Synthetic Methods

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Lewis Base Assisted Brønsted Base Catalysis: Bidentate Phosphine Oxides as Activators and Modulators of Brønsted Basic Lanthanum–Aryloxides**

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Dedicated to Professor E. J. Corey on the occasion of his 80th birthday

Combining catalysts having different or similar properties is currently an important topic in catalysis development.[1] Various catalyst combinations, such as Lewis acid/Brønsted base,[2] Lewis acid/Lewis base,[3,4] Lewis acid/Brønsted acid,[5] Lewis acid/Lewis acid,[5] and transition metal/Lewis acid[6] have been developed to provide unique catalytic activities. Herein we describe a different class of combination catalysts, in which Brønsted base catalysis is assisted by a Lewis base catalyst (Figure 1). A catalytic amount of Lewis basic bidentate phosphine oxide **1** effectively activated and modified the properties of Brønsted basic rare-earth metal aryloxide catalysts, switching the diastereoselectivity from *syn* to *anti* in the lanthanum-catalyzed direct Mannich-type reaction. The mechanistic studies, a preliminary trial in a catalytic asymmetric reaction, and the extension of the Lewis base/Brønsted base catalysis to Michael and nitroaldol reactions are also described.

We recently reported an *i*Pr–pybox/La(OAr^1)$_3$ (Ar^1 = 4-MeO-C$_6$H$_4$) complex which catalyzed the *syn*-selective direct asymmetric Mannich-type reactions[7] of imines **2**[8] with trichloromethyl ketone **3a**, an ester donor equivalent (Table 1, entry 1).[9,10] During the mechanistic studies of the reaction, we found that the reaction did not proceed with either La(OAr^1)$_3$ alone (Table 1, entry 2,) or *i*Pr–pybox alone (Table 1, entry 3). In addition, an electron-donating Me$_2$N group appended to *i*Pr–pybox, which is sterically similar to the standard *i*Pr–pybox, significantly decreased the diastereoselectivity (Table 1, entry 4). On the basis of these results, we hypothesized that the pybox acts not only as a simple chiral ligand to provide a steric bias in the transition state, but also as a Lewis base to electronically modify the properties of the Brønsted basic La(OAr)$_3$.[11] To test this hypothesis involving Lewis base assisted Brønsted base catalysis, we decided to search for a new catalyst system.

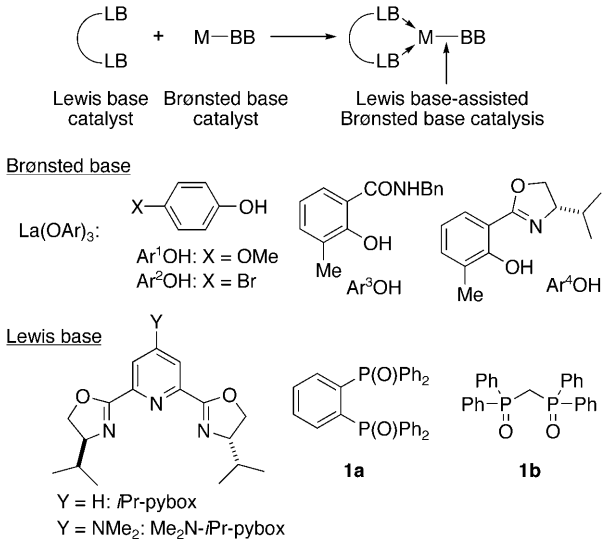
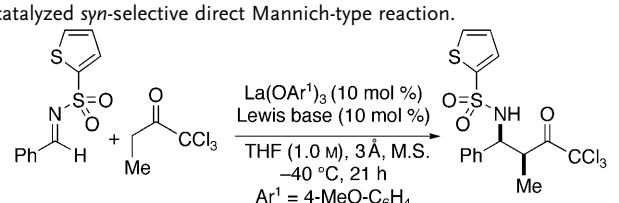


Figure 1. The concept of Lewis base assisted Brønsted base catalysis, and the structures of Brønsted bases and Lewis bases.

