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Synthesis and Evaluation of Enantiopure HMPA Analogs in Samarium-Diiodide-Promoted Dearomatizations of N-Acylated Indole Derivatives

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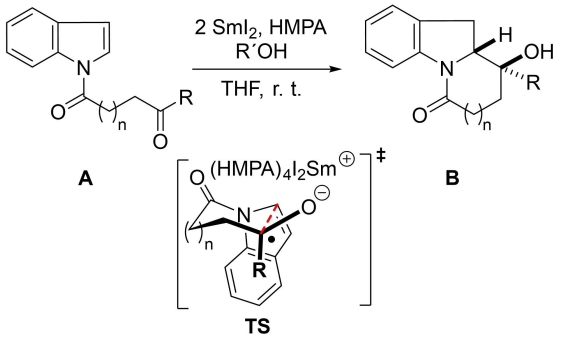
In memory of Klaus Hafner – a committed supporter of the Alexander von Humboldt Foundation

A series of (*S*)-proline-based enantiopure phosphorus triamide derivatives were prepared and evaluated as HMPA alternative in samarium diiodide cyclization reactions of *N*-acylated indole derivatives. The expected tricyclic indoline derivatives were generally obtained in good to excellent yields, however, the induced enantioselectivities were at best moderate. In our model reaction, the phosphorus triamide derivative with a (dimethyl)hydroxymethyl group at the stereogenic center provided the cyclization product in almost quantitative yield and with an enantiomeric excess of approximately 24%. No separate proton source is required by applying this chiral Lewis base which was recovered in 93% yield. Bulkier substituents at the stereogenic center did not furnish improved results. Although in our preliminary study only low to moderate enantioselectivities could be achieved, the observed fast conversions and the high yields demonstrate the basic suitability of chiral pyrrolidine-based phosphoramide Lewis bases in samarium(II)-induced reactions.

Introduction

Dearomatization reactions of indole derivatives are currently investigated in much detail since they lead to functionalized indolines suitable for many applications. The examples include syntheses of natural products or bioactive compounds.[1] Quite a number of methods applying asymmetric catalysis have recently been developed for this useful transformation.[2] Our group found that *N*-acylated indole derivatives such as **A** undergo smooth samarium diiodide-promoted dearomative cyclization reactions to tricyclic or tetracyclic indolines **B** in high yields (Scheme 1).[3,4] The mechanistic details of these reactions involving samarium ketyls have been discussed in several reports and a preferred transition state with an arrangement such as **TS** has been suggested to explain the observed excellent diastereoselectivity.[5] By developing a cascade process, these efforts allowed us to elaborate a very short and efficient route to strychnos alkaloids.[6] These investigations with indoles or other heterocycles were based on the earlier discovery of closely related dearomatization reactions of benzene and naphthalene derivatives.[7]



Scheme 1. Reductive dearomatization of *N*-acylated indole derivatives **A** with samarium diiodide leading to indolines **B** and the proposed transition state **TS** of these reactions; the coordination of ligands at the samarium center is presented in a simplified version.

In general, all these samarium diiodide-promoted reactions[8] require a proton source and a strong Lewis base to achieve high yields. Hexamethylphosphortriamide (HMPA) is traditionally employed as additive which strongly raises the reducing ability of samarium diiodide.[9] Due to the metabolism of the *N*-methyl groups of HMPA, this useful reagent is known to be carcinogenic and teratogenic and hence related additives without these harmful effects have been studied. We and others found that easily available tripyrrolidinophosphoramide (TPPA) can often serve as very good substitute (Figure 1).[10] Since a pyrrolidine group should have a stronger electron-donating effect compared with a dimethylamino substituent[11] TPPA should even be more Lewis basic than HMPA. The comparison of few typical examples depicted in Scheme 2 clearly reveals that HMPA can be substituted by TPPA in most cases.[12] It

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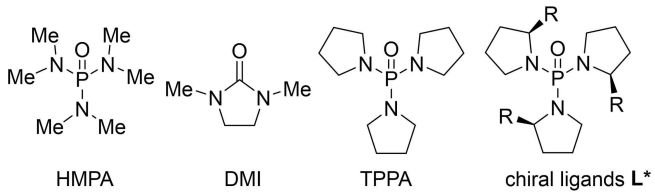
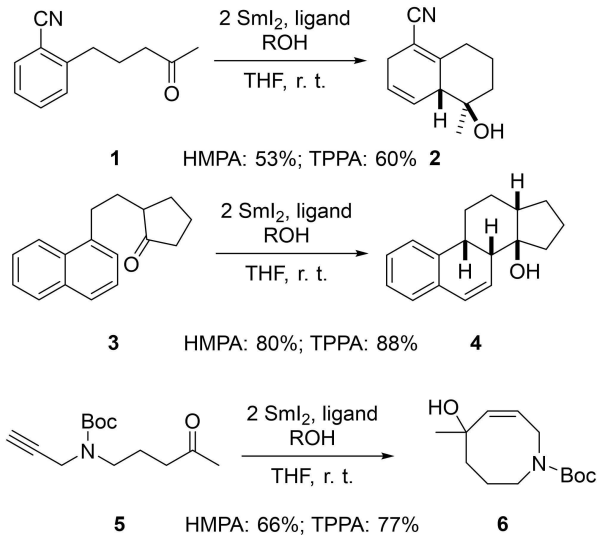


Figure 1. Suitable Lewis basic ligands for samarium diiodide-promoted cyclization reactions including chiral ligands **L***.



Scheme 2. Comparison of typical samarium diiodide-promoted cyclizations of ketones in the presence of HMPA or TTPA leading to cyclic compounds (ca. 18 equivalents of ligands were employed); all cyclization products are racemic mixtures.

should also be mentioned that in a few reactions HMPA could also be replaced by LiBr/1,3-dimethyl-2-imidazolidinone (DMI)[13] or by use of a LiBr/water system,[14] but these variations are not generally applicable.

