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Direct Catalytic Asymmetric Addition of Allyl Cyanide to Ketones via Soft Lewis Acid/Hard Brønsted Base/Hard Lewis Base Catalysis

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Abstract: We report that a hard Lewis base substantially affects the reaction efficiency of direct catalytic asymmetric γ-addition of allyl cyanide (**1a**) to ketones promoted by a soft Lewis acid/hard Brønsted base catalyst. Mechanistic studies have revealed that Cu/(*R*,*R*)-Ph-BPE and Li(OC_6H_4-*p*-OMe) serve as a soft Lewis acid and a hard Brønsted base, respectively, allowing for deprotonative activation of **1a** as the rate-determining step. A ternary catalytic system comprising a soft Lewis acid/hard Brønsted base and an additional hard Lewis base, in which the basicity of the hard Brønsted base Li(OC_6H_4-*p*-OMe) was enhanced by phosphine oxide (the hard Lewis base) through a hard−hard interaction, outperformed the previously developed binary soft Lewis acid/hard Brønsted base catalytic system, leading to higher yields and enantioselectivities while using one-tenth the catalyst loading and one-fifth the amount of **1a**. This second-generation catalyst allows efficient access to highly enantioenriched tertiary alcohols under nearly ideal atom-economical conditions (0.5−1 mol % catalyst loading and a substrate molar ratio of 1:2).

Introduction

Catalytic asymmetric construction of stereogenic tetrasubstituted carbon centers is a stimulating challenge in modern organic synthesis.[1] In particular, the manifestation of the above transformation via proton-transfer conditions will provide a truly advanced methodology in terms of atom economy[2] and environmentally benign synthetic processes.[3] Various methodologies based on the addition of preactivated nucleophiles to ketones have been developed for catalytic asymmetric synthesis of enantioenriched tertiary alcohols, which have a broad utility in organic synthesis.[4] Most of these methods rely on the high nucleophilicities of organometallic reagents (B,[5] Si,[6] Zn,[7] Sn,[8] etc.[9]) or enol silyl ethers[10] to compensate for the attenuated reactivity of ketones accompanied by the inevitable generation of (more than) stoichiometric amounts of unwanted waste, which

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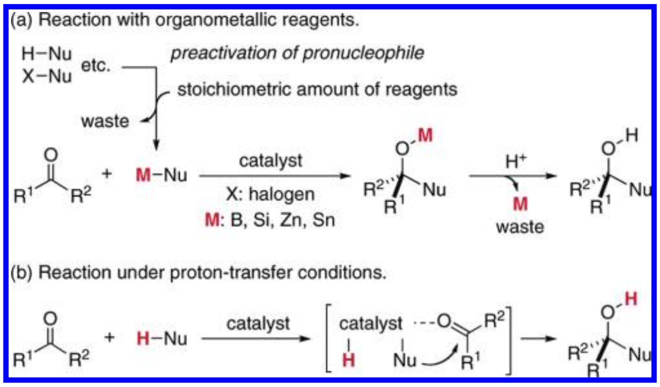
Scheme 1. Catalytic Asymmetric Addition to Ketones with (a) Reactive Organometallic Reagents and (b) Pronucleophiles Activated in Situ



significantly decreases the overall reaction efficiency (Scheme 1a). Catalytic generation of a nucleophile by simple deprotonation that is sufficiently active to attack ketones without the retro-reaction is the key to overcoming the above-mentioned drawback (Scheme 1b).[11−13] Until recently, HCN has been the only pronucleophile that meets the criteria,[14] likely because the generation of highly active nucleophiles by deprotonation requires harsh Brønsted basic conditions, which compromise the catalytic turnover and induce undesirable side reactions. In this context, we directed our attention toward the cooperative use of a soft Lewis acid and a hard Brønsted base to achieve chemoselective activation/deprotonation of a soft Lewis basic pronucleophile under mild conditions (Figure 1). Particular focus was placed on allylic cyanides as potential pronucleophiles for this purpose because (1) the minimal steric bias of the nitrile group is beneficial for the highly congested transition state anticipated for the reaction with ketones; (2) the soft Lewis basic character of the nitrile functionality allows for chemoselective activation in the presence of a soft Lewis acid; and (3) the adjacent vinyl group enhances the acidity of the α-hydrogen of the nitrile to facilitate deprotonation under mild basic conditions and serves as a useful handle for further elaboration of the reaction products.[15−19] On the basis of this hypothesis, we developed a chiral soft Lewis acid/hard Brønsted base catalytic system consisting of $[Cu(CH_3CN)_4]ClO_4$/(*R*,*R*)-Ph-BPE/LiOAr that enables direct catalytic asymmetric γ-addition of allyl cyanide (**1a**) to ketones,[20] producing a tetrasubstituted stereogenic center bearing a *Z*-configured olefin via proton-transfer conditions in conjunction with C−C bond formation (Scheme

