Development of a new Lewis base-tolerant chiral LBA and its application as a catalyst to asymmetric protonation reaction

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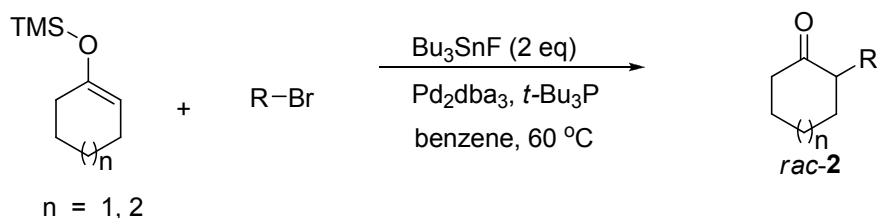
General Procedures:

All reactions were carried out in oven- or flame-dried glassware under an atmosphere of dry nitrogen unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin layer chromatography (TLC) using Whatman pre-coated silica gel flexible plates (0.25 mm) with F254 indicator or Merck pre-coated silica gel plates with F254 indicator. Visualization was accomplished by UV light (254 nm), with combination of potassium permanganate and/or phosphomolybdic acid solution as an indicator. Flash column chromatography was performed according to the method of Still using silica gel 60 (mesh 230-400) supplied by Silicycle. Yields refer to chromatographically and spectrographically pure compounds, unless otherwise noted.

Commercial grade reagents and solvents were used without further purification except as indicated below. Toluene (anhydrous, 99.8 %, 18 L in Pure-Pac[TM]), dichloromethane (anhydrous, 99.9%, 18L in Pure-Pac[TM]), hexanes (anhydrous, 99.9%, 18L in Pure-Pac[TM]), and THF (anhydrous, 99.9%, 18L in Pure-Pac[TM]) purchased from Aldrich were purified by M. BRAUN solvent purification system (A2 Alumina).

^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were recorded on a Bruker Avance 500 (500 MHz ^{1}H, 125 MHz ^{13}C, 202 MHz ^{31}P). Tetramethylsilane was used as an internal standard for ^{1}H NMR (δ: 0.0 ppm), CDCl$_3$ and H$_3$PO$_4$ for ^{13}C NMR (δ: 77.0 ppm) and ^{31}P NMR (δ: 0.0 ppm) as external standards, respectively. The proton spectra are reported as follows δ (position of proton, multiplicity, coupling constant J, number of protons). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (septet), m (multiplet) and br (broad). High-performance liquid chromatography (HPLC) was performed on a Varian ProStar Series equipped with a variable wavelength detector using chiral stationary columns (0.46 cm x 25 cm) from Daicel. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter.

1. Synthesis of racemic 2-aryl substituted cyclic ketones (*rac*-2a-i)

All α-aryl cyclic ketones were prepared by α-arylation of trimethylsilyl (TMS) enol ethers with aryl halides, except commercially available *rac*-2a and *rac*-2h.[1]


General Procedure: To a solution of TMS enol ether of cyclic ketone (20 mmol), Pd$_2$(dba)$_3$ (0.23 g, 0.25 mmol), and Bu$_3$SnF (6.18 g, 20 mmol) under nitrogen was added a solution of ^{t}Bu$_3$P (1.0 M, 0.6 mL) in benzene (40 mL) at room temperature. The resultant mixture was heated to reflux for 24 h. After cooling to room temperature, the reaction mixture was diluted with ether (200 mL) (when tin residue precipitated, it was removed by decantation with ether), washed with 1 *N*

aqueous NaOH twice, followed by brine (50 mL x 2), dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc, 10/1) on silica gel.
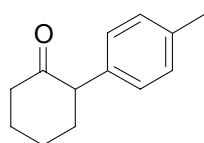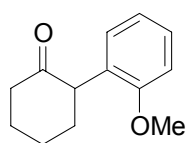
2-(4-Methylphenyl)cyclohexanone (*rac*-**2b**) was obtained as a white solid (1.34 g, 72 % yield) and ^{1}H NMR was in agreement with the literature.[2] ^{1}H NMR (CDCl₃, 500 MHz) δ: 1.78-1.84 (m, 2H), 1.95-2.05 (m, 2H), 2.12-2.17 (m, 1H), 2.22-2.27 (m, 1H), 2.22 (s, 3H), 2.39-2.56 (m, 2H), 3.56 (dd, *J* = 5.4, 12.0 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H).
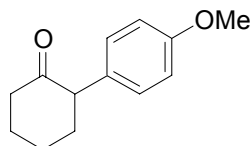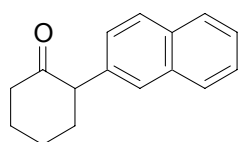
2-(4-Methoxyphenyl)cyclohexanone (*rac*-**2c**) was obtained as a white solid (1.34 g, 72 % yield) and ^{1}H NMR was in agreement with the literature.[1,2] ^{1}H NMR (CDCl₃, 500 MHz) δ: 1.75-1.85 (m, 2H), 1.94-2.02 (m, 2H), 2.10-2.15 (m, 1H), 2.22-2.26 (m, 1H), 2.49-2.53 (m, 2H), 3.56 (dd, *J* = 5.5, 12.5 Hz, 1H), 3.78 (s, 3H), 6.87 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 8.5 Hz, 2H).
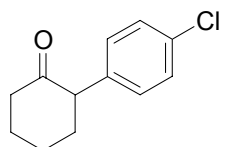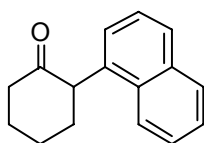
2-(4-Chlorophenyl)cyclohexanone (*rac*-**2d**) was obtained as a white solid (1.29 g, 62 % yield), and ^{1}H NMR was in agreement with the literature.[2] ^{1}H NMR (CDCl₃, 500 MHz) δ: 1.79-1.91 (m, 2H), 1.95-2.02 (m, 2H), 2.15-2.28 (m, 2H), 2.41-2.54 (m, 2H), 3.59 (dd, *J* = 5.4, 12.4 Hz, 1H), 7.07 (d, *J* = 9.0 Hz, 2H), 7.30 (d, *J* = 9.0 Hz, 2H).