Despite of their strong effects, the exact role of ligands such as HMPA is quite complex in solution and still not fully understood. The ligands at samarium(II) (iodide, THF, Lewis base) undergo fast exchange reactions and the equilibria are strongly dependent on the concentration of the components and other factors.[15] On the other hand, a solid state structure of the SmI_2-$(HMPA)_4$ complex revealed that the four phosphoramide ligands coordinate via their oxygen atoms and are located in the equatorial positions of a distorted octahedral geometry with the two iodide anions being in the axial positions.[16] The reactions at the samarium(II) center probably occur by dissociation of one of the iodide ligands and by approach of the oxygen of the substrate to allow the required inner sphere electron transfer.

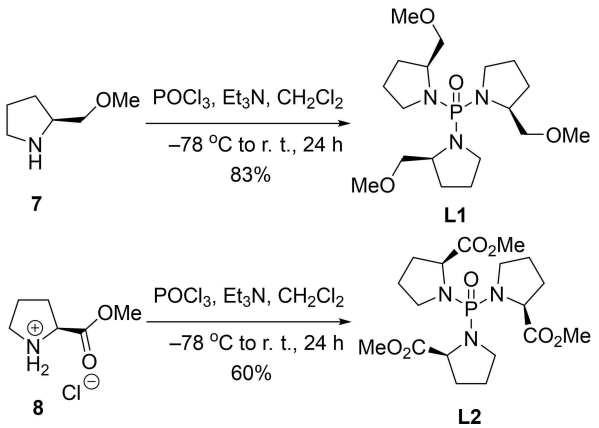
Regardless of these uncertain details, it is interesting to recognize that the samarium(II) ion is surrounded by the ligands like the active center in an enzyme. Therefore, introduction of chiral elements to the Lewis bases should induce at least to some extent enantioselectivity in the cyclization event. The examples of Schemes 1 and 2 show that achiral precursor compounds are converted into chiral products and that the stereogenic centers are generated in the first step (e.g. via transition state **TS**). We were therefore looking for enantiopure substitutes of HMPA and TPPA and a self-evident reasoning led to chiral derivatives of TPPA derived from L-proline (see ligands **L*** in Figure 1).[17] An earlier attempt to use phosphate and phosphinate esters bearing chiral alkoxy groups was not very promising; the cyclization yields were only moderate and the observed enantioselectivities were close to zero.[18]

Results and Discussion

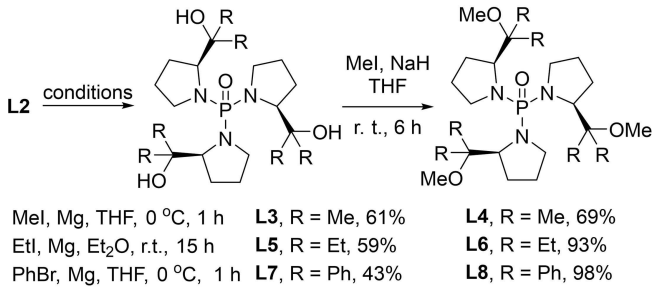
Following a literature procedure,[19] the synthesis of chiral phosphoramide ligand **L1** was achieved by treating phosphorus oxychloride at low temperature with six equivalents of commercially available (*S*)-prolinol methyl ether in the presence of an excess of triethylamine (Scheme 3). After routine work-up and chromatography the chiral HMPA analog **L1** was obtained in 83% yield. Similarly, the corresponding ligand **L2**, bearing methoxycarbonyl groups at the stereogenic centers, was prepared starting from the hydrochloride of (*S*)-proline methyl ester **8** in 60% yield.

Since no satisfactory enantioselectivities could be achieved with Lewis bases **L1** and **L2** (see below), we therefore assumed that sterically more demanding derivatives were required. For this purpose, phosphorus triamide **L2** was treated with three different Grignard reagents (ca. eight equivalents) and after aqueous work-up and purification the literature known tertiary alcohols **L3**, **L5**, and **L7** were isolated in reasonable yields (43–61%, Scheme 4).

The deprotonation of compounds **L3**, **L5**, and **L7** with sodium hydride in tetrahyrofuran followed by *O*-alkylation employing an excess of methyl iodide furnished the three new HMPA analogs **L4**, **L6**, and **L8** which are characterized by (dialkyl)methoxymethyl or (diphenyl)methoxymethyl moieties at the stereogenic centers. The overall efficiency of this two-



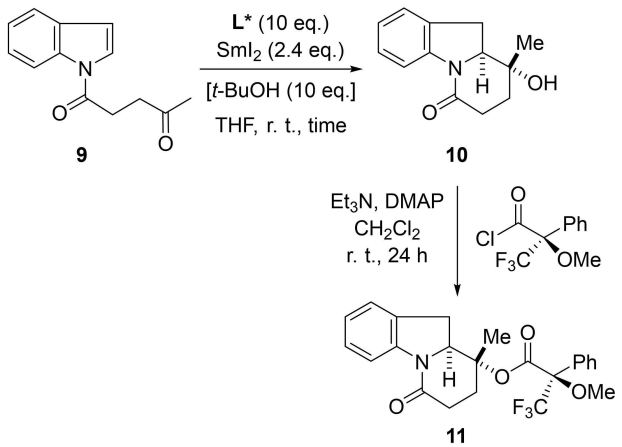
Scheme 3. Synthesis of chiral HMPA analogs **L1** and **L2** starting from (*S*)-proline derivatives.



Scheme 4. Synthesis of chiral phosphorus triamide ligands by addition of Grignard reagents to **L2** followed by deprotonation and *O*-methylation of **L3**, **L5**, **L7** to afford the chiral methyl ethers **L4**, **L6** and **L8**.

step route to the chiral phosphorus triamides is good (42–55% overall yield).

With eight structurally related chiral ligands **L1**–**L8** in hand, their influence on samarium diiodide-promoted cyclizations could be studied. As model reaction we selected the reaction



Scheme 5. Cyclization reaction of *N*-acylated indole derivative **9** with samarium diiodide in the presence of ligands **L*** to indoline **10** and conversion into Mosher ester **11**.

Table 1. Samarium diiodide-promoted reactions of *N*-acylated indole derivative **9** to indoline **10** in the presence of different Lewis bases and diastereomeric ratios determined for the corresponding Mosher ester **11**.

