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Chiral *N*-Phosphonylimine Chemistry: Asymmetric Synthesis of *N*-Phosphonyl β-Amino Weinreb Amides

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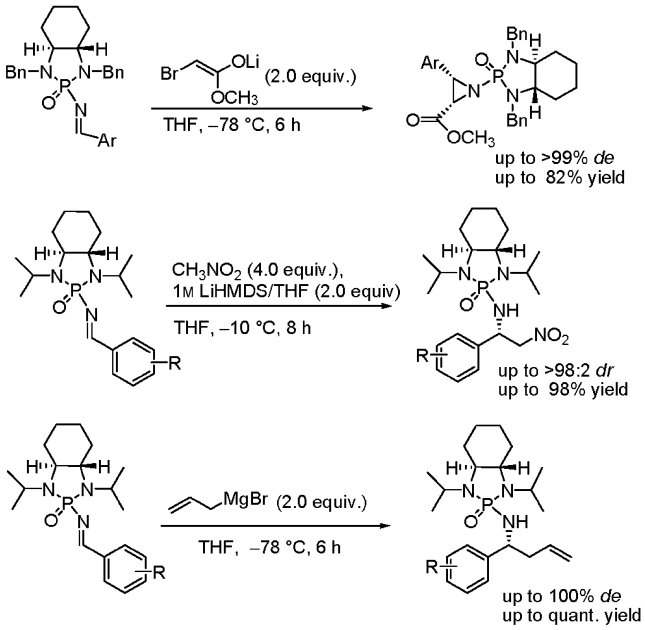
Various chiral *N*-phosphonyl β-amino Weinreb amides were synthesized by treating chiral *N*-phosphonyl imines with the lithium enolate of *N*-methoxy-*N*-methylacetamide. The *N*,*N*-protection groups on chiral *N*-phosphonyl imines and the types of deprotonation bases for enolate generation were found to be crucial for the successful synthesis. Eleven Weinreb amides were obtained in excellent chemical yields (92 to 98 %) and good to excellent diastereoselectivities (up to *dr* = 99:1). The absolute structures were unambiguously determined by converting the products into authentic samples and by comparing their optical rotation values.

Introduction

α-Amino aldehydes and ketones have been widely used in the synthesis of many natural products and related biologically important compounds, and they are also found to exist in many natural products.[1–3] In addition, they can be utilized as useful building blocks for general organic synthesis.[4–9] The syntheses of these compounds are usually conducted by using Mannich-type reactions, aminoalkylations, oxidations of γ-amino alcohols,[4] and the selective reductions of *N*-protected β-amino esters.[6] The asymmetric synthesis of chiral β-amino carbonyl derivatives sometime faces challenges because of the inherent instability and tendency of these compounds to undergo self condensation in the absence of suitable *N*-protection.[10–11] Among carbonyl derivatives, Weinreb amides have been paid special attention in organic synthesis, because they can be readily converted into ketones.[12–15] For example, Weinreb amides have been successfully utilized for the asymmetric synthesis of 1,3-aminoketals[14a] and α-amino ketones.[14b] Recently, several methods for the asymmetric synthesis of β-amino Weinreb amides have been reported,[15–17] which include the use of *N*-sulfinyl imine based carbonyl-type addition and lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide-based α,β-conjugate addition reactions.

Very recently, our group developed new chiral *N*-phosphonylimine chemistry. We successfully synthesized and utilized a series of chiral *N*-phosphonyl imines as electrophiles for several nucleophilic addition reactions, such as aza-Darzens reaction, aza-Henry reaction, and allylmagnesium bromide based addition (Scheme 1).[18]



Scheme 1. Asymmetric reaction with the use of chiral *N*-phosphonyl imines.

The resulting chiral products were isolated in excellent yields and good to excellent diastereoselectivities. Meanwhile, the C_2-symmetric diamine chiral auxiliary was easily recovered in quantitative yield.[18b] We now turn our attention to the use of Weinreb amide derived enolates for the electrophilic addition to chiral *N*-phosphonyl imines. Herein we report our preliminary results on this reaction and its application to the asymmetric synthesis of *N*-phosphonyl β-amino Weinreb amides (Scheme 2).

