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Rational Design of New Dihydrobenzooxophosphole-Based Lewis Base Organocatalysts

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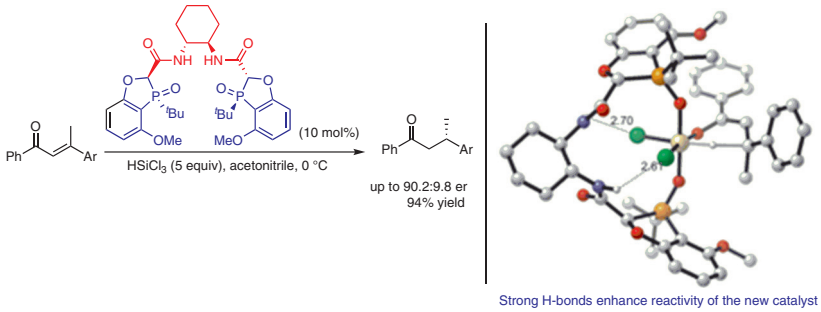

Strong H-bonds enhance reactivity of the new catalyst

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Abstract A series of new dihydrobenzooxophosphole-based Lewis base organocatalysts were designed and synthesized. They are shown to be effective in trichlorosilane-mediated stereoselective conjugate reductions of C=C bonds. DFT calculations reveal that the strong hydrogen bonds between the amide linker and the chloride on silicon in the transition state contribute to the high reactivity of the catalyst.

Key words chiral Lewis base, organocatalyst, enone reduction, hydrogen bonds

Chiral Lewis base catalysts have emerged as powerful organocatalysts in the past decade for the construction of C–C or C–X bonds.[2] Among them, phosphine oxide-containing Lewis base catalysts (Figure 1) have been applied extensively in a number of enantioselective transformations including Mukaiyama aldol and double aldol reactions,[3] trichlorosilane-mediated stereoselective reductions of C=N and C=C bonds,[4] bromoaminocyclization,[5] enantioselective allylation[6] and epoxide ring-opening reactions.[7]

The availability of diversified phosphine ligand libraries has enabled successful application of metal-catalyzed reactions on industrial scales. With increasing attention on developing organocatalyst-catalyzed asymmetric synthesis, the advancement of novel efficient catalyst systems remains an attractive endeavor. Recently, we reported a series of tunable *P*-stereogenic dihydrobenzooxophosphole-based bisphosphine ligands BIBOPs that are highly effective in a number of asymmetric transformations.[8] We reasoned that the corresponding bis-phosphine oxide BIBOPOs might be applicable as Lewis base organocatalysts. The conjugate reduction of (*E*)-1,3-diphenylbutenone (**1a**) in the presence of trichlorosilane[4] was selected as a model transformation to evaluate the effectiveness of such catalysts (Scheme 1). However, when BIBOPO was applied in the test reaction, only trace amount of product **2a** was observed (Scheme 1a). We rationalized that an increased coordinating angle of the Si atom to bis P=O might be required to accommodate the substrate coordination (Scheme 1b). C_2-Symmetric tetradentate bisphosphine/diamine (PNNP) ligands with NH-functionality have been reported as highly efficient catalyst systems for asymmetric hydrogenation/transfer hydrogenation of ketones[9] and other enantioselective reactions.[10] We therefore decided to apply the versatile features of a diamine linker and prepare new P(O)NNP(O)-based organocatalysts. We hypothesized that such a linker would not only increase the bite angle, but also lead to potential hydrogen bonding of $HSiCl_3$ with the hydrogen atoms on diamine.

The proposed catalysts were synthesized by coupling of the corresponding carboxylic acid[11] with diamines in the presence of propylphosphonic anhydride (T_3P) in aceton-

