“Alkenyl nonaflates from carbonyl compounds: New synthesis, elimination reactions, and systematic study of Heck and Sonogashira cross-couplings”

A thesis submitted to the Freie Universität Berlin
for the degree of
Dr. rer. nat.
Faculty of Chemistry and Biochemistry

2009

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Promotionsdatum: 19.06.2009

Contents

Abbreviations

Ac	acetyl
t-Bu	*tert*-butyl
BTEM	Band-Target Entropy Minimization
ca.	*circa*
cat.	catalytic
°C	degrees Celsius
cm^{-1}	wavenumber
DCE	dichloroethane
DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EI	electron ionisation
ESI	electrospray ionisation
Et	ethyl
et al.	*et alia*
eq. or equiv.	equivalent
GC	gas chromatography
GC-MS	gas chromatography–mass spectrometry
GP	general procedure
h	hour
HPLC	high performance liquid chromatography
HR	high resolution
ICES	Institute of Chemical and Engineering Sciences
IR	infrared
J	NMR coupling constant
lit.	literature
M	molar
MCPBA	meta-chloroperbenzoic acid
MeCN	acetonitrile
MHz	megahertz
min.	minute
ml	millilitre(s)
mmol	millimole(s)

m.p.		melting point
MS		mass spectroscopy
N		normal
NMR		nuclear magnetic resonance
NMR data:		
	s	singlet
	d	doublet
	dd	double doublet
	ddd	double double doublet
	t	triplet
	dt	double triplet
	quart.	quartet
	quint.	quintet
	m	multiplett
Ph		phenyl
ppm		parts per million
Pr		propyl
quant.		quantitative
R		unspecified group
RAMP		(*R*)-1-amino-2-methoxymethylpyrrolidine
rpm		revolutions per minute
r.t.		room temperature
SAMP		(*S*)-1-amino-2-methoxymethylpyrrolidine
STAB-H		sodium triacetoxy borohydride
TEMPO		2,2,6,6-tetramethylpiperidine-1-oxyl
tert		tertiary
TBAF		tetra *n*-butylammonium fluoride
TBDMS		*tert*-butyldimethylsilyl
TFA		trifluoroacetic acid
THF		tetrahydrofurane
TLC		thin layer chromatography
TMS		trimethylsilyl

Declaration and Copyright Statement

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In parts results described within this thesis have been published so far in peer reviewed journals or were presented on conferences as posters or oral presentations.

Publications in peer reviewed journals:

4.) Thieme Chemistry Journal Awardees – Where are they now?
“A General One-Step Synthesis of Alkynes from Enolisable Carbonyl Compounds”; Ilya M. Lyapkalo, Michael A. K. Vogel, Ekaterina V. Boltukhina, Jiri Vavrik, *Synlett*, **2009**, 4, 558-561.

3.) “A Straightforward Synthesis of Alkenyl Nonaflates from Carbonyl Compounds Using Nonafluorobutane-1-sulfonyl Fluoride in Combination with Phosphazene Bases”;
Michael A. K. Vogel, Christian B. W. Stark and Ilya M. Lyapkalo, *Synlett*, **2007**, 18, 2907-2911.

2.) “An Expedient Variant of Heck Reaction of Alkenyl Nonaflates: Homogeneous Ligand-Free Palladium Catalysis at Room Temperature”;
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1.) “A General and Versatile Method for C-C Cross-Coupling Synthesis of Conjugated Enynes: One-Pot Sequence Starting from Carbonyl Compounds”;
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9.) Michael A. K. Vogel, Christian B. W. Stark, Ilya M. Lyapkalo; “A New General One-step Methodology for the Synthesis of Alkynes from Enolizable Carbonyl Compounds”; 8th Tetrahedron Symposium; Berlin, **2007**, Poster presentation.

8.) Michael A. K. Vogel, Ilya M. Lyapkalo; “A New Expedient Variant of Heck Reaction of Alkenyl Nonaflates: Homogeneous Ligand- and Additive-free Pd-catalysis at Room Temperature”; German-Singapore Symposium; Singapore, **2007**, Oral presentation.

7.) Michael A. K. Vogel, Ilya M. Lyapkalo; “A New Expedient Variant of Heck Reaction of Alkenyl Nonaflates: Homogeneous Ligand- and Additive-free Pd-catalysis at Room

Temperature"; Asia Pacific Congress on Catalysis (APCAT-4); Singapore, **2006**, Oral presentation.

6.) Michael A. K. Vogel, Ilya M. Lyapkalo; "A Straightforward Synthesis of Alkenyl Nonaflates from Carbonyl Compounds using Nonafluorobutane-1-sulfonylfluoride in Combination with Phosphazene Bases."; International Kyoto Conference on New Aspects of Organic Chemistry (IKCOC – 10); Kyoto, **2006**, Poster presentation.

5.) Michael A. K. Vogel, Ilya M. Lyapkalo; "A New Expedient Variant of Heck Reaction of Alkenyl Nonaflates: Homogeneous Ligand- and Additive-free Pd-catalysis at Room Temperature"; International Kyoto Conference on New Aspects of Organic Chemistry (IKCOC – 10); Kyoto, **2006**, Oral presentation.

4.) Michael A. K. Vogel, Ilya M. Lyapkalo; "Alkenyl Nonaflates as a new entry in Transition Metal Catalysis - Highly robust and efficient ligand-free Heck Coupling Protocol starting from Carbonyl Precursors"; 231st ACS National Meeting, Atlanta, **2006**, Oral Presentation.

3.) Michael A. K. Vogel, Ilya M. Lyapkalo; "Alkenyl Nonaflates as a new entry in Transition Metal Catalysis - Highly robust and efficient ligand-free Heck Coupling Protocol starting from Carbonyl Precursors"; SICC-4 (Singapore International Chemical Conference – 4), Singapore, **2005**, Oral Presentation.

2.) Michael A. K. Vogel, Ilya M. Lyapkalo; "Alkenyl Nonaflates as a New Entry in Transition Metal Catalysis: Highly Robust, Fast and Efficient Ligand-free Heck Coupling Protocol at Ambient Temperature."; C&FC **2004** (International Symposium on Catalysis and Fine Chemicals 2004), HongKong, Poster Presentation.

1.) Michael A. K. Vogel, Ilya M. Lyapkalo; "Alkenyl Nonaflates as a New Entry in Transition Metal Catalysis: Highly Robust, Fast and Efficient Ligand-free Heck Coupling Protocol at Ambient Temperature."; C&FC **2004** (International Symposium on Catalysis and Fine Chemicals 2004), HongKong, Oral Presentation.

The Author

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the curriculum vitae is not included in the online version.

Acknowledgements

Firstly I wish to thank Dr. Ilya M. Lyapkalo, Prof. Dr. Christian B. W. Stark and Prof. Dr. H.-U. Reißig for making this thesis possible, based on a collaboration project between FU Berlin and ICES Singapore. Despite the fact it was not easy to run and finish the project, it was definitely worthwhile doing it.

Needless to say that I owe much to my supervisor and friend Ilya. It is indeed a long list. Thank you for making us the start in Singapore so easy and made us feel at home. I enjoyed a lot the funny time we had together (and the unforgettable moments). And not to forget for introducing us into the food court culture of this town, it is a really great thing.
Massive thanks for the endless ideas and inspiration. I fully enjoyed the talks and discussions we had. They were always fruitful and helpful. I simply enjoyed the time working with you. Thank you. Keep on going with the interesting topics we started here.

Christian, massive thanks for your support and to keep the things running. I know that was not easy. I hope(!) this little “adventure” was also for you a good and interesting experience. Your visit here was hilarious and I hope we can repeat that once.

I would never have survived this madhouse without the famous lunch table. Thousand thank you to Marc, Ludger, Asawin, Kanisha, Vu and Fabi. That was fun! Our enlightening talks were often the intellectual highlights of the day.

A big “Thank you!” to Ludger, Marc and Fabi for your intellectual input, the chemicals (your shelfs and drawers were a rich source for my work – I always asked!;-)) and the excellently maintained equipment I was allowed to make use of. Many thanks for the GC Fabi.

Thanks also to Ser Kiang and Simon. I appreciated a lot working with you. There was much to do to keep the lab running. I will never forget your kindness and humor guys.

Thank you PK. It was a great experience to get you known.

The late evenings and weekends were always the perfect antidote to the long working days. Thank you Steffi for your endless patience. There is nothing more to say.

Abstract

Within this thesis an efficient transformation of readily available carbonyl compounds to alkenyl nonaflates or alkynes is described. The particular advantage of this protocol is the use of the reagents NfF **7** and the phosphazene bases **29**/**30** under internal quenching conditions, therefore enabling to conduct this transformation in a single operational step. It was found that 5 to 7-membered cycloketones form cyclic alkenylnonaflates while acyclic ketones inevitable generate internal or terminal alkynes or allenes. Within systematic investigations we learnt that both reaction pathways are feasible for aldehydes and formation of either the alkenyl nonaflate or the terminal alkyne is temperature dependent.

As a model system the Heck reaction of cyclopentenyl nonaflate **28a** with methyl acrylate **44** was explored. Within systematic investigations the effect of solvents, bases, additives, ligands and different catalyst loadings was studied. It was found that the cross-coupling reaction features excellent efficiency and robustness as a ligand and additive free palladium catalysis. The optimization of the reaction conditions regarding reaction performance and practicability resultet in the use of NEt_3 as the base, $Pd(OAc)_2$ as the stable catalyst precursor and DMF as the solvent. The developed catalysis requires only the essential components for the Heck reaction without any further additives and due to its simplicicity it is suitable for up scaling or mechanistic investigations. In a comparative study cyclopentenyl nonaflate **28a** was found to provide a higher rate of conversion than cyclopentenyl iodide **46** and cyclopentenyl triflate **47**.

In a series of kinetic experiments the established ligand and additive free Heck cross-coupling could be identified as homogenous transition metal catalysis. Homogeneous catalysis with alkenyl sulfonates or halides is unprecedented so far and is the main reason for the robustness of the catalysis.

The developed Heck protocol could be extended to a variety of cyclic and acyclic alkenyl nonaflates and olefins. The desired products are formed in overall very good yields, while regioselectivities follow typically observed trends. During the systematic experiments a stabilizing effect of the diene products, formed during the Heck reaction course, on the catalytic active species could be demonstrated. Moreover, it could be shown further that the Heck- and Sonogashira cross-coupling methodology is compatible with the conditions of the alkenyl nonaflate and terminal alkyne formation. Therefore, the synthesis of dienes and enynes culminated in combining both synthetic steps in a *one-pot reaction sequence*. The developed one-pot protocol represents a straightforward methodology to generate highly functionalized dienes or enynes from readily available carbonyl compounds.

Zusammenfassung

Im Rahmen dieser Arbeit wird eine effiziente Umsetzung von leicht zugänglichen Carbonylverbindungen zu Alkenylnonaflaten oder Alkinen beschrieben. Der große Vorteil dieses Protokolls liegt in der Verwendung von NfF **7** und den Phosphazen Basen **29**/**30**, die unter „internal quenching“ Bedingungen angewendet werden und es daher erlauben, diese Transformationen in einem einzelnen operativen Schritt auszuführen. Es wurde festgestellt, daß fünf bis siebengliedrige cyclische Ketone zu cyclischen Alkenylnonaflaten führen, während lineare Ketone terminale oder interne Alkine, beziehungsweise Allene ergeben. In systematischen Untersuchungen konnte gezeigt werden, das für Aldehyde beide Reaktionswege offen stehen und die Bildung von entweder Alkenylnonaflaten oder terminalen Alkinen temperaturabhängig ist.

Als Modellsystem wurde die Heck-Reaktion von Cyclopentenylnonaflat **28a** mit Methylacrylat **44** untersucht. In systematischen Untersuchungen wurde der Effekt von Lösemitteln, Basen, Additiven, Liganden und unterschiedlichen Katalysatorladungen studiert. Die Kreuzkupplung als Liganden- und Additiv-freie Katalyse stellte sich als ausgesprochen effizient und robust heraus. Die Optimierung der Reaktionsbedingungen bezüglich Leistung und Praktikabilität führte zur Verwendung von NEt_3 als Base, $Pd(OAc)_2$ als Katalysatorvorläufer und DMF als das Lösemittel. Die entwickelte Katalyse benötigt ausschließlich die für die Heck-Reaktion essentiellen Komponenten und ist aufgrund der Einfachheit prädestiniert für große Maßstäbe oder mechanistische Untersuchungen. In einer vergleichenden Analyse wies Cyclopentenylnonaflat **28a** eine insgesamt höhere Umsetzungsgeschwindigkeit auf als Cyclopentenyliodid **46** oder Cyclopentenyltriflat **47**.

In einer Serie von kinetischen Experimenten konnte die entwickelte Liganden- und Additiv-freie Heck-Reaktion als homogene Übergangsmetallkatalyse identifiziert werden. Homogene Katalyse mit Alkenylsulfonaten und halogeniden ist bisher nicht berichtet und stellt den wesentlichen Grund für die Robustheit der Katalyse dar. Das entwickelte Heck-Protokoll konnte um eine Reihe von cyclischen und acyclischen Alkenylnonaflaten und verschiedenen Olefinen erweitert werden. Die gewünschten Produkte werden insgesamt in sehr guten Ausbeuten erhalten, während die Regioselektivitäten den üblichen Trends folgen. Bei systematischen Experimenten konnte ein stabilisierender Effekt der Diene, die bei der Heck-Reaktion gebildet werden, auf die katalytisch aktive Spezies nachgewiesen werden. Weiterhin konnte gezeigt werden, das die Heck- und Sonogashira Kreuzkupplungsmethodik mit den Bedingungen für die Bildung von Alkenylnonaflaten und terminalen Alkinen kompatibel ist. Dadurch kulminiert die Synthese von Dienen und Eninen in der Vereinigung beider synthetischer Schritte zu insgesamt einer *Eintopfsequenz*. Ausgehend von leicht zugänglichen Carbonylverbindungen stellt das entwickelte Eintopfprotokoll eine effiziente Methode zur Darstellung von hochfunktionalisierten Dienen oder Eninen dar.

Introduction and Objective

Introduction and Objective

Sulfonic esters and halides are important functional groups due to the ease of their accessibility, scope of applicability and high reactivity (Figure 1).[1] As leaving groups or as functionalities in transition metal catalyzed reactions they often represent key moieties in the synthetic organic conception and are found therefore frequently as part of important intermediates, designed for the generation of complex structures.

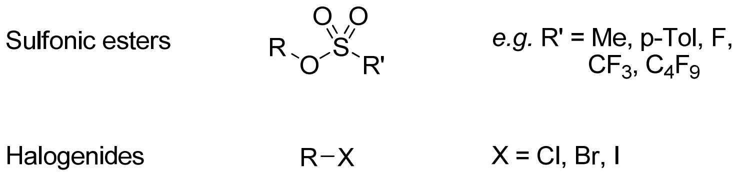


Figure 1 Sulfonic esters and halides as the most abundant functionalities in organic chemistry exhibiting an overall high reactivity and providing a wide scope of applicability.

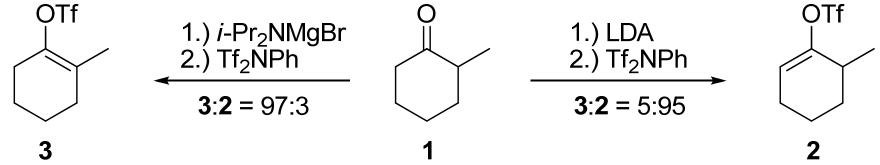
Similar to the halides (in this context this applies to chloride, bromide and iodide since the C-F bond with its high binding energy of 489 kJ/mol[2] shows a significantly different reactivity than the higher homologues) the corresponding sulfonic esters form bonds with sp^3- and sp^2-carbon centres. While the reactivity of the carbon-halide bond is naturally defined by the used halide, sulfonic esters feature a large scope of reactivity depending on the rest (R' in Figure 1). Within this structural motif a wide range in the relative leaving group ability of over 10^5 can be found.[3]

Among these compounds the perfluorinated sulfonic esters are functionalities of exceptional high reactivity and therefore the alkene perfluoroalkanesulfonic esters and aryl perfluoroalkanesulfonic esters are substrates of particular value.[4a-d] Since the corresponding acids of these groups are stronger Bronstedt acids than for instance sulphuric acid (pK_a = -2) or even perchloric acid (pK_a = -10), the anions generated from these substrates are some of the most non nucleophilic species known in organic chemistry.[5]

In general both halogens and sulfonic esters are readily available substrates, nevertheless significant differences exist. The introduction of a sulfonate group requires the presence of hydroxy or carbonyl functionality. Although these are common functional groups and a large number of methodologies for their synthesis exist, this requirement can represent a limiting factor for their preparation.

Aryl halides are abundant due to the ease of electrophilic halogenation of aromatic compounds. The synthesis is relatively cheap and practically any desired substitution pattern can be generated. In contrast the synthesis of aryl sulfonates implies the availability of the specific phenolic precursor. This considerably reduces the diversity of the available compounds and explains *e.g.* the predominant use of aryl halides in transition metal catalyzed reactions.

On the other hand, alkenyl halides are in general more difficult to prepare than the corresponding alkenyl sulfonates. While alkenyl halides are in principle accessible via addition reactions to alkynes the synthesis of highly substituted alkenes remains a difficult task. Particularly the generation of cycloalkenyl halides is problematic and proceeds with variable regioselectivity. In contrast cyclic and acyclic alkenyl sulfonates are readily available from enolizable carbonyl compounds without facing the same regioselectivity problems. A descriptive example represents the regioselective conversion of α-methyl cycloketones into the corresponding alkenyl triflates (Scheme 1). The transformation of 2-methyl-cyclohexanone **1** into either 6-methyl-cyclohex-1-enyl triflate **2** or 2-methyl-cyclohex-1-enyl triflate **3** is directed by either kinetic (yielding product **2**) or thermodynamic control (providing product **3**) of the enolate formation and affords the desired products in good yields and selectivities.[6]



Scheme 1 The regioselective conversion of 2-methyl-cyclohexanone **1** into either 6-methyl-cyclohex-1-enyl triflate **2** or 2-methyl-cyclohex-1-enyl triflate **3**; the differentiation between both products takes place by a kinetic (yielding product **2**) or thermodynamic (providing product **3**) controlled enolate formation.

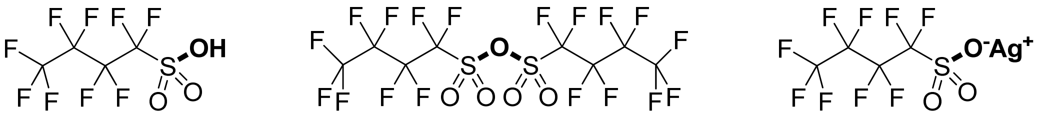
During the past 3 decades aryl and alkenyl halides and sulfonates became the most eminent groups in transition metal catalyzed reactions. Aryl halides and sulfonates meanwhile even became important substrates in Heck and Suzuki reactions on an industrial scale.[7a-b] Most frequently used substrates are aryl iodides and bromides or triflates. It is generally accepted that the catalytic cycle of the palladium catalyzed reactions starts with a Pd(0) insertion into the R-X or R-OSO_2R' bond. The commonly adopted order of reactivity for the above mentioned groups has been established to be I > OTf > Br >> Cl for aryl derivatives. However, scarce studies have been carried out so far in order to elucidate a rate of this step depending on the electronic effects of R' in sulfonates, and very little is known about the order of reactivity of alkenyl halides and alkenyl sulfonates in palladium catalyzed reactions.

Within the group of sulfonic esters, aryl and alkenyl triflates have found copious use in transition metal catalyzed reactions. In contrast, the corresponding nonaflates were not utilized for a long time to such an extent and just within the past two decades alkenyl and aryl nonaflates found a wider range of application in organic synthesis. However, meanwhile these substrates represent common tools in the field of transition metal catalysis, employed in various carbon-carbon as well as in carbon-nitrogen bond forming reactions.[8a-l]

This is an interesting circumstance since alkenyl nonaflates as well as phenyl nonaflates manifest some crucial advantages over the corresponding triflates. Often they show, depending on the catalytic system, a higher reactivity of in between 1.2 to 2 times greater than the triflates, in solvolytic reactions[9a-b] or in transition metal catalyzed transformations.[8d,10] Due to their long hydrophobic perfluorinated chain they are potentially easy to purify by flash chromatography with nonpolar solvents and therefore can be isolated in a straightforward manner. But the most significant advantage is the convenient preparation of alkenyl and aryl nonaflates from readily available enolates and phenolates, developed and further improved during the past three decades.

After the introduction of alkenyl nonaflates by Hanack *et al.* in 1972,[11] only a small number of practical methodologies of their preparation is reported in literature. Initially the most common procedures for the synthesis were either the addition of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid **4** to alkynes and certain allenes, and later the reaction of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid anhydride **5** with enolizable carbonyl compounds and enolates (Figure 2).[12a-c]

Although the addition of the perfluorinated sulfonic acid **4** is simple, it is limited to the preparation of mono- or disubstituted vinyl nonafluoroalkane sulfonates featuring a β-hydrogen atom. The most general and widely used procedure is the reaction of nonafluorobutanesulfonic acid anhydride **5** with enolizable carbonyl compounds or enolates. While use of the anhydride together with carbonyl compounds affords mono-, di-, or trisubstituted vinyl esters with different substituents in moderate to good yields, the later methodology is superior for the preparation of primary vinyl sulfonates.



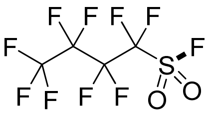
$CF_3(CF_2)_3SO_2$**-OH** **4** $[CF_3(CF_2)_3SO_2]_2$**-O** **5** $CF_3(CF_2)_3SO_2$**-O⁻Ag⁺** **6**

Figure 2 The nonaflating reagent 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid **4** and derivatives thereof, 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid anhydride **5** and silver-1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonate **6**.

Besides these two protocols a less commonly used method was the use of the silver salt **6** of nonafluorobutanesulfonic acid along with vinyl halides.[9b,13] Due to the restriction to reactive vinyl halides and the high cost of the silver salt, this protocol is naturally of limited practicability and got only applied to substrates which were not accessible by the two previously described procedures.

Altogether the above mentioned methodologies face restrictions in the synthetic potential, since they are of limited functional group tolerance and form the desired products only in moderate yields. In addition, they exhibit the disadvantage of being dependent upon harsh and costly reagents. For all these reasons a demand for more experimental simple and cost efficient procedures existed.

The major improvement in terms of manipulative simplicity and cleanness of the reaction was achieved with the introduction of the industrial product 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonylfluoride NfF **7** (Figure 3) as the trapping agent for preformed phenolates or enolates, to give the anticipated aryl or alkenyl nonaflates.[14]

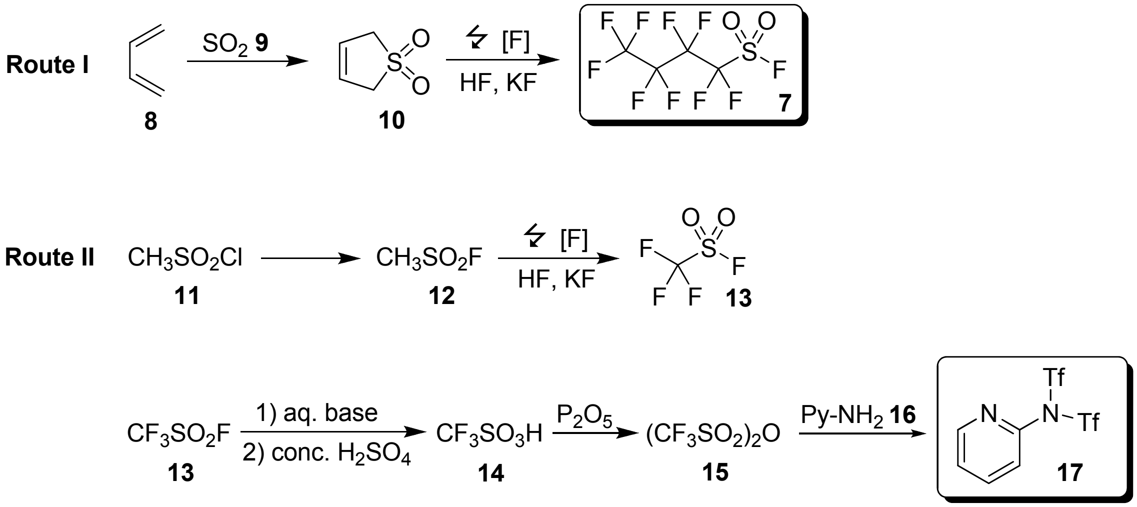


$CF_3(CF_2)_3SO_2$-F = Nf-F **7**

Figure 3 1,1,2,2,3,3,4,4,4-**N**ona**f**luorobutanesulfonyl**f**luoride = NfF **7**.

The major advantage of this transformation comes with the facile handling of this reagent. Compound **7** is a colourless, stable, moisture insensitive liquid with a boiling point of (65-66)°C and is therefore convenient to handle in the laboratory without any major precaution.

At this point it is worthwhile to take a closer look at the advantages of NfF **7**. The industrial scale synthesis of NfF **7** is depicted in Scheme 2, Route **I**. Starting from the multi ton products butadiene **8** and sulphur dioxide **9** the intermediate 3-sulfolene **10** is generated. Total electrochemical fluorination of **10** leads to NfF **7** in the second and already final step.[15] All the above mentioned nonaflating reagents are made thereof and require at least one additional synthetic step.



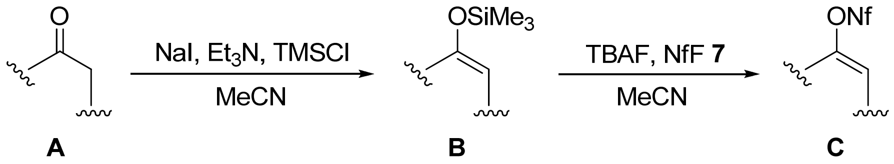
Scheme 2 Synthesis of the nonaflating agent NfF **7** (Route I) and the triflating agents triflic anhydride **15** and *N*-(2-pyridyl)triflimide **17** (Route II).

The synthesis of a comparatively mild triflating reagent is considerably more elaborate (Scheme 2, Route II).[16] Starting from methanesulfonyl chloride **11** the corresponding methanesulfonyl fluoride **12** is generated by halogen exchange. Total electrochemical fluorination of compound **12** leads to trifluoromethanesulfonyl fluoride **13**. This substrate has the major disadvantage that it is an aggressive gas with a boiling point of -23°C and therefore is difficult to handle. Transformation of **13** to its corresponding acid **14** and subsequent treatment with P_2O_5 gives triflic anhydride **15**, a liquid with a boiling point of 82°C. Reagent **15** is commonly used for the introduction of the CF_3SO_2 group; nevertheless it is a harsh reagent and often requires cryogenic conditions. Milder reagents, for instance *N*-(2-pyridyl)triflimide **17** are derived from the anhydride **15** and 2-aminopyridine **16**.

Overall the generation of mild triflating reagents requires at least three more synthetic steps. This makes NfF **7** competitive as compared with commercially available mild triflating reagents.

Variations in the synthesis of aryl and alkenyl nonaflates later on exclusively consisted in a different generation of the requisite anions. In the seminal publication by Hanack *et al.*, both enolates and phenolates were synthesized from either enolizable carbonyl compounds or phenol and its derivatives via reaction with NaH. While aryl nonaflates could be isolated in very good yields, the alkenyl nonaflates were obtained in overall low to moderate yields.[14]

A further improvement in the synthesis of alkenyl nonaflates was achieved by Hünig *et al.* based on their systematic investigations of enolate formation (Scheme 3).[17]



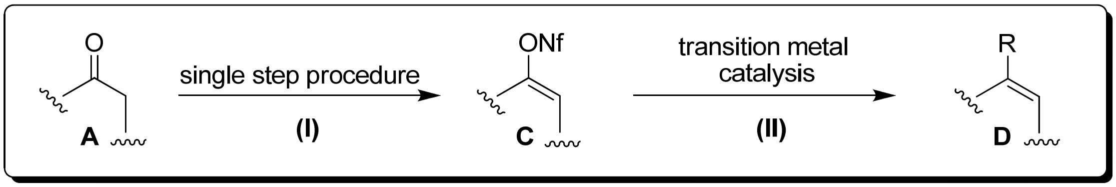
Scheme 3 The synthesis of alkenyl nonaflates **C** starting from enolizable ketones **A** via the isolable trimethyl silylenol ethers **B** as intermediates.

In a two step procedure enolizable carbonyl precursors **A** are transformed chemoselectively into the corresponding trimethylsilylenol ethers **B**. As thermally stable compounds they can be isolated in good to high yields. With the preservation of the configuration of the regioselectively formed C=C bond, alkenyl nonaflates **C** are formed by abstraction of the Me_3Si group from the silylenol ethers **B** with catalytic amounts of TBAF and O-sulfonylation by NfF **7** in overall good yields. Starting from the preformed silylenol ethers **B** this protocol was even successfully employed in various transition metal catalyzed coupling reactions in a one-pot sequence.[7b,18a-c]

Despite the accomplishments made in the regio- and chemoselective synthesis of alkenyl nonaflates further improvement is desirable. Especially if seen in the light of the central role of the carbonyl group in organic synthesis, new general transformations of the carbonyl functionality are always of particular importance.[1]

As consequence from the methodologies described so far, a more straightforward functionalization of enolizable carbonyl precursors **A** would be most desirable. A general and efficient transformation of enolizable carbonyl compounds **A** to yield alkenyl nonaflates **C**, accomplished within a single step did not exist at the outset of our study (Scheme 4, step I). The use in combination with NfF **7** does require a strong but non nucleophilic base in order to avoid substitution reactions with reagent **7**.

The development of such a protocol could even culminate in the subsequent utilization of the generated alkenyl nonaflate. This challenge would not be limited to a certain class of reaction. However, promising transformations would certainly be transition metal catalyzed cross-coupling reactions. This could result in an overall one-pot protocol for the preparation of complex structures from readily available carbonyl precursors (Scheme 4, step I + step II).



One-Pot Methodology

Scheme 4 Single step procedure for the synthesis of alkenyl nonaflates **C** from enolizable carbonyl compounds **A**, with a subsequent transition metal catalyzed cross-coupling. Compatibility of the alkenyl nonaflate formation with the transition metal catalysis provided would enable an overall one-pot methodology.

Such protocol makes considerable advances to more environmentally benign synthesis since one of the most important cost and waste factors is the use of solvents and purification steps. Combining several reactions in a one-pot manner does significantly help to reduce these factors.

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[1] “The chemistry of carbonyl compounds is virtually the backbone of synthetic organic chemistry”: J. D. Roberts, M. C. Caserio, Basic Principles of Organic Chemistry, Benjamin, New York, 1965, p. 426.

Alkenyl sulfonates became established substrates in organic synthesis. Nevertheless, only scant data exist about solvent, base and additive effects in transition metal catalyzed cross-coupling reactions of the alkenyl sulfonates. Also scarce data exists about differences in the reactivity of alkenyl halides and perfluoroalkenesulfonic esters. The same holds true for mechanistic studies. In particular, no data have been published verifying if these transformations are of homogeneous or heterogeneous nature. In remarkable contrast, numerous studies were published on the nature of Pd-catalysis in the Heck reaction of aryl halides.

Within this thesis the above mentioned desireable further progress in alkenyl nonaflate synthesis and even more straightforward cross-coupling methodologies employing alkenyl nonaflates will be addressed. Furthermore, this thesis shall help in a better understanding of solvent, base, and additive effects in transition metal catalyzed cross-coupling reactions of alkenyl sulfonates and to gain a better mechanistic insight of the catalysis.

Due to its promising synthetic potential the development and study of the scope of the direct generation of alkenyl nonaflates will be the beginning and a major part of the thesis (as depicted in Step 1, Scheme 4). In addition the potential of combining an established procedure with a subsequent transition metal catalyzed reaction, in an overall *one-pot* methodology, will be investigated (Scheme 4).

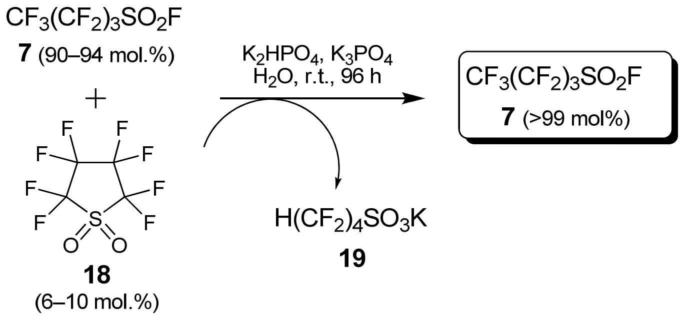
Furthermore, mechanistic investigations and the role of solvent, base, and additive effects in a model Heck reaction will be conducted. Depending on a successful method development and gained mechanistic insights also potential applications of the established procedures will be investigated.

Alkenyl nonaflates from enolizable carbonyl precursors – methodology, preparation, and elimination reactions

1. Alkenyl nonaflates from enolizable carbonyl precursors – methodology, preparation and elimination reactions

1.1. Purification of NfF and compatibility experiments with bases

The perfluorinated reagent NfF **7** is an industrial product and produced on a ton scale. The compound is obtained in 90-94% purity by the total electrochemical fluorination of 2,5-dihydrothiophene-1,1-dioxide **10** (Scheme 2, Route I), with the perfluorosulfolane **18** as side product (6–10%, see Scheme 5).[15] Although the presence of **18** has no apparent effect on the performance of NfF **7**, it may lead nevertheless to the formation of side products[19] in reactions when reagent **7** is involved or to a deterioration in the analytical characteristics of isolated nonaflates.

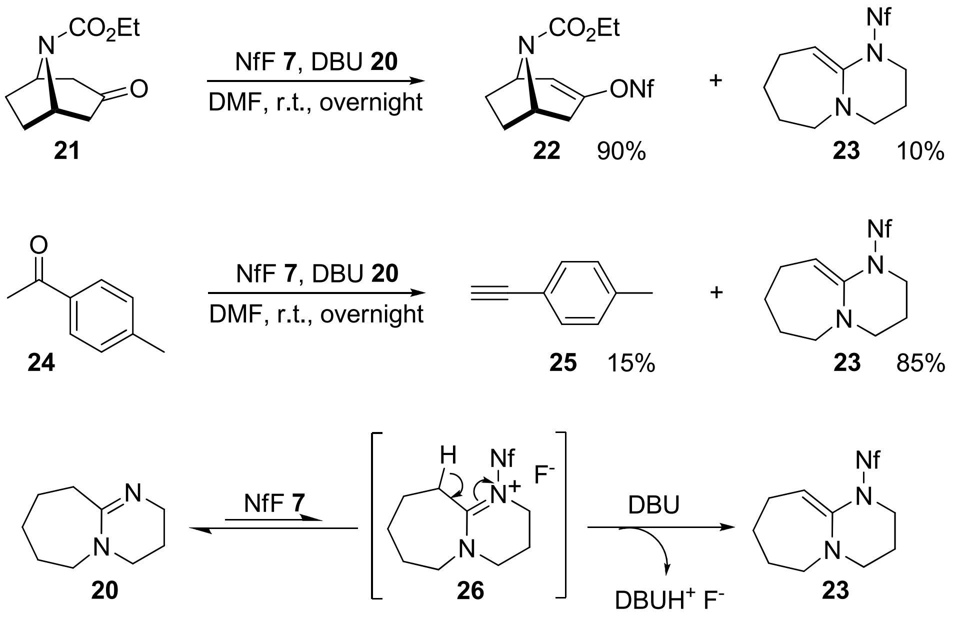


Scheme 5 Purification of NfF **7** via basic treatment by an aqueous phosphate buffer solution within a pH-range of 12-13.

We have found that vigorous stirring of the technical grade product, consisting of the perfluorinated compounds **7** and **18**, with a concentrated aqueous buffer solution of K_2HPO_4/K_3PO_4 (pH 12–13) for 96 hours at room temperature leads to the highly selective nucleophilic ring opening of the perfluorosulfolane **18** to give potassium 1,1,2,2,3,3,4,4-octafluorobutane-sulfonate **19**[20] with NfF **7** remaining essentially intact (Scheme 5). Phase separation followed by distillation over P_2O_5 furnishes **7** in 92% yield and of over 99% purity according to ^{19}F-NMR. Pure NfF **7** obtained this way was used for all further transformations.

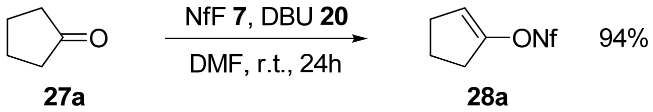
In our pursuit of the one-pot methodology (see Scheme 4), we aimed at finding a base compatible with NfF **7** and at the same time strong enough to effect deprotonation of a wide range of enolisable aldehydes and ketones. Since common lithium amide bases, widely used in the α-deprotonation of ketones, readily react with reagent **7** even at low temperature to give the anticipated nonafluorobutane-1-sulfonamides,[19] we turned our attention to metal-free nitrogen bases.

1,8-Diazabicyclo[5.4.0]undec-7-en (hereinafter called DBU **20**) represents a promising candidate due to its ready availability and a $pK_{BH}{}^{+} = 24.33$ in MeCN.[21a-b] *N*-Ethoxycarbonyl tropinone **21** smoothly produced the nonaflate **22** under the action of DBU **20** and NfF **7** (Scheme 6, top). However, 1-(4-methylphenyl)-ethanone **24** gave only 15% conversion to the anticipated 4-methylphenyl-acetylene **25** in the presence of the excess of DBU **20** (2.35 equivalent), whereas NfF **7** (1.30 equivalent) has been fully consumed resulting in unexpected product **23** (Scheme 6, center). Its formation was rationalized in terms of self-assisted nonaflation of DBU **20** via intermediate **26** (Scheme 6, bottom), and the structure was proven by independent synthesis and full characterisation.[22]



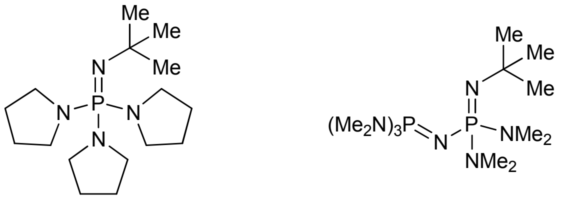
Scheme 6 An undesired side reaction: Formation of *N*-sulfonylated octahydro-pyrimido azepine **23** from the reaction of DBU **20** with NfF **7** (bottom); while *N*-ethoxycarbonyl tropinone **21** is transformed to the corresponding nonaflate **22** accompanied by a minor amount of compound **23** (top), the reaction of 1-(4-methylphenyl)-ethanone **24** with DBU **20** mainly results in the formation of substance **23** (center).

The competing formation of alkenyl nonaflate and *N*-sulfonyl octahydro pyrimido azepine **23** formation can be directed into the generation of alkenyl nonaflates in the case of relatively reactive enolizable ketones like cyclopentanone **27a**, which forms the corresponding alkenyl nonaflate **28a** still in high yields (Scheme 7). However, this approach lacks generality and the poor results achieved with DBU **20** in combination with carbonyl precursors like 1-(4-methylphenyl)-ethanone **24** prompted us to seek a base which would be free from intrinsic drawbacks of reagent **20**, namely it should be sterically congested at the basic centre and should not contain acidic hydrogen atoms at α- and β-positions.



Scheme 7 Transformation of cyclopentanone **27a** to the corresponding nonaflate **28a** using DBU **20** as the base.

We were pleased to find out that (*tert*-butylimino)tris(1-pyrrolidinyl)-phosphorane **29**[23] (hereinafter called P_1-base) as well as 1-(*tert*-butylimino)-1,1,3,3,3-pentakis(dimethylamino)-$1\lambda^5,3\lambda^5$-diphosphazene **30**[24] (hereinafter called P_2-base), commercially available representatives of the phosphazene bases family advantageously introduced and developed by R. Schwesinger *et al*. turned out to be fully compatible with NfF **7**.



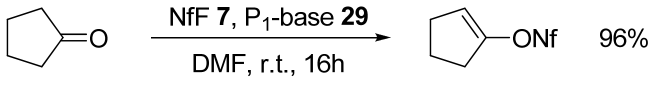
P_1-base **29**

P_2-base **30**

Figure 4 Phosphazene bases employed for the alkenyl nonaflate formation (nonaflation) of carbonyl compounds (according to the primary classification given by R. Schwesinger, the subscript designates the number of P-atoms in the molecule).

Within the phosphazene base family a wide range of high basicity is offered, giving the opportunity to select the appropriate base for a specific substrate.[25] When combined with

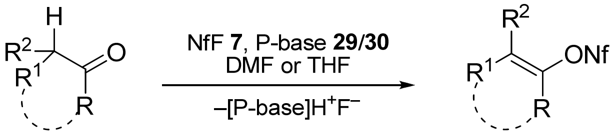
NfF **7** in dry dipolar aprotic solvents (typically DMF), the P_1-base **29** provides clean and complete conversion of cyclopentanone **27a** to form the desired cyclopent-1-enyl nonaflate **28a** in high yield (Scheme 8).



27a **28a**

Scheme 8 Smooth transformation of cyclopentanone **27a** to the corresponding nonaflate **28a** using the P_1-base **29** in dry dipolar aprotic solvents.

The phosphazene bases exhibit a basicity of $pK_{BH}{}^{+} = 28.35$ for the P_1-base **29**[26] and $pK_{BH}{}^{+} = 33.49$ for the P_2-base **30**[26] (both in acetonitrile), therefore enabling the deprotonation of aldehydes and ketones over a large substrate range. This allowed us to develop a novel synthesis of alkenyl nonaflates **C** achieved in a single operational step by having the electrophilic component NfF **7** present during the deprotonation of the enolizable carbonyl compound **A** by the phosphazene base (Scheme 9). This mode of reactivity, termed internal quenching, was originally described by Corey and Gross for highly regio- and stereoselective syntheses of silyl enolethers by deprotonation of the carbonyl compounds **A** with lithium dialkylamide bases in the presence of trialkylsilyl chlorides.[27]



A **C**

Scheme 9 Synthesis of alkenyl nonaflates **C** from enolizable carbonyl compounds **A** using the phosphazene bases **29**/**30** in combination with NfF **7** under internal quenching conditions.

The protocol is generally carried out in a 1 molar concentration, allowing monitoring of the reaction course by ^{1}H-NMR (one exemplary run was also successfully conducted using cyclopentanone **27a** in a 2 molar concentration). The transformations precede smoothly in common non-protogenic solvents like THF or DMF. The compounds are added consecutively to the chosen solvent, stirred for the designated amount of time and after completion of the reaction purified by a simple chromatographic workup with pentane or hexane as the eluent. The above described methodology comprises experimental simplicity with overall good to excellent yields. Taking all these beneficial attributes of the protocol into account, it can be stated that scale up should also be easily feasible for this transformation.

1.2. Application of the internal quenching protocol for the preparation of cyclic alkenyl nonaflates

The alkenyl nonaflate formation for a representative array of cyclic ketones **27a–i** using the phosphazene bases **29/30** and NfF **7** under internal quenching conditions is summarized in Table 1. The detailed investigation for the regioselective alkenyl nonaflate formation from ketones **27f,g** is summarized in the Tables 2 and 3.

The P_1-base **29** induces high-yielding conversion of cyclic, plane-symmetric ketones **27a**–**e** to the desired alkenyl nonaflates **28a**–**e** (Table 1, Entries 1-5). While the basicity of the P_1-base is sufficient to obtain full conversion for 5- and 6-membered cyclic ketones generally within 16 hours, 7-membered cyclic ketones require slightly longer reaction times or elevated temperature to obtain a nearly quantitative conversion.

Compared to six and seven membered rings the relatively higher acidity of cyclopentanone **27a** (Entry 1) and high acidity of 2-indanone **27e** (Entry 5) permits the use of even weaker bases. Ketone **27a** was successfully transformed with DBU **20** furnishing product **28a** in comparable yields to those achieved with the phosphazene base **29**, indicating that the side product formation of compound **23** is not significant. Equally efficient was the nonaflation of the substrate **27e** with DBU **20**. Due to the relatively high acidity of this carbonyl compound (pK_a = 16.9 in DMSO)[28] even the distinctly weaker base NEt_3 can be employed, albeit with somewhat lower yields. Further alkenyl nonaflate **28b** could be generated using DBU **20** with 1.40 equivalents of LiCl as additive. The reaction stalled after 20 hours at a conversion of 76%. However, the desired product **28b** could be isolated in 71% yield.

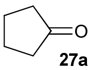
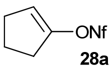
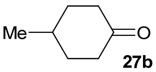
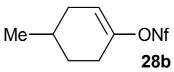
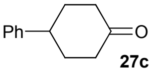
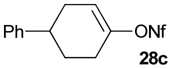
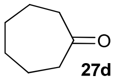
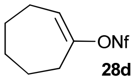
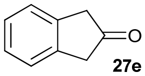
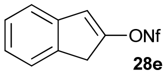
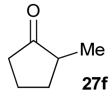
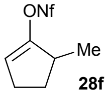
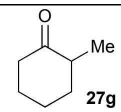
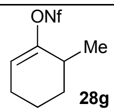
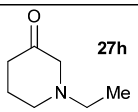
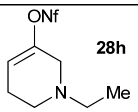
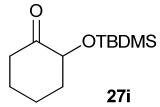
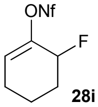
Entry	Ketone	Base	Reaction conditions	Product	% Yield / Ratio
1	 **27a**	P_1-base DBU^{a}	DMF, r.t., 16h DMF, r.t., 24h	 **28a**	**96** **94**
2	 **27b**	P_1-base DBU / LiCl^{b}	THF, r.t., 16h DMF, r.t., 30h^{c}	 **28b**	**96** **71**
3	 **27c**	P_1-base	THF, r.t., 20h	 **28c**	**95**
4	 **27d**	P_1-base	DMF, r.t., 24h	 **28d**	**77**^{d}
5	 **27e**	P_1-base DBU NEt_3^{e}	THF, r.t., 16h THF, r.t., 24h DMF, r.t., 22h	 **28e**	**95** **94** **72**
6	 **27f**	P_2-base P_1-base	DMF, –30°C, 17h DMF, 21h	 **28f**	**84** / (*ca*. 24:1^{f}) **89** / (1.2:1^{f})
7	 **27g**	P_2-base P_1-base	DMF, –20°C, 65h^{g} DMF, r.t., 111h	 **28g**	**93** / (99:1^{f})^{h} **84** / (1:1)
8	 **27h**	P_1-base LiHMDS	DMF, r.t., 18h THF, –78°C, 4h	 **28h**	**75** **91**^{i}
9	 **27i**	P_1-base	DMF, r.t., 62h	 **28i**	**61**

Table 1 Synthesis of alkenyl nonaflates **28** from enolizable cyclic ketones **27**: with the P-bases **29**/**30** (1.15 equiv.) and NfF **7** (1.15 equiv.) at room temperature unless stated otherwise; a) addition of NfF **7** 20 min after base addition, b) 1.40 equiv., c) after 20h the reaction stalled at 76% conversion, d) after 24 hours *ca.* 95% conversion were detected, e) 4 equiv., f) in favor of the less substituted regioisomer (see Table 2 and 3), g) 88% conversion after 24 h, h) 2.0 equiv. of the P_2-base **30** and NfF **7** were required in order to achieve complete conversion of the starting ketone, i) the crude material obtained was characterized without further purification.

The protocol was also successfully extended to the heterocycle 1-ethyl-piperidine-3-one **27h** (Entry 8). In order to investigate the reactivity of this substrate, an initial transformation was carried out employing lithium bis(trimethylsilyl)amide at –78°C. In order to avoid formation of the sulfonamide, ketone **27h** was added dropwise to a preformed solution of lithium bis(trimethylsilyl)amide in THF and quenched after 15 min with NfF **7** at the same temperature. The solution was stirred for 2 hours, allowing the warm up of the mixture to room temperature. After aqueous workup 91% of the isomer **28h** was obtained as crude product. Applying the P_1-base in the above described standard procedure furnished the pure compound in 75% yield also exclusively as the desired regioisomer **28h**.

The metal-free, non-coordinating nature of the P_1-base **29** provides perfect regioselectivity control in favour of the deprotonation of ketone **27h** at the position most remote to the ring nitrogen to give nonaflate **28h** as a single isomer. However, the P_1-base was found to be non-regioselective with respect to α-methine *vs.* α-methylene deprotonation of 2-methyl cyclopentanone **27f** (Entry 6 and Table 2, Entry 1) and 2-methyl cyclohexanone **27g** (Entry 7 and Table 3, Entry 1), respectively. While the P_1-base proved to be unselective (Table 2, Entry 1, Table 3, Entry 1), the regioselectivity was dramatically improved when the much stronger P_2-base **30** was employed under kinetically controlled conditions.

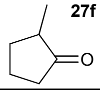
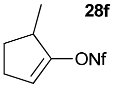
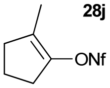
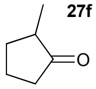
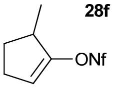
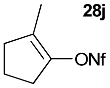
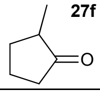
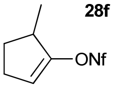
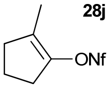
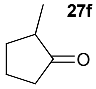
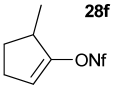
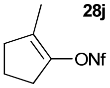
Entry	Ketone	Base	Reaction conditions	Product ratio[a]			% Yield
1	 **27f**	P_1-base	DMF, 21h -0°C → r.t. in 1h	 **28f**	**1.2 / 1**	 **28j**	**89**
2	 **27f**	P_2-base	THF, 16h addition at –78°C → r.t.	 **28f**	**6 / 1**	 **28j**	**84**
3	 **27f**	P_2-base	DMF addition at –40°C → -30°C -30°C for 17h	 **28f**	**24 / 1**	 **28j**	**85**
4	 **27f**	P_2-base	DMF addition at –50°C → -40°C -40°C for 19h	 **28f**	**16 / 1**	 **28j**	**83**

Table 2 Nonaflation of 2-methyl cyclopentanone **27f** under varying conditions with the P-bases **29**/**30** (1.15 equiv.) and NfF **7** (1.15 equiv.); a) determined by ^{1}H-NMR.

For both ketones addition of the P_2-base **30** at -78°C and subsequent warming up to room temperature resulted in an improved regioisomer ratio (Table 2, Entry 2 and Table 3, Entry 2). However, a defined temperature control over longer reaction times is excluded by using dry ice/acetone mixtures, but is of crucial importance in order to determine the ideal temperature range for the most effective regioisomeric discrimination. Therefore, a refrigerated circulator was used, enabling a precise temperature adjustment. With this modified experimental set-up the ideal temperature range was investigated in order to obtain both high yields and satisfactory regioisomer ratios.

The temperature providing the best regioselectivity and fastest conversion of starting material **27f** was identified with –30°C, affording the product **28f** in 85% yield (Table 2, Entry 3). Lowering the temperature further resulted in a less substantial increase in regioselectivity (Table 2, Entry 4).

Low temperatures applied to substrate **27g** resulted in long reaction times and unfortunately were also accompanied with base deactivation (Table 3, Entries 3-5). Keeping the temperature constantly at –20°C led to an increased rate of conversion but in all cases conversion was less then 70% after 24 hours (a representative example is presented in Table 3, Entry 6). Minimal reaction progress was observed even after additional days. Increasing the amount of the P$_2$-base **30** and NfF **7** up to 2.0 equivalents with an addition at -50°C under otherwise unchanged conditions gave finally full conversion and an excellent regioisomeric ratio of 99:1 in favour of the kinetically preferred product (Table 3, Entry 7).

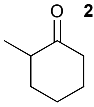
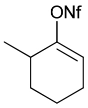
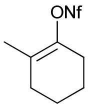
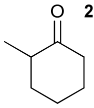
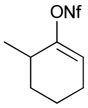
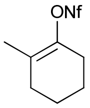
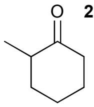
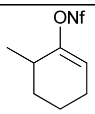
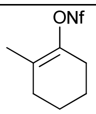
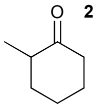
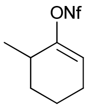
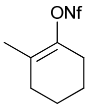
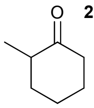
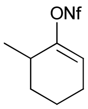
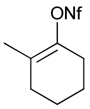
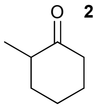
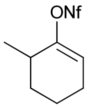
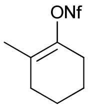
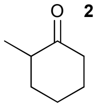
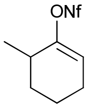
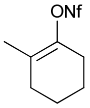
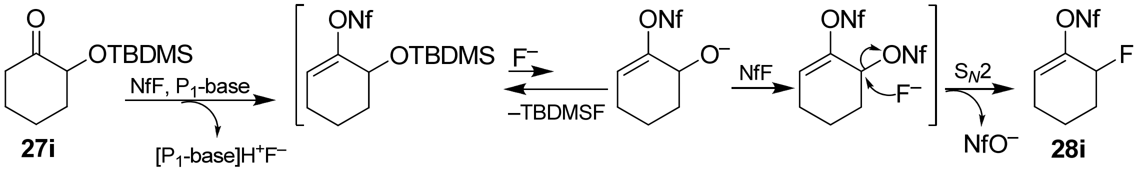
Entry	**Ketone**	**Base**	**Reaction conditions**	**Product ratio[a]**			**% Yield**
1	 **27g**	P$_1$-base	DMF, 111h -0°C → r.t. in 1h (~85% conversion)	 **28g**	**1/1**	 **28k**	**84**
2	 **27g**	P$_2$-base	THF, 16h addition at –78°C → r.t. slowly	 **28g**	**1.3/1**	 **28k**	**94**
3	 **27g**	P$_2$-base	THF, 63h addition at –70°C → -60°C; -60°C, no conversion	 **28g**	**—[b]**	 **28k**	**—[b]**
4	 **27g**	P$_2$-base	THF add. at –50°C → -40°C; 10% conv. after 16h; → -30°C, 50% conv. after 20h[c]	 **28g**	**—**	 **28k**	**—**
5	 **27g**	P$_2$-base	DMF add. at –40°C → -30°C, 41% conv. after 24h; → -20°C, 68% conv. after 48h[c]	 **28g**	**—**	 **28k**	**—**
6	 **27g**	P$_2$-base	DMF add. at –50°C → -20°C, 68% conv. after 21h; 100% conv. at r.t. within 5h	 **28g**	**5/1**	 **28k**	**—**
7	 **27g**	P$_2$-base[d] (2.0 equiv.)	DMF, 65h[e] add. at –50°C → -20°C	 **28g**	**99/1**	 **28k**	**93**

Table 3 Nonaflation of 2-methyl cyclohexanone **27g** under varying conditions with P-bases **29**/**30** (1.15 equiv.) and NfF **7** (1.15 equiv.) unless stated otherwise; a) determined by ^{1}H-NMR, b) "—" not determined, c) base inactive after this period, d) 2.3 equiv. NfF **7**, e) 88% conversion of ketone **27g** after 24h.

It must be emphasized that the use of DMF (m.p. -61°C) is limited to a temperature range of –40°C to –50°C since otherwise freezing of the reaction mixture is inevitable. The P$_2$-base **30** is used as a 2 molar solution in THF and therefore carrying out the transformation at slightly lower temperatures in THF/DMF mixtures is feasible. Carrying out the reaction at -78°C necessarily requires THF to be the sole solvent.

Kinetically controlled, highly regioselective nonaflation of 2-(*tert*-butyldimethylsiloxy) cyclohexanone **27i** triggered an unexpected replacement of the OTBDMS group by fluoride, resulting in a moderate yield of the nonaflate **28i** (Table 1, Entry 9). Presumably, fluoride-induced cleavage of the TBDMS group (The ^{1}H-NMR signals of TBDMS-F, detected in the spectrum of the crude reaction mixture, matched well those reported in the literature)[29] gives the intermediate bis-nonaflate and is followed by nucleophilic substitution of the ONf-group at the *sp*^{3}-carbon centre by the fluoride anion[2], as depicted in Scheme 10. Indicated by ^{1}H-NMR analysis product **28i** is formed along with a small amount of side product, which could neither be identified by HPLC-MS nor GC-MS analysis so far.



Scheme 10 Putative mechanism for the nonaflation – substitutive fluorination of ketone **27i** and the final generation of enol nonaflate **28i**.

After establishing this protocol for a number of representative cyclic ketones, including the nitrogen containing heterocycle **27h**, an extension to a larger number of synthetically interesting heterocycles was envisaged. Furanes, Pyranes and Oxepanes are structural entities found in numerous natural products and pharmaceuticals. Derivatives possessing such structural moieties could be generated from lactones of the respective ring size by the established protocol.

Compared to cyclic ketones lactones exhibit a comparable acidity of the α-methylene moiety. For example the 6-membered cycle δ-valerolactone **31b** displays a pK_a of 25.2[31] and is therefore slightly more acidic than cyclohexanone owing a pK_a = 26.4.[28] As representative examples γ-butyro- **31a**, δ-valero- **31b** and ε-caprolactone **31c** were chosen in order to study

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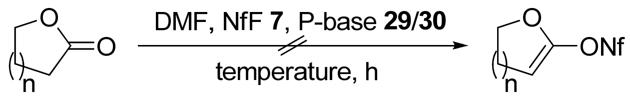
[2] A replacement of the OH group with fluoride using NfF in combination with a strong base was reported earlier.[30]

the formation of the corresponding alkenyl nonaflates by our protocol (Scheme 11). The experimental details of this investigation are summarized in Table 4.



n = 1 = **31a**
2 = **31b**
3 = **31c**

n = 1 = **32a**
2 = **32b**
3 = **32c**

Scheme 11 γ-Butyrolactone **31a**, δ-Valerolactone **31b**, and ε-caprolactone **31c** as representative oxygen containing heterocycles in the established nonaflation protocol.

The room temperature reaction of lactones **31a**-**c** (Entries 1-3) with the P_1-base **29** and NfF **7** for 19 and 22 hours in the case of γ-Butyrolactone **31a** and ε-caprolactone **31c**, and even up to 4 days for δ-Valerolactone **31b** afforded no product formation for the candidates at all. Warming up the reaction mixtures to 50°C and even 70°C for up to 24 hours did not lead to the formation of the desired products **32a**-**c** as well. ^{1}H-NMR reaction control indicated in all cases the presences of the unaffected starting materials **31a**-**c** in all cases.

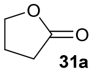
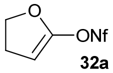
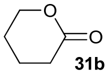
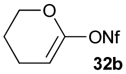
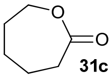
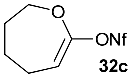
Entry	Ketone	Base & Reaction conditions	Product	% Yield
1	 **31a**	P_1-base, DMF, r.t., 19h additionally at 50°C for 16h additionally at 70°C for 16h	 **32a**	—
2	 **31b**	P_1-base, DMF, r.t., 4d additionally at 50°C for 16h	 **32b**	—
3	 **31c**	1.) P_1-base, DMF, r.t., 22h additionally at 50°C for 24h 2.) P_2-base, THF, r.t., 18h	 **32c**	—

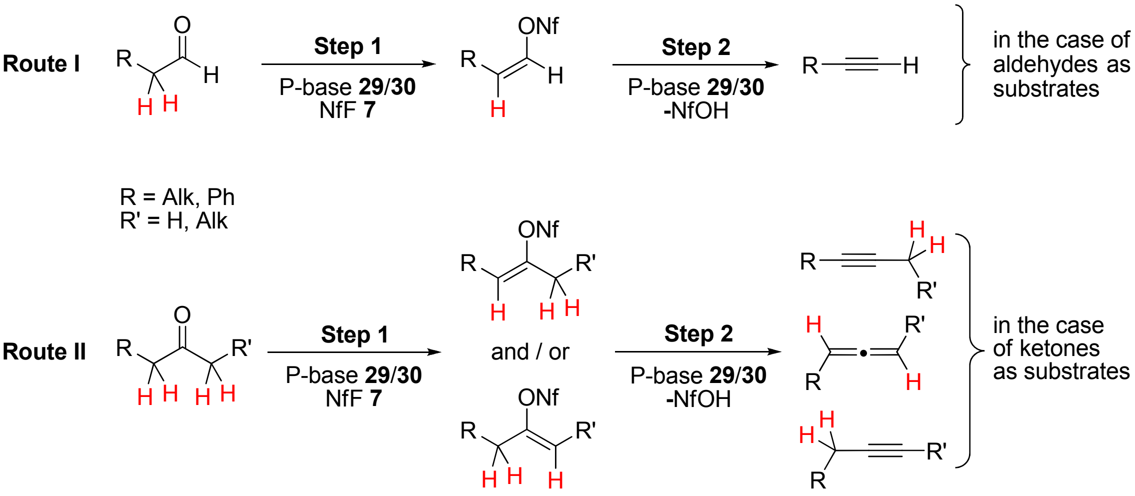
Table 4 Attempts to generate the alkenyl nonaflates from γ-Butyrolactone **31a**, δ-Valerolactone **31b**, and ε-caprolactone **31c** under internal quenching conditions.

In order to rule out lacking basicity of the P_1-base **29** under the applied reaction conditions causing the negative experimental outcome, the stronger P_2-base **30** was applied using caprolactone **31c** as a starting material. After 18 hours reaction time again exclusively the unaffected starting material **31c** was identified. Without being too speculative the experimental failure can be most likely explained by the lacking tendency of carbocylic esters to form enolates as it is described for instance for the highly acidic cyclic dilactone Meldrums acid.[31]

1.3. Reactions of acyclic ketones with NfF and phosphazene bases

1.3.1. General remarks

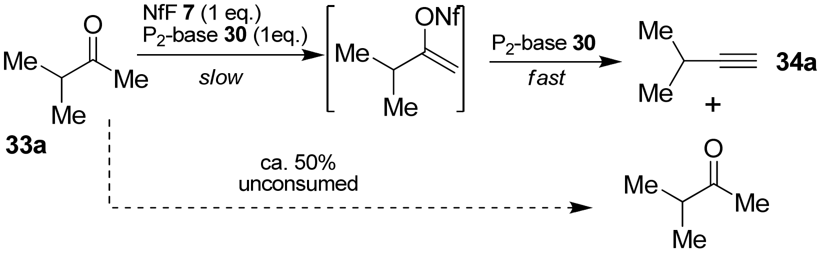
While 5 to 7-membered cyclic ketones form alkenyl nonaflates under the described reaction conditions, aldehydes and linear ketones can undergo further transformations. Treatment of an acyclic carbonyl compound with NfF **7** and phosphazene bases **29**/**30** leads in any case to alkenyl nonaflate formation first (Scheme 12; Route I, II; Step 1). Additionally a subsequent base-induced elimination of formally NfOH resulting in the formation of alkynes or allenes is feasible for these substrates (Scheme 12, Route I, II; Step 2). This pathway is disabled for the 5-7 membered cyclic ketones since it would lead to highly strained products possessing sp-hybridized carbon centers confined in the 5-7 membered cycles.



Scheme 12 Illustration of the possible elimination pathways of aldehydes (Route I) and acyclic ketones (Route II), exhibiting α-methylene groups, in the nonaflation-elimination protocol.

If the elimination reaction (Step 2) is the rate determining step and only 1 equivalent of the base is used, the reaction can potentially lead to alkenyl nonaflates as the final products. On the other hand, if formation of the alkenyl nonaflate is the rate limiting step (Step 1), the reaction will inevitably end up in the elimination of formally NfOH. In this specific case aldehydes will exclusively give terminal alkynes as the final products (Scheme 12, Route I). Ketones generally offer two reaction pathways, if more than one methylene or methyl moiety adjacent to the carbonyl functionality is available for proton abstraction (Scheme 12, Route II). The first deprotonation forms either a sole or two different alkenyl nonaflates, depending on differences in the availability and acidity of the protons adjacent to the carbonyl functionality (Step 1). At least a sole regioisomer formed has the chance to react in the second deprotonation step to give a single alkyne, or if deprotonation takes place at the β-position to the alkenyl moiety to form an allene (Step 2). Mixtures of alkenyl nonaflates generated after the first deprotonation step, will lead in most cases to mixtures of different alkynes, or alkynes and allenes.

In order to accomplish the complete transformation of a carbonyl precursor to an alkyne or allene, at least 2 equivalent of the base are required. In a typical example the linear ketone 3-methyl-2-butanone **33a** was mixed with equimolar amounts of NfF **7** and P_2-base **30** at -78°C (Scheme 13). When the solution was allowed to warm up to room temperature, the reaction led to formation of a *ca*. 1:1 mixture of the starting material and isopropyl acetylene **34a**, thus clearly pointing out that the generation of the alkenyl nonaflate is the rate determining step.[22] This experimental finding was later verified for other ketones as well.

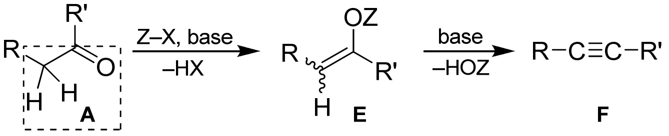


Scheme 13 A typical example for acyclic ketones: Competing deprotonation reactions of the starting material **33a** and the intermediary formed alkenyl nonaflate. The resulting *ca.* 1:1 mixture of ketone **33a** and terminal alkyne **34a** using 1 equiv. of P_2-base **30** suggest that the alkenyl nonaflate formation must be the rate determining step in this reaction.

It must be emphasized that the elimination of formally H_2O from enolizable ketones and aldehydes generates the C,C-triple bond directly at the position of the parent carbonyl functionality within the given carbon backbone, in contrast to such established methodologies for C,C-triple bond formation like the Corey-Fuchs sequence or the Seyferth-Gilbert homologation, in which the alkyne formation takes place by a C_1-extension.[32a-d]

1.3.2. Synthesis of alkynes: reactivity and selectivity

No general one-pot procedure for the conversion of enolizable carbonyl functionalities to C,C-triple bonds encompassing both ketones and aldehydes has been described at the outset of our study. In view of the synthetic potential of alkynes and the existing abundance and accessibility of ketones and aldehydes, such a method would be of particular interest. As long as formation of the C,C-triple bond within the given carbon backbone is concerned, elimination of (formally) H_2O from enolizable carbonyl group looks very attractive due to the apparent simplicity of this non-redox transformation (Scheme 14).



Scheme 14 General approach towards the synthesis of alkynes **F** starting from enolizable carbonyl compounds **A** by incorporating carbonyl oxygen into a good leaving group OZ in the intermediate enolate **E**.

Different procedures for the conversion of ketones **A** (R' ≠ H) to alkynes **F** have been reported to date. A protocol originally developed by Negishi *et al.* is most frequently used.[33] It consists of sequential treatment of the ketone with LDA or Li-2,2,6,6-tetramethylpiperidide and $(EtO)_2P(O)Cl$, with the intermediate enol phosphate treated with an excess of the Li-amide base again. The protocol features good regioselectivity, but the substrate is exposed to the excess of the exceedingly strong base so that base-labile functionalities must be avoided. The elimination could be induced by a somewhat milder Me_3COK, but it necessitates the presence of an electron-withdrawing functionality.[34] Eliminations induced by trialkylamines, via enol triflates using Tf_2O / *i*-Pr_2NEt[35] or via *N*-methyl-2-(alken-1-yloxy)pyridinium salts using 2-chloro-*N*-methylpyridinium iodide / Et_3N[36a-b] are limited to substrates with electron-withdrawing groups (R' = Ar or *R*$_2$N, see Scheme 14). Moreover, the one-pot conversion of aldehydes **A** (R' = H) to terminal acetylenes **F** seems to be unprecedented at the outset of our study (a complex, multistep redox transformation involving *n*-Bu_3SnLi, CBr_4, PPh_3, DBU and $Pb(OAc)_4$ is reported).[37]

The procedure for the elimination of carbonyl compounds to alkynes resembles the protocol for the alkenyl nonaflate formation of cyclic ketones. The phosphazene base **29**/**30** is added to the 1 molar mixture of the carbonyl compound and NfF **7** in DMF at slightly lower temperature and the solution is allowed to warm up to room temperature afterwards. Since the elimination consists of two separate deprotonation steps, 2 equivalents of the base are used for the full conversion of the starting material. In most cases a clean transformation is observed by ^{1}H-NMR analysis and usually the desired alkynes are furnished in overall very good yields, taking into account that two subsequent reaction steps are carried out one-pot.

The outcome of the reaction is strongly substrate dependent (Scheme 12, Route II). It was thought that the availability of α-protons or the differences in the acidity of the protons adjacent to the carbonyl functionality direct the elimination step towards either alkyne or allene formation. The reaction outcome is generally predictable if exclusively on one side of the carbonyl group protons are available for abstraction. This is for example the case if one quaternary carbon atom or aryl substituent is adjacent to the carbonyl functionality and in this instance deprotonation leads solely to either internal or terminal alkynes.

The protocol was first applied to some representative ketones with either one sterically hindered or one quaternary carbon atom adjacent to the carbonyl moiety (Table 5). As a general trend steric hindrance at the α-position was found to hamper proton abstraction for all substrates. If the elimination is for example carried out with pinacolon **33b** and the P_1-base **29** no reaction takes place (Entry 1). This is in line with an appreciably reduced acidity of **33b** (pK_a 27.7)[38] as compared to acetone (pK_a 26.5)[38]. Use of the P_2-base **30** instead led to a clean and complete transformation of **33b** to the expected alkyne **34b** according to ^{1}H-NMR control. However, isolation of the product turned out to be difficult. Due to its low boiling point of 37°C aqueous workup[3] with *n*-pentane as eluent in order to extract the compound is not feasible. In order to obtain the pure product distillation of the generated alkyne **34b** directly out of the reaction solution was applied. This procedure turned out to be unsatisfying, since the involved P_2-base **30** is used as a 2 molar solution in THF and the

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[3] Within this thesis, aqueous workup is referred to the following procedure: Quenching of the reaction solution with water and multiple extraction with an organic solvent. After aqueous washing and drying of the organic phase finally evaporation of the solvent in order to obtain crude product.

product was found to be accompanied by this solvent in any case. In addition small amounts of alkyne **34b** could be still detected in the reaction solutions. Nevertheless, the desired product **34b** could be isolated in 38% yield accompanied by THF and DMF.

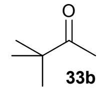
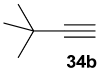
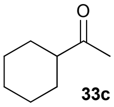
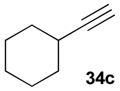
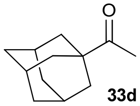
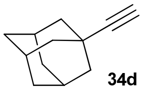
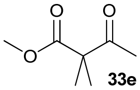
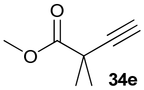
Entry	Ketone	Base	Reaction conditions	Product	% Yield
1	 **33b**	P$_2$-base[a]	DMF, 5h Addition at 0°C → r.t.	 **34b**	**38**[b]
2	 **33c**	P$_2$-base[a]	DMF, 18h Addition at -10°C → r.t.	 **34c**	**80**
3	 **33d**	P$_2$-base[a]	DMF, 14h Addition at -20°C → r.t.	 **34d**	**72**
4	 **33e**	P$_1$-base (3 equiv.)	DMF, 19h Addition at 0°C → r.t.	 **34e**	**44**

Table 5 Alkynes **34** derived from ketones **33** with the P-bases **29**/**30** (2.4 equiv.) and NfF **7** (1.2 equiv.) unless stated otherwise; a) no reaction occurred with P$_1$-base **29**, b) the product is accompanied by THF and DMF (see experimental section).

Using the P$_1$-base **29** in the transformation of cyclohexyl methyl ketone **33c** gave no conversion even upon heating to 50°C overnight (Entry 2). The P$_2$-base **30** instead afforded the desired product **34c** in 80% yield at room temperature. The same result was obtained for substrate **33d** (Entry 3). No conversion was observed at room temperature with the P$_1$-base after 19 hours. Again also heating to 50°C for 19 hours afforded no product **34d**. However, subsequent addition of the P$_2$-base to the same reaction mixture at room temperature led to complete consumption of the starting material. Based on this result the elimination was carried out with the P$_2$-base **30** in order to give alkyne **34d** in 72% yield.

In contrast to the preliminary carbonyl precursors the β-ketoester **33e** could be converted to the corresponding terminal alkyne **34e** making use of the P$_1$-base **29** (Entry 4). Reaction of 2.3 equivalents of the base relative to the starting material **33e** resulted in a somewhat slow transformation. After 19 hours 92% conversion could be detected. After 3 days of additional stirring the conversion increased to 98%. A faster transformation of **33e** was obtained by using 3.0 equivalents of the base **29**, leading to the complete conversion of compound **33e** within 19 hours. Despite the fact that ^{1}H-NMR control indicated a clean and complete transformation, only 44% of product **34e** could be finally isolated. To a certain extend the low yield may be due to losses during aqueous workup accompanied with the subsequent Kugelrohr distillation. Compound **34e** exhibits a relatively low boiling point of 141°C.[39] Therefore losses during any purification procedure involving reduced pressure are inevitable. Consequently a different purification methodology would be recommendable, such as exclusively flash chromatography of the crude reaction mixture with low boiling point solvents in order to minimize the operational steps.

Aryl groups adjacent to the carbonyl functionality as in acetophenones and alkyl aryl ketones increase the acidity of the ketones (illustrated by the pK_a's of acetophenone exhibiting a pK_a=24.7[38] *vs.* acetone owing a pK_a=26.5[38]), and ruling out the possibility of the generation of regioisomers in the formation of the enol nonaflate, which favourably affects the outcome of the reaction. In general, these substrates are conveniently transformed to alkynes in overall good to excellent yields (Table 6).

The investigated transformations exhibit a good functional group tolerance as demonstrated for substrates **35a** (Entry 1), **35b** (Entry 2) and **35c** (Entry 3). ^{1}H-NMR control indicates a clean transformation and the resulting α-aryl alkynes **36a**, **36b** and **36c** are isolated in all cases in yields equal or higher than 90%. The latter product **36c** exhibits two functionalities amenable without further modification, suitable in consecutive transition metal catalyzed cross-coupling reactions.

As mentioned exemplarily for the ketones **33b-d** steric hindrance does affect the reactivity of the carbonyl compounds. Therefore it is of interest to investigate also the effect of steric hindrance for α-aryl ketones, resulting from different ring substitutions. In a representative series the effect of methyl groups in ortho position to the acyl functionality was investigated. It is reported that 4-methyl-acetophenone can be transformed to 1-ethynyl-4-methylbenzene in isolated 86% yield employing the P_1-base **29** overnight at room temperature.[22] Complete conversion of ketone **35d** (Entry 4), exhibiting a methyl group in the ortho position is observed within 15 hours, albeit with an overall slightly lower yield of 77% compared to the unsubstituted substrate. Furthermore, substitution of both ortho positions with methyl groups as in substrate **35e** (Entry 5), leads to a considerably lower rate of conversion in comparison to the transformation of **35d**. 2.25 equivalents of the P_1-base led to 78% conversion after 19 hours and 83% after 44 hours. In order to obtain a higher rate of conversion 3.4 equivalents of the base were used. However, the measured conversion was practically the same with 81% after 20 hours at room temperature. Therefore elevated temperature was applied to obtain a complete transformation of **35e** within a reasonable time scale. The reaction mixture was additionally stirred at 50°C for overall 32 hours, leading to 90%

conversion. Finally stirring for additional 10 days at room temperature did not lead to full consumption of the starting material. Workup of the reaction mixture afforded 63% of the product **35e**. Thus, either higher temperatures or a change to the P_2-base **30** is required in order to obtain full conversion of **35e**.