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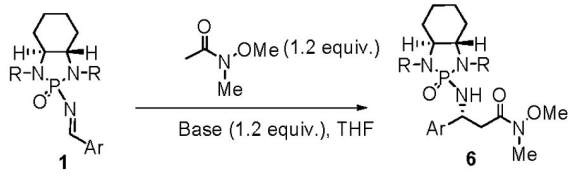


Scheme 2.

Results and Discussion

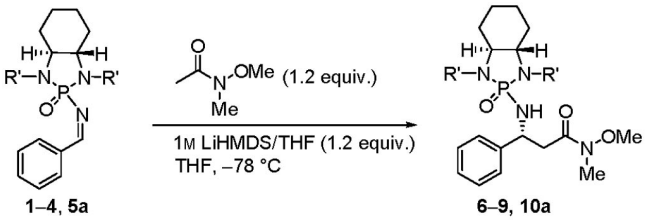
Chiral *N*-phosphonyl imine **1** having a benzyl group in its *N*,*N*-positions was employed as the electrophile for the model reaction. The enolate was first generated by treating *N*-methoxy-*N*-methylacetamide (0.02 mL, 0.30 mmol) with KHMDS (20% solution in toluene, 1.5 mL, 0.30 mmol) at –78 °C in dry THF (2 mL). The reaction was performed by adding chiral *N*-phosphonyl imine **1** (0.087 g, 0.25 mmol, 2 mL of solution in THF) into the resulting mixture. The reaction was stirred at –78 °C for 2 h and constantly monitored by TLC (EtOAc/MeOH, 9:1). After the starting materials were consumed completely, the reaction was quenched with the addition of saturated NH_4Cl. Surprisingly, only moderate yields (40%) and very poor diastereoselectivities (<55:45) were observed. To improve the yields and selectivities, the reaction was optimized by using different bases at different temperatures and reaction times. LiHMDS was thus used as the base for enolate generation. This modification resulted in an improved yield of 60% and a slightly higher diastereoselectivity (60:40) when the reaction was conducted at –78 °C. The use of other bases including LDA did not give any further improvements in either the chemical yield or the diastereoselectivity.

We then turned our attention to modification of *N*,*N*-protection groups on the chiral auxiliary. Five different *N*,*N*-protection substituents, such as benzyl, isobutyl, neopentyl, naphthyl, and isopropyl were examined. The optimization results with the use of these *N*,*N*-protection groups are summarized in Table 1.

As revealed in Table 1, when the isobutyl group (in auxiliary **2**) was used to replace the benzyl counterpart, no selectivity was observed. The same situation was encountered when the neopentyl group (in auxiliary **3**) was employed. For these two cases, a large amount of unreacted imine remained, as revealed by TLC, even after a prolonged reaction period. The third attempt was to use the naphthyl group as the *N*,*N*-protection group (in auxiliary **4**), where an improved diastereoselectivity (70:30) was observed, but the reaction conversion was only 50%. Pleasantly, when the isopropyl group (in auxiliary **5a**) was used the diastereoselectivity increased to 87:13 and the yield increased to 96%. The diastereoselectivity enhancement obtained with the use of the isopropyl group should be attributed to the larger steric effect from the secondary alkyl group. This observation is in accordance with our previous observations in the aza-Henry and Grignard reactions.[18b–18c]

On the basis of the above-encouraging results with the use of the isopropyl group in the chiral auxiliary, a series of chiral *N*-phosphonyl imines **5a**–**k** derived from various aromatic aldehydes were then synthesized[18b] and subjected to reactions with the lithium enolate of *N*-methoxy-*N*-methylacetamide. The results are summarized in Table 2. Excellent chemical yields were achieved for all the cases that we studied. The highest diastereoselectivities (*dr* = 96:4 to 99:1) were observed in those cases where *ortho* substituents