2-(2-Methoxyphenyl)cyclohexanone (*rac*-**2e**) was obtained as oil (1.02 g, 50 %) and ^{1}H NMR was in agreement with the literature.[1,2] ^{1}H NMR (CDCl₃, 500 MHz) δ: 1.73-1.84 (m, 2H), 1.98-2.05 (m, 2H), 2.13-2.21 (m, 2H), 2.44-2.53 (m, 2H), 3.78 (s, 3H), 3.94 (dd, *J* = 5.5, 12.5 Hz, 1H), 6.88 (d, *J* = 8 Hz, 1H), 6.96 (t, *J* = 8 Hz, 1H), 7,12 (d, *J* = 8 Hz, 1H), 7.24 (t, *J* = 8 Hz, 1H).

2-(2-naphthyl)cyclohexanone (*rac*-**2f**) was obtained as a white solid (1.54 g, 70 % yield) and ^{1}H NMR was in agreement with the literature.[2] ^{1}H NMR (CDCl₃, 500 MHz) δ: 1.81-1.91 (m, 2H), 2.00-2.07 (m,1H), 2.12-2.21 (m, 2H), 2.31-2.36 (m, 1H), 2.46-2.58 (m, 2H), 3.77 (dd, *J* = 5.6, 12.2 Hz, 1H), 7.27 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.41-7.46 (m, 2H), 7.60 (s, 1H), 7.77-7.83 (m, 3H).

2-(1-naphthyl)cyclohexanone (*rac*-**2g**) was obtained as a white solid (1.54 g, 70 % yield) and ^{1}H NMR was in agreement with the literature.[3] ^{1}H NMR (CDCl₃, 500 MHz) δ: 1.89-1.97 (m, 2H), 2.10-2.15 (m, 1H), 2.24-2.31 (m, 2H), 2.39-2.44 (m, 1H), 2.61-2.69 (m, 2H), 4.33-4.37 (dd, *J* = 5.5, 12.5 Hz, 1H), 7.35-7.36 (d, *J* = 8.0 Hz, 1H), 7.43-7.48 (m, 3H), 7.70-7.72 (m, 1H), 7.77-7.79 (d, *J* = 8.0 Hz, 1H), 7.84-7.87 (m, 1H).
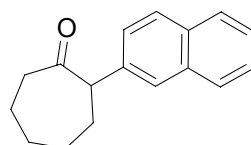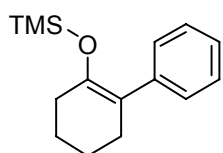
2-(2-Naphthyl)cyclohexanone (*rac*-**2i**) was obtained as oil (1.37 g, 57 %) and ^{1}H NMR was in agreement with the literature.[2] ^{1}H NMR (CDCl₃, 500 MHz,) δ: 1.49-1.53 (m, 2H), 1.66-1.73 (m, 1H), 1.99-2.15 (m, 4H), 2.20-2.23 (m, 1H), 2.55-2.58 (m, 1H), 2.72-2.78 (td, *J* = 12.8, 3.1 Hz, 1H), 3.88 (dd, *J* = 4.2, 11.4 Hz, 1H), 7.37 (dd, *J* = 1.7, 8.5 Hz, 1H), 7.42-7.48 (m, 2H), 7.67 (s, 1H), 7.79-7.81 (m, 3H).

2. Synthesis of silyl enol ethers of 2-substituted cyclic ketones (1a-i)

All silyl enol ethers of 2-aryl substituted cyclic ketones were synthesized by the following method.
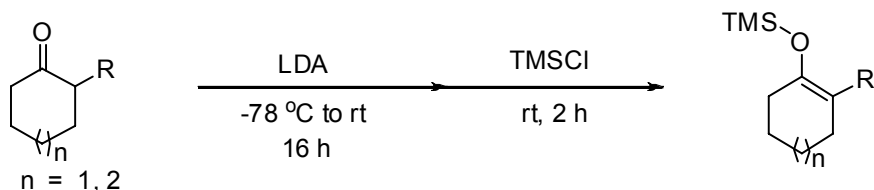