Entry	Ligand	Time [h]	Yield of **10**	d. r. of Mosher ester **11**	e. e. calcd. for **10**
1	HMPA	16	73%[a]	n. a.	n. a.
2	**L1**, R = CH_2OMe	0.5	88%	50:50	0%
3	**L2**, R = CO_2Me	–[b]	–	–	–
4	**L3**, R = CMe_2OH	0.5	97%	62:38	24%
5	**L4**, R = CMe_2OMe	18	74%	55:45	10%
6	**L5**, R = CEt_2OH	24	83%	44:56	−12%
7	**L6**, R = CEt_2OMe	38	52%	52:48	4%
8	**L7**, R = CPh_2OH	20	55%	53:47	6%
9	**L8**, R = CPh_2OMe	27	55%	57:43	14%

[a] Ref. 3a,e, phenol was used as proton source. [b] See text.

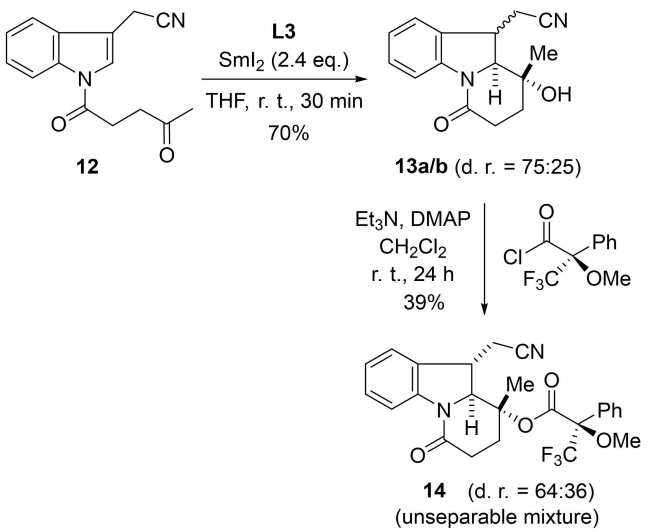
of *N*-acylated indole derivative **9** which is a moderately active substrate bearing only one electron-withdrawing group at the indole nitrogen (Scheme 5). Its cyclization to tricyclic indoline **10** requires the support by strong Lewis bases whereas indole derivatives with an additional methoxycarbonyl group at the C-3 of the indole ring are more reactive, undergoing the samarium diiodide-promoted cyclization even in the absence of HMPA.[3a,e] The reference reaction of **9** with samarium diiodide under standard conditions (HMPA, proton source, room temperature) furnished **10** in 73% yield (Table 1, entry 1).[3e] Employing ligand **L1** in presence of *tert*-butanol this reaction required only 30 minutes for complete decolorization of the samarium diiodide solution and after work-up product **10** was isolated in excellent 88% yield (Table 1, entry 2). By chromatography, 66% of the chiral ligand **L1** could be recovered. The short reaction time and the high yield demonstrate that TPPA-related ligands such as **L1** are excellent Lewis bases to activate samarium diiodide. However, are they good reagents for enantioselective cyclizations? For determination of its enantiomeric excess indoline **10** was converted into the Mosher ester **11** under standard conditions. By NMR spectroscopy, in particular by ^{19}F NMR-spectroscopy, the diastereomeric ratio (d. r.) of **11** could be determined.[20] Disappointingly, for this first sample a 50:50 mixture of the two diastereomers was determined (NMR estimated error ±3%) showing that **10** was formed essentially without any enantioselectivity under the influence of **L1**.

With ligand **L2** the samarium diiodide solution was decolorized before substrate could be added (Table 1, entry 3). Although no definite product was isolated, we assume that the C–N bonds of **L2** which are activated by the PO and the CO_2Me moieties were reductively cleaved in this case. A related reaction of *N*-acylated proline derivatives has been reported by Honda, who could isolate products with cleaved pyrrolidine ring.[21] When this strong activating effect of the methoxycarbonyl group was absent, as in highly substituted ligands **L3**–**L8**, samarium diiodide was not consumed before the cyclization process. With ligand **L3** again a very fast reaction was observed and indoline derivative **10** was isolated in excellent yield (entry 4); **L3** was recovered in 93% yield. It should be noted, that for this ligand (and the related compounds **L5** and **L7**) no *tert*-butanol was added since the free hydroxy groups of the ligand can serve as proton source. Analysis of the Mosher ester **11** of this sample revealed a diastereomeric ratio of 62:38 which refers to an enantiomeric excess of 24%. By comparison, employing the *O*-methylated analog **L4** (in presence of *t*-butanol) resulted in a slower conversion of **9** into the desired product **10** which was isolated in 74% yield. The Mosher ester of this sample revealed a d. r. of 55:45 (entry 5).

Although the enantioselectivity induced by ligand **L3** was only very moderate this result encouraged us to prepare and study the sterically more hindered derivatives **L5** and **L7**. Unfortunately, both gave inferior results (entries 6 and 8), both reactions proceed slower, the yield of **10** employing **L5** was still very good, but with **L7** it was considerably lower. Even more relevant for our goal were the low diastereomeric ratios of the

prepared Mosher esters of these samples. Whether the "inversed" selectivity as indicated for entry 6 (compared with entry 4) has any meaning is uncertain. The value of 44:56 is too close to a 1:1 ratio to be seriously discussed.

Employing the most promising ligand **L3** we also examined the cyclization of *N*-acylated indole derivative **12** bearing a cyanomethyl group at C-3 (Scheme 6). The reaction proceeded smoothly providing the expected product **13a/b** as a 75:25 mixture of two diastereomers which differ in the relative configuration at C-3. This stereogenic center is established by the final protonation of the intermediate carbanion. The reference reaction employing HMPA as Lewis base in the presence of *tert*-butanol afforded this product in similar yield, but with higher diastereoselectivity; the relative configuration of the major *trans*-diastereomer has been established by an X-ray analysis.[3d] The example presented in Scheme 6 demonstrates that ligand **L3** is an excellent Lewis base, however, its ability to induce enantioselectivity could not be determined unequivocally in this case. The mixture of diastereomers **13a/b** could not be separated and its conversion into the Mosher ester **14** was low yielding, furnishing again an inseparable mixture of two diastereomers. We assume that the esters derived from the major *trans*-diastereomer were isolated, which would refer to a d. r. of 64:36 and hence an e. e. of cyclization product **13a** of ca. 28%. This value is close to the e. e. of entry 4 (Table 1) with the simple model compound **9** as precursor. Nevertheless, this result needs confirmation and extension to other model substrates. Due to the low enantioselectivities observed no attempts were made to establish the configuration of the slightly predominating enantiomer of **13a** and **10**.