Table 1: Unexpected effects of Lewis basic pybox in the La(OAr^1)$_3$-catalyzed *syn*-selective direct Mannich-type reaction.



2a **3a** (2 equiv) **4aa**

Entry	Brønsted base	Lewis base	Yield [%]	*anti*/*syn*[a]	*ee* [%][b]
1	La(OAr^1)$_3$	*i*Pr–pybox	90	1:19	93
2	La(OAr^1)$_3$	none	0	–	–
3	none	*i*Pr–pybox	0	–	–
4	La(OAr^1)$_3$	Me$_2$N–*i*Pr–pybox	86	1:5	90

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Value is for the *syn* adduct.

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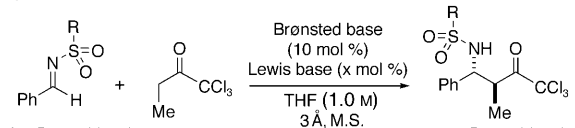
Among the Lewis bases screened in combination with $La(OAr^1)_3$ for a direct Mannich-type reaction of imines **2** with **3a**, a catalytic amount of bidentate phosphine oxide was promising. The optimization studies are summarized in Table 2. Bidentate bis(phosphine oxide) **1a**[12] gave Mannich adduct **4aa** in 80% yield with *anti* selectivity (Table 2, entry 2).[13–15] Additional optimization of the reaction conditions were investigated because an undesirable side product was formed in the reaction reported as entry 2 in Table 2. Screening included N-substituted imine **2b** (Table 2, entry 3),[16] which when used with $La(OAr^3)_3$ improved the yield of Mannich adduct **4ba** to 98% after 15 hours, while maintaining the high *anti* selectivity (Table 2, entry 6). Neither monodentate Lewis base $Ph_3P(O)$ (20 mol%) nor $La(OAr^2)_3$ ($Ar^2 = 4\text{-Br-}C_6H_4$) gave good results; **4ba** was obtained in low yield and *syn* selectivity (Table 2, entries 4 and 5). The use of Lewis base **1b** significantly accelerated the reaction, and **4ba** was obtained in 97% yield and good *anti* selectivity after 3 hours (Table 2, entry 7). To confirm that the positive effects resulted from using either Lewis base **1a** or **1b**, rather than from the *N*-substituent on the imine or the structure of the aryloxide, control experiments using the best imine, **2b**, and Brønsted base $La(OAr^3)_3$ were performed. In the absence of Lewis base **1b**, $La(OAr^3)_3$ alone gave poor reactivity and diastereoselectivity (Table 2, entry 8) and $LiOAr^3$ alone promoted the Mannich-type reaction, but with *syn* selectivity (Table 2, entry 9). In addition, reactions did not proceed with the Lewis base alone (Table 2, entries 10 and 11). Thus, the combination of bidentate Lewis base **1a** or **1b** with the Brønsted base $La(OAr^3)_3$ was important for achieving good reactivity and *anti* selectivity (Table 2, entries 6 and 7).

Table 2: Optimization of the *anti*-selective Mannich-type reaction using phosphine oxides as Lewis bases.



2a: R = 2-thienyl
2b: R = 2-pyridyl
3a (2 equiv)
4aa: R = 2-thienyl
4ba: R = 2-pyridyl