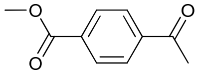
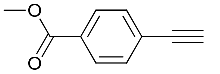
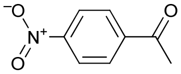
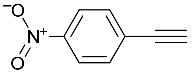
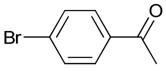
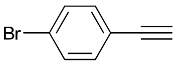
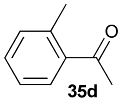
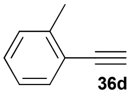
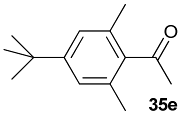
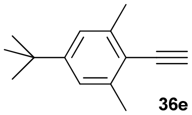
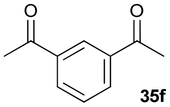
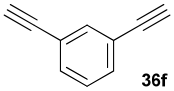
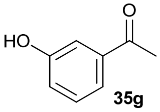
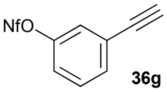
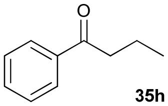
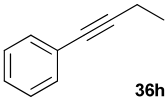
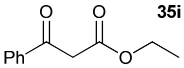
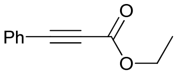
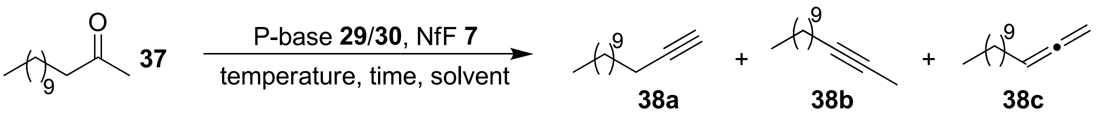
Entry	Ketone	Base	Reaction conditions	Product	% Yield
1	 **35a**	P_1-base	DMF, 5h -10°C for 30min → r.t.	 **36a**	**97**
2	 **35b**	P_1-base	DMF, 15h -20°C for 30min → r.t.	 **36b**	**90**
3	 **35c**	P_1-base	DMF, 13h -10°C for 30min → r.t.	 **36c**	**92**
4	 **35d**	P_1-base	DMF, 15h 0°C for 30min → r.t.	 **36d**	**77**
5	 **35e**	P_1-base	DMF -10°C for 30min → r.t. 15h r.t,, 32h at 50°C, 10d at r.t. additionally	 **36e**	**63**[a]
6	 **35f**	P_1-base[b]	DMF, 14h -10°C for 30min → r.t.	 **36f**	**78**
7	 **35g**	P_1-base	DMF, 17h 0°C for 30min → r.t.	 **36g**	**49**
8	 **35h**	P_1-base	DMF, 18h -10°C for 30min → r.t.	 **36h**	**95**
9	 **35i**	P_1-base	DMF, 5h 0°C for 60min → r.t.	 **36i**	**82**

Table 6 Alkynes **36** derived from acetophenones **35** or α-phenyl ketones **35** with the P_1-base **29** (2.4 equiv.) and NfF **7** (1.2 equiv.) unless stated otherwise; a) obtained with 90% conversion of **35e**, b) 4.6 equiv.

In conclusion, steric hindrance adjacent to the carbonyl functionality leads to the deterioration of the reaction course with decreased rates of conversion and lower yields. This can be seen as a general trend for the ketones **33b-d** (Table 5) and the acetophenones **35d-e** (Table 6). Nevertheless more experimental data need to be collected in order to receive a more detailed picture of this effect. The problem can be adressed by the use of either a larger amount of the P_1-base **29** and/or the application of elevated temperature or the use of the stronger P_2-base **30**.

Both acetyl groups in 1,3-Diacetylbenzene **35f** can be simultaneously converted to terminal alkyne functionalities in excellent 77% yield, taking into account that four single reaction steps take place in one-pot (Entry 6). A different outcome of the elimination reaction was obtained for m-hydroxyacetophenone **35g** (Entry 7). Product **36g** represents an interesting building block, since it exhibits (analogously to **36c**) two functionalities which can be directly employed in transition metal catalyzed cross-coupling reactions. The P_1-base **29** was added in a temperature range of -20°C to 0°C to give the product **36g** only in low yields ranging from 27% to 49% in repetitive runs. 1-Phenylbutane-2-one **35h** could be smoothly transformed to the internal alkyne **36h** in excellent 95% yield (Entry 8), while elimination of the ß-ketoester **35i** forms the desired alkyne **36i** in slightly lower yield of 82% (Entry 9).

Acyclic ketones exhibiting a second α-methylene or a methyl moiety adjacent to the carbonyl functionality are able to form, terminal alkynes, internal alkynes or allenes (Scheme 12, Route II). We already found the P_2-base **30** to be regioselective with respect to α-methine *vs.* α-methylene deprotonation under kinetically controlled conditions (Table 2, 3). Likewise, it is of interest to investigate if the regioselective outcome of the elimination of α-methylene *vs.* α-methyl moieties can be influenced, if the P_2-base **30** is used at lower temperatures. Tridecan-2-one **37** was chosen as a representative example (Scheme 15) and different reaction conditions were applied for the transformation, in order to identify optimal reaction conditions for the generation of exclusively one of the three possible regioisomers **38a**, **38b**, and **38c**.



Scheme 15 The elimination reaction of tridecan-2-one **37** using the P-bases **29**/**30** and NfF **7** under varying conditions generally makes three different products feasible, the terminal alkyne **38a**, the internal alkyne **38b** and the allene **38c**.

The results are summarized in Table 7. As a reference reaction the P_1-base **29** was applied in the elimination and a mixture of the regioisomers **38a** and **38b** in a ratio of 2.2:1 was obtained (Entry 1). Considering the statistically given ratio of methyl to methylene protons of

1.5:1 a slight discrimination of the proton abstraction in favour of the methyl group is observed. In addition to the alkynes **38a** and **38b** also a small amount of the allene **38c** is formed. However, a synthetically useful reaction requires a higher regioselectivity of the elimination. Therefore the P$_2$-base **30** was applied in order to obtain an improved selectivity favouring the formation of terminal alkyne **38a**.

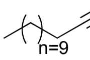
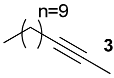
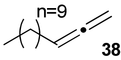
Entry	Base	Reaction conditions	Product ratio[a]	%Yield
			 **38a**  **38b**  **38c**	
1	P$_1$-base	DMF, 20h -10°C → r.t. in 2h	**1.0 / 0.49 / 0.09 (≈6%)**	**75[b]**
2	P$_2$-base	DMF, 14h add. at –30°C → -20°C -20°C → r.t. in 1h	**1.0 / 0.81 / —**	**95**
3	P$_2$-base	DMF, 16h add. at –50°C → -20°C -20°C	**0.81 / 1.0 / ≤1%**	**95**
4	P$_2$-base[c] (2.8 equiv.)	THF, 25h add. at –60°C → -50°C -50°C	**1.0 / 0.42 / —**	**94**
5	P$_2$-base[c] (2.5 equiv.)	THF, 48h add. at –70°C → -60°C -60°C for 24h [d] -50°C for 24h	**1.0 / 0.39 / —**	**—[e]**
6	P$_2$-base[f] (3.4 equiv.)	THF, 48h add. at –65°C → -60°C -60°C	**1.0 / 0.39 / —**	**98**

Table 7 Elimination reaction of tridecan-2-one **37** under varying conditions; a) determined by ^{1}H-NMR, b) result obtained by Dr. I. M. Lyapkalo, c) 1.4 equiv. NfF **7**, d) 42% conversion, e) no workup was carried out for this experiment, f) 1.7 equiv. NfF **7**.

Addition of the P$_2$-base **30** at –30°C and stirring at -20°C for one hour in DMF, with subsequent warming up of the reaction mixture, resulted in the formation of a nearly equimolar amount of terminal and internal alkyne with the terminal one slightly favoured (Entry 2). Addition of the base at –50°C and conducting the reaction at a constant temperature of -20°C under otherwise identical conditions led to a basically reversed regioselectivity (Entry 3). Compared to the reference reaction the use of the P$_2$-base **30** leads in both cases to a higher overall yield and interestingly practically no formation of allene is observed. Lowering the reaction temperature to -50°C and -60°C in THF resulted in an only slightly improved selectivity compared to the reference reaction (Entries 4-6). Full conversion is obtained at -50°C with 2.5-2.8 equivalents of the P_2-base **30** within 25 hours (Entry 4). Lowering the temperature to -60°C significantly slows down the rate of conversion and with 2.5 equivalents of the P_2-base **30** only circa 42% conversion is observed after 24 hours (Entry 5). The reaction reaches completion when stirred for additional 24 hours at -50°C. In order to obtain full conversion at -60°C within a reasonable time scale 3.4 equivalents of the P_2-base **30** and 1.7 equivalent NfF **7** are required (Entry 6). In experiments 4-6, a ratio of at least 2.4:1 in favour of the terminal alkyne **38a** was achieved, while no formation of allene is observed.

Conducting the elimination at lower temperatures of –50°C or below offers a slightly beneficial outcome of the regioselectivity in favour of terminal alkyne **38a** formation. Nevertheless, the differentiation of the P_2-base **30** is overall unsatisfactory to bestow the reaction a preparative value. However, the considerably higher yields and the absence of allene is encouraging. While the enol nonaflate formation obviously exhibits low regioselectivity, the subsequent elimination of (formally) NfOH is indeed highly regioselective, since both enol nonaflate regioisomers formed could afford the same allene.

1.4. The formation of allenes

Beside the formation of alkynes, the base-induced elimination of NfOH from alkenyl nonaflates can also lead to allenes (Scheme 12, Route II, Step 2). This pathway depends on the properties of the substrate and the course of the reaction is predictable with a high chance for two specific conditions. It will be most likely the case for compounds bearing two methyl or methylene groups adjacent to the carbonyl moiety with little or no differences in the pK_a values and if the transformation results in a gain in conjugation. Or if the proton abstraction can exclusively take place between a α-methine and a α-methylene group, with the α-methine entity being significantly more acidic. In this case the first deprotonation step will take place at the α-methine and the second at the α-methylene group, thus directly leading to an allene. A small array of carbonyl precursors was applied in the elimination reaction to study the formation of allenes under internal quenching conditions (Table 8).

The symmetric ketone 1,3-diphenylacetone **39a** is an excellent example for a substrate exhibiting two chemically equivalent methylene groups adjacent to the carbonyl functionality. Compound **39a** undergoes a smooth conversion into the expected racemic allene **40a** in excellent yield (Entry 1). A surprising outcome was observed for the elimination reaction with 3-phenylpropanal **39b** (Entry 2). In this case first terminal alkyne formation takes place according to Scheme 12 (Route I). Subsequent base induced 1,3-shift of one of the two remaining methylene protons finally forms allene **40b** in good yield.[40a-b]

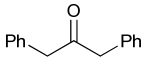
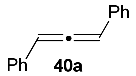
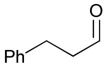
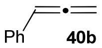
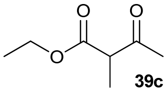
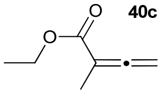
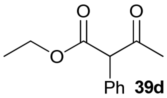
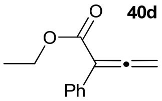
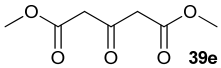
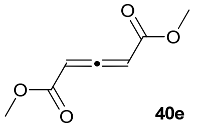
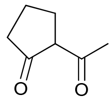
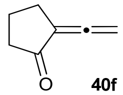
Entry	Ketone	Base	Reaction conditions	Product	% Yield
1	 **39a**	P_1-base	DMF, 5h Addition at -20°C -10°C for 30min → r.t.	 **40a**	**97**
2	 **39b**	P_1-base	DMF, 13h Addition at -20°C -10°C for 30min → r.t.	 **40b**	**77**
3	 **39c**	P_1-base	DMF, 3h Addition at -30°C -20°C for 30min → r.t.	 **40c**	**81**
4	 **39d**	P_1-base	DMF, 21h Addition at -30°C -20°C for 30min → r.t.	 **40d**	**—**
5	 **39e**	P_1-base and DBU	DMF, 3h Addition at -30°C -20°C for 30min → r.t.	 **40e**	**<10**[a]
6	 **39f**	P_1-base	DMF, 22h Addition at -30°C -20°C for 30min → r.t.	 **40f**	**—**

Table 8 Allenes **40** derived from carbonyl compounds **39** with the P_1-base **29** (2.4 equiv.) and NfF **7** (1.2 equiv.) in DMF unless stated otherwise; a) accompanied with side products.

The protocol was applied also to the β-ketoesters **39c**, **39d** (Entries 3 and 4) and the symmetric ketodiester **39e** (Entry 5) in order to make activated allenes accessible. Since the C*H*-R hydrogens in the β-ketoesters **39c**, **39d** are several orders of magnitude more acidic than the terminal methyl group deprotonation takes place at this position first. Subsequent reaction with NfF **7** should form the intermediate alkenyl nonaflate. As a result of the first defined transformation the second deprotonation step can exclusively take place at the adjacent methyl group and therefore lead to the desired activated allenes.

Ethyl-2-methylacetoacetate **39c** was converted into the allene **40c** as outlined (Entry 3). Full conversion was detected after 4 hours, indicated by the disappearance of the sole C*H*-Me proton at 3.5 ppm and formation of the allene **40c** can be monitored by the arising signal of the allene protons at 5.1 ppm. The reaction proceeds to completion in a clean manner. Since compound **40c** was found to be stable on silica gel, it was purified by a quick flash chromatographic workup of the whole reaction mixture and obtained in 81% yield.

A different result was obtained with ethyl-2-phenylacetoacetate **39d** (Entry 4). As in the previous case, ^{1}H-NMR control indicated a fast disappearance of the sole C*H*-Ph proton of the ketoester while applying the P_1-base **29**. However, stirring of the reaction solution up to 21 hours afforded neither a significant amount of the intermediate alkenyl nonaflate nor of the desired allene **40d**. In contrast, several quartet signals in between 3.5 to 4.3 ppm appear alongside with several triplet signals between 0.7 to 1.3 ppm, indicating the formation of several side products containing the ethylester functionality. Partially also starting material **39d** seems to be unaffected, suggesting an incomplete conversion. Workup of the reaction solution by a quick flash column chromatography afforded a yellow oil, consisting of starting material and various unidentified side products, but not of the desired allene **40d** (^{1}H-NMR signals as described in literature[41] could not be identified in the NMR monitoring of the reaction).

Taking the relatively high C*H*-R acidity of both **39c** and **39d** into account, the equilibrium between anion and starting material must exist completely on the side of the anion for both substrates if the P_1-base **29** is employed. Both anions are stabilized by mesomeric structures which lower the nucleophilicity of the negatively charged oxygen. Nevertheless, the only difference between substrates **39c** and **39d** is the methyl *vs.* the phenyl substitutent. Apparently, a contribution of Ph in the negative charge stabilization effectively reduces the nucleophilicity of the enolate oxygen in the anion of **39d** to such extent, that O-sulfonylation with NfF **7** becomes sluggish and/or reversible, thus paving a way to the formation of side products.

Employing the protocol to dimethyl 3-oxopentanedioate **39e** with the P_1-base **29** led to a similar result (Entry 5). Deprotonation of the starting material takes place rapidly. Within 3 hours **39e** is fully consumed according to ^{1}H-NMR control, giving rise to the immediate formation of side products. Workup of the reaction solution resulted in the isolation of traces of the desired allene (<10%), still accompanied by at least one unidentified side product. Practically the same result was obtained using DBU **20** as an alternative base under otherwise identical conditions. The elimination protocol was also carried out with 2-acetyl-cyclopentanone **39f** (Entry 6). For this substrate no alkenyl nonaflate or allene **40f** formation could be detected after 4 and 22 hours. The starting material was consumed mostly after

4 hours, fully after 22 hours, to give a mixture of side products the structures of which were not further investigated.

In summary, the allene formation using the P_1-base **29** and NfF **7** under internal quenching conditions is not applicable to the substrates **39d-f**. The failure of the transformations might be explained by two reasons. The stable non-nucleophilic enolates, formed under the applied reaction conditions, only sluggishly if at all react with NfF **7**, thus opening up pathway(s) to the formation of side products. Alternatively, the anticipated reactive allenes **40d-f** may be unstable under the reaction conditions, presumably owing to F^- / base induced (poly)condensations initiated by a nucleophilic attack of the nucleophile / base on the electrophilic sp-carbon centre of the allenes.

Since the nucleophilic substitution may represent the rate determining step, the use of a weaker base such as a trialkylamine was viewed as an approach to generate an equilibrium between the deprotonated and protonated species, with a reduced interaction of the generated nucleophiles and the base with reactive allene products. Consequently, more acidic trialkylammonium cation formed would effectively reduce a nucleophilicity of F^- by forming stronger hydrogen bonds.

The behavior of the weaker base NEt_3 was investigated in the reaction with compound **39d**. The reaction progress was monitored by ^{1}H-NMR, the results are summarized in Table 9.

Entry	**Conditions**			**Conversion [%]**					
	T [°C]	base	solvent	16h	22h	45h	93h	114h	7d
1	r.t.	NEt_3 3 equiv.	DMF	7				39	
2	58	NEt_3 4 equiv.	DMF		23	29	dec[a]		dec[a]
3	r.t.	NEt_3 5 equiv.	—				—		

Table 9 Conversion of ethyl-2-phenylacetoacetate **39d** with NEt_3 as alternative base and NfF **7** under internal quenching conditions; a) dec = decomposition of the product is observed.

The use of 3.0 equivalents of NEt_3 resulted in a very slow conversion of **39d**. After 114 hours 39% of the desired product **40d** was formed (Entry 1). Applying elevated temperature of

58°C led to an increased rate of conversion (Entry 2). However, a significant decomposition of the formed product **40d** was observed after 93 hours. Interestingly, an attempt to carry out the reaction in the five-fold excess of neat NEt$_3$ resulted in no conversion of the starting material **39d** at all (Entry 3). This observation manifests the necessity of the dipolar solvent DMF for the reaction to occur and can be satisfyingly explained by the required stabilization of the charged reaction intermediates by a polar component in the reaction mixture.

The most straightforward approach to address this requirement is the use of a more polar base, exhibiting the same or an even slightly higher basicity than NEt$_3$. A higher polarity than NEt$_3$ (ε_o = 2.418), but a comparable basicity is given for *N*-methylpyrrolidine (ε_o = 32.2), and therefore this base was used for further elimination reaction of **39d** under otherwise identical conditions in order to check the polarity effect (Table 10).

Entry	Conditions			Conversion [%]								
	T[°C]	Base	solvent	22h	42h	45h	68h	87h	112h	114h	158h	18d
1	r.t.	NMP 5 equiv.	DMF	32		47	55		60		47 dec[a]	
2	r.t.	NMP[b] 9 equiv.	DMF		33			58		50 dec[a]		—
3	40	NMP 9 equiv.	DMF	~49% conversion after 31h Complete decomposition of the product after 56h								

Table 10 Conversion of ethyl-2-phenylacetoacetate **39d** with *N*-methylpyrrolidine as the base and NfF **7**; a) dec = decomposition of the product is observed, b) 4 equiv. of NfF **7**.

Indeed an appreciably higher rate of conversion could be measured with *N*-methylpyrrolidine and after 22 hours 32% conversion of the starting material **39d** were determined at room temperature (Entry 1). Nevertheless, the rate of conversion slows down at a later stage of the reaction and a presumably maximum conversion of *ca.* 60% is measured at 112 hours. Additionally, degradation of the product **40d** is observed at extended reaction times.

In order to obtain a higher rate of conversion and less decomposition of the product **40d** larger amounts of the base (9.0 equivalents) and NfF **7** (4 equivalents) were employed, but without detecting the desired acceleration effect (Entry 2). The decomposition of the product could also not be avoided by higher dilution and was detected after 114 hours. Warming the reaction solution to 40°C led to a higher conversion of 49% after 31 hours, followed by complete decomposition of the product after 56 hours (Entry 3).

Despite the obvious improvement, the elimination of **39d** using *N*-methylpyrrolidine is not fully satisfying from a synthetic point of view. The rate of conversion is still too little and in addition, product formation competes with its decomposition at a later stage of the reaction. However, at least 60% conversion are achievable with this methodology and since the conversion of **39d** seems to proceed in a clean manner as demonstrated by the ^{1}H-NMR control, product **40d** might be obtained in an overall moderate yield.

A possible solution to circumvent the inherent drawbacks of the internal quenching protocol using NfF **7** could be the substitution of this reagent with the more electrophilic Tf_2O, which does not generate nucleophilic fluoride, and should form the required intermediate alkenyl sulfonate instantaneously. Subsequent addition of an appropriate base, inducing elimination of the intermediate alkenyl triflate, could potentially lead directly to the desired allenes.

1.5. Conversion of aldehydes with NfF and phosphazene bases

1.5.1. Alkenyl nonaflate formation

As determined above (see chapter 1.3.1, Scheme 13), the generation of enol nonaflates appears to be the rate-determining step in the conversion of acyclic ketones to alkynes with the P_1-base **29** and NfF **7**. In contrast, careful control of the reaction conditions in the conversion of aldehydes allows stopping of the transformation at the stage of the enol nonaflate and enables the isolation of these intermediates at wish. Thus, optimisation experiments carried out with heptanal **41b** as the model substrate, within a temperature range of –60°C to –10°C, resulted in the perfect kinetic discrimination between the alkenyl nonaflate formation and the NfOH elimination step in favour of the former at ≤–30°C. The reactions were conducted analogously as for the cyclic ketones 2-methyl cyclopentanone **27f** (Table 2) and 2-methyl cyclohexanone **27g** (Table 3).

A small set of aldehydes **41a**-**d** was then successfully converted to the corresponding nonaflates **42a**-**d** employing the developed procedure (Table 11). The nonaflation of aldehydes proceeds appreciably faster than that of the cyclic ketones, apparently owing to the higher acidity of the α-hydrogens of the aldehydes (*cf.* Tables 1&11).

The conversion of the aldehydes **41a-c** takes place in a clean manner according to ^{1}H-NMR-control and the desired alkenyl nonaflates **42a**-**c** (Entries 1-3) were obtained in good yields. Due to the unavailability of a second proton in α-position to the carbonyl functionality the aldehyde **41a** could be transformed to the alkenyl nonaflate **42a** at room temperature (Entry 1). The desired product **42a** was isolated in 89% yield. The low temperature conversion of heptanal **41b** proceeds smoothly within 21 hours and affords the desired alkenyl nonaflate **42b** as a mixture of (*E*/*Z*)-stereoisomers in 84% yield (Entry 2). Noteworthy, that the low-temperature transformation of 6-oxo-heptanal **41c** into the corresponding nonaflate **42c** was successfully accomplished, with the unprotected ketone functionality remaining intact (Entry 3). The double bond geometry for both alkenyl nonaflates **42b** and **42c** is formed with a (*Z*/*E*)-ratio slightly higher than 4:1 in favour of the (*Z*)-configuration. Most likely the observed moderate (*Z*)-selectivities are owing to the stabilizing antiperiplanar overlap of the $\sigma_{C\text{-}H}$ orbital and the incipient $\sigma^*_{C\text{–}ONf}$ orbital in the open-chain transition state.

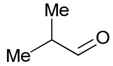
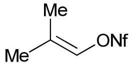
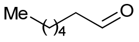
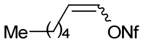
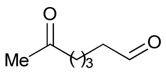
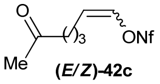
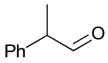
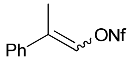
Entry	Aldehyde	Base	Reaction conditions	Product	% Yield / Ratio
1	 **41a**	P_1-base	DMF, 4h, r.t.	 **42a**	**89**
2	 **41b**	P_1-base	DMF, 21h, –30°C	 **(*E*/*Z*)-42b**	**84** / (*Z*:*E* = 4.2:1)
3	 **41c**	P_1-base	DMF, 21h, –30°C	 **(*E*/*Z*)-42c**	**73** / (*Z*:*E* = 4.7:1**)**
4	 **41d**	P_1-base	DMF, 17h, r.t.^{a}	 **(*E*/*Z*)-42d**	**44^b /** (*E*:*Z* = 5.5:1**)**

Table 11 Synthesis of alkenyl nonaflates **42** from aldehydes **41** with the P_1-base **29** (1.15 equiv.) and NfF **7** (1.15 equiv.); a) the base was added at –40°C, after complete addition the temperature was kept for 30 min at –30°C and allowed to come to room temperature within 3 hours, b) the product is accompanied by prop-1-ynyl-benzene **42e**, the ratio of (*E*/*Z*)-**42d**:**42e** = 2.2:1.

A different outcome of the reaction was observed for the nonaflation of 2-phenyl propionaldehyde **41d** (Entry 4). The desired nonaflate **42d** is obtained as a mixture of the stereoisomers (*E*)-**42d**, (*Z*)-**42d** and prop-1-ynyl-benzene **42e** in a ratio of 5.5:1.0:2.9. The intermediary generated alkenyl nonaflates (*E*/*Z*)-**42d** obviously suffer a base induced rearrangement to prop-1-ynyl-benzene **42e** under the applied internal quenching conditions.

The base induced rearrangement of the cognate triflates using *t*-BuOK via a free carbene intermediate is reported.[42a-b] For the corresponding triflates the formation of the alkyne was found to be nonstereoselective with respect to the (*E*)- and the (*Z*)-stereoisomers. However, due to the fast and extensive conversion of the (*E*/*Z*)-alkenyl nonaflates **42d** neither the (*E*/*Z*)-ratio of their generation nor a preferred consumption of one of the stereoisomers in the subsequent rearrangement can be determined in this experiment. Further investigations using weaker bases might raise the opportunity to circumvent the formation of prop-1-ynyl-benzene **42e** and give the chance to determine the (*E*/*Z*)-stereoisomer ratio.

1.5.2. Formation of terminal alkynes

If the nonaflation of aldehydes is carried out at room temperature with at least a two fold excess of the auxiliary base, the intermediary alken-1-yl nonaflates are subjected to the base-induced elimination of NfOH to give terminal alkynes. The results for a set of representative aldehydes are summarized in Table 12.

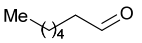
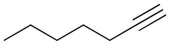
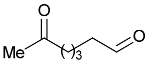
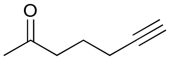
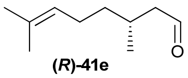
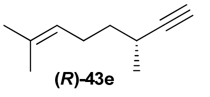
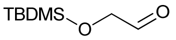
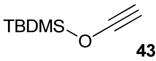
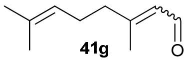
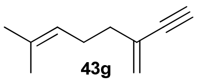
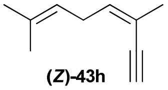
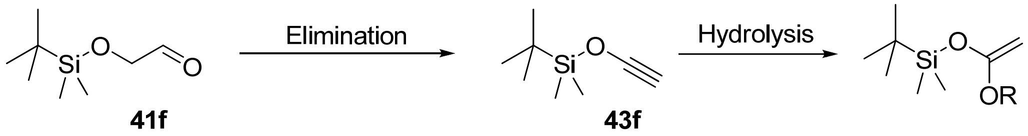
Entry	Aldehyde	Reaction conditions	Product	% Yield / Ratio
1	 **41b**	DMF, 14h, P_1-base -10°C for 30min → r.t.	 **43b**	**66**
2	 **41c**	DMF, 16h, P_1-base -10°C for 30min → r.t.	 **43c**	**76**
3	 **(*R*)-41e**	DMF, 18h, P_1-base 0°C for 30min → r.t.	 **(*R*)-43e**	**76**
4	 **41f**	DMF, 2.5h, P_1-base -20°C for 30min → r.t.	 **43f**	—
5	 **41g**	DMF, 18h, P_1-base -10°C for 30min → r.t.	 **43g**  **(*Z*)-43h**	**87** **43g**:**43h** = 3.6:1

Table 12 Reaction of aldehydes **41** with the P_1-base **29** (2.4 equiv.) and NfF **7** (1.2 equiv.) at room temperature leading to terminal alkynes **43.**

^{1}H-NMR-analysis generally indicates a clean conversion of the starting material. Heptanal **41b** and 6-oxo-heptanal **41c** gave good yields of 1-heptyne **43b** (Entry 1) and 6-oxo-heptyne **43c** (Entry 2), respectively. Somewhat lower yield of the alkyne **43b** is attributed to losses during workup due to the low boiling point of 99°C.[43] This conclusion can be directly verified by comparison with the result for the less volatile but otherwise similar product 6-oxo-heptyne **43c** with a considerably higher boiling point of 174°C.[44] Again the transformation of 6-oxo-heptanal **41c** did not require protection of the second carbonyl functionality. (*R*)-Citronellal **41e** was converted to **43e** in 76% yield with the chiral centre in β-position remaining intact (Entry 3).

(*t*-Butyl-dimethyl-silanyloxy)-acetaldehyde **41f** is an interesting starting material from a synthetic point of view (Entry 4). A successful elimination of this compound would lead to the terminal silanyloxy-alkyne **43f** as shown in Scheme 16. This building block is useful in two different ways. Firstly it could be employed as coupling component in the Sonogashira reaction to introduce a silanyloxy alkyne entity. Secondly, this compound exhibits a masked alkoxy-vinyloxysilane moiety which can be obtained by hydrolysis of **43f** and is otherwise difficult to access.



Scheme 16 Elimination reaction of **41f** forming the synthetically useful building block **43f.** This substrate represents a masked alkoxy-vinyloxysilane, which can be obtained via hydrolysis.

The elimination of **41f** under the established conditions is somewhat delicate, since highly activated F$^-$ is generated during the reaction course in anhydrous DMF and is potentially leading to the cleavage of the TBDMS-group. The elimination protocol for this aldehyde was carried out under the established reaction conditions. ^{1}H-NMR-control indicated complete conversion of the starting aldehyde after 2.5 hours. However, after aqueous workup with subsequent distillation exclusively *t*-butyldimethylfluorosilane was obtained instead of the desired product **43f** as a direct comparison with the literature spectra proved.[45] Cleavage of the TBDMS-group takes place fast, since during the reaction course more than just two singlets for each of the *t*-butyl and the two methyl groups between 0 ppm and 1 ppm arise.

Citral **41g** afforded the elimination product in form of the two regioisomers **43g** and (*Z*)-**43h** in the ratio of 3.6:1 in favour of the product exhibiting the terminal double bond (Entry 5). Also for this substrate it could be interesting to study the outcome of the reaction applying lower temperatures, in order to obtain a further improvement of the ratio in favour of the formation of alkyne **43g**.

1.6. Conclusions

The successful transformation of carbonyl compounds to alkenyl nonaflates, alkynes and allenes using the phosphazene bases **29**/**30** and NfF **7** under internal quenching conditions comprises the advantages of conveniently to handle and readily available substrates and reagents with high efficency and experimental simplicity.

The synthesis of cyclic alkenyl nonaflates is versatile and can be applied to a variety of compounds. The problem of regioselective double bond formation was addressed and solved for the representative model substrates 2-methyl cyclopentanone **27f** (Table 2) and 2-methyl cyclohexanone **27g** (Table 3).

Aldehydes can be elegantly transformed into either alkenyl nonaflates or terminal alkynes, simply by adjusting the required reaction temperature and amount of the P_1-base **29**. Due to their high reactivity, the transformation of aldehydes into either alkenyl nonaflates or terminal alkynes can be carried out in the presence of unprotected ketone functionality.

Limitations of the protocol exist for the generation of alkenyl nonaflates from acyclic ketones. For such substrates in any case either allene or alkyne formation is inevitable under the applied internal quenching conditions. However, employing this procedure to selected ketones led to the successful formation of a series of synthetically interesting alkynes.

Unfortunately we could not achieve a synthetically viable kinetic selectivity in favour of terminal alkynes from methyl *n*-alkyl ketones as shown exemplarily for tridecan-2-one **37**.

The formation of allenes bearing electron-withdrawing groups lacks generality. Highly stabilised enolate anions seem to react sluggishly and/or reversibly with NfF **7** so that the contribution of the side reactions becomes substantial. Alternatively, nucleophilic phosphazenium fluoride formed as a by-product in the course of the reaction may trigger oligomerisation of the electron-deficient allene products. A possible solution to this obstacle could be the application of the more electrophilic Tf_2O, which does not generate nucleophilic fluoride. Subsequent addition of an appropriate base, inducing elimination of the intermediate alkenyl triflate, could potentially lead directly to the desired allenes.

The alkenyl nonaflates in the Heck reaction – methodology and reactivity

2. The alkenyl nonaflates in the Heck reaction – methodology and reactivity

2.1. General remarks

Since their introduction aryl and alkenyl triflates attracted considerable attention as alternatives to the corresponding halides in transition metal catalyzed cross-coupling reactions.[16,46] The nonaflate counterparts have been only scarcely explored, which is reflected in an overall lower number of publications. However, the latest trend is such that the synthetic applications are steadily growing for both aryl and alkenyl nonaflates, and they are often found advantageous compared to the analogous triflates.

Knochel *et al.* highlighted aryl nonaflates as superior alternatives to aryl triflates in Negishi, Suzuki and Stille coupling reactions as a result of their more efficient preparation and cleaner reactions. The authors also indicated a slightly higher reactivity of the aryl nonaflates as compared to the corresponding triflates.[8d] Aryl nonaflates are reported to be effective alternatives to triflates in palladium-catalyzed C−N bond-forming processes due to their increased stability under the applied reaction conditions.[8k-l] Also they show beneficial properties in terms of stability against the reaction conditions, when used in the palladium catalyzed cross-coupling reaction with alkenylsilanols to form geminal disubstituted styrene derivatives.[47] Even in the Pd(0)-catalyzed synthesis of unsymmetric triarylphosphine boranes a higher reactivity of 2-naphtyl nonaflate *vs.* the corresponding triflate is reported.[48] As described for aryl nonaflates[8d] also a slightly higher reactivity is reported for alkenyl nonaflates of 8-oxabicyclo-[3.2.1]octan-3-ones in the Heck, Suzuki and Sonogashira reaction compared to the analogous triflates.[8j,10]

Meanwhile, alkenyl and aryl nonaflates are used in all the synthetically important cross-coupling reactions, such as Stille, Sonogashira, Negishi, Suzuki and Heck couplings.[8a-l] In addition one-pot-strategies have been developed generating the alkenyl nonaflate *in situ* from preformed silyl enol ethers and a subsequent C-C-coupling reaction by transition metal catalysis.[8b] Aryl nonaflates even found application in the rare palladium catalyzed synthesis of methyldiphenylphosphine-boranes[49] and unsymmetric triarylphosphine boranes[48], using the aryl nonaflates to introduce the final phenyl moiety into the phosphine borane complexes.

Routinely, the coupling reactions are carried out in an inert gas atmosphere, with purified compounds and solvents, mainly DMF. Most frequently, either (primarily) phosphine ligands or additives such as tetrabutylammonium halides or LiCl are employed. Both ligands and additives are believed to stabilize the catalytically active palladium species throughout the reaction course. Over the years the development of palladium catalyzed reactions bifurcated into “ligated” and “ligandless” catalysis. Latter term is strongly associated with the work of Jeffery *et al.*[50] who introduced tetrabutylammonium salts as additives in palladium catalyzed reactions. Therefore this variant of catalysis is generally referred to as “Jeffery conditions”.

The term “ligandless” implies the existence of a non-coordinated palladium species. However, coordination necessarily takes place at least with the solvent molecules. This notion points out the common perception that stabilization of the catalytic active species is required, either to sustain full activity throughout the reaction course or to achieve higher reactivity, resulting in an increasing rate of the reaction. In fact the term „ligandless” is somewhat misleading, but this formal definition helps to highlight two different concepts of catalysis associated with its advantages as well as its drawbacks.

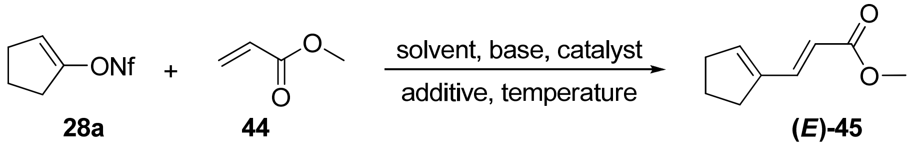
In the past decades phosphine type ligands turned out to be advantageous and therefore are used predominantly. Pursuant to their role, ligands are employed in a comparable amount related to the metal catalyst and should therefore be cost efficient. Notwithstanding, ligands often require an elaborate synthesis and turn out to be a significant cost factor.

In contrast, additives like simple salts, *e.g.* LiCl are readily available and considerably cheaper than ligands, but generally are used in at least stoichiometric amount. While reactions in a small scale do not pose a problem in terms of experimental effort and costs, upscaling may turn into a difficult task in terms of process handling and generation of waste. For these reasons catalytic protocols avoiding both ligands and additives are of particular interest.[8c]

A straightforward process development of catalytic systems, or the optimisation of the catalysis requires as much as possible detailed information about the influence of the various components participating in the reaction. To date, very little investigations can be found in literature, with only scarce data concerning the properties of sulfonate groups in transition metal catalyzed reactions being available.

2.2. Methodology and initial experiments

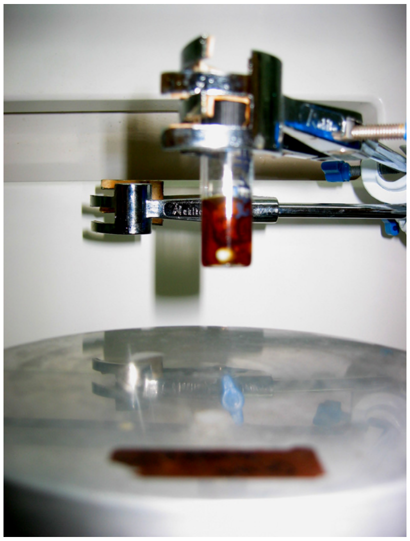
The aforementioned lack of systematic research prompted us to carry out kinetic studies of cross-coupling reactions by varying the reaction components to determine their role and effect. Since the coupling of alkenyl halides with olefins, simply known as Heck reaction, has been widely employed for sulfonates and especially for alkenyl triflates and nonaflates, we decided to carry out the study with alkenyl nonaflates in this transformation. The Heck reaction of cyclopentenyl nonaflate **28a** with methyl acrylate **44** is known to proceed cleanly resulting in (*E*)-methyl 3-cyclopentenylacrylate **45** as the sole product.[8b] Therefore, it was chosen as the model reaction (Scheme 17).



Scheme 17 The model Heck reaction. For all kinetic experiments the following standardised reaction conditions were applied (unless stated otherwise): 1.0 mmol of alkenyl nonaflate **28a**, 1.3 mmol of methyl acrylate **44**, 2.0 mmol of the base, 5 mol% of the palladium salt, 1.0 mmol of additive if applied, 1 ml of solvent.

In the initial experiments, the rates of conversion in *N*-methylformamide and DMF as the solvents in combination with LiCl and tetrabutylammonium halides as the additives were studied in order to obtain leadoff information. The reactions using NEt_3 as the base and $PdCl_2$ as the catalyst precursor indicated sound conversion and catalytic sustainability in the formamide solvents. Most importantly, the reference reaction carried out without any additive turned out to be at least as robust as those conducted with the additives. Throughout the reaction course no formation of Pd_{black} could be observed. The rate of conversion resembled that of the reactions in the presence of LiCl or tetrabutylammonium halides. Additionally we learned that even inert gas protection of the reaction mixture from atmospheric oxygen or moisture was not required.

Thus, we were able to simplify the whole experimental set up. In the preliminary experiments the reactions were carried out in a round bottom flask, equipped with a three way tap in order to enable evacuation and inert gas filling steps. The reaction itself was conducted in a protected atmosphere of argon. For the amended conditions we switched to simple glass vial, equipped only with a magnetic stirring bar and did not apply any protection from atmospheric oxygen or moisture (Picture 1). The catalysis turned out to be exceptionally robust so that even unpurified compounds and solvents were employed in the modified experimental procedure. All the components were simply used as purchased, and compared to the reference experiments employing purified components neither the reaction course nor the rate of the conversion was affected.



Picture 1 Typical kinetic study carried out in a sample vial equipped with magnetic stirring bar. The vial is placed *ca.* 2 cm above the plate.[4]

After measuring on a precision balance the liquid components were added consecutively via syringe. The Pd(II)-salt was added to the reaction mixture last and the bottle was subsequently affixed above a magnetic stirring plate. Samples were taken from the reaction solution by a Pasteur pipette and analysed either via ^{1}H-NMR or GC.

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[4] Conventional magnetic stirrers show over a longer period of stirring (several hours) a significant warm up of the metal plate. In order to avoid heat transfer from the stirrer to the glass wall the sample bottles were fixed above the plate in order to maintain a constant reaction temperature.

2.3. Systematic investigations

2.3.1. The solvent effect

The first systematic set of experiments was carried out to study the effects of different solvents, primarily to obtain information on changes in the kinetic profile depending on varying polarity. Assuming that the catalytic cycle of the Heck reaction consists of a series of positively charged intermediates,[5] it is reasonable to suggest that solvents exhibiting a higher polarity should more efficiently stabilize these reactive intermediates more efficiently, and therefore lead to a higher rate of conversion. The relative polarity of the solvents is defined by the dielectric constant ε_o: the larger ε_o for the pure solvent the higher the polarity.[52] In addition to the polarity also specific coordinating properties may influence the overall stability of the catalyst throughout the reaction course and may show rate accelerating effects. Amides are known to coordinate to transition metals[53a-d] and therefore three different solvents with an amide moiety, namely DMF (ε_o = 38.2), *N*-methylacetamide (ε_o = 179.0) as well as *N*-methylformamide (ε_o = 189.0) were selected. In order to cover a wide range of the dielectric constant ε_o propylene carbonate (ε_o = 66.1), DMSO (ε_o = 47.2), MeCN (ε_o = 36.6), NMP (ε_o = 32.6) and THF (ε_o = 7.5) were additionally chosen.

By covering a wide range of the dielectric constant ε_o, starting from THF with ε_o = 7.52 and ascending to the very high value of ε_o = 189.0 for *N*-methylformamide the effect of polarity can be examined. In case of a predominant interrelationship between polarity and the rate of conversion, a higher value of ε_o should lead to a higher rate. In addition, this selection of solvents might allow distinguishing between polarity and specific solvation effects.

The reactions were carried out in parallel at room temperature. The results are summarized in Table 13. For this experimental series $PdCl_2$ was used as the catalyst precursor with one exception (Entry 9), and NEt_3 as the base with the exception of Entry 8.

The fastest conversion of nonaflate **28a** is obtained in *N*-methylformamide (Entry 3) and *N*-methylacetamide (Entry 2). Both solvents exhibiting by far the highest dielectric constants. Interestingly, the rate of conversion in DMF (Entry 1) is only slightly inferior. Moreover, DMF

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[5] It is generally believed that the catalytic cycle of the Heck reaction consists of alternating changes in the oxidation state of Pd(0) and Pd(II). Alternatively also a cycle exhibiting the oxidation states of Pd(II) and Pd(IV) is predicted,[51] but so far this hypothesis is lacking any experimental evidence.

provides a faster conversion of **28a** compared to the more polar solvent propylene carbonate (Entry 4) and DMSO (Entry 5). The reaction in DMSO proceeds slightly slower and reaches completion within 22 hours, comparable to the reaction in DMF. In contrast propylene carbonate shows a significant slow down effect during the reaction course and even after 22 hours conversion does not exceed 63%. The kinetic profiles in MeCN and NMP are similar to that in DMF: 71% conversion of **28a** after 7 hours in MeCN (Entry 6) and 80% after 8 hours in NMP (Entry 7). Both reactions are complete after 22 hours. MeCN and NMP are commonly used solvents in the chemical industry as alternatives to DMF. The reaction in *N*-methylformamide using *N*-methyl-pyrrolidine (Entry 8) lead to a fast conversion of the starting material. Unfortunately a precise integration of the characteristic signals in ^{1}H-NMR could not be accomplished in this particular experiment, but it can be clearly seen that the reaction proceeds slightly slower than with NEt_3 as the base. In contrast the reaction in THF (Entry 9) was found to be very slow and after 22 hours only circa 5% conversion is obtained.

Entry	**Components**				**Conversion in %**					
	solvent / ε_o		catalyst	base	2h	4h	6h	7h	8h	22h
1	DMF	38.25	$PdCl_2$	NEt_3	21	46		73		√
2	AcNHMe	179.0	$PdCl_2$	NEt_3	26	62		84		√
3	HCONHMe	189.0	$PdCl_2$	NEt_3	34	83		≥99%		√
4	Propylene carbonate	66.14	$PdCl_2$	NEt_3	23	33		44		63
5	DMSO	47.24	$PdCl_2$	NEt_3	16	42		63		√
6	MeCN	36.64	$PdCl_2$	NEt_3	25	50		71		√
7	NMP	32.55	$PdCl_2$	NEt_3	25	42	65		80	√
8	HCONHMe	189.0	$PdCl_2$	N-Methyl-Pyrrolidin		~70		≥98 %[a]		
9	THF	7.52	$Pd(OAc)_2$	NEt_3	—	—	—		—	~5[b]

Table 13 Conversion of **28a** according to the model reaction (Scheme 17) with NEt_3 as the base, $PdCl_2$ as the catalyst precursor and a variation of solvents, at 24°C (unless stated otherwise); a) accurate integration of the product signals was not possible by ^{1}H-NMR, b) additional heating at 50°C for 16h lead to a conversion of 52%. "√" indicates that no starting material could be detected by ^{1}H-NMR anymore.

The most noteworthy results are the fast conversion of **28a** in HCONHMe with two different bases and the good performance of the reactions in DMF, MeCN and NMP. The latter solvents exhibit an appreciably lower dielectric constant than DMSO or propylene carbonate and even a 4-5 fold lower value in comparison with AcNHMe. Nevertheless they show a rate of conversion for nonaflate **28a** comparable to those in DMSO or in AcNHMe, and a considerably higher rate than that in propylene carbonate.

The experiments indicate that a certain degree of polarity is required in order to obtain a reasonable reaction rate as demonstrated for THF (see Entry 9). However, not only the polarity of the solvent plays a role in the reaction kinetics. Obviously a specific coordinating ability of the amide functionality seems to be beneficial for the rate of conversion since in general the amide type solvents provide the fastest rate of conversion.

Heck reactions of alkenyl halides or sulfonates are often conducted under Jeffery conditions,[50] using tetrabutylammonium chloride in combination with the inorganic base K_2CO_3. Most often the reactions are carried out in DMF forming a heterogeneous system due to the low solubility of the base in the organic medium. We were interested to investigate K_2CO_3 in our model reaction, while varying the solvent of different polarities analogously to the series utilizing NEt_3 (compare with Table 13). The results are summarized in Table 14.

Entry	**Components**			**Conversion in %**		
	solvent	catalyst	base	2h	4h	7h
1	DMF	$PdCl_2$	K_2CO_3	27	56	87
2	AcNHMe	$PdCl_2$	K_2CO_3	5		37
3	HCONHMe	$PdCl_2$	K_2CO_3	side reaction, little conversion[a]		
4	Propylen carbonate	$PdCl_2$	K_2CO_3	—		~6
5	DMSO	$PdCl_2$	K_2CO_3	—		
6	MeCN	$PdCl_2$	K_2CO_3	—		~2

Table 14 Conversion of **28a** according to the model reaction (Scheme 17) with K_2CO_3 as the base, $PdCl_2$ as the catalyst precursor and variation of the solvent, at 24°C; a) the exact amount could not be determined via ^1H-NMR.

The rate of conversion for nonaflate **28a** is notably slower in all of the solvents with exception of DMF, in which K_2CO_3 provides an even higher rate compared to the use of NEt_3 (Entry 1). Using *N*-methylacetamide leads to a dramatic slow down effect (Entry 2), whereas in *N*-methylformamide a crucial retardation of the desired Heck coupling is accompanied by an unspecified side reaction. No conversion at all is observed for the reaction in DMSO (Entry 5) and the conversions in propylene carbonate (Entry 4) and acetonitrile (Entry 6) are found to be negligible. These results clearly indicate a fully substituted amide functionality to be beneficial for the course of the reaction. The reason for the observed reactivity differences within the single amide type solvents and K_2CO_3 remains unclear. Taking into account that even the more polar solvents propylene carbonate and DMSO, as well as the slightly less polar solvent MeCN show either no or very little conversion, DMF seems to be unique within the given array for being able to provide a fast conversion with both K_2CO_3 and NEt_3.

The highest rates of conversion for **28a** within these two reaction sets are obtained with K_2CO_3 in DMF and with NEt_3 in *N*-methylformamide. In addition, another common palladium source, $Pd(OAc)_2$ was investigated using Et_3N as a base in DMF *vs.* *N*-methylformamide (Table 15). In DMF a nearly quantitative conversion was detected already after 6 hours reaction time (Entry 1). In contrast to $PdCl_2$ (see Table 13, Entries 1 and 3), $Pd(OAc)_2$ induces a slightly higher rate of conversion in DMF than in *N*-methylformamide. Summarizing all the kinetic experiments described above, we conclude that the fastest rate of conversion is achieved in DMF, with $Pd(OAc)_2$ as the palladium source and NEt_3 as a the base (Table 15, Entry 1).

Entry	**Components**			**Conversion in %**			
	solvent	catalyst	base	2h	4h	6h	8h
1	DMF	$Pd(OAc)_2$	NEt_3	33	81	98	≥99
2	HCONHMe	$Pd(OAc)_2$	NEt_3	41		81	95

Table 15 Conversion of **28a** according to the model reaction (Scheme 17) with $Pd(OAc)_2$ as an alternative catalyst precursor and NEt_3 as the base, at 24°C.

Amide type solvents show as a general trend a faster rate of conversion in comparison to the alternative solvents tested. Since DMF provides good to excellent conversion in all of the above described catalytic systems and is additionally advantageous in terms of handling and price compared to the competing amide type solvents, it became the solvent of choice while stable, non-hygroscopic $Pd(OAc)_2$ was selected as catalytic Pd source for all further experiments.

2.3.2. The effect of different bases

The two most commonly used bases in the Heck reaction K_2CO_3 and NEt_3 interestingly gave a very different kinetic profile in our model reaction for each of the solvents with the exception of DMF. As the next step of our study, we deemed advisable to examine the effect of further bases on the course of the model Heck reaction in DMF and $Pd(OAc)_2$ (Table 16).

Entry	**Components**		**Conversion in %**										
	base	additive	1h	2h	4h	5h	6h	7h	9h	10h	24h	27h	48h
1	Pyridine	—	—	—	—				—			1-2	~3
2	NEt_3	Toluene[a]	11	33	77								
3	NEt_3	—	12	36	78								
4	NEt_3	Pyridine[b]	—	—					5		12		
5	2,6-Lutidin	—	—	—	—				—			—	—
6	DIPEA	—	11	34	65	75	82	87	94			√	
7	CH_3COONa	—	3	6	14				27			58	67
8	P_1-base	—	16	32	53		63			71	81[c]		

Table 16 Conversion of **28a** according to the model reaction (Scheme 17) with DMF as solvent and $Pd(OAc)_2$ as the catalyst precursor, at 24°C; a) 1.0 equiv. relative to **28a**, b) 3.7 equiv. related to the catalyst, c) full conversion could be obtained after heating the reaction solution overnight at 50°C. "√" indicates that no starting material could be detected by ^{1}H-NMR anymore.

The use of pyridine results in a negligible conversion (~3%) of **28a** after 48 hours (Entry 1). This experimental finding can in principle be explained by inhibition through coordination of the catalyst either to the lone pair of the sp^2-nitrogen atom or to the 6π-aromatic ring system. In order to exclude the latter less likely possibility the model reaction was carried out with toluene, added in a 1 millimolar amount (Entry 2). The reaction shows a conversion of 77% after 4 hours, being in a good agreement with the reference reaction (Entry 3). This clearly indicates that the lone pair nitrogen orbitals coordinates to the palladium metal and thereby hampers the catalysis. This assumption is additionally supported since even the small amount of 3.7 equivalents of pyridine related to the catalyst led to a nearly complete inhibition of the reaction with only 12% conversion after 24 hours (Entry 4). This also rules out that eventually the considerably lower basicity of pyridine causes the low rate of conversion when used as the sole base (Entry 1). As a readily available alternative to pyridine, 2,6-lutidine was tried in the model reaction (Entry 5). The steric hindrance resulting from the two methyl groups in the vicinity of the nitrogen centre is obviously insufficient to prevent coordination to the metal, since no conversion is observed using this base.

In contrast, organic bases possessing a sp^3-nitrogen centre like NEt_3 (Entry 3) or sterically hindered Hünig's base (Entry 6) provide high rates of conversion, latter one with a similar kinetic profile than the reference reaction. Sodium acetate shows a conversion of 67% after 48 hours (Entry 7), which is significantly less than reactions with NEt_3 or K_2CO_3. It is unlikely that this results from the low solubility and therefore heterogeneous nature of the reaction in DMF, since K_2CO_3 is poorly soluble as well and shows a distinctly higherr rate of conversion (Table 14, Entry 1). Therefore, we would attribute the observed slowdown effect to its lower basicity compared to K_2CO_3.

On the other hand, when P_1-base was employed (Entry 8), the significant increase in strength of the organic base as compared to Et_3N (P_1-base is *ca.* 10^9 times stronger than NEt_3 in MeCN)[26] did not lead to a higher rate of conversion. In contrast, some slowdown effect became evident towards the end of the reaction (81% after 24 hours) which however may be due to deactivation of the base by moisture and CO_2. The result might be explained by the latter assumption, since heating of the reaction mixture at 50°C over night resulted in full conversion of **28a**.

Combining the obtained experimental results with practical considerations suggest that the reaction of cyclopentenyl nonaflate **28a** with methyl acrylate **44** in DMF as the solvent, $Pd(OAc)_2$ as the catalyst precursor and NEt_3 as the base comprises fast conversion with conveniently to handle substrates. Therefore this optimised system was used on a regular basis for all the following investigations.

2.3.3. The effect of additives

As evidenced from studies by Jeffrey *et al.* and other authors,[50] tetraalkylammonium halides often accelerate Heck couplings of aryl halides and sulfonates and stabilize the Heck catalytic systems. While the concept of ligand assisted catalysis is understood quite well and is backed up with experimental data,[54a-b] significantly less is known about the effect of salts on the reaction course. Often *per se* a beneficial effect is taken for granted, without being in possession of any supporting kinetic data. For this reason, we decided to test additives in our model reaction. First the effect of tetrabutylammonium salts, most often used in "ligandless" catalysis, on the model system was investigated by adding tetrabutylammonium chloride, bromide and iodide salts (Table 17).

Entry	Components			Additive[a]	Conversion in %			
	solvent	catalyst	base		2h	4h	6h	22h
1	DMF	$Pd(OAc)_2$	NEt_3	$(n\text{-}Bu)_4NCl$	8	17	29	√
2	DMF	$Pd(OAc)_2$	NEt_3	$(n\text{-}Bu)_4NBr$	29	62	96	√
3	DMF	$Pd(OAc)_2$	NEt_3	$(n\text{-}Bu)_4NI$	27	48	67	√
4	DMF	$Pd(OAc)_2$	NEt_3	—	34	81	98	√

Table 17 Conversion of **28a** according to the model reaction (Scheme 17) in the presence of tetrabutylammonium salts, at 24°C; a) 1 equiv. of the salt related to the substrate **28a** was added. "√" indicates that no starting material could be detected by ^{1}H-NMR anymore.

Surprisingly the most frequently used additive in „ligandless" Heck catalysis tetrabutylammonium chloride showed the lowest rate of conversion (Entry 1). It is significantly slower than the reference reaction (Entry 4), or those carried out in the presence of bromide or iodide (Entries 2 and 3). The fastest conversion in the presence of a salt was obtained with tetrabutylammonium bromide, which is overall comparable but not faster than the reference reaction. The conversion of alkenyl nonaflate **28a** with tetrabutylammonium iodide lies in between. Therefore the following order of declining reactivity for the anions can be given as follows: *without additive* $\approx Br^- > I^- > Cl^-$.

It is not possible to exhaustively explain the results solely with the kinetic data obtained so far. It can be assumed that the type of catalysis either heterogeneous or homogeneous is affected differently by the employed anions. For heterogeneous catalysis it is generally believed that tetraalkylammonium halides stabilize Pd clusters by building up a "protective layer" and preventing them from agglomeration in order to form Pd_{black}.[55] As a direct consequence of this model the reactants must overcome an activation barrier, to allow for a reaction with the active metal species. Therefore, it is reasonable to assume that the highest rate of conversion is to be expected for systems in which a balance between stabilization and reactivity of the catalytic species is optimal. Apparently, for the alkenyl nonaflates the stabilization by the amide solvent molecules must be better in this respect than by halide anions. As a result the additive free catalytic system (Entry 4) exhibits the highest reactivity. On the other hand, in the case of a homogeneous catalysis deactivation of an intermediate palladium complex can take place if salts are employed, caused by specific halogen anion effects.[6] Indeed, the above results can be taken as a hint for homogeneous catalysis since an improved reaction outcome is reported for tetrabutylammonium salts in heterogeneous systems.[56a-b] In contrast, the above results show a reduced activity for the catalytic species if tetrabutylammonium salts are used and the highest rate of conversion if the catalysis is not affected by salts.

Usually tetrabutylammonium salts are used together with K_2CO_3 as the base. $(n\text{-Bu})_4NCl$ is the most common additive in the ligand free Heck reaction, and the question arose if a negative chloride effect can also be found in the reaction with K_2CO_3 in place of NEt_3 (Table 18). The reaction containing $(n\text{-Bu})_4NCl$ (Entry 1) shows a dramatically higher rate of conversion as without additive (Entry 2). Nearly complete conversion is obtained in repetitive, reproducible runs after only 30 minutes.

Entry	**Components**			**Additive**[a]	**Conversion in %**			
	solvent	catalyst	base		½h	1h	2h	24h
1	DMF	$Pd(OAc)_2$	K_2CO_3	$(n\text{-Bu})_4NCl$	98	√		
2	DMF	$Pd(OAc)_2$	K_2CO_3	—		7	21	93
3	DMF	$Pd(OAc)_2$	K_2CO_3	$(n\text{-Bu})_4NBF_4$	5	17		84
4	DMF	$Pd(OAc)_2$	Cs_2CO_3	—		12		23
5	DMF	$Pd(OAc)_2$	$K_3PO_4 * H_2O$	—	5	8		50

Table 18 Conversion of nonaflate **28a** according to the model reaction (Scheme 17) with different inorganic bases and additive combinations, at 23°C; a) 1 equiv. of the additive related to the substrate **28a** was added. "√" indicates that no starting material could be detected by ^{1}H-NMR anymore.

The dramatic acceleration effect resulting from the combination of chloride anion with the K_2CO_3 base for this specific system can be suspected already by direct comparison of the additive free model reaction employing $Pd(OAc)_2$ and K_2CO_3 (Table 18, Entry 2) with the reaction using $PdCl_2$ and K_2CO_3 (Table 14, Entry 1), with latter reaction showing a higher rate of conversion, with only catalytic amounts of chloride present. Nevertheless, a rate enhancing effect could also result from the tetrabutylammonium cation, working as a phase

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[6] It is well documented that the type of halogen ion can significantly influence the outcome of an organic reaction. For an excellent review covering this topic see K. Fagnou, M. Lautens, Angew. Chem. Int. Ed. **2002**, 41, 26-47.

transfer agent for the poorly soluble base K_2CO_3 in DMF. In order to confirm or rule out this hypothesis, tetrabutylammonium tetrafluoroborate was employed in which the BF_4^- ion represents an inert "dummy" counteranion (Entry 3). However, essentially no faster rate of conversion was observed (*cf.* reference reaction, Entry 2), which means that the acceleration effect is more than just due to phase-transfer co-catalysis and that it uniquely pertains to the combination of $(n\text{-Bu})_4NCl$ with K_2CO_3. Even with stronger inorganic bases than K_2CO_3 like Cs_2CO_3 (Entry 4) or $K_3PO_4{*}H_2O$ (Entry 5) the reaction exhibits a lower rate of conversion than the reaction making use of a combination of $(n\text{-Bu})_4NCl$ and K_2CO_3 or the additive free system with NEt_3 as the base.

So far inorganic bases were always applied together with additives containing the tetrabutyl ammonium cation. To obtain kinetic data in the absence of this common phase transfer catalyst counterion, and to investigate further the beneficial effect of the chloride anion the chloride source was changed to LiCl as the additive. As a cheap and non hygroscopic salt LiCl represents also a useful alternative to the tetrabutylammonium halilde, if providing a fast catalysis.

Compared to the reference reaction using solely K_2CO_3 (Table 19, Entry 1) the catalysis with LiCl as the additive shows an interesting kinetic profile (Entry 2). The reaction exhibits an unusually long induction period, but a high rate of conversion at the end of the reaction course. While only 4% of the starting material is consumed after 4 hours, already 95% of conversion is obtained after 9 hours.

Entry	**Components**			**Additive**	**Conversion in %**								
	solvent	catalyst	base		1/4h	1/2h	1h	2h	2.5h	4h	6h	9h	29h
1	DMF	$Pd(OAc)_2$	K_2CO_3	—			7	20		40	52	71	93
2	DMF	$Pd(OAc)_2$	K_2CO_3	LiCl		—	—	—		4		95	√
3	DMF	$Pd(OAc)_2$	K_2CO_3	$(n\text{-Bu})_4NCl^a$	61	74	85		√				

Table 19 Conversion of nonaflate **28a** according to the model reaction (Scheme 17) in the presence of K_2CO_3 as the base and LiCl and $(n\text{-Bu})_4NCl$ as additives, at 23°C; a) 0.5 equiv. related to the substrate **28a**. "√" indicates that no starting material could be detected by ^1H-NMR anymore.

Due to the long induction period the catalysis is overall considerably slower than the reaction with $(n\text{-Bu})_4NCl$ as the additive (Table 18, Entry 1). Nevertheless, with a conversion of 95% after 9 hours the catalysis is still clearly faster than for the reference reaction. Also of importance is the $(n\text{-Bu})_4NCl$ to K_2CO_3 ratio (Entry 3). Lowering the ratio of additive to base from 1:2 to 1:4 results in a lower rate of conversion compared to the reaction exhibiting a ratio of 1:2 (Table 18, Entry 1).

Taking the results from Table 14, Entry 1 and the Tables 17, 18 and 19 into account, the dramatic acceleration effect of the combination of $(n\text{-Bu})_4NCl$ and K_2CO_3 (Table 18, Entry 1) cannot be explained in terms of an isolated anion or base effect. In contrast it must be attributed to a unique synergy resulting from the combination of K_2CO_3 with $(n\text{-Bu})_4NCl$, as neither of the components alone is able to render the observed degree of acceleration. At this point, we are unable to provide a rational explanation for this effect which requires further experimental studies.

The limitations of the catalysis using the combination of K_2CO_3 and $(n\text{-Bu})_4NCl$ were tested by varying the temperature and the catalyst loading. For cost reasons it is desirable to apply lower catalyst loadings, but ideally run the reaction still at room temperature. In addition it would be attractive to carry out the reaction at lower temperature, enabling the smooth conversion of temperature sensitive substrates or to influence stereoselective transformations. To investigate both options the model reaction with $(n\text{-Bu})_4NCl$ and K_2CO_3 was conducted at 0°C and 5 mol% catalyst loading and with 0.5 mol% $Pd(OAc)_2$ at room temperature (Table 20).

Entry	**Components**			**T**	**Conversion in %**								
	catalyst	base	additive[a]		1/2h	1h	2h	3h	4h	5h	6h	9h	29h
1	$Pd(OAc)_2$	K_2CO_3	$(n\text{-Bu})_4NCl$	0°C	5		13	23	28	39	55[b]		
2	$Pd(OAc)_2$[c]	K_2CO_3	$(n\text{-Bu})_4NCl$	r.t.		2	4		9		11	18	53

Table 20 Conversion of nonaflate **28a** according to the model reaction (Scheme 17) in DMF with K_2CO_3 as base and $(n\text{-Bu})_4NCl$ as additive; a) 1 equiv. of the additive related to the substrate **28a** was added, b) the reaction is completed after one additional hour at r.t., c) 0.5 mol% catalyst loading. "√" indicates that no starting material could be detected by ^{1}H-NMR anymore.

Performing the catalysis at 0°C slows down the rate of conversion significantly and 55% conversion are obtained after 6 hours (Entry 1). The reaction reaches completion within 1 hour when the mixture is taken out of the ice bath and is allowed to warm up to room temperature. Lowering the catalyst loading tenfold leads to a dramatic lower rate of conversion (Entry 2). After 29 hours only circa half of the starting material is consumed. At this catalyst loading elevated temperature is required to get the reaction to completion within a reasonable time scale.

The catalysis itself is largly unaffected by the presence of small amounts of H_2O as demonstrated by a simple qualitative experiment shown in Table 21. Compared to the reference reaction (Entry 1) the addition of 1 drop = 40 mg ≈ 3 vol% of deionised H_2O has practically no effect on the reaction outcome (Entry 2).

Entry	Components			Additive	Conversion in %				
	solvent	catalyst	base		1/4h	1/2h	4h	6h	24h
1	DMF	$Pd(OAc)_2$	K_2CO_3	$(n\text{-Bu})_4BF_4$	2	4	67	79	91
2	DMF	$Pd(OAc)_2$	K_2CO_3	$(n\text{-Bu})_4BF_4$ + 40 mg H_2O	2	4	62	71	84

Table 21 Conversion of nonaflate **28a** according to the model reaction (Scheme 17) in the presence of a small amount of H_2O, at 22°C.

In general the reactions are carried out without drying of any of the components. Hence water is already present at the beginning of the reaction, particularly from the solvent DMF. This experiment testifies the robustness of the catalytic species and therefore confirms that solvents can be used as purchased, without drying prior to the use in the catalysis.

2.3.4. The effect of triphenylphosphine

To the best of our knowledge kinetic investigations have not been conducted for the Heck reaction of alkenyl sulfonates or halides in the presence of phosphine ligands. In order to obtain first kinetic data the model reaction was carried out in the presence of varying amounts of PPh_3, and the reaction outcome studied (Table 22).

A small amount of PPh_3 (0.05 equivalents) relative to the catalyst has no effect on the rate of conversion (Entry 2) compared to the reference reaction without PPh_3 (Entry 1). 1 equivalent of the ligand has only a marginal effect on the overall outcome of the reaction (Entry 3). The catalytic system exhibits some induction period, but full conversion is achieved in nearly the same time as for the reference reaction. While amounts smaller or equal than 1 equivalent give full and essentially clean conversion similar to the reference reaction, a very different kinetic profile is obtained with amounts of 2 and 4 equivalents of PPh_3. In the first case a side reaction takes place which even overruns the main coupling reaction (Entry 4). The side product was not further investigated. In the latter reaction no conversion at all can be monitored over 6 hours.

Entry	**Ligand**[a]	**Conversion in %**					
		1h	2h	3h	4h	5h	6h
1	—	26	61	85	96	≥99	√
2	PPh_3 - 0.05 equiv.	24	61	86	97	99	√
3	PPh_3 - 1 equiv.	4	23	54	80	94	≥99
4	PPh_3 - 2 equiv.	—	—		—		small amount of **45**[b]
5	PPh_3 - 4 equiv.	—	—		—		—

Table 22 Conversion of **28a** according to the model reaction (Scheme 17) in DMF as the solvent, $Pd(OAc)_2$ as the catalyst precursor and NEt_3 as the base in the presence of PPh_3 as ligand, at 24°C; a) amount relative to $Pd(OAc)_2$, b) from the very beginning the formation of side product could be observed, emerging to the main product during the reaction course. "√" indicates that no starting material could be detected by ^{1}H-NMR anymore.

Obviously amounts of *ca.* 1 equivalent of PPh_3 (related to the catalyst precursor) start affecting the reaction course, incipient with the occurance of an induction period and accompanied with an acceleration effect in the end of the reaction. Using an amount of PPh_3 exceeding 1 equivalent the Heck reaction is superseded by at least one side reaction, while 4 equivalents of phosphine already act as a catalyst poison. A similar observation is described for the reaction of *p*-bromoanisole with *n*-butylacrylate at 135°C and a varying amount of PPh_3.[57] The highest activity is obtained using 1 equivalent of PPh_3. With increasing amounts of phosphine the catalytic activity is gradually reduced, until cessation of the catalysis is observed using 6 equivalents of phosphine. The result is explained by the hypothesis that PPh_3 loadings higher than 1 equivalent suppress the formation of underligated Pd-phosphine complexes which are required for the catalysis to take place. However, at that time we refrain from speculating too much about the observed effect of phosphines. Since different substrates and reaction conditions were applied this explanation does not necessarily translate to our investigation.

2.3.5. Lower catalyst loading

The ligand- and additive-free model system using 5 mol% of the catalyst precursor provides full conversion of the starting material generally within 6-9 hours. Nevertheless it is advisable to work with lower catalyst loadings and therefore 1 mol% as well as 0.5 mol% of $Pd(OAc)_2$ were applied, and the conversion of **28a** at room temperature and elevated temperature determined. The results are summarized in Table 23 and 24.

The solutions appear homogeneous and essentially clear throughout the whole reaction course and no loss of activity is seen. Gentle heating to 50°C at the end of the reaction course with 0.5 mol% loading of $Pd(OAc)_2$ results in full conversion (Table 23, Entry 2).

Entry	**Catalyst**	**Conversion in %**									
	$Pd(OAc)_2$	2h	4h	22h	32h	52h	60h	3d 9h	6d	2h at 50°C	3h at 50°C
1	1 mol%	8	15	46	56	70	76	93	√		
2	0.5 mol%	5		18	22	30	36	50	88	97	√

Table 23 Conversion of **28a** according to the model reaction (Scheme 17) in DMF and NEt_3 as the base with 1mol% and 0.5mol% catalyst loading, at 22°C. "√" indicates that no starting material could be detected by ^{1}H-NMR anymore.

The investigation was also conducted with the catalytic most active systems from Table 15 (Entry 1) and Table 13 (Entry 3) using 0.5 mol% of the catalyst precursor and elevated temperature from the very beginning (Table 24).

Entry	**Components**			**T**	**Conversion in %**							
	solvent	catalyst	base		2h	4h	6h	7h	8h	9h	+15h at r.t.	+66h at r.t.
1	DMF	$Pd(OAc)_2$ 0.5 mol%	NEt_3	50°C	39	70	86	90	91	95	97	√
2	HCONHMe	$PdCl_2$ 0.54 mol%	NEt_3	50°C	45	72	83			94	not done[a]	√

Table 24 Conversion of **28a** according to the model reaction (Scheme 17) at 50°C in DMF and *N*-methylformamide as solvents; a) the precise amount could not be determined via ^{1}H-NMR. "√" indicates that no starting material could be detected by ^{1}H-NMR anymore.

Both reactions show the same high conversion after 9 hours under these conditions and completion of the catalysis even at room temperature. Neither Pd_{black} formation nor any loss of catalytic activity could be observed during the reaction course.

2.3.6. *A short discussion about the role of the solvent*

The specific, beneficial role of the amide solvents is unclear. First of all the solvent could act as the reducing agent for the formation of Pd(0) from Pd(II) after the dissolution of the metal salt. In addition, it seems to exhibit stabilizing effects on the catalytically active species due to a dynamic ligation to the metal centre.

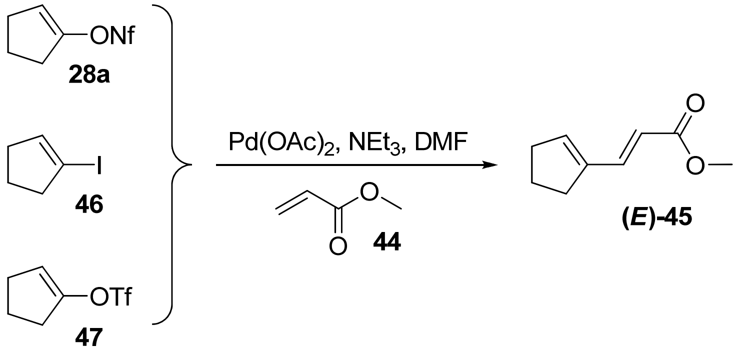
DMF acting as the reducing agent would be oxidized to dimethylcarbamic acid. As an unstable compound it quickly decomposes into CO_2 and dimethylamine. A single experiment was carried out mixing cyclopentenyl nonaflate **28a**, $Pd(OAc)_2$ and DMF in a NMR tube. Subsequent ^1H and ^{13}C-NMR studies indicated no reduction. Addition of NEt_3 did not show any change either. With addition of methylacrylate **44** immediately the coupling reaction took place, indicating that the olefin may trigger the reduction. The experiment as it was conducted must be interpreted with caution since the intensity of the possibly formed dimethylamine signals is expected to be very small.

Since all the components of the model Heck reaction with exception of the catalyst precursor are liquids, and therefore the components of the reaction can form a homogeneous mixture, the reaction was performed excluding DMF (otherwise identical to those conditions described in Scheme 17). Interestingly catalysis can be observed a few hours after the addition of the catalyst precursor even without the presence of the solvent, although the overall rate of conversion is small. Pd_{black} is formed as a thin film on the sample bottle within one day, indicating a loss of stability in the catalytic system. However, full conversion is accomplished within 161 hours.

Considering the results of these experiments, reduction of the Pd salt at least exclusively by the formamide solvent can be excluded. Nevertheless, the solvent obviously exerts a beneficial effect on the rate of the reduction and the rate of conversion. To receive more clarity for these important matters additional experiments are required, in order to fully elucidate the role of the formamide solvents.

2.4. A comparison of cyclopentenyl nonaflate, triflate and iodide

Only scarce kinetic measurements of palladium catalyzed C,C-bond forming reactions are reported for alkenyl triflates, nonaflates or even halides.[8j,10] We learned already that protection from atmospheric oxygen and moisture is not required and additives or ligands are not essential to maintain the catalysis for the model Heck coupling and therefore we became interested in comparing the nonaflate **28a** with the iodide **46** and triflate **47** counterparts using these conditions (Scheme 18). In the previous Chapter we already introduced a new procedure for the generation of alkenyl nonaflates from enolizable carbonyl precursors, advantageous compared to the reported synthesis of vinyl triflates or the corresponding iodides. Therefore more kinetic data attesting a superior kinetic reactivity could make the nonaflates substrates of choice for a wide range of applications.



Scheme 18 Comparison of cyclopentenyl nonaflate **28a**, cyclopentenyl iodide **46** and cyclopentenyl triflate **47** in the model Heck reaction: 1.0 mmol of **28a**/**46**/**47**, 1.3 mmol of **44**, 5 mol% of $Pd(OAc)_2$, 2.0 mmol of NEt_3 in 1 ml of DMF at 20°C; the experiments were conducted in parallel runs to acquire comparative kinetic data.

The kinetic investigation was conducted in two sets of reactions. In the first set, a comparison of cyclopentenyl nonaflate **28a** with cyclopentenyl iodide **46** was carried out. The reaction solution containing **46** turned greyish already at an early stage of the reaction course, while the mixture containing the nonaflate **28b** essentially remained a clear solution. Unfortunately the Heck coupling of the iodide **46** could not be monitored satisfactorily by ^{1}H-NMR due to signal overlap of the vinylic proton of **46** with the olefinic protons of methylacrylate **44** in the ^{1}H-NMR spectra. However, the end of the transformation could be clearly determined and the catalysis using alkenyl nonaflate **28a** was completed within 9 hours, while compound **46** required 12 hours for full conversion (corresponding to a 1.3 times overall lower rate of conversion).

A second set of reactions included as the starting materials cyclopentenyl nonaflate **28a**, cyclopentenyl iodide **46** and cyclopentenyl triflate **47** (Scheme 18). This time the progress of the reaction was monitored by GC-analysis. Immediately with addition of the $Pd(OAc)_2$ salt Pd_{black} was formed in the reaction mixture containing cyclopentenyl iodide **46** and the catalysis stalled. Compared with cyclopentenyl triflate **47** the corresponding nonaflate **28a** shows an appreciably faster initial and overall rate of conversion (Figure 5 and Table 25). In addition the reaction with nonaflate **28a** reaches full conversion within 25 hours in contrast to the reaction mixture containing the triflate **47** (Figure 5).

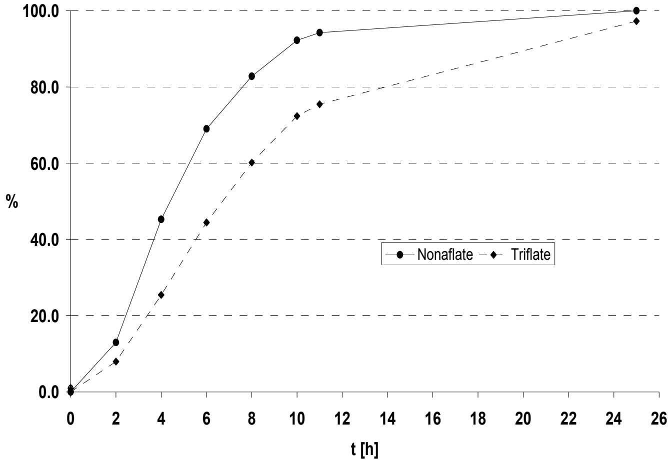


Figure 5 Kinetic profiles for the conversion of cyclopentenyl nonaflate **28a** and cyclopentenyl triflate **47** according to Scheme 18, at 20°C.