Scheme 6. Cyclization reaction of *N*-acylated indole derivative **12** with samarium diiodide in the presence of ligand **L3** to indoline **13a/b** and conversion into Mosher ester **14**.

Conclusion

The easily available (*S*)-proline-based chiral phosphorus triamides **L1** and **L3**–**L8** are excellent Lewis bases that can substitute the harmful additive HMPA in samarium diiodide-promoted cyclizations. As a model reaction we investigated the dearomatizing cyclization of *N*-acylated indole **9** that gave tricyclic indoline derivative **10** in good to excellent yields. In particular, ligands **L1** and **L3** with methoxymethyl or (dimethyl)hydroxy-methyl groups, respectively, at the stereogenic center induced very high reactivity and consumption of samarium(II) in less than 30 minutes. No separate proton source is required when **L3** containing a tertiary alcohol moiety is used in these transformations[22] and the chiral ligand was recovered to a very high degree. At the moment, it is premature to discuss the reaction mechanism in detail, but the high cyclization rate induced by the sterically least hindered ligand **L3** suggests that proton-coupled electron transfer (PCET) processes are involved.[23] Unfortunately, the investigated chiral ligands **L*** induce only low to moderate enantioselectivities in the studied model reaction. With **L3** as best ligand, an e. e. of ca. 24% could be determined. We are convinced that our study can be regarded as lead to design Lewis bases for samarium diiodide-promoted reactions providing higher enantioselectivities.[24]

Experimental Section

Reactions were generally performed under argon in flame-dried flasks. Solvents and reagents were dried using standard procedures. Tetrahydrofuran (THF) was transferred from a MB SPS-800-dry solvent system directly into a flame-dried flask. SmI_2 was freshly prepared in THF (see general procedure) or taken from a previously prepared stock solution (ca. 0.1 M in THF). Other reagents were purchased and were used as received without further purification unless otherwise stated. Products were purified by flash chromatography on silica gel (230–400 mesh, Merck or Macherey and Nagel). Unless otherwise stated, yields refer to analytically pure samples.

NMR spectra were recorded on Bruker (AC 500, AVIII 700) and JEOL (ECX 400, Eclipse 500) instruments. Chemical shifts are reported relative to TMS (^{1}H: $\delta = 0.00$ ppm) and $CDCl_3$ (^{13}C: $\delta = 77.0$ ppm). Integrals are in accordance with assignments and coupling constants are given in Hz. All ^{13}C-NMR spectra are proton-decoupled. For detailed peak assignments 2D spectra were measured (COSY, HMQC, HMBC, GOESY if necessary). IR spectra were measured with a Nexus FT-IR spectrometer equipped with a Nicolet Smart DuraSample IR ATR. Mass and HRMS analyses were performed with Finnigan MAT 711 (EI, 80 eV, 8 kV), MAT CH7 A (EI 80 eV, 3 kV) and Varian Ionspec QFT-7 (ESI-FT ICRMS) instruments. Elemental analyses were carried out with CHN-Analyzer 2400 (Perkin-Elmer) and Elementar Vario EL Elemental Analyzer. Melting points were measured with a Reichert apparatus Themovar and are uncorrected. Optical rotations were determined with a Perkin-Elmer 241 polarimeter at the temperatures given.

Tris((*S*)-2-(methoxymethyl)pyrrolidin-1-yl)phosphine Oxide (L1): Following ref. 19, (*S*)-2-(methoxymethyl)pyrrolidine **7** (30.0 g, 260 mmol) and triethylamine (65.9 g, 651 mmol, 90.9 mL) were dissolved in dichloromethane (100 mL) and the mixture was cooled

to −78 °C. Then phosphorus oxychloride (6.66 g, 43.4 mmol, 4.1 mL) in dichloromethane (20 mL) was added via an addition funnel during 45 min. The reaction mixture was slowly allowed to warm to room temperature. After 24 h, the solvent was evaporated and the residue was dissolved in ethyl acetate (100 mL) and filtered through a silica pad. After evaporation of the solvent under reduced pressure, the crude product mixture was purified by column chromatography (silica gel, 60–80% ethyl acetate in hexanes) to obtain **L1** (83%, 14.0 g) as viscous liquid. $[\alpha]_D^{25} = -28.1$ ($c = 0.74$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.76-1.98$ (m, 12 H, 3-H, 4-H), 3.03–3.23 (m, 6 H, 5-H), 3.30 (s, 9 H, OMe), 3.24–3.33 (m, 3 H, 2-H), 3.43–3.98 (m, 2 H, 2-CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 24.4$, 24.5, 25.1, 25.2, 28.85, 28.92, 29.2, 29.3, 47.87, 47.91, 48.35, 48.37 (12 t, C-3, C-4, C-5), 57.97, 58.01, 58.18, 58.22 (4 d, C-2), 58.96, 59.03 (2 q, OMe), 74.37, 74.40, 75.20, 75.23 (4 t, 2-C) ppm; according to these ^{1}H- and ^{13}C-NMR data the C-3 symmetry of this compound is disturbed; ^{31}P NMR (162 MHz, $CDCl_3$) $\delta = 22.59$ ppm; IR (ATR): $\nu =$ 2975–2870 (C–H), 1200, 1270 (P=O) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{18}H_{37}N_3O_4P$: 390.2522; found: 390.2537.