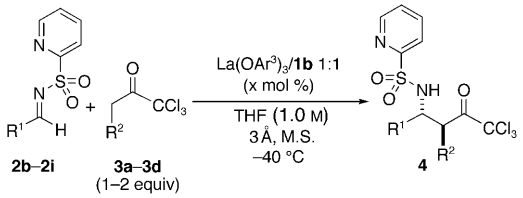
Entry	Imine	Lewis base (mol%)	Brønsted base	*t* [h]	Yield[a] [%]	*anti*/*syn*[a]
1	**2a**	none (0)	$La(OAr^1)_3$	21	0	–
2	**2a**	**1a** (10)	$La(OAr^1)_3$	21	80[b]	18:1
3	**2b**	**1a** (10)	$La(OAr^1)_3$	21	89[b]	42:1
4	**2b**	$Ph_3P(O)$ (20)	$La(OAr^1)_3$	21	10	1:18
5	**2b**	**1a** (10)	$La(OAr^2)_3$	21	34	1:2
6	**2b**	**1a** (10)	$La(OAr^3)_3$	15	98	26:1
7	**2b**	**1b** (10)	$La(OAr^3)_3$	3	97	20:1
8	**2b**	none (0)	$La(OAr^3)_3$	3	7	3:1
9	**2b**	none (0)	$LiOAr^3$	7	46	1:10
10	**2b**	**1a** (10)	none	21	0	–
11	**2b**	**1b** (10)	none	21	0	–

[a] Determined by ^{1}H NMR analysis of the crude mixture. [b] Approximately 10% of a by-product was obtained in addition to **4**, see the Supporting Information.

The optimized reaction conditions were applicable to various imines and donors (Table 3). Imines containing aryl, heteroaryl, and alkenyl groups afforded products in good yields and with *anti* selectivity (Table 3, entries 1–10). Good yields were obtained even when a reduced amount of trichloromethyl ketone was used (Table 3, entries 1 and 2). The catalyst loading was reduced to 5–2.5 mol% without a loss in yield or selectivity (Table 3, entries 3 and 4). An isomerizable aliphatic imine could also be used (Table 3, entry 11), and trichloromethyl ketones **3b**–**3d** gave products with high *anti* selectivity (Table 3, entries 12–14). A preliminary trial with an enantioselective variant is shown in Scheme 1. Although the enantioselectivity has not yet been fully optimized, the use of chiral lanthanum aryloxide $La(OAr^4)_3$ in combination with a slight excess of Lewis base **1b** (20 mol%) afforded **4ba** in 93% yield, *anti*/*syn* 23:1, and 71% *ee* (*anti*-**4ba**).[15b,17] In the absence of Lewis base **1b**, the catalytic enantioselective reaction did not proceed, indicating the importance of the Lewis base. Additional improvement of the enantioselectivity will be reported in due course as a full paper.

To demonstrate the synthetic utility of the products, transformations of the trichloromethyl ketone moiety were investigated (Scheme 2). The Mannich adduct with the trichloromethyl ketone moiety can be a good precursor of

Table 3: Substrate scope of the *anti*-selective direct catalytic Mannich-type reaction.[a]

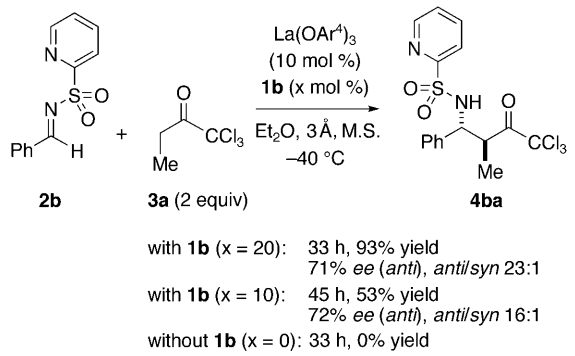


2b–2i **3a–3d** (1–2 equiv) **4**

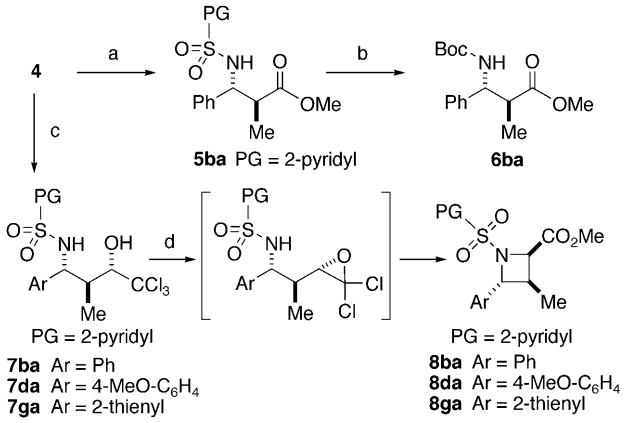
3a: R^2 = Me, **3b**: R^2 = Et
3c: $R^2 = CH_2Ph$, **3d**: $R^2 = CH_2CH_2OCH_2Ph$