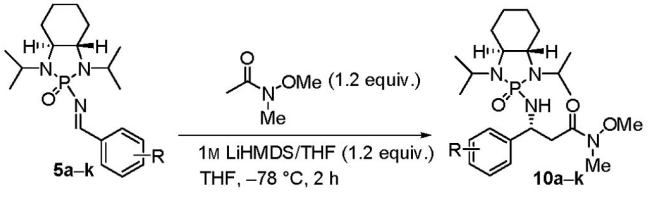
Table 1. Optimization results by using different R groups on the chiral *N*-phosphonyl imines.[a]



Entry	Substrate	R′	Product	Time [h]	Yield[b,c] [%]	*dr*[d]
1	**1**	benzyl	**6**	2	60	60:40
2	**2**	isobutyl	**7**	2	30	50:50
				10	40	50:50
3	**3**	neopentyl	**8**	2	30	50:50
				10	30	50:50
4	**4**	1-naphthyl	**9**	2	40	70:30
				10	50	70:30
5	**5a**	isopropyl	**10a**	2	96	87:13

[a] All reactions were carried out at –78 °C in 0.06 M solution of THF. [b] Yield calculated by ^{1}H NMR spectroscopic analysis of the crude product. [c] Combined yields of both isomers. [d] Diastereomeric ratio determined by ^{31}P and ^{1}H NMR spectroscopic analysis of the crude products.

Table 2. Results of the synthesis of *N*-phosphonyl-β-amino Weinreb amides with the use of chiral *N*-phosphonyl imines **5a**–**k**.

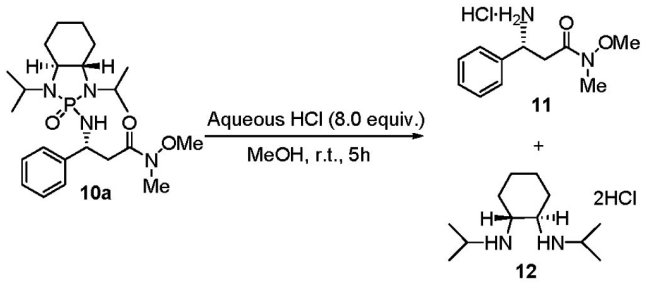


Entry	Substrate	R	Product	Yield[a,b] [%]	*dr*[c]
1	**5a**	H	**10a**	96	87:13
2	**5b**	4-fluoro	**10b**	96	86:14
3	**5c**	4-chloro	**10c**	94	85:15
4	**5d**	4-bromo	**10d**	95	88:12
5	**5e**	2-fluoro	**10e**	98	96:4
6	**5f**	2-methoxy	**10f**	93	99:1
7	**5g**	2-nitro	**10g**	95	99:1
8	**5h**	2-methyl	**10h**	96	98:2
9	**5i**	2-chloro	**10i**	93	98:2
10	**5j**	2-bromo	**10j**	95	98:2
11	**5k**	thienyl	**10k**	92	78:22

[a] Yields after standard aqueous workup. [b] Combined yields of both isomers. [c] Diastereomeric ratio determined by ^{31}P and ^{1}H NMR spectroscopic analysis of the crude sample.

are present on the aromatic rings (Table 2, Entries 5–10). However, for those cases where *para* substituents are attached to the aromatic rings (Table 2, Entries 2–4), the diastereoselectivity decreased to *dr* = 88:12 to 86:14. In contrast, chiral *N*-phosphonyl imines derived from a heteroaromatic aldehyde gave relatively low diastereoselectivity (*dr* = 78:22; Table 2, Entry 11).

The absolute configuration of the product was determined by removing the chiral auxiliary from compound **10a** followed by treatment with aqueous HCl in methanol as shown in Scheme 3. The optical rotation value of the deprotected product was proven to be comparable to that of known compound **11**.[14a]



Scheme 3. Removal of the chiral *N*-phosphonyl auxiliary from product **10a**.

Conclusions

Chiral *N*-phosphonyl imines were found to react with Weinreb amide derived enolates under convenient conditions. The deprotonation base and the *N*,*N*-protection groups were proven to be crucial for the success of this reaction. The secondary protection group, isopropyl, resulted in excellent chemical yields and good to excellent diastereoselectivities. The new method provides easy access to *N*-phosphonyl β-amino Weinreb amides. Further modifications by using various other *N*-substituents in *N*-phosphonyl imines under different conditions will be studied in the future.