Trimethyl (Oxo-λ^5-phosphanetriyl) (2'*S*,2''*S*)-tri-L-prolinate (L2): According to ref. 19, an oven-dried two neck round bottom flask was charged with methyl L-prolinate hydrochloride **8** (50.0 g, 302 mmol) in dichloromethane (200 mL) and triethylamine (91.6 g, 906 mmol, 126 mL) was added at room temperature. After 1 h, the precipitated triethylamine hydrochloride was filtered off and the filtrate was cooled to −78 °C. Then phosphorus oxychloride (7.68 g, 50.1 mmol, 4.7 mL) in dichloromethane (10 mL) was added via an addition funnel during 45 min. The reaction mixture was slowly allowed to warm to room temperature. After 24 h, the solvent was evaporated and the residue was dissolved in ethyl acetate (100 mL) and filtered through a silica pad. After evaporation of the solvent under reduced pressure, the crude product mixture was purified by column chromatography (silica gel, 60–80% ethyl acetate in hexanes) to obtain **L2** (60%, 12.9 g) as viscous liquid which solidified on cooling. The given yield is based on recovered methyl L-prolinate **8** (30 g). M. p. 56–57 °C; $[\alpha]_D^{20} = -92.5$ ($c =$ 2.53, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.76-1.88$ (m, 9 H, 4-H, 3-H), 2.12–2.19 (m, 3 H, 3-H), 3.46 (ddd, $J = 9.6$, 6.8, 5.8 Hz, 3 H, 5-H), 3.20 (ddd, $J = 14.3$, 9.6, 5.8 Hz, 3 H, 5-H), 3.64 (s, 9 H, CO_2Me), 4.25 (dd, $J = 12.0$, 6.0 Hz, 3 H, 2-H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 25.5$, 25.6, 31.05, 31.11, 46.85, 46.88 (6 t, C-4, C-3, C-5), 51.8 (q, CO_2Me), 59.6, 59.7 (2 d, C-2), 175.59, 175.62 (2 s, CO_2Me) ppm; ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = 14.95$ ppm; IR (ATR): $\nu =$ 2955–2870 (C–H), 1740 (C=O), 1210, 1280 (P=O) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{30}N_3NaO_7P$: 454.1719; found: 454.1716; $C_{18}H_{30}N_3O_7P$ (431.4): calcd. C 50.11, H 7.01, N 9.74; found: C 50.11, H 7.35, N 9.75.

Typical experimental procedure for the preparation of triols of the triphosphorusamide derivatives (**GP1**), **tris((*S*)-5-(2-hydroxypropan-2-yl)pyrrolidin-1-yl)phosphine oxide (L3)**: Following ref. 19, an oven-dried two neck round bottom flask was charged with magnesium turnings (0.50 g, 20.4 mmol) in THF (40 mL) and connected to a cooling condenser. The magnesium metal was activated with a pinch of iodine and methyl iodide (2.90 g, 20.4 mmol) was then added during 30 min at 0 °C. The reaction mixture was stirred for another 30 min at this temperature. In a second round bottom flask triphosphoramide **L2** (1.10 g, 2.55 mmol) was dissolved in THF (10 mL) and then the solution was transferred to the MeMgI reagent flask via syringe at 0 °C. After 1 h, the reaction mixture was quenched with saturated NH_4Cl solution at 0 °C. The solids were filtered off and washed with diethyl ether. The combined organic layers were washed with brine and dried (Na_2SO_4). After evaporation of the solvent, the crude material was recrystallized from hexanes/dichloromethane (3:1) to provide pure triol **L3**[19] (colorless solid, 675 mg, 61%). M. p. 212–213 °C; $[\alpha]_D^{30} = -61.2$ ($c = 5.0$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.10$, 1.21 (2 s, 9 H each, Me), 1.62–1.79 (m, 6 H, 4-H), 1.84–2.11 (m, 6 H, 3-H), 3.23 (ddd, $J \approx 9.7$, 7.7, 4.6 Hz, 6 H, 5-H), 3.66 (dd, $J = 11.9$, 7.2 Hz, 3 H, 2-H), 5.96 (s, 3 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 22.8$ (q, Me), 25.4, 25.5 (2 t, C-4), 27.5 (q, Me), 30.7, 30.8 (2 t, C-3), 48.6, 48.7 (2 t, C-5), 69.67, 69.71 (2 d, C-2), 72.7 (s, 2-C); ^{31}P NMR (202 MHz, $CDCl_3$): $\delta = 21.91$ ppm; IR (ATR): $\nu = 3360$ (O–H), 2970–2830 (C–H), 1205, 1245 (P=O) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd for $C_{21}H_{42}N_3NaO_4P$: 454.2811; found: 454.2811; $C_{21}H_{42}N_3O_4P$ (431.5): calcd. C 58.45, H 9.81, N 9.74; found: C 58.47, H 9.81, N 9.84.

Tris((*S*)-5-(3-hydroxypent-3-yl)pyrrolidin-1-yl)phosphine Oxide (L5): Following **GP1**, compound **L2** (2.00 g, 4.63 mmol), magnesium turnings (901 mg, 37.1 mmol), Et_2O (50 mL), I_2 (pinch), ethyl iodide (5.78 g, 37.1 mmol, 2.98 mL) afforded pure product **L5**[19] (colorless solid, 1.40 g, 59%). Ethylmagnesium iodide was generated at room temperature with cooling condenser setup. M. p. 204–206 °C; $[\alpha]_D^{20} = -32.3$ ($c = 1.9$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.91$ (m, 18 H, CH_2CH_3), 1.16–1.29 (m, 6 H, 4-H), 1.58–1.96 (m, 15 H, 3-H, CH_2CH_3), 2.02–2.10 (m, 3 H, 3-H), 3.09–3.24 (m, 6 H, 5-H), 3.84 (dd, $J = 13.8$, 5.4 Hz, 3 H, 2-H), 5.46 (s, 3 H, OH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 7.5$ (q, CH_2CH_3), 25.4, 25.5 (2 t, C-4), 27.1 (t, CH_2CH_3), 29.17, 29.24, 48.5, 48.6 (4 t, C-3, C-5), 66.7, 66.8 (2 d, C-2), 75.5 (s, 2-C) ppm; ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = 22.27$ ppm; IR (ATR): $\nu =$ 3415, 3300 (O–H), 2965–2850 (C–H), 1200, 1285 (P=O) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd. for $C_{27}H_{54}N_3NaO_4P$: 538.3750; found: 538.3738; $C_{27}H_{54}N_3O_4P$ (515.7): calcd. C 62.88, H 10.55, N 8.15, found: C 62.89, H 10.55, N 8.17.

