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Diastereoselective Mannich Reaction of Chiral Enolates Formed by Enantioselective Conjugate Addition of Grignard Reagents

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Cu–Taniaphos-catalyzed enantioselective addition of Grignard reagents to cyclic enones leads to chiral magnesium enolates. These enolates add to *N*-protected imines directly, or through in situ transformation to silyl enol ethers. Diastereoselectivity of the addition depends on the nitrogen protecting group of the imine. Diastereoisomers of the resulting β-amino carbonyl compounds can be separated and are obtained in acceptable yields and in high enantiomeric purities (up to 99:1 *er*).

Introduction

Stereoselective catalytic synthesis of complicated molecules possessing several stereogenic centers is still a considerable challenge. Tandem or domino catalytic reactions, by combining several reactions into a one-pot sequence, try to minimize the number of necessary synthetic and purification operations thus to improve the overall efficiency.[1] Although various tandem or domino reactions are known, the use of conjugate addition as an initiating reaction seems particularly appealing. Generation of chiral enolates by catalytic conjugate addition of organometallic reagents to enones is a useful and practical method for the preparation of reactive carbon nucleophiles. Such nucleophilic species are useful synthetic building blocks and can be added to various electrophiles.[2] Zinc enolates produced by Cu-catalyzed addition of dialkylzinc reagents to cyclic enones were successfully trapped by aldehydes,[3] allyl bromide or acetate,[4] alkyl iodide,[5] nitroso compounds,[6] bromine,[7] or acid anhydride.[8] These enolates also open epoxides[9] or take part in cross-coupling[10] or cyclopropanation reactions.[11] Chiral metal enolates can also be trapped intramolecularly to form cycles.[12] This was realized by another conjugate addition[13] or a nucleophilic displacement of a remote halogen atom.[11] Intramolecular enolate trapping is also useful for Rh-catalyzed additions, although these reactions typically run without a chiral ligand.[14] Hayashi developed an intermolecular enantioselective version of rhodium enolate trapping in the aldol reaction.[15] Further transformations can be performed by conversion of the metal enolate to a silyl enol ether.[16] Imines bearing electron-withdrawing groups also react with zinc enolates. Gonzales-Gómez and co-workers used Cu–phosphoramidite-catalyzed addition of dialkylzinc reagents to enones, and the resulting enolates reacted with chiral sulfinyl imine.[17] The use of a chiral imine ensured high diastereoselectivity of enolate addition to the imine. Huang and co-workers used a phosphoramidite–amide ligand for Et_2Zn addition to acyclic enones. They were able to control the enantioselectivity as well as the diastereoselectivity of the reaction with a chiral catalyst.[18] On the other hand, magnesium enolates, resulting from the conjugate addition of Grignard reagents, have been utilized to a much lesser extent.[19] The synthetic scope and utility of chiral magnesium enolates is potentially much broader, as there is a large number of Grignard reagents available, either commercially or though simple synthetic procedures. Inspired by the work of Feringa and co-workers[20] on Cu–Taniaphos-catalyzed conjugate addition of Grignard reagents to enones, we have developed an extension of this methodology by trapping the resulting magnesium enolates with imines. The Cu–Taniaphos complex was able to catalyze the highly enantioselective conjugate addition of Grignard reagents to cyclohex-2-enone followed by a one-pot reaction with *N*-benzylidenetoluenesulfonamide.[21] With this imine, however, diastereoselectivity of the addition was poor. Therefore, we decided to study this transformation with the aim of addressing the problem of low diastereoselectivity. In this paper we investigated an array of imines with various *N*-protecting groups and also studied the effects of various additives. We have found an interesting influence of the imine protecting group on the diastereoselectivity of enolate addition. The study led to overall improvement of the methodology.