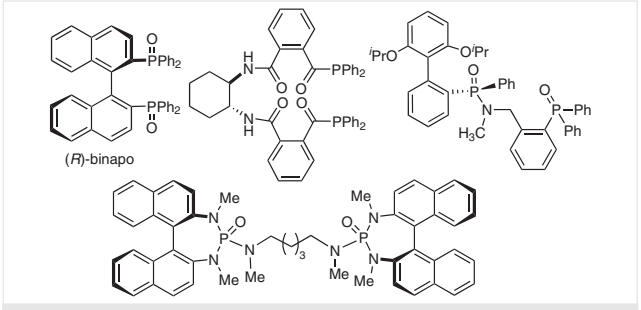

Figure 1 Selected P=O containing Lewis base organocatalysts

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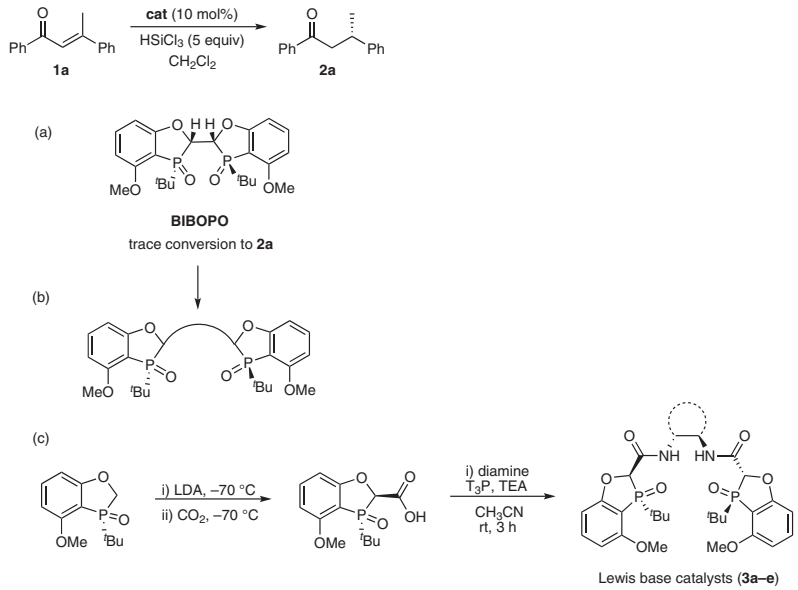
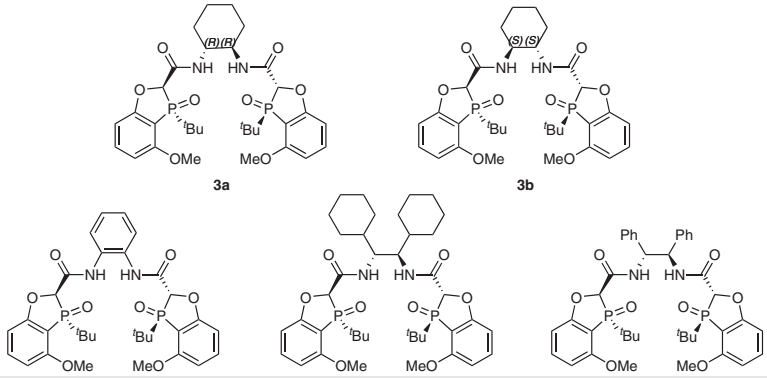


entry	catalyst	Conversion (%)	er
1	**3a**	90	82.5:17.5
2	**3a**[a]	100	89.6:10.4
3	**3b**[a]	49	67.8:32.2
4	**3c**[a]	10	69.0:31.0
5	**3d**[a]	100	87.5:12.5
6	**3e**[a]	100	73.8:26.2



Scheme 1 Conjugate reduction of **1a** with P(O)NNP(O) Lewis base catalysts. *Reagents and conditions*: **1a** (0.27 mmol), $HSiCl_3$ (1.35 mmol), catalyst (0.027 mmol) in CH_2Cl_2 at 0 °C for 20 h unless specified otherwise. Conversion of **1a** into **2a**, and enantioselectivity were analyzed on SFC at 220 nm UV wavelength with a chiral stationary phase. (a) Application of BIBOPO catalyst; (b) rational design of new catalysts; (c) synthesis and evaluation of the new catalysts. [a] Reaction was run in acetonitrile.

trile (Scheme 1c).[12] In each case, only one diastereomer product was obtained under the coupling conditions, without any racemization. We first synthesized the bis-amide catalyst **3a**, featuring a (*R*,*R*)-diaminocyclohexane linker. Pleasingly, (*S*)-1,3-diphenylbutan-1-one (**2a**)[13] was furnished in 90% conversion and an 82.5:17.5 enantiomeric ratio in CH_2Cl_2 (entry 1). Several environmentally friendly solvents were tested, and acetonitrile was found to provide the highest selectivity (89.6:10.4 er; entry 2). Interestingly, the corresponding diastereomeric (*S*,*S*)-diaminocyclohexyl-containing catalyst **3b** provided incomplete conversion and 67.8:32.2 er, indicating that the conformation of the bis-amide linker is integral to both turnover and selectivity. When the rigidity of the catalyst backbone linker was increased with phenyl diamine, however, low reactivity and selectivity were observed for catalyst **3c**. On the other hand, the (*R*,*R*)-1,2-dicyclohexyl ethylene diamine-containing catalyst **3d** provided the product **2a** with 100% conversion