Tris((*S*)-5-(hydroxydiphenylmethyl)pyrrolidin-1-yl)phosphine Oxide (L7): Following **GP1**, compound **L2** (2.00 g, 4.63 mmol), magnesium turnings (901 mg, 37.1 mmol), THF (50 mL), I_2 (pinch), bromobenzene (5.82 g, 37.1 mmol, 3.89 mL) provided pure product **L7**[19] (colorless solid, 1.60 g, 43%). M. p. >250 °C (decomposition); $[\alpha]_D^{25} = -63.3$ ($c = 6.58$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.05-1.56$ (m, 6 H, 4-H), 2.01–2.19 (m, 9 H, 3-H, 5-H), 2.76 (td, $J = 13.4$, 9.6 Hz, 3 H, 5-H), 4.61 (dd, $J = 15.3$, 3.1 Hz, 3 H, 2-H), 7.15 (s, 3 H, OH), 7.31–7.43 (m, 24 H, Ph), 7.61 (m_c, 6 H, Ph) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 24.0$, 24.1, 30.5, 30.6, 47.6, 47.7 (6 t, C-3, C-4, C-5), 67.46, 67.49 (2 d, C-2), 81.1 (s, 2-C), 127.2, 127.3, 127.4, 128.1, 128.5, 129.1, 144.3, 146.1 (6 d, 2 s, Ph) ppm; ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = 24.16$ ppm; IR (ATR): $\nu = 3310$ (O–H), 3085, 3030 (=C–H), 2955–2855 (C–H), 1600, 1500 (C=C), 1215 (P=O) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd. for $C_{51}H_{54}N_3NaO_4P$: 826.3750; found: 826.3743; $C_{51}H_{54}N_3O_4P$ (803.9): calcd. C 76.19, H 6.77, N 5.23; found: C 76.27, H 6.86, N 5.13.

Typical experimental procedure for *O*-Methylation of triphosphorusamide derivatives (**GP2**), **tris((*S*)-5-(2-methoxyprop-2-yl)pyrrolidin-1-yl)phosphine oxide (L4)**: To a stirred solution of triol **L3** (1.00 g, 2.32 mmol) in THF (15 mL) was added NaH (334 mg, 13.9 mmol, 60% in paraffin oil) at 0 °C. The mixture was stirred for 30 min at this temperature then methyl iodide (1.97 g, 13.9 mmol, 0.86 mL) was added drop-wise over a period of 10–15 min. After 6 h stirring at room temperature, the reaction mixture was quenched with water at 0 °C and extracted with ethyl acetate. The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude material was purified by column chromatography (silica gel, ethyl acetate/hexanes 3:7) to furnish the pure product **L4** (colorless solid, 750 mg, 69%). M. p. 110–111 °C; $[\alpha]_D^{20} = -37.7$ ($c = 1.06$, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.14$, 1.19 (2 s, 18 H, Me), 1.78–1.90 (m, 9 H, 3-H, 4-H), 1.95–1.99 (m, 3 H, 3-H), 2.98–3.07 (m, 3 H, 5-H), 3.17 (s, 9 H, OMe), 3.45 (ddd, $J = 14.8$, 9.9, 5.2 Hz, 3 H, 5-H), 3.80 (dd, $J = 11.9$, 5.6 Hz, 3 H, 2-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 22.1$, 22.8 (2 q, Me), 25.55, 25.58, 26.42, 26.45, 47.67, 47.68 (6 t,

C-3, C-4, C-5), 49.2 (q, OMe), 66.07, 66.09 (2 d, C-2), 78.60, 78.63 (2 s, 2-C) ppm; ^{31}P NMR (202 MHz, $CDCl_3$): δ = 20.87 ppm; IR (ATR): ν = 2965–2830 (C–H), 1200, 1240 (P=O) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd for $C_{24}H_{48}N_3NaO_4P$: 496.3280; found: 496.3355; $C_{24}H_{48}N_3O_4P$ (473.6): calcd. C 60.86, H 10.22, N 8.87; found: C 60.90, H 10.07, N 8.94.

Tris((*S*)-5-(3-methoxypent-3-yl)pyrrolidin-1-yl)phosphine oxide (L6): Following **GP2**, the triol **L5** (400 mg, 0.77 mmol), NaH (149 mg, 6.20 mmol, 60%), methyl iodide (881 mg, 6.20 mmol, 0.39 mL) afforded pure **L6** (colorless viscous liquid, 403 mg, 93%). $[\alpha]_D^{20} = -30.0$ ($c = 2.87$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (m, 18 H, CH_2CH_3), 1.47 (m_c, 3 H, 4-H), 1.61–1.73 (m, 9 H, 3-H, 4-H), 1.79–1.95 (m, 12 H, CH_2CH_3), 2.90–3.01 (m, 3 H, 5-H), 3.18 (s, 9 H, OMe), 3.52 (ddd, J = 14.9, 11.7, 7.4 Hz, 3 H, 5-H), 3.83 (dd, J = 9.9, 8.4 Hz, 5 H, 2-H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 8.5, 8.7 (2 q, CH_2CH_3), 25.3, 25.6, 25.7, 26.3, 26.5, 26.6, 48.1 (7 t, CH_2CH_3, C-3, C-4, C-5), 50.3 (q, OMe), 64.29, 64.31 (2 d, C-2), 81.59, 81.63 (2 s, 2-C), ppm; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 24.24 ppm; IR (ATR): ν = 2970–2830 (C–H), 1200 (P=O) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+Na]^+$calcd. for $C_{30}H_{60}N_3NaO_4P$: 580.4219; found: 580.4232.