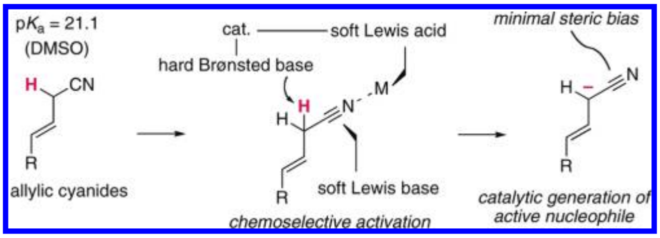


Figure 1. Chemoselective activation of allylic cyanides with a soft Lewis acid/hard Brønsted base catalyst.

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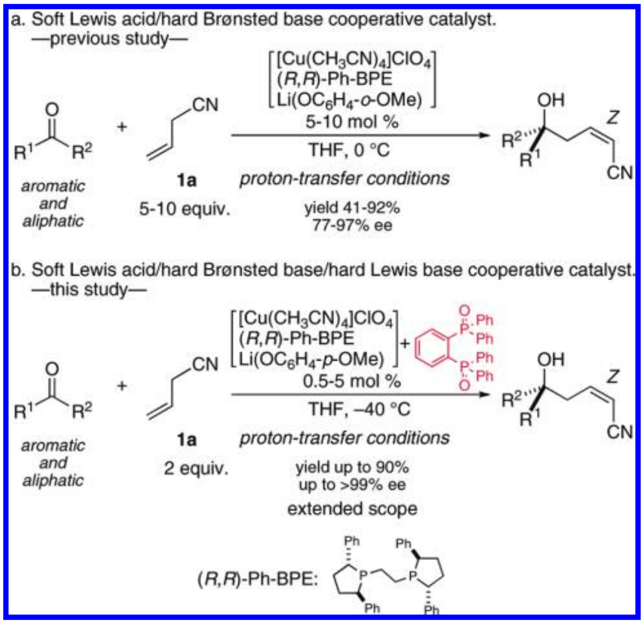
Scheme 2. Catalytic Asymmetric γ-Addition of Allyl Cyanide (**1a**) to Ketones

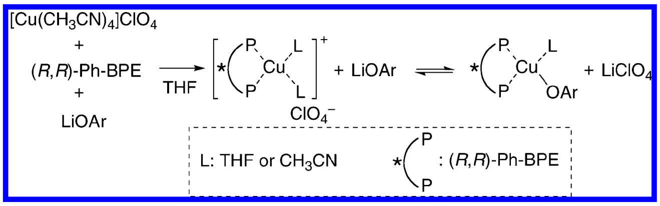


2a).[21] Although this methodology utilizing soft Lewis acid/hard Brønsted base cooperative catalysis allows for the direct catalytic asymmetric addition of **1a** via proton-transfer conditions, high catalyst loading (5−10 mol %) and an excess amount of pronucleophile **1a** significantly decrease the utility of the reaction as an atom-economical/environmentally benign synthetic methodology.[22] Herein, we report mechanistic studies of the reaction that led us to develop a second-generation catalytic system involving a soft Lewis acid/hard Brønsted base/hard Lewis base ternary catalyst. The third component of the catalyst, the hard Lewis base, substantially improved the catalytic performance, accomplishing the above reaction with higher enantioselectivity in most cases by using 2 equiv of **1a** and 1 mol % catalyst loading (Scheme 2b). Various spectroscopic analyses provided insight into the role of the hard Lewis base.