Results and Discussion

The reaction of cyclohex-2-enone (**1**) with methylmagnesium bromide followed by enolate addition to imine **2a** af-

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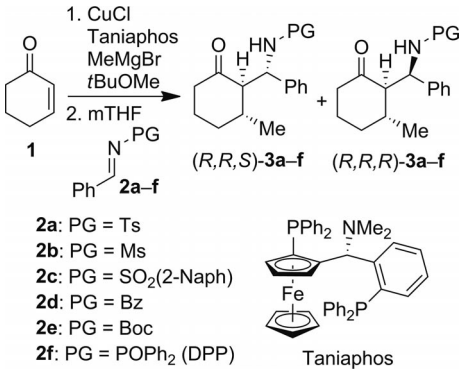
forded diastereomeric products **3a** (Scheme 1). Although the enantioselectivity, controlled by the chiral Taniaphos ligand, was high (94:6 and 96:4 *er*), the diastereoselectivity was low (56:44 *dr*). Therefore, we decided to examine the tandem reaction with imines having other nitrogen protecting groups with the aim of improving the diastereoselectivity. A range of *N*-protected benzylideneamines **2**, either commercially available or synthesized according to literature procedures, were evaluated. We started our investigation with previously established optimal reaction conditions (Scheme 1).[21] The reaction with ketone **1** and methylmagnesium bromide in *t*BuOMe followed by the addition of imines in 2-methyltetrahydrofuran (mTHF) afforded a range of products **3b**–**f**. In all instances, only two major diastereoisomers, (*R*,*R*,*S*)-**3** and (*R*,*R*,*R*)-**3**, were isolated.



Scheme 1.

Surprisingly, the addition to the majority of the imines proceeded with similar results in terms of chemical yield, diastereoselectivity, and enantioselectivity. A typical example is imine **2b**, which afforded product **3b** in 65% yield with 2:1 *dr* and 96:4 *er* for (*R**,*R**,*S**)-**3b** and 89:11 *er* for (*R**,*R**,*R**)-**3b**. The reaction with imine **2c** was more enantioselective, but product **3c** was isolated in lower yield (Table 1, Entry 5). The same is true also for imines **2d** and **2e** (Table 1, Entries 6 and 7). Only imine **2f**, with a diphenylphosphorane protecting group (DPP), behaved differently. Imine **2f** afforded product **3f** with markedly higher diastereoselectivity (22:78 *dr*). Furthermore, the major diastereomer was (*R*,*R*,*R*)-**3f**, whereas in all other instances isomer (*R*,*R*,*S*)-**3** prevailed. Isolated yields of the diastereomers of **2f** were 18 and 40%. Separation and purification of the diastereomers was often difficult and usually led to some product loss. This was demonstrated by an experiment in which diastereomers (*R*,*R*,*S*)-**3f** and (*R*,*R*,*R*)-**3f** were isolated together in 67% yield (Table 1, Entry 10). Practicality of the tandem reaction with imine **2f** was evaluated also by a reaction on a larger scale (3 mmol), which resulted in 626 mg (50%) of pure diastereomer (*R*,*R*,*R*)-**3f**. Imines without an electron-withdrawing group, such as *N*-benzylidene-*tert*-butylamine or (benzylidene)(trimethylsilyl)amine, did not react at all. We also evaluated several Lewis acidic additives, but without success. In situ transformation of the magnesium enolate to the silyl enol ether with trimethylsilyl triflate (TMSOTf) led to a slight increase in the diastereoselectivity for imine **2a** and had little effect on imines **2b** and **2e**. Addition of TMSOTf also led to lower yields of products **3**, because silyl enol ethers have intrinsically lower nucleophilicities than metal enolates. On the other hand, with imine **2f**, addition of TMSOTf resulted in a further increase in the diastereoselectivity (up to 7:93 *dr*). The results of the screening of the nitrogen protecting groups are summarized in Table 1.

Table 1. One-pot conjugate addition of MeMgBr to cyclohex-2-enone (**1**) followed by reaction with imines **2a**–**f**.

Entry	Imine	Additive	Yield of **3**[a] (*R*,*R*,*S*)/(*R*,*R*,*R*)	*dr*[b]	*er*[c]
1	**2a**	–	35/24	56:44	94:6/96:4
2	**2a**	TMSOTf	25/11	67:33	98:2/98:2
3	**2b**	–	32/33	64:36	96:4/89:11
4	**2b**	TMSOTf	32/13	70/30	93:7/90:10
5	**2c**	–	23/24	63/37	98:2/97:3
6	**2d**	–	24/14	66:34	96:4/96:4
7	**2e**	–	23/22	60:40	97:3/92:8
8	**2e**	TMSOTf	11/9	60:40	92:8/97:3
9	**2e**	$Cu(OTf)_2$	(11)[d]	70:30	n.d.
10	**2f**	–	18/40 (67)[e]	22:78	81:19/98:2
11	**2f**	TMSOTf	3/29	7:93	97:3/98:2
12	**2f**	TIPSCl	n.d.	18:82	n.d.