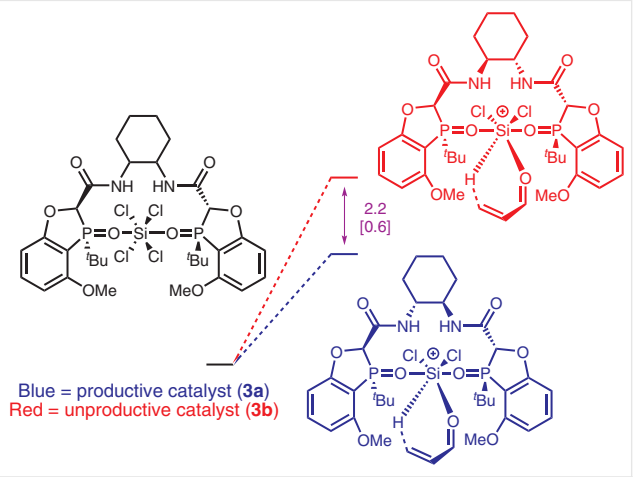
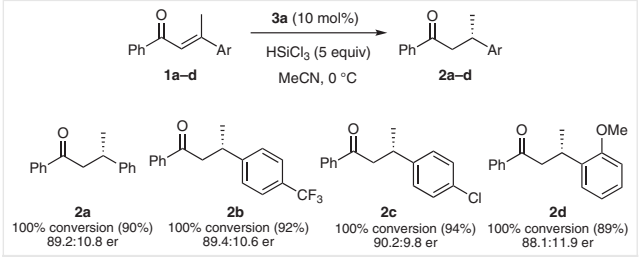


Figure 2 Relative activation energies of the reduction of the simplified enone by both diastereomeric catalysts **3a** (blue) and **3b** (red). Computed at B3LYP/6-31G(d) level. Free energy values are reported in kcal/mol, and enthalpies are given in brackets. Acrolein was used as a model for the enone.



Scheme 2 Conjugate 1,4-enone reduction using organocatalyst **3a**. *Reagents and conditions*: enone **1** (0.27 mmol), $HSiCl_3$ (1.35 mmol), catalyst **3a** (0.027 mmol) in acetonitrile at 0 °C for 20 h; the yields in parenthesis are isolated yields after silica gel purification.

and 87.5:12.5 er. When the bis-cyclohexyl group was replaced with a bis-phenyl group in catalyst **3f**, the same reactivity of 100% conversion was achieved, but diminished enantioselectivity of 74:26 er was observed.

We initiated a DFT study with Gaussian 16[14] at the B3LYP/6-31G(d) level[15] to understand the origin of the catalyst reactivity in these reductions. According to the proposed mechanism,[16] the stereodetermining step involves a 1,4-addition of a silicon hydride to the enone via a six-membered transition state. In this transition state, the cationic silicon coordinates to the carbonyl oxygen, geometrically placing the silicon hydride near the β-carbon of the enone. Upon reduction, the enolate remains coordinated to the cationic silicon. Possible transition states differ in the position of the hydride on the catalyst, the position of the enone on the catalyst, the orientation of the hydride relative to the enone, and the geometry of the enone (since it can undergo isomerization under the reaction conditions). Detailed conformational analyses of these transition states were undertaken to identify the relevant lowest energy transition states for the different catalysts.

Amongst the catalysts screened, there was a notable difference in behavior of the diastereomeric compounds obtained from the two enantiomers of cyclohexane diamine (matched **3a**, mismatched **3b**). To assess the reactivity of these diastereomeric catalysts, the activation energies for hydride transfer in the respective systems were analyzed. Calculations showed that a higher activation energy is required for the reduction of the enone using the (*S*,*S*)-isomer of the catalyst **3b** by 2.2 kcal/mol, which is consistent with the observed reactivity (Figure 2).