Experimental Section

General Methods: All solvents, unless otherwise mentioned, used for the reactions were purified and dried by passing through an alumina column prior to use. THF was distilled from sodium/benzophenone ketyl. All the glassware used was dried overnight at 100 °C. NMR spectra were recorded at 500, 125, and 202 MHz for ^{1}H, ^{13}C, and ^{31}P nuclei, respectively. Shifts are reported in ppm on the basis of an internal TMS standard (for ^{1}H/$CDCl_3$) or on residual solvent peaks (for ^{13}C/$CDCl_3$). ^{31}P NMR spectra were referenced to external H_3PO_4 (δ =0.00 ppm). Lithium bis(trimethylsilyl-amide) (1 M in THF) was obtained from Aldrich and used as obtained from commercial sources without further purification.

Typical Procedure for the Synthesis of *N*-Phosphonyl β-Amino Weinreb Amides by Using Chiral *N*-Phosphonyl Imines: In a dry vial, under inert gas protection, was loaded *N*-methoxy-*N*-methylacetamide (0.70 mmol) and THF (4 mL). The reaction vial was cooled to –78 °C and LiHMDS (1 M in THF, 0.70 ml, 0.70 mmol) was added dropwise. The reaction solution was stirred at –78 °C for 1 h. At this time, phosphonyl imine (0.2 g, 0.60 mmol) in THF (4 mL) was added to the reaction mixture. The reaction mixture stirred for another 1 h. Further, the reaction was quenched by adding saturated NH_4Cl solution followed by water (10 mL). The reaction mixture was then transferred to the separatory funnel and extracted with diethyl ether (2 × 20 mL). The combined organic layer was washed with water (1 × 20 mL) and dried with anhydrous sodium sulfate. Sodium sulfate was filtered off, and the organic layer was concentrated to obtain the desired products as oils. For the 4-fluoro and 4-chloro derivatives, the product was purified by flash chromatography (EtOAc/MeOH, 5:1).

10a: Yellow oil. Yield: 0.26 g, 96%. $[\alpha]_D^{25}$ = –30.1 (*c* = 0.62, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 7.5 Hz, 2 H), 7.28 (t, *J* = 7.0 Hz, 2 H), 7.18 (t, *J* = 7.5 Hz, 1 H), 4.83–4.77 (m, 1 H), 3.86 (t, *J* = 10.5 Hz, 1 H, NH), 3.43–3.38 (m, 1 H), 3.36 (s, 3 H), 3.13–3.07 (m, 1 H), 3.03 (s, 3 H), 2.97–2.78 (m, 4 H), 2.07–1.96 (m, 2 H), 1.75 (s, 3 H), 1.34–1.28 (m, 4 H), 1.20 (d, *J* = 7.0 Hz, 4 H), 1.15 (d, *J* = 7.0 Hz, 2 H), 1.09 (d, *J* = 6.5 Hz, 2 H), 1.05 (d, *J* = 10 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.8, 144.1, 128.1 (2 C), 126.7, 126.5 (2 C), 60.9, 59.8 (d, *J* = 11.3 Hz), 58.9 (d, *J* = 9.8 Hz), 52.7, 45.7, 43.9 (d, *J* = 3.0 Hz), 43.8 (d, *J* = 3.8 Hz), 31.4 (d, *J* = 11.8 Hz), 30.8 (d, *J* = 10 Hz), 24.3 (d, *J* = 12.5 Hz), 23.6 (d, *J* = 7.8 Hz), 23.1, 23.0, 19.6, 19.5 (d, *J* = 2.0 Hz) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 22.6 ppm.