Results and Discussion

Control Experiments and Kinetic Profile of the Direct Catalytic Asymmetric Addition of Allyl Cyanide (1a) to Acetophenone (2a). To gain insight into the prospective improvement of the reaction efficiency with regard to catalyst loading and amount of **1a**, we proceeded to dissect the reaction profile through systematic control experiments and kinetic studies. We initially focused on identifying the actual active species formed by mixing the three catalyst components

Scheme 3. Expected Equilibrium of the Catalyst Components



$[Cu(CH_3CN)_4]ClO_4$, (*R*,*R*)-Ph-BPE, and $Li(OC_6H_4$-*p*-OMe) in THF (Scheme 3). Analyses of a 1:1 mixture of $[Cu(CH_3CN)_4]ClO_4$ and (*R*,*R*)-Ph-BPE in THF-d_8 using ^1H NMR spectroscopy and electrospray ionization mass spectrometry (ESI-MS) indicated that a 1:1 Cu/(*R*,*R*)-Ph-BPE complex [Cu/(*R*,*R*)-Ph-BPE]ClO_4 was formed without the formation of a 1:2 Cu/(*R*,*R*)-Ph-BPE complex.[23] Subsequent addition of $Li(OC_6H_4$-*p*-OMe) led to the formation of a $Cu(OC_6H_4$-*p*-OMe)/(*R*,*R*)-Ph-BPE complex and $LiClO_4$,[24] which was presumably in equilibrium with the [Cu/(*R*,*R*)-Ph-BPE]ClO_4 complex and $Li(OC_6H_4$-*p*-OMe). The existence of an equilibrium between {[Cu/(*R*,*R*)-Ph-BPE]ClO_4 + $Li(OC_6H_4$-*p*-OMe)} and {$Cu(OC_6H_4$-*p*-OMe)/(*R*,*R*)-Ph-BPE + $LiClO_4$} was supported by the coalescing peaks in a variable-temperature ^1H NMR experiment on a solution of $[Cu(CH_3CN)_4]ClO_4$ and $Li(OC_6H_4$-*p*-OMe) in THF-d_8 (Figure 2),[25] suggesting that the equilibrium shown in Scheme 3 is valid.

To determine which species in Scheme 3 is responsible for the effective promotion of the reaction, a series of control experiments was performed using **1a** and acetophenone (**2a**) as model substrates. In the absence of either the hard Brønsted base $Li(OC_6H_4$-*p*-OMe) or the soft Lewis acid $[Cu(CH_3CN)_4]ClO_4$, the reaction did not proceed at all (Scheme 4a,b). The candidates for the Brønsted base in the catalyst solution that initiates the reaction by the deprotonation of **1a** were $Li(OC_6H_4$-*p*-OMe) and $Cu(OC_6H_4$-*p*-OMe)/(*R*,*R*)-Ph-BPE (Scheme 3). To clarify which was the actual Brønsted base, the reaction was conducted using $Cu(OC_6H_4$-*p*-OMe)/(*R*,*R*)-Ph-BPE as the Brønsted base in the absence of Li cations.[26] $Cu(OC_6H_4$-*p*-OMe)/(*R*,*R*)-Ph-BPE, which was prepared by mixing equimolar amounts of mesitylcopper(I) and HOC_6H_4-*p*-OMe,[27] exhib-

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(26) For selected examples of catalytic asymmetric C−C or C−B bond formation using copper alkoxides, see: (a) Pagenkopf, B. L.; Krüger, J.; Stojanovic, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3124. (b) Suto, Y.; Tsuji, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 3757. (c) Asano, Y.; Hara, K.; Ito, H.; Sawamura, M. *Org. Lett.* **2007**, *9*, 3901. (d) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034. (e) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687. (f) Motoki, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 2997. (g) Lee, J.-E.; Yun, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 145. (h) Chen, I.-H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 11664. (i) Sasaki, Y.; Zhong, C.; Sawamura, M.; Ito, H. *J. Am. Chem. Soc.* **2010**, *132*, 1226. Also see ref 16h,i.

(27) For the synthesis, characterization, and application of mesitylcopper, see: (a) Tsuda, T.; Yazawa, T.; Watanabe, K.; Fujii, T.; Saegusa, T. *J. Org. Chem.* **1981**, *46*, 192. (b) Tsuda, T. *Encyclopedia of Reagents for Organic Synthesis*: Paquette, L., Ed.; Wiley: New York, 1995; p 3271. (c) Eriksson, H.; Håkansson, M. *Organometallics* **1997**, *16*, 4243.