As projected, both catalysts form hydrogen bonds between the amide linker and the chlorine ligands of the silicon in the transition state. The productive catalyst **3a** forms stronger hydrogen bonds than the unproductive catalyst **3b**, as determined by bond lengths (Figure 3). These hydrogen bonds would be expected to enhance the Lewis acidity of the silicon center and thereby enhance reactivity. It thus appears that the mismatched catalyst, **3b**, must engage in greater deformation (i.e., is more strained) to achieve such

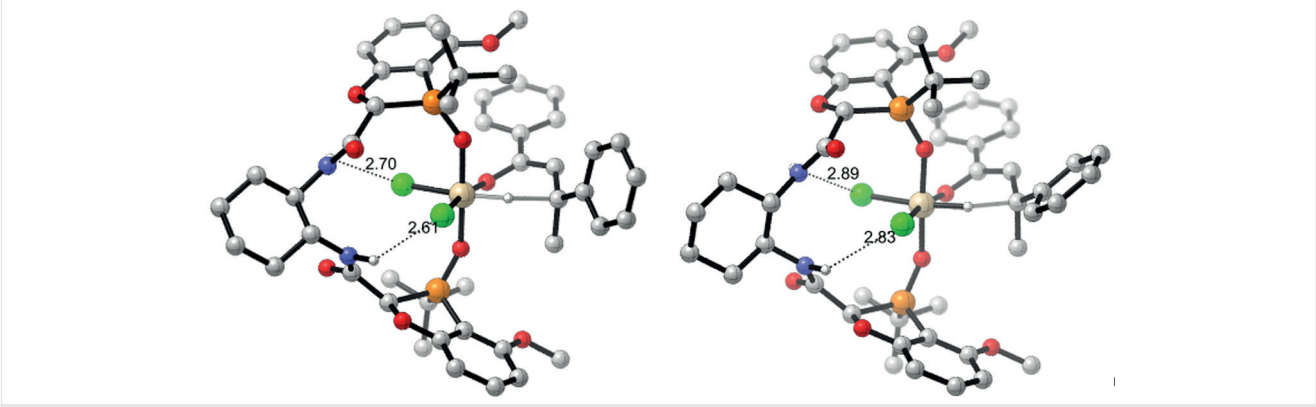


Figure 3 CYL view of the transition-state structures with productive (**3a**, left) and unproductive (**3b**, right) diastereomeric catalysts. Hydrogen bonds between the amide linker and chlorine atoms are indicated with dashed lines, distances are given in Angstroms.

hydrogen bonds, which are also weaker, causing less activation. Together, these factors account for the much lower reactivity of **3b** (49% conversion) relative to **3a** (100% conversion).

The conjugate reduction conditions with catalyst **3a** are compatible with (*E*)-1,3-diphenylbutenones bearing both electron-rich and electron-poor functional groups and give similar enantioselectivity (**2a–d**) in acetonitrile (Scheme 2).

In conclusion, we have developed new Lewis base organocatalysts derived from a *P*-stereogenic dihydrobenzooxophosphole core structure by coupling with (*R*,*R*)-dicyclohexyl ethylene diamine, which provides a conformational match for the enantioselective reduction of enone derivatives mediated with $HSiCl_3$. The asymmetric transformation is effected by the *P*-stereogenic center and the selectivity is tunable by the substituents on the catalyst. This class of catalysts has potential as tunable Lewis base catalysts in terms of reactivity and selectivity. Further work to identify catalysts that are more efficient is ongoing, and such tuning will be reported in due course.

