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

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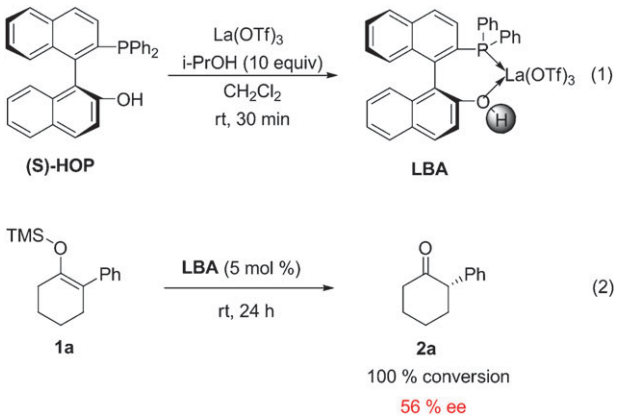
A new Lewis base-tolerant LBA (Lewis Acid Assisted Brønsted Acid) derived from La(OTf)$_3$ and (*S*)-HOP has been developed as a new chiral Brønsted acid. This acid has been successfully applied as a catalyst to asymmetric protonation reactions of silyl enol ethers of 2-substituted cyclic ketones.

Chiral Brønsted acid catalysis has been one of the growing fields in modern organic synthesis.[1] Urea/thioureas,[2] TADDOL,[3] and phosphoric acids[4] have been widely used as catalysts in various asymmetric syntheses. Despite the recent progress in asymmetric Brønsted acid catalysis, utility of these acids is somewhat limited to reactive substrates due to their lower reactivities compared to metal based Lewis acid catalysts. Thus, the development of a new Brønsted acid with high reactivity is still one of the most urgent tasks in Brønsted acid catalysis in order to extend the utility of these acids to more general substrates.[5]

The combined acid system is an excellent method to increase the reactivity of Brønsted acids.[6] The coordination of a Brønsted acid to a Lewis acid activator increases its acidity, and thus increases its reactivity. Based on this idea, our group has developed Lewis acid-assisted Brønsted acids (LBAs) as strong chiral proton reagents and successfully applied these LBAs as effective proton reagents for enantioselective protonation[7] and polyene cyclization[8] reactions. Unfortunately, however, the previous LBA systems,[9] where $SnCl_4$ and $TiCl_4$ have been used as Lewis acid activators, have some limitations; these LBAs have poor stability toward Lewis bases such as moisture, alcohols and amines. Thus, highly anhydrous reaction conditions are needed to maintain the reactivity of LBAs. Furthermore, although a LBA has been used as a catalyst in asymmetric protonation reaction with a bulky phenol as an achiral Brønsted acid, poor stability of this LBA has rendered catalytic systems almost unrealistic.[10] Herein, we describe the development of a new chiral LBA bearing remarkable stability towards Lewis bases and its application as a catalyst to asymmetric protonation reactions of silyl enol ethers of 2-substituted cyclic ketones.

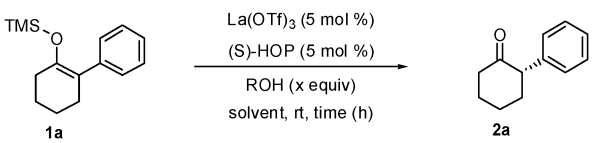
Chiral LBA was generated *in situ* from optically active (*S*)-2-hydroxy-2′-diphenylphosphino-1,1′-binaphthyl ((*S*)-HOP) as a chiral Brønsted acid[11] and a metal triflate as a Lewis acid activator in the presence of superstoichiometric amount of 2-propanol (eqn (1), Scheme 1). With this LBA in hand, we attempted to apply this LBA as a catalyst to the asymmetric protonation reaction[12,13] of the silyl enol ether derived from 2-phenyl cyclohexanone. Among the metal triflates tested,[14] La(OTf)$_3$ was found to be the best choice of Lewis acid activator;[15] 5 mol% of LBA derived from La(OTf)$_3$ afforded the desired protonation product in quantitative yield and 56% enantiomeric excess (ee) (eqn (2)).



Scheme 1 Generation of chiral LBA from La(OTf)$_3$ and (*S*)-HOP and its application to asymmetric protonation reaction.