Tris((*S*)-5-(methoxydiphenylmethyl)pyrrolidin-1-yl)phosphine oxide (L8): Following **GP2**, the triol **L7** (600 mg, 0.75 mmol), NaH (60%, 143 mg, 5.97 mmol), methyl iodide (847 mg, 5.97 mmol, 0.37 mL) furnished pure **L8** (colorless solid, 620 mg, 98%). M. p. 149–152 °C; $[\alpha]_D^{20} = -73.5$ ($c = 2.51$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78–0.95 (m, 3 H, 4-H), 1.56–1.95 (m, 6 H, 3-H, 4-H), 1.95 (m_c, 3 H, 3-H), 2.20–2.38 (m, 3 H, 5-H), 2.94 (s, 9 H, OMe), 3.43–3.58 (m, 3 H, 5-H), 5.09 (t, J = 9.5 Hz, 3 H, 2-H), 7.23–7.37, 7.42–7.50 (2 m, 18 H, 12 H, Ph) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 24.77, 24.78, 29.20, 29.21, 48.0 (5 t, C-3, C-4, C-5), 52.2 (q, OMe), 64.29, 64.32 (2 d, C-2), 86.38, 86.44 (2 s, 2-C), 127.10, 127.12, 127.5, 127.7, 130.0, 130.3, 141.6, 142.1 (6 d, 2 s, Ph) ppm; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.17 ppm; IR (ATR): ν = 3085, 3025 (=C–H), 2960–2855 (C–H), 1600 (C=C), 1210 (P=O) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd. for $C_{54}H_{60}N_3NaO_4P$: 868.4219; found: 868.4198.

Typical experimental procedure for the SmI_2-induced cyclizations of ketone **9** in presence of chiral triphosphoramide derivative **L*** leading to **(9*R**,9a*S**)-9-hydroxy-9-methyl-8,9,9a,10-tetrahydropyrido[1,2-*a*]indol-6(7*H*)one (10)** (**GP3**): Use of ligand **L1**: under an atmosphere of argon, freshly prepared SmI_2 (225 mg, 0.56 mmol, 5.6 mL) in 0.1 M THF solution was added to the chiral phosphoramide ligand **L1** (904 mg, 2.32 mmol). The resulting purple solution was stirred for 5 minutes at room temperature and then was transferred to a mixture of ketone **9** (50 mg, 0.23 mmol) and *t*-BuOH (172 mg, 2.32 mmol) in THF (3 mL) in single portion via syringe. After 30 min, the solvent was removed under reduced pressure. The crude material was purified by column chromatography (silica gel, ethyl acetate/hexanes 7/3) to obtain the pure cyclization product **10** (44 mg, 88%) and the recovered ligand **L1** (600 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 3 H, Me) 1.98–2.06 (m, 2 H, 8-H), 2.16 (s, 1 H, OH), 2.58 (ddd, J = 18.5, 10.4, 8.4 Hz, 1 H, 7-H), 2.73 (ddd, J = 18.5, 6.9, 3.4 Hz, 1 H, 7-H), 3.13 (d, J = 9.7 Hz, 2 H, 10-H), 4.26 (t, J = 9.7 Hz, 1 H, 9a-H), 7.04 (t, $J \approx 7.4$ Hz, 1 H, Ar), 7.19 (t, $J \approx 7.7$ Hz, 1 H, Ar), 7.20 (d, J = 7.9 Hz, 1 H, Ar), 8.16 (d, J = 8.0 Hz, 1 H, Ar) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 20.3 (q, Me), 30.1, 31.3, 36.8 (3 t, C-8, C-7, C-10), 67.6 (d, C-9a), 70.4 (s, C-9), 117.0, 124.3, 124.8, 127.7, 129.7, 142.7, 167.6 (4 d, 3 s, Ar, C=O) ppm. These data agree with those reported in the literature.[3e] The conversion into the corresponding Mosher ester **11** revealed a 50:50 ratio of the two enantiomers.

Use of ligand **L3**: following **GP3**, but omitting addition of *t*-BuOH, freshly prepared SmI_2 (48.5 mg, 0.12 mmol, 1.2 mL) in 0.1 M THF solution was added to the chiral phosphoramide ligand **L3** (216 mg, 0.50 mmol). The resulting mixture was stirred for 5 minutes at room temperature and was then transferred to ketone **9** (10.8 mg, 0.050 mmol) in THF (8.8 mL, under argon) in single portion via syringe. After 30 min, the solvent was removed under reduced pressure. The crude material was purified by column chromatography (silica gel, ethyl acetate/hexanes 7/3) to obtain the pure cyclization product **10** (10.5 mg, 97%) and the recovered ligand **L3** (200 mg, 93%). The NMR data agree with the data above and those reported in ref. 3e.

Typical experimental procedure for the formation of Mosher ester (GP4): Compound **10** (10.5 mg, 0.048 mmol) as obtained in the preceding experiment was dissolved in dichloromethane (0.5 mL) and at room temperature were added triethylamine (14.6 mg, 0.14 mmol), DMAP (5.9 mg, 0.05 mmol) and (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (18.0 mg, 0.07 mmol). After 24 h, the solvent was removed and the crude mixture was purified by chromatography (silica gel, hexanes/ethyl acetate 9/1) to obtain the corresponding esters **11** (19.5 mg, 93%, d. r. = 62:38) as colorless viscous liquid.