Funding Information

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Supporting Information

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(12) **General procedure for catalyst preparation**: To a solution of carboxylic acid phosphine oxide (5.0 g, 17.6 mmol, 2.2 equiv), diamine (8.0 mmol, 1 equiv) and triethylamine (32.0 mmol, 4 equiv) in acetonitrile at room temperature was added propylphosphonic anhydride (T_3P) solution in DMF (16.0 mmol, 2 equiv) in portions over 3 h. The reaction was stopped after complete consumption of the carboxylic acid. The mixture was then treated with 50% aqueous NaOH (10 mL) and stirred at 35 °C for 3 h. The suspension was diluted with water and the resulting clear solution was extracted three times with EtOAc. The combined organic layer was washed with brine, dried with $MgSO_4$ and concentrated, and the crude mixture was purified by chromatography on silica (100% EtOAc to 10% MeOH/EtOAc) to obtain a white solid after drying.
(2*R*,2′*R*,3*S*,3′*S*)-*N*,*N*′-((1*R*,2*R*)-cyclohexane-1,2-diyl)bis(3-(*tert*-butyl)-4-methoxy-2*H*-benzo[*d*][1,3]oxaphosphole-2-carboxamide 3-oxide) (3a): Yield: 3.67 g (71%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46 (t, *J* = 8.23 Hz, 2 H), 6.80 (br d, *J* = 6.70 Hz, 2 H), 6.71 (dd, *J* = 8.3, 2.8 Hz, 2 H), 6.54 (dd, *J* = 8.2, 4.4 Hz, 2 H), 4.93 (s, 2 H), 3.88 (s, 6 H), 3.80 (br s, 2 H), 2.11 (br d, *J* = 7.3 Hz, 2 H), 1.65 (br s, 2 H), 1.37 (d, *J* = 17.0 Hz, 18 H), 1.25–1.23 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.2 (d, *J* = 2.7 Hz), 164.5 (d, *J* = 14.2 Hz), 161.1 (d, *J* = 2.4 Hz), 136.9 (d, *J* = 0.87 Hz), 106.6 (d, *J* = 5.3 Hz), 104.1 (d, *J* = 5.7 Hz), 102.70 (d, *J* = 90.8 Hz), 75.4 (d, *J* = 48.4 Hz), 55.6, 53.7, 34.07 (d, *J* = 74.5 Hz), 32.4, 25.1 (d, *J* = 0.96 Hz), 24.5. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 62.83. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{45}O_8N_2P_2$: 647.26457; found: 647.26495.
(2*R*,2′*R*,3*S*,3′*S*)-*N*,*N*′-((1*S*,2*S*)-cyclohexane-1,2-diyl)bis(3-(*tert*-butyl)-4-methoxy-2*H*-benzo[*d*][1,3]oxaphosphole-2-carboxamide 3-oxide) (3b): Yield: 3.36 g (65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (t, *J* = 8.2 Hz, 2 H), 6.86 (br d, *J* = 6.0 Hz, 2 H), 6.62 (dd, *J* = 8.2, 3.0 Hz, 2 H), 6.50 (dd, *J* = 8.1, 4.4 Hz, 2 H), 5.22 (s, 2 H), 3.80 (s, 6 H), 3.73 (br s, 2 H), 2.12 (br d, *J* = 6.6 Hz, 2 H), 1.69 (br s, 2 H), 1.31–1.26 (overlapping d, *J* = 17.0 Hz, and m, 22 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7 (d, *J* = 2.0 Hz), 165.3 (d, *J* = 15.3 Hz), 161.3 (d, *J* = 2.1 Hz), 136.8, 106.4 (d, *J* = 5.4 Hz), 103.8 (d, *J* = 5.8 Hz), 101.6 (d, *J* = 91.6 Hz), 74.6 (d, *J* = 48.3 Hz), 55.6, 53.5, 34.3 (d, *J* = 74.0 Hz), 32.2, 24.6, 24.5. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 62.36. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{45}O_8N_2P_2$: 647.26457; found: 647.26433.
(2*R*,2′*R*,3*S*,3′*S*)-*N*,*N*′-(1,2-phenylene)bis(3-(*tert*-butyl)-4-methoxy-2*H*-benzo[*d*][1,3]oxaphosphole-2-carboxamide 3-oxide) (3c): Yield: 3.07 g (60%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65 (s, 2 H), 7.54 (m, 2 H), 7.44 (t, *J* = 8.2 Hz, 2 H), 7.16 (m, 2 H), 6.68 (dd, *J* = 8.3, 2.8 Hz, 2 H), 6.54 (dd, *J* = 8.2, 4.4 Hz, 2 H),

5.33 (s, 2 H), 3.86 (s, 6 H), 1.34 (d, *J* = 17.1 Hz, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.2 (d, *J* = 14.9 Hz), 164.5 (d, *J* = 2.6 Hz), 161.3 (d,*J* = 2.2 Hz), 137.0, 129.9, 126.7, 126.2, 106.5 (d, *J* = 5.4 Hz), 104.1 (d, *J* = 5.8 Hz), 102.0 (d, *J* = 91.6 Hz), 75.5 (d, *J* = 47.5 Hz), 55.7, 34.4 (d, *J* = 73.8 Hz), 24.7. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 63.9. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{39}O_8N_2P_2$: 641.21762; found: 641.21767.