Compound	T	conversion in %						
		2h	4h	6h	8h	10h	11h	25
28a	20°C	13	45	69	83	92	94	√
47	20°C	8	25	44	60	72	75	97

Table 25 Conversion of cyclopentenyl nonaflate **28a** *vs.* cyclopentenyl triflate **47** in the model Heck reaction according to Scheme 18 at 20°C; the reaction was monitored with GC and p-xylene as internal standard.

Admittedly, as a single experiment, the order of relative reactivity of the cyclopentenyl derivatives **28a**, **46** and **47** established above is by implication not conferrable to other acyclic- or cyclic alkenyl derivatives. Nevertheless this result - together with literature data - confirms the trend of an overall slightly higher reactivity for alkenyl nonaflates compared to the corresponding triflates and even over iodides.

2.5. Conclusions

The developed ligand and additive free Heck coupling protocol employing NEt_3 as the base, $Pd(OAc)_2$ as the stable catalyst precursor salt and DMF as the solvent features excellent performance in terms of manipulative simplicity, catalytic activity and robustness.

The catalytic activity can be significantly increased by employing tetrabutylammonium chloride as an additive in combination with K_2CO_3 as the base. While the reason for the increased rate of conversion remains unclear, it is obvious that this characteristic depends on a synergistic effect of both components. Interestingly, additives as tetrabutylammonium halides have a slightly inhibitory effect if applied in the presence of NEt_3 as the base. This might suggests that the catalysis is a matter of a homogenous reaction and the anions involved deteriorate the rate of the conversion.

It must be emphasized that the catalytic system operates with conveniently to handle components and due to its 1M concentration is ideal for scale up. Nevertheless, for large scale applications it would be necessary to work with a reduced amount of the required palladium catalyst. In this case gentle heating is required in order to enable full conversion within a reasonable time scale.

Within this investigation alkenyl nonaflate **28a** proved to be superior compared to alkenyl triflate **47** in terms of reactivity and iodide **46** in terms of activity and stability of the catalytic system.

The Heck coupling with alkenyl nonaflates: principles, scope, and the proof of homogeneity

3. The Heck coupling with alkenyl nonaflates: principles, scope, and the proof of homogeneity

3.1. General remarks

Transition metal catalysis has rapidly evolved to an extensive and multifaceted area within organic chemistry. As a result the number of catalytic systems became unmanageable and meanwhile countless transition metal complexes are known, readily available for various transformations in organic synthesis.

However, the metal complex added to a reaction mixture is often not the true catalyst. While - for example - asymmetric transformations and the activation of substrates apparently require, that the ligand system is preserved throughout the catalysis, this must not necessarily be the case for other C-C bond forming reactions. Especially under reducing conditions the transformation of the metal complex to a colloidal metal species is a likely process. For obvious reasons it is of importance to distinguish between heterogeneous and homogeneous catalysis. The catalytic properties of both systems vary decisively. While a homogeneous species typically owns just one reaction site, metal particles exhibit multiple reaction sites. Therefore catalytic activity, selectivity and the tendency for side reactions, as well as stability and endurance of the catalytic system will differ significantly. For instance a colloidal metal species must be prevented from agglomeration by the right choice and concentration of stabilizers, in order to obtain the longest possible lifetime. As consequence for a rational design or the improvement of a catalytic system, it is of fundamental importance to learn if the catalysis is performed by a homogeneous or a heterogeneous species.[58]

Within the pool of transition metal catalysis the Heck reaction represents one of the basic tools in contemporary organic synthesis.[59a-i] As mentioned in the previous chapter the existing vast realm of the Heck chemistry can be conventionally subdivided to ligand-assisted and ligand-free catalysis. While ligands are essential for enantioselective variants of the Heck reaction[60] or activation of otherwise unreactive aryl chlorides,[61a-b] it often tends to deteriorate the desired coupling and causes side reactions or it may even deactivate the catalyst (see *e.g.* results of PPh_3 addition prior to the start of the Heck reaction summarized in Chapter 2.3.4., Table 22, Entries 4 and 5),[57] in particular when aryl iodides are used as substrates.[62] From this standpoint, it is of no surprise that the fastest versions of Heck reaction known so far are described for ligand-free systems, employing additives in form of tetrabutyl ammonium halides or LiCl containing free halides ($Cl^{\ominus}$ or $Br^{\ominus}$) which are believed to stabilize the Pd(0)-species.[50,56a-b]

Later on, it was shown that intermediary Pd nanoparticles as colloids are likely to be the true catalytic species in such systems.[55] Owing to the recent advancements in mechanistic study and design of robust and efficient low Pd-loading systems,[56a,63] the ligand-free Heck reaction became an emerging trend with particular promise for industrial applications.[7a-b] On the other hand, it was demonstrated in a number of well-documented cases that palladacycles[56a,64a-d] and pincer Pd(II) complexes[65a-b] are pre-catalysts and not the actual active species catalyzing the Heck reaction of aryl halides, as it was believed earlier.[51] Compelling evidences based on kinetic studies and quantitative poisoning experiments were obtained that the above complexes decompose under the reaction conditions generating the actual catalytic species, Pd nanoparticles.[65a,66]

The above achievements in a better understanding of the nature of catalysis in the Heck chemistry of aryl halides,[67] the lack of mechanistic insight in the underligated Heck reaction of aryl- and alkenyl perfluoroalkanesulfonates[68a-g] and the findings described in the previous chapter prompted us to scrutinize the nature of Pd-catalysis for these substrates, with the primary objective to establish whether the reaction is effected by heterogeneous or homogeneous catalysis.

3.2. The proof of homogeneity

Since catalysis is a “kinetic phenomenon”[7], it has been generally accepted that quantitative kinetic data provide the most compelling evidences for the identity of the true catalyst.[58] Our kinetic investigations were again performed with cyclopentenyl nonaflate **28a** and methyl acrylate **44** (Scheme 19). The ligand- and additive-free Heck reaction was carried out under the optimized conditions at ambient temperature (20-24°C). All the kinetic experiments were carried out using GC monitoring with p-xylene as internal standard.

First and foremost the idea of a likely homogeneity of our catalytic system emerged from the observations described in Chapter 2, that is, the catalytic system features excellent reproducibility, robustness and insensitivity towards atmospheric oxygen and moisture. The

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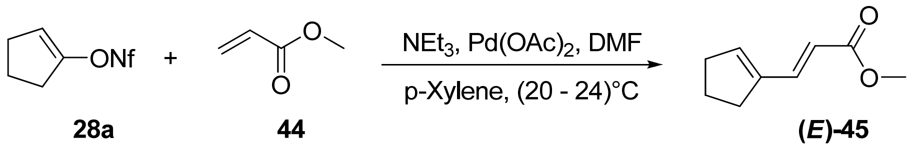
[7] Taken from J. A. Widegren, R. G. Finke, *J. Mol. Catal. A: Chem.* **2003**, *198*, 317–341.[58]

idea was additionally supported by kinetic measurements carried out in the presence of tetrabutylammonium chloride, which is reported to have a beneficial effect on the reaction outcome in the case of a heterogeneous catalysis, while it showed in contrast a considerable slow down effect for the model Heck reaction under the optimized reaction conditions (Chapter 2, Table 17, Entry 1 and 4). Noteworthy, the reaction mixtures remain essentially homogeneous during the entire course of the reactions, regardless to the amount of Pd taken and despite the absence of Pd colloid stabilizers.



Scheme 19 The model Heck reaction for kinetic investigations and poisoning experiments: 1.0 mmol of cyclopentenyl nonaflate **28a**, 1.3 mmol of methylacrylate **44**, 5 mol% of $Pd(OAc)_2$, 2.0 mmol of NEt_3 in 1 ml of DMF; the reactions were monitored via GC and p-xylene as internal standard; a detailed description of the single experiments can be found in the experimental section under “7.4.2 Poisoning Experiments”.

Another hint for a homogeneous type of catalysis arose from the interpretation of the kinetic profile of the reaction. Not a single experiment showed a sigmoidal curve, universally accepted as a strong indication of a heterogeneous type of catalytic system (as representative graphs see Chapter 2, Figure 5 (curve of the alkenyl nonaflate **28a**); Figure 7, 8 and 9, see reference curves). A slightly lower slope in the beginning of the reaction curves can be satisfyingly explained by the required time for dissolution of the $Pd(OAc)_2$ salt followed by the subsequent reduction of Pd(**II**) to Pd(0) prior to the start of the reaction.

The first indirect evidence for the homogeneous nature of the catalytic system came from the comparative analysis of the rate of conversion as a function of catalyst loading in the model Heck reaction of nonaflate **28a** *vs*. that of bromobenzene studied earlier.[56a,63] In the latter case, the reaction slows down significantly and stops finally at an early stage when the Pd loading is increased. This result is explained by the aggregation of Pd(0) at a certain stage of the reaction, leading to Pd cluster formation of low catalytic activity which outruns the desirable Heck coupling. This is why the increase in the catalytic loading leads to a seemingly paradoxal decrease of the conversion (as the aggregation process is higher order in Pd concentration than Heck coupling, by reasonable lowering the catalyst-to-substrate ratio significant improvement of the kinetics in favour of the Heck reaction was achieved).[56a,63]

A significantly different kinetic profile was obtained using our protocol with nonaflate **28a** and methyl acrylate **44** as the substrates (Figure 6). It manifests a steady increase of the rate of conversion with raising the catalyst-to-substrate ratio to even high Pd concentrations (10 mol%). In addition, the rate of the reaction features consistent linear dependence related to the catalyst loading. This result can be regarded as evidence for a kinetically stable, homogeneous catalytic species lacking clustering.

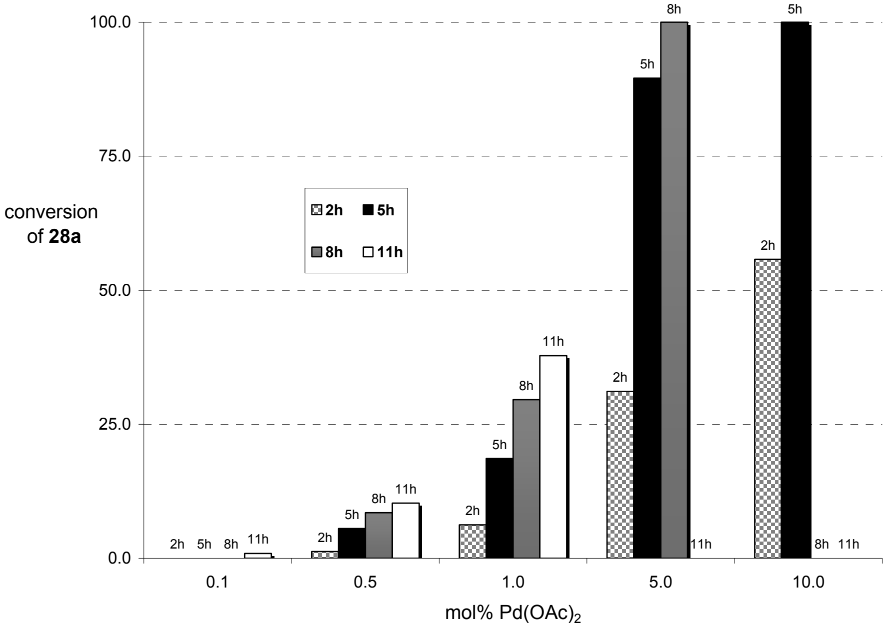


Figure 6 The effect of the Pd(OAc)$_2$/alkenyl nonaflate **28a** ratio on the conversion of the model Heck reaction (Scheme 19) at 24°C; for the purpose of clarity the bars indicating 100% conversion for 11 hours at 5 and 10 mol% and 8 hours at 10 mol% are not displayed.

A compelling proof for either homogeneous or heterogeneous catalysis can result from poisoning experiments, if carried out quantitatively.[58] Various approaches have been developed giving the opportunity to choose the appropriate catalyst poison for the transformation in question. Undoubtedly, the most commonly applied approaches are based on mercury and ligand poisoning. The ability of mercury to poison metal surfaces by amalgamation is known for circa a century, the Hg(0) poisoning has been established in transition metal catalysis since the early eighties.[69] The suppression of catalysis after addition of Hg(0) is a strong indication for a heterogeneous system and a negative proof for homogeneous catalysis.

Nevertheless, the experimental data has to be interpreted carefully since Hg(0) is used in large excess in order to avoid incomplete poisoning. It is reported that Hg(0) is able to react with transition metal complexes leading to the formation of side products under these conditions.[69,70a-c] This stands for a false negative proof of homogeneous catalysis, that is, it may impede the homogeneous catalysis if it forms intermetallic bonds with the ligated metal. The conclusion is that if it does not hamper or poison the catalyst then it is surely a proof for a homogeneous catalysis, but if it does then it is likely but not necessarily heterogeneous. Thus additional control experiments are of crucial importance, in order to obtain a definite result. Established poisons of heterogeneous catalysts are CS_2, PPh_3 or thiophene. These compounds are known to effectively bind and to inactivate metal surfaces. Since only a small number of metal atoms within a single cluster is involved in the catalytic processes, already a much lower quantity than 1 equivalent of the poison relative to the catalyst taken will effectively quell the catalytic activity, while poisoning of a homogeneous catalyst requires at least 1 equivalent of the poison.

In a number of quantitative studies, well-established catalyst poisons such as PPh_3, CS_2 or thiophene taken in amounts smaller or equal to 1 equivalent (hereinafter, the amounts of the additives are expressed in equivalent relative to the Pd catalyst) or a large excess of metallic mercury (~300 equivalents) were found to effectively quell the catalytic activity thus proving the heterogeneous nature of the Pd(0)-catalysts in the Heck reactions of aryl halides.[65a-b] For this reason, we decided to apply these protocols to the model Heck reaction of alkenyl nonaflate **28a** and methyl acrylate **44** and studied the reaction course (Scheme 19).

The first set of poisoning experiments was carried out with thiophene, added in amounts of 0.1 to 2.0 equivalents (Figure 7). The catalyst poison was added after 2.5 hours, when the system reached highest catalytic activity.[8]

The kinetic profile of the reaction shows practically no effect of the catalyst poison. The curves of the reference reaction and of that carried out in the presence of 0.1 equiv. of

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[8] In order to avoid systematic errors it is advisable to add the catalyst poison when it can be assured that the catalyst precursor is fully transformed into the catalytically active species. A detailed discussion about systematic failures reported in literature and recommendations for a sound experimental design can be found in the excellent review of J. A. Widegren, R. G. Finke, *J. Mol. Catal. A: Chem.* **2003**, *198*, 317–341.[57]

thiophene are almost identical. The graphs employing 0.5, 1.0 and 2.0 equivalents of the catalyst poison show a marginal slow down effect after the addition, but also exhibit overall the same kinetic profile as the reference reaction.

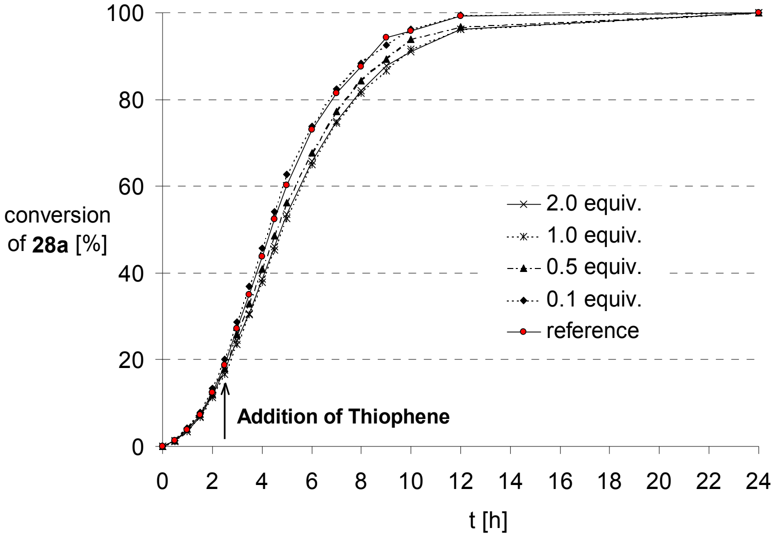


Figure 7 Kinetic profiles of the model reaction in the presence of different amounts of thiophene (from 0.1 to 2.0 equivalents), at 20°C.

This experiment clearly demonstrates that the heterogeneous catalyst poison thiophene, added in amounts of up to 2.0 equivalents has minimal to no effect on the reaction outcome and the rate of conversion for the Heck reaction of nonaflate **28a**. This observation dramatically contrast results obtained by Eberhard *et al.* who demonstrated that already much smaller amounts than 1 equivalent of thiophene are sufficient to fully suppress the activity of the heterogeneous Pd catalyst, apparently resulted from decomposition of pincer Pd(II) complexes.[65b]

A very similar result was obtained with PPh_3 as the catalyst poison (Figure 8). Adding phosphine after 2.5 hours in a range of 0.1 to 0.5 equivalents resulted in a marginal affected kinetic profile of the catalysis (for the sake of clarity only one representative curve is shown in Figure 8, employing 0.5 equivalents of PPh_3). The graphs are in accordance to the reference reaction. 1.0 equivalent of poison led to a slight slow down of the rate of conversion from the point of addition onwards. Nevertheless, the catalysis fully recovers during the reaction course and reaches full conversion at practically the same time as the reference reaction.

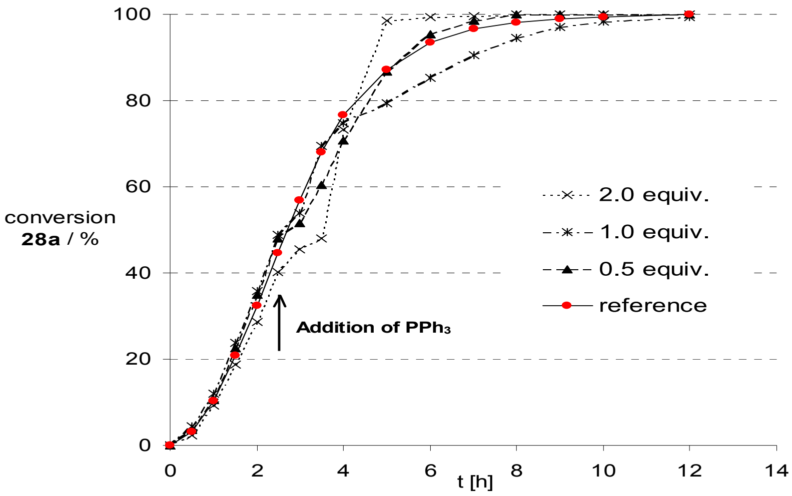


Figure 8 Kinetic profiles of the model reaction in the presence of different amounts of PPh_3 (for the sake of clarity the graphs of the reactions employing 0.1 and 0.25 equivalents were taken out of the figure, since they show the identical kinetic profile as the reaction with 0.5 equivalents), at 20°C.

Given the earlier data by Eberhard *et al.* described above, our results obtained for alkenyl nonaflates with both thiophene and PPh_3 can be regarded as negative proof for the homogeneous nature of the Heck catalysis. The inability of poisoning the catalytically active species with the described additives can be regarded as an evidence of a kinetically stable form of the *homogeneous* Pd(0)-catalytic species throughout the entire reaction course.

The catalysis in the presence of 2.0 equivalents of PPh_3 deserves a separate discussion. It results in a more pronounced effect (Figure 8). The reaction slows down after the addition, but from 210 min on the reaction rate accelerates and full conversion of the starting nonaflate is obtained already after circa 7 hours. This kinetic profile can be explained by side product formation from the point of addition onwards, leading to a faster consumption of the starting material **28a** which gives rise to the desired cross-coupling product, the diene **45**, and the unidentified side product the formation of which is induced by the phosphine.

It is interesting to compare these results with the observation made earlier by adding phosphine in the same amounts prior to the addition of $Pd(OAc)_2$ (Chapter 2, Table 22). With addition of 1.0 equivalent of PPh_3 an induction period was observed with a fast conversion of the substrate taking place afterwards. With 2 equivalents of the catalyst poison already a considerable suppression of the catalysis took place mainly with formation of side products. This is in accordance to the experimental data obtained with addition of PPh_3 after 2.5 hours. Obviously, with more than 1.0 equivalents of phosphine the reaction starts to drift into a different pathway, leading to an increasing amount of the side products the more phosphine is added, regardless whether the catalytic species is already generated (addition after 2.5 hours) or still to be formed (addition prior to the start of the reaction). The cause for this observation remains unclear and requires further investigation, starting with the identification of the side products. Nonetheless, also this result clearly demonstrates the robustness of the ligandless catalytic system in the presence of large amounts of the catalyst poison.

Despite certain limitations on the applicability of Hg(0) poisoning tests,[69,70] we decided to investigate its effect on our model reaction. Whereas the Heck reactions catalyzed by Pd colloids are instantaneously and completely suppressed after addition of mercury,[65a-b] no such dramatic effect was observed under our conditions (Figure 9, curve *a*).

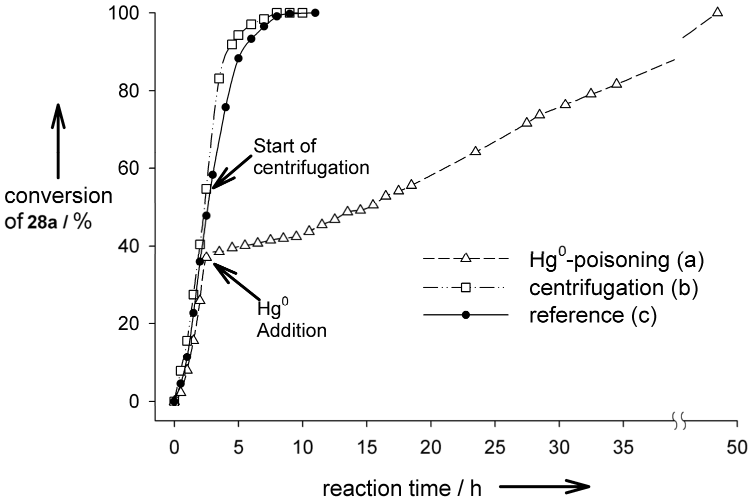


Figure 9 Kinetic profiles of the model reaction (curve c) subjected to Hg(0) poisoning (curve a) and centrifugation (curve b), at 24°C.

As shown in Figure 9, treatment with 300 equivalents Hg(0) resulted in an appreciable slow-down effect. However, no irreversible loss of catalytic activity was observed, and the reaction reached full conversion. This experimental finding could be confirmed within repetitive runs applying an excess of 300 equivalents of Hg(0) related to the catalyst precursor.

A non-invasive method to test for metal clusters represents the precipitation of colloids by centrifugation, possible due to their relatively high density and molecular weight. Therefore the centrifugation of a reaction mixture containing metal clusters will lead to a precipitate. Separation of the supernatant solution from the precipitate should give a catalytically inactive solution and catalytically active sediment. A major problem of this methodology is the quantitative separation of the precipitate from the supernatant solution. Moreover, it must be ensured that the catalyst loading is high enough to enable the formation of a visible precipitate. However, if a catalytically active precipitate is formed in any case a significantly reduced catalytic activity in the supernatant solution can be expected, indicating a heterogeneous catalyst.[58,71a-b]

The centrifugation of the slightly turbid reaction mixture at 55% conversion (after 2.5 hours) at 14.500 rpm for 25 minutes resulted in the formation of a tiny amount of a very fine dark-brown precipitate. The residue proved to be catalytically inactive after exposure to the freshly added reactants for 24 hours at room temperature. The reaction rate in the clear homogeneous solution after centrifugation matched well that of the reference reaction, indicating that the true catalytic species fully remains in solution (Figure 9, curve *b* and *c*). A slightly increased rate of conversion after centrifugation of the sample (curve b) compared to the reference reaction (curve c) results from a slight warm up of the reaction mixture during centrifugation.

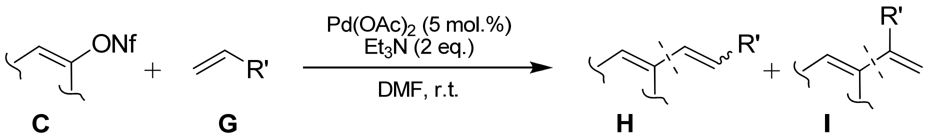
In summary each of the above described experiments clearly indicates the homogeneous nature of the catalytic species present in the Heck reaction of alkenyl nonaflate **28a**. Taken all the results into account it can be clearly stated that the Pd(0)-catalyzed Heck reaction of alkenyl nonaflates is taking place under homogeneous conditions, in contrast to the reaction of aryl halides mentioned earlier.

At this stage, we would refrain from speculating on the structure of the catalyst in the Heck reaction of alkenyl nonaflates. As a working hypothesis, we suggest that Pd(0) exists in kinetically stable form, PdL_n in a dynamic equilibrium with the reaction components (L = olefin **44** or 1,3-diene **45** or DMF or Et_3N) playing the role of weak ligands readily coordinating and dissociating and thus enabling an easy access of substrate to the coordinating sphere of the Pd(0)-centre. A fast oxidative insertion helps to keep the palladium species in the catalytic cycle and ensures its stability under the applied reaction conditions. With all likelihood, low-nucleophilic nonaflate anion accumulated during the reaction course does not coordinate to the catalytic Pd-species and thus does not affect the catalyst activity. In contrast to the inert nonaflate anion one could envisage a beneficial role of the dienes, formed during the reaction course, since this moiety is known to coordinate to transition metal catalysts to form stable complexes, used in stereoselective transformations.[72]

3.3. The Heck reaction with alkenyl nonaflates

The Heck reaction has been recognized as sharpening stone of palladium catalysis[59g] and became an indispensable tool in contemporary organic synthesis spawning even new applications for the industrial production of fine chemicals.[7a-b] Originally described as Pd-catalysed coupling of olefins with organic halides, the reaction significantly gained in versatility and scope after alkenyl perfluoroalkanesulfonates (mainly triflates) were found to undergo efficient Pd-catalysed cross-couplings. Straightforward regio- and stereospecific access to the desired alkenyl building blocks from readily available carbonyl compounds represents an essential advantage of the enol sulfonate methodology.

The generality of the new ligand and additive free cross-coupling protocol was tested in reactions of a series of alkenyl nonaflates **C** with various olefins **G** (Scheme 20). Gratifyingly, a number of alkenyl nonaflates were found to react under the optimized reaction conditions with terminal alkenes to give the expected dienes (**H**, **I**) in overall high yields.



Scheme 20 General scheme for the conversion of alkenyl nonaflates **C** with olefins **G** to the Heck cross-coupling products **H** and/or **I**; the catalysis was conducted without protection from atmospheric oxygen or moisture, the reagents were used as purchased under the following conditions: 1 mmol of nonaflate **C**, 1.3 mmol of olefin **G**, 2.0 mmol NEt_3, 5 mol% $Pd(OAc)_2$ in 1 ml DMF at room temperature.

As representative substrates the cycloalkenyl nonaflates **28a-d** with varying ring size, the indanone derived nonaflate **28e**, the heterocyclic alkenyl nonaflate **28h** and the acyclic alkenyl nonaflate **42b** were selected (Figure 10). The series of olefins included the activated substrates **44**, **48-50**, the slightly electron rich compound styrene **51** and the inactivated olefin 1-hexene **52**. This selection gave the opportunity to evaluate qualitatively the activity of the catalytic system against olefins with different electronic characteristics.

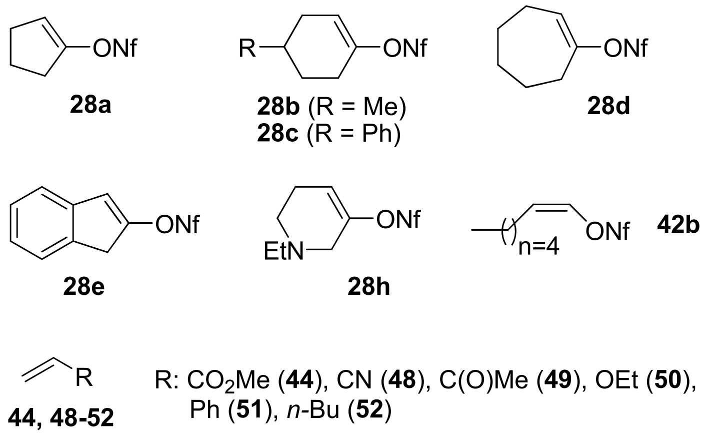


Figure 10 The selection of alkenyl nonaflates and olefins employed in the ligand and additive free cross-coupling protocol according to Scheme 20.

Based on the results obtained in the preliminary investigations (Chapter 2, Scheme 17), the scope of the catalytic system was first explored with cyclopentenyl nonaflate **28a** and all of the aforementioned olefins (Table 26).

Methylacrylate **44** (Entry 1), acrylonitrile **48** (Entry 2) and methyl vinyl ketone **49** (Entry 3) could be coupled in excellent yields, while selectivities follow the typically observed trends.[59b,c,g] The coupling with ethyl vinyl ether **50** afforded the synthetically interesting terminal olefin **55a** as the main product in very good yield (Entry 4). As accompanying compound the (*E*)-isomer **55b** is formed in overall 6%. Electron-rich 1,3-dienes such as **55a** are not easily accessible, therefore this procedure represents a truly straightforward protocol to generate this type of products.

The catalytic system is active enough to cross-couple styrene **51** (Entry 5) or inactivated 1-hexene **52** (Entry 6) at room temperature. The reaction with styrene **51** is completed within 13 hours and mainly affords the (*E*)-isomer **56a** with the terminal olefin **56b** as an accompanying product of always circa 7% in 3 repetitive runs. The reaction of **28a** with 1-hexene **52** is completed within 15 hours, comparable to the activated olefins. The desired coupling product is generated in form of three isomers. Primarily as a mixture of the

(*E*)-regioisomer **57a** and the terminal olefin **57b**, accompanied by 13 mol.% of 1-hex-2-enyl-cyclopentene **57c**.

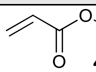
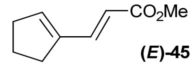
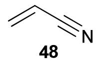
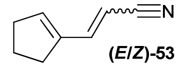
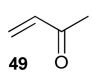
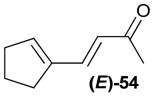
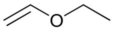
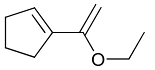
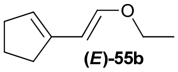
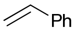
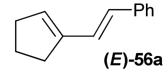
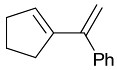
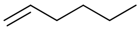
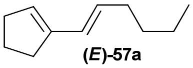
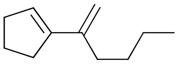
Entry	Nonaflate	Olefin	t [h]	Product	% Yield / Ratio
1	**28a**	 **44**	11	 **(*E*)-45**	**94**
2	**28a**	 **48**	16	 **(*E*/*Z*)-53**	**92** (*E*/*Z*) = 3.8:1
3	**28a**	 **49**	13	 **(*E*)-54**	**90**
4	**28a**	 **50**	18	 **55a**  **(*E*)-55b**	**86** **55a**:**55b** = 15.7:1
5	**28a**	 **51**	13	 **(*E*)-56a**  **56b**	**86** **56a**:**56b** = 13.3:1
6	**28a**	 **52**	15	 **(*E*)-57a**  **57b**	**84** **57a**:**57b** = 2.1:1[a]

Table 26 Heck coupling according to Scheme 20 with 5-membered ring alkenyl nonaflate **28a** and all above mentioned olefins; a) the product mixture contains 13 mol.% of the 1,4-diene product, 1-hex-2-enyl-cyclopentene **57c**.

Both results (Entry 5 and 6) illustrate the remarkably high activity of the catalytic system. The room temperature, ligand and additive free Heck reaction of an inactivated or electron rich alkene with alkenyl sulfonates or halides is unprecedented so far. Both coupling reactions give the products in very good yields and also exhibit excellent reproducibility.

As representative substrates for 6-membered ring nonaflates 4-methyl-cyclohexenyl nonaflate **28b**, 4-phenyl-cyclohexenyl nonaflate **28c** and the piperidine derivative **28h** were chosen (Table 27). As a general trend the cross-coupling affords the desired products in good to excellent yields with comparable selectivities as observed for the 5-membered ring nonaflates, although longer reaction times are observed for some examples.

The coupling of **28b** with methylacrylate **44** gave the diene (*E*)-**58** in excellent 98% yield (Entry 1). The coupling with styrene **51** afforded the product as a mixture of the (*E*)-regioisomer **59a** and the terminal olefin **59b** in a ratio of 5.3:1 (Entry 2). Thus, the reaction forms the product composition in a somewhat worse ratio as it is observed for the coupling with cyclopentenyl nonaflate **28a** (Table 26, Entry 5). For both reactions a slightly elongated reaction time of 24 hours was observed. Reaction of 4-phenyl-cyclohexenyl nonaflate **28c** and methyl vinyl ketone **47** (Entry 3) gave the diene (*E*)-**60** as the sole isomer in excellent 98% yield. The piperidine derivative **28h** could be coupled with methyl acrylate **44** to give the (*E*)-diene **61** in a yield of 82% (Entry 4).

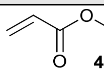
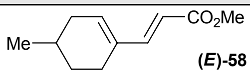
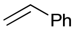
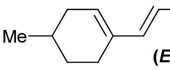
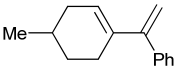
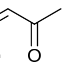
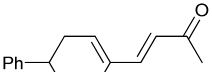
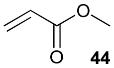
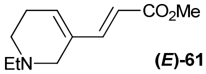
Entry	Nonaflate	Olefin	t [h]	Product	% Yield / Ratio
1	**28b**	 **44**	24	 **(*E*)-58**	**98**
2	**28b**	 **51**	24	 **(*E*)-59a**  **59b**	**98** **59a**:**59b** = 5.3:1
3	**28c**	 **49**	15	 **(*E*)-60**	**98**
4	**28h**	 **44**	16	 **(*E*)-61**	**82**

Table 27 Heck coupling according to Scheme 20 with the 6-membered ring alkenyl nonaflates **28b**, **28c** and **28h** and olefins **44**, **49** and **51**.

Similar to the 5- and 6-membered alkenyl nonaflates, cycloheptenyl nonaflate **28d** undergoes a clean coupling with the olefins **44**, **48**, **49** and **50**, and again the products are generally obtained in high yields (Table 28).

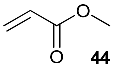
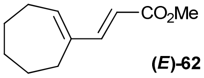
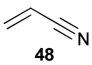
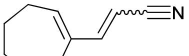
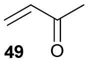
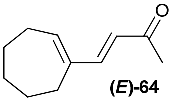
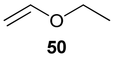
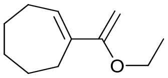
Entry	Nonaflate	Olefin	t [h]	Product	% Yield / Ratio
1	**28d**	 **44**	13	 **(*E*)-62**	**99**
2	**28d**	 **48**	14	 **(*E/Z*)-63**	**87** E/Z = 2:1
3	**28d**	 **49**	13	 **(*E*)-64**	**94**
4	**28d**	 **50**	37^{a}	 **65**	**91**

Table 28 Heck coupling according to Scheme 20 with the 7-membered ring alkenyl nonaflate **28d** and olefins **44**, **48**, **49** and **50**; a) the reaction with ethyl vinyl ether **50** proceeds considerably slower than with the other olefins employed (Entries 1-3), the conversion of **28d** at 24 h could be determined to 91%.

The cross-coupling of **28d** with acrylonitrile **48** gave the product **63** as usual in a high yield but compared to the 5- and 6-membered alkenyl nonaflates in a poor (*E*)-selectivity of 2:1. In contrast, the reaction using ethyl vinyl ether **50** affords the interesting terminal olefin **65** in this case as the sole product (Entry 4, compare with Table 26, Entry 4). However, in order to obtain full conversion of nonaflate **28d** at room temperature a long reaction time of 37 hours is observed for this cross-coupling.

In addition to the 5-7-membered alkenyl nonaflates 2-indenyl nonaflate **28e** was coupled with the two olefins methylacrylate **44** (Entry 1) and styrene **51** (Table 29, Entry 2). Again the reaction proceeds in a clean manner to give high yields of the coupling products, formed as the (*E*)-isomers exclusively.

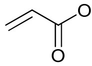
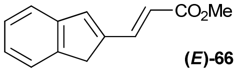
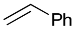
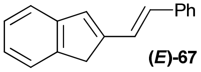
Entry	Nonaflate	Olefin	t [h]	Product	% Yield
1	**28e**	 **44**	13	 **(*E*)-66**	**93**
2	**28e**	 **51**	15	 **(*E*)-67**	**94**

Table 29 Heck coupling according to Scheme 20 employing the aromatic 2-indenyl nonaflate **28e** and the olefins **44** and **51**.

It should be noted that the ring size seems to influence the rate of conversion of the cross-coupling reaction. Generally longer reaction times are observed for the 6-membered cyclic alkenyl nonaflates compared to the 5- or 7-membered cycles. This effect is in particular pronounced for 4-methyl-cyclohexenyl nonaflate **28b** which required 24 hours for the room temperature coupling reactions (Table 27, Entries 1 and 2) and so requires *ca.* double the time as compared to the reactions with nonaflates **28a** or **28d** and the same olefins (Table 26, Entries 1 and 5; Table 28, Entry 1). This trend becomes even more prominent when lower Pd loadings are employed. Table 30 summarizes a series of coupling reactions with 1 mol% $Pd(OAc)_2$ and elevated temperature, under otherwise identical conditions.

Cyclopentenyl nonaflate **28a** fully reacts with methylacrylate **44** within 5 hours at 50°C (Entry 1). Cycloheptenyl nonaflate **28d** even does not require elevated temperatures to reach nearly quantitative conversion with 1 mol% of the catalyst precursor (Entry 2). In contrast 4-methyl-cyclohexenyl nonaflate **28b** requires 30 hours for the total consumption at 50°C (Entry 3).

Elevated temperature seems to have practically no effect on the stereo- and regioselective outcome of the cross-coupling (Entries 4 and 5; compare with Table 26, Entries 2 and 5).

Nevertheless, a lower Pd loading seems to have a beneficial effect for the selective formation of the terminal diene **55a** (Entry 6). Full conversion of **28a** is obtained within 24 hours at 50°C and product **55a** is obtained in this case as the sole product (compare with Table 26, Entry 4).

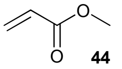
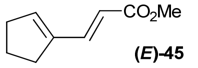
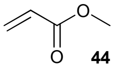
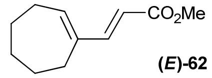
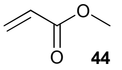
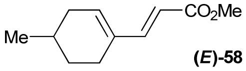
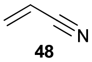
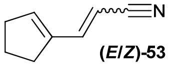
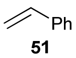
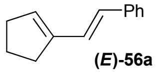
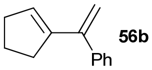
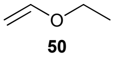
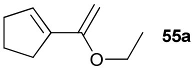
Entry	Nonaflate	Olefin	T [°C]	t [h]	Product	% Conversion [a]
1	**28a**	 **44**	50	5	 **(*E*)-45**	√
2	**28d**	 **44**	25	23	 **(*E*)-62**	**~97**
3	**28b**	 **44**	50	30	 **(*E*)-58**	√
4	**28a**	 **48**	50	24	 **(*E*/*Z*)-53**	**99** (*E*/*Z*) = 3:1
5	**28a**	 **51**	50	12	 **(*E*)-56a**  **56b**	√ **56a**:**56b** = 13:1[b]
6	**28a**	 **50**	50	24	 **55a**	**84**

Table 30 Heck coupling with the selected alkenyl nonaflates **28a**, **28b** and **28d** and the olefins **44**, **48**, **50**, **51** employing lower catalyst loading at room or elevated temperature: 1 mmol of nonaflate, 1.3 mmol of olefin, 2.0 mmol of NEt_3, 1 mol% $Pd(OAc)_2$ in 1 ml DMF; a) the products were not isolated, b) also 3% of the (*E*)-isomer can be detected according to ^{1}H-NMR; "√" indicates that no starting material could be detected by ^{1}H-NMR anymore.

However, these results can and must be seen as a rough guideline, and more coupling reactions with a larger variety of olefins in combination with different 5-, 6-, and 7-membered cyclic alkenyl nonaflates need to be conducted, in order to gain ground for a better understanding of reactivity and selectivity trends.

The cross-coupling protocol, successfully developed for alkenyl nonaflates derived from cyclic ketones, was subsequently extended to acyclic alkenyl nonaflates. 1-heptenyl nonaflate **42b** obtained as a mixture of both stereoisomers in a (*Z*/*E*) ratio of 4:1 (Chapter 1, Table 11) served as an exemplary substrate in the coupling reactions employing the olefins methylacrylate **44**, methyl vinyl ketone **49** and ethyl vinyl ether **50** (Table 31).

Also for the acyclic alkenyl nonaflate **42b** the coupling reactions proceed in a clean conversion and give the desired acyclic dienes in very good yields. The observed reaction times are slightly longer as compared to 5- or 7-membered cyclic nonaflates. Unfortunately, a loss of (*E*/*Z*)-stereoselectivity for the internal double bond is observed, most likely due to a palladium induced isomerization. For all three entries a final (*E*/*Z*)-ratio of circa 2:1 is determined, still in favor of the (*Z*)-configuration of the double bond originating from the alkenyl nonaflate.

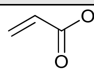
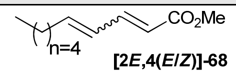
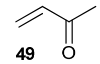
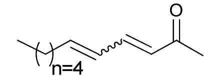
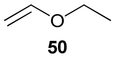
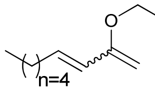
Entry	Nonaflate	Olefin	t [h]	Product	% Yield / Ratio
1	**42b**	 **44**	24	 **[2*E*,4(*E*/*Z*)]-68**	**92**[a]
2	**42b**	 **49**	18	 **[3*E*,5(*E*/*Z*)]-69**	**88**[b]
3	**42b**	 **50**	18	 **(*E*/*Z*)-70**	**89**[c]

Table 31 Heck coupling according to Scheme 20 with 1-heptenyl nonaflate **42b** and the olefins **44**, **49** and **50**; a) product **68** is obtained as a mixture of (4*Z*/4*E*)-stereoisomers in a ratio of 2.2:1, b) product **69** is obtained as a mixture of (5*Z*/5*E*)-stereoisomers in a ratio of 1.7:1, c) product **70** is obtained as a mixture of (*Z*/*E*)-stereoisomers in a ratio of 2.1:1.

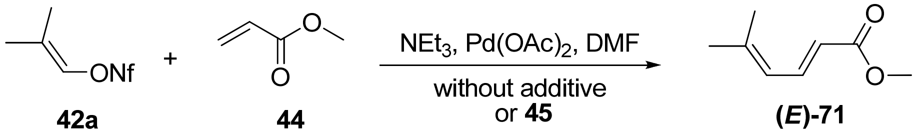
Besides the above mentioned, this type of protocol exhibits an additional advantage. Analogously to the generation of alkenyl nonaflates or alkynes the purification can be conducted in a straightforward way. Since the coupling reaction is carried out in a concentrated 1 molar solution basically consisting of polar components and salts, the formation of an unpolar or slightly polar product gives the opportunity to pour the whole reaction mixture on top of a chromatographic column, with a following flash chromatography using an unpolar or slightly polar eluent, in order to obtain the pure product. In the worst case, an additional simple aqueous extraction may be needed to remove traces of DMF.

3.4. Difficulties and limitations

3.4.1. Reactions of 2-methyl propenyl nonaflate 42a with different olefins

The developed Heck coupling protocol works well for a variety of cyclic and acyclic alkenyl nonaflates. In contrast 2-methyl propenyl nonaflate **42a** shows a considerably different performance compared to 1-heptenyl nonaflate **42b** (Scheme 21). The coupling using the optimized reaction conditions with methyl acrylate **44** led to Pd_{black} formation within 13 hours and termination of the catalysis. Overall only a small amount (≤ 3%) of the desired coupling product (*E*)-**71** could be detected.

As mentioned previously it seems to be most likely that the catalytic species is stored safely in the catalytic cycle by means of a fast oxidative insertion into the alkenyl nonaflate. It might be the case that this process is impeded for 2-methyl propenyl nonaflate **42a** due to steric hindrance, resulting from the methyl group present in the α-position of this substrate. As a consequence stabilization of the Pd(0)-species is obviously essential.

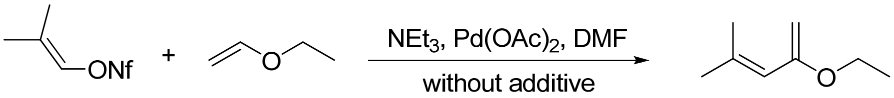


Scheme 21 If no additives were used the desired olefin **71** was generated only in traces since the catalysis was terminated by Pd_{black} formation at an early stage of the coupling of **42a** and **44**; with 1 mmol of diene **45** a considerable amount of product **71** could be generated at elevated temperatures: 1 mmol of **42a**, 1.3 mmol of olefin **44**, 2.0 mmol of NEt_3, 5 mol% $Pd(OAc)_2$ in 1 ml DMF at room- or elevated temperature.

It was already speculated that diene formation during the reaction course could provide an additional stabilization of the catalytically active species. To kill two birds with one stone and to obtain an efficient catalysis with the simultaneous proof of the hypothesis, that the diene generated throughout the Heck reaction course stabilizes the catalytically active species, the product diene of the model reaction 3-cyclopent-1-enyl-acrylic acid methyl ester **45** was used as an additive.

Addition of 1 mmol of **45** to the reaction mixture (Scheme 21) led to circa 10% conversion of the starting material at room temperature within 48 hours. Increasing the temperature to 40°C led to more than 50% conversion overnight. The catalytic system remained stable and neither loss of activity nor Pd_{black} formation was observed. The product was generated exclusively as the (*E*)-isomer **71** according to ^{1}H-NMR.

The effect of diene **45** on the Heck cross-coupling was also investigated for the reaction of **42a** with ethyl vinyl ether **50** (Scheme 22).



Scheme 22 Heck coupling of alkenyl nonaflate **42a** and olefin **50** with or without diene **45**; 1 mmol of **42a**, 1.3 mmol of olefin **50**, 2.0 mmol of NEt_3, 5 mol% $Pd(OAc)_2$ in 1 ml DMF at room temperature.

The catalysis was conducted without additive, with 0.2 mmol (4 equivalents related to the catalyst) and 1.0 mmol of **45**. The results are summarized in Table 32.

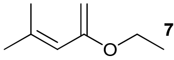
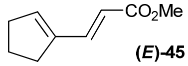
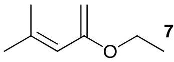
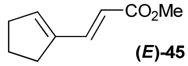
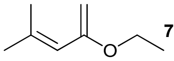
Entry	Nonaflate	Olefin	Additive	Equiv.[a]	t [h]	Product	% Yield / Ratio
1	**42a**	**50**	**—**	—	46	 **72**	√[b]
2	**42a**	**50**	 **(*E*)-45**	1.0	20	 **72**	**69**[c]
3	**42a**	**50**	 **(*E*)-45**	0.2	16	 **72**	**77**

Table 32 Heck coupling of **42a** with olefin **50** and with or without additive **45**: 1 mmol of **42b**, 1.3 mmol of olefin **50**, 2.0 mmol of NEt_3, 5 mol% $Pd(OAc)_2$ in 1 ml DMF at room temperature; "√" indicates that no starting material could be detected by ^{1}H-NMR anymore; a) related to alkenyl nonaflate **42a**, b) the product was not isolated, c) the product was accompanied by a small amount of DMF.

In contrast to the coupling reaction with methyl acrylate **44** full conversion is obtained using the olefin **50** without the presence of the diene **45**. Even though the reaction is slow, it is completed within 46 hours without any indication of Pd_{black} formation (Entry 1). Using the diene **45** in a 1 mmolar amount results in a significantly faster consumption of the starting material **42a**. After 20 hours full conversion is obtained and distillation of the product directly out of the reaction mixture gave **72** in 69% yield, accompanied by a small amount of DMF (Entry 2). Employing **45** in 0.2 mmolar amounts gave a similar result. The reaction proved to be stable throughout the whole reaction course and after 16 hours full conversion was detected. Aqueous workup and subsequent Kugelrohr distillation afforded product **72** in 77% yield (Entry 3). The slightly lower yield obtained for Entry 2 must be attributed to the less efficient way of product isolation.

Despite the fact this investigation is lacking generality both reactions clearly indicate a beneficial effect of the 1,3-diene **45** on the reaction outcome. Nevertheless, from a synthetic point of view the use of larger amounts of conjugated dienes for the stabilization of a palladium catalyzed reaction is not satisfying and cheaper additives like LiCl are naturally more attractive. For this reason the reaction of **42a** with methylacrylate **44** was investigated with varying amounts of LiCl.

Addition of 1 equivalent LiCl related to the catalyst enabled the slow but full conversion of **42a** to give the coupling product **71** within 6 days at room temperature. The reaction was found to be stable throughout the reaction course. A faster conversion of the starting material was obtained by heating to 44°C. Full conversion was detected after 15 hours, though with accompanied Pd_{black} formation. Aqueous workup afforded the product in 68% yield. In order to avoid Pd_{black} formation and to obtain a more efficient transformation at elevated temperature 4 equivalents of LiCl related to the catalyst were employed. Full conversion was obtained after 21 hours at 45°C, but still accompanied with Pd_{black} formation.

The amount of LiCl was further increased to 8 equivalents and the reaction carried out again at 45°C. Now full conversion was obtained within 15 hours, accompanied only by traces of Pd_{black}. After aqueous workup the diene **71** was obtained in 92% yield (Table 33, Entry 1). The product is formed in any case as a mixture of (*E*/*Z*)-stereoisomers. The overall amount of (*Z*)-**71** was determined to 6% according to ^{1}H-NMR. Within the described experimental set up the LiCl loading did not have an obvious effect on the ratio of both stereoisomers.

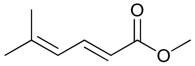
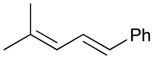
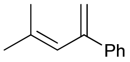
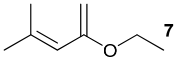
Entry	Nonaflate	Olefin	Additive	Equiv.[a]	T [°C]	t [h]	Product	% Yield/ratio
1	**42a**	**44**	LiCl	8	45	15	 **(*E*)-71**	**92**[b]
2	**42a**	**51**	**—**	—	45	15	 **(*E*)-73a**  **73b**	**84** **73a**:**73b** = 4:1
3	**42a**	**50**	**45**	4	25	16	 **72**	**77**

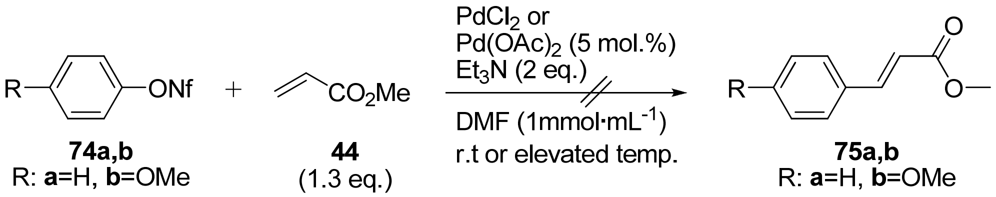
Table 33 Synthetically useful Heck couplings of **42a** with different olefins and with or without additives: 1 mmol of **42b**, 1.3 mmol of olefin, 2.0 mmol of NEt_3, 5 mol% $Pd(OAc)_2$ in 1 ml DMF at room temperature; a) equivalent related to $Pd(OAc)_2$, b) the (*E*)-stereoisomer **71** is accompanied by 6 mol% of the (*Z*)-stereoisomer **71** (1H-NMR control).

Interestingly the reaction of 2-methyl propenylnonaflate **42a** with styrene **51** does not require any assistance of additives (Table 33, Entry 2). The reaction runs to completion within 15 hours if kept at 45°C. Aqueous workup afforded the diene **73a** in 84% yield, accompanied by the terminal olefin (4-methylpenta-1,3-dien-2-yl)benzene **73b** in a ratio of 4:1. Preparative useful is the coupling reaction of **42a** and ethyl vinyl ether **50**, affording the diene **72** as the sole product in 77% yield, with 3-cyclopent-1-enyl-acrylic acid methyl ester **45** as an additive in 4 equivalents relative to the catalyst (Entry 3).

3.4.2. The Heck reaction with aryl nonaflates

Attempts to extend the ligand- and additive free Heck cross-coupling protocol to aryl nonaflates met with no general success. Thus, exposure of phenyl nonaflate **74a** with methyl acrylate **44** for 4 days at room temperature or heating for 24 hours at 50°C did not lead to the formation of the desired phenyl-acrylic acid methyl ester **75a**, but with the reactants remaining intact (Scheme 23).

The same result was obtained for 4-methoxyphenyl nonaflate **74b** (Scheme 23). Stirring of the reaction mixture for 24 hours at room temperature did not lead to product formation and stirring for 28 hours at 50°C resulted in the formation of a palladium mirror on the surface of the vial. Additional stirring of the reaction solution for 15 hours at 75°C resulted in a brown reaction mixture again with no indication of product formation.

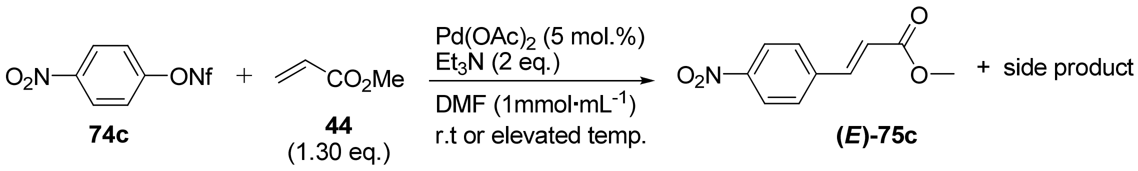


Scheme 23 Attempted ligandless cross-coupling of methyl acrylate **44** with the aromatic substrates phenyl nonaflate **74a** and p-methoxyphenyl nonaflate **74b**.

For both substrates the catalytic system remained stable at room temperature for days or at slightly elevated temperature for a few hours. However, in the case of phenyl nonaflate **74a** as substrate Pd$_{black}$ formation was observed while stirring the reaction solution at 50°C to

65°C overnight. Using 4-methoxyphenyl nonaflate **74b** this effect was observed already after a few minutes at the same temperature range.

A different outcome of the reaction was obtained employing 4-nitrophenyl nonaflate **74c** (Scheme 24). No conversion was monitored while stirring the reaction solution for 24 hours at room temperature. Heating of the mixture for 40 hours to 60°C led to a conversion of the starting aryl nonaflate **74c** of ≥99%. However, both ^{1}H-NMR and GC-MS analysis of the reaction mixture indicated the formation of the (*E*)-isomer of product **75c** accompanied by a large amount of an unidentified aromatic side product owing the molecular mass 252. This is indeed an interesting result since it provides an indication for a second different reaction mechanism taking place. In any case a further examination of this reaction would have gone beyond the scope of this investigation at that stage, and since large amounts of the side product made the reaction preparative worthless it was not further analyzed.



Scheme 24 Attempted ligandless cross-coupling of *p*-nitrophenyl nonaflate **74c** and methyl acrylate **44** to give (*E*)-**75c** at room temperature or elevated temperature; the product (*E*)-**75c** is accompanied by a large amount of an unidentified side product.

The results obtained with aryl nonaflates **74a-c** are in accordance with literature reports, describing phenyl nonaflates less reactive than the corresponding iodides. While the use of aryl iodies in ligandless procedures is reported, aryl nonaflates apparently require ligands or additives for an efficient transformation.[8d]

3.5. Conclusions

Unlike the relevant ligand-free systems established for the Heck coupling of aryl halides, the room temperature ligand- and additive-free Heck reactions of alkenyl nonaflates do not indicate signs of heterogeneous (colloidal Pd(0)) catalysis. The established methodology features remarkable endurance and insensitivity to the established heterogeneous catalyst poisons. All the results obtained from the kinetic experiments combined strongly suggest that the coupling reactions are catalyzed by homogeneous Pd(0)-complex(es) of yet unidentified nature.

From the synthetic viewpoint, the protocol described herein is simple, robust and generally applicable to the coupling of alkenyl nonaflates with electron-withdrawing, electron-rich as well as non-activated alkenes. All the dienes are formed in overall good to excellent yields. While selectivities follow typically observed trends, we were surprised to learn that the catalytic system is active enough to effect the room-temperature Heck coupling even with poorly activated (styrene **51**: Table 26, Entry 5; Table 27, Entry 2; Table 29, Entry 2; Table 33, Entry 2) or non-activated olefins (1-hexene **52**: Table 26, Entry 6), unprecedented so far for ligandless Heck reactions. The procedure therefore represents one of the most active catalytic systems in the Heck chemistry. Ethyl vinyl ether **50** as olefinic compound gives the terminal olefin in good regioselectivity (Table 26, Entry 4) or exclusively (Table 28, Entry 4; Table 30, Entry 6; Table 31, Entry 3).

Limitations of the protocol are encountered for the cross-coupling of sterically hindered substrates like **42a** and aromatic nonaflates **74a**-**c**. In the case of alkenyl nonaflate **42a** the utilization of additives like LiCl is required for the successful cross-coupling with certain olefins. Moreover, the use of the diene 3-cyclopent-1-enyl-acrylic acid methyl ester **45** has an overall beneficial effect on the reaction outcome. Thus it appears that diene formation during the Heck cross-coupling reactions has a stabilizing effect on the catalytic active species.

The aryl nonaflates **74a**-**c** are significantly less reactive than the alkenyl nonaflates. While unactivated aryl nonaflates do not cross-couple at all, the reaction with activated substrate **74c** led to the formation of a mixture of the desired product **75c** and a side product, making this protocol useless as a general procedure. To gain generality in the cross-coupling for these substrates the use of additives or ligands is apparently inevitable.

One-pot cross-coupling reactions

4. One-pot cross-coupling reactions

4.1. General remarks

During the past two decades an emerging need for more environmentally friendly and cost efficient organic transformations became apparent. This trend basically arose from demands in chemical industry and considerably influenced fundamental research in chemistry. This led to an increased interest in the methodological improvement of organic synthesis and the development of new synthetic techniques.[73]

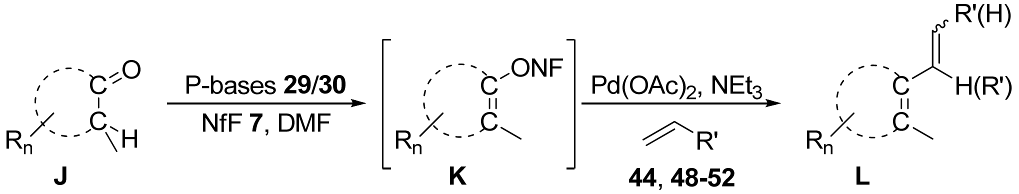
Important cost and environmental factors are organic solvents used in the reactions and the subsequent workup procedures. For this reason it is of interest to reduce the amount of solvent by working in concentrated solutions and to lessen isolation and purification steps in between the single transformations. To achieve this target the most effective strategy is to perform as many synthetic transformations as possible in “one-pot” procedures.

So far the cross-coupling protocol starting from aldehydes or ketones comprised at least 2 steps. Traditional approaches involve the synthesis of the enol sulfonates followed by Pd-coupling.[8a-c,8d-j] Alternatively, the carbonyl precursors are converted to trimethylsilyl enol ethers which subsequently undergo one-pot transformation to the coupling products via intermediacy of the corresponding alkenyl nonaflates.[8b,18a-c] In both cases, isolation and often the purification of the intermediates, either the enol sulfonates or trimethylsilyl enol ethers, is required. This necessity highlights the major challenge for the development of a more general and straightforward methodology, that is to combine the alkenyl nonaflate synthesis with a subsequent C,C-cross-coupling step in an *one-pot synthetic operation*. The main requirement for such a protocol is the compatibility of the phosphazene bases **29**/**30** and the salts thereof, formed during the alkenyl nonaflate or alkyne formation, with the catalytically active transition metal species present during the subsequent coupling reaction.

In Chapter 1 the straightforward synthesis of alkenyl nonaflates and alkynes from readily available carbonyl compounds was described. Furthermore, the suitability of alkenyl nonaflates in the ligand and additive free version of the Heck reaction could be demonstrated in Chapter 3. A straightforward protocol would consist of a combination of both methodologies in one-pot, avoiding intermediary isolation and purification steps. With these efficient procedures in hand, we decided therefore to investigate the combination of nonaflation/elimination reactions with transition metal catalyzed cross-couplings.

4.2. One-pot Heck reactions

The reactions are conducted according to the general Scheme 25. First the cycloalkenyl nonaflates **K** are generated by treatment of enolizable cyclic ketones **J** with NfF **7** and phosphazene bases **29**/**30** under internal quenching conditions as described in Chapter 1. Upon reaction completion, NEt_3, the olefin and $Pd(OAc)_2$ are consecutively added and the cross-coupling is carried out to form the desired dienes **L**. While the nonaflation procedure requires an inert gas atmosphere with dry DMF in order to avoid partial degradation of the phosphazene bases **29**/**30** and NfF **7** by H_2O, the addition of the coupling components is conducted without any inert gas protection. The components are used as purchased.



Scheme 25 One-pot synthesis starting from enolizable cyclic ketones **J** via the intermediary alkenyl nonaflates **K** and subsequent Heck coupling to the desired dienes **L**; unless stated otherwise the following reaction conditions were applied for the alkenyl nonaflate preparation: 1.0 mmol of the cyclic ketone **J**, 1.2 mmol of the phosphazene base **29**/**30**, 1.2 mmol of NfF **7** in 1 ml of DMF; for the Heck-coupling: 1.3 mmol of olefins **44**, **48**-**52**, 5 mol% of the $Pd(OAc)_2$, 2.0 mmol of NEt_3; the conversion for the single reaction steps is controlled by ^1H-NMR.

Initially the one-pot Heck protocol was investigated using the established reaction conditions for the formation of cyclopentenyl nonaflate **28a** and subsequent coupling with methyl acrylate **44** according to Scheme 25. We were pleased to find that neither the remaining P_1-base **29** nor the generated phosphazenium salt did hamper the desired Heck coupling and the catalysis proceeded without a loss of catalytic activity.

Therefore we decided to screen a larger amount of substrates in order to examine the scope of the reaction. The compounds are summarized in Figure 11. All the reactions were conducted according to Scheme 25 (unless otherwise stated).

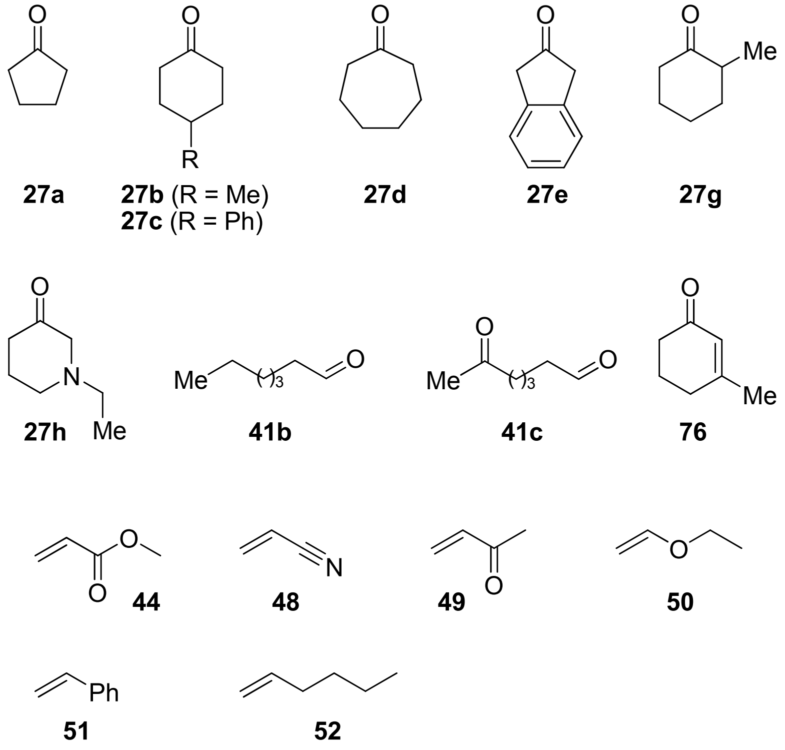


Figure 11 The array of enolizable ketones and olefins employed in the one-pot Heck protocol.

The reactions using cyclopentanone **27a** are summarized in Table 34. Full conversion of the intermediately formed cyclopentenyl nonaflate **28a** in the cross-coupling reaction with methylacrylate **44** is obtained within the same time frame as for the isolated alkenyl nonaflate **28a** (Entry 1). The product (*E*)-**45** is isolated in 80% yield. A clean transformation was also observed for the reactions using acrylonitrile **48** (Entry 2) and methyl vinyl ketone **49** (Entry 3). The diene **53** is obtained as a mixture of (*E*/*Z*)-stereoisomers in a ratio of (*E*:*Z*) = 3.5:1. The required time for the cross-coupling as well as the (*E*/*Z*)-selectivity outcome for the product **53** matches the reaction employing the corresponding isolated nonaflate. The pure products could be obtained in overall very good yields of 77% for (*E*/*Z*)-**53** and 92% for (*E*)-**54**.

A different outcome of the reaction was observed with styrene **51** (Entry 4). No conversion was obtained during the room temperature cross-coupling. In repetitive runs elevated temperature of up to 60°C only led to the formation of a small amount of product. The dramatic loss of catalytic activity can be clearly attributed to the presence of free P_1-base **29** in the Heck coupling step under ligand- and additive-free conditions since CF_3CO_2H added after the completion of the alkenyl nonaflate formation fully restored the catalysis. The effect may be attributed to complete removal of the strong P_1-base **29** under the Et_3NH^+/Et_3N buffer conditions or to hydrogen bond activation with Et_3NH^+ as described recently.[74] In addition also the generated anion $CF_3CO_2^-$ might stabilise the catalytic species during the course of the palladium catalysis. Applying these modified conditions to the cross-coupling with styrene **51** lead to the full conversion of the starting material after 32 hours at room temperature and the desired diene (*E*)-**56a** could be isolated in excellent 88% yield as the single isomer.

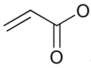
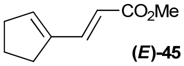
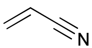
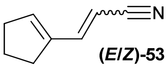
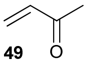
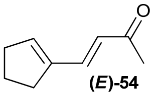
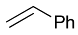
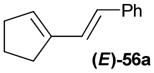
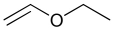
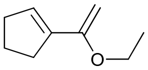
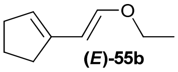
Entry	Ketone	Olefin	Coupling t [h]	Product	% Yield / Ratio
1	**27a**	 **44**	14	 **(*E*)-45**	**80**
2	**27a**	 **48**	18	 **(*E*/*Z*)-53**	**77** (*E*/*Z*) = 3.5:1
3	**27a**	 **49**	21	 **(*E*)-54**	**92**
4[a]	**27a**	 **51**	32	 **(*E*)-56a**	**88**
5	**27a**	 **50**	16[b]	 **55a**  **(*E*)-55b**	**53** **55a**/**55b** = 5.9:1

Table 34 One-pot Heck coupling of cyclopentanone **27a** with various olefins; the nonaflation of the ketone was conducted as described in Chapter 1; a) 0.5 equiv. of CF_3CO_2H were added to the reaction mixture prior to the addition of NEt_3 and styrene **51**, b) the coupling reaction was carried out at 50°C.

Also a lower catalytic activity was observed for the cross-coupling with ethyl vinyl ether **50** (Entry 5). The catalysis at room temperature showed little conversion of 20% within 20 hours. Heating of the reaction mixture to 50°C led to full conversion of alkenyl nonaflate **28b** within 16 hours. However, in repetitive runs considerably lower yields of the desired diene **55a** compared to the coupling operating with the isolated alkenyl nonaflate **28a** were obtained (Chapter 3, Table 26, Entry 4, 86% yield for the reaction at r.t.). In a representative run the desired diene **55a** could be isolated in 53% yield accompanied by the (*E*)-regioisomer **55b** (Entry 5). The diene **55a** and the isomer **55b** were obtained in a diminished selectivity of

5.9:1 in favour of **55a**. Addition of CF_3CO_2H after completion of the alkenyl nonaflate formation led to an improved catalytic activity. Thus, full conversion of nonaflate **28a** was already observed at room temperature within 70 hours. However, aside from the generation of the desired product **55a** this modification led to the formation of not further identified side products in repetitve runs.

The one-pot protocol applied to 6-membered cyclic alkenyl nonaflates follows the trends observed so far. The catalysis nonetheless shows an overall slightly reduced activity for the selected olefins (Table 35).

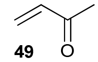
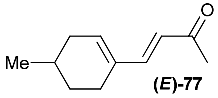
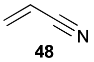
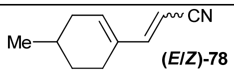
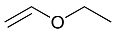
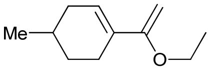
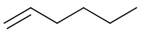
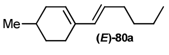
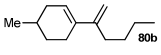
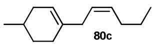
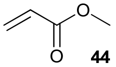
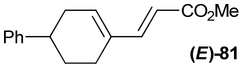
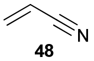
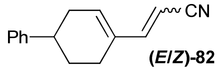
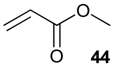
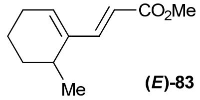
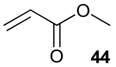
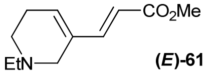
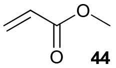
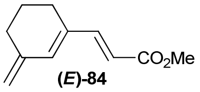
Entry	Ketone	Olefin	Coupl. t [h]	Product	% Yield / Ratio
1	**27b**	 **49**	19	 **(*E*)-77**	**85**
2	**27b**	 **48**	24[a] (40°C)	 **(*E*/*Z*)-78**	**95** (*E*/*Z*) =2.9:1
3	**27b**	 **50**	24 (40°C)	 **79a**	**80**[b]
4	**27b**	 **52**	17 (40°C)	 **(*E*)-80a**  **80b**  **80c**	**88** **80a**:**80b**:**80c** = 62:18:20
5	**27c**	 **44**	18	 **(*E*)-81**	**90**
6	**27c**	 **48**	40	 **(*E*/*Z*)-82**	**85** (*E*/*Z*) =1.7:1
7[c]	**27g**	 **44**	18	 **(*E*)-83**	**96**
8	**27h**	 **44**	14	 **(*E*)-61**	**82**
9	**76**	 **44**	22	 **(*E*)-84**	**78**

Table 35 One-pot Heck coupling with the 6-membered cyclic ketones **27b**, **27c**, **27g**, **27h** and **76** and a representative selection of olefins; nonaflation of the ketones was conducted as described in Chapter 1; a) the conversion after 24h was at least *ca.* 99%, b) The product is accompanied by 10 mol% of (*E*)-1-(2-ethoxyvinyl)-4-methylcyclohex-1-ene (*E*)-**79b**, c) [The alkenyl nonaflate formation was conducted at –20°C according to Table 3, Entry 7 with 2.0 equiv. of the P_2-base **30** and 2.0 equiv. of NfF **7**; the coupling reaction was initiated when ~99% conversion (65h) were obtained; <<1% of the undesired regioisomer **28k** could be detected].

While the intermediate 4-methyl-cyclohexenyl nonaflate **27b** could be coupled with methyl vinyl ketone **49** at room temperature within 19 hours, to give the product (*E*)-**77** in 85% yield (Entry 1), the transformation with acrylonitrile **48** (Entry 2), ethyl vinyl ether **50** (Entry 3) and 1-hexene **52** (Entry 4) required already a longer reaction time. For practical reasons these reactions were carried out at slightly elevated temperature of 40°C. Under these conditions the products were formed as usual in high yields of 95% for (*E*/*Z*)-**78** (Entry 2), 80% for **79a** (Entry 3) and 88% for **80a**-**c** (Entry 4). The ratios of the isomers for the products (*E*/*Z*)-**78** and **80a**-**c** follow the trends observed before.

4-Phenyl-cyclohexenyl nonaflate **27c** was cross-coupled at room temperature with methylacrylate **44** (Entry 5) and acrylonitrile **48** (Entry 6). While the catalysis using olefin **44** could be carried out in a similar time scale as with isolated alkenyl nonaflates, the reaction using acrylonitrile **48** required already 40 hours for completion. The dienes (*E*)-**81** and (*E*/*Z*)-**82** were obtained in 90% and 85% yield. In the reaction with acrylonitrile **48** 4-phenyl-cyclohexenyl nonaflate **27c** gave in comparison to 4-methyl-cyclohexenyl nonaflate **27b** a slightly diminished stereoisomeric outcome (Entries 6 *vs.* 2).

The regioselective formation of alkenyl nonaflates as described in Chapter 1 (Tables 2 and 3) could be successfully utilized in the one-pot protocol (Entry 7). In this representative example 2-methyl-cyclohexanone **27g** could be regioselectively converted into the desired nonaflate **28g**, accompanied with less then 1% of the undesired regioisomer **28k**. Subsequent coupling with methylacrylate **44** gave 3-(6-methyl-cyclohex-1-enyl)-acrylic acid methyl ester (*E*)-**83** in excellent 96% yield. The piperidine derivative (*E*)-**61** could be generated from 1-ethyl-piperidin-3-one **27h** in 82% yield. This matches the result obtained for the reaction employing the isolated nonaflate (Chapter 3, Table 27, Entry 4).

A slightly different reaction pathway is observed for the reaction of 3-methyl-cyclohex-2-enone **76**. In this case deprotonation occurs at the 3-methyl position of the enone **76**. The intermediately formed 3-methylene-cyclohex-1-enyl anion reacts with NfF **7** at the O-centre to give the 1,3-dienyl nonaflate exhibiting an exocyclic C,C-double bond geometry. Cross-coupling with methyl acrylate **44** forms the triene (*E*)-**84** in 78% yield.

The protocol was applied to cycloheptanone **27d** with methyl acrylate **44** (Table 36, Entry 1) and acrylonitrile **48** (Entry 2). For both reactions the catalysis is completed within 19 hours. The product (*E*)-**62** is formed in 78% yield. The diene (*E*/*Z*)-**63** is isolated in 80% yield in form of its two (*E*/*Z*)-stereoisomers exhibiting a ratio of 2.74:1 in favour of the (*E*)-isomer. The result is comparable to the reaction using the isolated nonaflate **28d** (Chapter 3, Table 28, Entry 2).

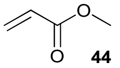
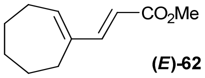
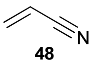
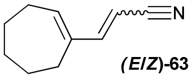
Entry	Ketone	Olefin	Coupling t [h]	Product	% Yield / Ratio
1	**27d**	 **44**	19	 **(*E*)-62**	**78**
2	**27d**	 **48**	19	 **(*E*/*Z*)-63**	**80** (*E*/*Z*) = 2.74:1

Table 36 One-pot Heck coupling with the 7-membered cyclic ketone **27d** and the olefins **44** and **48**; the nonaflation of the ketones was conducted as described in Chapter 1.

The one-pot protocol using 2-indanone **27e** was performed with a 4-fold excess of NEt_3 related to the substrate, used as the sole base in both the nonaflate formation and the Heck coupling steps (Table 37). This resulted in a satisfactory formation of the alkenyl nonaflate **28e** (Table 1, Chapter 1) and enabled the subsequent cross-coupling step with the remaining NEt_3 base. The product (*E*)-**66** was isolated in moderate 62% yield.

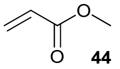
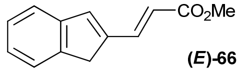
Entry	Ketone	Olefin	Coupling t [h]	Product	% Yield / Ratio
1[a]	**27e**	 **44**	14	 **(*E*)-66**	**62**

Table 37 One-pot Heck coupling with 2-indanone **27e** and olefin **44**; nonaflation of the ketone is conducted as described in Chapter 1; a) in total 4 equiv. of NEt_3 are used in order to perform both the nonaflation and the subsequent coupling.