General procedure: To a solution of lithium diisopropylamide (LDA) (4.8 mmol) in THF was added 2-substituted cyclic ketone (5.0 mmol) at -78 °C. The reaction mixture was warmed up to room temperature and stirred for 16 h. After 16h, trimethylsilyl chloride (TMSCl) was added to the reaction mixture. The reaction mixture was allowed to stir for additional 2 h. After then, the reaction mixture was quenched with saturated aqueous NaHCO₃, extracted with ether, followed by brine, dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc, 20:1) on silica gel.
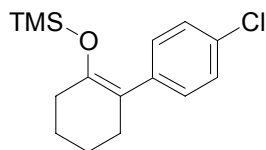
The silyl enol ether (**1a**) was obtained as oil (1.15 g, 93 %) and ^{1}H NMR was in agreement with the literature.[2] ^{1}H NMR (CDCl₃, 500 MHz) δ: -0.05 (s, 9H), 1.64-1.77 (m, 4H), 2.15-2.19 (m, 2H), 2.34-2.38 (m, 2H), 7.12-7.15 (m, 1H), 7.25-7.28 (m, 2H), 7.34-7.36 (dd, J = 1.3, 8.2 Hz, 2H).
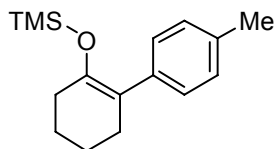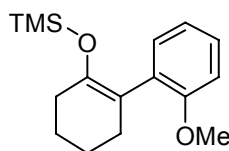
The silyl enol ether (**1b**) was obtained as oil (1.10 g, 84 %) and ^{1}H NMR was in agreement with the literature.[2] ^{1}H NMR (CDCl₃, 500 MHz) δ: -0.04 (s, 9H), 1.65-1.76 (m, 4H), 2.15-2.18 (m, 2H), 2.31 (s, 3H), 2.32-2.36 (m, 2H), 7.07-7.09 (d, J = 7.9 Hz, 2H), 7.25-7.26 (d, J = 7.9 Hz, 2H).
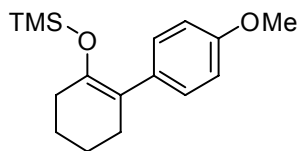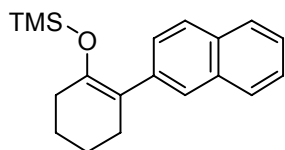
The silyl enol ether (**1c**) was obtained as oil (1.18 g, 85 %) and ^{1}H NMR was in agreement with the literature.[2] ^{1}H NMR (CDCl₃, 500 MHz) δ: -0.04 (s, 9H), 1.65-1.77 (m, 4H), 2.14-2.17 (m, 2H), 2.31-2.35 (m, 2H), 3.80 (s, 3H), 6.80-6.85 (d, J = 8.8 Hz, 2H), 7.28-7.31 (d, J = 8.8 Hz, 2H).

The silyl enol ether (**1d**) was obtained as oil (1.13 g, 80 %). ^{1}H NMR (CDCl₃, 500 MHz) δ: -0.02 (s, 9H), 1.67-1.75 (m,4H), 2.15-2.18 (m, 2H), 2.31-2.34 (m, 2H), 7.22-7.24 (d, J = 8.6 Hz, 2H), 7.30-7.32 (d, J = 8.6 Hz, 2H).

The silyl enol ether (**1e**) was obtained as oil (1.05 g, 76 %) and ^{1}H NMR was in agreement with the literature.[2] ^{1}H NMR (CDCl₃, 500 MHz)) δ: -0.12 (s, 9H), 1.64-1.68 (m, 2H), 1.74-1.79 (m, 2H), 2.13-2.16 (m, 2H), 2.26-2.28 (m, 2H), 3.78 (s, 3H), 6.84-6.90 (m, 2H), 7.11-7.19 (m, 2H).

The silyl enol ether (**1f**) was obtained as oil (1.24 g, 84 %) and ^{1}H NMR was in agreement with the literature.[2] ^{1}H NMR (CDCl₃, 500 MHz) δ: -0.06 (s, 9H), 1.72-1.82 (m, 4H), 2.21-2.24 (m, 2H), 2.47-2.49 (m, 2H), 7.38-7.43 (m, 2H), 7.57-7.59 (dd, J = 1.7, 8.5 Hz, 1H), 7.73-7.80 (m,

4H).

The silyl enol ether (**1g**) was obtained as oil (1.32 g, 89 %) and ^{1}H NMR was in agreement with the literature.[2] ^{1}H NMR (CDCl$_3$, 500 MHz) δ: -0.34 (s, 9H), 1.76-1.81 (m, 2H), 1.85-1.90 (m, 2H), 2.17-2.21 (m, 1H), 2.27-2.34 (m, 1H), 2.37-2.40 (m, 2H), 7.26-7.29 (d, J = 7.0 Hz, 1H), 7.41-7.48 (m, 3H), 7.70-7.72 (d, J = 8.0 Hz, 1H), 7.81-7.83 (m, 1H), 7.88-7.90 (m, 1H).
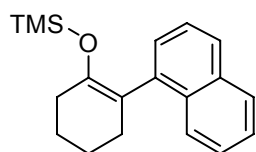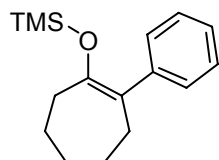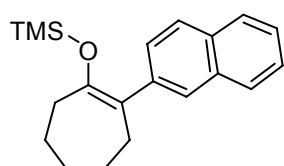
The silyl enol ether (**1h**) was obtained as oil (1.06 g, 81 %) and ^{1}H NMR was in agreement with the literature.[2] ^{1}H NMR (CDCl$_3$, 500 MHz) δ: -0.07 (s, 9H), 1.63-1.70 (m, 4H), 1.78-1.82 (m, 2H), 2.42-2.47 (m, 4H), 7.11-7.14 (t, , J = 7.2 Hz, 1H), 7.25-7.32 (m, 4H).
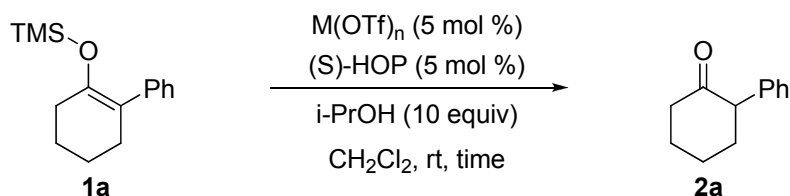
The silyl enol ether (**1i**) was obtained as a white solid (1.12 g, 72 %) and ^{1}H NMR was in agreement with the literature.[2] ^{1}H NMR (CDCl$_3$, 500 MHz) δ: -0.09 (s, 9H), 1.67-1.76 (m, 4H), 1.82-1.87 (m, 2H), 2.45-2.50 (m, 2H), 2.56-2.62 (m, 2H), 7.39-7.45 (m, 2H), 7.50-7.54 (d, J = 8.5 Hz, 1H), 7.68-7.82 (m, 4H).