(2*R*,2′*R*,3*S*,3′*S*)-*N*,*N*′-((1*R*,2*R*)-1,2-dicyclohexylethane-1,2-diyl)bis(3-(*tert*-butyl)-4-methoxy-2*H*-benzo[*d*][1,3]oxaphosphole-2-carboxamide 3-oxide) (3d): Yield: 3.03 g (50%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (t, *J* = 8.2 Hz, 2 H), 6.72–6.68 (overlapping s and dd, *J* = 8.2, 3.0 Hz, 4 H), 6.54 (dd, *J* = 8.1, 4.3 Hz, 2 H), 4.92 (d, *J* = 0.48 Hz, 2 H), 4.06–4.00 (m, 6 H), 3.88 (s, 6 H), 1.74–1.67 (m, 9 H), 1.54–1.34 (overlapping d, *J* = 17.0 Hz, and m, 24 H), 1.22–1.02 (m, 10 H), 0.9–0.81 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1 (d, *J* = 2.3 Hz), 164.4 (d, *J* = 13.9 Hz), 161.1 (d, *J* = 2.1 Hz), 136.7, 106.5 (d, *J* = 5.2 Hz), 104.1 (d, *J* = 5.7 Hz), 103.1 (d, *J* = 90.5 Hz), 75.6 (d, *J* = 48.9 Hz), 55.6, 54.7, 38.9, 34.1 (d, *J* = 74.4 Hz), 30.5, 27.3, 26.2, 26.16, 26.11, 25.2. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 61.64. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{40}H_{59}O_8N_2P_2$: 757.37412; found: 757.37417.

(2*R*,2′*R*,3*S*,3′*S*)-*N*,*N*′-((1*R*,2*R*)-1,2-diphenylethane-1,2-diyl)bis(3-(*tert*-butyl)-4-methoxy-2*H*-benzo[*d*][1,3]oxaphosphole-2-carboxamide 3-oxide) (3e): Yield: 2.98 g (50%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52 (br d, *J* = 2.8 Hz, 2 H), 7.43 (t, *J* = 8.2 Hz, 2 H), 7.11–7.06 (m, 10 H), 6.70 (dd, *J* = 8.3, 2.5 Hz, 2 H), 6.50 (dd, *J* = 8.1, 4.3 Hz, 2 H), 5.40–5.38 (m, 2 H), 5.00 (s, 2 H), 3.85 (s, 6 H), 1.35 (d, *J* = 16.9 Hz, 18 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5 (d, *J* = 2.4 Hz), 164.5 (d, *J* = 14.1 Hz), 161.1 (d, *J* = 2.3 Hz), 137.7, 136.8, 128.5, 127.74, 127.69, 106.5 (d, *J* = 5.3 Hz), 104.0 (d, *J* = 5.8 Hz), 102.7 (d, *J* = 91.1 Hz), 75.3 (d, *J* = 48.8 Hz), 59.1, 55.6, 34.1 (d, *J* = 74.5 Hz), 25.1 (d, *J* = 0.8 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ = 62.13. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{40}H_{47}O_8N_2P_2$: 745.28022; found: 745.28012.

General procedure for enone reduction: To a stirring solution of **1a** (60 mg, 0.27 mmol) and catalyst **3a** (0.027 mmol, 10 mol%) in acetonitrile (2 mL) at 0 °C was added $HSiCl_3$ (1.35 mmol, 5 equiv) dropwise, and the mixture was stirred at 0 °C for 20 h. The reaction was then quenched with a solution of 5N aqueous NaOH (2 mL), and the mixture was warmed to room temperature then diluted with EtOAc and water. The phases were separated, and the aqueous phase was further extracted once with EtOAc. The combined organic layers were washed with water followed by brine, dried with Na_2SO_4 and concentrated. The product was purified on silica with a mixture of hexanes/EtOAc (10:1) to obtain a colorless oil after drying.