10b: Colorless oil. Yield: 0.269 g, 96%. $[\alpha]_D^{25}$ = –33.2 (*c* = 2.23, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.32 (m, 2 H), 7.00–6.95 (m, 2 H), 4.84–4.78 (m, 1 H), 3.96 (t, *J* = 10.0 Hz, 1 H, NH), 3.41 (s, 3 H), 3.35–3.27 (m, 3 H), 3.04 (s, 3 H), 2.96–2.77 (m, 4 H), 2.07–2.00 (m, 2 H), 1.74 (s, 2 H), 1.40 (t, *J* = 7.5 Hz, 1 H), 1.34–1.25 (m, 3 H), 1.19 (d, *J* = 7.0 Hz, 3 H), 1.14 (d, *J* = 7.0 Hz, 3 H), 1.08 (dd, *J* = 6.5, 12.5 Hz, 5 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.7, 160.6, 140.0, 128.1, 128.0, 114.9, 114.7, 61.0, 59.8 (d, *J* = 10.8 Hz), 58.8 (d, *J* = 9.8 Hz), 52.0, 45.7, 43.9 (d, *J* = 4.0 Hz), 43.8 (d, *J* = 4.0 Hz), 31.3 (d, *J* = 11.8 Hz), 30.7 (d, *J* = 10 Hz), 24.3, 24.2, 23.6 (d, *J* = 7.8 Hz), 23.0 (d, *J* = 3.5 Hz), 19.6, 19.5 (d, *J* = 2.0 Hz) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 22.6 ppm.

10c: Colorless oil. Yield: 0.276 g, 94%. $[\alpha]_D^{25}$ = –35.3 (*c* = 1.72, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.30 (m, 2 H), 7.27–7.24 (m, 2 H), 4.84–4.71 (m, 1 H), 3.97 (t, *J* = 10.0 Hz, 1 H, NH), 3.43 (s, 3 H), 3.39–3.26 (m, 2 H), 3.04 (s, 3 H), 2.96–2.90 (m, 2 H), 2.87–2.76 (m, 2 H), 2.07–1.97 (m, 3 H), 1.74 (s, 2 H), 1.31–1.23 (m, 4 H), 1.18–1.08 (m, 10 H), 0.82 (d, *J* = 6.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.7, 142.8, 132.4, 128.2 (2 C), 128.0 (2 C), 61.0, 59.8 (d, *J* = 11.3 Hz), 58.9 (d, *J* = 9.8 Hz), 52.1, 44.0 (d, *J* = 3.3 Hz), 43.9 (d, *J* = 4.0 Hz), 39.9, 31.3 (d, *J* = 11.8 Hz), 30.7 (d, *J* = 9.3 Hz), 24.3, 24.2, 23.7 (d, *J* = 7.3 Hz), 23.0 (d, *J* = 3.5 Hz), 19.64, 19.61 (d, *J* = 2.0 Hz) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 22.4 ppm.

10d: Colorless oil. Yield: 0.288 g, 95%. $[\alpha]_D^{25}$ = –27.1 (*c* = 4.70, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 8.5 Hz, 2 H), 7.29 (d, *J* = 8.5 Hz, 2 H), 4.81–4.76 (m, 1 H), 4.09 (t, *J* = 8.0 Hz, 1 H, NH), 3.43 (s, 3 H), 3.40–3.26 (m, 3 H), 3.04 (s, 3 H), 2.96–2.85 (m, 3 H), 2.80–2.77 (m, 1 H), 2.07–1.97 (m, 2 H), 1.74 (s, 2 H), 1.31–1.27 (m, 3 H), 1.18 (d, *J* = 7.0 Hz, 4 H), 1.15 (d, *J* = 7.0 Hz, 4 H), 1.08 (d, *J* = 6.5 Hz, 3 H), 0.78 (d, *J* = 7.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.5, 143.2, 130.9 (2 C), 128.3 (2 C), 120.3, 60.9, 59.6 (d, *J* = 10.8 Hz), 58.7 (d, *J* = 9.8 Hz), 51.9, 43.8 (d, *J* = 3.5 Hz), 43.7 (d, *J* = 4.3 Hz), 39.8, 31.2 (d, *J* =

11.8 Hz), 30.5 (d, J = 9.3 Hz), 24.1, 24.0, 23.5 (d, J = 7.8 Hz), 22.8 (d, J = 3.3 Hz), 19.49, 19.46 (d, J = 2.0 Hz) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 22.6 ppm.