3. Catalytic Asymmetric Protonation Reactions of Silyl Enol Ethers with Chiral LBA

3-1. Optimization of Reaction Conditions

1) Screening of M(OTf)$_n$

$$\text{M(OTf)}_n \text{ (5 mol \%)}$$
$$\text{(S)-HOP (5 mol \%)}$$
$$\text{i-PrOH (10 equiv)}$$
$$\text{CH}_2\text{Cl}_2\text{, rt, time}$$

entry	M(OTf)$_n$ (5 mol %)	time (h)	% conversion[a]	ee (%)[b]
1	La(OTf)$_3$	5	100	56 (S)
2	Yb(OTf)$_3$	5	100	23 (S)
3	Eu(OTf)$_3$	36	100	20 (S)
4	Sc(OTf)$_3$	12	100	rac
5	In(OTf)$_3$	12	100	rac
6	Zn(OTf)$_2$	12	100	rac
7	Cu(OTf)$_2$	12	100	rac

[a] Isolated yield after column chromatography separation. [b] Enantiomeric excess (ee) was determined by HPLC analysis using chiral OD-H column.

Various other metal triflates were investigated as Lewis acid activators with (*S*)-HOP in the presence of superstiochiometric amount of isopropanol. Although all the metal triflates provide the protonation product in quantitative yield, enantioselectivity highly depended on the choice of metal triflates. Yb(OTf)$_3$ and Eu(OTf)$_3$ provided the protonation product

in 23 and 20 % ee, respectively, whereas $Sc(OTf)_3$, $In(OTf)_3$, $Zn(OTf)_2$, and $Cu(OTf)_2$ provided only the racemic product. Among the metal triflates tested, $La(OTf)_3$ gave the best result in terms of enantioselectivity.

2) Screening of Ligand

Reaction scheme: TMS-enol ether **1a** (with Ph substituent on cyclohexene) → La(OTf)$_3$ (5 mol %), Ligand (5 mol %), i-PrOH (10 equiv), CH$_2$Cl$_2$, rt, time → ketone **2a** (2-Ph cyclohexanone)
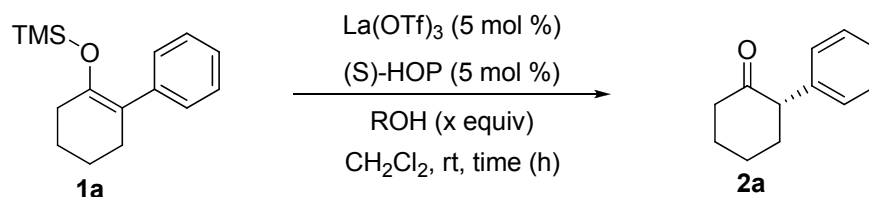
Ligand box:

(S)-BINOL:	X = Y = OH
(S)-Me-BINOL:	X = OH, Y = OMe
(S)-HOP:	X = PPh$_2$, Y = OH
(S)-Me-HOP:	X = PPh$_2$, Y = OMe
(S)-Ox-HOP:	X = P(O)Ph$_2$, Y = OH
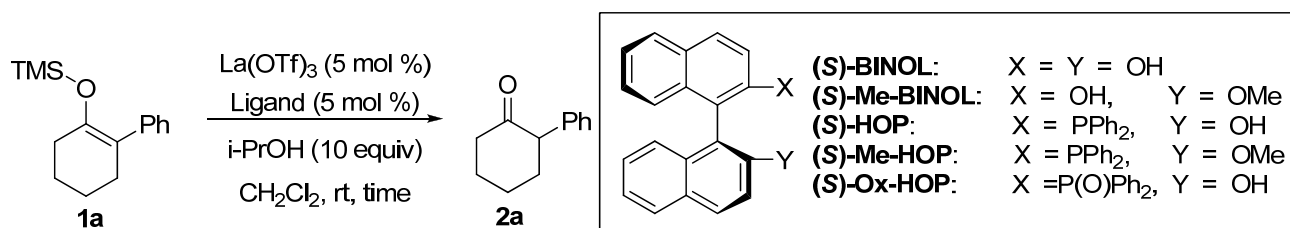
entry	ligand (5 mol %)	time (h)	% conversion[a]	ee (%)[b]
1	(S)-HOP	24	100	56 (S)
2	(S)-BINOL	5	100	rac
3	(S)-Me-BINOL	5	100	rac
4	(S)-Me-HOP	12	100	rac
5	(S)-Ox-HOP	12	100	28 (S)

[a] Isolated yield after column chromatography separation. [b] Enantiomeric excess (ee) was determined by HPLC analysis using chiral OD-H column.