Utilizing (*S*)-HOP and La(OTf)$_3$ as a chiral ligand and a Lewis acid activator, respectively, we further optimized the reaction conditions in the protonation reaction (Table 1). As expected, various alcohols could be used as achiral proton

Table 1 Optimization of reaction conditions



Entry	Solvent	ROH (equiv.)	Time/h	% Yield[a]	ee (%)[b]
1	CH_2Cl_2	i-PrOH (10)	24	93	56
2	CH_2Cl_2	MeOH (10)	18	97	68
3	CH_2Cl_2	EtOH (10)	24	76	8
4	CH_2Cl_2	*t*-BuOH (10)	48	94	18
5	CH_2Cl_2	CF_3CH_2OH (10)	36	30	Rac
6	CH_2Cl_2	PhOH (2)	12	96	Rac
7	Et_2O	MeOH (10)	48	93	68
8	THF	MeOH (10)	48	53	32
9	Hexanes	MeOH (10)	48	Trace	ND
10	Toluene	MeOH (10)	36	52	24

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

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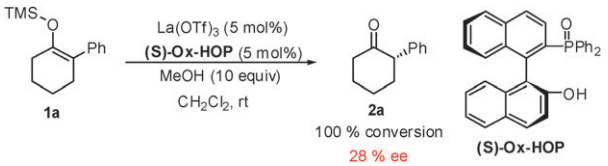
sources in the protonation reaction with LBA, although both reactivity and enantioselectivity showed a strong dependence on the choice of achiral Brønsted acid (entries 1–5). Among the alcohols examined, methanol gave the best enantioselectivity (entry 2). However, phenol was not able to be used as achiral Brønsted acid presumably due to the small pK_a difference between the chiral Brønsted acid and phenol (entry 6). Then, we further optimized solvents in protonation reaction (entries 2, 7–10). Interestingly, the reactivity of LBA in the protonation reaction displayed a strong dependence on 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. Although CH_2Cl_2 and Et_2O provided the protonation product in similar levels of enantioselectivities, CH_2Cl_2 was chosen as the optimal solvent because the reactivity of LBA significantly increased in a non-coordinating halogenated solvent than a coordinating solvent (entries 2 and 7).

To further improve enantioselectivity of the protonation reaction and understand the role of chiral and achiral Brønsted acids, we carried out several control experiments (Table 2). Interestingly, the MeOH activated by $La(OTf)_3$ is acidic enough to protonate the silyl enol ether (entry 1). However, without any achiral Brønsted acid, no protonation product was obtained even with stoichiometric amount of $La(OTf)_3$ and chiral Brønsted acid presumably due to poor solubility of $La(OTf)_3$ in CH_2Cl_2 in the absence of methanol (entry 2). Furthermore, when methylated chiral Brønsted acid, (*S*)-Me-HOP, was used instead of chiral Brønsted acid (*S*)-HOP, still the protonation reaction proceeded but only racemic product was obtained.[16,17] These results suggested that enantioselecitivity of the protonation reaction could be increased by minimizing the protonation with the activated methanol by $La(OTf)_3$ and maximizing the protonation from (*S*)-HOP activated by $La(OTf)_3$. It is therefore expected that increase in the ratio of ligand to metal would have a beneficial effect on enantioselectivity presumably because (*S*)-HOP will occupy the available sites on $La(OTf)_3$, which decreases the amount of methanol activated by $La(OTf)_3$. To our delight, increasing the ratio of ligand to metal indeed increased enantioselectivity (entries 3–5).

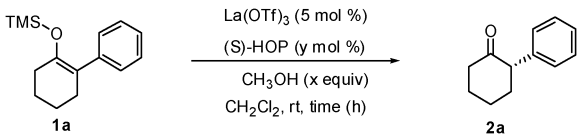
However, even in the standard conditions, sometimes the enantioselectivity fluctuated from 40 to 74% ee. We assumed that this inconsistency in enantioselectivity might result from the oxidation of the chiral Brønsted acid to the corresponding phosphine oxide ligand ((*S*)-Ox-HOP) during the protonation reaction. ^{31}P NMR of the crude mixture providing low enantioselectivity showed a new peak around 30 ppm, which is corresponding to the corresponding phosphine oxide.[18] Furthermore, LBA from (*S*)-Ox-HOP gave the protonation product in quantitative yields but with much lower enantioselectivity (eqn (3)).[19] In order to avoid the less-enantioselective protonation reaction through LBA with the oxidized ligand, (*S*)-Ox-HOP, the protonation reaction was carried out under an argon atmosphere. To our delight, the protonation reaction was reproducible without any fluctuation in enantioselectivity (entry 6).