In this investigation the reactions using cyclohexanones imposingly confirm the observation described in Chapter 3, that comparatively longer cross-coupling times are required for the 6-membered alkenyl nonaflates. Exemplarily this can be seen for the reactions using acrylonitrile **48** as the olefin (Table 35, Entry 2 and Entry 6). With an overall reaction time of at least 24 hours at 40°C in the first case and 40 hours at room temperature for the latter one, the cross-coupling requires a significantly longer reaction time as compared to the reactions of the same olefin with 5- (Table 34, Entry 2) or 7-membered (Table 36, Entry 2) cycloalkenyl nonaflates.

In addition to the room temperature experiments with 5 mol% of the catalyst precursor the methodology was also investigated with 1 mol% of $Pd(OAc)_2$ and elevated temperature in order to prove if the catalytic activity is affected under reduced catalyst loadings. The reactions were carried out with some representative substrates listed in Table 38.

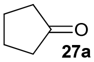
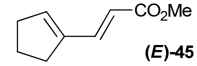
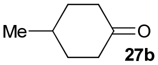
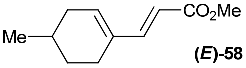
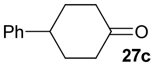
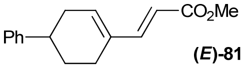
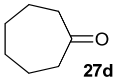
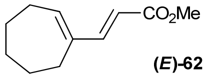
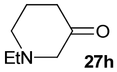
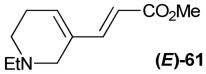
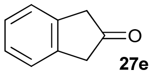
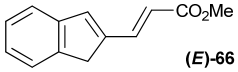
Entry	Ketone	Olefin	Coupling t [h]	Product	% Yield / Ratio
1	 **27a**	**44**	5	 **(*E*)-45**	**82**
2	 **27b**	**44**	7	 **(*E*)-58**	**94**
3	 **27c**	**44**	18	 **(*E*)-81**	**97**
4	 **27d**	**44**	4	 **(*E*)-62**	**72**
5	 **27h**	**44**	17[a]	 **(*E*)-61**	**87**
6	 **27e**	**44**	14	 **(*E*)-66**	**58[b]**

Table 38 One-pot Heck coupling with selected ketones and methyl acrylate **44** employing 1 mol% of $Pd(OAc)_2$ at 50°C; the nonaflation of the ketones was conducted as described in Chapter 1; a) the coupling reaction was carried out at 60°C, b) the reaction was conducted in the presence of overall 4 equiv. of NEt_3.

The experiments show that the catalytic activity is preserved under reduced catalyst loadings. Also the yields are practically the same compared to the room temperature reaction and 5 mol% $Pd(OAc)_2$ loading.

As described in Chapter 1 aldehydes can be transformed to the corresponding alkenyl nonaflates if the reaction is conducted at -30°C. Heptanal **41b** and 6-oxoheptanal **41c** were subjected to the protocol to test the aldehydes **41b**,**c** in the one-pot methodology (Table 39). The alkenyl nonaflates were generated according to the procedure described in Chapter 1 (Table 11). Subsequent cross-coupling with methylacrylate **44**, methyl vinyl ketone **49** or ethyl vinyl ether **50** showed no conversion at ambient or slightly elevated temperature. Analogously to the experiments using cyclopentenylnonaflate **28a** with styrene **51** (Table 34, Entry 4) the loss of catalytic activity can be attributed to the presence of the P_1-base **29** in the

Heck coupling step. Again the addition of CF_3CO_2H prior to the addition of NEt_3 restored the catalytic activity and full conversion of the intermediately formed alkenyl nonaflates **42b** and **42c** at room temperature was obtained within 22 hours.

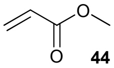
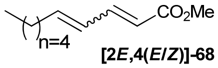
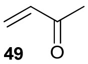
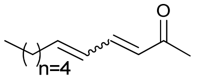
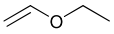
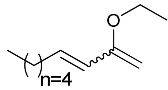
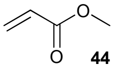
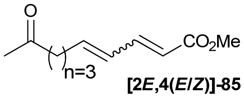
Entry [a]	Ketone	Olefin	Coupling t [h]	Product	% Yield / Ratio
1	**41b**	 **44**	20	 **[2*E*,4(*E*/*Z*)]-68**	**81** (4*Z*/4*E*)=2.2:1
2	**41b**	 **49**	22	 **[3*E*,5(*E*/*Z*)]-69**	**82** (5*Z*/5*E*)=1.6:1
3	**41b**	 **50**	18	 **(*E*/*Z*)-70**	**78** (*Z*/*E*)=2.1:1
4	**41c**	 **44**	22	 **[2*E*,4(*E*/*Z*)]-85**	**72** (4*Z*/4*E*)=2.5:1

Table 39 One-pot Heck coupling with heptanal **41b** and 6-oxoheptanal **41c** and the olefins methylacrylate **44**, methyl vinyl ketone **49** and ethyl vinyl ether **50**; the nonaflation of the ketones was conducted as described in Chapter 1; a) in all cases 0.5 equiv. of CF_3CO_2H were added to the reaction mixture prior to the addition of NEt_3, the olefin and the catalyst precursor.

Again a loss of (*E*/*Z*)-selectivity of the internal double bond geometry during the transition metal catalyzed cross-coupling was observed. ^{1}H-NMR control after completed alkenyl nonaflate formation indicated similar to the isolated acyclic alkenyl nonaflates (Table 11, Entries 2 and 3) a selectivity of ≥4:1 in favour of a (*Z*)-configuration for all the products. After the palladium catalyzed cross-coupling step a (*E*/*Z*)-ratio of in average 2:1 in favour of the (*Z*)-configuration was determined (analogous to the palladium catalysis with isolated alkenyl nonaflates; see Chapter 3, Table 31).

4.3. One-pot Sonogashira reactions

The enyne moiety is a versatile functionality and useful structural element,[75] and is often encountered within natural products with biological function or potent pharmacological activity. A selection of interesting natural compounds is given in Figure 12.[76a-j] It is the bioactivity that triggered a great deal of interest towards the straightforward assembly of enyne and endiyene structural motifs.

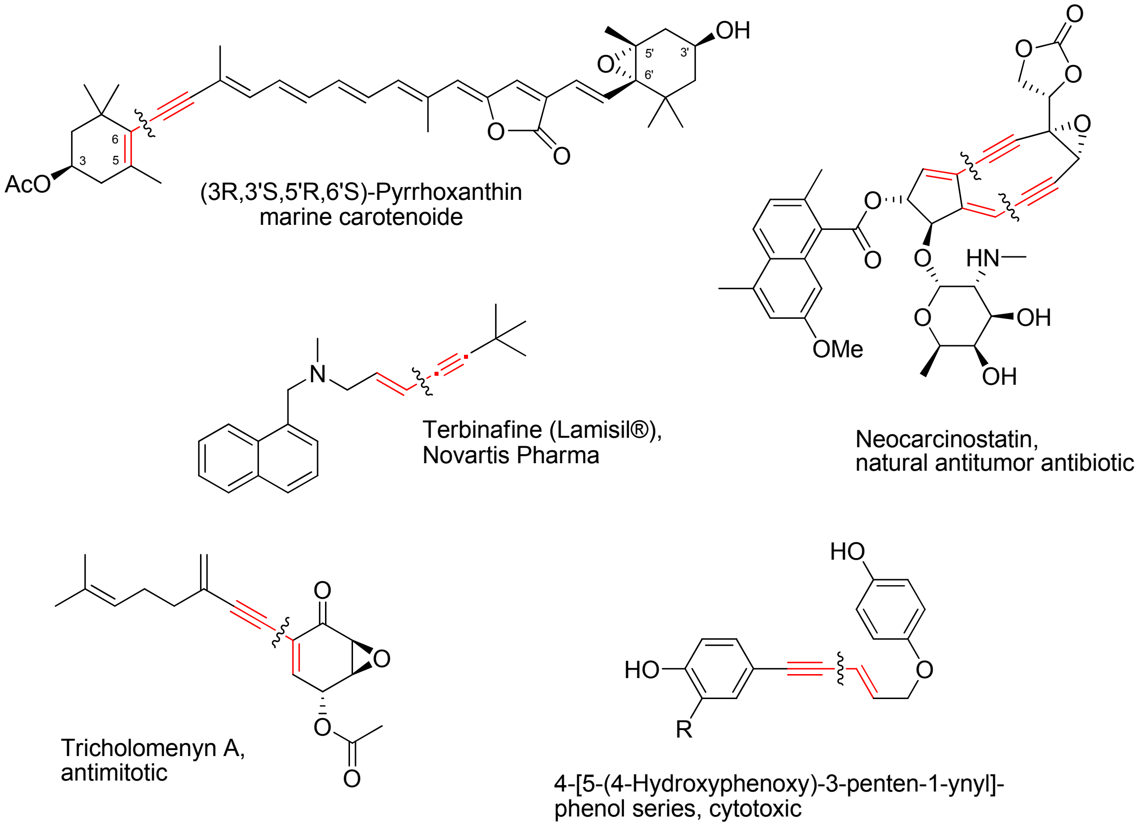


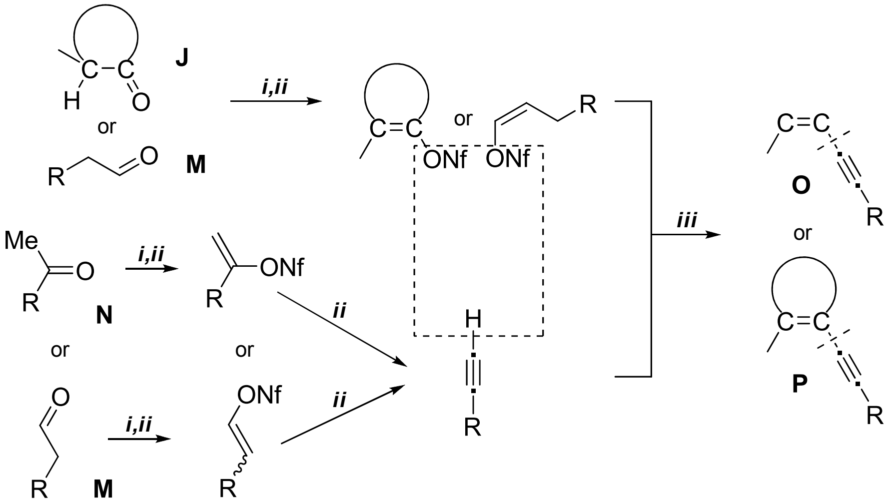
Figure 12 (3R,3'S,5'R,6'S)-Pyrrhoxanthin[76a], Neocarcinostatin[76b-d], Terbinafine[76e-f], Tricholomenyn A[76g-h] and the 4-[5-(4-hydroxyphenoxy)-3-penten-1-ynyl]-phenol series[76i-j] as examples of natural products of biological importance or potent pharmacological activity exhibiting the enyne motif, a key structural unit for the synthesis of these compounds.

The Sonogashira reaction was originally introduced by K. Sonogashira and N. Hagihara in 1975 as a palladium catalyzed reaction of copper-acetylides with bromoalkenes, iodoarenes and bromopyridines to form the conjugated enynes.[77] Further major changes of the methodology consisted in the variation of the halides employed, the extension to alkenyl or aryl sulfonates and copper free variants.[78a-b]

If alkenyl sulfonates are used the coupling protocol routinely consists of two different steps. First O-sulfonylation of the starting carbonyl compounds is conducted followed by the Pd-catalyzed C-C cross-coupling of the isolated alkenyl sulfonate. This requirement serves to highlight the challenge as described in the previous section, to combine both the conversion of the carbonyl compound to the corresponding alkenyl nonaflates and the subsequent C-C cross-coupling step with a terminal alkyne in an overall one-pot operation.

In the one-pot Heck procedure, the alkenyl nonaflate is prepared *in situ* with a subsequent cross-coupling step. In our own design of a straightforward Sonogashira coupling protocol, both coupling components, cycloalkenyl nonaflates and terminal acetylenes are to be generated from carbonyl precursors in one pot (Scheme 26). The former would be produced from cyclic ketones **J** whereas the latter one from aldehydes **M** or methyl ketones **N** via intermediacy of the acyclic nonaflates, followed by base induced E2-elimination of NfOH as depicted in the Scheme 26. With completion of the alkenyl nonaflate and terminal alkyne formation, the addition of the Sonogashira coupling reagents would finally lead to the formation of the desired enynes (**O** or **P**).

The protocol can be extended to acyclic alkenyl nonaflates as coupling components as well. Therefore the required aldehyde **M** needs to be transformed to the desired alkenyl nonaflate after formation of the terminal alkyne, in order to avoid E2-elimination of NfOH from the acyclic alkenyl nonaflate.



Scheme 26 *One-pot* synthesis of the enynes **O** or **P** starting from cyclic ketones **J** or aldehydes **M** and methyl ketones **N** or aldehydes **M** as the carbonylic substrates, in any case at least 4 operational steps are combined in a single one-pot sequence within this protocol; ***i***: NfF **7**, ***ii***: phosphazene base **29**/**30**, ***iii***: *i*-Pr_2NH (excess), $Pd(OAc)_2$ (5 mol.%), PPh_3 (10 mol.%), CuI (10 mol.%), LiCl, r.t. or slightly elevated temperature.

It must be emphasized that within this protocol at least 4 operational steps are combined in a single one-pot sequence. The outlined reaction sequence has been successfully conducted with selected substrates listed in the Tables 40, 41 and 42. The conditions and the reaction course follow the description in Scheme 26 unless stated otherwise.

The reaction of 2-methyl cyclopentanone **27f** with 6-oxo-heptanal **41c** in order to give the desired enyne **86** was conducted one-pot in 3 consecutive steps (Table 40, Entry 1). First the ketone **27f** was transformed to the alkenyl nonaflate **28f** using the P_2-base **30** under kinetically controlled conditions by adding the base to the reaction solution at -78°C with subsequent slow warm up. With completed alkenyl nonaflate formation aldehyde **41c** was added and the corresponding terminal alkyne **43c** generated under the above described conditions using the P_1-base **29**. Final cross-coupling of the generated intermediates at 50°C led to the enyne **86** in 74% yield (Entry 2). Employing this alkenyl nonaflate formation a >95:<5 selectivity in favour of the kinetically controlled double bond regioisomer shown is obtained.

The synthesis of enyne **87** was carried out analogously using ketone **27f** and acetophenone **35j** as the starting material. Cross-coupling at 45°C for 17 hours afforded the product in 81% yield with a similar regioselective outcome.

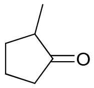
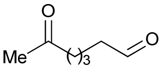
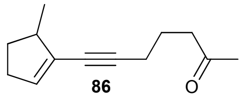
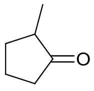
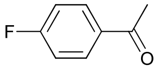
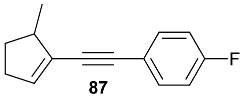
Entry	Cyclic ketone	Aldehyde or methyl ketone	Base	Coupling t [h]	Product	% Yield
1	 **27f**	 **41c**	P_2-base then P_1-base	20 (50°C)	 **86**	**74**[a]
2	 **27f**	 **35j**	P_2-base then P_1-base	17 (45°C)	 **87**	**81**[a]

Table 40 One-pot Sonogashira coupling with 2-methyl cyclopentanone **27f** and the carbonyl precursors **41c** and **35j**; cross-coupling conditions: *i*-Pr_2NH (excess), $Pd(OAc)_2$ (5 mol.%), PPh_3 (10 mol.%), CuI (10 mol.%), LiCl; the nonaflation and elimination of the substrates was conducted as described in Chapter 1; a) >95 : <5 selectivity in favour of the kinetically controlled double bond regioisomer shown.

For the following examples regioselectivity considerations are irrelevant and therefore the 6-membered ketones could all be transformed using the P_1-base **29**, reducing the overall number of operational steps to 2 steps (Table 41).

Cyclohexanone **27j** and p-tolyl-ethanone **35k** could be fully transformed into the required intermediates cyclohexenyl nonaflate and 1-ethynyl-4-methylbenzene and subsequent cross-coupling at room temperature lead to the product **88** in 67% yield (Entry 1). Applying the protocol analogously to 1-ethyl-piperidin-3-one **27h** and 1-(2-bromo-phenyl)-ethanone **35l** lead to enyne **89** in 75% yield (Entry 2). In addition 4-*t*-butyl cyclohexanone **27k** and *n*-pentanone **41h** gave the desired product **90** in excellent 90% yield (Entry 3).

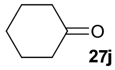
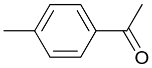
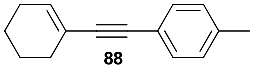
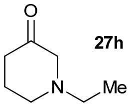
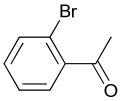
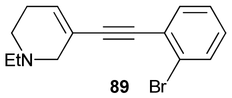
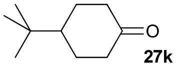
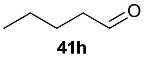
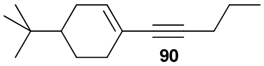
Entry	Cyclic ketone	Aldehyde or methyl ketone	Base	Coupling t [h]	Product	% Yield
1	 **27j**	 **35k**	P_1-base	24	 **88**	**67**
2	 **27h**	 **35l**	P_1-base	15 (45°C)	 **89**	**75**
3	 **27k**	 **41h**	P_1-base	24	 **90**	**83**

Table 41 One-pot Sonogashira coupling with the 6-membered cyclic ketones **27j**, **27h** and **27k** with the acetophenones **35k**, **35l** and the aldehyde **41h**; cross-coupling conditions: *i*-Pr_2NH (excess), $Pd(OAc)_2$ (5 mol.%), PPh_3 (10 mol.%), CuI (10 mol.%), LiCl; the nonaflation of the substrates was conducted as described in Chapter 1.

Two different 7-membered cyclic ketones were successfully employed in the methodology (Table 42). *N*-ethoxycarbonyl tropinone **27l** was submitted to the protocol with both 1-(2-fluorophenyl)ethanone **35m** and 4-methyl-4-(trimethylsilyloxy)pentan-2-one **33f** to give the desired enynes **91** and **92** in excellent yields after a short cross-coupling of 6 hours and 4 hours at 60°C.

Cycloheptanone **27e** was employed in the protocol with the sterically hindered ketones **33b**, **33c** and the aldehyde **41c**. As shown in Chapter 1 (Table 5, Entry 1 and 3) ketones **33b** and **33c** require the P_2-base **30** for the conversion into the terminal alkynes and since alkenyl nonaflate formation with cycloheptanone **27d** proceeds significantly faster with base **30** both reactions were conducted using the P_2-base **30** exclusively. While the conversion of cycloheptanone **27d** and pinacolone **33a** occurred in a clean manner according to ^{1}H-NMR control, the room temperature Sonogashira coupling of the substrates proceeded slow and sluggishly and took 48 hours for completion (Entry 3). Despite the fact full conversion was indicated, after aqueous workup only 39% of the product could be isolated (in order to avoid losses of the intermediate 3,3-dimethyl-but-1-yne **34b** due to its low boiling point of 37°C, the coupling was carried out at room temperature). In contrast, the use of ketone **33c** gave the desired enyne **94** in 71% yield after carrying out the cross-coupling at 50°C for 24 hours

(Entry 4). Elevated temperature was required in order to obtain full conversion within a reasonable time scale. The reaction using aldehyde **41c** was conducted with P_1-base **29** exclusively (Entry 5). After cross-coupling at 40°C the enyne **95** was obtained in 75% yield. Also for this transformation elevated temperature was required.

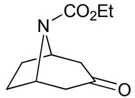
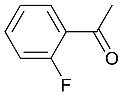
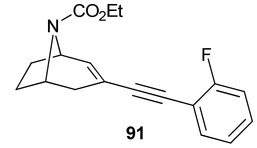
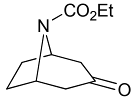
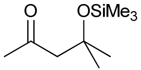
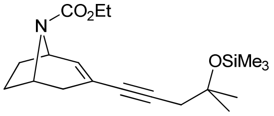
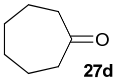
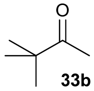
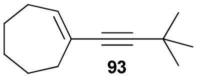
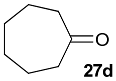
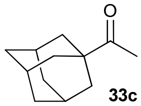
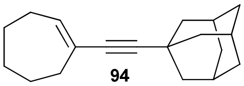
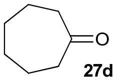
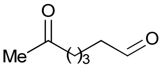
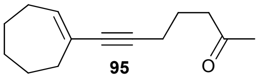
Entry	Cyclic ketone	Aldehyde or methyl ketone	Base	Coupling t [h]	Product	% Yield
1	 **27l**	 **35m**	P_1-base	6 (60°C)	 **91**	**97**
2	 **27l**	 **33f**	P_1-base	4 (60°C)		**82**
3	 **27d**	 **33b**	P_2-base	48	 **93**	**39**
4	 **27d**	 **33c**	P_2-base	24 (50°C)	 **94**	**71**
5	 **27d**	 **41c**	P_1-base	24 (40°C)	 **95**	**75**

Table 42 One-pot Sonogashira coupling with *N*-ethoxycarbonyl tropinone **27l** and cycloheptanone **27d** and the ketones **33b,c,f** and **35m** as well as the aldehyde **41c**; cross-coupling conditions: *i*-Pr_2NH (excess), $Pd(OAc)_2$ (5 mol.%), PPh_3 (10 mol.%), CuI (10 mol.%), LiCl; the nonaflation of the substrates was conducted as described in Chapter 1.

4.4. Conclusions

The experiments described in Chapter 4 clearly demonstrate the compatibility of the Heck- and Sonogashira cross-coupling methodology with the conditions of the alkenyl nonaflate and terminal alkyne formation, using phosphazene bases **29**/**30** and NfF **7** under internal quenching conditions. The established methodology comprises operational simplicity, paired with a high robustness of the palladium catalysis as shown for the one-pot Heck reactions. The protocol could be applied to a variety of substrates, proving the generality for application in Heck- and Sonogashira cross-coupling reactions.

In some cases a loss of activity or deactivation of the transition metal catalyst caused by the phosphazene base **29** was observed. This synthetic problem could be addressed by either using slightly elevated temperature or by quenching of the remaining phosphazene base **29** with CF_3CO_2H, prior to the addition of the reagents that are required for the transition metal catalysis.

The methodology opens up a straightforward synthesis of highly functionalized dienes or enynes from readily available carbonyl precursors. The protocol is conducted in a concentrated 1 molar solution, therefore facile scale up should be feasible.

Towards the total synthesis of Stenusin

5. Towards the total synthesis of Stenusin

5.1. Introduction

The developed one-pot methodology provides an efficient protocol to generate highly functionalized structures, exhibiting a diene or enyne moiety as the key functional unit. Therefore we looked for a synthetic target to apply this protocol in a natural product synthesis. As promising compound 1-ethyl-3-(2-methyl-butyl)-piperidine, named Stenusin **96** was identified, a piperidine derivative generated from the staphylinid *Stenus comma*.[79] As a proof of concept the synthesis of compound **96** also serves as an exemplary model for a general approach to access *N*-alkylated, ring substituted piperidines (Figure 13).

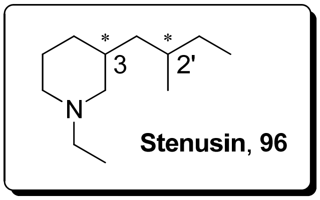
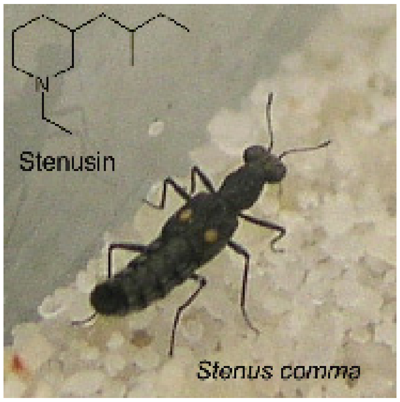


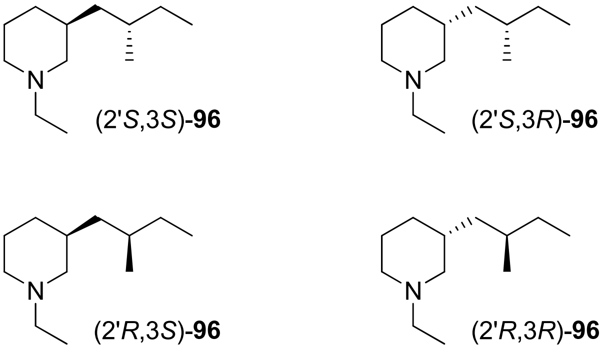
Figure 13 The natural product Stenusin **96**. The compound is generated by the staphylinid *Stenus comma* as a mixture of all the four possible stereoisomers.

The genus *Stenus* comprises 1990 species worldwide and around 120 in Central Europe.[80] The most common species of the genus *Stenus comma*, a slim black staphylinid weighing around 2.5 mg and measuring circa 5 mm, inhabits the sandy banks of stagnant ponds or sluggishly flowing waters (Picture 2). The beetle is able to propel itself over the water by immersing the tip of its abdomen into the water and expelling oil out of its two paired pygidial defence glands. This enables the animal to slide on a thin film over the surface with a speed of 45 to 75 cm/s.[81] Among the four compounds isolated from the two smaller glands, Stenusin **96** was identified by Schildknecht *et al.* as the main spreading agent. Due to its low solubility in water (0.2 wt.%) the compound exhibits the lowest surface tension and exerts the highest surface pressure among the isolated structures. Interestingly Stenusin **96** exhibits high spreading ability also on materials such as wood, plastics and glass.[81]



Picture 2 *Stenus comma* on an artificial river bank. In average the black staphylinid weighs around 2.5 mg and measures circa 5 mm.

The beetle generates Stenusin **96** in all the four possible stereoisomers (Scheme 27). Chiral GC analysis of both the natural as well the samples synthesized by Enders and Kimbe *et al.* helped to establish that *Stenus comma* generates this compound in an enantiomeric ratio of 43:40:13:4 = (2’*S*,3*S*):(2’*S*,3*R*):(2’*R*,3*R*):(2’*R*,3*S*).[82]



Scheme 27 The four possible stereoisomers of Stenusin **96**.

Due to the low concentrations of the compounds, these values need to be considered with some reservation since integration of the signals turned out to be difficult. Nevertheless, it can be clearly stated that the epimers possessing (*S*)-configuration in the side chain are present in a large excess (83:17), whereas there seems to be no preference for diastereomers with (*S*)- or (*R*)-configuration at the ring stereogenic centre (53:47). It is reasoned that the enantiomeric ratio seems to vary between different genera.[83] According to most recent investigations Stenusin **96** does not only serve as the main spreading agent for the beetle, it also exhibits an antimicrobial effect on entomopathogenic bacteria and fungi.[84]

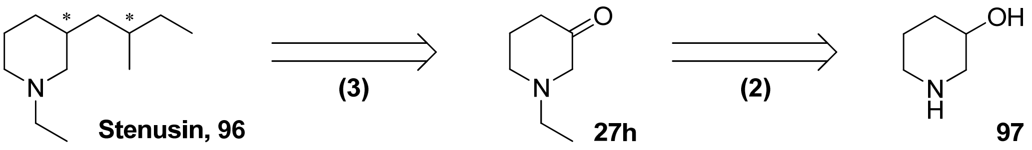
Since its isolation from *genus comma*, the definite biosynthetic pathway for the synthesis of Stenusin **96** remained unclear for nearly 30 years. It is known that many piperidine alkaloid core structures are derived from the natural amino acid lysine. Husson *et al.* were the first group supposing a potential biosynthetic pathway of **96** derived from lysine and isoleucine.[85] Final confirmation of this synthesis results from latest investigations making use of labelled substrates. In feeding experiments employing deuterated L-lysine, L-isoleucine and acetate with subsequent analysis of the biosynthetic products, the synthesis of Stenusin **96** from L-lysine forming the piperidine ring, with the side chain originating from L-isoleucine could be confirmed.[86] *N*-ethylation results from reaction with acetate followed by the final reduction of the intermediary formed amide.

Beginning with the seminal publication by Schildknecht *et al.* in 1975,[78] a number of different preparations of Stenusin **96** have been reported based on racemic{79,80,84,86a-b] and on stereoselective[82,88a-b] strategies. The earlier protocols based on a racemic synthesis lack of either generality or suffer from a laborious strategy in combination with the use of expensive or highly sensitive substrates.[81,87a-b] Following a possible biogenetic pathway Husson *et al*. were able to synthesize Stenusin **96** elegantly in 3 steps starting from (*R*)-(-)-phenylglycinol in overall 10% yield.[85] Considering the overall low yield and the long reaction time of 6 days this strategy is essentially of academic interest. The most recent and straightforward synthesis is reported by Seifert *et al.*, employing 3-picoline as the starting material. Deprotonation of the methyl group and reaction of the generated anion with (*R*)-2-bromobutane affords 3-(2'-methybutyl)pyridine. Reaction of this intermediate with acetaldehyde under hydrogenating conditions led to Stenusin **96**.[80] The natural product can be obtained in overall 74% yield as a mixture of all the four possible stereoisomers in a ratio of 54:29:10:7 = (2'*S*,3*S*):(2'*S*,3*R*):(2'*R*,3*R*):(2'*R*,3*S*).

So far 2 of the 4 possible stereoisomers have been synthesized. The first enantioselective synthesis is described by Enders *et al.* making use of their chiral SAMP/RAMP-auxiliars. The synthesis afforded (2'*S*,3*S*)- and (2'*S*,3*R*)-Stenusin in a diastereomerical excess of ≥95% for both diastereoisomers with an enantiomeric excess of higher than 99%.[82] In subsequent publications the stereoselective synthesis of (2'*S*,3*R*)-Stenusin using different approaches is reported as well.[88a-b]

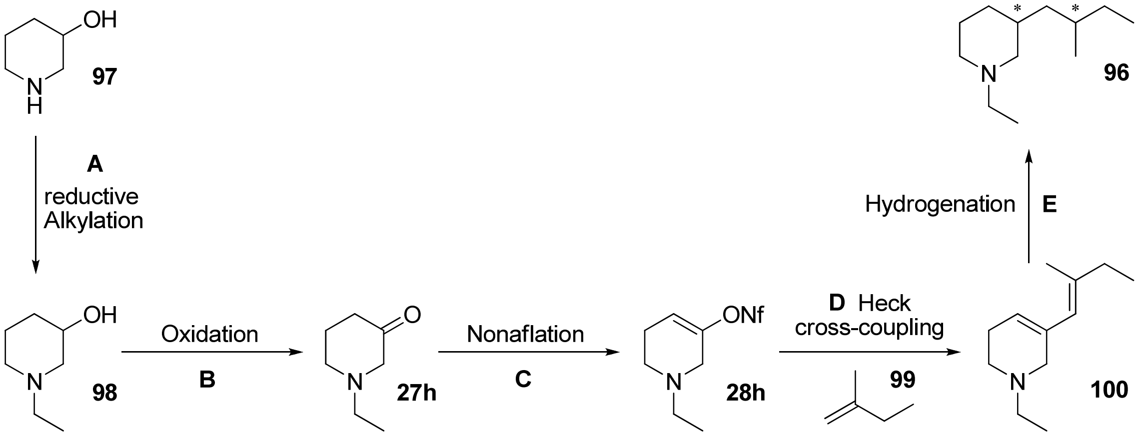
5.2. General reaction outline

The retrosynthetic pathway for the envisaged synthesis of Stenusin **96** is described in Scheme 28, consisting of in total 5 single experimental steps. As the key intermediate serves the piperidinone derivative **27h**. Following the retrosynthetic strategy the details of the synthesis are described in Scheme 29.



Scheme 28 The retrosynthetic pathway envisages the synthesis of Stenusin **96** in overall 5 single reaction steps. As a key intermediate serves the piperidinone **27h.**

Piperidinol **97** is a stable solid and serves as an inexpensive starting material. Reductive alkylation introduces the *N*-ethyl substituent in the first step (Step **A**), followed by the oxidation of the resulting *N*-ethyl piperidinol **98** (Step **B**). For both transformations, a number of closely related literature analogies are described. The resulting ketone **27h** should be transformable into alkenyl nonaflate **28h** as described in Chapter 1 (Step **C**).



Scheme 29 The strategy planned for the synthesis of Stenusin **96** consists of 5 steps (**A**-**E**). While the steps **A** and **B** require isolation of the intermediates, steps **C**, **D** and **E** could be ideally conducted in an one-pot sequence.

Submitting **28h** to the Heck cross-coupling reaction with 2-methyl-1-butene **99** would lead to the diene **100** (Step **D**). The proof of the concept for this coupling step has already been conducted with the reaction of alkenyl nonaflate **28h** with methyl acrylate **44** leading to the piperidine derivative (*E*)-**61** (Chapter 3, Table 27, Entry 4). Total hydrogenation of the resulting diene would finally lead to Stenusin **96** (Step **E**), most likely as a mixture of all four stereoisomers.

The Heck cross-coupling of **28h** and 2-methyl-1-butene **99** might produce the diene **100** along with other isomers of different location of the exocyclic C=C bond as it was observed for the reaction of cyclopentenyl nonaflate **28a** with 1-hexene **52** (Chapter 3, Table 26, Entry 6). This regioselectivity problem caused by the Heck chemistry will be resolved by the total hydrogenation in the final step.

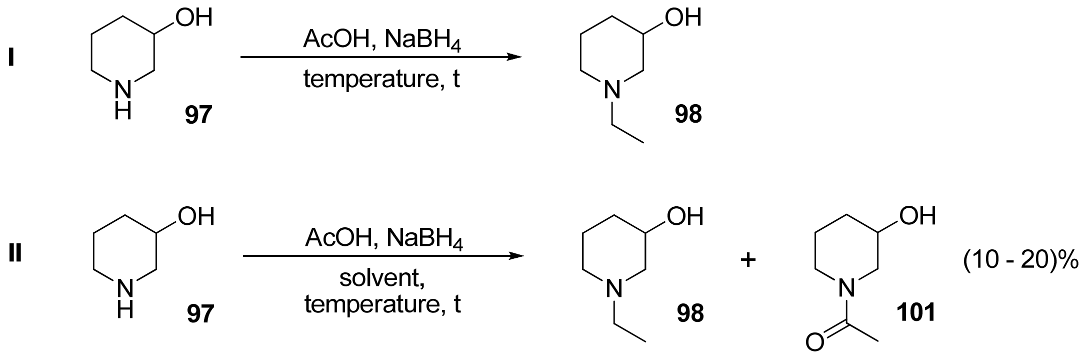
Steps **C** and **D** could potentially be carried out in an one-pot sequence as demonstrated for ketone **27h** and methyl acrylate **44** in Chapter 4 (Table 35, Entry 8). The overall coupling sequence could even be culminated by inclusion of the final Pd-catalyzed total hydrogenation into the one-pot procedure, justifying even higher palladium loadings throughout the cross-coupling step, if applied in a larger scale.

As briefly mentioned in the introduction it must be emphasized that the outlined strategy represents a general approach to 3- or 4-substituted piperidine derivatives, starting from 3- or 4-hydroxypiperidine, respectively. The approach is not restricted to Heck chemistry and could be extended to Suzuki, Sonogashira or Negishi cross-coupling reactions as well. In conclusion, the strategy presented in the Schemes 28 and 29 could become a short and flexible pathway towards 3- and 4-substituted *N*-alkylated piperidines.

5.3. Synthesis

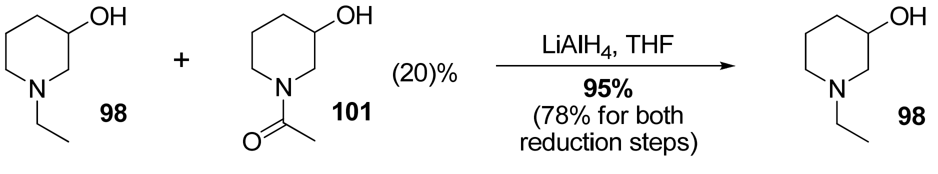
5.3.1. Reductive alkylation

A variety of different methodologies for the reductive alkylation of piperidine derivatives is reported. Due to its simplicity the reaction using sodium borohydride as the reducing agent in neat acetic acid seems to be most attractive (Scheme 30, I). This procedure is described to give excellent results for a variety of amines, by clean transformations of the starting materials to give the pure products in overall good yields.[89] However, application of this protocol to piperidinol **97** always led to a by-product, amide **101** in an amount of up to 20% (Scheme 30, **II**). Variation of the concentration of the reducing agent and the reaction temperature did not improve the reaction selectivity. As an additional obstacle the separation of the compounds **98** and **101** turned out to be difficult, making this protocol unattractive.



Scheme 30 Reductive alkylation of piperidinol **97** in neat AcOH with NaBH$_4$ leading to *N*-ethyl piperidinol **98**. The result as described in literature (I) and the experimental finding with the accompanying amide **101** as the side product (II).

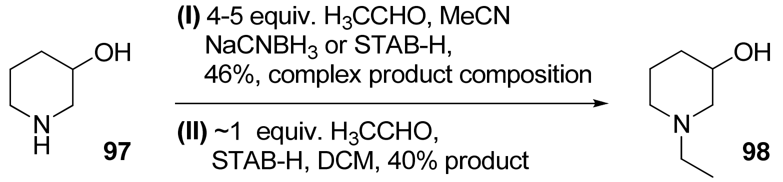
Our results are supported by the detailed experimental survey of this protocol reported by another synthetic chemistry group.[90] The systematic investigation of the described procedure, by varying the temperature, the ratio of the applied substrates, the order of addition of the single compounds and the effect of solvents, afforded the alkylated amine consistently with accompanying amide of varying amount. As a consequence the isolated product mixture composed of compounds **98** and **101** (with 20% amide **101**) was reduced additionally with LiAlH$_4$ to obtain **98** finally as the sole product in overall 79% yield for both reduction steps (Scheme 31). Nevertheless due to the inherent drawback of the procedure described above, a different approach was required.



Scheme 31 Reduction of the product mixture **98** and **101** with LiAlH$_4$ finally affords pure **98** in 95% yield (78% yield for both reduction steps).

Milder reducing agents such as sodium cyano borohydride or sodium triacetoxy borohydride (STAB-H) allow the conduction of the reaction in the presence of aldehydes. This variation potentially enables the reductive alkylation of 3-piperidinol **97** with acetaldehyde.[91] In a reported standard procedure the reduction consists of the dissolution of the amine in a aprotic polar solvent like MeCN, with the subsequent addition of an equimolar amount of the aldehyde followed by the reducing agent.[92]

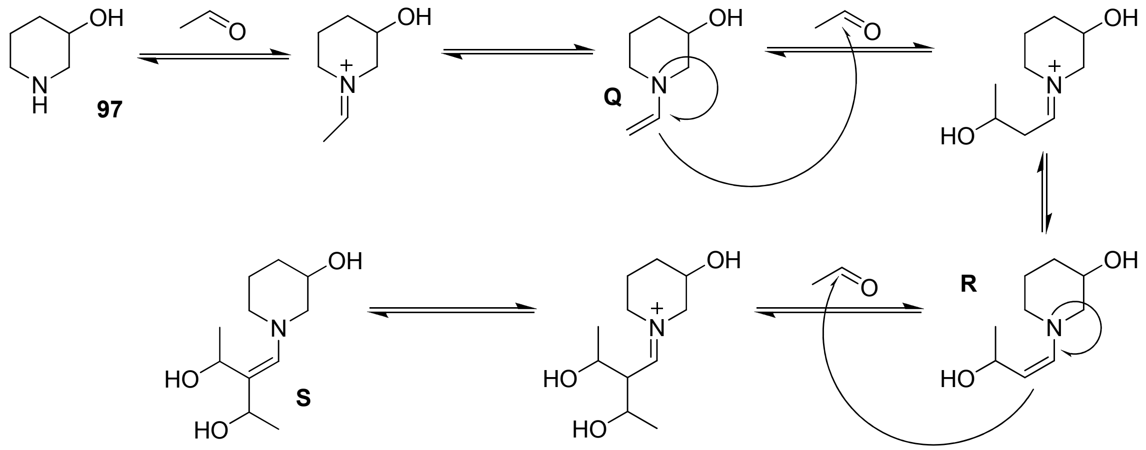
In repetitive experiments, the *N*-alkylation of **97** with sodium cyano borohydride afforded after aqueous workup and subsequent Kugelrohr distillation up to 46% of a complex compound composition, containing only small amounts of the product (Scheme 32, I). Use of sodium acetoxyborohydride under otherwise unchanged conditions led to the same result.



Scheme 32 Reductive alkylation of piperidinol **97** using $NaCNBH_3$ or STAB-H and an excess of acetaldehyde (I); alternatively the reaction was conducted with STAB-H and an equimolar amount of acetaldehyde (II); the reaction progress was controlled via GC.

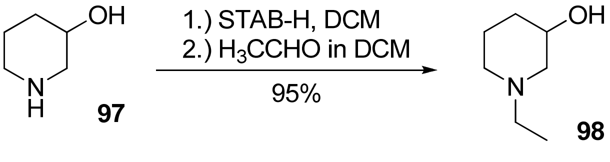
Working instead with a nearly equimolar mixture of acetaldehyde and the aminoalcohol **97** reduced significantly the side product formation and the reaction finally carried out in DCM as the solvent led to the isolation of around 40% of pure product (Scheme 32, II). GC-MS reaction control indicated fast formation of the product, but accompanied with several side products. Mass spectroscopic analysis of the reaction components and the crude product identified the compounds as intermediates resulting from several side reactions, taking place with the starting material 3-piperidinol **97** and acetaldehyde.

The putative reaction pathway is outlined in Scheme 33. Reaction of acetaldehyde with 3-piperidinol **97** results in the formation of the enamine **Q** via an intermediary iminium ion. As an excellent nucleophile it is able to react further with a second aldehyde forming the intermediate **R**. Going through the same reaction sequence even a second transformation can take place, leading to the tri-hydroxy amine **S**. For all the side products M^+ and the characteristic fragmentation patterns could be identified.



Scheme 33 Putative mechanism of enamine formation **Q** suffering the undesired consecutive side reaction with acetaldehyde, resulting in the formation of several side products as determined by GC-MS analysis.

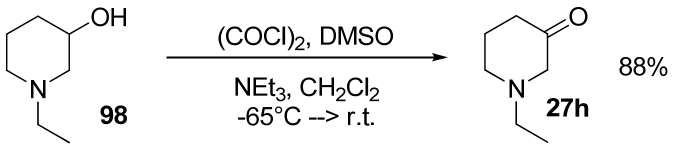
A simple change in the order of addition eliminated the side reactions, nonetheless the experimental simplicity was maintained (Scheme 34). Therefore, sodium triacetoxy borohydride and 3-piperidinol **97** were first mixed together in one half of the overall solvent volume. Acetaldehyde, diluted in the other half of the solvent volume, was added slowly dropwise to the reaction mixture while vigorous stirring. A slight excess of aldehyde in a range of 1.1 to 1.4 equivalents and an amount of 1.5 to 2.0 equivalent of STAB-H in an overall 0.15 molar concentration of the substrate **97** were identified as suitable reaction conditions. Using this experimental procedure, product **98** could be isolated in repetitive runs in yields equal or higher than 95%, owing a purity of circa 98% after aqueous workup. *N*-ethyl piperidinol **98** was used in the following oxidation without further purification.



Scheme 34 Mixing of aminoalcohol **97** and STAB-H prior to the slow addition of diluted acetaldehyde led to the nearly quantitative formation of the desired *N*-ethyl piperidinol **98**.

5.3.2. Oxidation

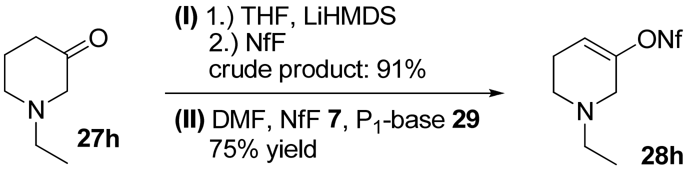
A robust and frequently used protocol for the oxidation of secondary alcohols to the corresponding ketones is the use of activated dimethyl sulfoxide. Originally introduced by Swern *et al.* oxalyl chloride is still the most efficient and common reagent for the activation. The Swern oxidation of **98** was carried out using standard conditions and afforded the aminoketone **27h** in 88% yield (Scheme 35).[93]



Scheme 35 Swern oxidation of *N*-ethylpiperidin-3-ol **98** to give *N*-ethyl-piperidine-3-one **27h**.

5.3.3. Synthesis of the alkenyl nonaflate

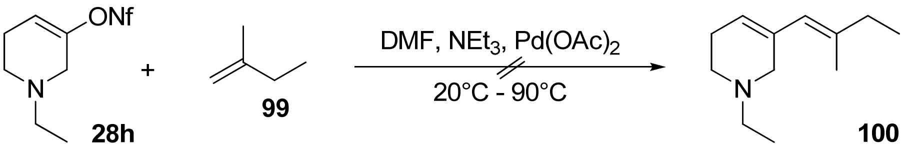
With the ketone **27h** in hand the nonaflation step was examined according to Scheme 36. The systematic investigations are described in Chapter 1, Table 1.



Scheme 36 Synthesis of alkenyl nonaflate **28h** via two different routes. The details of the reactions are given in Chapter 1, Table 1.

5.3.4. Heck cross-coupling methodology

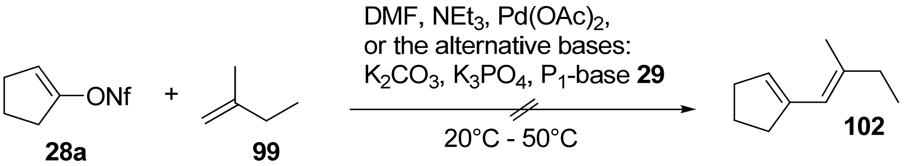
Alkenyl nonaflate **28h** has already successfully been utilized in the room temperature Heck reaction with methyl acrylate **44** to give compound (*E*)-**61** in 82% yield (Chapter 3, Table 27, Entry 4). Also the inactivated olefin 1-hexene **52** could be effectively coupled with representative cyclic alkenyl nonaflates to give the anticipated dienes in overall good yields (Chapter 3, Table 26, Entry 6 and Chapter 4, Table 35, Entry 4). These previously obtained results suggest the potential application of building block **28h** in the developed Heck procedure with inactivated olefin 2-methyl-1-butene **99** for the synthesis of the desired diene **100** (Scheme 37).



Scheme 37 Attempted synthesis of the diene **100** via the Heck cross-coupling of **28h** with 2-methyl-1-butene **99** at different temperatures using the optimised reaction conditions: 1 mmol of **28a**, 1.3 mmol of olefin, 2.0 mmol of NEt$_3$, 5 mol% Pd(OAc)$_2$ in 1 ml DMF.

The cross-coupling of 2-methyl-1-butene **99** with alkenyl nonaflate **28h** was first carried out using the optimised reaction conditions. The course of the reaction was monitored by GC-MS. Reaction at room temperature showed no conversion of the starting material with the compounds remaining intact. Also no obvious Pd$_{black}$ formation was observed. Exposure to elevated temperature of 50°C or heating of the reaction mixture up to 90°C did not result in the generation of the desired product. Even worse, carrying out the reaction at higher temperature led to the formation of various unidentified side products with full consumption of the nonaflate **28h**.

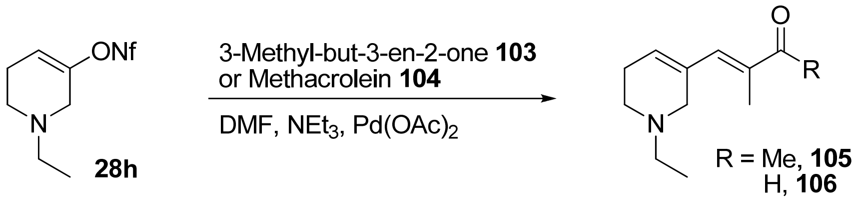
The failure of the reaction could be explained by adverse effect caused by two alkyl substituents in the position 2 of 2-methyl-1-butene **99**. To find out whether the failing of the Heck reaction is owing to 2-methyl-1-butene or just its unfortunate combination with the heterocyclic nonaflate **28h**, we decided to replace compound **28h** with cyclopentenyl nonaflate **28a** (Scheme 38), which was found earlier to react smoothly with 1-hexene **52** (Chapter 3, Table 26, Entry 6).



Scheme 38 Reactivity testing for 2-methyl-1-butene: Attempted cross-coupling with cyclopentenyl nonaflate **28a** and 2-methyl-1-butene **99** to form the diene **102** at different temperatures and with various bases: 1 mmol of **28a**, 1.3 mmol of olefin **99**, 2.0 mmol of NEt_3, 5 mol% $Pd(OAc)_2$ in 1 ml DMF; as alternative bases K_2CO_3, K_3PO_4 and the P_1-base were chosen.

While the transformation of 1-hexene **52** and nonaflate **28a** provided a clean transformation, the reaction with 2-methyl-1-butene **99** showed no conversion at room temperature or at 50°C. To test if the failure of the catalysis is maybe caused by a hindered proton abstraction in the final β-elimination step the stronger bases K_2CO_3, K_3PO_4, and P_1-base **29** were used in the latter reaction under otherwise identical conditions. This modification had no beneficial effect on the outcome of the reaction.

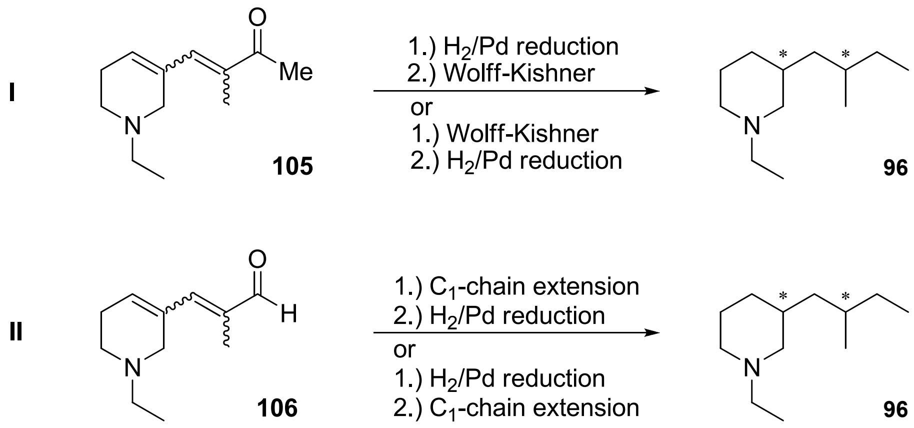
The above comparison between olefins 1-hexene **52** and 2-methyl-1-butene **99** in the coupling reaction with cyclopentenyl nonaflate **28a** clearly shows that the introduction of a methyl group in position 2 of an inactivated olefin leads to the total suppression of the desired cross-coupling. As a solution to obviate this adverse deactivation effect while keeping with the proposed cross-coupling route towards Stenusin **96**, it was thought about an electronic activation of the C,C-double bond. Appropriate substrates therefore are commercially available 3-methyl-but-3-en-2-one **103** and methacrolein **104**. This would lead to the synthesis of the alternative target compounds **105** and **106**, respectively (Scheme 39).



Scheme 39 The alternative route using the activated olefins 3-methyl-but-3-en-2-one **103** and methacrolein **104.** The generation of the expected coupling products **105** and **106** requires an extra step to finalize the synthesis of Stenusin **96.**

As a result of this modification an additional synthetic step is required to obtain Stenusin **96** (Scheme 40). Supposing the successful formation of compound **105**, two options of a further modification to Stenusin **96** are conceivable (Scheme 40, Route I). First reduction of the carbonyl moiety by Wolff-Kishner followed by hydrogenation of the conjugated double bonds.

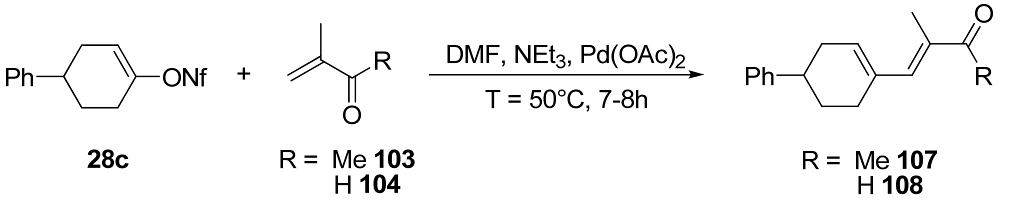
Alternatively this sequence can be carried out in a reversed order. The latter methodology exhibits the advantage still to enable alkenyl nonaflate formation, Heck coupling and the hydrogenation within a one-pot procedure. If methacrolein **104** is used, an additional C_1-chain extension is required. This can be applied prior to the final total hydrogenation or after the reduction of the conjugated double bonds (Scheme 40, Route II).



Scheme 40 Proposed transformations of the unsaturated carbonyl compounds **105** and **106** to the final product Stenusin **96**.

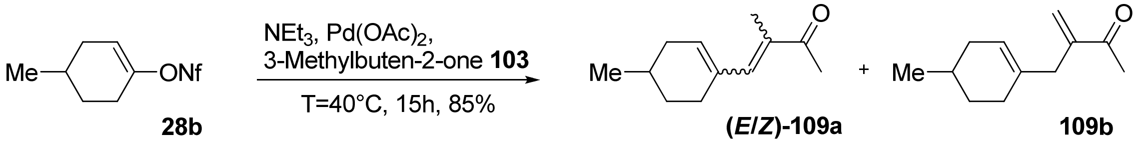
For both routes a satisfactory repertoire of synthetic methodologies is available. Reduction of the ketone could be carried out by a variety of variants of the Wolff-Kishner reduction.[94] Carbon chain extension for instance can be achieved by the Wittig or Tebbe olefination[95] or by the reductive coupling of aldehydes via their sulfonylated hydrazones and alkyllithium reagents.[96] Since all routes offer a potential pathway to Stenusin **96** the coupling was tried with both olefins.

The olefins **103** and **104** were tested first in the reaction with 4-phenyl-cyclohexenyl nonaflate **28c** as described in Scheme 41. This allows the direct comparison of these substrates to the successful reaction of nonaflate **28c** with the structural related methyl vinyl ketone **49** as described in Chapter 3 (Table 27, Entry 3). While the catalysis with olefin **49** takes place at room temperature and full conversion is obtained within 15 hours, the reaction employing olefins **103** and **104** with nonaflate **28c** showed a low rate of conversion at room temperature. However, carrying out the reaction at 50°C full conversion of **28c** was observed within 7 hours using ketone **103**. In the reaction employing methacrolein **104** still at least 2% of the starting nonaflate were present at the same time. Further, the GC-MS reaction control indicated an overall cleaner reaction course for 3-methyl-but-3-en-2-one **103** as the substrate. Aqueous workup afforded compound **107** as a practically pure compound while diene **108** was accompanied by the starting nonaflate **28c** and side products. For this reason 3-methyl-but-3-en-2-one **103** was chosen as the substrate for the envisaged coupling step.



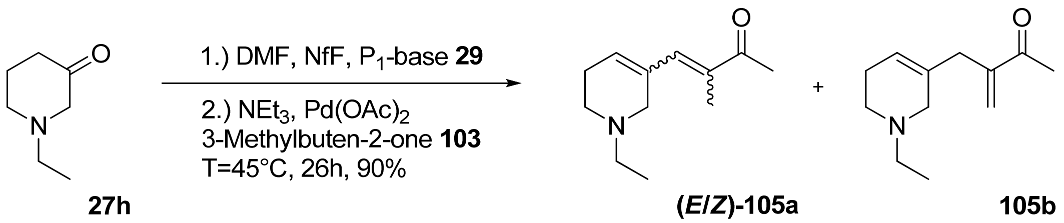
Scheme 41 Test reactions of 4-phenyl-cyclohexenyl nonaflate **28c** and the olefins 3-methyl-but-3-en-2-one **103** and acrolein **104**: 1 mmol of **28a**, 1.3 mmol of olefin, 2.0 mmol of NEt_3, 5 mol% $Pd(OAc)_2$ in 1 ml DMF. The reaction showed no conversion at room temperature, elevated temperature of 50°C furnished complete conversion of the starting nonaflate **28c** and olefin **103** within 7h.

In a set of reactions the ideal temperature range for the coupling of 4-methyl-cyclohexenyl nonaflate **28b** and 3-methyl-but-3-en-2-one **103** was identified as 40-45°C. Full conversion was obtained at 40°C within 15 hours and the desired coupling product **109** was isolated in 85% yield (Scheme 42). The product is obtained as a mixture of the isomers (*E*)-**109a**, (*Z*)-**109a** and the 1,4-diene **109b** in a ratio of 6.3:1.0:4.4. The product mixture is accompanied by a small amount of an unidentified compound.



Scheme 42 Cross coupling of 4-methyl-cyclohexenyl nonaflate **28b** and 3-methyl-but-3-en-2-one **103** to give the diene **109** on 85% yield as a mixture of three isomers. The ratio of the isomers could be determined to (*E*)-**109a**:(Z)-**109**:**109b** = 6.3:1.0:4.4.

Finally the results obtained for the coupling of olefin **103** with the alkenyl nonaflates **28b** and **28c** were applied in the one-pot Heck reaction with amino ketone **27h** (Scheme 43). The catalysis was carried out at 45°C and full conversion of the nonaflate **28b** was achieved after 26 hours.

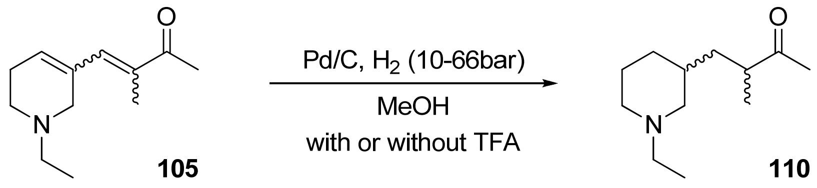


Scheme 43 Cross coupling of aminoketone **27h** with 3-methyl-but-3-en-2-one **103** to give the diene **105** as a mixture of three isomers. In order to obtain a sufficient high rate of conversion the reaction was conducted at a temperature of 45°C.

The one-pot sequence afforded the desired product **105** in overall 90% yield as a mixture of stereoisomers (*E*)-**105a**, (*Z*)-**105a**, and the 1,4-diene **105b** in the ratio of 2.9:1.7:1.0. The desired product is accompanied by an unidentified side product, but used as such in the subsequent hydrogenation reaction.

5.3.5. Hydrogenation of the diene

The first attempt for the total hydrogenation of **105** was carried out using palladium on carbon (10%) in a methanolic solution under 10 bar hydrogen pressure (Scheme 44).



Scheme 44 Palladium on charcoal catalyzed hydrogenation of diene **105**. The reaction was carried in a methanolic solution applying H$_2$ pressures in between 10 to 66 bar; the first experiment was carried without TFA, the second reaction in the presence of TFA.

The reaction mixture was stirred in an autoclave for overall 16 hours (overnight). At the end a reduced pressure of less than 2 bars was observed. ^{1}H-NMR reaction control indicated an uncompleted conversion of the substrate (monitoring of the olefinic protons). Therefore a second hydrogenation was carried out using 66 bars as the starting hydrogen pressure in the presence of TFA. The overnight reaction (15 hours) showed a final pressure of 5 bars.

^{1}H-NMR control after a quick extraction of the product **110** from the methanolic solution into MTBE indicated complete conversion. Evaporation afforded the crude product **110**, but still with the same unidentified impurity present as determined in the generation of product **105**.

5.4. Summary and outlook

Unfortunately the total synthesis of Stenusin **96** could not be accomplished within the granted time frame. Determination of the impurity, generated in the Heck cross coupling step of the aminoketone **27h** with 3-methyl-but-3-en-2-one **103**, and the final Wolff-Kishner reduction are the missing final steps for the synthesis of Stenusin **96** using the above described strategy.

Nevertheless, it could be demonstrated that the described protocol represents a general approach to 3- or 4-substituted *N*-alkylated piperidine derivatives via the Heck cross-coupling methodology. A solution to the above described reactivity problem using sterically hindered inactivated olefins like 2-methyl-1butene **99** is the introduction of an activating functionality, as the carbonyl group in 3-methyl-but-3-en-2-one **103**.

However, the most straightforward solution to this problem is the extension of the protocol to alternative cross-coupling procedures like Suzuki and Negishi couplings. This would give the chance for the specific example of the Stenusin **96** synthesis, to use the commercially available substrate 1-iodo-2-methylbutane in a Negishi coupling or 9-(2-methylbutyl)-9-borabicyclo[3.3.1]nonane, generated from 2-methyl-1butene **99** and 9-BBN, in the Suzuki coupling. This modification would directly lead to the desired natural product **96** in overall 4 synthetic steps.

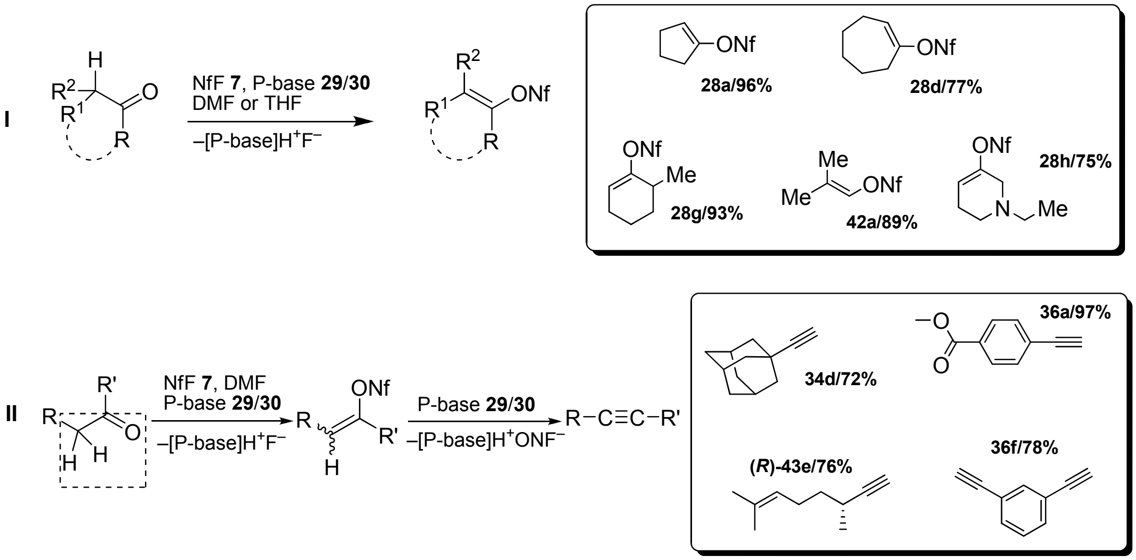
Key achievements and perspective

6. Key achievements and perspective

6.1. Key achievements

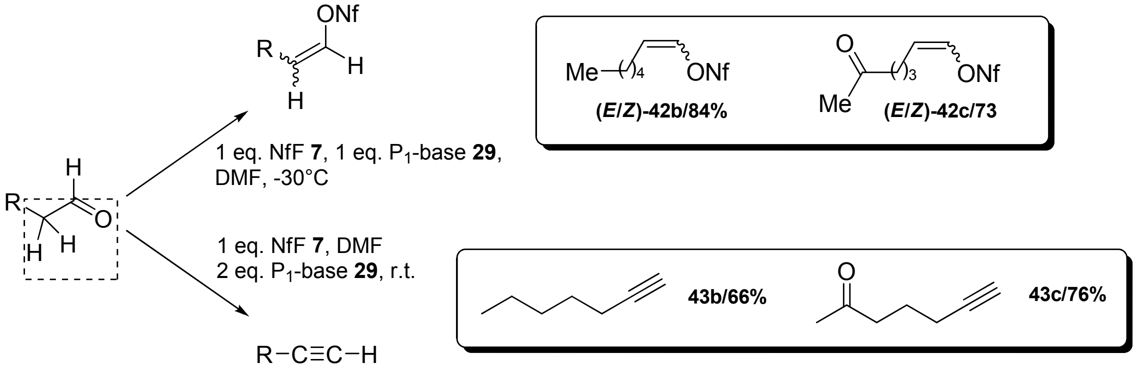
Within this thesis a number of synthetic innovations and new insights regarding the palladium mediated transformations employing alkenyl nonaflates are described.

A straightforward transformation of readily available carbonyl compounds to either alkenyl nonaflates or alkynes has been developed. The particular advantage of this protocol is the use of the reagent NfF **7** and the phosphazene bases **29**/**30** under convenient internal quenching conditions. Cyclic ketones (or aldehydes with only one hydrogen adjacent to the carbonyl functionality) are transformed to the corresponding cyclic (acyclic) alkenyl nonaflates (Scheme 45, I), while acyclic ketones inevitable form internal or terminal alkynes (Scheme 45, II).



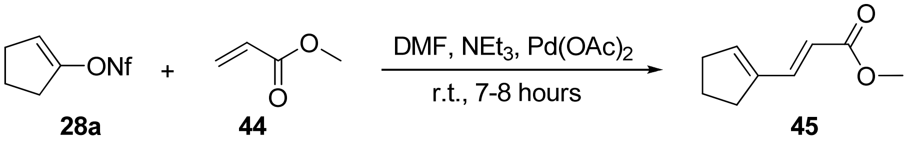
Scheme 45 Transformation of carbonyl compounds with NfF **7** and the P-bases **29**/**30** under internal quenching conditions. The outcome of the reaction is substrate dependend and can lead to alkenyl nonaflates (I) or to alkynes (II). Representative examples with yields are shown in the boxes (the reaction can also lead to allenes; since this transformation lacks generality examples are not given here).

A different situation was identified for the use of aldehydes. It could be shown that the reaction pathway for either alkenyl nonaflate or terminal alkyne formation is temperature dependent, enabling an effective differentiation of both transformations. This allows the exclusive synthesis of one of the potential products, simply by conducting the reaction at the appropriate temperature with the required amount of base **29**/**30** (Scheme 46).



Scheme 46 Depending on the reaction conditions aldehydes give the chance to form either alkenyl nonaflates or terminal alkynes under internal quenching conditions. Products formed from heptanal **41b** or 6-oxoheptanal **41c** are given in the boxes.

As a model system for the cross-coupling of alkenyl nonaflates and olefins the Heck reaction of cyclopentenyl nonaflate **28a** with methyl acrylate **44** was explored (Scheme 47). It was found that the coupling reaction features excellent efficiency and robustness as a ligand and additive free palladium catalysis. The optimization of the reaction conditions regarding reaction performance and practicability resulted in the use of NEt_3 as the base, $Pd(OAc)_2$ as the stable catalyst precursor and DMF as the solvent (Scheme 47).



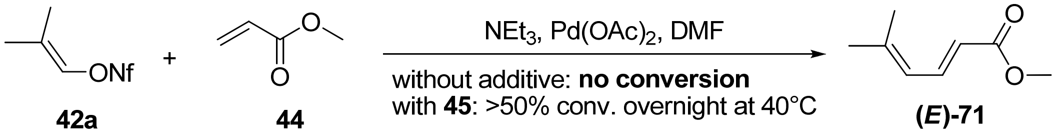
Scheme 47 “Model Heck reaction”; systematic investigations of solvent, base and additive effects led to the use of 2 eq. NEt_3 as the base, 5 mol% of $Pd(OAc)_2$ as the catalyst precursor and DMF as the solvent. These conditions were further used for systematic mechanistic investigations and for the Heck coupling with different alkenyl nonaflates and olefins.

The developed catalysis requires only the essential components for the Heck reaction and due to its simplicity it is particularly suited for up scaling or mechanistic investigations. In a comparative study cyclopentenyl nonaflate **28a** was found to provide a higher rate of conversion than cyclopentenyl iodide **46** and cyclopentenyl triflate **47**.

While testing the robustness of the Heck model reaction and the investigation of additive effects, the Heck reaction using K_2CO_3 as the base with $(n\text{-Bu})_4NCl$ as the additive in DMF was found to provide an extraordinary high rate of conversion. To the best of our knowledge the full conversion of an alkenyl sulfonate practically within one hour using 5 mol% of the catalyst precursor at room temperature is unprecedented so far.

In a series of kinetic experiments the established ligand and additive free Heck cross-coupling protocol (Scheme 47) could be identified as homogenous transition metal catalysis. Homogeneous catalysis with alkenyl sulfonates or halides is - to the best of our knowledge - unprecedented so far.

The developed ligandless and additive free Heck protocol could be extended to a variety of cyclic and acyclic alkenyl nonaflates and olefins. The desired products are formed in overall very good yields, while regioselectivities follow typically observed trends. Experiments employing the sterically hindered 2-methyl propenyl nonaflate **42a** indicated qualitatively the stabilizing effect of the diene products, formed during the Heck reaction course, on the catalytic active species (Scheme 48).



Scheme 48 The dienes formed during the course of the Heck cross-coupling reaction exhibit a stabilizing effect on the catalytically active species.

Moreover, the compatibility of the Heck- and Sonogashira cross-coupling methodology with the conditions of the alkenyl nonaflate and terminal alkyne formation could be demonstrated. Therefore alkenyl nonaflate and terminal alkyne formation, as well as transition metal catalysis can be conducted consecutively in a *one-pot* fashion. The developed protocol represents a straightforward methodology to generate highly functionalized conjugated dienes and enynes from simple, readily available carbonyl precursors.

6.2. Perspective

With the achieved goals and the questions opened up, this thesis gives copious room for further investigations and developments. In the following few sections some ideas are outlined, how these achievements can be further worthwhile spanned into different areas of organic synthesis and mechanistic investigations.

So far exclusively the Heck- and the Sonogashira reaction have been applied in the one-pot procedure. Based on the positive results obtained so far it is obvious to extend the one-pot protocol to other efficient palladium mediated transformations like Suzuki and Negishi reactions, in order to extend the synthetic scope of the developed methodology. The protocol could even culminate in adding on a second transition metal catalyzed step on top of the palladium catalysis, enabling a multi step transition metal catalyzed one-pot methodology. One interesting example is the alkine directed Ni-catalyzed coupling reaction of enynes with aldehydes or epoxides to give the corresponding conjugated addition products.[97]

The ligand and additive free Heck cross-coupling protocol is identified as a homogenous transformation. Due to its homogeneity and simplicicity it is suitable for further mechanistic investigations and could simplify mass spectrometry, BTEM[98a-b] or solution NMR measurements for the *in situ* monitoring of the transformations and the characterisation of reaction intermediates. In this context the Heck catalysis with K_2CO_3 and tetrabutylammonium chloride deserves further investigations in order to explain the high catalytic activity. A better mechanistic understanding of this reaction might enable the optimization of this remarkable catalysis or could allow the modification of other catalytic systems.

The synthesis of alkenyl nonaflates, alkynes or allenes by the established internal quenching protocol from carbonyl precursors with NfF **7** and phosphazene bases **29**/**30** represents a convenient and straightforward methodology. However, with the use of phosphazene bases **29**/**30** cost issues arise, and most important for an attractive generally applicable transformation - especially on a large scale - are cheap and enviromental benign reagents (recycling of the phosphazene base is a potential option, even though it cannot be the first choice). Therefore the quest for alternative bases exhibiting the same beneficial entities, but coming along with a considerable cheaper price would constitute a great improvement of the protocol.

Alkynes and allenes are valuable starting materials for the synthesis of complex molecules. Exciting areas are for instance intermolecular cyclization reactions employing alkynes or allenes or intramolecular reactions of enynes catalyzed by various transition metals. Compatibility of promising transformations with the phosphazene bases **29**/**30** could lead to further attractive one-pot procedures for the generation of complex ring systems starting from simple carbonyl precursors. The use of alkynes and activated allenes as candidates in *e.g.* dipolar additions[99] is promising and could extend the present protocol to further preparative interesting one-pot methodologies.

By all means this thesis represents an interesting matrix for future work in the field of preparative organic chemistry and transition metal catalysis. It just depends on the imagination.

Experimental part

7. Experimental part

7.1. General

- NMR spectra were recorded on *Bruker 400 UltraShield* instrument in $CDCl_3$ as a solvent unless stated otherwise. ^1H and ^{13}C chemical shifts are expressed as ppm downfield from $SiMe_4$ ($\delta = 0$) used as an internal standard.
- Mass spectra were registered with *Varian* MAT 711 and with *Finnigan MAT 95XP* (HRMS) spectrometers.
- Microanalyses were performed with *Euro Elemental Analyser*.
- IR spectra were measured with spectrometer *FTIR-Bio Rad Excalibur*.
- TLC-analysis was performed using *Merck* silica gel *60* F_{254} plates.
- Column chromatography was conducted on silica gel 60 (40–63 μm, *Fluka*).
- GC-analysis was performed on *Agilent Technologies 6890N* (FID-detector; Agilent 190915-413 HP-5 column; 5% Phenylmethylsiloxane capillary, 30 m × 0.32 mm, 0.25 micron).
- GC-MS-analysis was performed on Agilent *Technologies G1540N* (Agilent 190915-413 HP-5 column; 5% Phenylmethylsiloxane capillary, 30 m × 0.32 mm, 0.25 micron).
- Melting points were determined with a *Büchi Melting Point B-540*.
- Low temperature experiments were conducted using a *Julabo FT902* immersion cooler (temperature stability ±1.0°C, Pt100 external sensor).
- Ozone for ozonolysis reactions was generated with the Ozone generator *OL80W/FM500* from *Ozone Services Canada*.
- If required dry and purified solvents were generated by standard procedures and equipment. THF and Et_2O were distilled over sodium/benzophenone, DMF was distilled over CaH_2. At a later stage of the thesis all solvents were purified using a *Glass Contour 6* – solvent purification system to obtain purified and dry THF, DMF and toluene. No obvious differences in the reactivity were observed.
- DMF (*Riedel-de Haën*) and NEt_3 (*Riedel-de Haën*) were used as purchased without further purification. $Pd(OAc)_2$ and $PdCl_2$ were purchased from *Alfa Aesar*. The carbonyl compounds and olefins were purchased from various suppliers and used without further purification.

7.2. Procedures and analytical details

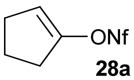
7.2.1. Reactions of Chapter 1

GP-1 General procedure for the synthesis of cyclic alkenyl nonaflates (unless stated otherwise):

Into a dry one-necked round bottom flask equipped with magnetic stirring bar and a three way tap either DMF or THF (as stated in Table 1), the carbonyl compound **27** and NfF **7** are added consecutively in an argon atmosphere (all via syringe). The reaction mixture is cooled to 0°C and under vigorous stirring the P-base **29**/**30** is added dropwise. With completed addition the three way tap is replaced by a glass stopper and the flask is closed tightly. The solution is allowed to warm to room temperature slowly and is stirred for the stated time (reaction control via ^{1}H-NMR). The reaction mixture is diluted with water (5 ml / mmol compound **27**) followed by extraction of the aqueous phase with *n*-pentane (4 * 25 ml / mmol compound **27)**. The combined organic phases are washed with water (20 ml / mmol compound **27**) and dried over $MgSO_4$. Careful evaporation of the solvent under reduced pressure (despite their high molecular weight the alkenyl nonaflates exhibit a considerably volatility) generates a crude oil which is finally purified by flash column chromatography (*n*-pentane) over a short column of silica gel.

Relatively high amounts of solvent are used for the aqueous workups of small scale reactions in order to avoid losses during the purification steps. This volume is gradually lowered with higher substrate loadings. If more than 10 mmol of the carbonyl compound **27** are used the amount of each solvent contribution is reduced to a fifth.

Synthesis of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid cyclopent-1-enyl ester <u>28a</u>



28a

The synthesis was carried out according to the general procedure GP-1.

Cyclopentanone **27a**: 4.210 g, 50.0 mmol,

NfF **7**: 18.881 g, 62.5 mmol,

P_1-base **29**: 16.40 g, 52.5 mmol,

40 ml DMF.

After column chromatography **28a** was obtained as colorless oil (17.58 g, 48.0 mmol, 96% yield).

^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 1.99-2.07 (m, 2 H, CH_2), 2.39-2.45 (m, 2 H, CH_2), 2.55-2.61 (m, 2 H, CH_2), 5.64 (t, $^3J_{H,H}$ = 2.3 Hz, 1 H, CH=C);

^{13}C-NMR (100.65 MHz): δ = 20.9 (CH$_2$), 28.1 (CH$_2$), 31.0 (CH$_2$), 117.9 (CH), 149.9 (C=CH).

Analytical data match well those described in literature.[17]

The synthesis was carried out according to the general procedure GP-1 alternatively with DBU **20**.