Utilizing La(OTf)$_3$ as a Lewis acid activator, next we investigated various other ligands. The ligands without phosphinyl group, although a chiral ligand has acidic protons, afforded the protonation product with no enantioselectivity (entries 2 and 3). These results imply that the importance of the phosphinyl moiety to achieve enantioselectivity presumably because this moiety provides rigid conformation to the LBA. Furthermore, when (S)-Me-HOP was used in place of (S)-HOP, no enantioselectivity was obtained, which implies the importance of OH group in the asymmetric protonation reaction (entry 4). The oxidized (S)-HOP, (S)-Ox-HOP, provided the protonation product only in moderate enantioselectivity (entry 5). From these results suggested two important findings: 1) phosphonyl group is needed to induce stereoselectivity in asymmetric protonation reaction, 2) the protonation reaction with the alcohol activated by La(OTf)$_3$ may be less or non enantioselective pathway regardless of the structure of chiral ligands.

3) Screen of achiral Brønsted acid

Reaction scheme: TMS-enol ether **1a** → La(OTf)$_3$ (5 mol %), (S)-HOP (5 mol %), ROH (x equiv), CH$_2$Cl$_2$, rt, time (h) → ketone **2a**

entry	ROH (equiv)	time (h)	% yield[a]	ee (%)[b]
1	MeOH (10)	18	97	68
2	EtOH (10)	24	76	8
3	i-PrOH (10)	24	93	56
4	t-BuOH (10)	48	94	18
5	CF$_3$CH$_2$OH (10)	36	30	rac
6	PhOH (2)	12	96	rac

[a] Isolated yield after column chromatography separation. [b] Enantiomeric excee (ee) was determined by HPLC analysis using chiral OD-H column.

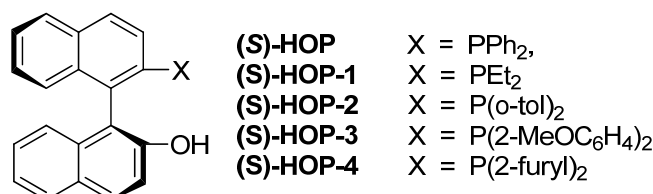We further screened the role of achiral Brønsted acid on enantioselectivity in the protonation reaction. As expected, although both reactivity and enantioselectivity showed a strong dependence on the choice of achiral Brønsted acid, various alcohols could be used as achiral proton sources in the protonation reaction with LBA (entries 1-5). However, phenol was not able to be used as an achiral Brønsted acid, presumably due to little difference in the acidity between (S)-HOP and phenol (entry 6). Among the achiral Brønsted acids examined, methanol gave the best enantioselectivity (entry 1).

4) Optimization of (S)-HOP
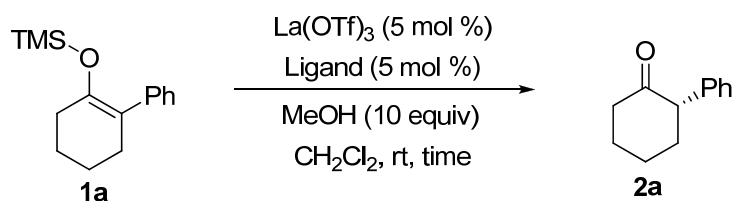
entry	ligand (5 mol %)	time (h)	% conversion[a]	ee (%) [b]
1	(S)-HOP	18	100	68
2	(S)-HOP-1	18	100	31
3	(S)-HOP-2	24	100	47
4	(S)-HOP-3	18	100	54
5	(S)-HOP-4	12	100	52

(S)-HOP	X = PPh$_2$,
(S)-HOP-1	X = PEt$_2$
(S)-HOP-2	X = P(o-tol)$_2$
(S)-HOP-3	X = P(2-MeOC$_6$H$_4$)$_2$
(S)-HOP-4	X = P(2-furyl)$_2$

[a] Isolated yield after column chromatography separation. [b] Enantiomeric excee (ee) was determined by HPLC analysis using chiral OD-H column.