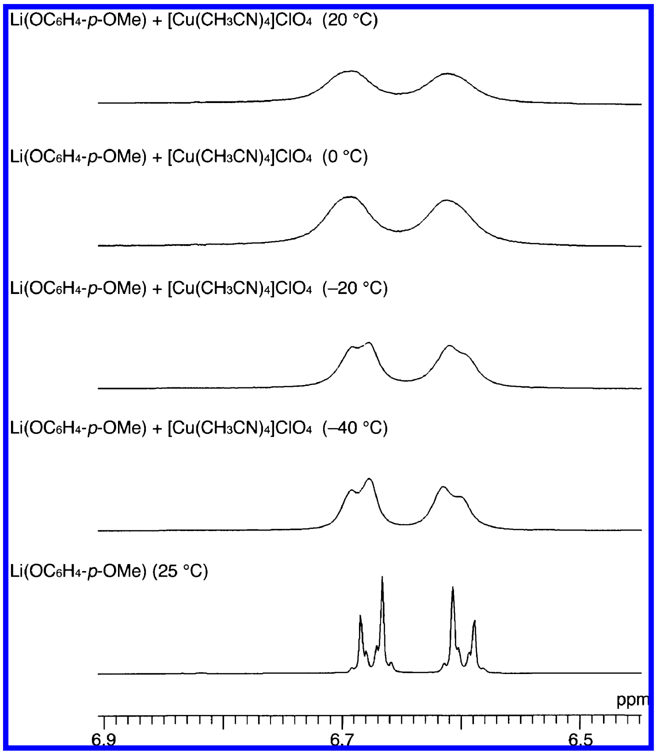
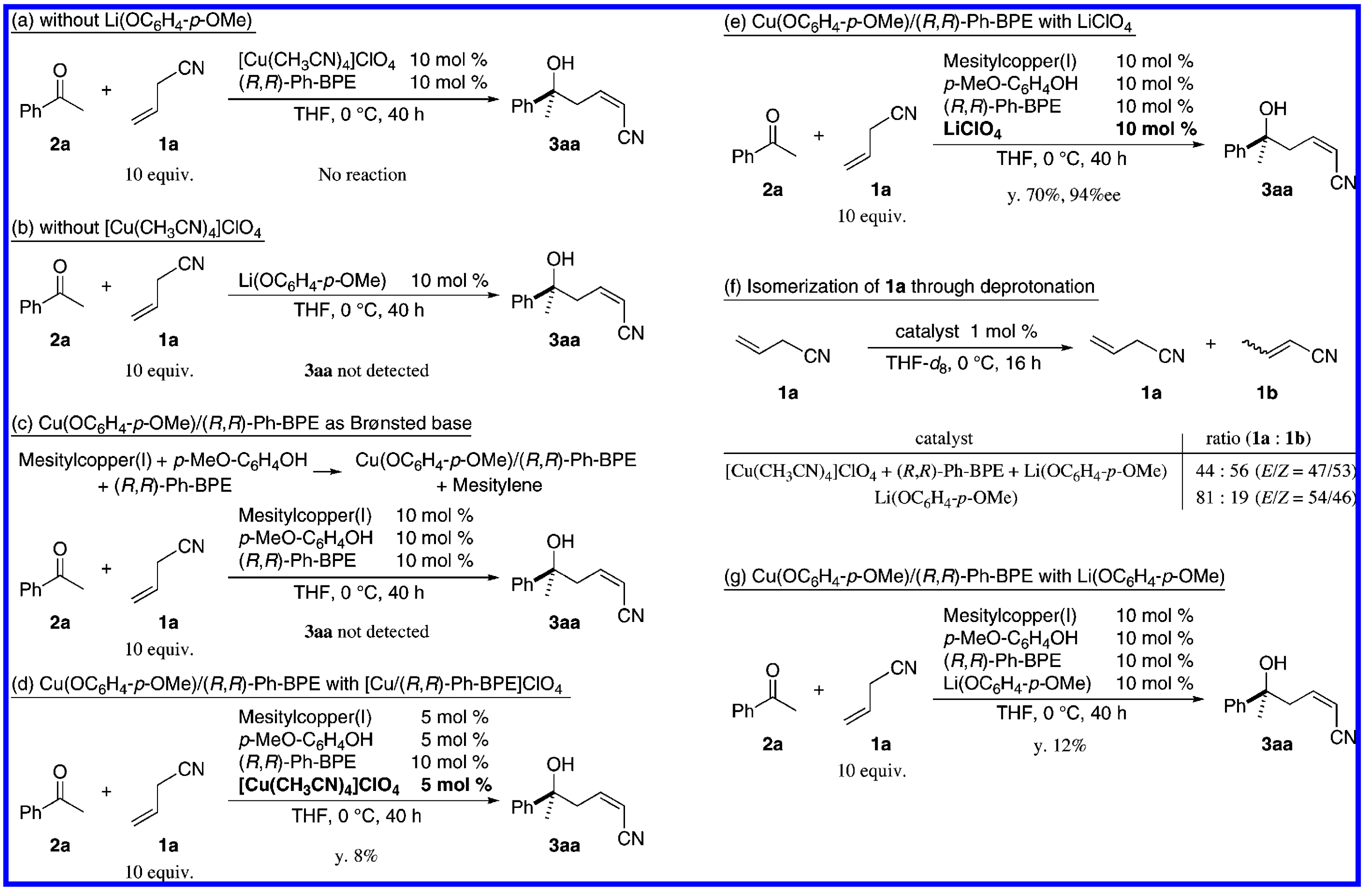