Cyclopentanone **27a**: 4.267 g, 50.7 mmol,

NfF **7**: 18.887 g, 62.5 mmol,

DBU **20**:8.776 g, 57.7 mmol,

40 ml DMF.

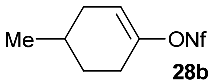
After column chromatography **28a** was obtained as colorless oil (17.45 g, 47.7 mmol, 94% yield).

^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 2.00-2.07 (m, 2 H, CH_2), 2.39-2.44 (m, 2 H, CH_2), 2.55-2.61 (m, 2 H, CH_2), 5.64 (t, $^3J_{H,H}$ = 2.3 Hz, 1 H, CH=C);

^{13}C-NMR (100.65 MHz): δ = 20.9 (CH$_2$), 28.1 (CH$_2$), 31.0 (CH$_2$), 117.9 (CH), 149.9 (C=CH).

Analytical data match well those described in literature.[17]

Synthesis of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-methyl-cyclohex-1-enyl ester 28b



28b

The synthesis was carried out according to the general procedure GP-1.

4-Methylcyclohexanone **27b**: 2.243 g, 20.0 mmol,

NfF **7**: 7.70 g, 25.5 mmol,

P$_1$-base **29**: 7.245 g, 24.0 mmol,

20 ml THF.

After column chromatography **28b** was obtained as colorless oil (7.58 g, 19.2 mmol, 96% yield).

^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 0.99 (d, $^3J_{C,H}$ = 6.4 Hz, 3 H, CH_3), 1.39-1.49 (m, 1 H, CH_2), 1.68-1.87 (m, 3 H, CH), 2.20-2.34 (m, 2 H, CH_2) 2.35-2.46 (m, 1 H, CH-CH$_3$), 5.73 (t, $^3J_{H,H}$ = 2.6 Hz, 1 H, CH=C);

^{13}C-NMR (100.65 MHz): δ = 20.6 (*C*H$_3$), 27.2 (*C*H-CH$_3$), 27.3 (*C*H$_2$), 30.6 (*C*H$_2$), 32.0 (*C*H$_2$), 118.0 (*C*H), 149.3 (*C*=CH);

MS (EI, 70 eV): m/z (%) = 55 ([M$^+$ – 339], [C$_4$H$_7$•], 100), 94 ([M$^+$ – 300], [C$_7$H$_{10}$•], 45), 95 ([M$^+$ – 299], [C$_7$H$_{11}$•], 35), 394 (M$^+$, 30);

HRMS: calculated for C$_{11}$H$_{11}$O$_3$F$_9$S (M$^+$) 394.0285, found 394.0297.

The synthesis was carried out according to the general procedure GP-1 alternatively with DBU **20**.

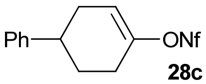
4-Methylcyclohexanone **27b**: 114.8 mg, 1.02 mmol,
NfF **7**: 377 mg, 1.25 mmol,
DBU **20**: 184.3 mg, 1.21 mmol,
LiCl: 60 mg, 1.42 mmol
1 ml DMF.

After column chromatography **28b** was obtained as colorless oil (288 mg, 0.73 mmol, 71% yield).

^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 0.99 (d, $^3J_{C,H}$ = 6.4 Hz, 3 H, C*H*$_3$), 1.39-1.49 (m, 1 H, C*H*$_2$), 1.68-1.87 (m, 3 H, C*H*), 2.20-2.34 (m, 2 H, C*H*$_2$) 2.35-2.46 (m, 1 H, C*H*-CH$_3$), 5.73 (t, $^3J_{H,H}$ = 2.6 Hz, 1 H, C*H*=C);

^{13}C-NMR (100.65 MHz): δ = 20.6 (*C*H$_3$), 27.2 (*C*H-CH$_3$), 27.3 (*C*H$_2$), 30.6 (*C*H$_2$), 32.0 (*C*H$_2$), 118.0 (*C*H), 149.3 (*C*=CH).

Synthesis of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-phenyl-cyclohex-1-enyl ester 28c



28c

The synthesis was carried out according to the general procedure GP-1.

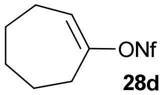
4-Methylcyclohexanone **27c**: 3.486 g, 20.0 mmol,
NfF **7**: 7.506 g, 24.85 mmol,
P$_1$-base **29**: 6.620 g, 21.2 mmol,
20 ml THF.

After column chromatography **28c** was obtained as colorless oil (8.673 g, 19.0 mmol, 95% yield).

^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 1.92-2.02 (m, 1 H, C*H*$_2$), 2.05-2.12 (m, 1 H, C*H*$_2$), 2.30-2.61 (m, 4 H, C*H*$_2$), 2.82-2.90 (m, 1 H, C*H*$_2$), 5.87 (t, $^3J_{H,H}$ = 2.75 Hz, 1 H, C*H*=C), 7.21-7.26 (m, 3 H, C$_6$*H*$_5$), 7.31-7.35 (m, 2 H, C$_6$*H*$_5$);

^{13}C-NMR (100.65 MHz): δ = 27.9 (CH_2), 29.7 (CH_2), 31.6 (CH_2), 38.8 (CH-CH_3), 118.2 (CH), 126.6 ($C_{Ar}H$), 126.7 ($C_{Ar}H$), 128.6 ($C_{Ar}H$), 144.6 (C_{Ar}-CH), 149.1 (C=CH);
MS (EI, 70 eV): m/z (%) = 157.2 ([M^+ – 299], [$C_{12}H_{13}$•] 100), 118.9 ([M^+ – 337], [C_2F_5•] 25);
HRMS: calculated for $C_{16}H_{13}O_3F_9S$ (M^+) 456.0442, found 456.0450.

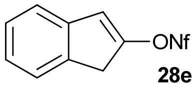
Synthesis of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid cyclohept-1-enyl ester 28d



28d

The synthesis was carried out according to the general procedure GP-1.
Cycloheptanone **27d**: 451.4 mg, 4.0 mmol,
NfF **7**: 1.537 g, 5.10 mmol,
P_1-base **29**: 1.5 g, 4.8 mmol,
4 ml DMF.
After column chromatography **28d** was obtained as slightly yellowish oil (1.226 g, 3.1 mmol, 77% yield).
^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 1.61-1.75 (m, 6 H, CH_2), 2.14-2.19 (m, 2 H, CH_2), 2.49-2.55 (m, 2 H, CH_2), 5.90 (t, $^3J_{H,H}$ = 6.4 Hz, 1 H, CH=C);
^{13}C-NMR (100.65 MHz): δ = 24.7 (CH_2), 24.8 (CH_2), 26.3 (CH_2), 29.8 (CH_2), 33.3 (CH_2), 123.2 (CH), 150.7 (C=CH).
Analytical data match well those described in literature.[14]

Synthesis of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 1H-inden-2-yl ester 28e



28e

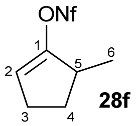
The synthesis was carried out according to the general procedure GP-1. The P_1-base **29** was added at -10°C dropwise.
2-Indanone **27e**: 1.189 g, 9.0 mmol,
NfF **7**: 3.136 g, 10.4 mmol,
P_1-base **29**: 3.093 g, 9.9 mmol,
10 ml THF.
After column chromatography **28d** was obtained as orange-yellow oil (3.542 g, 8.6 mmol, 95% yield).

^{1}H-NMR (400.23 MHz, C_6D_6): δ = 2.99 (s, 2 H, C*H*$_2$), 6.17 (t, $^4J_{H,H}$ = 1.5 Hz, 1 H, C*H*), 6.87 (d, $^3J_{H,H}$ = 7.4 Hz, 1 H, C_{Ar}*H*), 6.94-7.07 (m, 3 H, C_{Ar}*H*);
^{13}C-NMR (100.65 MHz, C_6D_6): δ = 37.5 (*C*H$_2$), 119.8 (*C*H), 122.4 (*C*$_{Ar}$H), 123.9 (*C*$_{Ar}$H), 126.3 (*C*$_{Ar}$H), 127.3 (*C*$_{Ar}$H), 137,7 (*C*$_{Ar}$-CH$_2$), 140.3 (*C*$_{Ar}$-CH), 153.7 (*C*=CH);
MS (EI, 70 eV): m/z (%) = 103 ([M$^+$ – 311], [C_8H_7•] 100), 131 ([M$^+$ – 283], [C_9H_7O•] 94), 69 ([M$^+$ – 345], [CF_3•] 43), 414 (M$^+$, 22), 219 ([M$^+$ – 195], [C_4F_9•] 5);
HRMS: calculated for $C_{13}H_7O_3F_9S$ (M$^+$) 413.9972, found 413.9976.

The synthesis was carried out according to the general procedure GP-1 alternatively with DBU **20**. NfF **7** and DBU **20** were added in reversed order.
2-Indanone **27e**: 1.330 g, 10.1 mmol,
NfF **7**: 4.030 g, 13.3 mmol,
DBU **20**: 1.776 g, 11.7 mmol,
11 ml THF.
After column chromatography **28d** was obtained as orange-yellow oil (3.68 g, 8.9 mmol, 94% yield).
^{1}H-NMR (400.23 MHz, C_6D_6): δ = 2.99 (s, 2 H, C*H*$_2$), 6.17 (t, $^4J_{H,H}$ = 1.5 Hz, 1 H, C*H*), 6.87 (d, $^3J_{H,H}$ = 7.4 Hz, 1 H, C_{Ar}*H*), 6.94-7.07 (m, 3 H, C_{Ar}*H*);
^{13}C-NMR (100.65 MHz, C_6D_6): δ = 37.5 (*C*H$_2$), 119.8 (*C*H), 122.4 (*C*$_{Ar}$H), 123.9 (*C*$_{Ar}$H), 126.3 (*C*$_{Ar}$H), 127.3 (*C*$_{Ar}$H), 137,7 (*C*$_{Ar}$-CH$_2$), 140.3 (*C*$_{Ar}$-CH), 153.7 (*C*=CH).
MS (EI, 70 eV): m/z (%) = 103 ([M$^+$ – 311], [C_8H_7•] 100), 131 ([M$^+$ – 283], [C_9H_7O•] 96), 69 ([M$^+$ – 345], [CF_3•] 33), 414 (M$^+$, 20), 219 ([M$^+$ – 195], [C_4F_9•] 3);
HRMS: calculated for $C_{13}H_7O_3F_9S$ (M$^+$) 413.9972, found 413.9979.

The synthesis was carried out according to the general procedure GP-1 alternatively with NEt_3. NfF **7** and NEt_3 were added in reversed order.
2-Indanone **27e**: 397.7 mg, 3.0 mmol,
NfF **7**: 1.13 g, 3.7 mmol,
NEt_3: 1.281 g, 12.7 mmol,
3 ml DMF.
After column chromatography **28e** was obtained as orange-yellow oil (901 mg, 2.2 mmol, 72% yield).
^{1}H-NMR (400.23 MHz, C_6D_6): δ = 2.99 (s, 2 H, C*H*$_2$), 6.17 (t, $^4J_{H,H}$ = 1.5 Hz, 1 H, C*H*), 6.87 (d, $^3J_{H,H}$ = 7.4 Hz, 1 H, C_{Ar}*H*), 6.94-7.07 (m, 3 H, C_{Ar}*H*);
^{13}C-NMR (100.65 MHz, C_6D_6): δ = 37.5 (*C*H$_2$), 119.8 (*C*H), 122.4 (*C*$_{Ar}$H), 123.9 (*C*$_{Ar}$H), 126.3 (*C*$_{Ar}$H), 127.3 (*C*$_{Ar}$H), 137,7 (*C*$_{Ar}$-CH$_2$), 140.3 (*C*$_{Ar}$-CH), 153.7 (*C*=CH).

Synthesis of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 5-methyl-cyclopent-1-enyl ester 28f



28f

2-Methylcyclopentanone **27f**: 98.7 mg, 1.02 mmol,
NfF **7**: 391 mg, 1.29 mmol,
P_2-base **30**: 0.6 ml, 1.20 mmol, (2.0 M solution in THF),
1 ml DMF.

Into a dry one-necked round bottom flask equipped with magnetic stirring bar and a three way tap DMF, **27f** and NfF **7** are added subsequently via syringe. The reaction mixture is cooled to ≤-40°C and under vigorously stirring the P_2-base **30** is slowly added dropwise. With the completed addition the three way tap is replaced quickly by a glass stopper and the flask is closed tightly. The solution is slowly warmed to -30°C and stirred at this temperature for 17 hours (reaction control via ^{1}H-NMR). The mixture is quenched at 5°C with 5 ml of water and gets extracted 4 times with 20 ml of *n*-pentane. The combined organic phases are washed with 20 ml of water and dried over $MgSO_4$. Careful evaporation of the solvent under reduced pressure furnished the crude orange colored oil. After flash column chromatography with *n*-pentane as the eluent **28f** was obtained as a slightly yellowish oil (326 mg, 0.86 mmol, 84% yield, ratio **28f**:**28j** = 24:1).

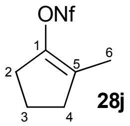
^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 1.14 (d, $^3J_{C,H}$ = 6.9, 3 H, CH_3), 1.52-1.62 (m, 1 H, CH_2), 2.22-2.41 (m, 3 H, CH_2), 2.90 (m, 1 H, C*H*-CH_3), 5.62 (m_c, 1 H, C*H*=C);

^{13}C-NMR (100.65 MHz): δ = 18.1 (6-*C*), 26.5 (CH_2), 30.0 (CH_2), 38.0 (5-*C*), 116.2 (2-*C*), 153.5 (1-*C*);

MS (EI, 70 eV): m/z (%) = 107 ([M^+ – 273], 100), 153 ([M^+ – 227], 64), 136 ([M^+ – 244], 40), 301 ([M^+ – 79], 39), 380 (M^+, 37);

HRMS: calculated for $C_{10}H_9O_3F_9S$ (M^+) 380.0129, found 380.0099.

Synthesis of 2-methylcyclopent-1-enyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate 28j



28j

Compound **28j** accompanied the formation of the desired alkenyl nonaflate **28f** and was obtained in varying amounts (see Chapter 7.3.1.). Alkenyl nonaflates **28j** and **28f** were not separated.

Signals are taken from the experiment described in Table 2, Entry 1:

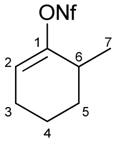
^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 1.72 (s, 3 H, C*H*$_3$), 1.93-2.02 (m, 2 H, C*H*$_2$), 2.21-2.45 (m, 2 H, C*H*$_2$), 2.54-2.64 (m, 2 H, C*H*$_2$);

^{13}C-NMR (100.65 MHz): δ = 12.2 (6-*C*), 19.4 (*C*H$_2$), 30.9 (*C*H$_2$), 33.1 (*C*H$_2$), 128.7 (5-*C*), 142.9 (1-*C*);

MS (EI, 70 eV): m/z (%) = 107 ([M$^+$ – 273], 100), 153 ([M$^+$ – 227], 64), 136 ([M$^+$ – 244], 40), 301 ([M$^+$ – 79], 39), 380 (M$^+$, 37);

HRMS: calculated for $C_{10}H_9O_3F_9S$ (M$^+$) 380.0129, found 380.0099.

Synthesis of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 6-methyl-cyclohex-1-enyl ester 28g



28g

2-Methylcyclohexanone **27g**: 114.5 mg, 1.021 mmol,

NfF **7**: 695 mg, 2.30 mmol,

P$_2$-base **30**: 1.0 ml, 2.0 mmol, (2.0 M solution in THF),

1 ml DMF.

Into a dry one-necked round bottom flask equipped with magnetic stirring bar and a three way tap DMF, **27g** and NfF **7** are added subsequently via syringe. The reaction mixture is cooled to ≤-50°C and under vigorously stirring the P$_2$-base **30** is slowly added dropwise. With the completed addition the three way tap is replaced quickly by a glass stopper and the flask is closed tightly. The solution is warmed to -20°C within 1 hour and stirred at this temperature for 65 hours (reaction control via ^{1}H-NMR). The mixture is quenched at 5°C with 6 ml of water and gets extracted 4 times with 25 ml of *n*-pentane. The combined organic phases are washed with 20 ml of water and dried over $MgSO_4$. Careful evaporation of the solvent under reduced pressure furnished a colorless oil. After flash column chromatography with *n*-pentane as the eluent **28g** was obtained as colorless oil (376 mg, 0.95 mmol, 93% yield, ratio **28g**:**28k** = 99:1).

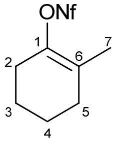
^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 1.15 (d, $^3J_{C,H}$ = 6.9, 3 H, C*H*$_3$), 1.43-1.71 (m, 3 H, C*H*$_2$), 1.90-1.97 (m, 1 H, C*H*$_2$), 2.18 (m, 2 H, C*H*$_2$), 2.54 (m, 1H, C*H*-CH$_3$), 5.75 (m$_c$, 1 H, C*H*=C);

^{13}C-NMR (100.65 MHz): δ = 17.8 (7-*C*), 19.2 (4-*C*), 24.5 (3-*C*), 31.5 (5-*C*), 32.6 (6-*C*), 118.3 (2-*C*), 153.5 (1-*C*);

MS (EI, 70 eV): m/z (%) = 394 (M^+, 100), 128 ([M^+ – 266], 94), 288 ([M^+ – 106], 45), 219 ([M^+ – 175], [C_4F_9•], 43), 131 ([M^+ – 263], 37), 153 ([M^+ – 241], 34) , 315 ([M^+ – 79], 23) , 234 ([M^+ – 160], 22) , 301 ([M^+ – 93], 15);

HRMS: calculated for $C_{11}H_{11}O_3F_9S$ (M^+) 394.0285, found 394.0285.

Synthesis of 2-methylcyclohex-1-enyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate 28k



28k

Compound **28k** accompanied the formation of the desired alkenyl nonaflate **28g** and was obtained in varying amounts (see Chapter 7.3.2.). Alkenyl nonaflates **28k** and **28g** were not separated.

Selected signals are taken from the experiment described in Table 3, Entry 1:

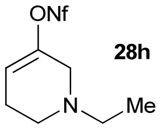
^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 1.76 (s, 3 H, CH_3), 2.09-2.16 (m, 2H, CH_2), 2.26-2.35 (m, 2H, CH_2);

^{13}C-NMR (100.65 MHz): δ = 16.9 (7-*C*), 21.8 (CH_2), 23.3 (CH_2), 27.7 (CH_2), 30.8 (CH_2), 126.8 (6-*C*), 143.5 (1-*C*);

MS (EI, 70 eV): m/z (%) = 394 (M^+, 100), 128 ([M^+ – 266], 94), 288 ([M^+ – 106], 45), 219 ([M^+ – 175], [C_4F_9•], 43), 131 ([M^+ – 263], 37), 153 ([M^+ – 241], 34) , 315 ([M^+ – 79], 23) , 234 ([M^+ – 160], 22) , 301 ([M^+ – 93], 15);

HRMS: calculated for $C_{11}H_{11}O_3F_9S$ (M^+) 394.0285, found 394.0285.

Synthesis of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 1-ethyl-1,2,5,6-tetrahydro-pyridin-3-yl ester 28h



28h

The synthesis was carried out according to the general procedure GP-1.

1-Ethylpiperidin-3-one **27h**: 130.8 mg, 1.03 mmol,

NfF **7**: 387 mg, 1.28 mmol,

P_1-base **29**: 402.1 mg, 1.29 mmol,
1 ml DMF.

After column chromatography **28h** was obtained as yellowish oil (315 mg, 0.77 mmol, 75% yield). The chromatography was conducted with 5% of NEt_3 in the eluent *n*-pentane.

The product turned out to be slightly unstable even if stored in the fridge at 4°C. At this temperature the previously yellowish compound turns into an orange to deep red coloured oil within a few days. ^{1}H-NMR analysis showed the formation of side products which were not further analyzed. Therefore compound **28h** was either used within a short time after preparation or stored at –80°C (systematic investigations were not carried out, but it seems to be the case that the compound can be stored at this temperature for several weeks without signs of degradation).

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 1.13 (t, $^3J_{H,H}$ = 7.2, 3 H, CH_2-C*H*$_3$), 2.30-2.35 (m, 2 H, C*H*$_2$), 2.53-2.60 (m, 4 H, C*H*$_2$), 3.13 (s, 2 H, C-C*H*$_2$) 5.85 (m, 1 H, C*H*=C);

^{13}C-NMR (100.65 MHz): δ = 12.2 (*C*H$_3$), 24.2 (*C*H$_2$), 48.4 (N-*C*H$_2$), 51.2 (N-*C*H$_2$), 52.5 (N-*C*H$_2$), 116.5 (*C*H), 146.0 (*C*=CH);

MS (EI, 70 eV): m/z (%) = 126 ([M^+ – 282], [$C_7H_{12}NO$•], 100), 407 (M^+, 86), 306 ([M^+ – 102], 55), 69 ([M^+ – 339], [CF_3•], 51), 97 ([M^+ – 311], 47), 82 ([M^+ – 326], 36), 98 ([M^+ – 310], 27);

HRMS: calculated for $C_{11}H_{12}O_3NF_9S$ (M^+) 408.0310, found 408.0317.

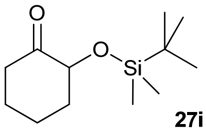
The synthesis was alternatively carried out with lithium bis(trimethylsilyl)amide as the base.
1-Ethylpiperidin-3-one **27h**: 255 mg, 2.0 mmol,
NfF **7**: 1.090 g, 3.60 mmol,
n-BuLi (2.5 M): 1.12 ml, 2.8 mmol,
HMDS: 0.6 ml, 452 mg, 2.8 mmol
18 ml THF.

In a dry one-necked round bottom flask equipped with magnetic stirring bar and a three way tap 15 ml of THF are cooled to 5°C and *n*-BuLi gets added via syringe in an argon atmosphere. The solution is cooled to -5°C and HMDS is added dropwise under vigorous stirring. The resulting yellowish mixture is stirred for 15 minutes at 0°C and subsequently cooled to -78°C. Within 5 minutes the ketone is added dropwise in 3 ml of THF. The solution is stirred for 1 hour at the same temperature. NfF **7** is added slowly and the mixture is stirred for additional 30 minutes at -78°C. Within 90 minutes the solution is warmed up slowly to room temperature. THF gets removed and the residue is taken up into 25 ml of *n*-pentane. The organic phase is washed with 10 ml of a 10% $NaHCO_3$ solution. The aqueous phase is washed 3 times with 10 ml of *n*-pentane. The unified organic phases are washed with 25 ml of brine and get dried over Na_2SO_4. The solvent gets evaporated at 50 mbar and the crude product is obtained as orange colored oil. The compound is characterized as such without further purification (742 mg, 1.81 mmol, 91% yield).

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 1.13 (t, $^3J_{H,H}$ = 7.2, 3 H, CH_2-C*H_3*), 2.30-2.35 (m, 2 H, C*H_2*), 2.53-2.60 (m, 4 H, C*H_2*), 3.13 (s, 2 H, C-C*H_2*) 5.85 (m, 1 H, C*H*=C);

^{13}C-NMR (100.65 MHz): δ = 12.2 (*C*H_3), 24.2 (*C*H_2), 48.4 (N-*C*H_2), 51.2 (N-*C*H_2), 52.5 (N-*C*H_2), 116.5 (*C*H), 146.0 (*C*=CH).

Synthesis of 2-(*tert*-butyl-dimethyl-silanyloxy)-cyclohexanone 27i



27i

As the starting material for the synthesis of **27i** served dodecahydrodibenzo[b,e][1,4]dioxine-4a,9a-diol (2-hydroxycyclohexanone dimer).

2-Hydroxycyclohexanone dimer: 571.8 mg, 5.0 mmol (related to the monomer),
TBDMSCl: 1.04 g, 7.0 mmol,
DBU **20**: 1.144 g, 7.50 mmol,
6 ml THF.

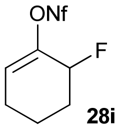
In a dry one-necked round bottom flask equipped with magnetic stirring bar and a three way tap the 2-hydroxycyclohexanone dimer gets suspended in 5 ml of THF in an argon atmosphere. TBDMSCl is added in 1 ml of THF. While stirring DBU **20** is added dropwise. Subsequently the reaction mixture is warmed to 40°C and stirred for 16 hours maintaining this temperature. The suspension is cooled to 5°C and 6 ml of water are added. The aqueous phase is extracted 4 times with each 30 ml of *n*-hexane. The unified organic phases are washed with 25 ml brine, dried over Na_2SO_4 and the solvent gets evaporated. Kugelrohr distillation of the resulting crude yellow oil furnishes **27i** as colorless oil (1.056 g, 0.95 mmol, 4.62 mmol, 92% yield).

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 0.02 (s, 3 H, Si-C*H_3*), 0.09 (s, 3 H, Si-C*H_3*), 0.89 (s, 9 H, Si-C(C*H_3*)$_3$), 1.54-1.80 (m, 3 H, C*H_2*), 1.86-1.94 (m, 2 H, C*H_2*), 2.03-2.13 (m, 1 H, C*H_2*), 2.18-2.26 (m, 1 H, C*H_2*), 2.50-2.57 (m, 1 H, C*H_2*), 4.10 (m, 1 H, C*H*);

^{13}C-NMR (100.65 MHz): δ = -5.3 (Si-*C*H_3), -4.7 (Si-*C*H_3), 18.4 (Si-*C*(CH_3)$_3$), 22.9 (*C*H_2), 25.8 (Si-C(*C*H_3)$_3$), 27.5 (*C*H_2), 37.1 (*C*H_2), 40.1 (*C*H_2), 76.8 (*C*-OSiC(CH_3)$_3$), 209.9 (*C*=O).

Analytical data match well those described in literature.[100]

Synthesis of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 6-fluoro-cyclohex-1-enyl ester 28i



28i

The synthesis was carried out according to the general procedure GP-1.

2-(*tert*-Butyl-dimethyl-silanyloxy)-cyclohexanone **27i**: 228.4 mg, 1.0 mmol,
NfF **7**: 708 mg, 2.34 mmol,
P_1-base **29**: 718.6 mg, 2.30 mmol,
1 ml DMF.

After column chromatography **28h** was obtained as colorless oil (242 mg, 0.61 mmol, 61% yield).

^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 1.68-2.43 (m, 6 H, C*H*$_2$), 5.0 (d, $^2J_{H,F}$ = 50 Hz, 1 H, C*H*-F), 6.16 (m, 1 H, C*H*);

^{13}C-NMR (100.65 MHz): δ = 16.2 (d, $J_{C,F}$ = 0.9 Hz, CH$_2$), 24.4 (d, $J_{C,F}$ = 2.8 Hz, CH$_2$), 29.5 (d, $^2J_{C,F}$ = 21.1 Hz, CH$_2$), 84.3 (d, $^1J_{C,F}$ = 173.2 Hz, CHF), 126.0 (d, $^3J_{C,F}$ = 6.6 Hz, *C*H=C), 145.6 (d, $^2J_{C,F}$ = 17.5 Hz, CH=*C*);

MS (EI, 70 eV): m/z (%) = 288 ([M$^+$ – 110], 100), 69 ([M$^+$ – 329], [CF$_3$•], 50), 95 ([M$^+$ – 303], 20), 131 ([M$^+$ – 267], 20), 398 (M$^+$, 18);

HRMS: calculated for $C_{10}H_8O_3F_{10}S$ (M$^+$) 398.0034, found 397.9995.

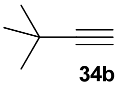
GP-2 General procedure for the synthesis of terminal alkynes and allenes from carbonyl precursors (unless stated otherwise):

Into a dry one-necked round bottom flask equipped with magnetic stirring bar and a three way tap DMF, the carbonyl compound and NfF **7** are added consecutively under an argon atmosphere (all via syringe). The reaction mixture is cooled to 0°C and under vigorous stirring the P-base **29**/**30** is added dropwise. The mixture is stirred for additional 30 min while maintaining the temperature. The three way tap is replaced with a glass stopper and the flask gets closed tightly. The solution is warmed up to room temperature and is stirred for the stated time (see Table 5, 6 and 7 for alkynes, Table 8 for allenes and Table 12 for aldehydes; reaction control via ^{1}H-NMR). The reaction mixture is either poured directly onto a column packed with silica gel and flash chromatographed with *n*-pentane to obtain the pure product or diluted with water (5 ml / mmol carbonyl compound) followed by extraction of the aqueous phase with n-pentane (4 * 25 ml / mmol carbonyl compound). The combined organic phases are subsequently washed with water (20 ml / mmol carbonyl compound) and dried over

$MgSO_4$. In this case a crude compound is obtained after careful evaporation of the solvent and final flash chromatography with *n*-pentane over a short column of silica furnishes the pure product.

The stated solvent amounts for aqueous workup were employed for 1-2 mmol reactions in order to minimize potential losses during the purification steps. This amount is reduced to the half for 3-4 mmol batches.

Synthesis of 3,3-dimethyl-but-1-yne 34b



34b

The synthesis was carried out according to the general procedure GP-2.

Pinacolone **33b**: 102 mg, 1.02 mmol,

NfF **7**: 372 mg, 1.23 mmol,

P_2-base **30**: 1.15 ml, 2.3 mmol,

1 ml DMF.

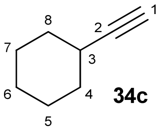
Distillation (200 mbar, 30 minutes) of alkyne **34b** out of the reaction solution and condensation into a cold trap (dry ice / methanol) afforded 80 mg of a colorless liquid consisting of compound **34b**, THF and DMF in a ratio of 0.4:0.52:0.08 (^{1}H-NMR). These numbers correspond to a calculated amount of 32 mg of **34b** (0.39 mmol, 38% yield). Product **34b** could still be detected in the reaction mixture after the distillation.

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 1.25 (s, 9 H, C*H*$_3$), 2.07 (s, 1 H, C*H*);

^{13}C-NMR (100.65 MHz): δ = 27.2 (*C*-$(CH_3)_3$), 30.9 (*C*H$_3$), 66.4 (C≡*C*H), 93.2 (*C*≡CH).

Analytical data match well those described in literature.[101]

Synthesis of ethynyl-cyclohexane 34c



34c

The synthesis was carried out according to the general procedure GP-2. The P_2-base **30** was added slowly dropwise at -10°C.

1-Cyclohexylethanone **33c**: 259.5 mg, 2.06 mmol,

NfF **7**: 745 mg, 2.47 mmol,

P_2-base **30**: 2.4 ml, 4.8 mmol, (2.0 M solution in THF),

2 ml DMF.

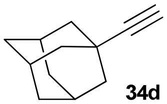
After column chromatography of the crude reaction mixture **34c** was obtained as yellowish oil (177.4 mg, 1.64 mmol, 80% yield).

^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 1.23-1.37 (m, 3 H, CH$_2$-C*H*$_2$), 1.39-1.56 (m, 3 H, CH$_2$-C*H*$_2$), 1.66-1.75 (m, 2 H, CH-C*H*$_2$), 1.78-1.85 (m, 2 H, CH-C*H*$_2$), 2.04 (d, $^4J_{HH}$ = 2.3 Hz, 1 H, C≡C*H*), 2.34-2.41 (m, 1 H, CH$_2$-C*H*);

^{13}C-NMR (100.65 MHz): δ = 24.8 (5,7-*C*H$_2$), 25.8 (6-*C*H$_2$), 28.8 (3-*C*H), 32.5 (4,8-*C*H$_2$), 67.8 (1-*C*H), 89.0 (2-*C*).

Analytical data match well those described in literature.[101]

Synthesis of 1-ethynyl-adamantane 34d



34d

The synthesis was carried out according to the general procedure GP-2. The P$_2$-base **30** was added slowly dropwise at -10°C.

1-Adamantylethanone **33d**: 180.2 mg, 1.010 mmol,

NfF **7**: 371 mg, 1.23 mmol,

P$_2$-base **30**: 1.2 ml, 2.40 mmol, (2.0 M solution in THF),

1 ml DMF.

After aqueous workup and column chromatography **34d** was obtained as white crystals (116.4 mg, 0.73 mmol, 72% yield).

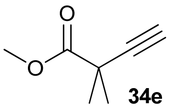
^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 1.69 (dd, $^3J_{H,H}$ = 2.8 Hz, 6 H, CH-C*H*$_2$-CH), 1.89 (d, $^3J_{H,H}$ = 2.8 Hz, 6 H, CH-C*H*$_2$-C), 1.96 (bs, 3 H, C*H*), 2.10 (s, 1 H, C≡C*H*);

^{13}C-NMR (100.65 MHz): δ = 27.9 (*C*H), 29.4 (*C*-(CH$_2$-)$_3$), 36.3 (*C*H$_2$), 42.8 (*C*H$_2$), 66.6 (C≡*C*H), 93.1 (*C*≡CH);

MS (EI, 80 eV): m/z (%) = 160 (M$^+$, 100), 117 ([M$^+$ – 43], 45), 145 ([M$^+$ – 15], 41), 91 ([M$^+$ – 69], 37), 103 ([M$^+$ – 57], 31) 131 ([M$^+$ – 29], 30), 79 ([M$^+$ – 81], 27).

Analytical data match well those described in literature.[102]

Synthesis of 2,2-dimethyl-but-3-ynoic acid methyl ester 34e



34e

The synthesis was carried out according to the general procedure GP-2.

Methyl 2,2-dimethyl-3-oxobutanoate **33e**: 434.3 mg, 3.01 mmol,

NfF **7**: 1.38 g, 4.57 mmol,

P_1-base **29**: 2.840 g, 9.10 mmol,

3 ml DMF.

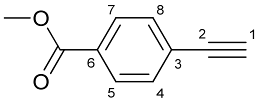
After aqueous workup *n*-pentane was removed under reduced pressure of ≥300 mbar and subsequent Kugelrohr distillation (54°C, 75 mbar) afforded **34e** as colorless oil (166 mg, 1.32 mmol, 44% yield).

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 1.50 (s, 6 H, C-(C*H*$_3$)$_2$, 2.29 (s, 1 H, C≡C*H*), 3.77 (s, 3 H, O-C*H*$_3$);

^{13}C-NMR (100.65 MHz): δ = 27.2 (*C*H$_3$), 38.0 (*C*-CH$_3$), 52.9 (O-*C*H$_3$), 70.0 (C≡*C*H), 86.2 (*C*≡CH), 173.9 (*C*=O).

Analytical data match well those described in literature.[103]

Synthesis of 4-ethynyl-benzoic acid methyl ester 36a



36a

The synthesis was carried out according to the general procedure GP-2.

Methyl 4-acetylbenzoate **35a**: 179 mg, 1.0 mmol,

NfF **7**: 367 mg, 1.21 mmol,

P_1-base **29**: 747 mg, 2.39 mmol,

1 ml DMF.

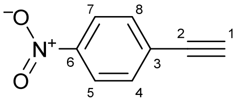
After column chromatography (*n*-pentane : MTBE = 15 : 1) of the crude reaction mixture **36a** was obtained as white solid (156 mg, 0.97 mmol, 97% yield).

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 3.16 (s, 1 H, C≡C*H*), 3.84 (s, 3 H, O-C*H*$_3$), 7.47 (d, $^3J_{H,H}$ = 8.0, 2 H, C_6H_5), 7.92 (d, $^3J_{H,H}$ = 8.0, 2 H, C_6H_5);

^{13}C-NMR (100.65 MHz): δ = 52.3 (O-CH$_3$), 80.1 (C≡CH), 82.8 (*C*≡CH), 126.8 (3-*C*), 129.5 (5,7-*C*), 130.2 (6-*C*), 132.1 (4,8-*C*), 166.4 (*C*=O).

Analytical data match well those described in literature.[104]

Synthesis of 1-ethynyl-4-nitro-benzene 36b



36b

The synthesis was carried out according to the general procedure GP-2. The P_1-base **29** was added slowly dropwise at -20°C.

1-(4-Nitrophenyl)ethanone **35b**: 200 mg, 1.21 mmol,

NfF **7**: 460 mg, 1.52 mmol,

P_1-base **29**: 914 mg, 2.93 mmol,

1 ml DMF.

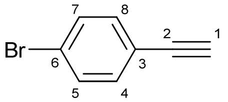
After column chromatography (*n*-pentane : MTBE = 2 : 1) of the crude reaction mixture **36b** was obtained as ochre colored solid (160.2 mg, 1.09 mmol, 90% yield).

^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 3.36 (s, 1 H, C≡C*H*), 7.64 (d, $^3J_{H,H}$ = 8.8, 2 H, C_6H_5), 8.20 (d, $^3J_{H,H}$ = 8.8, 2 H, C_6H_5);

^{13}C-NMR (100.65 MHz): δ = 81.6 (*C*≡CH), 82.3 (C≡*C*H), 123.6 (5,7-*C*), 128.9 (3-*C*), 133.0 (4,8-*C*), 147.5 (6-*C*).

Analytical data match well those described in literature.[104]

Synthesis of 1-bromo-4-ethynyl-benzene 36c



36c

The synthesis was carried out according to the general procedure GP-2. The P_1-base **29** was added slowly dropwise at -10°C.

1-(4-Bromophenyl)ethanone **35c**: 202 mg, 1.02 mmol,

NfF **7**: 370 mg, 1.22 mmol,

P_1-base **29**: 750 mg, 2.40 mmol,

1 ml DMF.

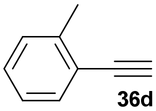
After column chromatography of the crude reaction mixture **36c** was obtained as yellow solid (169 mg, 0.93 mmol, 92% yield).

^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 3.12 (s, 1 H, C≡C*H*), 7.35 (d, $^3J_{H,H}$ = 8.5, 2 H, C_6H_5), 7.46 (d, $^3J_{H,H}$ = 8.5, 2 H, C_6H_5);

^{13}C-NMR (100.65 MHz): δ = 78.4 (C≡*C*H), 82.6 (*C*≡CH), 121.1 (3-*C*), 123.2 (6-*C*), 131.7 (5,7-*C*), 133.6 (4,8-*C*).

Analytical data match well those described in literature.[105]

Synthesis of 1-ethynyl-2-methyl-benzene 36d


36d

The synthesis was carried out according to the general procedure GP-2.

1-Tolylethanone **35d**: 136.5 g, 1.02 mmol,

NfF **7**: 368 mg, 1.22 mmol,

P_1-base **29**: 750 mg, 2.40 mmol,

1 ml DMF.

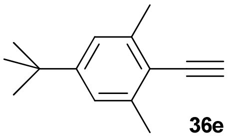
After aqueous workup and column chromatography **36d** was obtained as yellowish oil (91 mg, 0.78 mmol, 77% yield).

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 2.37 (s, 3 H, C_{Ar}-C*H*$_3$), 3.18 (m, 1 H, C≡C*H*), 7.03-7.06 (m, 1 H, C_6*H*$_5$), 7.01-7.17 (m, 2 H, C_6*H*$_5$), 7.37 (d, $^3J_{H,H}$ = 7.6, 1 H, C_6*H*$_5$);

^{13}C-NMR (100.65 MHz): δ = 19.5 (*C*H_3), 79.9 (C≡*C*H), 81.5 (*C*≡CH), 120.9 (*C*$_{Ar}$-C≡CH), 124.5 (*C*$_{Ar}$H), 127.7 (*C*$_{Ar}$H), 128.4 (*C*$_{Ar}$H), 131.5 (*C*$_{Ar}$H), 139.7 (*C*$_{Ar}$-CH_3).

Analytical data match well those described in literature.[106]

Synthesis of 5-*tert*-butyl-2-ethynyl-1,3-dimethyl-benzene 36e


36e

The synthesis was carried out according to the general procedure GP-2. Reaction control after 20 hours indicated 81% conversion. The reaction mixture was heated for additional 32 hours at 50°C leading to a final conversion of 90%.

1-(4-*tert*-Butyl-2,6-dimethylphenyl)ethanone **35e**: 204.5 mg, 1.0 mmol,

NfF **7**: 375 mg, 1.24 mmol,

P_1-base **29**: 1.040 g, 3.33 mmol,

1 ml DMF.

After aqueous workup and column chromatography **36e** was obtained as yellowish oil (117 mg, 0.63 mmol, 63% yield).

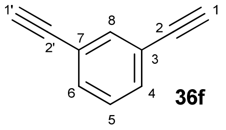
^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 1.29 (s, 9 H, C_{Ar}-(C*H*$_3$)$_3$), 2.44 (s, 6 H, C_{Ar}-C*H*$_3$), 3.44 (s, 1 H, C≡C*H*), 7.06 (s, 2 H, C_6*H*$_5$);

^{13}C-NMR (100.65 MHz): δ = 21.3 (*C*H_3), 31.2 (C-(*C*H_3)$_3$), 34.5 (*C*-(CH_3)$_3$), 81.4 (*C*≡CH), 84.5 (C≡*C*H), 119.1 (*C*$_{Ar}$-C≡CH), 123.8 (*C*$_{Ar}$H), 140.5 (*C*$_{Ar}$-CH_3), 151.3 (*C*$_{Ar}$-C(CH_3)$_3$);

MS (EI, 80 eV): m/z (%) = 171 ([M^+ – 15], [CH_3•], 100), 186 (M^+, 25), 143 ([M^+ – 43], 10), 128 ([M^+ – 58], 10), 156 ([M^+ – 30], 2x[CH_3•], 8), 115 ([M^+ – 71], 7);

HRMS: calculated for $C_{14}H_{18}$ (M^+) 186.1409, found 186.1421.

Synthesis of 1,3-diethynyl-benzene 36f



The synthesis was carried out according to the general procedure GP-2. The P_1-base **29** was added slowly dropwise at -20°C.

1,1'-(1,3-Phenylene)diethanone **35f**: 175 mg, 1.08 mmol,

NfF **7**: 788 mg, 2.61 mmol,

P_1-base **29**: 1.57 g, 5.0 mmol,

1 ml DMF.

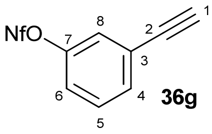
After aqueous workup and column chromatography **36f** was obtained as yellowish oil (105.5 mg, 0.84 mmol, 78% yield).

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 3.09 (s, 2 H, C≡C*H*), 7.28 (t, $^3J_{H,H}$ = 7.8 Hz, 1 H, 4-C_6H_5), 7.46 (d, $^3J_{H,H}$ = 7.8 Hz, 2 H, 3,5-C_6H_5), 7.62 (s, 1 H, 7-C_6H_5);

^{13}C-NMR (100.65 MHz): δ =78.1 (C≡*C*H), 82.7 (*C*≡CH), 122.6 (3,7-C_{Ar}), 128.6 (5-C_{Ar}), 132.5 (4,6-C_{Ar}), 135.8 (8-C_{Ar});

Analytical data match well those described in literature.[107]

Synthesis of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 3-ethynyl-phenyl ester 36g



The synthesis was carried out according to the general procedure GP-2.

1-(3-Hydroxyphenyl)ethanone **35g**: 545 mg, 4.0 mmol,

NfF **7**: 2.185 g, 7.23 mmol,

P_1-base **29**: 4.530 g, 14.5 mmol,

4 ml DMF.

After aqueous workup and column chromatography **36g** was obtained as slightly yellowish oil (780 mg, 1.95 mmol, 49% yield).

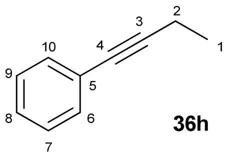
^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 3.18 (s, 1 H, C≡C*H*), 7.25-7.7.32 (m, 1 H, C_6H_5), 7.39-7.46 (m, 2 H, C_6H_5), 7.48-7.54 (m, 1 H, C_6H_5);

^{13}C-NMR (100.65 MHz): δ = 79.5 (1-*C*), 81.4 (2-*C*), 121.9 (4-*C*), 124.7 (3-*C*), 124.9 (C_{Ar}H), 130.2 (C_{Ar}H), 132.1 (C_{Ar}H), 149.4 (5-*C*);

MS (EI, 80 eV): m/z (%) = 89 ([M$^+$ – 311], [C_7H_5•], 100), 101 ([M$^+$ – 298.9], [C_8H_5•], 90), 117 ([M$^+$ – 117], [C_8H_5O•], 58), 399.9 (M$^+$, 55) 131 ([M$^+$ – 269], 31), 336 ([M$^+$ – 64], 26);

HRMS: calculated for $C_{12}H_5O_3F_9S$ (M$^+$) 399.9816, found 399.9840.

Synthesis of but-1-ynyl-benzene 36h



36h

The synthesis was carried out according to the general procedure GP-2. The P$_1$-base **29** was added slowly dropwise at -10°C.

1-Phenylbutan-1-one **35h**: 148.3 mg, 1.0 mmol,
NfF **7**: 380 mg, 1.25 mmol,
P$_1$-base **29**: 755 mg, 2.42 mmol,
1 ml DMF.

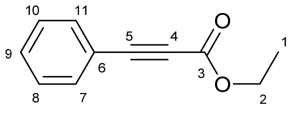
After column chromatography of the crude reaction mixture **36h** was obtained as colorless oil (123.4 mg, 0.95 mmol, 95% yield).

^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 1.10 (t, $^3J_{H,H}$ = 7.5 Hz, 3 H, CH$_2$-C*H*$_3$), 2.28 (q, $^3J_{H,H}$ = 7.5 Hz, 2 H, C*H*$_2$-CH$_3$), 7.09-7.17 (m, 3 H, C_6H_5), 7.23-7.28 (m, 2 H, C_6H_5);

^{13}C-NMR (100.65 MHz): δ = 13.1 (2-*C*), 13.9 (1-*C*), 79.9 (4-*C*), 91.7 (3-*C*), 124.0 (5-*C*), 127.5 (8-*C*), 128.2 (C_{Ar}H), 131.5 (C_{Ar}H).

Analytical data match well those described in literature.[108]

Synthesis of phenyl-propynoic acid ethyl ester 36i



36i

The synthesis was carried out according to the general procedure GP-2.

Ethyl 3-oxo-3-phenylpropanoate **35i**: 390 mg, 2.03 mmol

NfF **7**: 750 mg, 2.48 mmol,

P_1-base **29**: 1.42 g, 4.54 mmol,

2 ml DMF.

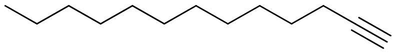
After column chromatography of the crude reaction mixture **36i** was obtained as yellowish oil (290 mg, 1.66 mmol, 82% yield).

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 1.35 (t, $^3J_{H,H}$ = 7.2, 3 H, CH_2-CH_3), 4.29 (q, $^3J_{H,H}$ = 7.2, 2 H, CH_2-CH_3), 7.36 (dd, $^3J_{H,H}$ = 7.4 Hz, 2 H, C_6H_5), 7.44 (dd, $^3J_{H,H}$ = 7.4 Hz, 1 H, C_6H_5) 7.58 (d, $^3J_{H,H}$ = 7.4 Hz, 2 H, 7,11-C*H*);

^{13}C-NMR (100.65 MHz): δ = 14.1 (1-*C*), 62.1 (2-*C*), 80.7 (4-*C*), 86.0 (5-*C*), 119.6 (6-*C*), 128.6 (8,10-*C*), 130.6 (9-*C*), 133.0 (7,11-*C*), 154.1 (3-*C*).

Analytical data match well those described in literature.[109]

Synthesis of tridec-1-yne 38a



38a

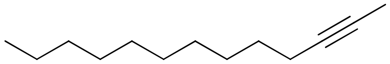
The detailed reaction data for the experimental series is stated in Chapter 7.3.3.

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, C*H*$_3$), 1.20-1.57 (m, 18 H, C*H*$_2$), 1.93 (t, $^4J_{H,H}$ = 2.6 Hz, 1 H, C≡C*H*), 2.18 (dt, $^3J_{H,H}$ = 7.1 Hz, $^4J_{H,H}$ = 2.6 Hz, 2 H, HC≡C-C*H*$_2$-);

^{13}C-NMR (100.65 MHz): δ = 14.1, 18.4, 22.7, 28.5, 28.8, 29.2, 29.4, 29.6, 29.7 (2C), 32.0, 68.2 (C≡*C*H), 84.9 (*C*≡CH).

Analytical data match well those described in literature.[110]

Synthesis of tridec-2-yne 38b



38b

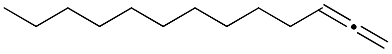
Compound **38b** accompanied the desired tridec-1-yne **38a** formation and was obtained in the systematical investigations in varying amounts (for detailed reaction description see Chapter 7.3.3.). Alkynes **38a** and **38b** were not separated.

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 0.88 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, C*H*$_3$), 1.20-1.57 (m, 18 H, C*H*$_2$),1.78 (t, $^5J_{H,H}$ = 2.5 Hz , 3 H, C≡C-C*H*$_3$), 2.11 (m, 2 H, -C≡C-C*H*$_2$-);

^{13}C-NMR (100.65 MHz): δ = 3.6 (C≡C-*C*H$_3$), 18.8, 29.0, 29.1, 29.2, 29.6, 29.65, 75.4 (C≡*C*-CH$_3$), 79.6 (*C*≡C-CH$_3$).

Analytical data match well those described in literature.[111]

Synthesis of trideca-1,2-diene 38c



38c

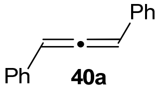
Within the systematical investigations compound **38c** was detected as side product in one reaction (Table 7, Entry 3) in circa 1% (for detailed reaction description see Chapter 7.3.3.). Allene **38c** was not separated from the major product alkynes **38a** and **38b**.

Selected signals:

^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 2.0 (qt, $J_{H,H}$ = 6.8, 1 H, CH_2-CH), 4.64 (dt, $J_{H,H}$ = 6.8, $J_{H,H}$ = 3.2, 2 H, C=CH_2), 5.09 (q, $J_{H,H}$ = 6.8, 1 H, CH=C=CH_2);

Analytical data match well those described in literature.[112]

Synthesis of 1,3-diphenyl-propa-1,2-diene 40a



40a

The synthesis was carried out according to the general procedure GP-2. The P$_1$-base **29** was added slowly dropwise at -10°C.

1,3-Diphenylpropan-2-one **39a**: 225 mg, 1.07 mmol

NfF **7**: 390 mg, 1.29 mmol,

P$_1$-base **29**: 735 mg, 2.41 mmol,

1 ml DMF.

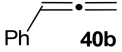
After column chromatography of the crude reaction mixture **40a** was obtained as yellowish oil (199 mg, 1.035 mmol, 97% yield).

^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 6.51 (s, 2 H, C=CH), 7.12-7.16 (m, 2 H, C$_6H_5$), 7.21-7.29 (m, 8 H, C$_6H_5$);

^{13}C-NMR (100.65 MHz): δ = 98.5, 127.0, 127.4, 128.8, 133.6, 207.8.

Analytical data match well those described in literature.[113]

Synthesis of propa-1,2-dienyl-benzene 40b



40b

The synthesis was carried out according to the general procedure GP-2. The P_1-base **29** was added slowly dropwise at -10°C.

3-Phenylpropanal **39b**: 135.7 mg, 1.01 mmol,

NfF **7**: 367 mg, 1.22 mmol,

P_1-base **29**: 752 mg, 2.40 mmol,

1 ml DMF.

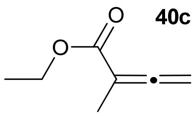
After column chromatography of the crude reaction mixture, washing of the eluent with 10 ml of water and drying over Na_2SO_4 **40a** was obtained as slightly yellowish oil (90 mg, 0.78 mmol, 77% yield).

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 5.13 (d, $^4J_{H,H}$ = 6.8 Hz, 2 H, $C{=}CH_2$), 6.16 (t, $^4J_{H,H}$ = 6.8 Hz, 1 H, C=CH), 7.13-7.24 (m, 1 H, C_6H_5), 7.28-7.31 (m, 4 H, C_6H_5);

^{13}C-NMR (100.65 MHz): δ = 78.8, 94.0 (both allene), 126.7, 126.9, 128.6, 133.9, 209.8 (=*C*=).

Analytical data match well those described in literature.[114]

Synthesis of 2-methyl-buta-2,3-dienoic acid ethyl ester 40c


40c

The synthesis was carried out according to the general procedure GP-2. The P_1-base **29** was added slowly dropwise at -20°C.

Ethyl 2-methyl-3-oxobutanoate **39c**: 290.6 mg, 2.02 mmol,

NfF **7**: 742 mg, 2.45 mmol,

P_1-base **29**: 1.5 g, 2.40 mmol,

2 ml DMF.

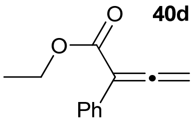
After aqueous workup with MTBE as the extraction solvent and subsequent column chromatography (*n*-pentane : MTBE = 5 : 1) **40c** was obtained as slightly yellowish oil (223 mg, 1.77 mmol, 88% yield).

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 1.28 (t, $^3J_{H,H}$ = 7.1, 3 H, $CH_2\text{-}CH_3$), δ = 1.88 (t, $^5J_{H,H}$ = 3.1, 3 H, $C\text{-}CH_3$), 4.21 (q, $^3J_{H,H}$ = 7.1, 2 H, $CH_2\text{-}CH_3$), 5.07 (q, $^5J_{H,H}$ = 3.1, 2 H, $C{=}CH_2$);

^{13}C-NMR (100.65 MHz): δ = 14.3, 14.8, 61.0, 77.8, 95.5, 167.6, 214.0.

Analytical data match well those described in literature.[115]

Synthesis of 2-phenyl-buta-2,3-dienoic acid ethyl ester 40d

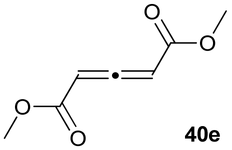

40d

The synthesis was carried out according to the general procedure GP-2. The P_1-base **29** was added slowly dropwise at -20°C.

Ethyl 2-phenyl-3-oxobutanoate **39d**: 433 mg, 2.10 mmol,
NfF **7**: 743 mg, 2.45 mmol,
P_1-base **29**: 1.48 g, 2.39 mmol,
2 ml DMF.

After flash column chromatography (MTBE : *n*-hexane = 20 : 1) of the crude reaction mixture various not further identified side products were obtained.

Synthesis of penta-2,3-dienedioic acid dimethyl ester 40e


40e

The synthesis was carried out according to the general procedure GP-2. The P_1-base **29** was added slowly dropwise at -20°C.

Dimethyl 3-oxopentanedioate **39e**: 407.7 mg, 2.016 mmol,
NfF **7**: 735 mg, 2.433 mmol,
P_1-base **29**: 1.520 g, 4.865 mmol,
2 ml DMF.

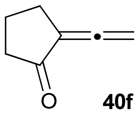
After flash column chromatography of the crude reaction mixture **40e** was obtained as the third of four fractions as yellowish oil accompanied by various side products (58.0 mg, <10% yield).

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 3.74 (s, 6 H, O-C*H*$_3$), 5.99 (s, 2 H, C*H*);

^{13}C-NMR (100.65 MHz): δ = 53.0 (2 x *C*H$_3$), 92.3 (d, 2 x *C*H), 164.0 (2 x *C*=O), 220.0 (=*C*=).

Analytical data match well those described in literature.[116]

Synthesis of 2-vinylidene-cyclopentanone 40f



40f

The synthesis was carried out according to the general procedure GP-2. The P_1-base **29** was added slowly dropwise at -20°C.

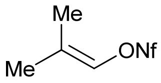
2-Acetylcyclopentanone **39f**: 131 mg, 1.04 mmol,
NfF **7**: 385 mg, 1.27 mmol,
P_1-base **29**: 756 mg, 2.42 mmol,
1 ml DMF.
No product formation was observed for this experiment (see Table 8, discussion for Entry 6).

The synthesis was alternatively carried out with the P_2-base **30** according to the general procedure GP-2. The P_2-base **29** was added slowly dropwise at -30°C.

2-Acetylcyclopentanone **39f**: 256 mg, 2.03 mmol,
NfF **7**: 744 mg, 2.46 mmol,
P_2-base **30**: 2.4 ml, 4.8 mmol, (2.0 M solution in THF),
2 ml DMF.
No product formation was observed for this experiment (see Table 8, discussion for Entry 6).

Alkenyl nonaflates derived from aldehydes were generated by using the general procedure GP-1 (unless stated otherwise):

Synthesis of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 2-methyl-propenyl ester 42a



42a

The synthesis was carried out according to the general procedure GP-1. The P_1-base **29** was added slowly dropwise at -10°C.

2-Methylpropanal **41a**: 731.8 mg, 10.15 mmol,
NfF **7**: 3.489 g, 11.55 mmol,
P_1-base **29**: 3.683 g, 11.79 mmol,
10 ml DMF.

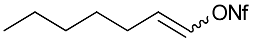
Kugelrohr distillation (84°C, 41 mbar) afforded **42a** as colorless oil (3.205 g, 9.05 mmol, 89% yield).

^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 1.70 (s, 3 H, (*Z*)-C*H*$_3$), δ = 1.76 (s, 3 H, (*E*)-C*H*$_3$), 6.44 (s, 1 H, C*H*);

^{13}C-NMR (100.65 MHz): δ = 15.6 ((*Z*)-CH$_3$), 19.0 ((*E*)-CH$_3$), 125.9 (H$_3$C-*C*), 130.9 (*C*H).

Analytical data match well those described in literature.[17]

Synthesis of (*E*/*Z*)-1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid hept-1-enyl ester (*E*/*Z*)-42b



(*E*/*Z*)-42b

1-Heptanone **41b**: 3.075 g, 26.93 mmol,

NfF **7**: 9.425 g, 31.2 mmol,

P$_1$-base **29**: 8.42 g, 26.95 mmol,

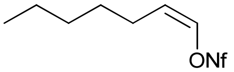
27 ml DMF.

Into a dry one-necked round bottom flask equipped with magnetic stirring bar and a three way tap DMF, 1-heptanone **41b** and NfF **7** are added subsequently via syringe. The reaction mixture is cooled to -35°C and under vigorously stirring the P$_1$-base **29** is added slowly dropwise. With the completed addition the three way tap is replaced by a glass stopper and the flask is closed tightly. The solution is slowly warmed to -30°C and stirred at this temperature for 21 hours (reaction control via ^{1}H-NMR indicated circa 99% conversion). The mixture is diluted with 100 ml of water at circa 10°C followed by 4 times extraction with 120 ml of *n*-pentane. The combined organic phases are washed with 150 ml of water and dried over Na$_2$SO$_4$. Careful evaporation of the solvent at ≥300 mbar pressure furnished a crude yellow colored oil.

After flash column chromatography of the crude product with *n*-pentane (*E*/*Z*)-**42b** was obtained as colorless oil (8.92 g, 22.5 mmol, 84% yield). The product **42b** is obtained as a mixture of the (*Z*)- and (*E*)-isomers in a ratio of 4.2:1.

The compounds (*Z*)-**42b** and (*E*)-**42b** were not separated and analyzed as a mixture:

(*Z*)-42b



(*Z*)-42b

^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 0.89 (t, $^3J_{H,H}$ = 6.9 Hz, 3 H, C*H*$_3$), δ = 1.24-1.45 (m, 6 H, C*H*$_2$), 2.19 (dt, $^3J_{H,H}$ = 7.5 Hz, 2 H, C*H*$_2$-CH), 5.23 (m, 1 H, C*H*=CHONf), 6.58 (d, $^3J_{H,H}$ = 5.6 Hz, 1 H, CH=C*H*ONf);

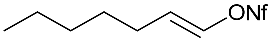
^{13}C-NMR (100.65 MHz): δ = 13.92 (*C*H_3), 22.4 (*C*H_2), 24.2 (*C*H_2), 28.2 (*C*H_2), 31.3 (CH-*C*H_2), 120.4 (*C*H=CHONf), 135.6 (CH=*C*HONf);

MS (EI, 80 eV): m/z (%) = 69 ([M$^+$ – 327], [CF_3•], 100), 275 ([M$^+$ – 121], 68), 81 ([M$^+$ – 315], 57), 131 ([M$^+$ – 265], 46), 219 ([M$^+$ – 177], [C_4F_9•], 40), 396 (M$^+$, 8);

HRMS: calculated for $C_{11}H_{13}O_3F_9S$ (M$^+$) 396.0442, found 396.0461;

C,H,S-analysis (%): calculated for $C_{11}H_{13}O_3F_9S$ (396.27): C, 33.34; H, 3.31; S, 8.09;
found C, 33.14; H, 2.88; S, 8.18.

(*E*)-42b


(*E*)-42b

^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 0.89 (t, $^3J_{H,H}$ = 6.9 Hz, 3 H, C*H*$_3$), δ = 1.24-1.45 (m, 6 H, C*H*$_2$), 2.04 (dt, $^3J_{H,H}$ = 7.2 Hz, 2 H, C*H*$_2$-CH), 5.77 (m, 1 H, C*H*=CHONf), 6.54 (d, $^3J_{H,H}$ = 11.8 Hz, 1 H, CH=C*H*ONf);

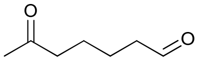
^{13}C-NMR (100.65 MHz): δ = 13.94 (*C*H_3), 22.4 (*C*H_2), 26.6 (*C*H_2), 28.4 (*C*H_2), 31.1 (CH-*C*H_2), 122.5 (*C*H=CHONf), 136.3 (CH=*C*HONf);

MS (EI, 80 eV): m/z (%) = 69 ([M$^+$ – 327], [CF_3•], 100), 275 ([M$^+$ – 121], 68), 81 ([M$^+$ – 315], 57), 131 ([M$^+$ – 265], 46), 219 ([M$^+$ – 177], [C_4F_9•], 40), 396 (M$^+$, 8);

HRMS: calculated for $C_{11}H_{13}O_3F_9S$ (M$^+$) 396.0442, found 396.0461;

C,H,S-analysis (%): calculated for $C_{11}H_{13}O_3F_9S$ (396.27): C, 33.34; H, 3.31; S, 8.09;
found C, 33.14; H, 2.88; S, 8.18.

Synthesis of 6-oxoheptanal 41c


41c

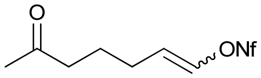
The synthesis is carried out in a three necked round bottom flask equipped with magnetic stirring bar, internal thermometer, condenser and gas inlet. The gas inlet is connected to the ozone generator with pure oxygen supply. 9.682 g (100.7 mmol) of 1-methylcyclohex-1-ene are dissolved in 700 ml dry CH_2Cl_2 and the solution is cooled to -75°C in a dry ice bath. While vigorous stirring ozone is bubbled through the reaction solution (the Ozone generator is adjusted to 9 and the gas flow is kept high so that a continuous strong gas flow is obtained). The reaction mixture is kept below -70°C and ozone is introduced further until the colorless solution turns into a pale blue color after 10 hours indicating saturation of CH_2Cl_2 with Ozone. The reaction mixture is freed from the dissolved Ozone by a stream of Argon (the blue color vanishes). To the solution 40.0 g (152.0 mmol) of PPh_3 dissolved in 40 ml of CH_2Cl_2 are added dropwise while the temperature is still kept at -70°C. The reaction mixture is continued to stir at this temperature for 30 minutes, allowed to come to room temperature slowly and stirred for additional 5 hours. The solvent is removed under reduced pressure and the obtained crude oil is distilled over a Vigreux column. 6-oxoheptanal **41c** is obtained as colorless oil (8.0 g, 62.4 mmol, 62% yield). The product **41c** is stored in the deep freezer at -80°C. No obvious degradation of the compound is observed within months (^{1}H-NMR control).

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 1.58-1.66 (m, 4 H, C*H*$_2$), 2.15 (s, 3 H, C*H*$_3$), 2.43-2.50 (m, 4 H, C*H*$_2$), 9.77 (t, $^3J_{H,H}$ = 1.6, 1 H, C*H*O);

^{13}C-NMR (100.65 MHz): δ = 21.5 (*C*H$_2$), 23.1 (*C*H$_2$), 29.9 (*C*H$_3$), 43.3 (C(O)-*C*H$_2$), 43.7 (C(O)-*C*H$_2$), 202.2 (*C*HO), 208.5 (*C*=O).

Analytical data match well those described in literature.[117]

Synthesis of (*E*/*Z*)-1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 6-oxo-hept-1-enyl ester (*E*/*Z*)-42c


(*E*/*Z*)-42c

6-Oxoheptanal **41c**: 262.2 mg, 2.05 mmol,

NfF **7**: 698 mg, 2.31 mmol,

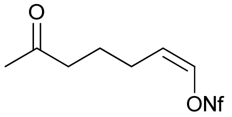
P_1-base **29**: 689 mg, 2.20 mmol,

2 ml DMF.

Into a dry one-necked round bottom flask equipped with magnetic stirring bar and a three way tap DMF, 6-Oxoheptanal **41c** and NfF **7** are added subsequently via syringe. The reaction mixture is cooled to -35°C and under vigorously stirring the P_1-base **29** is added slowly dropwise. With the completed addition the three way tap is replaced quickly by a glass stopper and the flask is closed tightly. The solution is slowly warmed to -30°C and stirred at this temperature for 21 hours (reaction control via ^{1}H-NMR indicated full conversion). The mixture is diluted with 8 ml of water at circa 5°C followed by 4 times extraction with 25 ml of *n*-pentane. The combined organic phases are washed with 20 ml of water and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure furnished a crude yellow colored oil.

After flash column chromatography (*n*-hexane : EtOAc = 1 : 1) of the crude reaction mixture (*E*/*Z*)-**42c** was obtained as yellowish oil (611.3 mg, 1.49 mmol, 73% yield). The product **42c** is obtained as a mixture of (*Z*)- and (*E*)-isomers in a ratio of 4.7:1.

(*Z*)-42c


(*Z*)-42c

^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 1.70 (quint., $^3J_{H,H}$ = 7.4 Hz, 2 H, C*H*$_2$), 2.15 (s, 3 H, C*H*$_3$), 2.21 (dt, $^3J_{H,H}$ = 7.6 Hz, 2 H, HC-C*H*$_2$), 2.46 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, C*H*$_2$-C(O), 5.23 (m, 1 H, C*H*=CHONf), 6.61 (d, $^3J_{H,H}$ = 5.6 Hz, 1 H, CH=C*H*ONf);

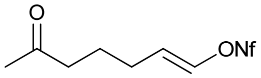
^{13}C-NMR (100.65 MHz): δ = 22.4 (*C*H$_2$), 23.6 (*C*H$_2$), 30.0 (*C*H$_3$), 42.6 (C(O)-*C*H$_2$), 119.4 (*C*H=CHONf), 136.2 (CH=*C*HONf), 208.0 (*C*(O)).

MS (EI, 80 eV): m/z (%) = 219 ([M$^+$ – 191], [C$_4$F$_9$•], 100), 275 ([M$^+$ – 135], 66), 288 ([M$^+$ – 122], 25), 352 ([M$^+$ – 58], 17),410 (M$^+$, 5);

HRMS: calculated for C$_{11}$H$_{11}$O$_4$F$_9$S (M$^+$) 410.0234, found 410.020;

C,H,S-analysis (%): calculated for C$_{11}$H$_{11}$O$_4$F$_9$S (410.253): C, 32.20; H, 2.70; S, 7.82;
found C, 32.57; H, 1.65; S, 7.81.

(*E*)-42c


(*E*)-42c

^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 1.70 (quint., $^3J_{H,H}$ = 7.4 Hz, 2 H, C*H*$_2$), 2.08 (dt, $^3J_{H,H}$ = 7.6 Hz, 2 H, C*H*$_2$-CH), 2.15 (s, 3 H, C*H*$_3$), 2.46 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, C*H*$_2$-C(O), 5.74 (m, 1 H, C*H*=CHONf), 6.56 (d, $^3J_{H,H}$ = 11.8 Hz, 1 H, CH=C*H*ONf);

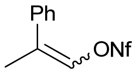
^{13}C-NMR (100.65 MHz): δ = 22.6 (*C*H$_2$), 26.0 (*C*H$_2$), 30.0 (*C*H$_3$), 42.3 (C(O)-*C*H$_2$), 121.7 (*C*H=CHONf), 136.8 (CH=*C*HONf), 207.9 (*C*(O)).

MS (EI, 80 eV): m/z (%) = 219 ([M$^+$ – 191], [C$_4$F$_9$•], 100), 275 ([M$^+$ – 135], 66), 288 ([M$^+$ – 122], 25), 352 ([M$^+$ – 58], 17),410 (M$^+$, 5);

HRMS: calculated for C$_{11}$H$_{11}$O$_4$F$_9$S (M$^+$) 410.0234, found 410.020;

C,H,S-analysis (%): calculated for C$_{11}$H$_{11}$O$_4$F$_9$S (410.253): C, 32.20; H, 2.70; S, 7.82;
found C, 32.57; H, 1.65; S, 7.81.

Synthesis of (*E*/*Z*)-1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 2-phenyl-propenyl ester (*E*/*Z*)-42d

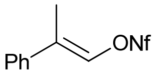

(*E*/*Z*)-42d

The synthesis was carried out according to the general procedure GP-1. The P_1-base **29** was added slowly dropwise at -40°C, kept at a temperature of -30°C for 30 minutes and the reaction was allowed to come to room temperature within 3 hours.

2-Phenylpropanal **41d**: 135 mg, 1.0 mmol,
NfF **7**: 365.5 mg, 1.21 mmol,
P_1-base **29**: 375 mg, 1.2 mmol,
1 ml DMF.

Kugelrohr distillation (80°C, 2.4 10^{-2} mbar) afforded the product (*E*/*Z*)-**42d** as slightly yellowish oil (185 mg, 0.44 mmol, 44% yield). The compound is accomapanied by Prop-1-ynyl-benzene **42e**. The ratio of the product composition of (*E*)-**42d**, (*Z*)-**42d** and **42e** is 5.5:1.0:2.9.

(*E*)-1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 2-phenyl-propenyl ester (*E*)-42d

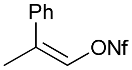

(*E*)-42d

^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 2.15 (d, $^4J_{H,H}$ = 1.4 Hz, 3 H, CH_3), 6.93 (s, 1 H, CH), 7.25-7.40 (m, 5 H, C$_{Ar}H$);

^{13}C-NMR (100.65 MHz): δ = 14.1 (Me), 126.2, 127.7, 128.7, 128.8, 133.4 (*C*H=CHONf), 136.6 (CH=*C*HONf).

Analytical data match well those described in literature.[118a-b]

(*Z*)-1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 2-phenyl-propenyl ester (*Z*)-42d

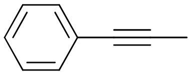

(*Z*)-42d

^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 2.05 (s, 3 H, CH_3), 6.71 (s, 1 H, CH), 7.25-7.40 (m, 5 H, C$_{Ar}H$);

^{13}C-NMR (100.65 MHz): δ = 19.0 (Me), 127.7, 128.41, 128.44, 129.0, 130.5.

Analytical data match well those described in literature.[118a-b]

Prop-1-ynyl-benzene 42e


42e

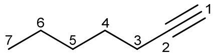
^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 2.05 (s, 3 H, CH_3), 7.25-7.40 (m, 5 H, C$_{Ar}H$);

^{13}C-NMR (100.65 MHz): δ = 4.2 (*C*H$_3$), 79.7 (*C*-CH$_3$), 85.7 (*C*-C$_{Ar}$), 124.0 (*C*$_{Ar}$-C), 127.5, 128.2 (2x*C*$_{Ar}$), 131.5 (2x*C*$_{Ar}$).

Analytical data match well those described in literature.[119]

Terminal alkynes from aldehydes were synthesized according to the general procedure GP-2 (unless stated otherwise):

Synthesis of hept-1-yne 43b



43b

The synthesis was carried out according to the general procedure GP-2.

Heptanal **41b**: 117 mg, 1.02 mmol,
NfF **7**: 356 mg, 1.18 mmol,
P_1-base **29**: 728 mg, 2.33 mmol,
1 ml DMF.

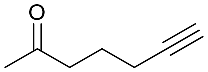
After aqueous work up and subsequent column chromatography **43b** was obtained as colorless oil (65 mg, 0.68 mmol, 66% yield).

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 0.91 (t, $^3J_{H,H}$ = 6.9, 3 H, CH_2-CH_3), δ = 1.64-1.26 (m, 6 H, CH_2), 1.93 (t, $^3J_{H,H}$ = 2.3, 1 H, CH_2-CH_3), 2.15-2.28 (m, 2 H, C-CH_2);

^{13}C-NMR (100.65 MHz): δ = 13.6 (7-*C*), 18.2 (3-*C*), 22.0 (6-*C*), 28.3 (4-*C*), 34.0 (5-*C*), 68.1 (1-*C*), 84.8 (2-*C*).

Analytical data match well those described in literature.[120]

Synthesis of hept-6-yn-2-one 43c



43c

The synthesis was carried out according to the general procedure GP-2.

6-Oxoheptanal **41c**: 259 mg, 2.02 mmol,
NfF **7**: 715 mg, 2.37 mmol,
P_1-base **29**: 1.455 g, 4.657 mmol,
2 ml DMF.

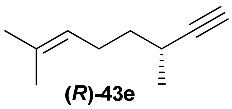
After aqueous workup and subsequent column chromatography **43c** was obtained as colorless oil (169 mg, 1.53 mmol, 76% yield).

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 1.79 (quint, $^3J_{H,H}$ = 7.01 Hz, 2 H, CH_2-CH_2-CH_2), δ = 1.97 (t, $^4J_{H,H}$ = 2.6 Hz, 1 H, C≡C*H*), 2.16 (s, 3 H, CH_2-CH_3), 2.24 (dt, $^3J_{H,H}$ = 6.9 Hz, $^4J_{H,H}$ = 2.6 Hz 2 H, C-CH_2), 2.59 (t, $^3J_{H,H}$ = 7.2 Hz, 2 H, (O=C)-CH_2);

^{13}C-NMR (100.65 MHz): δ = 17.7 (C-CH_2CH_2), 22.2 (CH_2), 30.0 (C(O)-CH_3), 42.0 (CH_2-C=O), 69.0 (C≡*C*H), 83.5 (*C*≡CH), 208.2 (*C*=O).

Analytical data match well those described in literature.[121]

Synthesis of (*R*)-3,7-dimethyl-oct-6-en-1-yne (*R*)-43e


(*R*)-43e

The synthesis was carried out according to the general procedure GP-2.

3,7-Dimethyloct-6-enal **41e**: 184.3 mg, 1.19 mmol,

NfF **7**: 498 mg, 1.65 mmol,

P_1-base **29**: 940 mg, 3.01 mmol,

1 ml DMF.

After column chromatography of the crude reaction mixture (*R*)-**43e** was obtained as colorless oil (124 mg, 0.91mmol, 76% yield).

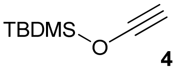
^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 1.18 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, CH-CH_3), δ = 1.38-1.54 (m, 2 H, CH-CH_2), 1.62 (s, 3 H, -C=C-C$_{cis}H_3$), 1.69 (s, 3 H, -C=C-C$_{trans}H_3$), 2.04 (d, $^4J_{H,H}$ = 2.4 Hz, 1 H, C≡CH), 2.13 (m$_c$, 2 H, =CH-CH_2), 2.43 (m$_c$, 1 H, C-CH), 5.10 (t, $^3J_{H,H}$ = 7.0 Hz, 1 H, C=CH);

^{13}C-NMR (100.65 MHz): δ = 17.7, 20.9, 25.2, 25.72, 25.75 (5-*C*), 36.8 (3-*C*), 68.2 (1-*C*), 89.1 (2-*C*), 123.8 (6-*C*), 132.1 (7-*C*);

$[\alpha_D]^{24}$ = -47.4° (c = 1.0, CHCl$_3$).

Analytical data match well those described in literature.[122]

Attempted synthesis of *tert*-butyl-ethynyloxy-dimethyl-silane 43f


43f

The synthesis was carried out according to the general procedure GP-2. The P_1-base **29** was added slowly dropwise at -20°C.

2-(*tert*-butyldimethylsilyloxy)acetaldehyde **41f**: 240 mg, 1.38 mmol, (the starting material was distilled prior to its use and obtained in 99% purity according to ^{1}H-NMR).

NfF **7**: 568 mg, 1.88 mmol,

P_1-base **29**: 999 mg, 3.2 mmol,

1.5 ml DMF.

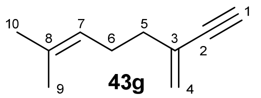
After complete conversion the crude reaction mixture was stored in the deep freezer at -18°C. Aqueous workup was performed after 16 hours. Kugelrohrdistillation (5 mbar / 65°C) afforded 92 mg of a colorless oil which was identified not to be the anticipated product **43f**; the NMR spectrum matches well with *t*-butyldimethylfluorosilane.