Entry	R^1	**2**	**3**	Cat. [mol%]	*t* [h]	**4**	Yield[b] [%]	*anti*/*syn*[c]
1[d]	Ph	**2b**	**3a**	10	22	**4ba**	87	17:1
2[e]	Ph	**2b**	**3a**	10	22	**4ba**	89	24:1
3[f]	Ph	**2b**	**3a**	5	7	**4ba**	95	20:1
4[f]	Ph	**2b**	**3a**	2.5	13	**4ba**	96	21:1
5	*p*-Me-C_6H_4	**2c**	**3a**	10	12	**4ca**	87	19:1
6	*p*-MeO-C_6H_4	**2d**	**3a**	10	12	**4da**	94	16:1
7	*p*-Cl-C_6H_4	**2e**	**3a**	10	12	**4ea**	80	16:1
8	2-furyl	**2f**	**3a**	10	12	**4fa**	87	37:1
9	2-thienyl	**2g**	**3a**	10	12	**4ga**	98	56:1
10	(*E*)-PhCH=CH	**2h**	**3a**	10	12	**4ha**	90	20:1
11[g]	Cy	**2i**	**3a**	10	24	**4ia**	64	>30:1
12	Ph	**2b**	**3b**	10	12	**4bb**	95	25:1
13	Ph	**2b**	**3c**	10	12	**4bc**	98	18:1
14	Ph	**2b**	**3d**	10	12	**4bd**	88	14:1

[a] Reaction was performed with 2 equivalents of **3** in THF (1.0 M) unless otherwise noted. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] 1.2 equivalents of **3a** were used. [e] 1.0 equivalents of **3a** was used. [f] Reaction was performed in THF (2.0 M). [g] 2-Thiophenesulfonyl imine and 5 equivalents of **3a** were used. Cy = cyclohexyl.



Scheme 1. Trial on the *anti*-selective catalytic enantioselective Mannich-type reaction.



Scheme 2. Transformations of *anti*-Mannich adducts into β-amino ester and azetidine esters. Reagents and conditions: a) NaOMe, MeOH, 0 °C, 10 min, >99% yield; b) 1. Boc_2O, DMAP, CH_3CN, RT, 2 h, 94% yield; 2. Mg^0, MeOH, RT, 2 h 93% yield; c) $LiAlH_4$, THF, −78 °C, 4 h, **7ba**: 80% yield; **7da**: 73% yield; **7ga**: 76% yield; d) 1. NaOH, DME/H_2O (1.6:1), RT, 5 h; 2. $TMSCHN_2$ in hexanes, MeOH, RT, **8ba**: 80% yield (2 steps from **7ba**); **8da**: 73% yield (2 steps from **7da**); **8ga**: 71% yield (2 steps from **7ga**). Boc = *tert*-butoxycarbonyl; DMAP = 4-(dimethylamino)pyridine; DME = 1,2-dimethoxyethane.

not only a β-amino acid, but also of an azetidine-2-carboxylic acid, which is not readily accessible from Mannich adducts lacking the trichloromethyl ketone moiety. β-Amino ester **5ba** was obtained in greater than 99% yield from **4ba** by treatment with NaOMe in MeOH at 0 °C for 10 minutes. Removal of the 2-pyridinesulfonyl group proceeded smoothly with Mg^0 in MeOH at room temperature,[8] to give **6ba** in good yield. Stereoselective reduction of **4** with $LiAlH_4$, and subsequent dichlorooxirane formation and stereoselective intramolecular cyclization using NaOH in DME at room temperature gave azetidine carboxylic acids.[18] Epimerization was not observed during cyclization under basic conditions. After methylation with $TMSCHN_2$, azetidine esters **8** were obtained in 80–71% yield (in 2 steps from **7**).