10e: Yellow oil. Yield: 0.265 g, 98%. $[\alpha]_D^{25}$ = –23.0 (c = 4.28, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51 (t, J = 8.0 Hz, 1 H), 7.21–7.16 (m, 1 H), 7.09 (t, J = 8.5 Hz, 1 H), 6.97 (t, J = 8.0 Hz, 1 H), 5.01–4.95 (m, 1 H), 4.04 (t, J = 11.5 Hz, 1 H, NH), 3.49 (s, 3 H), 3.41–3.32 (m, 2 H), 3.14–3.11 (m, 1 H), 3.01 (s, 3 H), 2.97–2.91 (m, 2 H), 2.83–2.79 (m, 1 H), 2.08–2.01 (m, 2 H), 1.75 (s, 2 H), 1.33–1.27 (m, 4 H), 1.21 (d, J = 6.5 Hz, 3 H), 1.17 (d, J = 6.5 Hz, 3 H), 1.07 (d, J = 6.5 Hz, 3 H), 1.04 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.8, 160.9, 158.9, 129.3 (d, J = 4.5 Hz), 128.4 (d, J = 7.8 Hz), 123.7 (d, J = 3.0 Hz), 115.0 (d, J = 21 Hz), 61.0, 59.8 (d, J = 11.3 Hz), 58.8 (d, J = 9.8 Hz), 48.0, 43.9 (d, J = 3.0 Hz), 43.7 (d, J = 4.5 Hz), 38.3, 31.3 (d, J = 11.3 Hz), 30.7 (d, J = 9.3 Hz), 24.2, 24.1, 23.7 (d, J = 8.3 Hz), 22.9 (d, J = 4.0 Hz), 19.5, 19.4 (d, J = 2.0 Hz) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 23.2 ppm.

10f: Colorless oil. Yield: 0.27 g, 93%. $[\alpha]_D^{25}$ = –24.1 (c = 1.65, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (d, J = 7.5 Hz, 1 H), 7.17 (t, J = 7.5 Hz, 1 H), 6.88 (t, J = 7.5 Hz, 1 H), 6.83 (d, J = 7.5 Hz, 1 H), 4.91–4.85 (m, 1 H), 4.21 (t, J = 12.0 Hz, 1 H, NH), 3.85 (m, 3 H), 3.42 (s, 3 H), 3.40–3.29 (m, 2 H), 2.99 (s, 3 H), 2.97–2.92 (m, 3 H), 2.86–2.82 (m, 1 H), 2.06–2.00 (m, 2 H), 1.75 (s, 2 H), 1.38–1.27 (m, 4 H), 1.25 (dd, J = 7.0, 10 Hz, 6 H), 1.17 (d, J = 7.0 Hz, 3 H), 1.03 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.1, 156.1, 130.9, 128.7, 127.7, 119.9, 109.9, 60.7, 59.7 (d, J = 11.3 Hz), 58.7 (d, J = 9.8 Hz), 54.8, 44.9, 43.7 (d, J = 2.8 Hz), 43.5 (d, J = 4.3 Hz), 37.8, 31.2 (d, J = 11.8 Hz), 30.6 (d, J = 8.8 Hz), 24.1, 24.0, 23.5 (d, J = 7.8 Hz), 22.8 (d, J = 3.3 Hz), 19.3, 8.8 ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 23.5 ppm.

10g: Colorless oil. Yield: 0.28 g, 95%. $[\alpha]_D^{25}$ = –28.9 (c = 0.39, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.89 (t, J = 8.0 Hz, 2 H), 7.60 (t, J = 7.5 Hz, 1 H), 7.38 (t, J = 7.5 Hz, 1 H), 5.43–5.36 (m, 1 H), 4.57 (t, J = 11.0 Hz, 1 H, NH), 3.46 (s, 3 H), 3.39–3.26 (m, 2 H), 3.21–3.17 (m, 1 H), 3.00 (m, 3 H), 2.95–2.91 (m, 2 H), 2.79–2.76 (m, 1 H), 2.08–1.97 (m, 3 H), 1.75–1.72 (m, 2 H), 1.38–1.25 (m, 3 H), 1.20 (dd, J = 6.5, 11.0 Hz, 6 H), 1.01 (d, J = 7.0 Hz, 3 H), 0.88 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.6, 147.9, 139.0, 132.8, 130.4, 127.8, 124.3, 61.1, 59.8 (d, J = 11.3 Hz), 58.7 (d, J = 9.8 Hz), 48.6, 43.9 (d, J = 3.5 Hz), 43.7 (d, J = 5.0 Hz), 38.0, 31.3 (d, J = 11.0 Hz), 30.9 (d, J = 8.8 Hz), 24.3, 24.1, 23.8 (d, J = 7.8 Hz), 23.2 (d, J = 3.0 Hz), 19.5, 19.2 (d, J = 2.0 Hz) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 23.2 ppm.