^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 0.10 (s, 6 H, Si-CH_3), 0.91 (s, 9 H, Si-C(CH_3)$_3$);

^{13}C-NMR (100.65 MHz, CDCl$_3$): δ = -4.7 [$^2J(^{19}F,^{13}C)$ = 14.9 Hz, F-Si-*C*H$_3$], 18.0 [$^2J(^{19}F,^{13}C)$ = 12.9 Hz, Me$_3$*C*-Si-F], 25.4 [$^3J(^{19}F,^{13}C)$ = 0.7 Hz, *Me$_3$*C-Si-F].

Analytical data match well those described in literature.[44]

Synthesis of 7-methyl-3-methylene-oct-6-en-1-yne 43g



43g

The synthesis was carried out according to the general procedure GP-2. The P$_1$-base **29** was added slowly dropwise at -10°C.

(*E*,*Z*)-3,7-Dimethylocta-2,6-dienal **41g**: 156 mg, 1.03 mmol,

NfF **7**: 471 mg, 1.56 mmol,

P$_1$-base **29**: 945 mg, 3.02 mmol,

1 ml DMF.

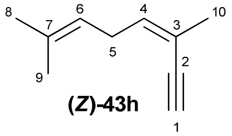
Aqueous workup and subsequent column chromatography afforded **43g** as slightly yellowish oil (120 mg, 0.89 mmol, 87% yield). The compound **43g** was obtained as the major product of a mixture of the regioisomers **43g** and (*Z*)-**43h** in a ratio of 3.2:1 in favor of **43g**.

^{1}H-NMR (400.23 MHz, CDCl$_3$): δ = 1.55 (s, 3 H, 9-CH_3), 1.62 (s, 3 H, 10-CH_3), 2.07-2.19 (m, 4 H, 5,6-CH_2), 2.82 (s, 1 H, 1-C*H*), 4.98-5.07 (m, 1 H, 7-C*H*), 5.22 (s, 1 H, 4-CH_2), 5.35 (s, 1 H, 4-CH_2); ;

^{13}C-NMR (100.65 MHz): δ = 17.7, 25.7, 26.6, 37.1, 76.8 (1-*C*), 84.1 (2-*C*), 122.8, 123.1, 130.5, 132.4.

Analytical data match well those described in literature.[123]

Synthesis of (*Z*)-3,7-dimethylocta-3,6-dien-1-yne (*Z*)-43h



(*Z*)-43h

The synthesis was carried out according to the general procedure GP-2. The P$_1$-base **29** was added slowly dropwise at -10°C.

(*E*,*Z*)-3,7-Dimethylocta-2,6-dienal **41g**: 156 mg, 1.03 mmol,

NfF **7**: 471 mg, 1.56 mmol,

P_1-base **29**: 945 mg, 3.02 mmol,

1 ml DMF.

Aqueous workup and subsequent column chromatography afforded **43h** as slightly yellowish oil (120 mg, 0.89 mmol, 87% yield). The compound **43h** was obtained as the minor product of a mixture of the regioisomers **43g** and (*Z*)-**43h** in a ratio of 3.6:1 in favor of **43g**.

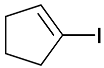
^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 1.58 (s, 3 H, 9-CH_3), 1.63 (s, 3 H, 10-CH_3), 1.78 (m, 3 H, 4'-CH_3), 2.83 (t, $^3J_{H,H}$ = 7.4 Hz 2 H, 6-CH_2), 3.03 (s, 1 H, 1-C*H*), 4.98-5.07 (m, 1 H, 7-C*H*), 5.61 (t, $^3J_{H,H}$ = 7.5 Hz, 1 H, 5'-C*H*);

^{13}C-NMR (100.65 MHz): δ = 17.8, 22.8, 25.7, 29.8, 80.5 (1-*C*), 102.5 (2-*C*), 116.5, 121.3, 132.9, 138.3.

Analytical data match well those described in literature.[123]

7.2.2. Reactions of Chapter 2

Synthesis of 1-iodo-cyclopentene 46



46

The synthesis of 1-iodo-cyclopentene **46** consists of a two step protocol starting from cyclopentanone **27a** via the isolated intermediate cyclopentylidenehydrazine.

Into a two necked round bottom flask equipped with magnetic stirring bar and condenser 6.443 g (76.6 mmol) of cyclopentanone are added slowly to a vigorously stirred solution of 22 ml (~ 450 mmol) hydrazine monohydrate under cooling with an ice bath. The reaction mixture is stirred at room temperature for 1 hour and refluxed for additional 7 hours. The solution is allowed to cool down and is subsequently poured into 80 ml of cold water. The aqueous phase is extracted 4 times with 100 ml of CH_2Cl_2 each. The unified organic phases are washed with 100 ml of brine and dried over $MgSO_4$. Filtration and evaporation of the solvent afforded 5.576g (74%) of cyclopentylidenehydrazine as colourless oil.

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 1.69-1.76 (m, 2 H, CH_2-CH_2), δ = 1.80-1.87 (m, 2 H, CH_2-CH_2), 2.16 (t, $^3J_{H,H}$ = 7.1, 2 H, C-CH_2), 2.34 (t, $^3J_{H,H}$ = 7.1, 2 H, C-CH_2), 4.82 (bs, 2 H, N-NH_2);

Analytical data match well those described in literature.[124]

The hydrazone was used without further purification.

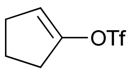
Into a dry three necked round bottom flask equipped with magnetic stirring bar, condenser and addition funnel 100 ml (681 mmol) of freshly distilled tetramethyl guanidine are added to a solution of 31.78 g (125.2 mmol) iodine in 200 ml of dry THF in an argon atmosphere under cooling with an ice bath. After addition the reaction is allowed to come to room temperature and is stirred for additional 2 hours. The reaction mixture is cooled to 0°C and 5.576 g (56.8 mmol) of the hydrazone dissolved in 100 ml of dry THF are added dropwise within 2 hours. The suspension is stirred for additional 13 hours at room temperature and is subsequently heated to 70°C for 2 hours. The reaction mixture is allowed to cool to room temperature and is filtered to remove solids and concentrated at 70 mbar. The solution is reheated for 3 hours to 85°C and after cooling to room temperature 250 ml of *n*-pentane are added. The organic phase is washed three times with 70 ml of a 2N HCl solution, three times with a 50 ml $Na_2S_2O_3$ solution and once with 50 ml of a saturated $NaHCO_3$ solution and 50 ml of brine. Drying over $MgSO_4$, evaporation of *n*-pentane and subsequent Kugelrohr distillation afforded 5.366g (49%) of alkenyl iodide **46** as a colourless oil.

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 1.89-1.97 (m, 2 H, CH_2-C*H*$_2$), δ = 2.29-2.35 (m_c, 2 H, C-C*H*$_2$), 2.57-2.63 (m_c, 2 H, CH-C*H*$_2$), 6.10 (m, 1 H, C=C*H*);

^{13}C-NMR (100.65 MHz): δ = 23.9 (*C*H$_2$), 34.0 (CH-C*H*$_2$), 43.7 (C-C*H*$_2$), 92.6 (*C*-I), 140.0 (C=C*H*).

Analytical data match well those described in literature.[124]

Synthesis of trifluoro-methanesulfonic acid cyclopent-1-enyl ester 47



47

In a 250 ml two necked round bottom flask equipped with magnetic stirrer, condenser and addition funnel a solution of 4.40 g (52.3 mmol) of cyclopentanone **27a** and 4.490 g (56.70 mmol) of pyridine in 50 ml of dry CH_2Cl_2 is cooled down to ≤-70°C and 16 ml (95.0 mmol) of triflic anhydride in 50 ml of dry CH_2Cl_2 are added within 45 minutes. The solution is additionally stirred at this temperature for 30 minutes and subsequently allowed to come to room temperature within 3 hours. After stirring for 14 hours at ambient temperature the solvent gets removed under reduced pressure and the crude viscous mixture is extracted three times with 75 ml *n*-pentane each. The unified organic phases get filtered, dried over Na_2SO_4 and evaporated under reduced pressure. Kugelrohr distillation (10 mbar / 60°C) affords 4.0 g (35%) of the cyclopentenyltriflate **47** as colourless oil.

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 2.0-2.07 (m, 2 H, CH_2-C*H*$_2$), δ = 2.39-2.45 (m_c, 2 H, C-C*H*$_2$), 2.54-2.60 (m_c, 2 H, CH-C*H*$_2$), 5.63 (m, 1 H, C=C*H*);

^{13}C-NMR (100.65 MHz): δ = 20.9 (CH_2), 28.0 (CH-CH_2), 30.9 (C-CH_2), 117.9 (C=*C*H), 149.7 (*C*-O).

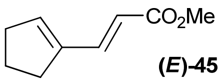
Analytical data match well those described in literature.[125]

7.2.3. Reactions of Chapter 3

GP-3 General procedure for the Heck coupling of isolated alkenyl nonaflates and olefins (unless stated otherwise):

DMF (1 mL), 1 mmol of the alkenyl nonaflate, 1.3 equivalent of the alkene, 2.0 equivalent of Et_3N and $Pd(OAc)_2$ (*ca*. 5 mol.%) are subsequently added to a screw-cap vial equipped with magnetic stirring bar. The reaction mixture is stirred for the designated amount of time (see Tables 26-33) at ambient temperature. Subsequently 4 ml of water are added to the reaction mixture and the aqueous phase is extracted 4 times with 20 ml of *n*-pentane. The combined organic layers are washed with 20 ml of brine and dried over Na_2SO_4. The solvent is removed under reduced pressure and the residue is purified by either column chromatography (silica gel, *n*-hexane : EtOAc = 20 : 1 as eluent unless stated otherwise) or Kugelrohr distillation to give the pure dienes.

Synthesis of (*E*)-methyl 3-cyclopentenyl acrylate (*E*)-45



(*E*)-45

The synthesis was carried out according to the general procedure GP-3.

Cyclopentenyl nonaflate **28a**: 368.8 mg, 1.01 mmol,

Methyl acrylate **44**: 117.4 mg, 1.36 mmol,

NEt_3: 207.5 mg, 2.05 mmol,

$Pd(OAc)_2$: 11.2 mg, 0.049 mmol, 5 mol%,

1 ml DMF.

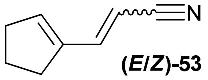
After column chromatography (*E*)-**45** was obtained as white solid (144.4 mg, 0.95 mmol, 94% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.94–2.01 (m, 2 H, CH_2-CH_2), 2.41–2.53 (m, 4 H, CH_2), 3.75 (s, 3 H, OMe), 5.74 (d, ^3J = 15.6 Hz, 1 H, CH=C*H*CO_2Me), 6.18 (m_c, 1 H, C*H*=C), 7.51 (d, ^3J = 15.6 Hz, 1 H, C*H*=CHCO_2Me);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 23.1, 30.8 and 33.5 (all *C*H_2), 51.5 (OMe), 117.7 (*C*H), 140.7, 141.1 (all *C*H), 141.4 (*C*H=*C*), 167.9 (*C*=O).

Analytical data match well those described in literature.[8b]

Synthesis of (*E/Z*)-3-cyclopentenyl-acrylonitrile (*E/Z*)-53



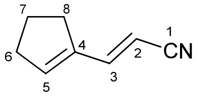
(*E*/*Z*)-53

The synthesis was carried out according to the general procedure GP-3.

Cyclopentenyl nonaflate **28a**: 373 mg, 1.02 mmol,
Acrylonitrile **48**: 73 mg, 1.38 mmol,
NEt_3: 208 mg, 2.05 mmol,
$Pd(OAc)_2$: 11.5 mg, 0.051 mmol, 5 mol%,
1 ml DMF.

Kugelrohr distillation at 65°C (1.0 mbar) furnished the product **53** (111.5 mg, 0.94 mmol, 92% yield, (*E/Z*) ratio = 79:21) as colorless oil.

(*E*)-3-cyclopentenyl-acrylonitrile (*E*)-53



(*E*)-53

^{1}H-NMR (C_6D_6, 400 MHz): δ = 1.47 (quint, ^3J = 7.5 Hz, 2 H, 7-CH_2), 1.71–1.77 (m, 2 H) and 1.94–2.01 (m, 2 H) (6-CH_2 and 8-CH_2), 4.47 (d, ^3J = 16.3 Hz, 1 H, 2-CH), 5.41 (br.s, 1 H, 5-CH), 6.55 (d, ^3J = 16.3 Hz, 1 H, 3-CH);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 22.9 (7-*C*H_2), 30.2 and 33.6 (6-*C*H_2 and 8-*C*H_2), 95.7 (2-*C*H), 118.6 (*C*N), 140.9 (4-*C*), 141.8 (5-*C*H), 146.7 (3-*C*H);

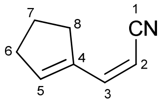
IR (film): $\tilde{\nu}$ = 2925, 2855 cm^{-1} (=C–H, C–H), 1665 cm^{-1} (C=C);

MS (EI, 80 eV): m/z (%) = 119 (M^+, 100), 91 ([M^+ – 28], 43);

HRMS: calculated for C_8H_9N (M^+) 119.0735, found 119.0736;

C,H,N-analysis (%): calculated for C_8H_9N (119.164): C, 80.63; H, 7.61; N, 11.75;
found C, 80.20; H, 7.43; N, 11.67.

(*Z*)-3-cyclopentenyl-acrylonitrile <u>(*Z*)-53</u>



(*Z*)-53

^{1}H-NMR (C_6D_6, 400 MHz): δ = 1.55 (quint, ^{3}J = 7.6 Hz, 2 H, 7-CH_2), 1.92–1.98 (m, 2 H) and 2.74 (m$_c$, 2 H) (6-CH_2 and 8-CH_2), 4.41 (d, ^{3}J = 11.7 Hz, 1 H, 2-CH), 5.58 (br.s, 1 H, 5-CH), 6.06 (d, ^{3}J = 11.7 Hz, 1 H, 3-CH);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 23.7 (7-*C*H_2), 31.5 and 32.6 (6-*C*H_2 and 8-*C*H_2), 93.4 (2-CH), 117.9 (*C*N), 141.4 (4-*C*), 143.6 and 145.2 (5-*C*H and 3-*C*H);

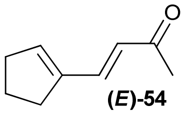
IR (film): $\tilde{\nu}$ = 2925, 2855 cm^{-1} (=C–H, C–H), 1665 cm^{-1} (C=C);

MS (EI, 80 eV): m/z (%) = 119 (M^{+}, 100), 91 ([M^{+} – 28], 43);

HRMS: calculated for C_8H_9N (M^{+}) 119.0735, found 119.0736;

C,H,N-analysis (%): calculated for C_8H_9N (119.164): C, 80.63; H, 7.61; N, 11.75;
found C, 80.20; H, 7.43; N, 11.67.

Synthesis of (*E*)-4-cyclopentenyl but-3-en-2-one <u>(*E*)-54</u>



(*E*)-54

The synthesis was carried out according to the general procedure GP-3.
Cyclopentenyl nonaflate **28a**: 369 mg, 1.0 mmol,
Methyl vinyl ketone **49**: 91.4 mg, 1.30 mmol,
NEt_3: 203 mg, 2.00 mmol,
$Pd(OAc)_2$: 11.2 mg, 0.049 mmol, 5 mol%,
1 ml DMF.

Kugelrohr distillation at 63-66°C (0.44 mbar) furnished the product (*E*)-**54** as colorless oil (124 mg, 0.90 mmol, 90% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.94–2.01 (m, 2 H, CH_2-C*H*$_2$), 2.29 (s, 3 H, C*H*$_3$), 2.43-2.54 (m, 4 H, C*H*$_2$), 6.0 (d, ^{3}J = 16.0 Hz, 1 H, CH=C*H*C(O)Me), 6.24 (m$_c$, 1 H, C*H*=C), 7.35 (d, ^{3}J = 16.0 Hz, 1 H, C*H*=CHC(O)Me);

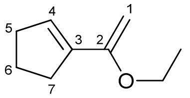
^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 23.1 (*C*H_2), 27.1 (*C*H_3), 30.8, 33.6 (both *C*H_2), 127.6, 139.8, 141.8 (all *C*H), 141.8 (CH=*C*), 199.1 (*C*=O).

Analytical data match well those described in literature.[126]

Synthesis of 1-(1-ethoxyethenyl)cyclopentene 55a and (*E*)-1-(2-ethoxyethenyl) cyclopentene (*E*)-55b

The synthesis was carried out according to the general procedure GP-3.
Cyclopentenyl nonaflate **28a**: 374.5 mg, 1.02 mmol,
Ethyl vinyl ether **50**: 91.4 mg, 1.30 mmol,
NEt_3: 204.0 mg, 2.02 mmol,
$Pd(OAc)_2$: 11.2 mg, 0.049 mmol, 5 mol%,
1 ml DMF.
Kugelrohr distillation at 62°C (4.0 mbar) furnished the product as a mixture of regioisomers **55a** and (*E*)-**55b** (94:6 ratio) as colorless oil (121.3 mg, 0.88 mmol, 86% yield).

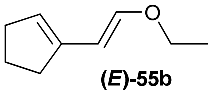
1-(1-ethoxyethenyl)cyclopentene 55a



55a

^{1}H-NMR (C_6D_6, 400 MHz): δ = 1.13 (t, ^3J = 7.0 Hz, 3 H, OCH$_2$*Me*), 1.75 (m$_c$, 2 H, 6-CH$_2$), 2.31 (m$_c$, 2 H) and 2.45 (m$_c$, 2 H) (5-CH$_2$ and 7-CH$_2$), 3.55 (q, ^3J = 7.0 Hz, 2 H, OC*H*$_2$Me), 4.07 (d, ^2J = 1.5 Hz, 1 H, 1-CH$_2$), 4.19 (d, ^2J = 1.5 Hz, 1 H, 1-CH$_2$), 5.07 (br.s, 1 H, =CH$_2$), 6.29 (quint, *J* = 2.2 Hz, 1 H, 4-CH);
^{13}C-NMR (C_6D_6, 100.65 MHz): δ = 14.6 (OCH$_2$*Me*), 23.6 (6-*C*H$_2$), 32.7 and 33.3 (5-*C*H$_2$ and 7-*C*H$_2$), 62.6 (O*C*H$_2$Me), 83.4 (1-*C*H$_2$), 127.98 (4-*C*H), 139.9 (3-*C*), 158.4 (2-*C*);
IR (film): $\tilde{\nu}$ = 2975, 2940, 2895 cm^{-1} (=C–H, C–H), 1680 cm^{-1} (C=C).
MS (EI, 80 eV): m/z (%) = 138 (M$^+$, 18), 123 ([M$^+$ – Me], 100), 110 ([M$^+$ – C_2H_4], 71);
HRMS: calculated for $C_9H_{14}O$ (M$^+$) 138.1045, found 138.1036;
C,H-analysis (%): calculated for $C_9H_{14}O$ (138.207): C, 78.21; H, 10.21; O, 11.58;
found C, 77.85; H, 9.96.

(*E*)-1-(2-ethoxyethenyl) cyclopentene (*E*)-55b



(*E*)-55b

NMR (selected signals):
^{1}H-NMR (C_6D_6, 400 MHz), δ = 1.02 (t, ^3J = 7.0 Hz, 3 H, OCH$_2$*Me*), 3.43 (q, ^3J = 7.0 Hz, 2 H, OC*H*$_2$Me), 5.50 (m$_c$, 1 H, C*H*=C), 5.89 (d, ^3J = 12.8 Hz, 1 H, C*H*=CHOEt), 6.49 (d, ^3J = 12.8 Hz, 1 H, CH=C*H*OEt);

^{13}C-NMR (C_6D_6, 100.65 MHz), δ = 14.8 (OCH$_2$*Me*), 23.7, 31.9 and 32.8 (all *C*H$_2$), 64.9 (O*C*H$_2$Me), 104.2, 125.0 and 148.5 (all *C*H);

IR (film): $\tilde{\nu}$ = 2975, 2940, 2895 cm^{-1} (=C–H, C–H), 1680 cm^{-1} (C=C).

MS (EI, 80 eV): m/z (%) = 138 (M$^+$, 18), 123 ([M$^+$ – Me], 100), 110 ([M$^+$ – C_2H_4], 71);

HRMS: calculated for $C_9H_{14}O$ (M$^+$) 138.1045, found 138.1036;

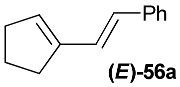
C,H-analysis (%): calculated for $C_9H_{14}O$ (138.207): C, 78.21; H, 10.21; O, 11.58;
found C, 77.85; H, 9.96.

Synthesis of (*E*)-(2-cyclopent-1-enyl-ethenyl)benzene 56a and (1-cyclopent-1-enyl-ethenyl)benzene 56b

The synthesis was carried out according to the general procedure GP-3.
Cyclopentenyl nonaflate **28a**: 366.9 mg, 1.0 mmol,
Styrene **51**: 141.5 mg, 1.36 mmol,
NEt_3: 205 mg, 2.03 mmol,
Pd(OAc)$_2$: 11.4 mg, 0.051 mmol, 5 mol%,
1 ml DMF.

Flash column chromatography with *n*-pentane furnished the product as a mixture of regioisomers (*E*)-**56a** and **56b** in the ratio of 93:7 as colorless solid (146.5 mg, 0.86 mmol, 86% yield).

(*E*)-(2-cyclopent-1-enyl-ethenyl)benzene (*E*)-56a



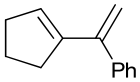
(*E*)-56a

^{1}H-NMR (CDCl$_3$, 400 MHz): δ = 1.97 (q, 2 H, CH$_2$-C*H$_2$*-CH$_2$), 2.47 (m, 2 H, C-C*H$_2$*), 2.55 (m, 2 H, CH-C*H$_2$*), 5.85 (m, 1 H, C-C*H*), 6.41 (d, ^3J = 16.1 1 H, C*H*), 7.01 (d, ^3J = 16.1 Hz, 1 H, C*H*), 7.16-7.23 (m, 1 H, C$_{Ar}$*H*), 7.26-7.34 (m, 2 H, C$_{Ar}$*H*), 7.41 (m, 2 H, C$_{Ar}$*H*);

^{13}C-NMR (CDCl$_3$, 100.65 MHz): δ = 23.2, 31.2, 33.1 (all *C*H$_2$), 125.8, 126.2 (*C*$_{Ar}$H), 127.1, 128.6 (*C*$_{Ar}$H), 128.7, 132.0, 137.8 (CH-*C*$_{Ar}$), 142.8 (CH-*C*).

Analytical data match well those described in literature.[8b]

(1-cyclopent-1-enyl-ethenyl)benzene 56b



56b

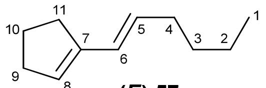
NMR (selected signals):

^{1}H-NMR ($CDCl_3$, 400 MHz), δ = 5.11 (d, ^2J = 30.3, 2 H, =CH_2), 5.58 (m, 1 H, =CH);
^{13}C-NMR ($CDCl_3$, 100.65 MHz), δ = 23.4, 33.0, 33.5 (all CH_2), 113.6 (C-CH_2), 126.2, 127.8, 128.5, 131.4 (all *C*H).

Synthesis of (*E*)-1-hex-1-enyl-cyclopentene (*E*)-57a, 1-hex-1-en-2-yl-cyclopentene 57b and 1-hex-2-enyl-cyclopentene 57c

The synthesis was carried out according to the general procedure GP-3.
Cyclopentenyl nonaflate **28a**: 367.8 mg, 1.0 mmol,
1-Hexene **52**: 113 mg, 1.34 mmol,
NEt_3: 207.5 mg, 2.05 mmol,
$Pd(OAc)_2$: 11.2 mg, 0.049 mmol, 5 mol%,
1 ml DMF.
Flash column chromatography with *n*-pentane furnished the product as a mixture of regioisomers (*E*)-**57a**, **57b** and **57c** (ratio: 56:31:13) as slightly yellowish oil (127.0 mg, 0.84 mmol 84% yield).
Analytical data match well those described in literature.[127]

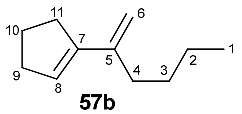
(*E*)-1-hex-1-enyl-cyclopentene 57a



(*E*)-57a

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 13.96 (1-Me), 22.28 and 23.13 (2- and 10-CH_2), 31.40, 31.70, 32.55 and 32.69 (3-, 4-, 9- and 11-CH_2), 126.91, 128.06 and 131.31 (5-, 6- and 8-*C*H), 142.71 (7-*C*).

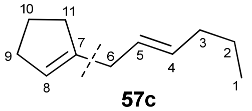
1-Hex-1-en-2-yl-cyclopentene 57b



57b

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 14.02 (1-Me), 22.75 and 23.12 (2- and 10-CH_2), 31.24, 32.72, 33.32 and 33.89 (3-, 4-, 9- and 11-CH_2), 111.01 (6-CH_2), 126.77 (8-*C*H), 143.60 and 144.74 (5- and 7-*C*).

1-Hex-2-enyl-cyclopentene 57c



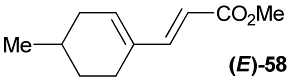
57c

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 13.68 (1-Me), 22.66 and 23.42 (2- and 10-CH_2), 32.49, 34.62 (double int.) and 35.10 (3-, 6-, 9- and 11-CH_2), 123.70, 127.74 and 131.42 (4-, 5- and 8-*C*H), 144.03 (7-*C*).

A mixture of all three isomers (56:31:13).

^{1}H NMR (C_6D_6, 400 MHz): δ = 0.86 (t, ^3J = 7.1 Hz, 3 H, Me, (*E*)-**57a**), 0.87 (t, ^3J = 7.4 Hz, 3 H, Me, **57c**), 0.89 (t, ^3J = 7.4 Hz, 3 H, Me, **57b**), 1.22–1.37 (m), 1.52 (m$_c$, 2 H, CH_2, **57b**), 1.73–1.85 (m), 1.96 (m$_c$, 2 H, 3-CH_2, **57c**), 2.06 (m$_c$, 2 H, 4-CH_2, (*E*)-**57a**), 2.22 (m$_c$, 2 H, CH_2, **57c**), 2.28–2.36 (m), 2.38–2.48 (m), 2.78 (br. d, ^3J = 6.4 Hz, 2 H, 6-CH_2, **57c**), 4.97 and 5.00 (both br. s, 1 H, 6-CH_2, **57b**) 5.40–5.61 (m), 5.71 (m$_c$, 1 H, 8-CH, **57b**), 6.36 (d, *J* = 15.6 Hz, 1 H, C*H*=CH).

Synthesis of (*E*)-methyl 3-(4-methylcyclohex-1-enyl) acrylate (*E*)-58



(*E*)-58

The synthesis was carried out according to the general procedure GP-3.

4-Methylcyclohex-1-enyl nonafluorobutanesulfonate **28b**: 396.5 mg, 1.01 mmol,

Methyl acrylate **44**: 114 mg, 1.32 mmol,

NEt_3: 206 mg, 2.04 mmol,

$Pd(OAc)_2$: 11.2 mg, 0.049 mmol, 5 mol%,

1 ml DMF.

After column chromatography, the pure product (*E*)-**58** was obtained as a white solid (179.5 mg, 1.0 mmol, 98% yield). M$_p$ = (34-35)°C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.98 (d, ^3J = 6.6 Hz, 3 H, Me), 1.27 (dtd, ^2J = 13.0 Hz, ^3J = 10.8, 5.8 Hz, 1 H, CH_{ax} of CH_2), 1.69 (m$_c$, 1 H, C*H*), 1.77–1.87 (m, 2 H, CH_2), 2.07–2.18 (m, 1 H, C*H* of CH_2), 2.20–2.34 (m, 2 H, CH_2), 3.74 (s, 3 H, OMe), 5.76 (d, ^3J = 15.8 Hz, 1 H, CH=C*H*CO_2Me), 6.14 (m$_c$, 1 H, C*H*=C), 7.30 (d, ^3J = 15.8 Hz, 1 H, C*H*=CHCO_2Me);

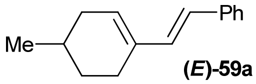
^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 21.5 (Me), 24.1 (CH_2), 28.2 (*C*H), 30.3 and 34.9 (both CH_2), 51.4 (OMe), 114.3, (*C*H), 134.6 (CH=*C*), 138.5 and 148.0 (both *C*H), 168.1 (*C*=O); IR (KBr): $\tilde{\nu}$ = 3010 cm^{-1} (=C–H), 2950, 2865 cm^{-1} (C–H), 1715 cm^{-1} (C=O), 1635 cm^{-1} (C=C);

MS (EI, 80 eV): m/z (%) = 180 (M^+, 14), 165 ([$M^+ - CH_3$], 61), 121 ([$M^+ - CO_2CH_3$], 100);
HRMS: calculated for $C_{11}H_{16}O_2$ (M^+) 180.1150, found 180.1151;
C,H-analysis (%): calculated for $C_{11}H_{16}O_2$ (180.224): C, 73.30; H, 8.95; O, 17.75;
found C, 72.88; H, 8.84.

Synthesis of (*E*)-1-[2-(4-methylcyclohex-1-enyl)ethenyl]benzene (*E*)-59a and 1-[1-(4-methylcyclohex-1-enyl)ethenyl]benzene 59b

The synthesis was carried out according to the general procedure GP-3.
4-Methylcyclohex-1-enyl nonafluorobutanesulfonate **28b**: 401 mg, 1.02 mmol,
Styrene **51**: 139.8 mg, 1.34 mmol,
NEt_3: 205 mg, 2.03 mmol,
$Pd(OAc)_2$: 11.2 mg, 0.049 mmol, 5 mol%,
1 ml DMF.
Flash chromatography with *n*-pentane furnished the product as a mixture of the regioisomers (*E*)-**59a** and **59b** in a ratio of 84:16 as colorless oil (198.6 mg, 1.0 mmol, 98% yield).

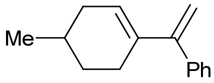
(*E*)-1-[2-(4-methylcyclohex-1-enyl)ethenyl]benzene (*E*)-59a



(*E*)-59a

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 0.98 (d, ^3J = 6.7 Hz, 3 H, Me), 1.24–1.35 (m, 1 H), 1.64–1.85 (m, 3 H), 2.15–2.32 (m, 2 H), and 2.32–2.42 (m, 1 H) (3 CH_2 and MeC*H*), 5.85 (m_c, 1 H, C*H*=C), 6.42 (d, ^3J = 16.2 Hz, C*H*=CH), 6.77 (d, ^3J = 16.2 Hz, CH=C*H*), 7.14–7.19 (m, 1 H, CH_p, Ph), 7.26–7.31 (m, 2 H, CH_m, Ph), 7.37–7.40 (m, 2 H, CH_o, Ph);
^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 21.71 (Me), 24.5 (*C*H_2), 28.6 (Me*C*H), 30.7 (*C*H_2), 34.6 (*C*H_2), 124.8 (*C*H), 126.1 and 128.5 (*C*H_m and *C*H_o), 126.8 (*C*H), 130.3 (*C*H), 132.3 (*C*H), 135.4 (*C*), 138.0 (*C*);
IR (film): $\tilde{\nu}$ = 3025, 2950, 2920, 2870 cm^{-1} (=C–H, C–H), 1635, 1600 cm^{-1} (C=C);
MS (EI, 80 eV): m/z (%) = 198 (M^+, 100), 183 ([$M^+ - CH_3$], 25), 91 (53);
HRMS: calculated for $C_{15}H_{18}$ (M^+) 198.1409, found 198.1410;
C,H-analysis (%): calculated for $C_{15}H_{18}$ (198.303): C, 90.85; H, 9.15;
found C, 90.71; H, 9.06.

1-[1-(4-Methylcyclohex-1-enyl)ethenyl]benzene 59b


59b

NMR (selected signals):

^{1}H-NMR ($CDCl_3$, 400 MHz), δ = 0.97 (d, ^3J = 7 Hz, 3 H, Me), 4.98 (1 H) and 5.18 (1 H) (both br.s, C*H*$_2$=C), 5.58 (m$_c$, 1 H, C*H*=C);

^{13}C-NMR ($CDCl_3$, 100.65 MHz), δ = 21.70 (Me), 26.4 (*C*H$_2$), 28.2 (Me*C*H), 31.1 (*C*H$_2$), 34.0 (*C*H$_2$), 111.1 (*C*H$_2$=C), 126.9 (*C*H), 127.8 and 128.7 (*C*H$_m$ and *C*H$_o$), 128.6 (*C*H), 136.7 (*C*), 142.1 (*C*), 151.4 (*C*=CH$_2$);

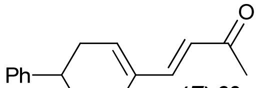
IR (film): $\tilde{\nu}$ = 3025, 2950, 2920, 2870 cm^{-1} (=C–H, C–H), 1635, 1600 cm^{-1} (C=C);

MS (EI, 80 eV): m/z (%) = 198 (M$^+$, 100), 183 ([M$^+$ – CH$_3$], 25), 91 (53);

HRMS: calculated for C_{15}H18 (M$^+$) 198.1409, found 198.1410;

C,H-analysis (%): calculated for $C_{15}H_{18}$ (198.303): C, 90.85; H, 9.15;
found C, 90.71; H, 9.06.

Synthesis of (*E*)-4-(4-phenylcyclohex-1-enyl) but-3-en-2-one (*E*)-60


(*E*)-60

The synthesis was carried out according to the general procedure GP-3.

4-Phenylcyclohex-1-enyl nonafluorobutanesulfonate **28c**: 458.7 mg, 1.01 mmol,
Methyl vinyl ketone **49**: 95.5 mg, 1.36 mmol,
NEt_3: 205 mg, 2.03 mmol,
$Pd(OAc)_2$: 11.3 mg, 0.05 mmol, 5 mol%,
1 ml DMF.

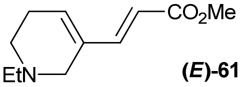
After column chromatography (*n*-hexane : EtOAc = 5 : 1) product (*E*)-**60**[27] was obtained as slightly yellowish solid (222.8 mg, 0.98 mmol, 98% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.76–1.87 (m, 1 H), 2.04–2.11 (m, 1 H), 2.25–2.42 (m, 3 H), and 2.50–2.59 (m, 1 H) (all CH$_2$), 2.30 (s, 3 H, Me), 2.80–2.88 (m, 1 H, PhC*H*), 6.09 (d, ^3J = 16.1 Hz, 1 H, C(O)C*H*=CH), 6.29–6.32 (m, 1 H, C*H*=C), 7.16–7.24 (m, 4 H, C(O)CH=C*H* and 3C*H*$_{Ph}$), 7.29–7.34 (m, 2 H, 2C*H*$_{Ph}$);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): 24.7 (*C*H$_2$), 27.3 (Me), 29.2 (*C*H$_2$), 34.5 (*C*H$_2$), 39.7 (Ph*C*H), 124.7 (*C*H), 126.3 (*C*H), 126.7 and 128.5 (*C*H$_m$ and *C*H$_o$), 135.0 (*C*=CH), 138.9 (*C*H), 145.9 (*C*-C$_{Ar}$), 146.2 (*C*H), 198.9 (*C*=O).

MS (EI, 80 eV): m/z (%) = 226 (M^+, 100), 183 ([M^+ – C(O)CH_3], 65);
HRMS: calculated for $C_{16}H_{18}O$ (M^+) 226.1358, found 226.1355.

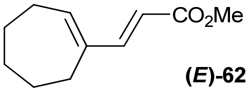
Synthesis of (*E*)-methyl 3-(1-ethyl-1,2,5,6-tetrahydropyridin-3-yl)acrylate (*E*)-61



(*E*)-61

The synthesis was carried out according to the general procedure GP-3.
1,1,2,2,3,3,4,4,4-Nonafluoro-butane-1-sulfonic acid 1-ethyl-1,2,5,6-tetrahydro-pyridin-3-yl ester **28h**: 409.3 mg, 1.0 mmol,
Methyl acrylate **44**: 114 mg, 1.32 mmol,
NEt_3: 206 mg, 2.04 mmol,
$Pd(OAc)_2$: 11.2 mg, 0.049 mmol, 5 mol%,
1 ml DMF.
After column chromatography the product (*E*)-**61** was obtained as slightly yellowish oil (160.1 mg, 0.82 mmol, 82% yield).
^{1}H NMR (C_6D_6, 400 MHz): δ = 0.94 (t, ^3J = 7.2 Hz, 3 H, CH_2-C*H*$_3$), 1.90-1.97 (m, 2 H, CH-C*H*$_2$), 2.18 (t, ^3J = 5.6 Hz, 2 H, N-C*H*$_2$), 2.22 (q, ^3J = 7.2 Hz, 2 H, N-C*H*$_2$-CH_3), 2.87 (m, 2 H, C-C*H*$_2$), 3.47 (s, 3 H, O-C*H*$_3$), 5.72 (m, 1 H, C=C*H*), 5.83 (d, ^3J = 16.0 Hz, 1 H, C(O)-C*H*), 7.48 (d, ^3J = 16.0 Hz, 1 H, C-C*H*=CH);
^{13}C-NMR (C_6D_6, 100.65 MHz): δ = 12.5 (CH_2-*C*H_3), 27.5 (CH-*C*H_2), 49.1 (N-*C*H_2), 51.0 (O-Me), 51.6 (N-*C*H_2), 52.2 (N-*C*H_2-C), 114.9 (C(O)-*C*H), 134.0 (CH-*C*), 136.1 (C-*C*H-CH_2), 145.6 (C-*C*H=CH), 167.3 (*C*=O);
MS (EI, 80 eV): m/z (%) = 180 ([M^+ – $C_{10}H_{14}NO_2$•], 100), 195 (M^+, 79), 136 ([M^+ – CO_2CH_3], 30), 79 ([M^+ – C_5H_5N•], 26), 164 ([M^+ – $C_9H_{10}NO_2$•], 14);
HRMS: calculated for $C_{11}H_{17}NO_2$ (M^+) 195.1259, found 195.1231.

Synthesis of (*E*)-methyl 3-cyclohept-1-enyl acrylate (*E*)-62



(*E*)-62

The synthesis was carried out according to the general procedure GP-3.
Cyclohept-1-enyl nonafluorobutanesulfonate **28d**: 394.3 mg, 1.0 mmol,
Methyl acrylate **44**: 119 mg, 1.38 mmol,
NEt_3: 203.5 mg, 2.01 mmol,

$Pd(OAc)_2$: 11.1 mg, 0.049 mmol, 5 mol%,

1 ml DMF.

Column chromatography furnished the product (*E*)-**62** as colorless oil (179.0 mg, 0.99 mmol, 99% yield).

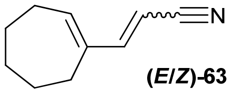
Analytical data match well those described in literature.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.50-1.56 (m, 4 H, 2 CH_2), 1.75-1.81 (m, 2 H, CH_2), 2.27-2.34 (m, 4 H, 2 CH_2), 3.74 (s, 3 H, Me), 5.80 (d, ^3J = 15.7 Hz, 1 H, C(O)C*H*=CH), 6.36 (t, ^3J = 6.8 Hz, 1 H, C*H*=C), 7.28 (d, ^3J = 15.7 Hz, 1 H, C(O)CH=C*H*);

^{13}C-NMR (C_6D_6), 100.65 MHz): δ = 26.1, 26.4, 27.3, 29.1, 32.0 (all *C*H_2), 51.0 (Me), 115.0 (*C*H), 142.1 (*C*=CH), 143.4 and 149.2 (both *C*H), 167.7 (*C*=O).

Analytical data match well those described in literature.[8b]

Synthesis of 3-cyclohept-1-enyl-acrylonitrile <u>(*E*/*Z*)-63</u>



(*E*/*Z*)-63

The synthesis was carried out according to the general procedure GP-3.

Cyclohept-1-enyl nonafluorobutanesulfonate **28d**: 395.7 mg, 1.0 mmol,

Acrylonitrile **48**: 76 mg, 1.43 mmol,

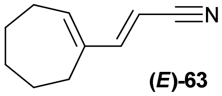
NEt_3: 204.6 mg, 2.02 mmol,

$Pd(OAc)_2$: 11.3 mg, 0.05 mmol, 5 mol%,

1 ml DMF.

Kugelrohr distillation at 100°C (5.0 mbar) furnished the product (*E*/*Z*)-**63**[14e] in a (*E*/*Z*)-ratio of 67:33 as colorless oil (127.8 mg, 0.87 mmol, 87% yield).

3-Cyclohept-1-enyl-acrylonitrile <u>(*E*)-63</u>



(*E*)-63

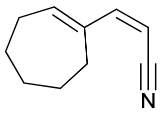
^{1}H-NMR (C_6D_6, 400 MHz): δ = 1.10–1.25 (m, 4 H, 2 CH_2), 1.36–1.47 (m, 2 H, CH_2), 1.67 (m_c, 2 H, CH_2), 1.81 (m_c, 2 H, CH_2), 4.56 (d, ^3J = 16.4 Hz, 1 H, CH=C*H*CN), 5.55 (t, ^3J = 6.8 Hz, 1 H, C*H*=C), 6.44 (d, ^3J = 16.4 Hz, 1 H, C*H*=CHCN);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 25.6, 25.93, 26.4, 29.0, and 31.5 (all *C*H_2), 92.3 (=*C*HCN), 119.1 (*C*N), 141.5 (*C*=CH), 144.7 (*C*H), 154.5 (*C*H).

MS (EI, 80 eV): m/z (%) = 147 (M^+, 100), 119 ([M^+ – 28], 33);

HRMS: calculated for $C_{10}H_{13}N$ (M^+) 147.1048, found 147.1033.

3-Cyclohept-1-enyl-acrylonitrile (*Z*)-63


(*Z*)-63

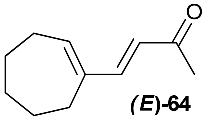
^{1}H-NMR (C_6D_6, 400 MHz): δ = 1.10–1.25 (m, 2 H, CH_2), 1.36–1.47 (m, 4 H, 2 CH_2), 1.86 (m_c, 2 H, CH_2), 2.57 (m_c, 2 H, CH_2), 4.42 (d, ^3J = 12.1 Hz, 1 H, CH=C*H*CN), 5.85 (t, ^3J = 6.8 Hz, 1 H, C*H*=C), 5.90 (d, ^3J = 12.1 Hz, 1 H, C*H*=CHCN);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 25.8, 25.96, 28.5, 28.8, and 31.6 (all *C*H_2), 90.9 (=*C*HCN), 117.5 (*C*N), 142.1 (*C*=CH), 144.6 (*C*H), 152.8 (*C*H).

MS (EI, 80 eV): m/z (%) = 147 (M^+, 100), 119 ([M^+ – 28], 33);

HRMS: calculated for $C_{10}H_{13}N$ (M^+) 147.1048, found 147.1033.

Synthesis of (*E*)-3-cyclohept-1-enyl but-3-en-2-one (*E*)-64


(*E*)-64

The synthesis was carried out according to the general procedure GP-3.

Cyclohept-1-enyl nonafluorobutanesulfonate **28f**: 395 mg, 1.0 mmol,

Methyl vinyl ketone **49**: 9276 mg, 1.31 mmol,

NEt_3: 204 mg, 2.02 mmol,

$Pd(OAc)_2$: 11.2 mg, 0.049 mmol, 5 mol%,

1 ml DMF.

Kugelrohr distillation at 80°C (0.026 mbar) furnished the product (*E*)-**64**[29] as colorless oil (154.8 mg, 0.94 mmol, 94% yield).

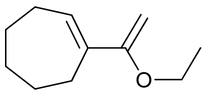
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.50–1.57 (m, 4 H, 2CH_2), 1.76–1.82 (m, 2 H, CH_2), 2.28 (s, 3 H, Me), 2.29–2.36 (m, 4 H, 2CH_2), 6.10 (d, ^3J = 16.0 Hz, 1 H, C(O)C*H*=CH), 6.36 (t, ^3J = 6.8 Hz, 1 H, C*H*=C), 7.12 (d, ^3J = 16.0 Hz, 1 H, C(O)CH=C*H*);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 25.9, 26.2 and 27.1 (all *C*H_2), 27.4 (Me), 29.3 and 31.9 (both *C*H_2), 124.2 (*C*H), 142.3 (*C*=CH), 144.9 and 148.1 (both *C*H), 199.0 (*C*=O).

MS (EI, 80 eV): m/z (%) = 149 ([M^+ – 15], 100), 95 ([M^+ – 69], 61), 164 (M^+, 49);

HRMS: calculated for $C_{11}H_{16}O$ (M^+) 164.1201, found 164.1202.

Synthesis of 1-(1-ethoxyethenyl)cycloheptene 65



65

The synthesis was carried out according to the general procedure GP-3.

Cyclohept-1-enyl nonafluorobutanesulfonate **28d**: 396.8 mg, 1.01 mmol,
Ethyl vinyl ether **50**: 102.5 mg, 1.42 mmol,
NEt_3: 207 mg, 2.05 mmol,
$Pd(OAc)_2$: 11.2 mg, 0.049 mmol, 5 mol%,
1 ml DMF.

Kugelrohr distillation at 70°C (1.1 mbar) furnished the product **65** as slightly yellowish oil (152.2 mg, 0.91 mmol, 91% yield).

^{1}H-NMR (C_6D_6, 400 MHz): δ = 1.11 (t, ^3J = 7.0 Hz, 3 H, OCH$_2$*Me*), 1.37–1.43 (m), 1.48–1.53 (m), 1.60–1.66 (m), 2.12 (m$_c$) and 2.41 (m$_c$) (all CH$_2$), 3.53 (q, ^3J = 7.0 Hz, 2 H, OC*H*$_2$Me), 4.00 (d, ^2J = 2.2 Hz, 1 H, =CH$_2$), 4.36 (d, ^2J = 2.2 Hz, 1 H, =CH$_2$), 6.67 (t, ^3J = 7.0 Hz, 1 H, C*H*=C);

^{13}C-NMR (C_6D_6, 100.65 MHz): δ = 14.7 (OCH$_2$*Me*), 26.86, 26.88, 28.5, 29.5 and 32.7 (all *C*H$_2$), 63.0 (O*C*H$_2$Me), 81.2 (=*C*H$_2$), 129.9 (C=*C*H), 140.6 (*C*=CH), 162.6 (*C*=CH$_2$);

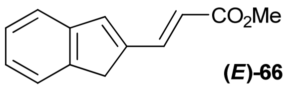
IR (film): $\tilde{\nu}$ = 2930, 2860 cm^{-1} (=C–H, C–H), 1665 cm^{-1} (C=C);

MS (EI, 80 eV): m/z (%) = 166 (M$^+$, 5), 151 ([M$^+$ – Me], 100), 138 ([M$^+$ – C_2H_4], 30) 123 (56).

HRMS: calculated for $C_{11}H_{18}O$ (M$^+$) 166.1358, found 166.1357;

C,H-analysis (%): calculated for $C_{11}H_{18}O$ (166.26): C, 79.46; H, 10.91; O, 9.62;
found C, 79.06; H, 10.84.

Synthesis of (*E*)-methyl 3-(1*H*-inden-2-yl) acrylate (*E*)-66



(*E*)-66

The synthesis was carried out according to the general procedure GP-3.

1*H*-inden-2-yl nonafluorobutanesulfonate **28d**: (422.8 mg, 1.020 mmol),
Methyl acrylate **44**: 118 mg, 1.37 mmol,
NEt_3: 204 mg, 2.02 mmol,
$Pd(OAc)_2$: 11.1 mg, 0.049 mmol, 5 mol%,
1 ml DMF.

After column chromatography the product (*E*)-**66** was obtained as an ochre colored solid (189.6 mg, 0.95 mmol, 93% yield). M$_p$ = (103–104)°C.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 3.57 (br.s, 2 H, CH_2), 3.79 (s, 3 H, OMe), 6.08 (d, ^3J = 15.6 Hz, 1 H, $CH{=}CHCO_2Me$), 7.11 (br.s, 1 H, C*H*=C), 7.23–7.30 (m, 2 H, 2 CH_{Ar}), 7.39–7.42 (m, 1 H, CH_{Ar}), 7.43–7.46 (m, 1 H, CH_{Ar}), 7.70 (d, ^3J = 15.6 Hz, 1 H, $CH{=}CHCO_2Me$);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 37.1 (CH_2), 51.6 (OMe), 117.8, 122.1, 124.0, 126.7, 126.9, 138.4, and 140.1 (*C*H=*C*H and all CH_{Ar}), 143.50, 143.52, and 144.0 (all *C*), 167.6 (*C*=O);

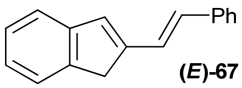
IR (KBr): $\tilde{\nu}$ = 3025, 2950, 2920, 2870 cm^{-1} (=C–H, C–H), 1635, 1600 cm^{-1} (C=C);

MS (EI, 80 eV): m/z (%) = 199 (M^+, 100), 183 ([$M^+ - CH_3$], 25), 91 (53);

HRMS: calculated for $C_{13}H_{12}O_2$ (M^+) 200.0837, found 200.0835;

C,H-analysis (%): calculated for $C_{13}H_{12}O_2$ (200.233): C, 77.98; H, 6.04; O, 15.98;
found C, 76.88; H, 5.82.

Synthesis of 2-(2-phenylethenyl)-1*H*-indene (*E*)-67



(*E*)-67

The synthesis was carried out according to the general procedure GP-3.

1*H*-inden-2-yl nonafluorobutanesulfonate **28e**: (421 mg, 1.020 mmol),
Styrene **51**: 140 mg, 1.34 mmol,
NEt_3: 207 mg, 2.04 mmol,
$Pd(OAc)_2$: 11.2 mg, 0.049 mmol, 5 mol%,
1 ml DMF.

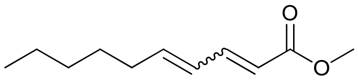
After flash column chromatography with *n*-pentane the product (*E*)-**67**[28] was obtained as yellowish solid (208.4 mg, 0.95 mmol, 94% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 3.65 (s, 2 H, CH_2), 6.77 (d, ^3J = 16.2 Hz, 1 H, CH=C*H*), 6.83 (br.s, 1 H, C*H*=C), 7.14–7.26 (m, 4 H), 7.31–7.36 (m, 3 H), 7.40–7.43 (m, 1 H), and 7.45–7.49 (m, 2 H) (all CH_{Ar}, CH_{Ph} and CH=C*H*);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 37.4 (CH_2), 120.9, 123.6, 124.9, and 125.0 (all *C*H), 126.4 and 128.7 (CH_m and CH_o), 126.6, 127.5, 129.4, and 131.4 (all *C*H), 137.3, 142.8, 145.2, and 146.3 (all *C*).

Analytical data match well those described in literature.[128]

Synthesis of (2*E*,4*E*/*Z*)-methyl deca-2,4-dienoate (2*E*,4*E*/*Z*)-68



[2*E*,4(*E*/*Z*)]- 68

The synthesis was carried out according to the general procedure GP-3.

1,1,2,2,3,3,4,4,4-Nonafluoro-butane-1-sulfonic acid hept-1-enyl ester **42b**: (397 mg, 1.0 mmol), the compound was used as obtained from the nonaflation procedure as a mixture of (*Z*/*E*)-stereoisomers in the ratio of 4.2:1.

Methyl acrylate **44**: 115 mg, 1.34 mmol,

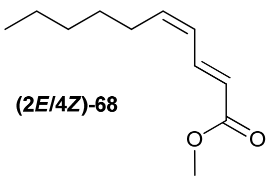
NEt_3: 210.5 mg, 2.08 mmol,

$Pd(OAc)_2$: 11.2 mg, 0.049 mmol, 5 mol%,

1 ml DMF.

Kugelrohr distillation (88°C at $5.2\ 10^{-2}$ mbar) afforded the product **68** as a mixture of (4*Z*/4*E*)-stereoisomers in a ratio of 2.2:1 as slightly yellowish oil (167.9 mg, 0.92 mmol, 92% yield).

Deca-(2*E*/4*Z*)-dienoic acid methyl ester (2*E*/4*Z*)-68



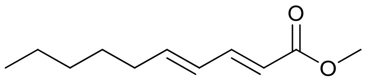
(2*E*/4*Z*)-68

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 0.89 (t, ^3J = 7.1 Hz, 3 H, C*H*$_3$), 1.24-1.48 (m, 6 H, C*H*$_2$), 2.30 (dt, ^3J = 7.8 Hz, ^3J = 7.4 Hz, 2 H, CH-C*H*$_2$), 3.75 (s, 3 H, O-C*H*$_3$), 5.87 (d, ^3J = 14.8 Hz, 1 H, C*H*), 5.83-5.90 (m, 1 H, C*H*), 6.13 (dd, ^3J = 11.5 Hz, ^3J = 10.5 Hz, 1 H, C*H*), 7.62 (ddd, ^3J = 15.3 Hz, ^3J = 11.6 Hz, ^4J = 1.2 Hz, 1 H, C*H*);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 14.0 (*C*H$_3$), 22.5, 28.2, 29.0 and 31.4 (all *C*H$_2$), 51.5 (O-*C*H$_3$), 120.6, 126.4, 139.8, and 141.9 (all *C*H), 167.7 (*C*=O).

Analytical data match well those described in literature.[129]

Deca-(2*E*/4*E*)-dienoic acid methyl ester (2*E*/4*E*)-68



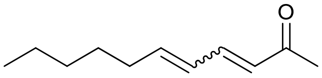
(2*E*/4*E*)-68

^{1}H-NMR ($CDCl_3$, 400 MHz), δ = 0.89 (t, ^{3}J = 7.0 Hz, 3 H, C*H*$_3$), 1.24-1.48 (m, 6 H, C*H*$_2$), 2.16 (dt, ^{3}*J* = 6.7 Hz, ^{3}*J* = 6.5 Hz, 2 H, CH-C*H*$_2$), 3.74 (s, 3 H, O-C*H*$_3$), 5.79 (d, ^{3}*J* = 15.3 Hz, 1 H, C*H*), 6.09-6.18 (m, 2 H, C*H*), 7.27 (dd, ^{3}*J* = 25.6 Hz, ^{3}*J* = 15.6 Hz, 1 H, C*H*);

^{13}C-NMR ($CDCl_3$, 100.65 MHz), δ = 14.0 (*C*H$_3$), 22.4, 28.4, 31.4 and 32.9 (all *C*H$_2$), 51.4 (O-*C*H$_3$), 118.6, 128.3, 145.0 and 145.4 (*C*H), 167.2 (*C*=O).

Analytical data match well those described in literature.[129]

Synthesis of [(*E*)-3,(*E*,*Z*)-5]-undeca-3,5-dien-2-one [(*E*)-3,(*E*,*Z*)-5]-69



[3*E*,5(*E*/*Z*)]-69

The synthesis was carried out according to the general procedure GP-3.

1,1,2,2,3,3,4,4,4-Nonafluoro-butane-1-sulfonic acid hept-1-enyl ester **42b**: (409.2 mg, 1.03 mmol), the compound was used as obtained from the nonaflation procedure as a mixture of (*Z*/*E*)-stereoisomers in the ratio of 4.2:1.

Methyl vinyl ketone **49**: 101 mg, 1.44 mmol,

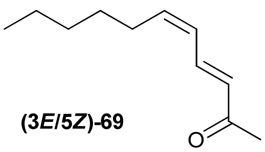
NEt_3: 206 mg, 2.04 mmol,

$Pd(OAc)_2$: 11.2 mg, 0.049 mmol, 5 mol%,

1 ml DMF.

Kugelrohr distillation (70°C at 3.7 10^{-2} mbar) afforded the product **69** as a mixture of (5*Z*/5*E*)-stereoisomers in a ratio of 1.7:1 as colorless oil (151.3 mg, 0.91 mmol, 88% yield).

Undeca-3*E*,5*Z*-dien-2-one (3*E*/5*Z*)-69



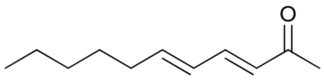
(3*E*/5*Z*)-69

^{1}H-NMR (C_6D_6, 400 MHz): δ = 0.83 (t, ^{3}*J* = 7.4 Hz, 3 H, C*H*$_3$), 1.05-1.27 (m, 6 H, C*H*$_2$), 1.89 (s, 3 H, C(O)-C*H*$_3$), 2.01 (dt, ^{3}*J* = 7.7 Hz, ^{3}*J* = 7.0 Hz, 2 H, CH-C*H*$_2$), 5.56-5.63 (m, 1 H, C*H*), 5.86-6.01 (m, 2 H, C*H*), 7.46 (ddd, ^{3}*J* = 15.4 Hz, ^{3}*J* = 11.5 Hz, ^{4}*J* = 1.0 Hz, 1 H, C*H*);

^{13}C-NMR (C_6D_6, 100.65 MHz): δ = 14.2 (*C*H$_3$), 22.8, 27.7, 28.3, 29.3, 31.5, 127.4, 130.7, 136.9 and 141.7 (all *C*H), 196.5 (*C*=O).

Analytical data match well those described in literature.[129]

Undeca-(3*E*,5*E*)-dien-2-one (3*E*/5*E*)-69



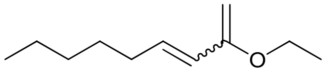
(3*E*/5*E*)-69

^{1}H-NMR (C_6D_6, 400 MHz), δ = 0.86 (t, ^{3}J = 7.0 Hz, 3 H, C*H*$_3$), 1.05-1.27 (m, 6 H, C*H*$_2$), 1.87 (dt, ^{3}*J* = 7.3 Hz, ^{3}*J* = 7.1 Hz, 2 H, CH-C*H*$_2$), 1.92 (s, 3 H, C(O)-C*H*$_3$), 5.70-5.78 (m, 1 H, C*H*), 5.86-6.01 (m, 2 H, C*H*), 6.95 (dd, ^{3}*J* = 26.31 Hz, ^{3}*J* = 15.6 Hz, 1 H, C*H*);

^{13}C-NMR (C_6D_6, 100.65 MHz), δ = 14.2 (*C*H$_3$), 22.8, 27.1, 28.7, 31.6, 33.2, 129.3 (2X), 142.9 and 144.6 (all *C*H), 196.5 (*C*=O).

Analytical data match well those described in literature.[129]

Synthesis of (*E*/*Z*)-2-ethoxynona-1,3-diene (*E*/*Z*)-70



(*E*/*Z*)-70

The synthesis was carried out according to the general procedure GP-3.

1,1,2,2,3,3,4,4,4-Nonafluoro-butane-1-sulfonic acid hept-1-enyl ester **42b**: (397.5 mg, 1.0 mmol), the compound was used as obtained from the nonaflation procedure as a mixture of Z/E-stereoisomers in the ratio of 4.2:1.

Ethyl vinyl ether **50**: 99 mg, 1.37 mmol,

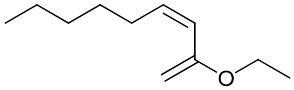
NEt$_3$: 209.5 mg, 2.07 mmol,

Pd(OAc)$_2$: 11.2 mg, 0.049 mmol, 5 mol%,

1 ml DMF.

Kugelrohr distillation (57°C at 3.0 10^{-2} mbar) afforded the product **70** as a mixture of (*Z*/*E*)-stereoisomers in a ratio of 2.1:1 as colorless oil (149.7 mg, 0.89 mmol, 89% yield).

(*Z*)-2-ethoxynona-1,3-diene (*Z*)-70

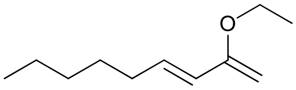


(*Z*)-70

^{1}H-NMR (C_6D_6, 400 MHz): δ = 0.87 (t, ^{3}*J* = 7.0 Hz , 3 H, C*H*$_3$), 1.09 (t, ^{3}*J* = 7.0 Hz , 3 H, O-CH$_2$-C*H*$_3$), 1.32-1.45 (m, 6 H, C*H*$_2$), 2.55 (m, 2 H, C*H*$_2$), 3.47 (q, ^{3}*J* = 7.0 Hz, 2 H, O-C*H*$_2$-CH$_3$), 4.07 (d, ^{4}*J* = 1.6 Hz, 1 H, =C*H*$_2$), 4.13 (d, ^{4}*J* = 1.6 Hz, 1 H, =C*H*$_2$), 5.46 (m, 1 H, C*H*), 5.86 (dt, ^{3}*J* = 12.0 Hz, ^{4}*J* = 1.6 Hz 1 H, C*H*);

^{13}C-NMR (C_6D_6, 100.65 MHz): δ = 14.3, 14.6 (both *C*H_3), 23.0, 29.4, 30.1, 32.0 and 62.7 (all *C*H_2), 84.8 (=*C*H_2), 125.7, 134.1 (all *C*H), 160.5 (*C*);
MS (EI, 80 eV): m/z (%) = 123 ([C_9H_{15}•], 100), 168 (M^+, 38);
HRMS: calculated for $C_{11}H_{20}O$ (M^+) 168.1514, found 168.1519.

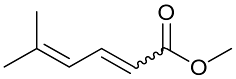
(*E*)-2-ethoxynona-1,3-diene <u>(*E*)-70</u>



(*E*)-70

^{1}H-NMR (CDCl$_3$, 400 MHz), δ = 0.82 (t, ^3J = 7.0 Hz , 3 H, C*H*$_3$), 1.11 (t, ^3J = 7.0 Hz, 3 H, O-CH$_2$-C*H*$_3$), 1.32-1.45 (m, 6 H, C*H*$_2$), 2.02 (m, 2 H, C*H*$_2$), 3.54 (q, ^3J = 7.0 Hz, 2 H, O-C*H*$_2$-CH$_3$), 4.01 (d, ^4J = 1.4 Hz, 1 H, =C*H*$_2$), 4.09 (d, ^4J = 1.5 Hz, 1 H, =C*H*$_2$), 5.95 (dt, ^3J = 15.5 Hz, ^4J = 1.4 Hz, 1 H, C*H*), 6.37 (m, 1 H, C*H*);
^{13}C-NMR (CDCl$_3$, 100.65 MHz), δ = 14.2, 14.6 (both *C*H$_3$), 22.9, 29.3, 31.8, 32.7 and 62.7 (all *C*H$_2$), 84.8 (=*C*H$_2$), 127.2, 131.3 (all *C*H), 159.1 (*C*);
MS (EI, 80 eV): m/z (%) = 123 ([C_9H_{15}•], 100), 168 (M^+, 38);
HRMS: calculated for $C_{11}H_{20}O$ (M^+) 168.1514, found 168.1519.

Synthesis of 5-methyl-hexa-(*E*,*Z*)-2,4-dienoic acid methyl ester <u>(*E*/*Z*)-71</u>



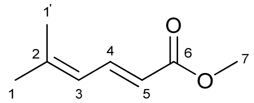
(*E*/*Z*)-71

The synthesis was carried out according to the general procedure GP-3. In addition LiCl was added as an additive prior to the addition of DMF. The coupling reaction was carried out at 45°C.

1,1,2,2,3,3,4,4,4-Nonafluoro-butane-1-sulfonic acid 2-methyl-propenyl ester **42a**: (358 mg, 1.01 mmol),
Methyl acrylate **44**: 115.2 mg, 1.34 mmol,
NEt$_3$: 210 mg, 2.08 mmol,
LiCl: 17 mg, 0.40 mmol,
Pd(OAc)$_2$: 11.2 mg, 0.049 mmol, 5 mol%,
1 ml DMF.

Kugelrohr distillation (65°C at 2.1 mbar) affords the (*E*)-stereoisomer **71** as the major product accompanied by the (*Z*)-isomer **71** (ratio 94:6, ^{1}H-NMR control) as colorless oil (130.7 mg, 0.93 mmol, 92% yield).

5-Methyl-hexa-(*E*)-2,4-dienoic acid methyl ester (*E*)-71



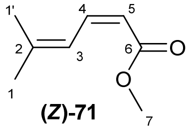
(*E*)-71

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.88 (s, 3 H, 1'-CH_3), 1.90 (s, 3 H, 1-CH_3), 3.74 (s, 3 H, O-CH_3), 5.77 (d, ^3J = 15.3 Hz, 1 H, 5-C*H*), 6.0 (d, ^3J = 11.6 Hz, 1 H, 3-C*H*), 7.57 (dd, $^3J_{H4H5}$ = 15.3 Hz, $^3J_{H3H4}$ = 11.6 Hz, 1 H, 4-C*H*);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 18.9 C-1', 26.5 C-1, 51.4 C-7, 118.0 C-5, 123.7 C-3, 141.2 C-4, 146.5 C-2, 168.1 C-6.

Analytical data match well those described in literature.[8b]

5-Methyl-hexa-(*Z*)-2,4-dienoic acid methyl ester (*Z*)-71



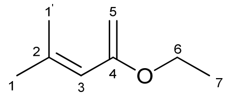
(*Z*)-71

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.86 (s, 3 H, 1'-CH_3), 1.92 (s, 3 H, 1-CH_3), 3.72 (s, 3 H, O-CH_3), 5.57 (d, ^3J = 11.3 Hz, 1 H, 5-C*H*), 6.87 (t, ^3J = 11.6 Hz, 1 H, 3-C*H*), 7.18 (dd, 1 H, ^3J = 11.6 Hz, ^3J = 1.2 Hz, 4-C*H*);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 18.2 C-1', 26.9 C-1, 51.0 C-7, 114.2 C-5, 121.9 C-3, 140.7 C-4, 146.9 C-2.

Analytical data match well those described in literature.[8b]

Synthesis of 2-ethoxy-4-methyl-penta-1,3-diene 72



72

The synthesis was carried out according to the general procedure GP-3. In addition to the reaction employing ligand and additive free conditions the coupling reaction was carried out with 0.2 and 1.0 equivalent of (*E*)-methyl 3-cyclopentenylacrylate **45** as additive. The components were added in the following amounts (a: no additive, b: 0.2 equivalent **45** c: 1.0 equivalent **45**):

a: Et_3N (205.8 mg, 2.03 mmol), **42a** (354.6 mg, 1.0mmol), **50** (93.7 mg, 1.30 mmol), $Pd(OAc)_2$ (11.2 mg, 0.048 mmol, 5 mol%);

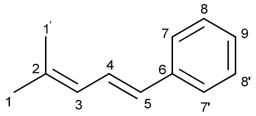
b: Et_3N (208 mg, 2.06 mmol), **42a** (355.2 mg, 1.0 mmol), **50** (102.5 mg, 1.42 mmol), **45** (30.4 mg, 0.2 mmol), $Pd(OAc)_2$ (11.2 mg, 0.048 mmol, 5 mol%);
c: Et_3N (212.4 mg, 2.10 mmol), **42a** (355.3 mg, 1.0 mmol), **50** (104 mg, 1.44 mmol), **45** (152.2 mg, 1.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.048 mmol, 5 mol%);

Isolation of the different reactions:

a: Full conversion was obtained after 46 hours. The product was not isolated.
b: Kugelrohr distillation (69°C at 66 mbar) affords the product **72** as colorless oil (97.2 mg, 0.77 mmol, 77% yield).
c: Distillation of the reaction solution at 1.5 mbar afforded 2 g of a colorless oil consisting of product **72** and DMF. Dissolution in water, extraction with 3 times of 25 ml of *n*-pentane and evaporation of the solvent afforded the product **72** as colorless oil accompanied by a small amount of DMF (87 mg, 0.69 mmol, 69%). Traces of product were still detectable in the reaction solution.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.33 (t, ^3J = 7.0 Hz, 3 H, CH_3), 1.78 (s, 3 H, 1'-C*H*$_3$), 1.91 (s, 3 H, 1-C*H*$_3$), 3.75 (q, ^3J = 7.0 Hz, 2 H, C*H*$_2$-CH_3), 3.95 (s, 1 H, C=C*H*$_2$), 4.07 (s, 1 H, C=C*H*$_2$), 5.62 (s, 1 H, C=C*H*);
^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 14.6 C-7, 19.8 C-1', 27.1 C-1, 62.6 C-6, 84.9 C-5, 121.4 C-3, 137.7 C-2, 159.6 C-4.
Analytical data match well those described in literature.[130]

Synthesis of (4-methyl-penta-(*E*)-1,3-dienyl)-benzene (*E*)-73a



(*E*)-73a

The synthesis was carried out according to the general procedure GP-3. The coupling reaction was carried out at 45°C.
1,1,2,2,3,3,4,4,4-Nonafluoro-butane-1-sulfonic acid 2-methyl-propenyl ester **42a**: (360 mg, 1.020 mmol),
Styrene **51**: 139 mg, 1.33 mmol,
NEt_3: 207 mg, 2.04 mmol,
$Pd(OAc)_2$: 11.2 mg, 0.049 mmol, 5 mol%,
1 ml DMF.

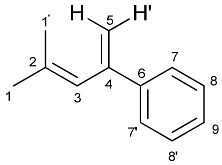
Kugelrohr distillation (70-73°C at 1.0 mbar) affords the product (*E*)-**73a** as the major product accompanied by **73b** (ratio of (*E*)-**73a**:**73b** = 4:1; ^{1}H-NMR analysis) as colorless oil (135.0 mg, 0.85 mmol, 84% yield).

^{1}H-NMR (CDCl$_3$, 400 MHz): δ = 1.84 (s, 3 H, 1'-CH$_3$), 1.86 (s, 3 H, 1-CH$_3$), 5.99 (d, ^3J = 11.0 Hz, 1 H, 3-C*H*), 6.42 (d, ^3J = 15.5 Hz, 1 H, 5-C*H*), 6.97 (dd, J_{H3H5} = 11.0 Hz, J_{H4H5} = 15.5 Hz, 1 H, 4-C*H*), 7.17 (m, 1 H, 9-C*H*), 7.29 (m, 2 H, 8,8'-C*H*), 7.38 (m, 2 H, 7,7'-C);

^{13}C-NMR (CDCl$_3$, 100.65 MHz): δ = 18.6 C-1', 26.3 C-1, 125.5, 125.7, 126.1, 126.9, 128.6, 129.6, 136.6, 138.1 C-2.

Analytical data match well those described in literature.[131]

Synthesis of (4-methylpenta-1,3-dien-2-yl)benzene 73b



73b

The synthesis was carried out according to the general procedure GP-3. The coupling reaction was carried out at 45°C.

1,1,2,2,3,3,4,4,4-Nonafluoro-butane-1-sulfonic acid 2-methyl-propenyl ester **42a**: (360 mg, 1.020 mmol),

Styrene **51**: 139 mg, 1.33 mmol,

NEt$_3$: 207 mg, 2.04 mmol,

Pd(OAc)$_2$: 11.2 mg, 0.049 mmol, 5 mol%,

1 ml DMF.

Kugelrohr distillation (70-73°C at 1.0 mbar) affords the terminal olefin **73b** as the minor product accompanied by (*E*)-**73a** (ratio of (*E*)-**73a**:**73b** = 4:1; ^{1}H-NMR analysis) as colorless oil (135.0 mg, 0.85 mmol, 84% overall yield).

NMR (selected signals):

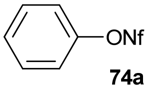
^{1}H-NMR (CDCl$_3$, 400 MHz): δ = 1.70 (s, 3 H, 1'-CH$_3$), 1.87 (s, 3 H, 1-CH$_3$), 5.06 (s, 1 H, 5'-C*H*$_2$), 5.51 (s, 1 H, 5-C*H*$_2$), 5.94 (s, 1 H, 3-C*H*), 7.23-7.40 (m, 5 H, C$_{Ar}$*H*);

^{13}C-NMR (CDCl$_3$, 100.65 MHz): δ = 19.7 C-1', 26.4 C-1, 114.3 C-5, 125.1, 126.6 C$_{Ar}$, 127.4, 128.2 C$_{Ar}$.

Analytical data match well those described in literature.[132]

Attempted synthesis of 3-phenyl-acrylic acid methyl ester 75a, 3-(4-methoxy-phenyl)-acrylic acid methyl ester 75b and 3-(4-nitro-phenyl)-acrylic acid methyl ester 75c.

Synthesis of phenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate 74a



74a

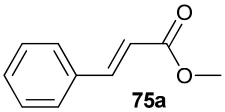
In a dry 100 ml one necked round bottom flask equipped with magnetic stirrer and three way tap with argon supply 4.71 g (50.0 mmol) of phenol are dissolved in 50 ml THF. The solution is cooled to 0°C and 7.588 g (75.0 mmol) of NEt_3 are added dropwise. The mixture is stirred for 10 minutes at the same temperature and 18.114 g (59.9 mmol) of NfF **7** are added dropwise within 3 minutes. With completed addition the reaction solution is allowed to come to room temperature. After stirring for 18 hours at ambient temperature ^{1}H-NMR-control indicates full conversion of the starting material. The solvent gets removed under reduced pressure, 50 ml of water are added and the product is extracted 3 times with 120 ml of *n*-hexane. The combined organic layers are washed with brine, dried over $MgSO_4$ and the solvent gets removed under reduced pressure. The crude yellow oil is submitted to flash column chromatography (*n*-hexane as eluent) to afford 18.471 g (49.1 mmol, 98%) of phenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate **74a** as a slightly yellowish oil.

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 7.27-7.30 (m, 2 H), 7.36-7.41 (m, 1 H), 7.43-7.47. (m, 2 H);

^{13}C-NMR (100.65 MHz): δ = 121.3 (2), 128.3, 130.2 (2), 149.7.

Analytical data match well those described in literature.[133]

Attempted synthesis of 3-phenyl-acrylic acid methyl ester 75a



75a

The synthesis was carried out according to the general procedure GP-3.

Phenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate **74a**: (379.3 mg, 1.0 mmol),

Methyl acrylate **44**: 114.7 mg, 1.33 mmol,

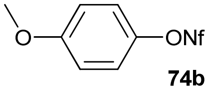
NEt_3: 203 mg, 2.0 mmol,

$PdCl_2$: 9.0 mg, 0.05 mmol, 5 mol%,

1 ml DMF.

The room temperature reaction showed no product formation within 4 days. Heating for 24 hours at 50°C did not indicate conversion of the starting material and heating of the reaction mixture to 60°C for 24 hours afforded also no product and led to the formation of Pd_{black}.

Synthesis of 4-methoxyphenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate 74b


74b

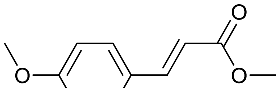
In a dry 100 ml one necked round bottom flask equipped with magnetic stirrer and three way tap with argon supply 6.207 g (50.0 mmol) of *p*-methoxyphenol are dissolved in 50 ml THF. The solution is cooled to 0°C and 7.590 g (75.0 mmol) of NEt_3 are added dropwise. The mixture is stirred for 15 minutes at the same temperature and 18.125 g (60 mmol) of NfF **7** are added dropwise within 2 minutes. With completed addition the reaction solution is allowed to come to room temperature. After stirring for 14 hours at ambient temperature ^{1}H-NMR-control indicates full conversion of the starting material. The solvent gets removed under reduced pressure, 50 ml of water are added and the product extracted 3 times with 125 ml of *n*-hexane. The combined organic layers are washed with brine, dried over $MgSO_4$ and the solvent gets removed under reduced pressure. The crude yellow oil is submitted to Kugelrohr distillation (7 mbar / 125°C) to afford 20.05 g (49.4 mmol, 99%) of 4-methoxyphenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate **74b** as slightly yellowish oil.

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 3.82 (s, 3 H, O-C*H*$_3$), 6.92 (d, ^3J = 9.2 Hz, 2 H), 7.20 (d, ^3J = 9.2 Hz, 2 H);

^{13}C-NMR (100.65 MHz): δ = 55.7, 115.0 (2), 122.4 (2), 143.3, 159.0.

Analytical data match well those described in literature.[134]

Attempted synthesis of 3-(4-methoxy-phenyl)-acrylic acid methyl ester 75b


75b

The synthesis was carried out according to the general procedure GP-3.

Methoxyphenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate **74b**: (406.5 mg, 1.0 mmol),

Methyl acrylate **44**: 112 mg, 1.30 mmol,

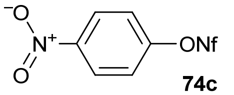
NEt_3: 202.6 mg, 2.0 mmol,

$Pd(OAc)_2$: 11.0 mg, 0.049 mmol, 5 mol%,

1 ml DMF.

The room temperature reaction showed no product formation within 25 hours. Heating of the reaction mixture to 50°C for 24 hours afforded no product and led to the formation of a Pd-mirror on the glass wall of the vial. Additional heating up to 75°C for 15 hours led to a partially removed Pd-mirror and a bright brown reaction mixture without product formation.