In the present system, the addition of a suitable bidentate phosphine oxide **1a** or **1b** was key to the increased reactivity of $La(OAr)_3$ and to the *anti* selectivity. ^{31}P NMR analysis of **1a** showed a downfield shift after complexation of **1a** with $La(OAr^1)_3$, indicating the coordination of the phosphine oxide to the lanthanum metal center. In Figure 2, the extent of a deuterium substitution[19] of the α protons in trichloromethyl ketone **3c** upon reaction with Ar^1OD catalyzed by

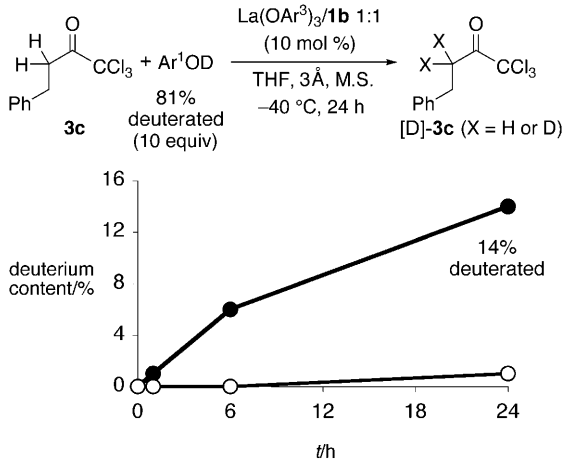


Figure 2. Deuterium exchange experiments with and without the Lewis base; ●: with Lewis base **1b**, ○: without Lewis base.

$La(OAr^3)_3$ was monitored by ^1H NMR spectroscopy. $La(OAr^3)_3$/Lewis base **1b** gave 14% deuteration after 24 hours, whereas $La(OAr^3)_3$ alone resulted in only a trace, if any, deuteration, providing direct evidence that the La–enolate-formation step by deprotonation was accelerated by Lewis base **1b**. With only Lewis base **1b**, deuteration was not observed after 24 hours. These results led us to assume that a catalytic amount of Lewis base **1b** coordinated to the lanthanum metal center and increased the Brønsted basicity of the lanthanum aryloxide moiety. The present $La(OAr)_3$/**1a** or **1b** system gives *anti* adducts,[20] whereas the previously reported $La(OAr)_3$/pybox afforded *syn* adducts. The observed *anti* selectivity in the present system can be explained by the difference in the nucleophilicity of the La–enolate. Strong Lewis bases such as **1a** and **1b** would increase the nucleophilicity of the La–enolate, therefore leading to a favorable sterically less-hindered acyclic *anti*-periplanar transition-state (Figure 3A) to give the *anti* adduct, analogous to a Lewis base promoted *anti*-Mannich reaction of silyl enolates.[21] With pybox ligands, a crowded cyclic transition state (Figure 3B) would be preferable because the imine is activated by the Lewis acidic lanthanum metal center to compensate for the lower nucleophilicity of the La–enolate. The $La(OAr^1)_3$/**1a** (Ar^1 = 4-MeO-C_6H_4) system gave **4ba** in a *anti*/*syn* 42:1 ratio (Table 2, entry 3), whereas the $La(OAr^2)_3$/**1a** (Ar^2 = 4-Br-C_6H_4) system resulted in poor diastereoselectivity (Table 2, entry 5). Moreover, the strongly electron-donating Me_2N substituted *i*Pr–pybox resulted in a significant loss of *syn* selectivity compared to *i*Pr–pybox (Table 1, entries 1 and 4). These results support the idea that the nucleophilicity of the La–enolate is one of the key factors in determining the diastereoselectivity. Additional mechanistic studies are ongoing to clarify the steric effects of the bidentate phosphine oxides and the difference in the Lewis acidity of the