With these optimized conditions, next we moved our attention to the optimization of ligand structure. Enantioselectivity showed strong dependence on electronic and steric effect of substituents on the phosphorous atom in (S)-HOP. Ligand bearing diethylphosphorous moiety showed much lower enantioselectivity (entry 2). Electron-rich aromatic substituent has a little deleterious effect on the enantioselectivity (entry 5). Ligands bearing bulky aromatic substituents displayed much lower selectivities (entries 3-4). Among the ligands examined, simple phenyl substituted (S)-HOP gave the best result in terms of enantioselectivity (entry 1).
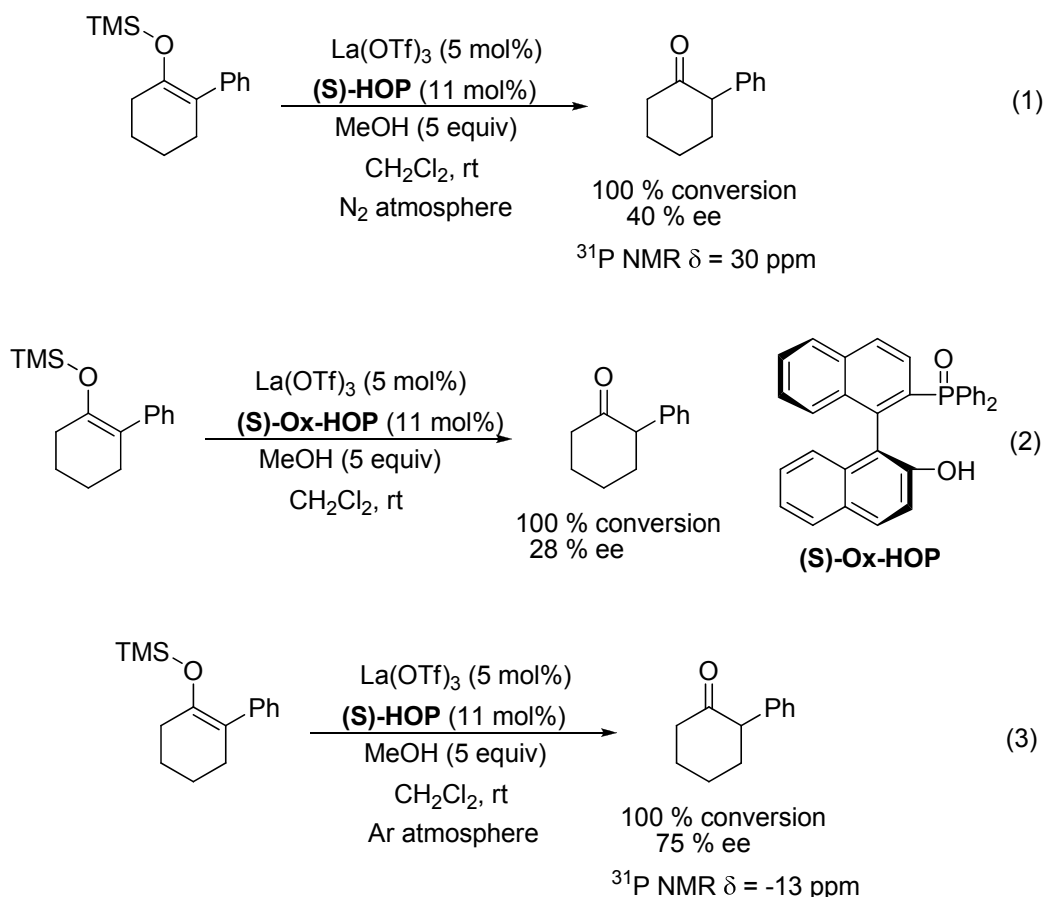
5) Screen of solvent
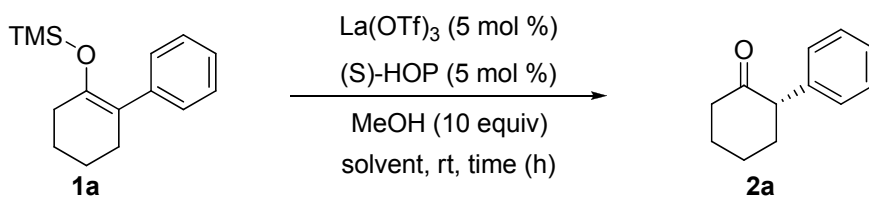
entry	solvent	time (h)	% yield [a]	ee (%) [b]
1	CH_2Cl_2	18	97	68
2	Et_2O	48	93	68
3	THF	48	53	32
4	hexanes	48	trace	N. D.
5	toluene	36	52	24

[a] Isolated yield after column chromatography separation. [b] Enantiomeric excess (ee) was determined by HPLC analysis using chiral OD-H column.

Next, solvents was further optimized in protonation reaction. Interestingly, the reactivity of LBA in the protonation reaction displayed a strong dependence of the solvent; the protonation reaction was significantly slow in coordinating solvents, such as ether and THF, whereas the protonation reaction is much faster in non-coordinating halogenated solvents, such as CH_2Cl_2 (entries 1-3). Although CH_2Cl_2 and Et_2O provided the protonation product in the similar levels of enantioselectivities (entries 1 and 2), CH_2Cl_2 was chosen as the optimal solvent because the reactivity of LBA significantly increased in non coordinating halogenated solvent than coordinating solvent.

**6) Asymmetric protonation reaction under an argon atmosphere**

however, even in the standard conditions, sometimes the enantioselectivity was fluctuated from 40 to 74 % ee. We assumed that this inconsistancy in enantioselectivity might result from the oxidation of the chiral Brønsted acid to the corresponding phosphine oxide ligand ((S)-Ox-HOP) during the protonation reaction. Indeed, the reaction mixture providing low enantioselectivity has a new peak at 30 ppm in ^{31}P NMR, which is corresponding to the oxidized (S)-HOP.[4] Furthermore, the protonation reaction with LBA from (S)-Ox-HOP gave the the protonation product with similar enantioselectivity (eq 1). The inconsistency in enantioselectivity might result from less selective protonation with the LBA from the oxidized (S)-HOP ligand. Thus, this might be avoided by by preventing (S)-HOP from oxidizing into (S)-Ox-HOP. To our delight, when the protonation reaction was carried out under an argon atmosphere, the desired product was obtained with 75 % ee without any inconstitancy.

$$\text{(1)}$$

TMS enol ether → La(OTf)$_3$ (5 mol%), **(S)-HOP** (11 mol%), MeOH (5 equiv), CH$_2$Cl$_2$, rt, N$_2$ atmosphere → 2-phenylcyclohexanone