(*S*)-1,3-Diphenylbutan-1-one (2a): Yield: 90%; 89.2:10.8 er; SFC (ES Industries CCA column 4.6 × 100 mm, 3 µm: 35 °C, A: CO_2, B: isopropanol; gradient: 1% B to 3% B in 3 min, to 50% B in 5 min; 3 mL/min, λ = 220 nm): t_R = 2.50 (major), 2.80 (minor) min. NMR data match those reported in the literature.[17] ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.9 Hz, 2 H), 7.57 (t, *J* = 7.3 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 2 H), 7.35–7.21 (m, 4 H), 7.35–7.28 (m, 2 H), 7.23 (t, *J* = 6.8 Hz, 1 H), 3.54 (sextet, *J* = 6.9 Hz, 1 H), 3.33 (dd, *J* = 16.5, 5.7 Hz, 1 H), 3.22 (dd, *J* = 16.5, 8.3 Hz, 1 H), 1.37 (d, *J*= 6.9 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.1, 146.6, 137.2, 133.0, 128.6, 128.5, 128.1, 126.9, 126.3, 47.0, 35.6, 21.9.

(*S*)-1-Phenyl-3-(4-(trifluoromethyl)phenyl)butan-1-one (2b): Yield: 92%; 89.4:10.6 er; SFC (ES Industries CCA column 4.6 × 100 mm, 3 µm: 35 °C, A: CO_2, B: isopropanol; gradient: 1% B to 3% B in 3 min, to 50% B in 5 min; 3 mL/min, λ = 220 nm): t_R = 1.69 (major), 1.91 (minor) min. NMR data match those reported in the literature.[18] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97–7.92 (m, 2 H), 7.60–7.56 (m, 3 H), 7.50–7.45 (m, 2 H), 7.41 (d, *J* = 8.3 Hz, 2 H), 3.69 (sextet, *J* = 6.9 Hz, 1 H), 3.35 (dd, *J* = 16.8, 6.4 Hz), 3.25 (dd, *J* = 16.9, 7.5 Hz, 1 H), 1.39 (d, *J* = 7.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.4, 150.6, 137.0, 133.2, 128.6, 128.0, 127.3, 125.5 (q, *J* = 3.8 Hz), 46.5, 35.3, 21.9.

(*S*)-3-(4-Chlorophenyl)-1-phenylbutan-1-one (2c): Yield: 94%; 90.2:9.8 er; SFC (ES Industries CCA column 4.6 × 100 mm, 3 µm: 35 °C, A: CO_2, B: methanol; gradient: 1% B to 3% B in 3 min, to 50% B in 5 min; 3 mL/min, λ = 220 nm): t_R = 2.93 (major), 3.51 (minor) min. NMR data match those reported in the literature.[18] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.92 (m, 2 H), 7.60–7.56 (m, 1 H), 7.50–7.45 (m, 2 H), 7.30–7.27 (m, 2 H), 7.25–7.21 (m, 2 H), 3.52 (sextet, *J* = 6.9 Hz, 1 H), 3.29 (dd, *J* = 16.7, 6.3 Hz), 3.2 (dd, *J* = 16.7, 7.7 Hz, 1 H), 1.35 (d, *J*= 7.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.7, 145.0, 137.1, 133.1, 131.9, 128.6, 128.3, 128.0, 46.8, 35.0, 22.0.

(*S*)-3-(2-Methoxyphenyl)-1-phenylbutan-1-one (2d): Yield: 89%; 88.1:11.9 er; SFC (Lux Cel 1 column 4.6 × 100 mm, 3 µm: 35 °C, A: CO_2, B: methanol; gradient: 1% B to 3% B in 3 min, to 50% B in 5 min; 3 mL/min, λ = 220 nm): t_R = 3.94 (major), 4.27 (minor) min. NMR data match those reported in the literature.[19] ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 7.8 Hz, 2 H), 7.45 (t, *J* = 7.3 Hz, 1 H), 7.36 (t, *J* = 7.6 Hz, 2 H), 7.15 (d, *J* = 7.3 Hz, 1 H), 7.11 (t, *J* = 7.7 Hz, 1 H), 6.85 (t, *J* = 7.4 Hz, 1 H), 6.77 (d, *J* = 8.1 Hz, 1 H), 3.78–3.73 (m, 1 H), 3.73 (s, 3 H), 3.27 (dd, *J* = 15.8, 4.8 Hz, 1 H), 2.97 (dd, *J* = 15.7, 9.2 Hz, 1 H), 1.23 (d, *J* = 7.0 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.7, 156.9, 137.3, 134.5, 132.8, 128.5, 128.2, 127.2, 126.9, 120.7, 110.6, 55.3, 46.0, 29.6, 19.7.

(13) (S)-isomer was assigned by comparison to the reported data in ref. 4b.

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