(9a*R*,9*S*)/(9*S*,9a*R*)-9-Methyl-6-oxo-6,7,8,9,9a,10-hexahydropyrido[1,2-*a*]-indol-9-yl-(*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (11): Data of a mixture of both isomers; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.64*, 1.65 (2 s, 3 H, 9-Me), 2.18–2.28 (m, 1 H, 8-H), 2.56–2.68 (m, 1 H, 8-H), 2.71–2.87 (m, 2 H, 7-H), 3.05–3.13 (m, 2 H, 10-H), 3.53* (s, 1.1 H, OMe), 3.56 (s, 1.9 H, OMe), 4.50 (t, $J \approx 9.4$, 1 H, 9a-H), 7.04 (t, $J \approx 7.4$ Hz, 1 H, Ar), 7.18 (m_c, 1 H, Ar), 7.42–7.56 (m, 6 H, Ar), 8.14 (d, $J \approx 8.0$ Hz, 1 H, Ar) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 17.5*, 17.9 (2 q, Me), 30.2*, 30.7, 30.81*, 30.83, 32.1, 32.5* (6 t, C-8, C-7, C-10), 55.3*, 55.4 (2 q, each J_{CF} = 1.2 Hz, OMe), 64.8, 65.3* (2 d, C-9a), 83.54*, 83.55 (2 s, C-9), 84.4, 84.7* (2 q, each J_{CF} = 28.3 Hz, C-2'), 116.8# (d, Ar), 123.4 (q, J_{CF} = 289.9 Hz, 2'-CF_3), 123.5* (q, J_{CF} = 289.9 Hz, 2'-CF_3), 124.47, 124.49*, 124.7#, 127.31, 127.39*, 127.9*, 128.0, 128.68, 128.71*, 129.0, 129.1* (13 d, Ar), 129.88, 129.91*, 132.1*, 132.2, 142.26*, 142.29 (6 s, Ar), 165.18*, 165.24, 167.3*, 167.4 (4 s, C=O, C-1') ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −70.91*, −70.98 ppm; *signals assigned to the minor isomer; #signal with higher intensity; IR (ATR): ν = 3075 (=C–H), 2955–2850 (C–H), 1745, 1670 (C=O), 1600 (C=C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$calcd. for $C_{23}H_{23}F_3NO_4$: 434.1579; found: 434.1588.

10-((9*R,9a*S**,10*S**)-9-Hydroxy-9-methyl-6-oxo-6,7,8,9,9a,10-hexahydropyrido[1,2-a]indol-10-yl)acetonitrile (13a)** and **10-((9*R**,9a*S**,10*R**)-9-hydroxy-9-methyl-6-oxo-6,7,8,9,9a,10-hexahydropyrido[1,2-a]indol-10-yl)acetonitrile (13b)**: Following **GP3**, SmI_2 (38.1 mg, 0.094 mmol, 0.94 mL), ligand **L3** (170 mg, 0.39 mmol), ketone **12** (10 mg, 0.039 mmol) furnished cyclization products **13a/b** (7 mg, 70%, d. r. = 75:25) and the recovered ligand **L3** (100 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 2.25 H, 9-Me), 1.50 (s, 0.75 H, 9-Me), 1.86–2.07 (m, 2 H, 8-H), 2.18 (s, 0.75 H, OH), 2.32 (s, 0.25 H, OH), 2.52–2.74 (m, 2.25 H, 7-H, 10-CH), 2.91 (dd, J = 17.0, 6.6 Hz, 0.75 H, 10-CH), 3.07 (dd, J = 17.0, 4.3 Hz, 0.75 H, 10-CH), 3.16 (dd, J = 16.2, 5.1 Hz, 0.25 H, 10-CH), 3.72 (dt, $J \approx 9.5$, 5.1 Hz, 0.75 H, 10-H), 3.78–3.84 (m, 0.25 H, 10-H), 3.98 (d, J = 9.7 Hz, 0.75 H, 9a-H), 4.33 (d, J = 8.7 Hz, 0.25 H, 9a-H), 7.13 (t, $J \approx 7.5$ Hz, 1 H, Ar), 7.30 (t, $J \approx 7.5$ Hz, 1 H, Ar), 7.38 (d, J = 7.5 Hz, 0.75 H, 1-H), 7.52 (d, J = 7.5 Hz, 0.25 H, 1-H), 8.19 (d, J = 8.1 Hz, 0.75 H, 4-H), 8.25 (d, J = 8.2 Hz, 0.25 H, 4-H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 20.8, 21.0* (2 q, Me), 21.8, 22.3*, 31.1, 31.4*, 37.2*, 38.9 (6 t, C-8, C-7, C-11), 40.0*, 40.1 (2 d, C-10), 68.6*, 70.8 (2 d, C-9a), 71.1*, 71.5 (2 s, C-9), 117.1*, 117.2 (2 s, CN), 118.0, 118.8*, 123.3, 123.4*, 124.8*, 124.9, 129.3, 129.5* (8 d, Ar), 129.8, 130.4*, 141.9*, 142.2, 167.2, 167.8* (6 s, Ar, C=O) ppm; *signals assigned to the minor isomer. The analytical data correlate with reported data.[3d]

(9*R,9a*S**,10*S**)-10-(Cyanomethyl)-9-methyl-6-oxo-6,7,8,9,9a,10-hexahydropyrido[1,2-a]indol-9-yl-(*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (14)**: Following **GP4**, compound **13a,b** (7.0 mg,

0.027 mmol), dichloromethane (1.2 mL), triethylamine (8.3 mg, 0.082 mmol), DMAP (3.3 mg, 0.027 mmol) and (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (41.4 mg, 0.16 mmol) afforded the corresponding Mosher esters **14** (5.0 mg, 39%, d. r. = 64:36, containing traces of other diastereomers) as an inseparable mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 1.92 H, 9-Me), 1.76* (s, 1.08 H, 9-Me), 2.13–2.24 (m, 2 H, 8-H), 2.31 (dt, J = 15.9, 4.6 Hz, 0.64 H, 7-H), 2.42* (dt, J = 15.9, 3.9 Hz, 0.36 H, 7-H), 2.65–2.80 (m, 1 H, 7-H), 2.90 (m_c, 2 H, 11-H), 3.48 (s, 1.92 H, 2'-OMe), 3.53–3.64 (m, 1 H, 10-H), 3.60 (s, 1.08 H, 2'-OMe), 4.49* (d, J = 8.5 Hz, 0.36 H, 9a-H), 4.56 (d, J = 8.5 Hz, 0.64 H, 9a-H), 7.13 (m_c, 1 H, Ar), 7.28–7.35 (m, 2 H, Ar), 7.47–7.59 (m, 5 H, Ar), 8.22 (d, $J \approx$ 8.0 Hz, 1 H, 4-H) ppm; *signals assigned to the minor diastereomer; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −69.71, −70.76 ppm. Due to the low amount of the sample and beginning decomposition no further purification and characterization was possible.

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Conflict of Interest

The authors declare no conflict of interest.

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