100 % conversion
40 % ee
^{31}P NMR δ = 30 ppm

$$\text{(2)}$$

La(OTf)$_3$ (5 mol%), **(S)-Ox-HOP** (11 mol%), MeOH (5 equiv), CH$_2$Cl$_2$, rt

100 % conversion
28 % ee

(S)-Ox-HOP

$$\text{(3)}$$

La(OTf)$_3$ (5 mol%), **(S)-HOP** (11 mol%), MeOH (5 equiv), CH$_2$Cl$_2$, rt, Ar atmosphere

100 % conversion
75 % ee
^{31}P NMR δ = -13 ppm

3-2 Substrate Scope

General Procedure: La(OTf)$_3$ (5.8 mg; 0.10 mmol; 0.050 eq) and (S)-HOP (10 mg; 0.22 mmol; 0.11 eq) were added to a flame dried test tube. The reaction flask was charged with an argon and then CH$_2$Cl$_2$ (2 mL) and MeOH (64 mg; 2.0 mmol; 10.0 eq) were added to the reaction mixture at room temperature. The reaction mixture was stirred for 30 min at room temperature. Silyl enol ether of 2-aryl cyclohexanone (0.20 mmol; 1.0 eq) was added dropwise to the reaction mixture at room temperature and the reaction was monitored by TLC. When all the silyl enol ether was completely comsumed, the reaction mixture was quenched with NaHCO$_3$ (aq), and extracted with ether. The organic layer was collected, dried over Na$_2$SO$_4$, and concentrated. Column chromatography on silica (15 % ethyl acetate in hexanes) gave the desired product. Enantiomeric ratio (er) was determined by HPLC analysis with a chiral column.

Substrate scope
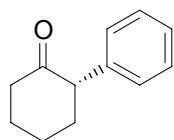
The product (**2a**)[2] was obtained as a white solid in 97 % yield (34.0 mg; 0.194 mmol) and 75 % ee. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 1.80-1.84 (m, 2H), 1.99-2.05 (m, 2H), 2.14-2.15 (m, 1H), 2.26-2.30 (m, 1H), 2.45-2.55 (m, 2H), 3.59-3.64 (dd, J = 5.0, 12.5 Hz, 1H), 7.11-7.16 (d, J = 7.5 Hz, 2H), 7.23-7.27 (t, J = 7.5 Hz, 1H), 7.31-7.35 (t, J = 7.5 Hz, 2H). Enantiomeric excess (ee) was determined by HPLC with a Chiralcel OD-H column equipped with an OD-H guard column (hexanes: 2-propanol = 99:1, flow rate = 1.0 mL/min, λ= 210 nm), t$_r$(major, S) = 15.7 min., t$_r$(minor, R) = 17.8 min.
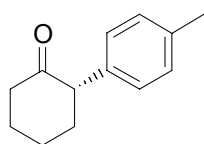
The product (**2b**)[2] was obtained as a white solid in 96 % yield (36.1 mg; 0.192 mmol) and 72 % ee. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 1.78-1.84 (m, 2H), 1.95-2.05 (m, 2H), 2.12-2.17 (m, 1H), 2.22-2.27 (m, 1H), 2.22 (s, 3H), 2.39-2.56 (m, 2H), 3.56 (dd, J = 5.4, 12.0 Hz, 1H), 7.02 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H). Enantiomeric excess (ee) was determined by HPLC with a Chiralcel OD-H column equipped with an OD-H guard column (hexanes:2-propanol = 95:5, flow rate = 1.0 mL/min, λ= 210 nm), t$_r$(major, S) = 14.9 min., t$_r$(minor, R) = 16.2 min.
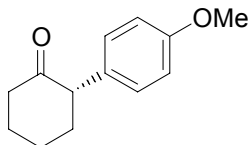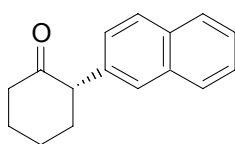
The product (**2c**)[2] was obtained as a white solid in 94 % yield (38.4 mg; 0.188 mmol) and 70 % ee. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 1.75-1.85 (m, 2H), 1.94-2.02 (m, 2H), 2.10-2.15 (m, 1H), 2.22-2.26 (m, 1H), 2.49-2.53 (m, 2H), 3.56 (dd, J = 5.5, 12.5 Hz, 1H), 3.78 (s, 3H), 6.87 (d, J = 8.5 Hz, 2H), 7.05 (d, J = 8.5 Hz, 2H). Enantiomeric excess (ee) was determined by HPLC with a Chiralcel OD-H column equipped with an OD-H guard column (hexanes:2-propanol = 95:5, flow rate = 1.0 mL/min, λ= 210 nm), t$_r$(major, S) = 12.2 min., t$_r$(minor, R) = 15.5 min.
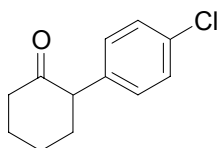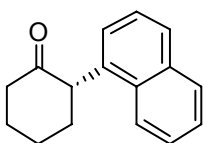
The product (**2d**)[2] was obtained as a white solid in 96 % yield (19.9 mg; 0.096 mmol) and 52 % ee. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 1.79-1.91 (m, 2H), 1.95-2.02 (m, 2H), 2.15-2.28 (m, 2H), 2.41-2.54 (m, 2H), 3.59 (dd, J = 5.4, 12.4 Hz, 1H), 7.07 (d, J = 9.0 Hz, 2H), 7.30 (d, J = 9.0 Hz, 2H). Enantiomeric excess (ee) was determined by HPLC with a Chiralcel OJ column equipped with an OJ guard column (hexanes:2-propanol = 90:10, flow rate = 0.7 mL/min, λ= 210 nm), t$_r$(major) = 32.3 min., t$_r$(minor) = 23.1 min.
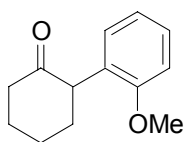
The product (**2e**)[2] was obtained as oil in 95 % yield (38.8 mg; 0.190 mmol) and 42 % ee. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 1.73-1.84 (m, 2H), 1.98-2.05 (m, 2H), 2.13-2.21 (m, 2H), 2.44-2.53 (m, 2H), 3.78 (s, 3H), 3.94 (dd, J = 5.5, 12.5 Hz, 1H), 6.88 (d, J = 8 Hz, 1H), 6.96 (t, J = 8 Hz, 1H), 7,12 (d, J = 8 Hz, 1H), 7.24 (t, J = 8 Hz, 1H); Enantiomeric excess (ee) was determined by HPLC with a Chiralcel OD-H column equipped with an OD-H guard column (hexanes:2-propanol = 95:5, flow rate = 1.0 mL/min, λ= 210 nm), t$_r$(major) = 8.6 min., t$_r$(minor) = 14.2 min.