[a] Isolated yield of pure diastereoisomers. [b] Ratio of (*R*,*R*,*S*)-**3**/(*R*,*R*,*R*)-**3** determined by ^{1}H NMR (^{31}P NMR for **3f**) spectroscopic analysis of the crude reaction mixture. [c] Enantiomeric purity of (*R*,*R*,*S*)-**3**/(*R*,*R*,*R*)-**3** determined by enantioselective HPLC (Daicel chiral columns). [d] Combined isolated yield of both diastereomers. [e] Yield given in parentheses is the isolated yield of **3f** without separation of diastereomers.

The absolute configuration of (*R*,*R*,*R*)-**3a** was previously established by X-ray crystallographic analysis.[21] The configurations of products **3b**–**e** were assigned by comparison of the H,H coupling constants within the series of compounds **3a**–**e**. Coupling constants between COCH and CHN are consistent within groups of both diastereomers (*R*,*R*,*S*)-**3** ($^3J_{H,H}$ = 3.0–4.3 Hz) and (*R*,*R*,*R*)-**3** ($^3J_{H,H}$ = 5.1–5.8 Hz). Because of the opposite sense of diastereoselectivity with imine **2f**, the relative configuration of its tandem reaction product, compound **3f**, was further ascertained by NOESY NMR experiments. Important interactions confirming the configurations of both diastereomers (*R*,*R*,*S*)-**3f** and (*R*,*R*,*R*)-**3f** are depicted in Figure 1.

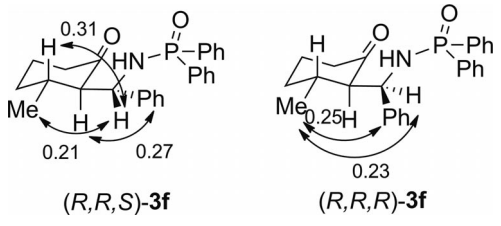
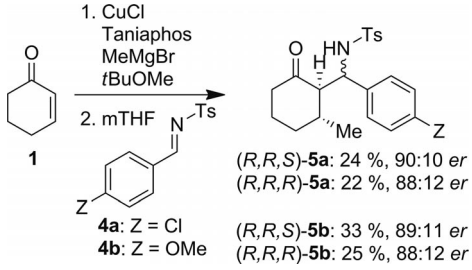


Figure 1. Important NOE interactions confirming relative configuration of product **3f** with calculated distances (nm). The lowest-energy conformers have been optimized by HF/3-21G calculations.

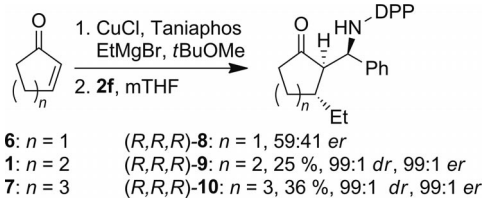
Tosyl-protected imines derived from substituted benzaldehydes were also evaluated in the tandem reaction (Scheme 2). Imines with both electron-withdrawing (i.e., **4a**) and -donating (i.e., **4b**) groups afforded tandem reaction

products **5a** and **5b**, respectively. The diastereoselectivity and enantioselectivity were slightly lower in comparison to those obtained with imine **2a**. Also in these experiments, diastereomers (*R*,*R*,*S*)-**5a**/(*R*,*R*,*R*)-**5a** and (*R*,*R*,*S*)-**5b**/(*R*,*R*,*R*)-**5b** were separated by column chromatography. An imine derived from ferrocene carboxaldehyde was unreactive under our reaction conditions, as only starting material was isolated. Also, a pyridine-derived imine did not afford the desired product of the tandem reaction.



Scheme 2.

Conjugate addition of ethylmagnesium bromide to cyclic enones **1**, **6**, and **7** followed by reaction with imine **2f** proceeded with high enantioselectivity (99:1 *er*) and diastereoselectivity with cyclohex-2-enone (**1**) and cyclohept-2-enone (**7**, Scheme 3). However, the chemical yields were somewhat lower than those obtained with methylmagnesium bromide. Product **8** of the reaction with cyclopent-2-enone (**6**) could not be isolated in pure form, and therefore, its *dr* was not determined; its enantiomeric ratio was also low (59:41 *er*).