Figure 2. Variable-temperature ^1H NMR spectra of a solution of $[Cu(CH_3CN)_4]ClO_4$ and $Li(OC_6H_4\text{-}p\text{-}OMe)$ in THF-d_8 and the ^1H NMR spectrum of $Li(OC_6H_4\text{-}p\text{-}OMe)$ in THF-d_8 at 25 °C.

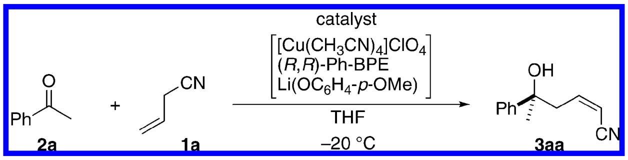
ited almost no catalytic activity in the reaction of **1a** with **2a** (Scheme 4c). Under the assumption that a cationic copper(I) salt is indispensable for activation of **1a** for deprotonation through a soft−soft interaction, a $Cu(OC_6H_4\text{-}p\text{-}OMe)$/(*R*,*R*)-Ph-BPE + $[Cu(CH_3CN)_4]ClO_4$ mixed catalytic system was studied (Scheme 4d). The resultant poor catalytic performance corroborated that $Cu(OC_6H_4\text{-}p\text{-}OMe)$/(*R*,*R*)-Ph-BPE is not the actual Brønsted base. When the reaction was conducted using $Cu(OC_6H_4\text{-}p\text{-}OMe)$/(*R*,*R*)-Ph-BPE with a catalytic amount of $LiClO_4$, the catalytic activity was restored, and product **3aa** was obtained in 70% yield with high enantioselectivity (94% ee) comparable to that obtained under the standard reaction conditions (Scheme 4e), presumably because $Li(OC_6H_4\text{-}p\text{-}OMe)$, a plausible acual Brønsted base, was generated by the equilibrium shown in Scheme 3. Undesirable isomerization of **1a** occurred gradually to give an *E*/*Z* mixture of crotononitrile (**1b**) triggered by deprotonation in the presence of a standard catalyst (Scheme 4f); **1b** did not act as a pronucleophile. $Li(OC_6H_4\text{-}p\text{-}OMe)$ itself induced the isomerization at a much lower rate than the standard catalyst, suggesting that [Cu/(*R*,*R*)-Ph-BPE]ClO_4 serves as a soft Lewis acid that activates **1a** through a soft−soft interaction to accelerate the deprotonation step. This assumption was further supported by the fact that the catalyst comprising the weak soft Lewis acid $Cu(OC_6H_4\text{-}p\text{-}OMe)$/(*R*,*R*)-Ph-BPE and the base $Li(OC_6H_4\text{-}p\text{-}OMe)$, in which cationic [Cu/(*R*,*R*)-Ph-BPE]ClO_4 as an effective soft Lewis acid was never formed, was far less efficient in promoting the reaction (Scheme 4g). On the basis of these observations, the most likely scenario for the present catalysis is that (1) {[Cu/(*R*,*R*)-Ph-BPE]ClO_4 + $Li(OC_6H_4\text{-}p\text{-}OMe)$} and {$Cu(OC_6H_4\text{-}p\text{-}OMe)$/(*R*,*R*)-Ph-BPE + $LiClO_4$} are in equilibrium; (2) the actual Brønsted base is $Li(OC_6H_4\text{-}p\text{-}OMe)$; and (3) [Cu/(*R*,*R*)-Ph-BPE]ClO_4 activates **1a** at the

Scheme 4. Series of Control Experiments Using **1a** and **2a** as Model Substrates