10h: Yellow oil. Yield: 0.264 g, 96%. $[\alpha]_D^{25}$ = –23.5 (c = 0.42, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, J = 8.0 Hz, 1 H), 7.17–7.14 (m, 1 H), 7.10–7.06 (m, 2 H), 5.06–5.00 (m, 1 H), 4.05 (t, J = 11.0 Hz, 1 H, NH), 3.37–3.24 (m, 5 H), 3.03 (s, 3 H), 3.00–2.90 (m, 1 H), 2.77–2.75 (m, 2 H), 2.42 (s, 3 H), 2.07–1.99 (m, 2 H), 1.74–1.73 (m, 2 H), 1.33–1.25 (m, 5 H), 1.16 (d, J = 7.0 Hz, 3 H), 1.12 (d, J = 7.0 Hz, 3 H), 1.08 (d, J = 7.0 Hz, 3 H), 1.01 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.7, 142.4, 134.1, 130.1, 126.6, 126.4, 125.8, 64.2, 60.8, 59.8 (d, J = 11.0 Hz), 58.8 (d, J = 9.8 Hz), 49.2, 45.4, 43.8 (d, J = 3.0 Hz), 38.5, 31.5 (d, J = 11.8 Hz), 30.8 (d, J = 9.3 Hz), 29.6, 24.3 (d, J = 7.3 Hz), 23.7 (d, J = 7.8 Hz), 23.0 (d, J = 3.5 Hz), 19.5, 19.2 (d, J = 2.5 Hz) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 23.3 ppm.

10i: Colorless oil. Yield: 0.271 g, 93%. $[\alpha]_D^{25}$ = –26.7 (c = 1.65, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63 (d, J = 8.0 Hz, 1 H), 7.29 (d, J = 10.0 Hz, 1 H), 7.24 (t, J = 8.0 Hz, 1 H), 7.15 (t, J = 8.0 Hz, 1 H), 5.07–5.02 (m, 1 H), 4.49 (t, J = 11.5 Hz, 1 H, NH), 3.42 (s, 3 H), 3.40–3.31 (s, 2 H), 3.27–3.24 (m, 1 H), 3.00 (s, 3 H), 2.98–2.93 (m, 1 H), 2.86–2.79 (m, 2 H), 2.09–2.08 (m, 1 H), 2.00 (d, J = 7.0 Hz, 1 H), 2.01 (m, 2 H), 1.75 (m, 2 H), 1.37–1.28 (m, 2 H), 1.21 (dd, J = 7.0, 5.0 Hz, 6 H), 1.04 (d, J = 6.5 Hz, 3 H), 0.92 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.6, 140.7, 131.8, 129.4, 129.0, 128.0, 126.4, 60.9, 59.8 (d, J = 11.3 Hz), 58.8 (d, J = 9.8 Hz), 50.0, 43.8 (d, J = 3.0 Hz), 43.5 (d, J = 4.5 Hz), 36.5, 31.4 (d, J = 11.8 Hz), 30.9 (d, J = 8.8 Hz), 24.2, 24.1, 23.8 (d, J = 7.8 Hz), 23.2 (d, J = 3.5 Hz), 19.5, 19.0 (d, J = 2.0 Hz) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 23.2 ppm.