Synthesis of 4-nitrophenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate 74c



74c

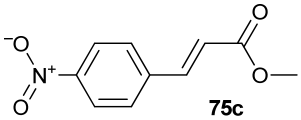
In a dry 50 ml one necked round bottom flask equipped with magnetic stirrer and three way tap with argon supply 3.50 g (25.2 mmol) of *p*-nitrophenol and 8.683 g (28.7 mmol) of NfF **7** are dissolved in 25 ml dry CH_2Cl_2. The solution is cooled to 10°C and 3.663 g (36.2 mmol) of NEt_3 are added dropwise leading immediately to a bright yellow solution. The mixture is stirred for 30 minutes at the same temperature and allowed to come to room temperature afterwards. TLC-control after stirring for 20 hours at ambient temperature indicates full conversion of the starting material. The solvent gets removed under reduced pressure, 40 ml of water are added and the product is extracted 4 times with 80 ml of MTBE. The combined organic layers are washed with brine, dried over $MgSO_4$ and the solvent gets removed under reduced pressure. The crude ivory coloured residue is submitted to flash column chromatography (MTBE : *n*-hexane = 1 : 20) to afford 9.05 g (21.5 mmol, 85%) of 4-nitrophenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate **74c** as white solid.

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 7.50 (d, ^3J = 9.2 Hz, 2 H), 8.37 (d, ^3J = 9.2 Hz, 2 H);

^{13}C-NMR (100.65 MHz): δ = 122.5 (2), 126.0 (2), 147.1, 153.4.

Analytical data match well those described in literature.[135]

Synthesis of 3-(4-nitro-phenyl)-acrylic acid methyl ester 75c



75c

The synthesis was carried out according to the general procedure GP-3.

4-Nitrophenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate **74c**: (422.8 mg, 1.0 mmol),

Methyl acrylate **44**: 120.5 mg, 1.40 mmol,

NEt_3: 211.3 mg, 2.09 mmol,

$Pd(OAc)_2$: 11.2 mg, 0.049 mmol, 5 mol%,

1 ml DMF.

The reaction progress was monitored by GC-MS and ^{1}H-NMR. No conversion was monitored while stirring the reaction solution for 24 hours at room temperature. Heating of the mixture to 60°C for 40 hours led to ≥99% conversion of the starting material. Among side product formation, circa 40% (by Peak Area %) of the desired 3-(4-nitro-phenyl)-acrylic acid methyl ester **75c** could be detected (this value has to be considered with some reservation since no response factors could be determined). The reaction mixture was not submitted to work up.

Selected peaks from ^{1}H-NMR reaction control:

For (*E*)-**75c** (400.23 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, O*Me*), 6.57 (d, ^3J = 16.1 Hz, 1 H), 7.68 (d, ^3J = 8.9 Hz, 2 H, $C_{Ar}H$), 7.72 (d, ^3J = 16.1 Hz, 1 H), 8.25 (d, ^3J = 8.9 Hz, 2 H, $C_{Ar}H$).

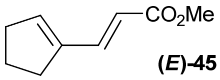
Analytical data for the double bond geometry match well those described in literature.[136]

7.2.4. Reactions of Chapter 4

GP-4 General procedure for the synthesis of alkenyl nonaflates from aldehydes and cyclic ketones and subsequent Heck-coupling to conjugated dienes – one-pot Heck cross-coupling protocol starting from carbonyl compounds (unless stated otherwise):

Into a dry one-necked round bottom flask equipped with magnetic stirring bar and a three way tap DMF, the carbonyl compound **27** or **41** and NfF **7** are added consecutively in an argon atmosphere (all via syringe). The reaction mixture is cooled to 0°C and under vigorous stirring the P-base **29**/**30** gets added dropwise. With complete addition the three way tap is replaced by a glass stopper and the flask is closed tightly. The solution is allowed to warm up to room temperature slowly and is stirred for the stated time (reaction control via ^{1}H-NMR). With completed alkenyl nonaflate formation 2.0 equivalent of Et_3N, 1.3 equivalent of the alkene and $Pd(OAc)_2$ (*ca*. 5 mol.%) are added. The reaction mixture is stirred for the designated amount of time (see Tables 34-37, 39) at ambient temperature. After full conversion is obtained the reaction mixture is quenched with water (5 ml / mmol carbonyl compound) and extracted with *n*-pentane (4 times 25 ml / mmol carbonyl compound). The combined organic phases are washed with water (20 ml / mmol carbonyl compound) and dried over Na_2SO_4. The solvent is removed under reduced pressure and the residue is purified by either column chromatography (silica gel, *n*-hexane : EtOAc = 20 : 1 as eluent unless stated otherwise) or Kugelrohr distillation to give the pure conjugated dienes.

Synthesis of (*E*)-methyl 3-cyclopentenyl acrylate (*E*)-45



(*E*)-45

The synthesis was carried out according to the general procedure GP-4.

1.) Cyclopentanone **27a**: 171 mg, 2.0 mmol,
NfF **7**: 814 mg, 2.7 mmol,
P_1-base **29**: 735 mg, 2.35 mmol,
2 ml DMF.

2.) NEt_3: 407.8 mg, 4.03 mmol,
Methyl acrylate **44**: 227.4 mg, 2.64 mmol,
$Pd(OAc)_2$: 22.45 mg, 0.1 mmol, 5 mol%.

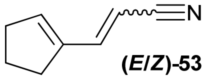
After column chromatography (*E*)-**45** was obtained as white solid (248 mg, 1.63 mmol, 80% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.94–2.01 (m, 2 H, CH_2-C*H*$_2$), 2.41–2.53 (m, 4 H, C*H*$_2$), 3.75 (s, 3 H, OMe), 5.74 (d, ^3J = 15.6 Hz, 1 H, CH=C*H*CO_2Me), 6.18 (m$_c$, 1 H, C*H*=C), 7.51 (d, ^3J = 15.6 Hz, 1 H, C*H*=CHCO_2Me);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 23.1, 30.8 and 33.5 (all CH_2), 51.5 (OMe), 117.7 (CH), 140.7, 141.1 (all CH), 141.4 (CH=*C*), 167.9 (C=O).

Analytical data match well those described in literature.[8b]

Synthesis of (*E*/*Z*)-3-cyclopentenyl-acrylonitrile (*E*/*Z*)-53



(*E*/*Z*)-53

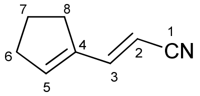
The synthesis was carried out according to the general procedure GP-4.

1.) Cyclopentanone **27a**: 87.2 mg, 1.04 mmol,
NfF **7**: 378 mg, 1.25 mmol,
P_1-base **29**: 383 mg, 1.22 mmol,
1 ml DMF.

2.) NEt_3: 208 mg, 2.06 mmol,
Acrylonitrile **48**: 75 mg, 1.41 mmol,
$Pd(OAc)_2$: 11.2 mg, 0.049 mmol, 5 mol%.

After column chromatography (*E*/*Z*)-**53** was obtained in a ratio of (*E*)-**53**:(*Z*)-**53** of 3.8:1 as slightly yellowish oil (95.1 mg, 0.8 mmol, 77% yield).

(*E*)-3-cyclopentenyl-acrylonitrile <u>(*E*)-53</u>



(*E*)-53

^{1}H-NMR (C_6D_6, 400 MHz): δ = 1.47 (quint, ^3J = 7.5 Hz, 2 H, 7-CH$_2$), 1.71–1.77 (m, 2 H) and 1.94–2.01 (m, 2 H) (6-CH$_2$ and 8-CH$_2$), 4.47 (d, ^3J = 16.3 Hz, 1 H, 2-CH), 5.41 (br.s, 1 H, 5-CH), 6.55 (d, ^3J = 16.3 Hz, 1 H, 3-CH);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 22.9 (7-CH$_2$), 30.2 and 33.6 (6-CH$_2$ and 8-CH$_2$), 95.7 (2-CH), 118.6 (CN), 140.9 (4-C), 141.8 (5-CH), 146.7 (3-CH);

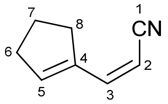
IR (film): $\tilde{\nu}$ = 2925, 2855 cm^{-1} (=C–H, C–H), 1665 cm^{-1} (C=C);

MS (EI, 80 eV): m/z (%) = 119 (M$^+$, 100), 91 ([M$^+$ – 28], 43);

HRMS: calculated for C_8H_9N (M$^+$) 119.0735, found 119.0739;

C,H,N-analysis (%): calculated for C_8H_9N (119.164): C, 80.63; H, 7.61; N, 11.75;
found C, 80.20; H, 7.43; N, 11.67.

(*Z*)-3-cyclopentenyl-acrylonitrile <u>(*Z*)-53</u>



(*Z*)-53

^{1}H-NMR (C_6D_6, 400 MHz): δ = 1.55 (quint, ^3J = 7.6 Hz, 2 H, 7-CH$_2$), 1.92–1.98 (m, 2 H) and 2.74 (m$_c$, 2 H) (6-CH$_2$ and 8-CH$_2$), 4.41 (d, ^3J = 11.7 Hz, 1 H, 2-CH), 5.58 (br.s, 1 H, 5-CH), 6.06 (d, ^3J = 11.7 Hz, 1 H, 3-CH);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 23.7 (7-CH$_2$), 31.5 and 32.6 (6-CH$_2$ and 8-CH$_2$), 93.4 (2-CH), 117.9 (CN), 141.4 (4-C), 143.6 and 145.2 (5-CH and 3-CH);

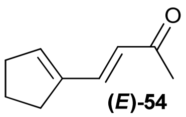
IR (film): $\tilde{\nu}$ = 2925, 2855 cm^{-1} (=C–H, C–H), 1665 cm^{-1} (C=C);

MS (EI, 80 eV): m/z (%) = 119 (M$^+$, 100), 91 ([M$^+$ – 28], 43);

HRMS: calculated for C_8H_9N (M$^+$) 119.0735, found 119.0739;

C,H,N-analysis (%): calculated for C_8H_9N (119.164): C, 80.63; H, 7.61; N, 11.75;
found C, 80.20; H, 7.43; N, 11.67.

Synthesis of (*E*)-4-cyclopentenyl but-3-en-2-one <u>(*E*)-54</u>



(*E*)-54

The synthesis was carried out according to the general procedure GP-4.

1.) Cyclopentanone **27a**: 84.3 mg, 1.0 mmol,
NfF **7**: 377 mg, 1.25 mmol,
P_1-base **29**: 370 mg, 1.18 mmol,
1 ml DMF.

2.) NEt_3: 204 mg, 2.02 mmol,
Methyl vinyl ketone **49**: 94 mg, 1.34 mmol,
$Pd(OAc)_2$: 11.2 mg, 0.049 mmol, 5 mol%.

Kugelrohr distillation (1 mbar, 73°C) afforded (*E*)-**54** as colorless oil (125.3 mg, 0.92 mmol, 92% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.94–2.01 (m, 2 H, CH_2-CH_2), 2.29 (s, 3 H, CH_3), 2.43-2.54 (m, 4 H, CH_2), 6.0 (d, ^3J = 16.0 Hz, 1 H, CH=C*H*C(O)Me), 6.24 (m_c, 1 H, C*H*=C), 7.35 (d, ^3J = 16.0 Hz, 1 H, C*H*=CHC(O)Me);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 23.1 (CH_2), 27.1 (CH_3), 30.8, 33.6 (both CH_2), 127.6, 139.8, 141.8 (all CH), 141.8 (CH=*C*), 199.1 (C=O).

Analytical data match well those described in literature.[137]

Synthesis of 1-(1-ethoxyethenyl)cyclopentene 55a and (*E*)-1-(2-ethoxyethenyl) cyclopentene (*E*)-55b

The synthesis was carried out in two ways, once according to the general procedure GP-4 (Synthesis A) and in a second manner with addition of TFA prior to the coupling step (Synthesis B).

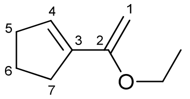
Synthesis A: The coupling step was carried out at 50°C.

1.) Cyclopentanone **27a**: 85.4 mg, 1.02 mmol,
NfF **7**: 362 mg, 1.16 mmol,
P_1-base **29**: 357 mg, 1.18 mmol,
1 ml DMF.

2.) NEt_3: 203 mg, 2.0 mmol,
Ethyl vinyl ether **50**: 102 mg, 1.41 mmol,
$Pd(OAc)_2$: 11.3 mg, 0.049 mmol, 5.0 mol%.

Kugelrohr distillation at 58°C (1.0 mbar) furnished the product as colorless oil (74 mg, 0.54 mmol, 53% yield, ratio of regioisomers **55a** and (*E*)-**55b** = 5.9:1).

1-(1-ethoxyethenyl)cyclopentene 55a



55a

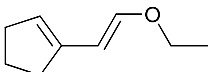
^{1}H-NMR (C$_6$D$_6$, 400 MHz): δ = 1.12 (t, ^{3}*J* = 7.0 Hz, 3 H, OCH$_2$*Me*), 1.75 (m$_c$, 2 H, 6-CH$_2$), 2.31 (m$_c$, 2 H) and 2.45 (m$_c$, 2 H) (5-CH$_2$ and 7-CH$_2$), 3.55 (q, ^{3}*J* = 6.9 Hz, 2 H, OC*H$_2$*Me), 4.07 (d, ^{2}*J* = 1.6 Hz, 1 H, 1-CH$_2$), 4.20 (d, ^{2}*J* = 1.6 Hz, 1 H, 1-CH$_2$), 5.07 (br.s, 1 H, =CH$_2$), 6.30 (quint, *J* = 2.2 Hz, 1 H, 4-CH);

^{13}C-NMR (C$_6$D$_6$, 100.65 MHz): δ = 14.6 (OCH$_2$*Me*), 23.6 (6-CH$_2$), 32.7 and 33.3 (5-CH$_2$ and 7-CH$_2$), 62.6 (O*C*H$_2$Me), 83.4 (1-CH$_2$), 127.98 (4-CH), 139.9 (3-C), 158.4 (2-C);

MS (EI, 80 eV): m/z (%) = 138 (M$^+$, 18), 123 ([M$^+$ – Me], 100), 110 ([M$^+$ – C$_2$H$_4$], 71);

HRMS: calculated for C$_9$H$_{14}$O (M$^+$) 138.1045, found 138.1049;

(*E*)-1-(2-ethoxyethenyl) cyclopentene (*E*)-55b



(*E*)-55b

NMR (selected signals):

^{1}H-NMR (C$_6$D$_6$, 400 MHz), δ = 1.01 (t, ^{3}*J* = 7.1 Hz, 3 H, OCH$_2$*Me*), 3.42 (q, ^{3}*J* = 7.0 Hz, 2 H, OC*H$_2$*Me), 5.50 (m$_c$, 1 H, C*H*=C), 5.90 (d, ^{3}*J* = 12.9 Hz, 1 H, C*H*=CHOEt), 6.49 (d, ^{3}*J* = 12.9 Hz, 1 H, CH=C*H*OEt);

^{13}C-NMR (C$_6$D$_6$, 100.65 MHz), δ = 14.8 (OCH$_2$*Me*), 23.7, 31.9 and 32.8 (all CH$_2$), 64.9 (O*C*H$_2$Me), 104.2, 125.0 and 148.5 (all CH);

MS (EI, 80 eV): m/z (%) = 138 (M$^+$, 18), 123 ([M$^+$ – Me], 100), 110 ([M$^+$ – C$_2$H$_4$], 71);

HRMS: calculated for C$_9$H$_{14}$O (M$^+$) 138.1045, found 138.1049;

Synthesis B: Subsequent to the formation of alkenyl nonaflate **28a** (Step 1) the reaction mixture was cooled to 0°C and acidified with trifluoroacetic acid (Step 2). The solution was stirred and allowed to come to room temperature within 15 minutes. The coupling components were added consecutively at room temperature and the reaction solution stirred for 70 hours (Step 3).

1.) Cyclopentanone **27a**: 84.7 mg, 1.01 mmol,
NfF **7**: 360 mg, 1.19 mmol,
P$_1$-base **29**: 361 mg, 1.16 mmol,
1 ml DMF.

2.) TFA: 67 mg; 0.59 mmol,

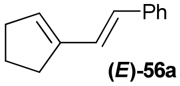
3.) NEt$_3$: 253 mg, 2.51 mmol,

Ethyl vinyl ether **50**: 100 mg, 1.38 mmol,
Pd(OAc)$_2$: 11.1 mg, 0.049 mmol, 4.9 mol%.

Kugelrohr distillation at 60°C (1.5 mbar) furnished the product as colorless oil but as a mixture of **55a**, (*E*)-**55b** and at least one unidentified side product in larger amount (104 mg, 0.84 mmol, 83% yield, ratio of regioisomers **55a** and (*E*)-**55b** = 9.1:1).

The analytical data obtained in this experiment for **55a** and (*E*)-**55b** matches well those described above.

Synthesis of (*E*)-(2-cyclopent-1-enyl-ethenyl)benzene (*E*)-56a



(*E*)-56a

The synthesis was carried out according to the general procedure GP-4. Subsequent to the formation of alkenyl nonaflate **28a** (Step 1) the reaction mixture was cooled to 0°C and acidified with trifluoroacetic acid (Step 2). The solution was stirred and allowed to come to room temperature within 15 minutes. The coupling components were added consecutively at room temperature (Step 3).

1.) Cyclopentanone **27a**: 84.3 mg, 1.0 mmol,
NfF **7**: 364 mg, 1.20 mmol,
P_1-base **29**: 364 mg, 1.16 mmol,
1 ml DMF.
2.) TFA: 67 mg; 0.59 mmol,
3.) NEt$_3$: 260 mg, 2.57 mmol,
Styrene **51**: 138 mg, 1.33 mmol,
Pd(OAc)$_2$: 11.3 mg, 0.049 mmol, 5 mol%.

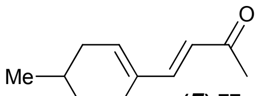
Flash column chromatography with *n*-pentane furnished as the sole product (*E*)-**56a** as white solid (150.3 mg, 0.88 mmol, 88% yield).

^{1}H-NMR (CDCl$_3$, 400 MHz): δ = 1.97 (q, 2 H, CH$_2$-C*H*$_2$-CH$_2$), 2.47 (m, 2 H, C-C*H*$_2$), 2.55 (m, 2 H, CH-C*H*$_2$), 5.85 (m, 1 H, C-C*H*), 6.41 (d, ^{3}J = 16.1 1 H, C*H*), 7.01 (d, ^3J = 16.1 Hz, 1 H, C*H*), 7.16-7.23 (m, 1 H, C$_{Ar}$*H*), 7.26-7.34 (m, 2 H, C$_{Ar}$*H*), 7.41 (m, 2 H, C$_{Ar}$*H*);

^{13}C-NMR (CDCl$_3$, 100.65 MHz): δ = 23.2, 31.2, 33.0 (all *C*H$_2$), 125.8, 126.2 (*C*$_{Ar}$H), 127.1, 128.6 (*C*$_{Ar}$H), 128.7, 132.0, 137.8 (CH-*C*$_{Ar}$), 142.8 (CH-*C*).

Analytical data match well those described in literature.[8b]

Synthesis of (*E*)-4-(4-methylcyclohex-1-enyl)but-3-en-2-one <u>(*E*)-77</u>



(*E*)-77

The synthesis was carried out according to the general procedure GP-4.

1.) 4-Methylcyclohexanone **27b**: 114 mg, 1.02 mmol,
NfF **7**: 357.4 mg, 1.18 mmol,
P_1-base **29**: 360 mg, 1.15 mmol,
1 ml DMF.

2.) NEt_3: 206.3 mg, 2.04 mmol,
Methyl vinyl ketone **49**: 94 mg, 1.34 mmol,
$Pd(OAc)_2$: 11.2 mg, 0.049 mmol, 5 mol%.

Kugelrohrdistillation (1.0 mbar at 80-88°C) afforded (*E*)-**77** as slightly yellowish oil (142 mg, 0.86 mmol, 85% yield).

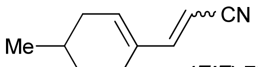
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 0.99 (d, ^3J =6.6 Hz, 3 H, CH-C*H*$_3$), 1.23–1.33 (m, 1 H, CH$_3$-C*H*), 1.64–1.76 (m, 1 H, C*H*$_2$), 1.78–1.89 (m, 2 H, C*H*$_2$), 2.08–2.19 (m, 1 H, C*H*$_2$), 2.21-2.36 (m, 2 H, C*H*$_2$), 2.28 (s, 3 H, C(O)-C*H*$_3$), 6.05 (d, ^3J = 16.0 Hz, 1 H, CH=C*H*C(O)Me), 6.19 (b r.s, 1 H, C*H*=C), 7.13 (d, ^3J = 16.1 Hz, 1 H, C*H*=CHC(O)Me);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 21.5 (CH-*C*H$_3$), 24.1 (*C*H$_2$), 27.2 (*C*H-CH$_3$), 28.2 (C(O)-*C*H$_3$), 30.3 (*C*H$_2$), 35.1 (*C*H$_2$), 124.4 (CH-*C*), 134.9 (*C*-CH), 139.5 (C=*C*H), 146.8 (C-*C*H), 199.1 (C=O);

MS (EI, 80 eV): m/z (%) = 121 ([C_9H_{13}•], 100), 164 (M^+, 68), 150 ([$M^+ - CH_3$], 31);

HRMS: calculated for $C_{11}H_{16}O$ (M^+) 164.1201, found 164.1206.

Synthesis of (*E*/*Z*)-3-(4-methylcyclohex-1-enyl)acrylonitrile <u>(*E*/*Z*) 78</u>



(*E*/*Z*)-78

The synthesis was carried out according to the general procedure GP-4. The cross-coupling reaction was carried out for 24 hours at 40°C.

1.) 4-Methylcyclohexanone **27b**: 137.6 mg, 1.23 mmol,
NfF **7**: 507 mg, 1.68 mmol,
P_1-base **29**: 448 mg, 1.43 mmol,
1 ml DMF.

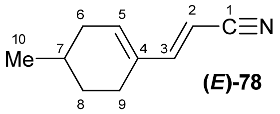
2.) NEt_3: 250 mg, 2.47 mmol,

Acrylonitrile **48**: 105 mg, 1.98 mmol,

$Pd(OAc)_2$: 11.2 mg, 0.049 mmol, 5 mol%.

After column chromatography (*n*-pentane : MTBE = 8 : 1) (*E*/*Z*)-**78** was obtained as yellowish oil (172 mg, 1.17 mmol, 95% yield, (*E*:*Z*)-ratio of 2.9:1).

(*E*)-3-(4-methylcyclohex-1-enyl)acrylonitrile (*E*)-78



(*E*)-78

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 0.99 (d, ^3J = 6.6 Hz, 3 H, 10-C*H*$_3$), 1.22-1.32 (m, 1 H, 7-C*H*), 1.62-1.74 (m, 1 H, C*H*$_2$), 1.78-1.88 (m, 2 H, C*H*$_2$), 2.01-2.21 (m, 2 H, C*H*$_2$), 2.32 (m, 1 H, C*H*$_2$), 5.18 (d, ^3J = 16.4 Hz, 1 H, 2-C*H*), 6.13 (br.s, 1 H, 5-C*H*), 7.0 (d, ^3J = 16.1 Hz, 1 H, 3-C*H*);

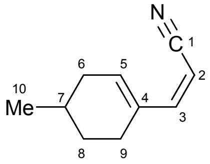
^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 21.4 (10-*C*H$_3$), 23.3 (*C*H$_2$), 28.0 (7-*C*H), 29.9 (*C*H$_2$), 34.7 (*C*H$_2$), 92.5 (2-*C*H), 119.0 (1-*C*N), 134.3 (4-*C*H), 139.6 (5-*C*H), 153.4 (3-*C*H);

MS (EI, 80 eV): m/z (%) = 69 ([M$^+$ – 78], 100), 131 ([M$^+$ – 17], 71), 118 ([M$^+$ – 29], 66), 147 (M$^+$, 50), 77 ([M$^+$ – 70], 47), 105 ([M$^+$ – 42], 45), 100 ([M$^+$ – 47], 40);

HRMS: calculated for $C_{10}H_{13}N$ (M$^+$) 147.1048, found 147.1033;

C,H,N-analysis (%): calculated for $C_{10}H_{13}N$ (147.217): C, 81.59; H, 8.90; N, 9.51;
found C, 78.53; H, 8.65; N, 9.03.

(*Z*)-3-(4-methylcyclohex-1-enyl)acrylonitrile (*Z*)-78



(*Z*)-78

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 0.99 (d, ^3J = 6.6 Hz, 3 H, 10-C*H*$_3$), 1.22-1.32 (m, 1 H, 7-C*H*), 1.62-1.74 (m, 1 H, C*H*$_2$), 1.78-1.88 (m, 2 H, C*H*$_2$), 2.32 (m, 1 H, C*H*$_2$), 2.46-2.58 (m, 1 H, C*H*$_2$), 2.32 (m, 1 H, C*H*$_2$), 5.04 (d, ^3J = 12.0 Hz, 1 H, 2-C*H*), 6.13 (br.s, 1 H, 5-C*H*), 6.61 (d, ^3J = 12.0 Hz, 1 H, 3-C*H*);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 21.5 (10-*C*H$_3$), 25.3 (*C*H$_2$), 27.6 (7-*C*H), 30.2 (*C*H$_2$), 34.8 (*C*H$_2$), 90.8 (2-*C*H), 118.1 (1-*C*N), 135.5 (4-*C*H), 140.3 (5-*C*H), 151.7 (3-*C*H);

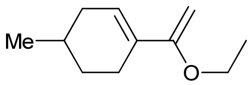
MS (EI, 80 eV): m/z (%) = 69 ([M$^+$ – 78], 100), 131 ([M$^+$ – 17], 71), 118 ([M$^+$ – 29], 66), 147 (M$^+$, 50), 77 ([M$^+$ – 70], 47), 105 ([M$^+$ – 42], 45), 100 ([M$^+$ – 47], 40);

HRMS: calculated for $C_{10}H_{13}N$ (M$^+$) 147.1048, found 147.1033;

C,H,N-analysis (%): calculated for $C_{10}H_{13}N$ (147.217): C, 81.59; H, 8.90; N, 9.51;

found C, 78.53; H, 8.65; N, 9.03.

Synthesis of 1-(1-Methoxy-vinyl)-4-methyl-cyclohexene 79a



79a

The synthesis was carried out according to the general procedure GP-4. The cross-coupling reaction was carried out for 24 hours at 40°C.

1.) 4-Methylcyclohexanone **27b**: 117.5 mg, 1.05 mmol,
NfF **7**: 390 mg, 1.29 mmol,
P_1-base **29**: 470 mg, 1.50 mmol,
1 ml DMF.

2.) NEt_3: 207 mg, 2.05 mmol,
Ethyl vinyl ether **50**: 105 mg, 1.46 mmol,
$Pd(OAc)_2$: 11.2 mg, 0.049 mmol, 5 mol%.

After Kugelrohr distillation (94°C at 5 mbar) **79a** was obtained as colourless liquid (140 mg, 0.84 mmol, 80% yield). The product **79a** is accompanied by 10% of the regioisomer (*E*)-1-(2-ethoxyvinyl)-4-methylcyclohex-1-ene (*E*)-**79b**.

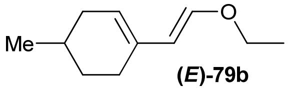
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 0.96 (d, ^3J = 6.5 Hz, 3 H, CH-C*H*$_3$), 1.19-1.31 (m, 1 H, C*H*-CH$_3$), 1.35 (t, ^3J = 7.0 Hz, 3 H, CH$_2$-C*H*$_3$), 1.59-1.80 (m, 3 H, C*H*$_2$), 2.08-2.29 (m, 3 H, C*H*$_2$), 3.79 (q, ^3J = 7.0 Hz, 2 H, OC*H*$_2$Me), 3.99 (d, ^2J = 2.2 Hz, 1 H, =C*H*$_2$), 4.16 (d, ^2J = 2.2 Hz, 1 H, =C*H*$_2$), 6.29 (m, 1 H, C*H*);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 14.6 (CH$_2$-*C*H$_3$), 21.7 (CH-*C*H$_3$), 25.2 (*C*H$_2$), 28.2 (*C*H-CH$_3$), 31.0 (*C*H$_2$), 33.9 (*C*H$_2$), 62.7 (O-*C*H$_2$), 80.8 (=*C*H$_2$), 124.4 (*C*H), 131.7 (*C*=CH), 160.4 (*C*=CH$_2$);

MS (EI, 70 eV): m/z (%) = 89 ([M$^+$ – 77], 100), 101 ([M$^+$ – 65], 97), 117 ([M$^+$ – 49], 72), 69 ([M$^+$ – 97], 48), 131 ([M$^+$ – 35], 20),166 (M$^+$, 4);

HRMS: calculated for $C_{11}H_{18}O$ (M$^+$) 166.1358, found 166.1343.

(*E*)-1-(2-ethoxyvinyl)-4-methylcyclohex-1-ene (*E*)-79b



(*E*)-79b

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 0.95 (d, ^3J = 6.4 Hz, 3 H, CH-C*H*$_3$), 1.19-1.31 (m, 1 H, C*H*-CH$_3$), 1.29 (t, ^3J = 7.0 Hz, 3 H, CH$_2$-C*H*$_3$), 1.59-1.80 (m, 3 H, C*H*$_2$), 2.08-2.29 (m, 3 H, C*H*$_2$), 3.79 (q, ^{3}*J* = 7.1 Hz, 2 H, OC*H*$_2$Me), 5.47 (m$_c$, 1 H, C*H*=C), 5.58 (d, ^{3}*J* = 12.9 Hz, 1 H, C*H*=CHOEt), 6.43 (d, ^{3}*J* = 12.9 Hz, 1 H, CH=C*H*OEt);

^{13}C-NMR (CDCl$_3$, 100.65 MHz): δ = 14.9 (CH$_2$-*C*H$_3$), 21.8 (CH-*C*H$_3$), 24.8 (*C*H$_2$), 28.7 (*C*H-CH$_3$), 30.8 (*C*H$_2$), 34.3 (*C*H$_2$), 65.2 (O-*C*H$_2$), 109.9 (*C*H), 123.3 (*C*H), 132.6 (*C*=CH), 145.0 (O-CH);

MS (EI, 70 eV): m/z (%) = 89 ([M$^+$ – 77], 100), 101 ([M$^+$ – 65], 97), 117 ([M$^+$ – 49], 72), 69 ([M$^+$ – 97], 48), 131 ([M$^+$ – 35], 20),166 (M$^+$, 4);

HRMS: calculated for $C_{11}H_{18}O$ (M$^+$) 166.1358, found 166.1343.

Synthesis of 1-hex-1-enyl-4-methyl-cyclohexene (*E*)-80a, 4-methyl-1-(1-pentyl-vinyl)-cyclohexene 80b and 1-hex-2-enyl-4-methylcyclohex-1-ene 80c

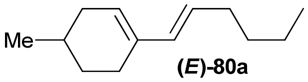
The synthesis was carried out according to the general procedure GP-4. The cross-coupling reaction was carried out for 17 hours at 40°C.

1.) 4-Methylcyclohexanone **27b**: 112.2 mg, 1.0 mmol,
NfF **7**: 375 mg, 1.24 mmol,
P$_1$-base **29**: 444 mg, 1.42 mmol,
1 ml DMF.

2.) NEt$_3$: 210 mg, 2.08 mmol,
1-hexene **52**: 120 mg, 1.43 mmol,
Pd(OAc)$_2$: 11.2 mg, 0.049 mmol, 5 mol%.

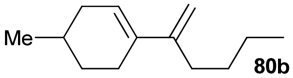
Flash column chromatography (*n*-hexane) furnished the product as a mixture of regioisomers (*E*)-**80a**, **80b** and **80c** (ratio: 62:18:20) as colorless oil (156 mg, 0.87 mmol, 87% yield).

1-Hex-1-enyl-4-methyl-cyclohexene (*E*)-80a



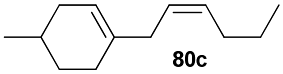
(*E*)-80a

4-Methyl-1-(1-pentyl-vinyl)-cyclohexene 80b



80b

1-Hex-2-enyl-4-methylcyclohex-1-ene 80c



80c

A mixture of all three isomers (*E*)-**80a**:**80b**:**80c** = 62:18:20.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.89 (t, ^3J = 7.4 Hz, 3 H, CH_2-CH_3), 0.89 (t, ^3J = 7.2 Hz, 3 H, CH_2-CH_3, **80a**), 0.90 (t, ^3J = 7.1 Hz, 3 H, CH_2-CH_3), 0.93 (d, ^3J = 6.1 Hz, 3 H, CH-CH_3), 0.96 (d, ^3J = 6.4 Hz, 3 H, CH-CH_3, **80a**), 0.96 (d, ^3J = 6.5 Hz, 3 H, CH-CH_3), 1.24 (m, 1 H, C*H*-CH_3, all),1.28–1.45 (m), 1.56-1.80 (m), 1.91–2.30 (m), 2.60 (m, 1 H, C-CH_2-CH, **80c**) 4.80 and 4.95 (both br. s, 1 H, C=CH_2, **80b**) 5.35-5.42 (m, 3 H, C*H*, **80c**), 5.54 (m, 1 H, CH=C*H*, **80a**), 5.59 (m_c, 1 H, C=C*H*-CH_2, **80a**), 5.85 (m_c, 1 H, C=C*H*-CH_2, **80b**), 6.03 (d, ^3J = 15.6 Hz, 1 H, C*H*=CH, **80a**);

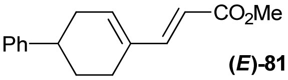
^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 13.7, 13.98 (**80a**), 14.0 (all CH_2-CH_3), 21.7, 21.81 (**80a**), 21.85 (all CH-CH_3), 22.3 (**80a**), 22.7, 22.8, 24.7 (**80a**), 26.1, 28.2, 28.50 (*C*H-CH_3), 28.53 (*C*H-CH_3), 28.7 (**80a**) (*C*H-CH_3), 30.9 (**80a**), 31.27, 31.30, 31.4, 31.9 (**80a**), 32.6 (**80a**), 33.5, 34.0, 34.3 (**80a**), 34.5, 34.7, 41.0 (C-CH_2-CH) (**80c**),108.6 (C-CH_2) (**80b**), 120.8 (*C*H) (**80c**), 123.7 (*C*H) (**80c**), 126.6 (*C*H) (**80a**), 127.0 (*C*H) (**80a**), 128.3 (*C*H) (**80a**), 131.6 (*C*H) (**80b**), 133.1 (*C*H) (**80a**), 135.3 (CH-*C*) (**80a**), 135.5 (*C*), 136.9 (*C*), 148.7 (*C*) (**80b**);

MS (EI, 80 eV): m/z (%) = 178 (M^+, 100), 79 ([M^+ – 99], 67), 93 ([M^+ – 85], 61), 103 ([M^+ – 75], 57), 131 ([M^+ – 47], 54), 135 ([M^+ – 43], [M^+-C_3H_7•], 35), 149 ([M^+ – 29], [M^+-C_2H_5•], 28);

HRMS: calculated for $C_{13}H_{22}$ (M^+) 178.1722, found 178.1709;

C,H-analysis (%): calculated for $C_{13}H_{22}$ (178.314): C, 87.56; H, 12.44;
found C, 83.00; H, 11.89.

Synthesis of (*E*)-methyl 3-(4-phenylcyclohex-1-enyl)acrylate (*E*)-81



(*E*)-81

The synthesis was carried out according to the general procedure GP-4.

1.) 4-Phenylcyclohexanone **27c**: 174.5 mg, 1.0 mmol,
NfF **7**: 378 mg, 1.25 mmol,
P_1-base **29**: 385 mg, 1.23 mmol,
1 ml DMF.

2.) NEt_3: 206 mg, 2.04 mmol,
Methyl acrylate **44**: 112.2 mg, 1.30 mmol,
$Pd(OAc)_2$: 11.2 mg, 0.049 mmol, 5 mol%.

After column chromatography (*n*-hexane : EtOAc = 30 : 1) (*E*)-**81** was obtained as white crystalline solid (219 mg, 0.90 mmol, 90% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.81 (m, 1 H, C*H*$_2$), 2.01-2.10 (m, 1 H, C*H*$_2$), 2.12-2.41 (m, 3 H, C*H*$_2$), 2.46-2.57 (m, 1 H, C*H*$_2$), 2.77-2.88 (m, 1 H, C$_{Ar}$-C*H*), 3.76 (s, 3 H, O-C*H*$_3$), 5.81 (d, ^3J = 15.7 Hz, 1 H, C(O)-C*H*), 6.25 (br.s, 1 H, C=C*H*), 7.22 (m, 3 H, C$_{Ar}$), 7.22 (m, 2 H, C$_{Ar}$), 7.35 (d, ^3J = 15.7 Hz, 1 H, C(O)-CH=C*H*);

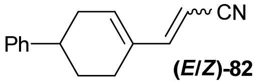
^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 24.7, 29.2, 34.4 (all *C*H$_2$), 39.7 (C$_{Ar}$-CH), 51.5 (O-*C*H$_3$), 114.9, 126.3, 126.8 (2x*C*$_{Ar}$), 128.5 (2x*C*$_{Ar}$), 134.7 (*C*=CH), 138.1, 146.1 (CH-*C*$_{Ar}$), 147.6, 168.0 (*C*=O);

MS (EI, 70 eV): m/z (%) = 104 ([M$^+$ – 138], [C_8H_8•], 100), 183 ([M$^+$ – 59], [$C_{14}H_{15}$•], 44), 242 (M$^+$, 37), 151 ([M$^+$ – 91], 26), 91 ([M$^+$ – 151], 15);

HRMS: calculated for $C_{16}H_{18}O_2$ (M$^+$) 242.1307, found 242.1271;

C,H-analysis (%): calculated for $C_{16}H_{18}O_2$ (242.313): C, 79.31; H, 7.49;
found C, 79.24; H, 7.54.

Synthesis of (*E*/*Z*)-3-(4-phenylcyclohex-1-enyl)acrylonitrile (*E*/*Z*)-82


(*E*/*Z*)-82

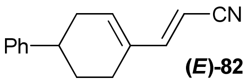
The synthesis was carried out according to the general procedure GP-4.

1.) 4-Phenylcyclohexanone **27c**: 174.2 mg, 1.0 mmol,
NfF **7**: 380 mg, 1.26 mmol,
P$_1$-base **29**: 380 mg, 1.22 mmol,
1 ml DMF.

2.) NEt$_3$: 207 mg, 2.05 mmol,
Acrylonitrile **48**: 88 mg, 1.66 mmol,
Pd(OAc)$_2$: 11.2 mg, 0.049 mmol, 5 mol%.

After column chromatography (*n*-hexane : EtOAc = 30 : 1) (*E*/*Z*)-**82** was obtained as white crystalline solid (178 mg, 0.85 mmol, 85% yield, (*E*:*Z*)-ratio of 1.74:1).

(*E*)-3-(4-phenylcyclohex-1-enyl)acrylonitrile (*E*)-82


(*E*)-82

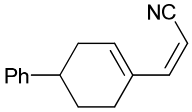
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.81 (m$_c$, 1 H, C$_{Ar}$-C*H*), 2.03-2.14 (m, 1 H, C*H*$_2$), 2.21-2.28 (m, 1 H, C*H*$_2$), 2.30-2.43 (m, 1 H, C*H*$_2$), 2.48-2.55 (m, 1 H, C*H*$_2$), 2.77-2.89 (m, 2 H, C*H*$_2$), 5.22 (d, ^3J = 16.4 Hz, 1 H, CN-C*H*), 6.25 (br.s, 1 H, C-C*H*), 7.05 (d, ^3J = 16.3 Hz, 1 H, C-C*H*=CH), 7.20-7.25 (m, 3 H, C_{Ar}), 7.30-7.34 (m, 2 H, C_{Ar});

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 23.9, 29.0, 34.3 (all CH_2), 39.5 (C_{Ar}-*C*H), 93.1 (CN-*C*H), 118.8 (*C*N), 126.4 (C_{Ar}), 126.8 (2xC_{Ar}H), 128.6 (2xC_{Ar}H), 134.4 (CH-*C*), 139.1 (C=*C*H), 145.6 (CH-C_{Ar}), 153.0 (C-*C*H);

MS (EI, 70 eV): m/z (%) = 104 ([M^+ – 105], [C_8H_8•], 100), 127 ([M^+ – 82], 49), 77 ([M^+ – 132], [C_6H_5•], 42), 209 (M^+, 32), 89 ([M^+ – 120], 23);

HRMS: calculated for $C_{15}H_{15}N$ (M^+) 209.1204, found 209.1182;

(*Z*)-3-(4-phenylcyclohex-1-enyl)acrylonitrile (*Z*)-82



(*Z*)-82

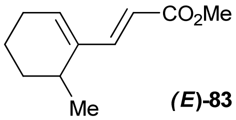
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.81 (m_c, 1 H, C_{Ar}-C*H*), 2.03-2.14 (m, 1 H, CH_2), 2.21-2.28 (m, 1 H, CH_2), 2.30-2.43 (m, 1 H, CH_2), 2.55-2.60 (m, 1 H, CH_2), 2.61-2.73 (m, 1 H, CH_2), 2.77-2.89 (m, 1 H, CH_2), 5.09 (d, ^3J = 12.1 Hz, 1 H, CN-C*H*), 6.25 (br.s, 1 H, C-C*H*), 6.65 (d, ^3J = 12.1 Hz, 1 H, C-C*H*=CH), 7.20-7.25 (m, 3 H, C_{Ar}), 7.30-7.34 (m, 2 H, C_{Ar});

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 26.1, 29.3, 34.4 (all CH_2), 39.1 (C_{Ar}-*C*H), 91.5 (CN-*C*H), 118.2 (*C*N), 126.4 (C_{Ar}), 126.8 (2xC_{Ar}H), 128.6 (2xC_{Ar}H), 135.6 (CH-*C*), 139.8 (C=*C*H), 145.8 (CH-C_{Ar}), 151.3 (C-*C*H);

MS (EI, 70 eV): m/z (%) = 104 ([M^+ – 105], [C_8H_8•], 100), 127 ([M^+ – 82], 49), 77 ([M^+ – 132], [C_6H_5•], 42), 209 (M^+, 32), 89 ([M^+ – 120], 23);

HRMS: calculated for $C_{15}H_{15}N$ (M^+) 209.1204, found 209.1182.

Synthesis of 3-(6-methyl-cyclohex-1-enyl)-acrylic acid methyl ester (*E*)-83



***(E)*-83**

The synthesis was carried out according to the general procedure GP-4. The alkenyl nonaflate formation was conducted at –20°C according to Table 3, Entry 7 with 2.0 equiv. of the P_2-base **30** and 2.0 equiv. of NfF **7**; <<1% of the undesired regioisomer **28k** could be detected after completed alkenyl nonaflate formation; the coupling reaction was initiated when ~99% conversion (65h) was obtained.

1.) 2-Methylcyclohexanone **27g**: 114 mg, 1.02 mmol,
NfF **7**: 625 mg, 2.07 mmol,

P$_2$-base **30**: 1.0 ml, 2.0 mmol,
1 ml DMF.

2.) NEt$_3$: 205.0 mg, 2.03 mmol,
Methyl acrylate **44**: 115 mg, 1.34 mmol,
Pd(OAc)$_2$: 11.4 mg, 0.051 mmol, 5 mol%.

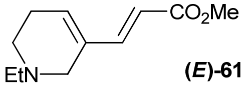
After column chromatography (*n*-hexane : EtOAc = 15 : 1) (*E*)-**83** was obtained as yellow oil (176 mg, 0.98 mmol, 96% yield).

^{1}H-NMR (CDCl$_3$, 400 MHz): δ = 1.10 (d, ^3J = 7.0 Hz, 3 H, CH-C*H*$_3$), 1.54–1.73 (m, 4 H, C*H*$_2$), 2.09-2.29 (m, 2 H, C*H*$_2$), 2.54 (m, 1 H, C*H*-CH$_3$), 3.75 (s, 3 H, O-C*H*$_3$), 5.82 (d, ^3J = 16.0 Hz, 1 H, C(O)-C*H*), 6.10 (t, ^3J = 4.0 Hz, 1 H, C=C*H*), 7.21 (d, ^3J = 16.0 Hz, 1 H, C-C*H*=CH);

^{13}C-NMR (CDCl$_3$, 100.65 MHz): δ = 17.2 (*C*H$_2$), 19.6 (CH-*C*H$_3$), 26.6 (*C*H$_2$), 27.5 (*C*H), 29.4 (*C*H$_2$), 51.4 (O-*C*H$_3$), 114.5 (C(O)-*C*H), 138.5 (C-*C*H-CH$_2$), 139.9 (CH-*C*), 147.8 (C-*C*H=CH), 168.2 (*C*=O).

Analytical data match well those described in literature.[138]

Synthesis of 3-(1-ethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-acrylic acid methyl ester (*E*)-61


(*E*)-61

The synthesis was carried out according to the general procedure GP-4.

1.) 1-Ethylpiperidin-3-one **27h**: 128.4 mg, 1.0 mmol,
NfF **7**: 366 mg, 1.21 mmol,
P$_1$-base **29**: 378 mg, 1.21 mmol,
1 ml DMF.

2.) NEt$_3$: 205 mg, 2.03 mmol,
Methyl acrylate **44**: 125.5 mg, 1.46 mmol,
Pd(OAc)$_2$: 11.2 mg, 0.049 mmol, 5 mol%.

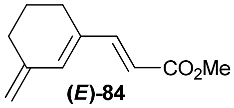
After column chromatography (*n*-hexane : EtOAc = 20 : 1) product (*E*)-**61** was obtained as yellow oil (161 mg, 0.82 mmol, 82% yield).

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 1.16 (t, ^3J = 7.4 Hz, 3 H, CH$_2$-C*H*$_3$), 2.39 (m, 2 H, CH-C*H*$_2$), 2.53-2.59 (m, 4 H, N-C*H*$_2$), 3.11 (m, 2 H, N-C*H*$_2$), 3.75 (s, 3 H, O-C*H*$_3$), 5.72 (d, ^3J = 15.6 Hz, 1 H, C(O)-C*H*), 6.20 (m, 1 H, C=C*H*), 7.27 (d, ^3J = 15.6 Hz, 1 H, C-C*H*=CH);

^{13}C-NMR (CDCl$_3$, 100.65 MHz): δ = 12.3 (CH$_2$-*C*H$_3$), 27.3 (CH-*C*H$_2$), 49.1 (*C*H$_2$), 51.46 (O-Me), 51.54 (*C*H$_2$), 52.1 (*C*H$_2$), 114.4 (C(O)-*C*H), 133.5 (CH-*C*), 136.1 (C-*C*H-CH$_2$), 145.4 (C-*C*H=CH), 167.8 (*C*=O);

Analytical data match well those obtained for the same compound in Chapter 3.

Synthesis of 3-(3-methylene-cyclohex-1-enyl)-acrylic acid methyl ester (*E*)-84



(*E*)-84

The synthesis was carried out according to the general procedure GP-4.

1.) 3-methylcyclohex-2-enone **76**: 113.5 mg, 1.03 mmol,
NfF **7**: 362.5 mg, 1.20 mmol,
P_1-base **29**: 380 mg, 1.21 mmol,
1 ml DMF.

2.) NEt_3: 205 mg, 2.03 mmol,
Methyl acrylate **44**: 116 mg, 1.35 mmol,
$Pd(OAc)_2$: 11.2 mg, 0.049 mmol, 5 mol%.

After flash column chromatography (*n*-pentane : MTBE = 15 : 1) (*E*)-**84** was obtained as orange colored oil (143 mg, 0.80 mmol, 78% yield).

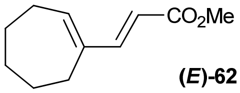
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.77 (quint, ^3J = 6.2 Hz, 2 H, C*H*$_2$), 2.24 (t, ^3J = 6.2 Hz, 2 H, C*H*$_2$), 2.34-2.38 (m, 2 H, C*H*$_2$), 3.76 (s, 3 H, O-C*H*$_3$), 5.02 (s, 1 H, =C*H*$_2$), 5.04 (s, 1 H, =C*H*$_2$), 5.91 (d, ^3J = 15.7 Hz, 1 H, C(O)-C*H*=CH), 6.46 (s, 1 H, C=C*H*), 7.34 (d, ^3J = 15.7 Hz, 1 H, C(O)-CH=C*H*);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 22.2, 24.2 and 30.1 (all *C*H$_2$), 51.5 (C(O)-*C*H$_3$), 115.7 (=*C*H$_2$), 116.5 (*C*H), 136.5 ($C_{\text{quart.}}$), 137.7 (*C*H), 143.3 ($C_{\text{quart.}}$), 147.1 (*C*H), 167.7 (C=O);

MS (EI, 70 eV): m/z (%) = 77 ([M^+- 101], 100), 89 ([M^+ – 89], 62), 153 ([M^+ – 25], 57), 105 ([M^+ – 73], 49), 136 ([M^+ – 42], 41);

HRMS: calculated for $C_{11}H_{14}O_2$ (M^+) 178.0994, found 178.0979.

Synthesis of (*E*)-methyl 3-cyclohept-1-enyl acrylate (*E*)-62



(*E*)-62

The synthesis was carried out according to the general procedure GP-4.

1.) Cycloheptanone **27d**: 112.4 mg, 1.0 mmol,
NfF **7**: 365 mg, 1.21 mmol,
P_1-base **29**: 375 mg, 1.20 mmol,
1 ml DMF.

2.) NEt_3: 202.5 mg, 2.0 mmol,
Methyl acrylate **44**: 118.4 mg, 1.38 mmol,

Pd(OAc)$_2$: 11.2 mg, 0.049 mmol, 5 mol%.

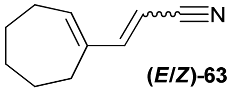
Column chromatography (*n*-hexane : EtOAc = 15 : 1) furnished the product (*E*)-**62** as colorless oil (140.1 mg, 0.78 mmol, 78 % yield).

^{1}H-NMR (CDCl$_3$, 400 MHz): δ = 1.50-1.57 (m, 4 H, 2 CH$_2$), 1.75-1.81 (m, 2 H, CH$_2$), 2.27-2.34 (m, 4 H, 2 CH$_2$), 3.74 (s, 3 H, Me), 5.80 (d, ^3J = 15.7 Hz, 1 H, C(O)C*H*=CH), 6.36 (t, ^3J = 6.8 Hz, 1 H, C*H*=C), 7.28 (d, ^3J = 15.7 Hz, 1 H, C(O)CH=C*H*);

^{13}C-NMR (C$_6$D$_6$), 100.65 MHz): δ = 26.1, 26.4, 27.3, 29.1, 32.0 (all *C*H$_2$), 51.0 (Me), 115.0 (*C*H), 142.1 (*C*=CH), 143.4 and 149.2 (both *C*H), 167.7 (*C*=O).

Analytical data match well those described in literature.[8b]

Synthesis of 3-cyclohept-1-enyl-acrylonitrile (*E/Z*)-63



(*E*/*Z*)-63

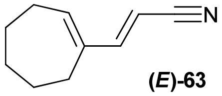
The synthesis was carried out according to the general procedure GP-4.

1.) Cycloheptanone **27d**: 115.4 mg, 1.03 mmol,
NfF **7**: 370 mg, 1.23 mmol,
P$_1$-base **29**: 367 mg, 1.18 mmol,
1 ml DMF.

2.) NEt$_3$: 202.5 mg, 2.0 mmol,
Acrylonitrile **48**: 118.4 mg, 1.38 mmol,
Pd(OAc)$_2$: 11.2 mg, 0.049 mmol, 5 mol%.

Column chromatography (*n*-hexane : EtOAc = 15 : 1) afforded (*E*/*Z*)**-63** as yellowish oil (121 mg, 0.82 mmol, 80% yield, (*E*/*Z*)-ratio = 2.74:1).

(*E*)-cycloheptenylacrylonitrile (*E*)-63



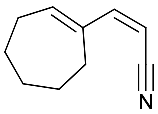
(*E*)-63

^{1}H-NMR (CDCl$_3$, 400 MHz): δ = 1.50–1.83 (m, 6 H, C*H$_2$*), 2.25-2.33 (m$_c$, 4 H, C*H$_2$*), 5.23 (d, ^3J = 16.4 Hz, 1 H, CH=C*H*CN), 6.27 (t, ^3J = 6.8 Hz, 1 H, C*H*=C), 6.97 (d, ^3J = 16.4 Hz, 1 H, C*H*=CHCN);

^{13}C-NMR (CDCl$_3$, 100.65 MHz): δ = 25.7, 26.0, 26.4, 29.0, and 31.6 (all *C*H$_2$), 92.3 (=*C*HCN), 119.1 (*C*N), 141.6 (*C*=CH), 144.8 (C=*C*H), 154.6 (C-*C*H).

Analytical data match well those obtained for the same compound in Chapter 3.

(*Z*)-cycloheptenylacrylonitrile <u>(*Z*)-63</u>



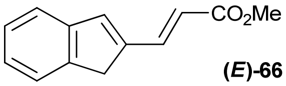
(*Z*)-63

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.50–1.82 (m, 4 H, C*H*$_2$), 2.28–2.33 (m, 2 H, C*H*$_2$), 2.50 (m$_c$, 2 H, C*H*$_2$), 2.70 (m$_c$, 2 H, C*H*$_2$), 5.05 (d, ^3J = 12.1 Hz, 1 H, CH=C*H*CN), 6.34 (t, ^3J = 6.7 Hz, 1 H, C*H*=C), 6.61 (d, ^3J = 12.1 Hz, 1 H, C*H*=CHCN);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 25.9, 26.0, 28.6, 28.9, and 31.7 (all *C*H$_2$), 91.0 (=*C*HCN), 117.6 (*C*N), 142.2 (*C*=CH), 144.7 (C=*C*H), 152.8 (C-*C*H).

Analytical data match well those obtained for the same compound in Chapter 3.

Synthesis of (*E*)-methyl 3-(1*H*-inden-2-yl) acrylate <u>(*E*)-66</u>



(*E*)-66

The synthesis was carried out according to the general procedure GP-4. Phosphazene bases **29**/**30** were substituted by 4 equivalent of NEt_3.

1.) 2-Indanone **27e**: 135 mg, 1.0 mmol,
NfF **7**: 362.5 mg, 1.20 mmol,
NEt_3: 404 mg, 4.0 mmol,,
1 ml DMF.

2.) Methyl vinyl ketone **49**: 116 mg, 1.34 mmol,
$Pd(OAc)_2$: 11.1 mg, 0.049 mmol, 5.0 mol%.

Workup was performed with $CHCl_3$. Flash column chromatography (*n*-hexane : EtOAc = 20 : 1) afforded (*E*)-**66** as yellowish solid (124 mg, 0.62 mmol, 62% yield). M$_p$ = (101–103)°C.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 3.57 (br.s, 2 H, CH_2), 3.79 (s, 3 H, OMe), 6.08 (d, ^3J = 15.6 Hz, 1 H, CH=C*H*CO$_2$Me), 7.11 (br.s, 1 H, C*H*=C), 7.23–7.30 (m, 2 H, 2 C*H*$_{Ar}$), 7.39–7.42 (m, 1 H, C*H*$_{Ar}$), 7.43–7.46 (m, 1 H, C*H*$_{Ar}$), 7.70 (d, ^3J = 15.6 Hz, 1 H, C*H*=CHCO$_2$Me);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 37.1 (*C*H$_2$), 51.6 (OMe), 117.8, 122.1, 124.0, 126.7, 126.9, 138.3, and 140.1 (*C*H=*C*H and all *C*H$_{Ar}$), 143.50, 143.52, and 144.0 (all *C*), 167.6 (*C*=O).

Analytical data match well those obtained for the same compound in Chapter 3.

The following compounds were coupled according to the general procedure GP-4 at 50°C and 1 mol% of Pd(OAc)$_2$ (experimental data for Table 38); the analytical data match well those already obtained for the same compounds in Chapter 3 and 4.

Synthesis of (*E*)-methyl 3-cyclopentenyl acrylate (*E*)-45

1.) Cyclopentanone **27a**: 88.1 mg, 1.04 mmol,
NfF **7**: 386.8 mg, 1.28 mmol,
P$_1$-base **29**: 390 mg, 1.25 mmol,
1 ml DMF.

2.) NEt$_3$: 206.8 mg, 2.03 mmol,
Methyl acrylate **44**: 117 mg, 1.36 mmol,
Pd(OAc)$_2$: 2.4 mg, 0.010 mmol, 1 mol%.

Column chromatography (*n*-hexane : EtOAc = 10 : 1) afforded (*E*)-**45** as white solid (129.3 mg, 0.85 mmol, 82% yield).

Synthesis of (*E*)-methyl 3-(4-methylcyclohex-1-enyl) acrylate (*E*)-58

1.) 4-Methylcyclohexanone **27b**: 113.2 mg, 1.0 mmol,
NfF **7**: 424.5 mg, 1.40 mmol,
P$_1$-base **29**: 397 mg, 1.27 mmol,
1 ml DMF.

2.) NEt$_3$: 203 mg, 2.0 mmol,
Methyl acrylate **44**: 116 mg, 1.35 mmol,
Pd(OAc)$_2$: 2.4 mg, 0.010 mmol, 1 mol%.

Column chromatography (*n*-hexane : EtOAc = 10 : 1) afforded the pure product (*E*)-**58** was obtained as a white solid (169 mg, 0.94 mmol, 94% yield). M$_p$ = (34-35)°C.

Synthesis of (*E*)-methyl 3-(4-phenylcyclohex-1-enyl)acrylate (*E*)-81

1.) 4-Phenylcyclohexanone **27c**: 175.3 mg, 1.0 mmol,
NfF **7**: 393 mg, 1.30 mmol,
P$_1$-base **29**: 380 mg, 1.22 mmol,
1 ml DMF.

2.) NEt$_3$: 211 mg, 2.09 mmol,

Methyl acrylate **44**: 119 mg, 1.38 mmol,
$Pd(OAc)_2$: 2.2 mg, 0.010 mmol, 1 mol%.

After column chromatography (*n*-hexane : EtOAc = 20 : 1) (*E*)-**81** was obtained as white crystalline solid (236.7 mg, 0.98 mmol, 97% yield).

3-(1-Ethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-acrylic acid methyl ester (*E*)-61

1.) 1-Ethylpiperidin-3-one **27h**: 128.2 mg, 1.0 mmol,
NfF **7**: 375 mg, 1.20 mmol,
P_1-base **29**: 369 mg, 1.22 mmol,
1 ml DMF.

2.) NEt_3: 204 mg, 2.01 mmol,
Methyl acrylate **44**: 121.5 mg, 1.41 mmol,
$Pd(OAc)_2$: 3.0 mg, 0.013 mmol, 1 mol%.

Column chromatography (*n*-hexane : EtOAc = 20 : 1, + 5 vol% NEt_3) product (*E*)-**61** was obtained as yellow oil (161 mg, 0.82 mmol, 82% yield).

(*E*)-methyl 3-cyclohept-1-enyl acrylate (*E*)-62

1.) Cycloheptanone **27d**: 113.6 mg, 1.0 mmol,
NfF **7**: 403 mg, 1.33 mmol,
P_1-base **29**: 395 mg, 1.26 mmol,
1 ml DMF.

2.) NEt_3: 210 mg, 2.08 mmol,
Methyl acrylate **44**: 115.5 mg, 1.34 mmol,
$Pd(OAc)_2$: 2.3 mg, 0.010 mmol, 1 mol%.

Column chromatography (*n*-hexane : EtOAc = 30 : 1) afforded (*E*)-**62** as yellowish oil (130.5 mg, 0.72 mmol, 72% yield).

(*E*)-methyl 3-(1*H*-inden-2-yl) acrylate (*E*)-66

Phosphazene base **29** was substituted by 4 equivalent of NEt_3.

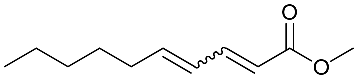
1.) 2-Indanone **27e**: 134.6 mg, 1.0 mmol,
NfF **7**: 366 mg, 1.21 mmol,
NEt_3: 406 mg, 4.0 mmol,,

1 ml DMF.

2.) Methyl acrylate **44**: 118 mg, 1.37 mmol,
Pd(OAc)$_2$: 2.2 mg, 0.010 mmol, 1.0 mol%.

Workup was performed with CHCl$_3$. Flash column chromatography (*n*-hexane : EtOAc = 20:1) afforded (*E*)-**66** as yellowish solid (117 mg, 0.58 mmol, 58% yield). M$_p$ = (101–103)°C.

Synthesis of (2*E*,4*E*/*Z*)-methyl deca-2,4-dienoate <u>(2*E*,4*E*/*Z*)-68</u>



[2*E*,4(*E*/*Z*)]- 68

The synthesis was conducted according to the general procedure GP-4 with the following modifications. The alkenyl nonaflate formation is carried out at -30°C as described for the synthesis of compound **42b**. Subsequent to the formation of alkenyl nonaflate **42b** (Step 1) the reaction mixture is kept at this temperature and acidified with trifluoroacetic acid (Step 2). The solution is stirred for 15 minutes and allowed to come to 0°C within 10 minutes. The coupling components were added consecutively at 0°C and the reaction mixture allowed coming to room temperature (Step 3).

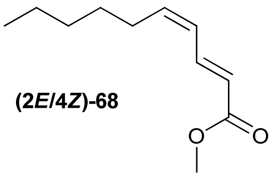
1.) 1-Heptanal **41b**: 342.6 mg, 3.0 mmol,
NfF **7**: 1.084 g, 3.59 mmol,
P$_1$-base **29**: 1.034 g, 3.31 mmol,
3 ml DMF.

2.) TFA: 192.5 mg; 1.69 mmol,

3.) NEt$_3$: 665.4 mg, 6.58 mmol,
Methyl acrylate **44**: 347 mg, 4.03 mmol,
Pd(OAc)$_2$: 33.8 mg, 0.150 mmol, 5 mol%.

Kugelrohr distillation (85°C at 4.5 10^{-2} mbar) afforded the product **68** as a mixture of (4*Z*/4*E*)-stereoisomers in a ratio of 2.2:1 as slightly yellowish oil (442 mg, 2.43 mmol, 81% yield).

Deca-(2*E*/4*Z*)-dienoic acid methyl ester <u>(2*E*/4*Z*)-68</u>



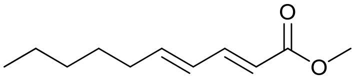
(2*E*/4*Z*)-68

^{1}H-NMR (CDCl$_3$, 400 MHz): δ = 0.89 (t, ^3J = 7.1 Hz, 3 H, CH_3), 1.24-1.48 (m, 6 H, CH_2), 2.30 (dt, ^3J = 7.8 Hz, ^3J = 7.4 Hz, 2 H, CH-CH_2), 3.75 (s, 3 H, O-CH_3), 5.87 (d, ^3J = 14.8 Hz, 1 H, CH), 5.83-5.90 (m, 1 H, CH), 6.13 (dd, ^3J = 11.5 Hz, ^3J = 10.5 Hz, 1 H, CH), 7.62 (ddd, ^3J = 15.3 Hz, ^3J = 11.6 Hz, ^4J = 1.2 Hz, 1 H, CH);

^{13}C-NMR (CDCl$_3$, 100.65 MHz): δ = 14.0 (CH$_3$), 22.5, 28.2, 29.0 and 31.4 (all CH$_2$), 51.5 (O-CH$_3$), 120.6, 126.4, 139.8, and 141.9 (all CH), 167.7 (C=O).

Analytical data match well those described in literature.[129]

Deca-(2*E*/4*E*)-dienoic acid methyl ester (2*E*/4*E*)-68



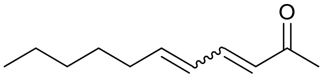
(2*E*/4*E*)-68

^{1}H-NMR (CDCl$_3$, 400 MHz), δ = 0.89 (t, ^{3}J = 7.0 Hz, 3 H, CH_3), 1.24-1.48 (m, 6 H, CH_2), 2.16 (dt, ^3J = 6.7 Hz, ^3J = 6.5 Hz, 2 H, CH-CH_2), 3.73 (s, 3 H, O-CH_3), 5.79 (d, ^3J = 15.3 Hz, 1 H, CH), 6.09-6.18 (m, 2 H, CH), 7.27 (dd, ^3J = 25.6 Hz, ^3J = 15.6 Hz, 1 H, CH);

^{13}C-NMR (CDCl$_3$, 100.65 MHz), δ = 14.0 (CH$_3$), 22.4, 28.4, 31.4 and 32.9 (all CH$_2$), 51.4 (O-CH$_3$), 118.6, 128.3, 145.0 and 145.4 (CH), 167.2 (C=O).

Analytical data match well those described in literature.[129]

Synthesis of [(*E*)-3,(*E*,*Z*)-5]-undeca-3,5-dien-2-one [(*E*)-3,(*E*,*Z*)-5]-69



[3*E*,5(*E*/*Z*)]-69

The synthesis was carried out according to the general procedure GP-4 with the following modifications. The alkenyl nonaflate formation is carried out at -30°C as described for the synthesis of compound **42b**. Subsequent to the formation of alkenyl nonaflate **42b** (Step 1) the reaction mixture is kept at this temperature and acidified with trifluoroacetic acid (Step 2). The solution is stirred for 15 minutes and allowed to come to 0°C within 10 minutes. The coupling components were added consecutively at 0°C and the reaction mixture allowed coming to room temperature (Step 3).

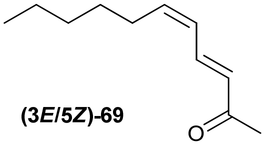
1.) 1-Heptanal **41b**: 344.6 mg, 3.02 mmol,
NfF **7**: 1.085 g, 3.59 mmol,
P$_1$-base **29**: 984.8 mg, 3.15 mmol,
3 ml DMF.

2.) TFA: 192 mg; 1.68 mmol,

3.) NEt_3: 665 mg, 6.57 mmol,
Methyl vinyl ketone **47**: 308 mg, 4.39 mmol,
$Pd(OAc)_2$: 33.9 mg, 0.150 mmol, 5 mol%.

Kugelrohr distillation (75°C at 4.0 10^{-2} mbar) afforded the product **69** as a mixture of (5*Z*/5*E*)-stereoisomers in a ratio of 1.6:1 as slightly yellowish oil (413 mg, 2.48 mmol, 82% yield).

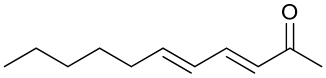
Undeca-3(*E*,5*Z*)-dien-2-one (3*E*/5*Z*)-69



(3*E*/5*Z*)-69

^{1}H-NMR (C_6D_6, 400 MHz): δ = 0.83 (t, ^3J = 7.4 Hz, 3 H, C*H*$_3$), 1.05-1.27 (m, 6 H, C*H*$_2$), 1.89 (s, 3 H, C(O)-C*H*$_3$), 2.01 (dt, ^3J = 7.7 Hz, ^3J = 7.0 Hz, 2 H, CH-C*H*$_2$), 5.56-5.63 (m, 1 H, C*H*), 5.86-6.01 (m, 2 H, C*H*), 7.46 (ddd, ^3J = 15.4 Hz, ^3J = 11.5 Hz, ^4J = 1.0 Hz, 1 H, C*H*);
^{13}C-NMR (C_6D_6, 100.65 MHz): δ = 14.2 (*C*H$_3$), 22.8, 27.7, 28.3, 29.3, 31.5, 127.4, 130.7, 136.9 and 141.7 (all *C*H), 196.5 (*C*=O).
Analytical data match well those described in literature.[129]

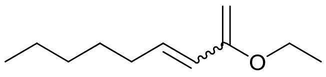
Undeca-(3*E*,5*E*)-dien-2-one (3*E*/5*E*)-69



(3*E*/5*E*)-69

^{1}H-NMR (C_6D_6, 400 MHz), δ = 0.86 (t, ^{3}J = 7.0 Hz, 3 H, C*H*$_3$), 1.05-1.27 (m, 6 H, C*H*$_2$), 1.87 (dt, ^3J = 7.3 Hz, ^3J = 7.1 Hz, 2 H, CH-C*H*$_2$), 1.92 (s, 3 H, C(O)-C*H*$_3$), 5.70-5.78 (m, 1 H, C*H*), 5.86-6.01 (m, 2 H, C*H*), 6.95 (dd, ^3J = 26.31 Hz, ^3J = 15.6 Hz, 1 H, C*H*);
^{13}C-NMR (C_6D_6, 100.65 MHz), δ = 14.2 (*C*H$_3$), 22.8, 27.1, 28.7, 31.6, 33.2, 129.3 (2X), 142.9 and 144.6 (all *C*H), 196.5 (*C*=O).
Analytical data match well those described in literature.[129]

Synthesis of (*E*/*Z*)-2-ethoxynona-1,3-diene **(*E*/*Z*)-70**



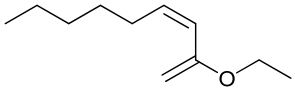
(*E*/*Z*)-70

The synthesis was carried out according to the general procedure GP-4 with the following modifications. The alkenyl nonaflate formation is carried out at -30°C as described for the synthesis of compound **42b**. Subsequent to the formation of alkenyl nonaflate **42b** (Step 1) the reaction mixture is kept at this temperature and acidified with trifluoroacetic acid (Step 2). The solution is stirred for 15 minutes and allowed to come to 0°C within 10 minutes. The coupling components were added consecutively at 0°C and the reaction mixture allowed coming to room temperature (Step 3).

1.) 1-Heptanal **41b**: 347 mg, 3.04 mmol,
    NfF **7**: 1.112 g, 3.68 mmol,
    P_1-base **29**: 982 mg, 3.14 mmol,
    3 ml DMF.
2.) TFA: 184 mg; 1.61 mmol,
3.) NEt_3: 695 mg, 6.87 mmol,
    Ethyl vinyl ether **50**: 297 mg, 4.12 mmol,
    $Pd(OAc)_2$: 34.1 mg, 0.150 mmol, 5 mol%.

Kugelrohr distillation (60°C at 3.0 10^{-2} mbar) afforded the product **70** as a mixture of (*Z*/*E*)-stereoisomers in a ratio of 2.1:1 as colorless oil (398.7 mg, 2.37 mmol, 78% yield).

(*Z*)-2-ethoxynona-1,3-diene **(*Z*)-70**



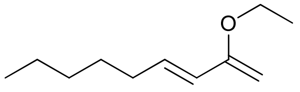
(*Z*)-70

^{1}H-NMR (C_6D_6, 400 MHz): δ = 0.87 (t, ^3J = 7.0 Hz , 3 H, C*H*$_3$), 1.09 (t, ^3J = 7.0 Hz , 3 H, O-CH$_2$-C*H*$_3$), 1.32-1.45 (m, 6 H, C*H*$_2$), 2.55 (m, 2 H, C*H*$_2$), 3.47 (q, ^3J = 7.0 Hz, 2 H, O-C*H*$_2$-CH$_3$), 4.07 (d, ^4J = 1.6 Hz, 1 H, =C*H*$_2$), 4.13 (d, ^4J = 1.6 Hz, 1 H, =C*H*$_2$), 5.46 (m, 1 H, C*H*), 5.86 (dt, ^3J = 12.0 Hz, ^4J = 1.6 Hz 1 H, C*H*);

^{13}C-NMR (C_6D_6, 100.65 MHz): δ = 14.3, 14.6 (both *C*H$_3$), 23.0, 29.4, 30.1, 32.0 and 62.7 (all *C*H$_2$), 84.8 (=*C*H$_2$), 125.7, 134.1 (all *C*H), 160.5 (*C*).

Analytical data match well those obtained for the same compound in Chapter 3.

(*E*)-2-ethoxynona-1,3-diene (*E*)-70



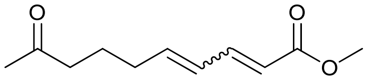
(*E*)-70

^{1}H-NMR (CDCl$_3$, 400 MHz), δ = 0.82 (t, ^3J = 7.0 Hz , 3 H, C*H*$_3$), 1.11 (t, ^3J = 7.0 Hz, 3 H, O-CH$_2$-C*H*$_3$), 1.32-1.45 (m, 6 H, C*H*$_2$), 2.02 (m, 2 H, C*H*$_2$), 3.54 (q, ^3J = 7.0 Hz, 2 H, O-C*H*$_2$-CH$_3$), 4.01 (d, ^4J = 1.4 Hz, 1 H, =C*H*$_2$), 4.09 (d, ^4J = 1.5 Hz, 1 H, =C*H*$_2$), 5.95 (dt, ^3J = 15.5 Hz, ^4J = 1.4 Hz, 1 H, C*H*), 6.37 (m, 1 H, C*H*);

^{13}C-NMR (CDCl$_3$, 100.65 MHz), δ = 14.2, 14.6 (both *C*H$_3$), 22.9, 29.3, 31.8, 32.7 and 62.7 (all *C*H$_2$), 84.8 (=*C*H$_2$), 127.2, 131.3 (all *C*H), 159.1 (*C*).

Analytical data match well those obtained for the same compound in Chapter 3.

Synthesis of 9-oxo-deca-(2*E*,4*E*/*Z*)-dienoic acid methyl ester [2*E*,4(*E*/*Z*)]-85



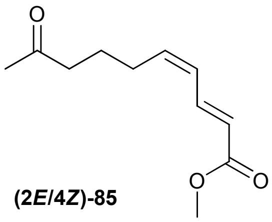
[2*E*,4(*E*/*Z*)]-85

The synthesis was carried out according to the general procedure GP-4 with the following modifications. The alkenyl nonaflate formation is carried out at -30°C as described for the synthesis of compound **42c**. Subsequent to the formation of alkenyl nonaflate **42c** (Step 1) the reaction mixture is kept at this temperature and acidified with trifluoroacetic acid (Step 2). The solution is stirred for 15 minutes and allowed to come to 0°C within 10 minutes. The coupling components were added consecutively at 0°C and the reaction mixture allowed coming to room temperature (Step 3).

1.) 6-Oxoheptanal **41c**: 257.7 mg, 2.01 mmol,
    NfF **7**: 716 mg, 2.37 mmol,
    P$_1$-base **29**: 683 mg, 2.19 mmol,
    2 ml DMF.
2.) TFA: 131 mg; 1.15 mmol,
3.) NEt$_3$: 463 mg, 4.57 mmol,
    Methyl acrylate **44**: 233 mg, 2.71 mmol,
    Pd(OAc)$_2$: 22.6 mg, 0.099 mmol, 5 mol%.

Flash column chromatography (*n*-hexane : EtOAc = 3 : 1) furnished the product **85** as a mixture of (4*Z*/4*E*)-stereoisomers in a ratio of 2.5:1 as yellow oil (282 mg, 1.44 mmol, 72% yield).

9-Oxo-deca-(2*E*/4*Z*)-dienoic acid methyl ester **(2*E*/4*Z*)-85**



(2*E*/4*Z*)-85

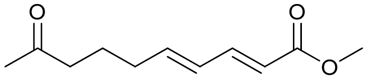
^{1}H-NMR (C_6D_6, 400 MHz): δ = 1.38 (dt, ^3J = 7.5 Hz, ^3J = 7.4 Hz, 2 H, C*H*$_2$), 1.60 (s, 3 H, C(O)-C*H*$_3$), 1.72 (t, ^3J = 7.4 Hz, 2 H, C*H*$_2$),), 1.86 (m, 2 H, C*H*$_2$), 3.44 (s, 3 H, O-C*H*$_3$), 5.42 (m, 2 H, C*H*), 5.80-5.87 (m, 1 H, C*H*), 5.92 (d, ^3J = 15.3 Hz, 1 H, C*H*), 7.78 (ddd, ^3J = 15.3 Hz, ^3J = 11.7 Hz, ^4J = 1.2 Hz, 1 H, C*H*);

^{13}C-NMR (C_6D_6, 100.65 MHz): δ = 23.3, 27.5, 29.3, 42.2, 51.1 (O-*C*H$_3$), 121.9, 127.3, 139.4, and 140.5 (all *C*H), 167.1 (MeO-*C*=O), 205.7 (*C*=O).

MS (EI, 70 eV): m/z (%) = 79 ([M$^+$ – 117], 100), 107 ([M$^+$ – 89], 45), 164 ([M$^+$ – 32], 32), 131 ([M$^+$ – 65], 20), 94 ([M$^+$ – 102], 16),196 (M$^+$, 4);

HRMS: calculated for $C_{11}H_{16}O_3$ (M$^+$) 196.1099, found 196.1096.