The product (**2f**)[2] was obtained as a white solid in 92 % yield (41.3 mg; 0.184 mmol) and 54 % ee. ^{1}H NMR (500 MHz, CDCl$_3$, ppm) δ: 1.81-1.91 (m, 2H), 2.00-2.07 (m,1H), 2.12-2.21 (m, 2H), 2.31-2.36 (m, 1H), 2.46-2.58 (m, 2H), 3.77 (dd, J = 5.6, 12.2 Hz, 1H), 7.27 (dd, J = 1.6, 8.4 Hz, 1H), 7.41-7.46 (m, 2H), 7.60 (s, 1H), 7.77-7.83 (m, 3H). Enantiomeric excess (ee) was determined by HPLC with a Chiralcel OD-H column equipped with an OD-H guard column (hexanes:2-propanol = 95:5, flow rate = 1.0 mL/min, λ= 210 nm), t$_r$(major, S) = 25.9 min., t$_r$(minor, R) = 32.1 min.

The product (**2g**)[4] was obtained as a white solid in 95 % yield (42.6 mg; 0.190 mmol) and 32 % ee. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 1.89-1.97 (m, 2H), 2.10-2.15 (m, 1H), 2.24-2.31 (m, 2H), 2.39-2.44 (m, 1H), 2.61-2.69 (m, 2H), 4.33-4.37 (dd, J = 5.5, 12.5 Hz, 1H), 7.35-7.36 (d, J = 8.0 Hz, 1H), 7.43-7.48 (m, 3H), 7.70-7.72 (m, 1H), 7.77-7.79 (d, J = 8.0 Hz, 1H), 7.84-7.87 (m, 1H). Enantiomeric excess

(ee) was determined by HPLC with a Chiralcel IC column equipped with an IC guard column (hexanes:2-propanol = 90:10, flow rate = 1.0 mL/min, λ= 225 nm), t_r(major, S) = 20.3 min., t_r(minor, R) = 31.8 min.
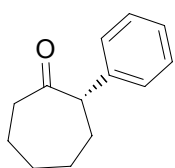
The product (**2h**)[2] was obtained as oil in 93 % yield (35.0 mg; 0.186 mmol) and 54 % ee. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 1.43-1.48 (m, 2H), 1.60-1.69 (m, 1H), 1.95-2.18 (m, 4H), 2.47-2.54 (m, 1H), 2.67-2.72 (m, 1H), 3.70-3.73 (dd, J = 4, 11 Hz, 1H), 7.20-7.26 (m, 3H), 7.30-7.33 (t, J = 7 Hz,2H). Enantiomeric excess (ee) was determined by HPLC with a Chiralcel AS column equipped with an AS guard column (hexanes:2-propanol = 95:5, flow rate = 1.0 mL/min, λ= 210 nm), t_r(major, *S*) = 9.8 min., t_r(minor, *R*) = 7.9 min.
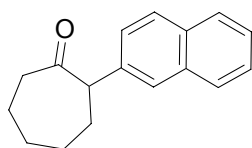
The product (**2i**)[2] was obtained as oil in 96 % yield (45.7 mg; 0.192 mmol) and 34 % ee. ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 1.49-1.53 (m, 2H), 1.66-1.73 (m, 1H), 1.99-2.15 (m, 4H), 2.10-2.23 (m, 1H), 2.55-2.58 (m, 1H), 2.72-2.78 (td, J = 12.8, 3.1 Hz, 1H), 3.88 (dd, J = 4.2, 11.4 Hz, 1H), 7.37 (dd, J = 1.7, 8.5 Hz, 1H), 7.42-7.48 (m, 2H), 7.67 (s, 1H), 7.79-7.81 (m, 3H); Enantiomeric excess (ee) was determined by HPLC with a Chiralcel AS column equipped with an AS guard column (hexanes:2-propanol = 99:1, flow rate = 1.0 mL/min, λ= 230 nm), t_r(major) = 18.9 min., t_r(minor) = 15.5 min.

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(3) For a chemical shift in ^{31}P NMR of (S)-HOP, see: Zhang, W.; Shi, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3467.
(4) Asensio, G.; Cuenca, A.; Rodriguez, N.; Medio-Simón, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3467.