Scheme 3.

Dependence of the diastereoselection of the Mannich reaction on the nitrogen protecting group is interesting but not unprecedented.[22] Different stereoselectivity of the enolate addition to imine **2f** in comparison to other imines led us to investigate possible transition states by computational methods. We assumed that the enolate reacts preferentially at its *anti* side with respect to the methyl group, and then we modeled two possible approaches of the imine. We found that the generally proposed six-membered Zimmerman–Traxler cyclic transition states were not possible to optimize and no proper transition states were found. Instead, geometrical optimization led to eight-membered cyclic transition states, in which Mg was bound to the oxygen atom of the DPP group or the oxygen atoms of the Ms group (Figure 2).

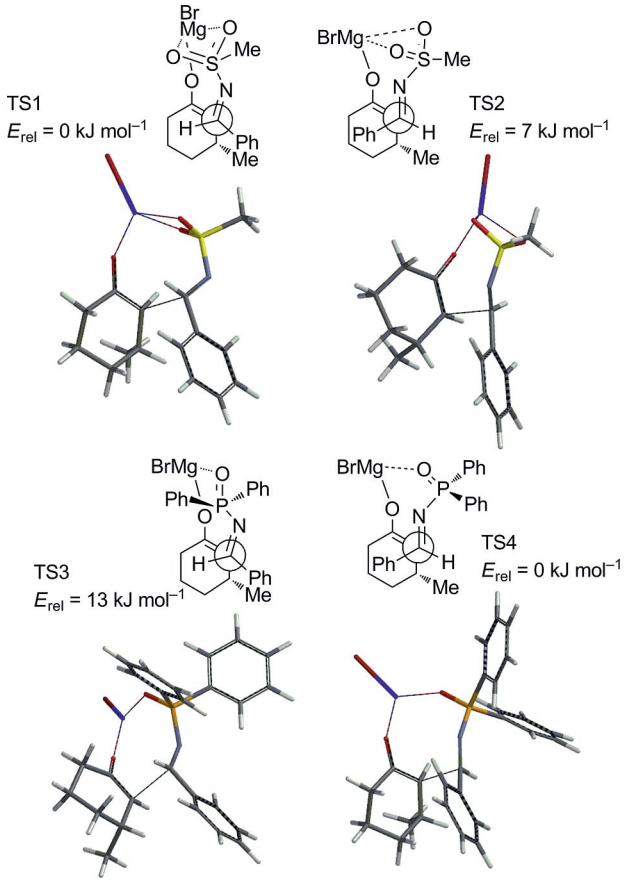


Figure 2. Calculated (HF/6-31G*) structures of the transition states of enolate addition to imines (TS1 and TS2 for imine **2b**; TS3 and TS4 for imine **2f**).

These eight-membered transition states are less rigid; therefore, the diastereoselectivities of enolate addition to imines are only moderate. For sterically less-congested imines, exemplified by **2b** with a Ms group, TS1 is preferred because steric interaction between the cyclohexane ring and the phenyl group of the imine is smaller than that in TS2. The preference of TS4 over TS3 seems to be in the more plausible conformation of imine **2f**. Thus, for sulfonate-, benzoyl-, and Boc-protected imines (i.e., **3a**–**e**), preferential attack is from the *Si* face, which leads to major isomers (*R*,*R*,*S*)-**3a**–**e**, and imine **2f** is attacked from its *Re* face, leading to (*R*,*R*,*R*)-**3f** as the major product (Figure 2).

The addition of TMSOTf after the addition of the Grignard reagent had an interesting effect: a higher diastereoselectivity was observed for the reaction of **1** with imine **2f**, although at the expense of chemical yield. With the addition of TMSOTf, conversion of the Mg-enolate to the silyl enol ether takes place, and the reaction likely proceeds through an open transition state. However, because of attractive interaction between the silicon and oxygen atoms of the protecting groups, *synclinal* arrangements of the enol ether and imine are preferred, and thus similar arguments as with Mg-enolates can be invoked. Figure 3 shows the transition states leading to the major diastereomers of **3**: TS5 to (*R*,*R*,*S*)-**3b** and TS6 to (*R*,*R*,*R*)-**3f**.