(3)

With these optimized conditions in hand, we next investigated the generality and limitations of this protonation reaction (Table 3). Various silyl enol ethers derived from 2-aryl cycloalkanones gave the desired protonation products in quantitative yields. However, enantioselectivity is strongly dependent on the electronic and steric properties of the aryl substituents. The silyl enol ethers carrying electron donating groups at the *para*-position of the aryl substituents gave almost the same levels of enantioselectivity (entries 1–3), whereas electron withdrawing substituent at the *para*-position of the aryl groups has deleterious effect on the enantioselectivity (entry 4). However, bulky aryl substituents had a deleterious effect on the enantioselectivities; only moderate enantioselectivities were obtained with cyclic ketones bearing bulky aryl and *ortho*-substituted aryl groups (entries 5–7). Furthermore, the ring size has an effect on enantioselectivity. 7-Membered ring silyl enol ethers provided the protonation

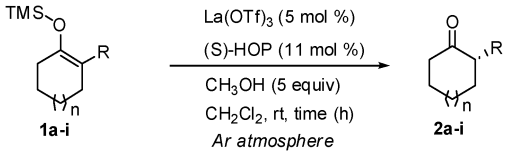
Table 2 Effect of ratio of (*S*)-HOP to $La(OTf)_3$ on enantioselectivity



Entry	(*S*)-HOP (*y* mol%)	CH_3OH (*x* equiv.)	L : M[e]	Time/h	% Yield[a]	ee (%)[b]
1	—	10	—	6	97	ND
2[c]	100	—	—	48	NR	ND
3	5	10	1 : 1	18	94	68
4	10	10	2 : 1	24	95	74
5	15	10	3 : 1	36	94	73
6[d]	10	5	2 : 1	18	96	75

[a] Isolated yield after column chromatography separation. [b] ee was determined by HPLC analysis using chiral OD-H column. [c] $La(OTf)_3$ was not soluble in this condition. [d] Reaction was carried out under an Ar atmosphere. [e] L : M means the ratio of (*S*)-HOP to $La(OTf)_3$.

Table 3 Substrate scope



Entry	*n*	R	Time/h	% Yield[a]	ee (%)[b]
1	1	Ph (**1a**)	18	97	75
2	1	4-MeC_6H_4 (**1b**)	18	96	72
3	1	4-MeOC_6H_4 (**1c**)	18	94	70
4	1	4-ClC_6H_4 (**1d**)	18	96	52
5	1	2-MeOC_6H_4 (**1e**)	12	95	42
6	1	2-naphthyl (**1f**)	18	92	54
7	1	1-naphthyl (**1g**)	12	95	32
8	2	Ph (**1h**)	16	93	54
9	2	2-naphthyl (**1i**)	18	96	34

[a] Isolated yield after column chromatography separation. [b] ee was determined by HPLC analysis using chiral column.

products in much lower enantioselectivity than those of six-membered rings counterparts (entries 1, 6, 8, and 9).

In conclusion, we have developed a LBA derived from (*S*)-HOP with $La(OTf)_3$ as a Lewis acid activator. The LBA is Lewis-base tolerant and was successfully applied to the catalytic enantioselective protonation reaction of silyl enol ether of 2-aryl cyclic ketones in the presence of a super-stoichiometric amount of methanol. The enantioselectivity of the protonation product was increased by decreasing the amount of MeOH activated by $La(OTf)_3$ and by preventing oxidation of chiral Brønsted acid to the corresponding phosphine oxide ligand. Further application of this Lewis base tolerant LBA is currently underway in our laboratory.

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Notes and references

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10 Catalytic usage of LBA for protonation reaction in the presence of stoichiometric amount of bulky phenol derivatives was reported, see: ref. 7*g*.

11 Other chiral ligands were also investigated, see ESI†.

12 For reviews of asymmetric protonation reaction, see: (*a*) C. Fehr, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2566; (*b*) J. T. Mohr, A. Y. Hong and B. M. Stoltz, *Nat. Chem.*, 2009, **1**, 359.

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14 Various other Lewis acids were investigated in the same condition. $Yb(OTf)_3$ and $Eu(OTf)_3$ provided the protonation product in 23, 20% ee, respectively, whereas $Sc(OTf)_3$, $In(OTf)_3$, $Zn(OTf)_2$, and $Cu(OTf)_2$ provided only the racemic product. For more detailed information, see ESI†.

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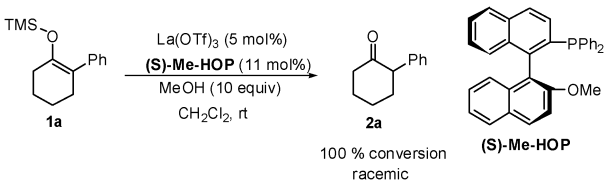
17 The Yanagisawa group reported an excellent example of asymmetric protonation reaction of silyl enol ethers through the protonation with activated MeOH by chiral LBA, see: ref. 9*b*.



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19 For more detailed information, see ESI†.