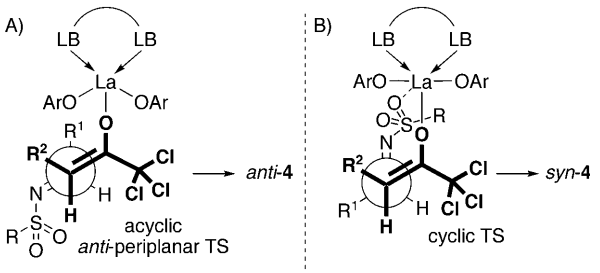
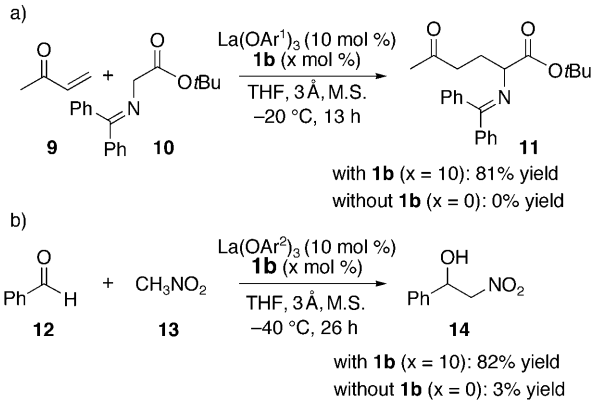


Figure 3. Postulated transition-state (TS) models. A) Acyclic TS leading to *anti*-**4** and B) cyclic TS leading to *syn*-**4**.

lanthanum metal center depending on the Lewis basic ligands, which might also be important for diastereo-switching.

To demonstrate that the Lewis base assisted Brønsted base catalysis is not restricted to the specific reaction using trichloromethyl ketones **3** and imines **2**, we performed additional experiments using different nucleophiles and electrophiles. Michael reaction of **9** with glycine Schiff base **10** at −20 °C proceeded only in the presence of Lewis base **1b** (Scheme 3 A). In a nitroaldol reaction of aldehyde **12** with nitromethane **13**, a significant difference in the reactivity was observed when using $La(OAr^2)_3$ (Ar^2 = 4-Br-C_6H_4) as the Brønsted base catalyst at −40 °C (Scheme 3 B). These results clearly indicate that Lewis base **1b** enhanced the catalytic activity of the $La(OAr)_3$ species.



Scheme 3. Reactivity difference observed for a) the Michael reaction and b) the nitroaldol reaction.

In summary, we described the utility of Lewis base assisted Brønsted base combined catalysis. A catalytic amount of Lewis basic bidentate phosphine oxides (**1**) effectively activated and modified the properties of Brønsted basic rare-earth metal aryloxide catalysts to realize the *anti*-selective direct catalytic Mannich-type reaction. The reactivity and selectivity of Brønsted basic rare-earth metal aryloxides were completely changed by a catalytic amount of Lewis base. The extension of this concept to other reactions, the improvement of the enantioselective reaction, and additional mechanistic studies are ongoing.

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[16] *N*-Ts imine derived from benzaldehyde was also suitable for *anti*-selective reactions under the optimized reaction conditions (98% yield, *anti*/*syn* > 20:1). We utilized *N*-heteroarenesulfonyl imines in this study because the removal of *N*-heteroarenesulfonyl is known to proceed under milder conditions than *N*-Ts group, see reference [8].

[17] We assume that 20 mol% of **1b** was favorable to form active species in Scheme 1 because Ar^4OH is sterically more crowded than other ArOH. Chiral phosphine oxides, such as a binap-dioxide (binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl), were not suitable to induce enantioselectivity in the present *anti*-selective Mannich-type reaction.

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