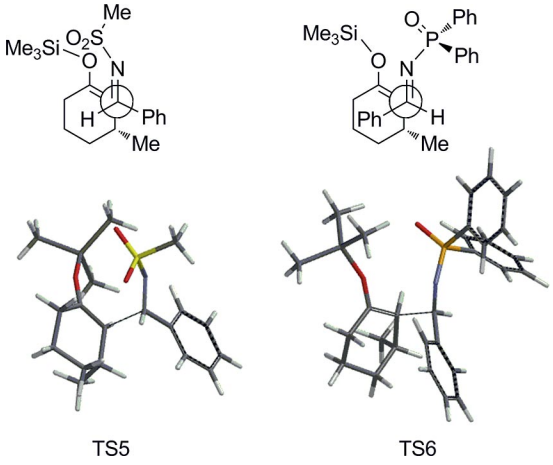


Figure 3. Calculated (HF/6-31G*) structures of the transition states of TMS-enol ether addition to imines (TS5 for imine **2b**; TS6 for imine **2f**).

Conclusions

Chiral enolates produced by the Cu–Taniaphos-catalyzed conjugate addition of Grignard reagents to cyclic enones add diastereoselectively to imines. The resulting β-amino carbonyl compounds are obtained in satisfactory overall yields and in high enantiomeric purities (up to 99:1). The relative configuration of the major diastereomer of the products can be controlled by the nitrogen protecting group and these diastereomers can be separated.

Experimental Section

General Methods: All reactions were carried out under an inert atmosphere of N_2. Solvents were dried and purified by standard methods before use.[23] NMR spectra were recorded with a Varian Mercury plus instrument (300 MHz for ^{1}H, 75 MHz for ^{13}C) and a Varian NMR System 600 (600 MHz for ^{1}H, 150 MHz for ^{13}C and 242.8 MHz for ^{31}P). Chemical shifts (δ) are given in ppm relative to tetramethylsilane for ^{1}H NMR and ^{13}C NMR spectroscopy. A unified chemical shift scale was used for ^{31}P NMR with 85% H_3PO_4 as the secondary standard (δ = 0.0 ppm, Ξ = 40.4807420). Specific optical rotations were measured with a Jasco instrument. Flash chromatography was performed on Merck silica gel 60. Thin-layer chromatography was performed on Merck TLC-plates silica gel 60, F-254. Enantiomeric ratios were determined by HPLC with Chiralpak AD-H, OD-H, AS-H, OJ-H, IA (Daicel Chemical Industries) columns by using hexane/*i*PrOH as the mobile phase and detection with a UV detector at 254 and 211 nm. The imines used in this work were commercially available or prepared according to the literature.[24]

Typical Procedure for the Tandem Reaction: Taniaphos (21 mg, 0.031 mmol) and CuCl (2.4 mg, 0.024 mmol) were dissolved in *t*BuOMe (6.0 mL), and the resulting solution was stirred for 30 min at room temperature. The reaction mixture was then cooled to –60 °C and cyclohex-2-enone (**1**; 47 μL, 47 mg, 0.489 mmol) was added. The solution was stirred for an additional 10 min at –60 °C. Then, the Grignard reagent (0.76 mmol, Et_2O solution) was added over 5 min, and the resulting mixture was stirred for an additional 2 h at –60 °C. Then, imine **2** (0.328 mmol) dissolved in mTHF (5.0 mL) was added, and the reaction mixture was allowed to slowly reach room temperature overnight. The mixture was then quenched with NH_4Cl and extracted with *t*BuOMe. The combined organic extracts were concentrated. The crude product was purified by column chromatography (SiO_2; hexane/EtOAc/CH_2Cl_2 or CH_2Cl_2/MeOH). Enantiomeric excess values were determined by HPLC with a chiral stationary phase.