10j: Yellow oil. Yield: 0.285 g, 95%. $[\alpha]_D^{25}$ = –30.6 (c = 4.15, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64 (d, J = 9.0 Hz, 1 H), 7.47 (d, J = 9.0 Hz, 1 H), 7.28 (t, J = 8.0 Hz, 1 H), 7.08 (t, J = 9.0 Hz, 1 H), 5.07–4.92 (m, 1 H), 4.62 (t, J = 11.2 Hz, 1 H, NH), 3.48–3.41 (m, 1 H), 3.40 (s, 3 H), 3.37–3.28 (m, 2 H), 3.00 (s, 3 H), 2.90–2.94 (m, 1 H), 2.84–2.76 (m, 2 H), 2.10 (d, J = 7.0 Hz, 1 H), 2.00 (d, J = 7.0 Hz, 1 H), 1.75–1.74 (m, 2 H), 1.34–1.28 (m, 4 H), 1.23 (dd, J = 7.0, 4.5 Hz, 6 H), 1.01 (d, J = 6.5 Hz, 3 H), 0.84 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.6, 142.2, 132.2, 129.6, 128.3, 127.0, 122.2, 60.9, 59.7 (d, J = 11.3 Hz), 58.8 (d, J = 9.9 Hz), 51.9, 43.8 (d, J = 3.0 Hz), 43.5 (d, J = 4.8 Hz), 36.3, 31.4 (d, J = 11.8 Hz), 30.9 (d, J = 8.7 Hz), 24.2, 24.1, 23.9 (d, J = 7.8 Hz), 23.3 (d, J = 3.0 Hz), 19.5, 18.8 (d, J = 2.0 Hz) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 23.2 ppm.

10k: Yellow oil. Yield: 0.238 g, 92%. $[\alpha]_D^{25}$ = –29.7 (c = 1.68, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.13–7.11 (m, 1 H), 6.96–6.95 (m, 1 H), 6.90–6.88 (m, 1 H), 5.10–5.04 (m, 1 H), 3.84 (t, J = 11.0 Hz, 1 H, NH), 3.53 (s, 3 H), 3.48–3.41 (m, 2 H), 3.11 (s, 3 H), 2.98–2.93 (m, 2 H), 2.84–2.80 (m, 1 H), 2.07–2.03 (m, 2 H), 1.74 (m, 2 H), 1.33–1.29 (m, 4 H), 1.25–1.22 (m, 4 H), 1.15 (dd, J = 6.5, 12.5 Hz, 8 H), 0.96 (d, J = 7.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.6, 148.8 (d, J = 2.5 Hz), 126.3, 123.9, 123.4, 61.0, 59.5 (d, J = 10.8 Hz), 58.8 (d, J = 9.8 Hz), 48.8, 43.9 (d, J = 2.8 Hz), 43.8 (d, J = 4.0 Hz), 40.3, 31.2 (d, J = 11.8 Hz), 30.7 (d, J = 9.3 Hz), 24.2, 24.1, 23.5 (d, J = 7.8 Hz), 23.1 (d, J = 4.0 Hz), 19.5, 19.4 (d, J = 2.0 Hz) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 22.6 ppm.

Procedure for the Removal of the Chiral *N*-Phosphonyl Group from 10a: Into a 50-mL round-bottomed flask was added product **10a** (0.438 g) and methanol (6.0 mL). To this solution was added aqueous HCl (8.0 equiv.), and the reaction mixture was stirred at room temperature for 5 h. The reaction was monitored by TLC, and completion of the reaction was indicated by the disappearance of the starting material on TLC. Volatiles were evaporated under vacuum, and the solid residue was extracted with ethyl acetate and saturated $NaHCO_3$. The organic layer was dried with sodium sulfate. Sodium sulfate was filtered off, and the organic layer was dried under vacuum to get the crude reaction mixture, which was further subjected to column chromatography to obtain pure product **11** as a yellow oil. $[\alpha]_D^{25}$ = +22.8 (c = 0.90, $CHCl_3$) {ref.[14a] [α] = –23.8 (c = 1.00, $CHCl_3$)}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.32 (m, 5 H, Ph), 4.50 (dd, J = 3.0, 9.0 Hz, 1 H), 3.62 (s, 3 H, OCH_3), 3.17 (s, 3 H, NCH_3), 2.91–2.76 (m, 2 H), 1.68 (s, 2 H, NH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.5, 144.0, 128.6 (2 C), 127.4, 126.7, 126.2, 61.1, 52.1, 41.0, 21.8 ppm.

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