9-Oxo-deca-(2*E*/4*E*)-dienoic acid methyl ester **(2*E*/4*E*)-85**



(2*E*/4*E*)-85

^{1}H-NMR (C_6D_6, 400 MHz): δ = 1.38 (dt, ^3J = 7.5 Hz, ^3J = 7.4 Hz, 2 H, C*H*$_2$), 1.62 (s, 3 H, C(O)-C*H*$_3$), 1.78 (t, ^3J = 7.2 Hz, 2 H, C*H*$_2$), 1.86 (m, 2 H, C*H*$_2$), 3.46 (s, 3 H, O-C*H*$_3$), 5.57 (m, 2 H, C*H*), 5.79-5.87 (m, 2 H, C*H*), 7.41 (dd, ^3J = 26.3 Hz, ^3J = 15.3 Hz, 1 H, C*H*);

^{13}C-NMR (C_6D_6, 100.65 MHz), δ = 22.7, 29.4, 32.2, 51.0 (O-*C*H$_3$), 119.8, 129.2, 143.4 and 145.1 (all *C*H), 167.1 (MeO-*C*=O), 205.7 (*C*=O).

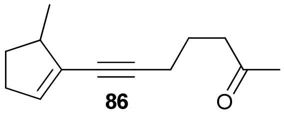
MS (EI, 70 eV): m/z (%) = 79 ([M$^+$ – 117], 100), 107 ([M$^+$ – 89], 45), 164 ([M$^+$ – 32], 32), 131 ([M$^+$ – 65], 20), 94 ([M$^+$ – 102], 16),196 (M$^+$, 4);

HRMS: calculated for $C_{11}H_{16}O_3$ (M$^+$) 196.1099, found 196.1096.

GP-5 General procedure for the Sonogashira coupling of alkenyl nonaflates and terminal olefins – one-Pot cross-coupling protocol starting from carbonyl compounds (unless stated otherwise):

Pre-dried LiCl was placed into a reaction flask equipped with a three-way tap and a magnetic stirrer coated with Teflon, and heated to *ca*. 250–300°C with a heat-gun under vacuum for 2-4 minutes. After cooling down under an atmosphere of dry argon, DMF, the carbonyl compound and NfF **7** are added consecutively (all via syringe). The reaction mixture is cooled to 0°C and under vigorous stirring the P-base **29**/**30** gets added dropwise. With completed addition the three way tap is replaced by a glass stopper and the flask is closed tightly. The solution is allowed to warm to room temperature slowly and is stirred for the stated time (reaction control via ^{1}H-NMR). With completed alkenyl nonaflate formation *i*-Pr_2NH in excess is added, followed by solid PPh_3, CuI and $Pd(OAc)_2$ (all together in one lot), and the reaction mixture is stirred for the designated amount of time and temperature (see Tables 40, 41 and 42). After full conversion is obtained the reaction mixture is diluted with water (5 ml / mmol carbonyl compound) and extracted with *n*-hexane (4 times with 25 ml / mmol carbonyl compound). The combined organic phases are washed with water (20 ml / mmol carbonyl compound) and dried over Na_2SO_4. The solvent is removed under reduced pressure and the residue is purified by column chromatography (silica gel, *n*-hexane : EtOAc = 20 : 1 as eluent unless stated otherwise) to give the pure conjugated enynes.

Synthesis of 7-(5-methyl-cyclopent-1-enyl)-hept-6-yn-2-one 86



86

The synthesis was carried out according to the general procedure GP-5.

Alkenyl nonaflate and terminal alkyne formation were conducted one-pot in two consecutive steps. The reaction mixture containing 2-methyl cyclopentanone **27f** and NfF **7** in THF was cooled to -78°C prior to the addition of the P_2-base **30**. The temperature was kept for 5 hours and then allowed to rise to room temperature slowly (within 2.5 hours). After completed alkenyl nonaflate formation 6-oxoheptanal **41c** was added to the reaction mixture and 2 equivalents of the P_1-base **29** at 0°C. After completed elimination reaction the cross-coupling was conducted at 50°C.

1.) LiCl: 95 mg, 2.25 mmol,
    2-Methylcyclopentanone **27f**: 98.3 mg, 1.0 mmol,
    6-Oxoheptanal **41c**: 129.3 mg, 1.0 mmol,
    NfF **7**: 790 mg, 2.62 mmol,
    P_2-base **30**: 0.6 ml, 1.2 mmol,
    P_1-base **29**: 857 mg, 2.7 mmol,
    1 ml THF.

2.) *i*-Pr_2NH: 1 ml, ~7 mmol,

PPh_3: 28 mg, 0.1 mmol,

CuI: 19 mg, 0.1 mmol,

$Pd(OAc)_2$: 11.2 mg, 0.05 mmol, 5 mol%.

Column chromatography afforded **86** as yellowish oil (148.3 mg, 0.78 mmol, 78% yield).

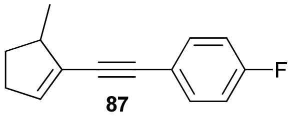
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.10 (d, ^3J = 6.9 Hz, 3 H, Me), 1.34–1.48 (1 H), 1.76–1.87 (2 H), 2.09–2.19 (1 H), 2.30–2.47 (4 H) (all m, all C*H*$_2$), 2.16 (s, 3 H, *Me*C=O), 2.59 (t, ^3J = 7.2 Hz, 2 H, C*H*$_2$C=O), 2.64–2.77 (m, 1 H C*H*Me), 5.91 (td, *J* = 2.5, 2.2 Hz, 1 H, C*H*=);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 18.7 (t, *C*H$_2$), 18.9 (q, CH*Me*), 22.7 (t, *C*H$_2$), 30.0 (q, *Me*C=O), 31.6, 32.0, 42.2 (all t, *C*H$_2$), 42.7 (d, *C*HMe), 77.9, 90.8 (both s, C≡C), 130.4 (s, CH=*C*), 135.3 (d, *C*H=C), 208.3 (*C*=O);

MS (EI, 70 eV): m/z (%) = 43 (CH_3CO^+, 100), 147 ([M^+ – CH_3CO], 45), 190 (M^+, 30), 175 ([M^+ - CH_3], 8);

HRMS: calculated for $C_{13}H_{18}O$ (M^+) 190.1358, found 190.1365.

Synthesis of 1-fluoro-4-(5-methyl-cyclopent-1-enylethynyl)-benzene 87



87

The synthesis was carried out according to the general procedure GP-5. The mixture of 2-methylcyclopentanone **27f,** LiCl and NfF **7** in THF was cooled down to –78°C under vigorous stirring, and P_2-base **30** was added dropwise for 3–4 min. After stirring at –75°C for 2 h, the reaction mixture was gradually allowed to warm up to ambient temperature for 2.5 h, and then 4-fluoroacetophenone **35j** was added. After dropwise addition of P_1-base **29** for 2-3 min, the resulting mixture was stirred overnight at room temperature (17 hours); the cross-coupling was carried out at 45-47°C (15 hours).

1.) LiCl: 85 mg, 2.0 mmol,

2-Methyl cyclopentanone **27f**: 98 mg, 1.0 mmol,

1-(4-Fluoro-phenyl)-ethanone **35j**: 166 mg, 1.2 mmol,

NfF **7**: 725 mg, 2.4 mmol,

P_2-base **30**: 0.6 ml, 1.2 mmol,

P_1-base **29**: 825 mg, 2.64 mmol,

3 ml THF.

2.) *i*-Pr_2NH: 1 ml, ~7 mmol,

PPh_3: 268 mg, 0.1 mmol,

CuI: 19 mg, 0.1 mmol,
Pd(OAc)$_2$: 11.2 mg, 0.05 mmol, 5 mol%.

Column chromatography (*n*-hexane) afforded **87** as yellowish oil (162 mg, 0.81 mmol, 81% yield).

^{1}H-NMR (CDCl$_3$, 270 MHz): d = 1.18 (d, ^{3}J = 6.9 Hz, 3 H, Me), 1.41–1.54 (m, 1 H), 2.13–2.25 (m, 1 H), 2.31–2.54 (m, 2 H), 2.83 (mc, 1 H) (both CH$_2$ and CHMe), 6.10 (td, J = 2.7, 2.1 Hz, 1 H, CH=), 7.00 (2 H, $^3J_{1H,19F}$ = 8.8 Hz, CHAr), 7.42 (2 H, $^4J_{1H,19F}$ = 5.4 Hz, CHAr) (both AA'BB' system, ^{3}J = 8.8 Hz, 4-FC$_6$H$_4$);

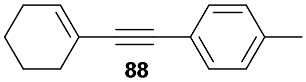
^{13}C-NMR (CDCl$_3$, 67.9 MHz): d = 19.7 (q, Me), 32.0, 32.2 (both t, CH$_2$), 42.8 (d, CHMe), 85.9, 90.2 (both s, C=C), 115.5 (dd, $^2J_{13C,19F}$ = 22.1 Hz, CHAr), 119.7 (d, $^4J_{13C,19F}$ = 3.4 Hz, CArC=C), 130.1 (s, C=CH), 133.3 (dd, $^3J_{13C,19F}$ = 8.2 Hz, CHAr), 137.2 (d, CH=C),
162.3 (d, $^1J_{13C,19F}$ = 249.0 Hz, CAr–F);

IR (film): $\tilde{\nu}$ = 2930, 2860, 2200, 1600, 1505, 1435 cm-1;

MS (EI, 80 eV): m/z (%) = 200 (M$^+$, 100), 185 ([M$^+$ – CH$_3$], 37), 172 ([M$^+$ – C$_2$H$_4$], 64), 133 ([M$^+$ – C$_5$H$_7$], 42).

C,H-analysis (%): calcd. for C$_{14}$H$_{13}$F (200.3): C 83.97, H 6.54;
found C 83.65, H 6.52.

Synthesis of 1-cyclohex-1-enylethynyl-4-methyl-benzene 88



88

The synthesis was carried out according to the general procedure GP-5. The nonaflation/elimination step was complete after 24 hours; the coupling reaction was carried out at room temperature for 24 hours.

1.) LiCl: 51 mg, 1.18 mmol,
Cyclohexanone **27j**: 99 mg, 1.01 mmol,
4-Methylacetophenone **35k**: 135.4 mg, 1.01 mmol,
NfF **7**: 814 mg, 2.7 mmol,
P$_1$-base **29**: 1.034 g, 3.31 mmol,
1 ml DMF.

2.) *i*-Pr$_2$NH: 1 ml, ~7 mmol,
PPh$_3$: 36 mg, 0.14 mmol,
CuI: 16 mg, 0.1 mmol,
Pd(OAc)$_2$: 11.3 mg, 0.05 mmol, 5 mol%.

Flash column chromatography (*n*-pentane) afforded **88** as yellowish oil (132 mg, 0.67 mmol, 67% yield).

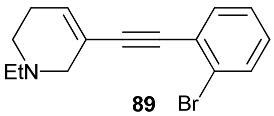
^{1}H-NMR (CDCl$_3$, 400 MHz): δ = 1.64 (m$_c$, 4 H), 2.09–2.17 (m, 2 H), 2.18–2.25 (m, 2 H) (all C*H*$_2$), 2.33 (s, 3 H, *Me*), 6.18 (tt, ^3J = 4 Hz, ^4J = 2 Hz, C*H*=), 7.09 (2 H, C$_{Ar}$*H*), 7.31 (2 H, C$_{Ar}$*H*) (both AA'BB' system, ^3J = 8.1 Hz, 4-MeC$_6$H$_4$);

^{13}C-NMR (CDCl$_3$, 100.65 MHz): δ = 21.4 (q, Me), 21.5, 22.3, 25.7, 29.3 (all t, *C*H$_2$), 86.9, 90.5 (both s, C≡C), 120.6, 120.8 (both s, *C*=CH, *C*$_{Ar}$C≡C), 128.9, 131.3 (both d, *C*$_{Ar}$H), 134.7 (d, C=*C*H), 137.7 (s, *C*$_{Ar}$Me);

MS (EI, 70 eV): m/z (%) = 196 (M$^+$, 100), 168 ([M$^+$ – C$_2$H$_4$], 61), 181 ([M$^+$ – CH$_3$], 54);

HRMS: calculated for C$_{15}$H$_{16}$ (M$^+$) 196.1252, found 196.1258.

Synthesis of 5-(2-bromo-phenylethynyl)-1-ethyl-1,2,3,6-tetrahydro-pyridine 89



89

The synthesis was carried out according to the general procedure GP-5. The nonaflation/elimination step was complete after 24 hours; the coupling reaction was carried out at 45-47°C for 15 hours.

1.) LiCl: 127 mg, 3.0 mmol,
 1-Ethylpiperidin-3-one **27h**: 255 mg, 2.0 mmol,
 2-Bromoacetophenone **35l**: 438 mg, 2.0 mmol,
 NfF **7**: 1.396 g, 4.62 mmol,
 P$_1$-base **29**: 2.20 g, 7.04 mmol,
 2 ml DMF.

2.) *i*-Pr$_2$NH: 3 ml, ~21 mmol,
 PPh$_3$: 52 mg, 0.2 mmol,
 CuI: 38 mg, 0.2 mmol,
 Pd(OAc)$_2$: 22.3 mg, 0.10 mmol, 5 mol%.

Column chromatography (Hexane : MTBE = 20 : 1, + 5 vol% NEt$_3$) afforded **89** as yellowish oil (435 mg, 0.67 mmol, 75% yield).

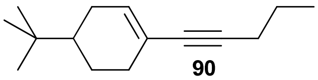
^{1}H-NMR (CDCl$_3$, 400 MHz): δ = 1.15 (t, ^3J = 7.2 Hz, 3 H, CH$_2$-C*H*$_3$), 2.33 (m, 2 H, C*H*$_2$, CH-C*H*$_2$), 2.54 (q, ^3J = 7.2 Hz, 1 H, N-C*H*$_2$-CH$_3$), 2.59 (t, ^3J = 5.8 Hz, 1 H, N-C*H*$_2$), 3.16 (q, ^3J = 2.8 Hz, 2 H, C-C*H*$_2$), 6.30 (hept., *J* = 1.95 Hz, 1 H, C*H*), 7.13 (dt, ^3J = 7.7 Hz, ^4J = 1.7 Hz, 1 H, C$_{Ar}$*H*), 7.24 (dt, ^3J = 7.6 Hz, ^4J = 1.2 Hz, 1 H, C$_{Ar}$*H*), 7.44 (dd, ^3J = 7.7 Hz, ^4J = 1.7 Hz, 1 H, C$_{Ar}$*H*), 7.57 (dd, ^3J = 8.0 Hz, ^4J = 1.3 Hz, 1 H, C$_{Ar}$*H*);

^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 12.3 (CH_2-*C*H_3), 26.5 (CH-*C*H_2), 48.7, 51.7, 54.8 (all N-*C*H_2), 86.8 (C-*C*≡C), 93.3 (C≡*C*-C_{Ar}), 119.6, 125.5, 125.6, 126.9, 129.1, 132.4, 133.1, 133.5;

MS (EI, 70 eV): m/z (%) = 232 ([M^+ – 57], [$C_{12}H_9{}^{79}Br$•], 100), 234 ([M^+ – 57], [$C_{12}H_9{}^{81}Br$•], 98), 152 ([M^+ – 137], 99), 154 ([M^+ – 137], 71), 289 (M^+, 49), 291 (M^+, 48), 210 ([M^+ – 79], 19), 212 ([M^+ – 81], 4);

HRMS: calculated for $C_{15}H_{16}N^{79}Br$ (M^+) 289.0461, found 289.0479;
calculated for $C_{15}H_{16}N^{81}Br$ (M^+) 291.0440, found 291.0457;
relative intensity: ($C_{15}H_{16}N^{79}Br$):($C_{15}H_{16}N^{81}Br$) = 30.9:29.9.

Synthesis of 4-*t*-butyl-1-pent-1-ynyl-cyclohexene <u>90</u>



90

The synthesis was carried out according to the general procedure GP-5. After completion of the nonaflation–elimination step (24 h at ambient temperature, then ^1H-NMR control showing 100% pentanal to 1-pentyne conversion and at least 90% 4-*t*-butylcyclohexanone to the nonaflate conversion) the coupling reaction was carried out at room temperature for 24 hours.

1.) LiCl: 64 mg, 1.5 mmol,
4-*t*-Butyl-cyclohexanone **27k**: 154 mg, 1.0 mmol,
Pentanal **44h**: 121 mg, 1.40 mmol,
NfF **7**: 798 mg, 2.64 mmol,
P_1-base **29**: 1.306 g, 4.18 mmol,
1.5 ml DMF.

2.) *i*-Pr_2NH: 2 ml, ~14 mmol,
PPh_3: 26 mg, 0.1 mmol,
CuI: 19 mg, 0.1 mmol,
$Pd(OAc)_2$: 11.3 mg, 0.05 mmol, 5 mol%.

After column chromatography (*n*-hexane) **90** was obtained as colorless oil (169 mg, 0.83 mmol, 83% yield).

^1H-NMR ($CDCl_3$, 270 MHz): d = 0.86 (s, 9 H, CMe_3), 0.99 (t, ^3J = 7.3 Hz, 3 H, Me), 1.11–1.30 (2 H), 1.76–1.91 (2 H), 2.04–2.20 (3 H) (all m, 3 CH_2 + CH) 1.54 (sextet, ^3J = 7.3 Hz, 2 H, CH_2Me), 2.27 (t, ^3J = 7.1 Hz, 2 H, CH_2C=C), 6.01 (mc, 1 H, CH=);

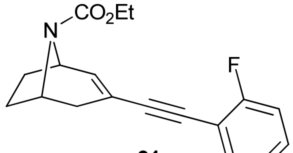
^{13}C-NMR ($CDCl_3$, 67.9 MHz): d = 13.5 (q, Me), 21.3, 22.4, 23.8 (all t, CH_2), 27.1 (q, CMe_3), 27.2, 31.1 (both t, CH_2), 32.1 (s, CMe_3), 43.3 (d, CH), 82.1, 87.4 (both s, C=C), 120.8 (s, C=CH), 133.4 (d, C=CH);

IR (film): $\tilde{\nu}$ = 2215, 1675, 1470, 1365 cm-1;

MS (EI, 80 eV): m/z (%) = 204 (M^+, 100), 189 ([$M^+ - CH_3$], 13), 161 ([$M^+ - C_3H_7$], 38), 147 ([$M^+ - C_4H_9$], 22);

C,H-analysis (%): calcd. for $C_{15}H_{24}$ (204.4): C 88.16, H 11.84;
found C 88.53, H 11.77.

Synthesis of 3-(2-fluoro-phenylethynyl)-8-aza-bicyclo[3.2.1]oct-2-ene-8-carboxylic acid ethyl ester <u>91</u>



91

The synthesis was carried out according to the general procedure GP-5. The nonaflation/elimination step was complete after 17 hours; the coupling reaction was carried out at 60°C for 6 hours.

1.) LiCl: 127 mg, 3.0 mmol,
3-Oxo-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester **27l**: 395 mg, 2.0 mmol,
1-(2-Fluoro-phenyl)-ethanone **35m**: 345 mg, 2.5 mmol,
NfF **7**: 1.495 g, 4.95 mmol,
P_1-base **29**: 2.41 g, 7.70 mmol,
2 ml DMF.

2.) *i*-Pr_2NH: 3 ml, ~20 mmol,
PPh_3: 52 mg, 0.2 mmol,
CuI: 38 mg, 0.2 mmol,
$Pd(OAc)_2$: 22.3 mg, 0.1 mmol, 5 mol%.

Column chromatography of the crude material (gradient elution: 1. *n*-hexane 2. toluene/*n*-hexane = 1:4 3. toluene/*n*-hexane = 1:1 4. toluene) afforded **91** as yellow oil (579 mg, 1.94 mmol, 97% yield).

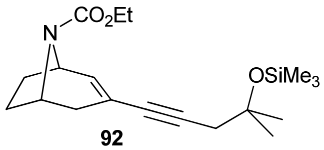
^{1}H NMR (C_6D_6, 500 MHz, 75°C): δ = 1.05 (t, *J* = 7.1 Hz, 3 H, Me), 1.29–1.36 (br.m, 1 H), 1.55 (ddd, *J* = 11.8, 9.0, 2.8 Hz, 1 H), 1.64 (m_c, 1 H), 1.77 (ddddd, *J* = 12.5, 12.5, 8.0, 2.8, 1.7 Hz, 1 H), 1.83 (br.d, *J* = 17 Hz, 1 H), 2.99 (br.d, *J* = 17 Hz, 1 H) (all CH_2), 4.06 (dq, *J* = 10.8, 7.1 Hz, 1 H), 4.09 (dq, *J* = 10.8, 7.1 Hz, 1 H) (both OCH_2), 4.29 (br.s, 1 H, CHN), 4.37 (br.s, 1 H, CHN), 6.29 (ddd, *J* = 5.3, 1.9, 1.8 Hz, 1 H, CH=C), 6.68 (td, *J* = 7.6, 1.3 Hz, 1 H), 6.74 (ddd, *J* = 9.5, 8.3, 1.3 Hz, 1 H), 6.78–6.73 (m, 1 H), 7.25 (td, *J* = 7.4, 1.8 Hz, 1 H) (all CH_{Ar}); ^{13}C (C_6D_6, 125.8 MHz, 75°C): δ = 14.8 (q, Me), 29.9, 34.5, 38.2 (all br.t., CH_2), 52.4, 53.7 (both d, CHN), 61.0 (t, OCH_2), 82.8 (s, C≡C), 95.0 (d, $^3J13_{C,}19_F$ = 3.2 Hz, C≡C), 112.8 (d, $^2J13_{C,}19_F$ = 15.7 Hz, C_{Ar}), 115.7 (dd, $^2J13_{C,}19_F$ = 21.0 Hz), 124.1 (dd, $^3J13_{C,}19_F$ = 3.8 Hz), 129.9 (dd, $^3J13_{C,}19_F$ = 7.9 Hz), 133.6 (dd, $^4J13_{C,}19_F$ = 1.3 Hz) (all CH_{Ar}), 118.6 (br.s, *C*=CH), 139.7 (br.d, C=*CH*), 154.4 (s, C=O), 163.2 (d, $^1J13_{C,}19_F$ = 251.6 Hz, C–F);

IR (film): $\tilde{\nu}$ = 3060–3035 cm^{-1} (=C-H), 2980–2835 (C-H), 2210 (C≡C), 1700 (C=O), 1620–1490 (C=C);

MS (EI, 80 eV): m/z (%) = 300 (M^+ + 1, 21), 299 (M^+, 100), 271 ([$M^+ - C_2H_4$], 37), 270 ([$M^+ - C_2H_5$], 91), 242 ([$M^+ - C_2H_5 - CO$], 45), 226 ([$M^+ - C_2H_5 - CO_2$], 28), 198 ([$M^+ - CO_2Et - C_2H_4$], 85), 183 ([$M^+ - CO_2Et - C_2H_4 - NH$], 10), 29 ($C_2H_5^+$, 44);

C,H,N-analysis (%): calcd. for $C_{18}H_{18}FNO_2$ (299.4): C 72.22, H 6.06, N 4.68;
found C 71.91, H 5.95, N 4.64.

Synthesis of 3-(4-methyl-4-trimethylsilanyloxy-pent-1-ynyl)-8-aza-bicyclo[3.2.1]oct-2-ene-8-carboxylic acid ethyl ester <u>92</u>



92

The synthesis was carried out according to the general procedure GP-5. The nonaflation/elimination step was complete after 24 hours; the coupling reaction was carried out at 60°C for 4 hours.

1.) LiCl: 64 mg, 1.50 mmol,
 3-Oxo-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester **27l**: 197 mg, 1.0 mmol,
 4-Methyl-4-trimethylsilanyloxy-pentan-2-one **33f**: 245 mg, 1.30 mmol,
 NfF **7**: 765 mg, 2.53 mmol,
 P_1-base **29**: 2.406 mg, 7.70 mmol,
 1 ml DMF.

2.) *i*-Pr_2NH: 1.5 ml, ~10 mmol,
 PPh_3: 26 mg, 0.1 mmol,
 CuI: 19 mg, 0.1 mmol,
 $Pd(OAc)_2$: 11.2 mg, 0.05 mmol, 5 mol%.

Column chromatography (gradient elution: hexane to *t*-BuOMe/*n*-hexane 1:20 to 1:10 to 1:8) afforded **92** as yellowish oil (286 mg, 0.82 mmol, 82% yield).

^{1}H-NMR ($C_6D_6Cl_3$, 400 MHz): δ = 0.15 (s, 9 H, $OSiMe_3$), 1.05 (t, J = 7.1 Hz, 3 H, OCH_2Me), 1.29 (s, 6 H, CMe_2), 1.32–1.38 (br.m, 1 H), 1.56 (br.mc, 1 H), 1.61–1.69 (m, 1 H), 1.75–1.82 (m, 2 H), 2.96 (br.d, J = 15 Hz, 1 H) (all CH_2), 2.42 (s, 2 H, $CH_2C{=}C$), 4.07 (mc, 2 H, OCH_2Me), 4.30 (br.s, 1 H, CHN), 4.37 (br.s, 1 H, CHN), 6.18 (br.d, J = 5 Hz, CH=);

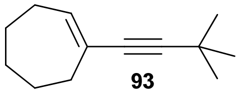
^{13}C-NMR ($C_6D_6Cl_3$, 125.8 MHz): δ = 2.5 (q, $OSiMe_3$), 14.7 (q, OCH_2Me), 29.7 (q, CMe_2), 29.9, 34.6, 38.8 (all br.t., CH_2), 36.3 (t, $C{=}CCH_2$), 52.4, 53.5 (both d, CHN), 60.8 (t, OCH_2Me), 73.9 (s, CMe_2), 82.9, 87.7 (both s, C=C), 120.5 (br.s, C=CH), 137.2 (br.d, C=CH), 154.4 (s, C=O);

IR (film): $\tilde{\nu}$: 2980–2860 cm-1 (C-H), 2220 cm-1 (C=C), 1700 cm-1 (C=O);

MS (EI, 80 eV): m/z (%) = 349 (M^+, 2.3), 334 ([M^+ – CH_3], 5.4), 291 ([M^+ – $SiMe_2$], 30), 131 ([$Me_3SiOCMe_2^+$], 100), 73 ([Me_3Si^+], 29), 29 ($C_2H_5^+$, 6.3);

C,H,N-analysis (%): calcd. for $C_{19}H_{31}NO_3Si$ (349.5): C 65.29, H 8.94, N, 4.01; found C 64.80, H 8.71, N, 3.99.

Synthesis of 1-(3,3-dimethyl-but-1-ynyl)-cycloheptene 93



93

The synthesis was carried out according to the general procedure GP-5. The nonaflation/elimination step was complete after 18 hours; the coupling reaction was carried out at room temperature for 48 hours.

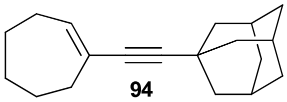
1.) LiCl: 50 mg, 1.18 mmol,
Cycloheptanone **27d**: 113 mg, 1.0 mmol,
Pinacolon **33b**: 103 mg, 1.03 mmol,
NfF **7**: 726 mg, 2.4 mmol,
P_2-base **30**: 1.8 ml, 3.6 mmol,
1 ml DMF.

2.) *i*-Pr_2NH: 1 ml, ~7 mmol,
PPh_3: 29 mg, 0.1 mmol,
CuI: 19.5 mg, 0.1 mmol,
$Pd(OAc)_2$: 11.3 mg, 0.05 mmol, 5 mol%.

Column chromatography (*n*-hexane) **93** was obtained as yellowish oil (68.7 mg, 0.39 mmol, 39% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.16 (s, 9 H, C-(C*H*$_3$)$_3$), 1.40–1.51 (m, 4 H, C*H*$_2$), 1.62–1.68 (m, 2 H, C*H*$_2$), 2.07 (m, 2 H, C*H*$_2$), 2.23 (m, 2 H, C*H*$_2$), 6.10 (t, ^3J = 6.7 Hz, 1 H, C*H*);
^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 26.6, 29.0, 30.6, 31.2 (3x*C*H$_3$), 32.2, 34.7, 82.3 (C-*C*≡C), 95.5 (C≡*C*-C(CH$_3$)$_3$), 127.2 (*C*=CH), 137.9 (*C*H);
HRMS: calculated for $C_{13}H_{20}$ (M^+) 176.1565, found 176.1559.

Synthesis of 1-cyclohept-1-enylethynyl-adamantane <u>94</u>


94

The synthesis was carried out according to the general procedure GP-5. The nonaflation/elimination step was complete after 19 hours; the coupling reaction was carried out at 50°C for 24 hours.

The coupling reaction was carried out at 50°C.

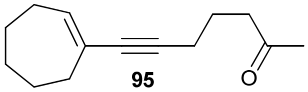
1.) LiCl: 46 mg, 1.08 mmol,
Cycloheptanone **27d**: 112.2 mg, 1.0 mmol,
1-Adamantan-1-yl-ethanone **33c**: 178.5 mg, 1.0 mmol,
NfF **7**: 735 mg, 2.43 mmol,
P_2-base **30**: 1.75 ml, 3.5 mmol,
1 ml DMF.

2.) *i*-Pr_2NH: 1 ml, ~7 mmol,
PPh_3: 26 mg, 0.1 mmol,
CuI: 19 mg, 0.1 mmol,
$Pd(OAc)_2$: 11.3 mg, 0.05 mmol, 5 mol%.

Flash column chromatography (*n*-hexane) afforded **94** as white solid (181 mg, 0.71 mmol, 71% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.47–1.58 (m, 2 H), 1.68 (m, 8 H), 1.86 (d, $^3J_{H,H}$ = 2.8 Hz, 6 H, CH-C*H*$_2$-C), 1.87 (d, $^3J_{H,H}$ = 2.8 Hz, 2 H), 1.95 (m, 3 H), 2.14 (m, 2 H, CH$_2$), 2.30 (m, 2 H), 6.17 (t, ^3J = 6.7 Hz, 1 H, C*H*=C);
^{13}C-NMR ($CDCl_3$, 100.65 MHz): δ = 26.6, 27.8, 28.1, 29.0, 29.9, 32.1, 34.9, 36.2, 36.4, 42.3, 42.7, 43.1, 82.7 (C≡*C*H), 95.5 (*C*≡CH), 127.2 (*C*-CH), 138.0 (C-*C*H);
MS (EI, 70 eV): m/z (%) = 254 (M^+, 100), 135 ([M^+ – 119], [$C_{10}H_{15}$•], 72), 55 ([M^+ – 199], 48), 91 ([M^+ – 163], 33), 95 ([M^+ – 159], [C_7H_{11}•], 27);
HRMS: calculated for $C_{19}H_{26}$ (M^+) 254.2035, found 254.2018.

Synthesis of 7-cyclohept-1-enyl-hept-6-yn-2-one 95



95

The synthesis was carried out according to the general procedure GP-5. The nonaflation/elimination step was complete after 20 hours; the coupling reaction was carried out at 40°C for 24 hours.

1.) LiCl: 51 mg, 1.18 mmol,
Cycloheptanone **27d**: 112.2 mg, 1.0 mmol,
6-Oxoheptanal **41c**: 129.3 mg, 1.0 mmol,
NfF **7**: 814 mg, 2.7 mmol,
P_2-base **30**: 1.5 ml, 3.0 mmol,
2 ml DMF.

2.) *i*Pr_2NH: 1 ml, ~7 mmol,
PPh_3: 48 mg, 0.2 mmol,
CuI: 38 mg, 0.2 mmol,
$Pd(OAc)_2$: 11.3 mg, 0.05 mmol, 5 mol%.

After column chromatography (*n*-pentane : MTBE = 20 : 1) **95** was obtained as yellowish oil (153 mg, 0.75 mmol, 75% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.45–1.60 (m, 4 H), 1.69–1.77 (m, 2 H), (all C*H*$_2$), 1.78 (quintet, ^3J = 7 Hz, 2 H, CH_2*CH*$_2$$CH_2$), 2.12–2.20 (m, 2 H, C*H*$_2$), 2.16 (s, 3 H, MeC=O), 2.27-2.32 (m, 2 H, C*H*$_2$), 2.33 (t, ^3J = 6.8 Hz, 2 H, *CH*$_2$C≡C), 2.57 (t, ^3J = 7.2 Hz, 2 H, C*H*$_2$C=O), 6.19 (tt, ^3J = 6.7 Hz, ^4J = 0.6 Hz);

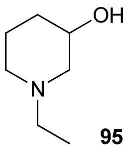
^{13}C-NMR ($CDCl_3$, 100.65 MHz): 18.7, 22.7, 26.48, 26.50, 28.9 (all t, *C*H2), 30.0 (q, *Me*C=O), 32.1, 34.4, 42.3 (all t, *C*H_2), 84.7, 86.0 (both s, C≡C), 127.0 (s, *C*=CH), 138.5 (d, C=*C*H), 208.4 (s, *C*=O);

MS (EI, 70 eV): m/z (%) = 43 (CH_3CO^+, 100), 161 ([M^+ – CH_3CO], 29), 204 (M^+, 16), 189 ([M^+ – CH_3], 5);

HRMS: calculated for $C_{14}H_{20}O$ (M^+) 204.1514, found 204.1519.

7.2.5. Reactions of Chapter 5

Synthesis of 1-ethylpiperidin-3-ol 95



95

In a dry 500 ml three necked round bottom flask equipped with magnetic stirrer, condenser, argon supply and addition funnel a solution of 7.349 g (72.7 mmol) of piperidin-3-ol **94** in 100 ml of dry CH_2Cl_2 is cooled to 0°C. While stirring 31.380 g (148 mmol) of STAB-H is added in one lot. Subsequently a solution of 4.770 g (108.3 mmol) of acetaldehyde in 150 ml of dry CH_2Cl_2 is added dropwise under vigorous stirring within 45 minutes. With completed addition the reaction mixture is allowed to warm to room temperature and stirred for additional 18 hours (GC-MS control indicicated complete conversion). To the reaction mixture 100 ml of ice cold water are added slowly and stirred for additional 15 minutes. The pH of the aqueous phase is adjusted to pH=12-13 via addition of a 1M NaOH solution and the phases get separated. The aqueous phase is extracted 3 times with 100 ml of CH_2Cl_2 and the unified organic phases are washed with 100 ml of water (pH=12), dried over Na_2SO_4 and evaporated under reduced pressure. Distillation (2 mbar / 77°C) afforded 8.896 g (68.9 mmol, 95%) of 1-ethylpiperidin-3-ol **95** as colorless oil.

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 1.06 (t, 3 H, ^3J = 7.2 Hz, CH_2-CH_3), 1.44-1.60 (m, 2 H, CH_2-CH_2-CH_2), 1.61-1.72 (m, 1 H, C(O)H-CH_2-CH_2), 1.73-1.86 (m, 1 H, C(O)H-CH_2-CH_2), 2.27-2.43 (m, 3 H, CH_2), 2.41 (q, 2 H, ^3J = 7.2 Hz, N-CH_2-CH_3), 2.47-2.60 (m, 1 H, CH_2), 2.68 (s_{br}, 1 H, O*H*), 3.81 (m_c, 1 H, C*H*(OH));

^{13}C-NMR (100.65 MHz): δ = 11.9 (*C*H_3), 21.9, 32.2, 52.3, 53.2 (all *C*H_2), 60.1 (N-*C*H_2-CH(OH), 66.4 (*C*H-OH);

MS (EI, 70 eV): m/z (%) = 114 ([M^+ – 15], [CH_3•], 100), 72 ([M^+ – 57], 21), 127 (M^+, 20), 57 ([M^+ – 72], 18).

Analytical data match well those described in literature.[139]

Synthesis of 1-ethylpiperidin-3-ol 95 using $NaBH_4$ in glacial acetic acid

In a dry 500 ml three necked round bottom flask equipped with magnetic stirrer, internal thermometer and condenser 8.05 g (79.6 mmol) of 3-piperidinol get suspended in 210 ml of glacial acetic acid. In order to obtain complete dissolution the suspension is warmed up to *ca.*

40°C for 10-15 minutes (by heat gun). The solution is cooled to room temperature again and under vigorous stirring 14.4 g (380 mmol) of $NaBH_4$ is added in portions while the temperature is kept below 40°C (cooling with an ice bath). After the addition is completed the reaction mixture is stirred for additional 20 hours while the temperature is kept in between 46°C-49°C. The solution is allowed to come to room temperature and is adjusted to pH=13 by addition of a 20% NaOH solution under cooling. The reaction mixture is extracted three times with 250 ml of DCM. The unified phases are washed with 750 ml brine and get dried over $NaSO_4$. After evaporation of the organic solvent 9.30 g of auburn oil are obtained. Distillation over a short column at 64°C (4-5 mbar) afforded 8.42 g (65.2 mmol, 82%) of the product **95** accompanied by *ca.* 20% of 1-(3-hydroxypiperidin-1-yl)ethanone **98**.

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 1.06 (t, 3 H, ^3J = 7.2 Hz, CH_2-CH_3), 1.44-1.60 (m, 2 H, CH_2-CH_2-CH_2), 1.61-1.72 (m, 1 H, C(O)H-CH_2-CH_2), 1.73-1.86 (m, 1 H, C(O)H-CH_2-CH_2), 2.27-2.43 (m, 3 H, CH_2), 2.41 (q, 2 H, ^3J = 7.2 Hz, N-CH_2-CH_3), 2.47-2.60 (m, 1 H, CH_2), 2.68 (s_{br}, 1 H, O*H*), 3.81 (m_c, 1 H, C*H*(OH));

^{13}C-NMR (100.65 MHz): δ = 11.9 (*C*H_3), 21.9, 32.2, 52.3, 53.2 (all *C*H_2), 60.1 (N-*C*H_2-CH(OH), 66.4 (*C*H-OH).

Selected NMR-data for compound **98**:

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 2.06 (C(O)-CH_3);

^{13}C-NMR (100.65 MHz): δ = 11.8 (*C*H_3), 170.6 (*C*=O).

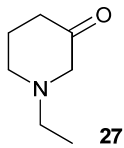
The reduction of 1-(3-hydroxypiperidin-1-yl)ethanone 98 in the presence of 95 with $LiAlH_4$ to give pure 1-ethylpiperidin-3-ol 95

In a dry 250 ml three necked round bottom flask equipped with magnetic stirrer, argon supply and condenser 3.80 g (100 mmol) of $LiAlH_4$ get suspended in 50 ml of THF and the suspension is cooled to 0°C. Under vigorous stirring 8.42 g (65.2 mmol) of **95** contaminated with amide **98** are added in 60 ml of THF dropwise. After completed addition the reaction is allowed to come to room temperature slowl and is refluxed for 4 hours. The reaction mixture is stirred for additional 16 hours at room temperature and the viscous solution diluted with 50 ml of THF. Subsequently 30 ml of a 1N NaOH solution is added. Finally 20 ml of a NaSO4 solution and 30 ml of THF are added. The THF phase gets seperated and the residue washed once with 100 ml of THF. The unified THF phases are washed with 150 ml of brine and the solvents gets removed. The resulting oil is dissolved in 200 ml of DCM, washed with 100 ml of brine and gets dried over $NaSO_4$. The solvent is removed and the resulting oil is submitted to Kugelrohr distillation at 96°C (7-8 mbar) to afford 8.05 g (62.6 mmol, 96% yield, 0.79% yield for both steps).

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 1.07 (t, 3 H, ^3J = 7.2 Hz, CH_2-CH_3), 1.45-1.62 (m, 2 H, CH_2-CH_2-CH_2), 1.61-1.72 (m, 1 H, C(O)H-CH_2-CH_2), 1.74-1.86 (m, 1 H, C(O)H-CH_2-CH_2), 2.27-2.43 (m, 3 H, CH_2), 2.42 (q, 2 H, ^3J = 7.2 Hz, N-CH_2-CH_3), 2.47-2.60 (m, 1 H, CH_2), 2.68 (s_{br}, 1 H, OH), 3.81 (m_c, 1 H, CH(OH));

^{13}C-NMR (100.65 MHz): δ = 11.9 (CH_3), 21.9, 32.2, 52.3, 53.3 (all CH_2), 60.1 (N-CH_2-CH(OH), 66.4 (CH-OH).

Synthesis of 1-ethylpiperidin-3-one 27h



27h

In a dry 500 ml three necked round bottom flask equipped with magnetic stirrer, condenser, internal thermometer, argon supply and addition funnel a solution of 6.3 ml (73.5 mmol) of oxalylchloride in 150 ml of dry CH_2Cl_2 is cooled to -64°C. While vigorous stirring a solution of 11.190 g (143.2 mmol) DMSO in 25 ml of dry CH_2Cl_2 is added dropwise within 15 minutes. With completed addition the reaction solution is stirred for additional 10 minutes and 8.0 g (62.0 mmol) of 1-ethylpiperidin-3-ol **95** in 10 ml of dry CH_2Cl_2 are added dropwise within 15 minutes. The solution is additionally stirred at this temperature for 20 minutes and 43 ml (31.37 g, 310 mmol) of NEt_3 are added dropwise. With completed addition the reaction is allowed to come to 0°C within 45 minutes and under vigorous stirring 80 ml of cold water is added slowly. The solution is stirred for additional 10 minutes and the pH of the aqueous solution gets adjusted to pH = 13 by addition of a 1M NaOH solution. The phases of the room temperature mixture are seperated and the aqueous phase is extracted 3 times with 100 ml of CH_2Cl_2. The unified organic phases are washed with 100 ml of water (pH=12), dried over Na_2SO_4 and evaporated under reduced pressure. Kugelrohr distillation (5 mbar / 70°C) with a subsequent vacuum distillation (3 mbar / 72°C) afforded 6.943 g (54.6 mmol, 88%) of 1-ethylpiperidin-3-one **27h** as yellowish oil.

^{1}H-NMR (400.23 MHz, $CDCl_3$): δ = 1.09 (t, 3 H, ^3J = 7.2 Hz, CH_2-CH_3), 1.94-2.00 (m, 2 H, CH_2-CH_2-CH_2), 2.37 (t, 2 H, ^3J = 6.9 Hz, N-CH_2-CH_2), 2.50 (q, 2 H, ^3J = 7.2 Hz, N-CH_2- CH_3), 2.66 (t, 2 H, ^3J = 5.6 Hz, C(O)-CH_2-CH_2), 3.00 (s, 2 H, C(O)-CH_2-N);

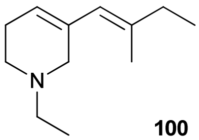
^{13}C-NMR (100.65 MHz, $CDCl_3$): δ = 12.1 (CH_3), 22.2, 40.2, 52.3, 53.2, 60.1 (all CH_2), 206.2 (C=O);

MS (EI, 70 eV): m/z (%) = 84 ([M^+ – 43], 100), 127 (M^+, 39);

HRMS: calculated for $C_7H_{13}NO$ (M^+) 127.0997, found 127.0991.

Analytical data match well those described in literature.[140]

Attempted synthesis of 1-ethyl-5-(2-methylbut-1-enyl)-1,2,3,6-tetrahydropyridine <u>100</u>



100

The synthesis was carried out according to the general procedure GP-3.

1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 1-ethyl-1,2,5,6-tetrahydro-pyridin-3-yl ester **28h**: 406 mg, 0.990 mmol,

2-Methyl-1-butene **99**: 247 mg, 3.50 mmol,

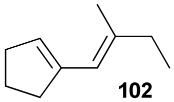
NEt_3: 202 mg, 2.0 mmol,

$Pd(OAc)_2$: 11.2 mg, 0.05 mmol, 5 mol%,

1 ml DMF.

The cross-coupling was carried at room temperature for 24 hours without the observation of product. Heating to 50°C led to Pd_{black} formation within 5 hours and to a precipitation of Pd_{black} at the glass vial after additional 15 hours. Heating to 90°C was applied overnight. No conversion of the starting material **28h** to the desired product **100** was observed. With stirring at 50°C impurities could be detected. Heating to 90°C led to the full transformation of starting material **28h** into not further identified side products. The reaction was monitored via ^{1}H-NMR and GC-MS.

Attempted synthesis of 1-(2-methylbut-1-enyl)cyclopent-1-ene <u>102</u>



102

The synthesis was carried out according to the general procedure GP-3.

Cyclopentenyl nonaflate **28a**: 371 mg, 1.01 mmol,

2-Methyl-1-butene **99**: 218 mg, 3.11 mmol,

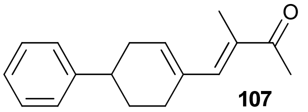
NEt_3: 203 mg, 2.0 mmol,

$Pd(OAc)_2$: 11.3 mg, 0.05 mmol, 5 mol%,

1 ml DMF.

The cross-coupling was carried at 20°C and 50°C. No conversion of the starting material **28a** to the desired product **102** was observed in both cases. The reaction was monitored via ^{1}H-NMR.

Synthesis of (*E*)-3-methyl-4-(4-phenylcyclohex-1-enyl)but-3-en-2-one 107



107

The synthesis was carried out according to the general procedure GP-3.

4-Phenylcyclohex-1-enyl nonafluorobutanesulfonate **28b**: 457.6 mg, 1.0 mmol,

3-Methylbut-3-en-2-one **103**: 119 mg, 1.415 mmol,

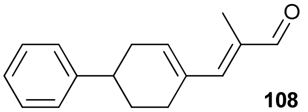
NEt_3: 208 mg, 2.06 mmol,

$Pd(OAc)_2$: 11.3 mg, 0.05 mmol, 5 mol%,

1 ml DMF.

The cross-coupling was conducted at 50°C. The transformation was monitored by GC-MS. Full conversion of the starting material **28b** was observed after 7 hours. The overall peak area (%) for product **107** in ratio to impurities could be determined to ≥95%. The product was obtained as a mixture of isomers. Also ^{1}H-NMR control indicated a clean transformation and full conversion of the starting material **28b** (but was not analyzed in detail).

Synthesis of (*E*)-2-methyl-3-(4-phenylcyclohex-1-enyl)acrylaldehyde 108



108

The synthesis was carried out according to the general procedure GP-3.

4-Phenylcyclohex-1-enyl nonafluorobutanesulfonate **28b**: 456.3 mg, 1.0 mmol,

Methacrolein **104**: 103 mg, 1.470 mmol,

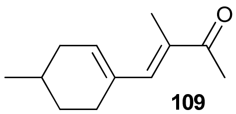
NEt_3: 206 mg, 2.036 mmol,

$Pd(OAc)_2$: 11.3 mg, 0.05 mmol, 5 mol%,

1 ml DMF.

The cross-coupling was conducted at 50°C. The transformation was monitored by GC-MS. After 7 hours at least 2% of the starting material **28b** was still present in the reaction solution. The overall peak area (%) for product **107** in ratio to impurities could be determined to <90% and >85%. The product was obtained as a mixture of isomers. ^{1}H-NMR control indicated as well the formation of several side products (but was not analyzed in detail).

Synthesis of (*E*)-3-methyl-4-(4-methylcyclohex-1-enyl)but-3-en-2-one 109



109

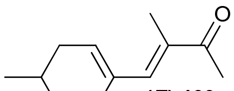
The synthesis was carried out according to the general procedure GP-3.

4-Methylcyclohex-1-enyl nonafluorobutanesulfonate **28b** 1.186 g, 3.01 mmol,
3-Methylbut-3-en-2-one **103**: 360 mg, 4.28 mmol,
NEt_3: 609 mg, 6.02 mmol,
$Pd(OAc)_2$: 33.7 mg, 0.15 mmol, 5 mol%,
3 ml DMF.

Column chromatography (*n*-hexane : MTBE = 15 : 1) and subsequent Kugelrohr distillation (90-100°C, 0.1 mbar) furnished the product **109** as colorless oil and as a mixture of the isomers (*E*)-**109a**:(*Z*)-**109a**:**109b** in the ratio of 6.3:1.0:4.4 (420 mg, 2.6 mmol, 85 % yield). The product mixture is accompanied by 7% of an unidentified compound (indicated by two singulets in the ^{1}H-NMR spectra at 3.48 ppm and 5.47 ppm, it is assumed that the signal at 5.47 represents a single proton).

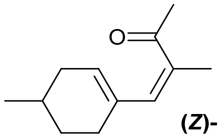
A mixture of three isomers (*E*)-**109a**:(*Z*)-**109a**:**109b**:

(*E*)-3-methyl-4-(4-methylcyclohex-1-enyl)but-3-en-2-one (*E*)-**109a**



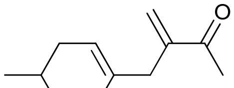
(*E*)-109a

(*Z*)-3-methyl-4-(4-methylcyclohex-1-enyl)but-3-en-2-one (*Z*)-**109a**



(*Z*)-109a

3-((4-methylcyclohex-1-enyl)methyl)but-3-en-2-one **109b**



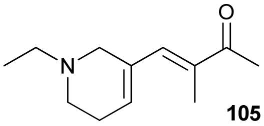
109b

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 0.93 (d, ^3J =6.2 Hz, 3 H, CH-C*H*$_3$, **109b**), 0.97 (d, ^3J =6.6 Hz, 3 H, CH-C*H*$_3$, (*Z*)-**109a**), 0.99 (d, ^3J =6.6 Hz, 3 H, CH-C*H*$_3$, (*E*)-**109a**), 1.12–1.32 (m, 1 H, CH$_3$-C*H*), 1.52-2.34 (m, CH$_2$), 1.94 (s, 3 H, C-C*H*$_3$, (*E*)-**109a**, (*Z*)-**109a**), 2.33 (s, 3 H, C(O)-C*H*$_3$, (*Z*)-**109a**), 2.338 (s, 3 H, C(O)-C*H*$_3$, **109b**), 2.34 (s, 3 H, C(O)-C*H*$_3$, (*E*)-**109a**), 2.90 (s, 2 H, C*H*$_2$-C, **109b**), 5.37 (br.s, 1 H, C*H*=C, **109b**), 5.71 (s, 1 H, C=C*H*$_2$, **109b**), 5.95 (br.s, 1 H, C*H*=C, (*E*)-**109a**), 5.97 (br.s, 1 H, C*H*=C, (*Z*)-**109a**), 6.05 (s, 1 H, C=C*H*$_2$, **109b**), 6.91 (s, 1 H, C*H*=C(Me)C(O)Me, (*E*)-**109a**), 7.01 (s, 1 H, C*H*=C(Me)C(O)Me, (*Z*)-**109a**);

^{13}C-NMR (CDCl$_3$), 100.65 MHz, selected signals): δ = 21.57 (CH-*C*H$_3$, (*Z*)-**109a**), 21.60 (CH-*C*H$_3$, (*E*)-**109a**), 21.74 (CH-*C*H$_3$, **109b**), 125.6 (C=C*H*$_2$, **109b**), 199.7 (*C*=O, **109b**), 200.4 (*C*=O, (*Z*)-**109a**), 200.8 (*C*=O, (*E*)-**109a**);

Due to technical difficulties no MS- and HRMS-spectra could be taken and compound **109** is not fully characterized.

Synthesis of (*E*)-4-(1-ethyl-1,2,5,6-tetrahydropyridin-3-yl)-3-methylbut-3-en-2-one 105



105

The synthesis was carried out according to the general procedure GP-4. The cross-coupling was performed at 45°C.

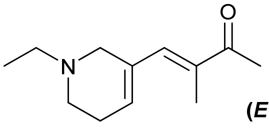
1.) 1-Ethylpiperidin-3-one **27h**: 2.545 g, 20.0 mmol,
NfF **7**: 7.25 g, 24.1 mmol,
P$_1$-base **29** 7.5 g, 24.2 mmol,
20 ml DMF.

2.) NEt$_3$: 4.048 g, 40.3 mmol,
3-Methylbut-3-en-2-one **103**: 2.271 g, 27 mmol,
Pd(OAc)$_2$: 224.5 mg, 1.0 mmol, 5 mol%.

Aqueous workup was performed with a basic aqueous solution of pH=12 (pH adjustment with 2N NaOH solution). Column chromatography (*n*-pentane : MTBE = 10 : 1 with 5 vol% NEt$_3$) and subsequent Kugelrohr distillation afforded **105** as yellowish oil and as a mixture of the isomers (*E*)-**105a**:(*Z*)-**105a**:**105b** in the ratio of 2.9:1.7:1.0 (3.49 g, 18.1 mmol, 90% yield). The product mixture is accompanied by *ca.* 34% of an unidentified compound (indicated by two singulets in the ^{1}H-NMR spectra at 3.39ppm and 5.48ppm, it is assumed that the signal at 5.48 represents a single proton).

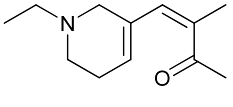
A mixture of three isomers (*E*)-**105a**:(*Z*)-**105a**:**105b**:

(*E*)-4-(1-ethyl-1,2,5,6-tetrahydropyridin-3-yl)-3-methylbut-3-en-2-one



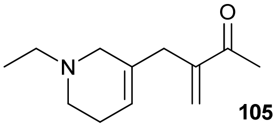
(*E*)-105a

(*Z*)-4-(1-ethyl-1,2,5,6-tetrahydropyridin-3-yl)-3-methylbut-3-en-2-one



(*Z*)-105a

3-((1-ethyl-1,2,5,6-tetrahydropyridin-3-yl)methyl)but-3-en-2-one



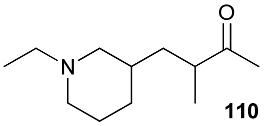
105b

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.05–1.20 (t, CH_2-CH_3), 1.55 (s, 3 H, C(O)-CH_3, **105b**), 1.81 (s, 3 H, C(O)-CH_3, (*Z*)-**105a**), 1.94 (s, 3 H, C(O)-CH_3, (*E*)-**105a**), 2.34 (s, 3 H, C-CH_3), 2.40-2.46 (m, CH_2), 2.71-2.90 (m, 2 H, C-CH_2), 5.69 (br.s, 1 H, C*H*=C, **105b**), 5.81 (s, 1 H, C=CH_2, **105b**), 6.03 (br.s, 1 H, C*H*=C, (*E*)-**105a**), 6.08 (br.s, 1 H, C=CH_2, **105b**), 6.09 (br.s, 1 H, C*H*=C, (*Z*)-**105a**), 6.85 (s, 1 H, C*H*=C(Me)C(O)Me, (*E*)-**105a**), 6.97 (s, 1 H, C*H*=C(Me)C(O)Me, (*Z*)-**105a**);

^{13}C-NMR ($CDCl_3$), 100.65 MHz, selected signals): δ = 21.2 (CH-CH_3, (*Z*)-**105a**), 21.45 (CH-CH_3, (*E*)-**105a**), 21.50 (CH-CH_3, **105b**), 124.9 (C=CH_2, **105b**), 198.1 (*C*=O, **105b**), 199.2 (*C*=O, (*Z*)-**105a**), 200.5 (*C*=O, (*E*)-**105a**);

Due to technical difficulties no MS- and HRMS-spectra could be taken and compound **105** is not fully characterized.

Synthesis of 4-(1-ethylpiperidin-3-yl)-3-methylbutan-2-one 110



110

Into a stainless steel reactor with stirrer 2.90 g (15.0 mmol) of the isomer mixture **105** is dissolved in 50 ml of MeOH. To this mixture 1.6 g of Pd/C are added in one lot and suspended. The vessel is closed and while stirring evacuated and filled with 2 bar of hydrogen twice. Afterwards the reactor is filled with hydrogen until a pressure of 10 bar is observed. The reaction mixture is stirred for 16 hours at room temperature. After 16 hours a pressure of 2 bar is observed, indicating a leak in the reactor system. The reaction solution was filtered and MeOH evaporated under reduced pressure. From the crude oil a ^{1}H-NMR sample was taken. It showed incomplete conversion of the starting material **105**.

A second reaction was conducted analogously to the above described hydrogenation, in the presence of 2.28 g (20 mmol) TFA and an overpressure of hydrogen of 66 bar. The reaction was stopped after 15 hours, the mixture was filtered, MeOH removed under reduced pressure and a ^{1}H-NMR sample taken from the crude orange colored oil. Disappearance of the olefinic protons indicated total hydrogenation of the starting material **105**. The same side product with a singulett signal at 5.48 ppm as seen in the reaction for the synthesis of **105** is observed here as well. The product **110** was not further analyzed.

7.3. Optimization reactions for regioselective product formation

GP-6 General procedure of the optimization reactions for the regioselective formation of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 5-methyl-cyclopent-1-enyl ester <u>28f</u> (Table 2), 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 6-methyl-cyclohex-1-enyl ester <u>28g</u> (Table 3) and tridec-1-yne <u>38a</u> (Table 7). Changes in the general procedure and details are stated for each single reaction.

To identify the optimum reaction conditions the experimental series required an accurate temperature control and the ability to keep the temperature constant for hours or even days. Therefore the reactions were carried out in a Dewar, equipped with the cooling coil of an immersion cooler for optimal temperature adjustment. The round bottom flasks were placed up to the neck in the methanol bath to allow effective temperature adjustment for the reaction solution. Every single adjustment of the temperature was followed by a period of at least 5 minutes of equilibration. The described experimental setup allowed a temperature control accurate to ±1°C.

Into a dry one-necked round bottom flask equipped with magnetic stirring bar and a three way tap either DMF or THF, one of the carbonyl compounds **27f, 27g** or **37** and NfF **7** are added consecutively in an argon atmosphere (all via syringe). The reaction mixture is cooled to the stated addition temperature and kept for 10 minutes. While vigorous stirring the P-base **29**/**30** gets added slowly dropwise. With the completed addition the temperature is kept for additional 5 minutes and the three way tap is replaced quickly by a glass stopper and the flask gets closed tightly. The reaction mixture is warmed up to the stated reaction temperature and stirred for the designated time (see Tables 2, 3 and 7). Samples are taken by fast dipping of a glass pipette into the reaction solution. Analysis for determination of the regioselectivity and conversion is conducted by ^{1}H-NMR. If workup is conducted the reaction mixture is quenched with 5 ml of water followed by 4 times extraction of the aqueous phase with 25 ml *n*-pentane. The combined organic phases are washed with 20 ml of water and dried over Na_2SO_4. The solvent is removed under reduced pressure and the residue is purified by column chromatography (*n*-pentane as eluent) to give the pure compounds for verification of the regioselective discrimination and determination of the yield.

7.3.1. Experimental data of the optimization reactions for the regioselective synthesis of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 5-methyl-cyclopent-1-enyl ester 28f

The alkenyl nonaflate formation was carried out according to the general procedure GP-6. The ratio of the regioisomers was determined by ^{1}H-NMR. The experimental results are stated in Table 2. The substrates were added in the following amounts:

Entry 1:
2-Methylcyclopentanone **27f** (99 mg, 1.01 mmol),
NfF **7** (365 mg, 1.21 mmol),
P_1-base **29** (359.4 mg, 1.15 mmol),
1 ml DMF.
The P_1-base **29** was added at 0°C (ice bath) and the reaction mixture warmed up to room temperature within 1 hour.
The alkenyl nonaflate **28f** was isolated as a mixture of **28f** and **28j** in a ratio of 1.2:1.0 as colorless oil (340 mg, 0.89 mmol, 89%).

Entry 2:
2-Methylcyclopentanone **27f** (99.7 mg, 1.02 mmol),
NfF **7** (355 mg, 1.18 mmol),
P_2-base **30** (0.6 ml, 1.20 mmol),
1 ml THF.
The P_2-base **30** was added at -78°C (dry ice bath) and the reaction solution was allowed to come to room temperature within several hours.
The alkenyl nonaflate **28f** was isolated as a mixture of **28f** and **28j** in a ratio of 6:1 as colorless oil (322.7 mg, 0.85 mmol, 84%).

Entry 3:
2-Methylcyclopentanone **27f** (98.7 mg, 1.0 mmol),
NfF **7** (391 mg, 1.29 mmol),
P_2-base **30** (0.6 ml, 1.2 mmol),
1 ml DMF.
The temperature was kept ≤-40°C while addition of the P_2-base **30**, the synthesis was carried out at -30°C.

The alkenyl nonaflate **28f** was isolated as a mixture of **28f** and **28j** in a ratio of 24:1 as slightly yellowish oil (326 mg, 0.86 mmol, 85%).

Entry 4:
2-Methylcyclopentanone **27f** (100 mg, 1.02 mmol),
NfF **7** (353.5 mg, 1.17 mmol),
P_2-base **30** (0.6 ml, 1.17 mmol),
1 ml DMF.
The temperature was kept ≤-50°C while addition of the P_2-base **30**, the synthesis was carried out at -40°C.
The alkenyl nonaflate **28f** was isolated as a mixture of **28f** and **28j** in a ratio of 16:1 as colorless oil (320 mg, 0.84 mmol, 83%).

7.3.2. Experimental data of the optimization reactions for the regioselective synthesis of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 6-methyl-cyclohex-1-enyl ester 28g

The alkenyl nonaflate formation was carried out according to the general procedure GP-6. The compound mixtures were analyzed and the ratio of the regioisomers determined by ^{1}H-NMR. The experimental results are stated in Table 3. The substrates were added in the following amounts:

Entry 1:
2-Methylcyclohexanone **27g** (112.3 mg, 1.0 mmol),
NfF **7** (356 mg, 1.18 mmol),
P_1-base **29** (368 mg, 1.17 mmol),
1 ml DMF.
The P_1-base **29** was added at 0°C (ice bath) and the reaction mixture warmed up to room temperature quickly, maximum conversion was reached with 85% after 111 hours and the reaction worked up as described.
The alkenyl nonaflate **28g** was isolated as a mixture of **28g** and **28k** in a ratio of 1:1 as colorless oil (330 mg, 0.84 mmol, 84%).

Entry 2:
2-Methylcyclohexanone **27g** (115.2 mg, 1.03 mmol),

NfF **7** (360 mg, 1.19 mmol),
P_2-base **30** (0.6 ml, 1.2 mmol),
1 ml THF.

The P_2-base **30** was added at -78°C (dry ice bath) and the reaction solution was allowed to come to room temperature within several hours.

The alkenyl nonaflate **28g** was isolated as a mixture of **28g** and **28k** in a ratio of 1.3:1.0 as colorless oil (381.1 mg, 0.97 mmol, 94%).

<u>Entry 3:</u>

2-Methylcyclohexanone **27g** (115.4 mg, 1.03 mmol),
NfF **7** (358 mg, 1.19 mmol),
P_2-base **30** (0.6 ml, 1.2 mmol),
1 ml THF.

The temperature was kept ≤-70°C while addition of the P_2-base **30** and adjusted to -60°C afterwards; no conversion was detected at this temperature for 63 hours; warm up to room temperature lead to a fast and nearly complete conversion of the starting material within 6 hours, indicating still active P_2-base **30** present in the reaction mixture.

The alkenyl nonaflates **28g** and **28k** were not isolated.

<u>Entry 4:</u>

2-Methylcyclohexanone **27g** (112.3 mg, 1.0 mmol),
NfF **7** (350 mg, 1.16 mmol),
P_2-base **30** (0.6 ml, 1.2 mmol),
1 ml DMF.

The temperature was kept ≤-50°C while addition of the P_2-base **30** and adjusted to -40°C afterwards; 10% conversion were detected after 16 hours at this temperature; the temperature was increased to -30°C and 50% conversion were obtained after 20 hours and 54% after additional 26 hours; warm up of the reaction mixture to room temperature lead to no further conversion of the starting ketone **27g**, indicating the total deactivation of the P_2-base **30**.

The alkenyl nonaflates **28g** and **28k** were not isolated.

<u>Entry 5:</u>

2-Methylcyclohexanone **27g** (112.8 mg, 1.01 mmol),
NfF **7** (354 mg, 1.17 mmol),
P_2-base **30** (0.6 ml, 1.2 mmol),
1 ml DMF.

The temperature was kept ≤-40°C while addition of the P_2-base **30** and adjusted to -30°C afterwards; 41% conversion were detected after 24 hours; the temperature was increased to -20°C and after overall 48 hours an conversion of 68% was obtained. Longer reaction time up to 67 hours did not lead to a higher conversion for the reaction.
The alkenyl nonaflates **28g** and **28k** were not isolated.

Entry 6:
2-Methylcyclohexanone **27g** (112.9 mg, 1.01 mmol),
NfF **7** (358.4 mg, 1.19 mmol),
P_2-base **30** (0.6 ml, 1.2 mmol),
1 ml DMF.
The temperature was kept ≤-50°C while addition of the P_2-base **30** and adjusted to -20°C within 1 hour afterwards; within 21 hours a conversion of 68% was detected; fast warm up of the reaction mixture to room temperature and additional stirring for 5 hours lead to a fast and complete conversion of the starting ketone **27g**.
The alkenyl nonaflates **28g** and **28k** were not isolated, the ratio of **28g** and **28k** was determined to 5:1.

Entry 7:
2-Methylcyclohexanone **27g** (114.5 mg, 1.02 mmol),
NfF **7** (695 mg, 2.30 mmol),
P_2-base **30** (1.0 ml, 2.0 mmol),
1 ml DMF.
The temperature was kept ≤-50°C while addition of the P_2-base **30** and adjusted to -20°C within 1 hour after completed addition; full conversion was detected within 65 hours at this temperature.
The alkenyl nonaflate **28g** was isolated as a mixture of **28g** and **28k** in a ratio of 99:1 as colorless oil (376 mg, 0.95 mmol, 93%).

7.3.3. Optimization reactions for the regioselective formation of the terminal alkyne tridec-1-yne 38a from tridecan-2-one 37

The elimination reactions were carried out according to the general procedure GP-6. Except for Entry 5 the products were isolated from the reaction mixtures and analyzed as pure compounds. The ratio of the obtained regioisomers was determined by ^{1}H-NMR. The experimental results are stated in Table 7 (Entry 2-6). The substrates were added in the following amounts:

Entry 2:

Tridecan-2-one **37** (198.8 mg, 1.0 mmol),
NfF **7** (371 mg, 1.23 mmol),
P_2-base **30** (1.15 ml, 2.30 mmol),
1 ml DMF.

The P_2-base **30** was added at -30°C and the temperature kept at -20°C for 10 minutes; subsequently the reaction mixture was warmed up to room temperature within 1 hour.

Tridec-1-yne **38a** was isolated as a mixture of **38a** and **38b** in a ratio of 1.0:0.81 as slightly yellowish oil (158 mg, 0.95 mmol, 95%).

Entry 3:

Tridecan-2-one **37** (206 mg, 1.04 mmol),
NfF **7** (380 mg, 1.26 mmol),
P_2-base **30** (1.2 ml, 2.40 mmol),
1 ml DMF.

The P_2-base **30** was added at -50°C and the reaction carried out at -20°C.

Tridec-1-yne **38a** was isolated as a mixture of **38a** and **38b** in a ratio of 0.81:1.0 as slightly yellowish oil (164 mg, 0.98 mmol, 95%); the product mixture is is accompanied by less then 1% of allene **38c**.

Entry 4:

Tridecan-2-one **37** (198.8 mg, 1.0 mmol),
NfF **7** (430 mg, 1.42 mmol),
P_2-base **30** (1.4 ml, 2.80 mmol),
1 ml THF.

The P_2-base **30** was added at -60°C and the reaction carried out at -50°C; full conversion was obtained within 25 hours.

Tridec-1-yne **38a** was isolated as a mixture of **38a** and **38b** in a ratio of 1.0:0.42 as slightly yellowish oil (156 mg, 0.94 mmol, 94%).

Entry 5:

Tridecan-2-one **37** (198.5 mg, 1.0 mmol),
NfF **7** (370 mg, 1.22 mmol),
P_2-base **30** (1.2 ml, 2.40 mmol),

1 ml THF.

The P_2-base **30** was added at -70°C and the reaction carried out at -60°C; stirring of the reaction mixture at -70°C turned out to be difficult due to solidification; after 24 hours 42% conversion could be detected; the reaction mixture was warmed up to -50°C and stirred for additional 24 hours with no further improvement of the conversion.

The generated alkynes **38a** and **38b** were not isolated, the product ratio of **38a**:**38b** was determined to 1.0:0.39 out of the reaction solution.

Entry 6:

Tridecan-2-one **37** (208.5 mg, 1.05 mmol),
NfF **7** (517 mg, 1.71 mmol),
P_2-base **30** (1.7 ml, 3.40 mmol),
1 ml THF.

The P_2-base **30** was added at -65°C and the reaction carried out at -60°C; full conversion was obtained within 48 hours.

Tridec-1-yne **38a** was isolated as a mixture of **38a** and **38b** in a ratio of 1.0:0.39 as yellowish oil (172.6 mg, 1.03 mmol, 98%).

7.4. Kinetic measurements

7.4.1. Variation of the catalyst loading (see Figure 6)

To screw cap vials equipped with magnetic stirring bars, DMF (1 mL), *p*-xylene (6 drops; added *via* syringe) as an internal standard, Et_3N, cyclopentenyl nonaflate **28a**, methyl acrylate **44** and $Pd(OAc)_2$ 10 mol.% (*a*), 5 mol.% (*b*) 1 mol.% (*c*) 0.5 mol.% (*d*) 0.1 mol.% (*e*) were subsequently added in the following amounts:

a: Et_3N (205.5 mg, 2.031 mmol), **28a** (372.0 mg, 1.016mmol), **44** (120.9 mg, 1.404 mmol), $Pd(OAc)_2$ (22.5 mg, 0.10 mmol);
b: Et_3N (203.2 mg, 2.008 mmol), **28a** (367.3 mg, 1.003 mmol), **44** (114.3 mg, 1.327 mmol), $Pd(OAc)_2$ (11.721 mg, 0.052 mmol);
c: Et_3N (205.5 mg, 2.031 mmol), **28a** (366.5 mg, 1.001 mmol), **44** (119.3 mg, 1.386 mmol), $Pd(OAc)_2$ (2.647 mg, 0.012 mmol);

d: Et_3N (204.4 mg, 2.020 mmol), **28a** (368.6 mg, 1.006 mmol), **44** (115.3 mg, 1.339 mmol), $Pd(OAc)_2$ (1.104 mg, 0.005 mmol);
e: Et_3N (205.5 mg, 2.031 mmol), **28a** (367.3 mg, 1.003 mmol), **44** (115.3 mg, 1.339 mmol), $Pd(OAc)_2$ (0.190 mg, 0.00085 mmol).

The mixtures were vigorously stirred at room temperature and the reaction progress was monitored after 0 hours, 2 hours, 5 hours, 8 hours and 11 hours by GC (p = 15 psi; t = 100°C const.; the samples taken were diluted with *n*-hexane before injection); R_t = 1.66 min (*p*-xylene), 2.79 min (**28a**), 8.55 min (product **45**).

7.4.2. Poisoning Experiments

General. The methods described in detail in the review by Widegren and Finke[58] suggest that the poisoning reagent be added at a certain time *after the reaction had started, and a catalytically active system had formed*, the kinetic profile being recorded before and after the addition of the catalyst poison. When applying this rule to our system, we chose to add the poisoning reagents at the highest conversion rate (maximum slope of the curve) that is routinely attained at *ca*. 2.5 hours after the beginning of the reaction.

With PPh_3 or thiophene: to screw cap vials equipped with magnetic stirring bars, DMF (1 ml), *p*-xylene (5 drops; added *via* syringe) as an internal standard, Et_3N, cyclopentenyl nonaflate **28a**, methyl acrylate **44** and $Pd(OAc)_2$ were subsequently added. The mixtures were vigorously stirred at room temperature, and the reaction progress was monitored as depicted in Figures 7 and 8 by GC as described above. After 2.5 hours reaction time, the poisoning reagent was added by volume using *Hamilton* syringe (thiophene) or by weight (PPh_3) in the amounts designated below. The reaction progress was further monitored by GC.

<u>Experiments with thiophene (see Figure 7)</u>:

a: Et_3N (206.5 mg, 2.041 mmol), **28a** (373.2 mg, 1.019 mmol), **44** (117.1 mg, 1.360 mmol), $Pd(OAc)_2$ (11.2 mg, 0.049 mmol), thiophene (8 µl, 0.1 mmol);
b: Et_3N (207.5 mg, 2.050 mmol), **28a** (368.6 mg, 1.007 mmol), **44** (117.0 mg, 1.360 mmol), $Pd(OAc)_2$ (11.2 mg, 0.049 mmol), thiophene (4 µl, 0.05 mmol);

c: Et_3N (207.5 mg, 2.050 mmol), **28a** (371.6 mg, 1.015 mmol), **44** (118.5 mg, 1.376 mmol), $Pd(OAc)_2$ (11.2 mg, 0.049 mmol), thiophene (2 µl, 0.025 mmol);
d: Et_3N (204.5 mg, 2.021 mmol), **28a** (369.2 mg, 1.008 mmol), **44** (113.1 mg, 1.314 mmol), $Pd(OAc)_2$ (11.2 mg, 0.049 mmol), thiophene (0.4 µl, 0.005 mmol);
e (reference run): Et_3N (207.5 mg, 2.050 mmol), **28a** (367.0 mg, 1.002 mmol), **44** (118.0 mg, 1.370 mmol), $Pd(OAc)_2$ (11.2 mg, 0.049 mmol).

Experiments with PPh_3 (see Figure 8):

a: Et_3N (207.4 mg, 2.052 mmol), **28a** (369.8 mg, 1.010 mmol), **44** (116.5 mg, 1.353 mmol), $Pd(OAc)_2$ (11.2 mg, 0.049 mmol), PPh_3 (26.4 mg, 0.10 mmol);
b: Et_3N (207.8 mg, 2.053 mmol), **28a** (370.0 mg, 1.010 mmol), **44** (114.2 mg, 1.326 mmol), $Pd(OAc)_2$ (11.2 mg, 0.049 mmol), PPh_3 (13.2 mg, 0.05 mmol);
c: Et_3N (205.3 mg, 2.029 mmol), **28a** (369.5 mg, 1.009 mmol), **44** (117.0 mg, 1.360 mmol), $Pd(OAc)_2$ (11.3 mg, 0.050 mmol), PPh_3 (6.6 mg 0.025 mmol);
d (reference run): Et_3N (209.2 mg, 2.067 mmol), **28a** (368.5 mg, 1.006 mmol), **44** (119.5 mg, 1.388 mmol), $Pd(OAc)_2$ (11.2 mg, 0.049 mmol).

With metallic mercury: the reaction in DMF (1 ml) with *p*-xylene (5 drops; added *via* syringe) as an internal standard, Et_3N (205.0 mg, 2.026 mmol), **28a** (366.3 mg, 1.0 mmol), **44** (117.0 mg, 1.36 mmol) and $Pd(OAc)_2$ (11.3 mg, 0.050 mmol) was carried out as described above. After 2.5 hours, mercury 3.047g (15.19 mmol) was added, and the two-phase mixture was *vigorously* stirred for 1 hour. The stirring was stopped, and the mercury phase was allowed to completely settle down to the bottom before the supernatant phase was carefully transferred into a new reaction vial, equipped with magnetic stirring bar. The reaction progress was monitored further by GC as depicted in Figure 9 (curve *a*).

7.4.3. Centrifugation

The reaction in DMF (1 ml) with *p*-xylene (6 drops; added *via* syringe) as internal standard, Et_3N (205.5 mg, 2.031 mmol), **28a** (372.6 mg, 1.017 mmol), **44** (115.0 mg, 1.336 mmol), and $Pd(OAc)_2$ (11.3 mg, 0.050 mmol) was carried out and monitored as described above. After 2.5 hours, the reaction solution was transferred into the centrifugation vial and centrifuged at 14.500 rpm for 25 minutes to give a small amount of dark-brown residue and a clear

yellowish supernatant solution. Approximately three quarter of the supernatant solution were carefully transferred into a new reaction vial and the reaction progress was monitored until the endpoint (see Figure 9, curve *b*).
Reference run (see Figure 9, curve *c*): DMF (1ml), Et_3N (205.8 mg, 2.034 mmol), **28a** (366.4 mg, 1.0 mmol), **44** (117.0 mg, 1.36 mmol), $Pd(OAc)_2$ (11.2 mg, 0.049 mmol).

The solid residue was separated from the rest of the reaction solution, washed with DMF two times (2 × 1.5 ml) followed by a centrifugation with 14.500 rpm for 15 minutes each time. It was then added to a freshly prepared reaction solution comprising DMF (1 ml), Et_3N (207.0 mg, 2.045 mmol), **28a** (367.0 mg, 1.002 mmol), **44** (114.7 mg, 1.332 mmol). The reaction mixture was monitored by GC after 6 hours, 20 hours and 24 hours indicating no product **45** formation.

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