***N*-[(2-Methyl-6-oxocyclohexyl)(phenyl)methyl]methanesulfonamide (3b)**

(*R*,*R*,*S*)-3b: White solid. M.p. 185–187 °C (hexane). $[\alpha]_D$ = –2.5 (*c* = 0.31, $CHCl_3$, 90%*ee*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 5 H, Ph), 6.26 (d, *J* = 10.5 Hz, 1 H, NH), 4.79 (dd, *J* = 10.5, 3.1 Hz, 1 H, CH-NH), 2.62 (s, 3 H, SO_2-CH_3), 2.50 (dd, *J* = 10.5, 3.1 Hz, 1 H, CH-CO), 2.36–2.11 (m, 3 H, 2 CH_2), 2.09–1.90 (m, 2 H, CH_2), 1.84–1.63 (m, 1 H, CH), 1.51–1.41 (m, 1 H, CH_2) 1.30 (d, *J* = 6.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.1 (C_q, CO) 140.6 (C_q, Ph), 128.6 (2 CH, Ph), 127.5 (CH, Ph), 127.1 (2 CH, Ph), 64.0 (CH), 55.6 (CH), 42.7 (CH_2), 42.0 (CH_3), 37.3 (CH), 33.6 (CH_2), 26.4 (CH_2), 20.3 (CH_3) ppm. HPLC (Chiralcel OJ-H, hexane/*i*PrOH = 85:15, 0.6 mL min^{-1}, 211 nm): t_R = 30.3 (major), 25.6 (minor) min. IR (ATR): $\tilde{\nu}$ = 3332 (w, NH), 1697 (s, CO), 1316 (s, SO_2), 1154 (s, SO_2) cm^{-1}. $C_{15}H_{21}NO_3S$ (295.4): calcd. C 60.99, H 7.17, N 4.74; found C 60.84, H 7.07, N 4.63.

(*R*,*R*,*R*)-3b: White solid. M.p. 151–153 °C (hexane). $[\alpha]_D$ = +48.8 (c 0.31, $CHCl_3$, 62%*ee*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.43 (m, 2 H, Ph), 7.38–7.29 (m, 3 H, Ph), 6.45 (d, *J* = 10.2 Hz, 1 H, NH), 4.75 (dd, *J* = 10.2, 5.2 Hz, 1 H, CH-NH), 2.71 (dd, *J* = 10.5, 5.2 Hz, 1 H, CH-CO), 2.45 (s, 3 H, SO_2-CH_3), 2.43–2.22 (m, 2 H, CH_2), 2.00–1.89 (m, 1 H, CH_2), 1.87–1.77 (m, 1 H, CH_2), 1.54–1.42 (m, 3 H, 2 CH_2), 1.15 (d, *J* = 5.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.0 (C_q, CO), 138.3 (C_q, Ph), 129.0 (2 CH, Ph), 128.9 (2 CH, Ph), 128.2 (CH, Ph), 61.9 (CH), 57.4 (CH), 42.1 (CH_2), 41.7 (CH_3), 35.0 (CH), 33.2 (CH_2), 24.0 (CH_2), 20.3 (CH_3) ppm. HPLC (Chiralpak AD-H, hexane/*i*PrOH = 85:15, 0.6 mL min^{-1}, 211 nm): t_R = 26.1 (major), 21.4 (minor) min. IR (ATR): $\tilde{\nu}$ = 3286 (w, NH), 1702 (s, CO), 1322 (s, SO_2), 1158 (s, SO_2) cm^{-1}. $C_{15}H_{21}NO_3S$ (295.4): calcd. C 60.99, H 7.17, N 4.74; found C 61.14, H 7.14, N 4.66.

***N*-[(2-Methyl-6-oxocyclohexyl)(phenyl)methyl]-*P*,*P*-diphenylphosphinic Amide (3f)**

(*R*,*R*,*S*)-3f: White solid. M.p. 184–186 °C (hexane). $[\alpha]_D$ = 0.08 (*c* = 0.34, $CHCl_3$, 96%*ee*). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.90–7.81 (m, 2 H, Ph), 7.69–7.60 (m, 2 H, Ph), 7.52–7.47 (m, 1 H, Ph), 7.46–7.41 (m, 2 H, Ph), 7.38–7.33 (m, 1 H, Ph), 7.30–7.27 (m, 4 H, Ph), 7.24–7.18 (m, 3 H, Ph), 4.76 (t, *J* = 11.3 Hz, 1 H, NH), 4.45 (dt, *J* = 11.3, 4.3 Hz, 1 H, CH-NH), 2.43 (ddd, *J* = 9.1, 4.3, 0.8 Hz, 1 H, CH-CO), 2.41–2.36 (m, 1 H, CH_2), 2.36–2.29 (m, 1 H, CH_2), 2.23 (m, 1 H, CH_2), 2.02–1.92 (m, 2 H, CH_2), 1.84–1.73 (m, 1 H, CH_2), 1.49–1.37 (m, 1 H, CH_2), 1.10 (d, *J* = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 213.9 (CO) 143.4 (d, *J* = 4.5 Hz, C_qPh), 133.4 (d, *J* = 130 Hz, C_qPh), 132.5 (d, *J* = 9.7 Hz, 2 CHPh), 131.7 (d, *J* = 130 Hz, C_qPh),131.7 (overlapped d, 2 CH with s, CHPh) 131.5 (d, *J* = 2.8 Hz, CHPh), 128.4 (d, *J* = 12.5 Hz, 2 CHPh), 128.1 (overlapped d, 2 CH with s, CHPh) 126.9 (s, 2 CHPh), 126.7 (s, CHPh), 64.6 (d, *J* = 2.8 Hz, CH), 53.5 (CH), 42.5 (CH_2), 36.1 (CH), 32.5 (CH_2), 25.5 (CH_2), 20.6 (CH_3) ppm. ^{31}P NMR (242.8 MHz, $CDCl_3$): δ = 21.6 ppm. IR (ATR): $\tilde{\nu}$ = 3146 (w, NH), 1705 (s, CO), 1186 (s, PO) cm^{-1}. HPLC (Chiralcel OD-H, hexane/*i*PrOH = 93:7, 0.7 mL min^{-1}, 211 nm) t_R = 14.8 (major), 18.8 (minor) min. $C_{26}H_{28}NO_2P$ (417.5): calcd. C 74.80, H 6.76, N 3.36; found C 74.59, H 6.82, N 3.10.

(*R*,*R*,*R*)-3f: White solid. M.p. 189–191 °C (hexane). $[\alpha]_D$ = 0.58 (*c* = 0.34, $CHCl_3$, 96%*ee*). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.83–7.77 (m, 2 H, Ph), 7.73–7.66 (m, 2 H, Ph), 7.51–7.36 (m, 4 H, Ph), 7.30 (m, 2 H, Ph), 7.24 (s, 5 H, Ph), 5.13 (t, *J* = 10.7 Hz, 1 H, NH), 4.41 (dt, *J* = 11.6, 5.1 Hz, 1 H, CH-NH), 2.87 (dd, *J* = 10.7, 5.1 Hz, 1 H, CH-CO), 2.31–2.29 (m, 2 H, CH_2), 1.93–1.84 (m, 1 H, CH), 1.79–1.72 (m, 1 H, CH_2), 1.69–1.36 (m, 3 H, 2 CH_2), 1.01 (d, *J* = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 213.7 (CO), 140.6 (d, *J* = 6.6 Hz, C_qPh), 133.3 (d, *J* = 126.4 Hz, C_qPh), 132.7 (d, *J* = 9.5 Hz, 2 CHPh), 132.4 (d, C_qPh), 131.7 (d, *J* = 2.4 Hz, 2 CHPh), 131.6 (d, *J* = 2.4 Hz, 2 CHPh), 131.5 (d, *J* = 9.5 Hz, 2 CHPh), 128.7 (s, CHPh), 128.4 (d, *J* = 12.5 Hz, 2 CHPh), 128.22 (d, *J* = 12.5 Hz, 2 CHPh), 128.20 (CHPh), 127.2 (CHPh), 63.2 (CH), 54.6 (CH), 42.4 (CH_2), 35.3 (CH), 33.1 (CH_2), 24.1 (CH_2), 20.1 (CH_3) ppm. ^{31}P NMR (242.8 MHz, $CDCl_3$): δ = 22.9 ppm. IR (ATR): $\tilde{\nu}$ = 3268 (w, NH), 1698 (s, CO), 1185 (s, PO) cm^{-1}. HPLC (Chiralcel OD-H, hexane/*i*PrOH = 93:7, 0.7 mL min^{-1}, 211 nm): t_R = 15.2 (major), 23.5 (minor) min. $C_{26}H_{28}NO_2P$ (417.5): calcd. C 74.80, H 6.76, N 3.36; found C 74.78, H 6.75, N 3.40.

Computational Details: Quantum chemical calculations were performed with Spartan.[25] Guess structures of the transition states were optimized at the semiempirical level (PM3 or AM1) and then geometrical optimization with HF/3-21G was performed. These structures were further refined with HF/6-31G* calculations.[26]

Supporting Information (see footnote on the first page of this article): Characterization data for all new compounds, copies of the NMR spectra and HPLC chromatograms, and additional discussion of calculated geometries of transition states.

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