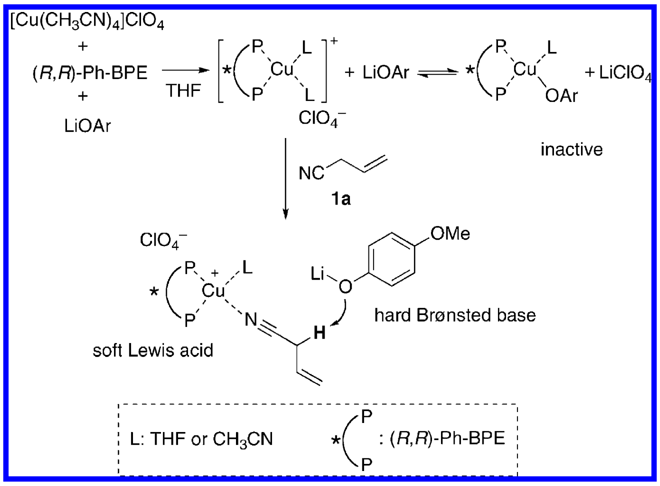
catalyst	ratio (**1a** : **1b**)
$[Cu(CH_3CN)_4]ClO_4$ + (*R*,*R*)-Ph-BPE + $Li(OC_6H_4\text{-}p\text{-}OMe)$	44 : 56 (*E*/*Z* = 47/53)
$Li(OC_6H_4\text{-}p\text{-}OMe)$	81 : 19 (*E*/*Z* = 54/46)

Table 1. Kinetic Profile of the Direct Catalytic Asymmetric Addition of **1a** to **2a**



species	order
catalyst	1.3
allyl cyanide (**1a**)	0.9
acetophenone (**2a**)	0.1

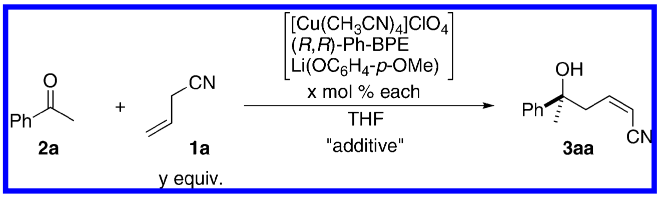
Scheme 5. Li(OC$_6$H$_4$-*p*-OMe) as the Actual Active Brønsted Base



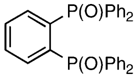
deprotonation stage, and the resultant allylcopper nucleophile is involved in the subsequent enantioselective addition to **2a**.

The initial-rate kinetic study of the reaction of **1a** and **2a** was performed at −20 °C in THF and revealed orders of 1.3, 0.9, and 0.1 with respect to the catalyst, **1a**, and **2a**, respectively (Table 1).[23] In view of the relatively high pK_a value of the α-proton of **1a**, the rate-determining step is likely the deprotonation step,[28] in which **1a**, after activation by [Cu/(*R*,*R*)-Ph-BPE]ClO$_4$ in an end-on fashion, is deprotonated by Li(OC$_6$H$_4$-*p*-OMe) (Scheme 5).[29,30]

Table 2. Enhancement of the Catalytic Activity in the Reaction of **1a** with **2a** in the Presence of a Hard Lewis Base[a]



entry	*x*	*y*	additive (mol %)	temp. (°C)	time (h)	yield (%)[b]	ee (%)
1	10	10	–	0	16	83	95
2	10	10	–	−40	16	22	99
3	10	10	Ph$_3$P=O (10)	−40	16	91	99
4	10	10	Ph$_3$P=O (20)	−40	16	89	99
5	1	2	Ph$_3$P=O (1)	−40	16	44	99
6	1	2	**4** (1)	−40	16	69	99
7[c]	1	2	**4** (1)	−40	40	86[d]	99



4

[a] Using 0.2 mmol of **2a** and 0.2*y* mmol of **1a**, unless otherwise noted. [b] Determined by ^{1}H NMR analysis using 2-methoxynaphthalene as an internal standard. [c] Using 0.4 mmol of **2a** and 0.4*y* mmol of **1a**. [d] Isolated yield.

Enhancement of the Basicity by the Action of a Hard Lewis Base. Examination of the catalytic system identified that the deprotonation step is likely to be the rate-determining step and that the active Brønsted base is Li(OC$_6$H$_4$-*p*-OMe). We hypothesized that enhancing the deprotonation process would increase the overall reaction rate and reduce both the catalyst loading and the requisite amount of **1a**, providing a more viable catalytic asymmetric approach for accessing enantioenriched tertiary alcohols under proton-transfer conditions. Extensive ligand screening suggested that the combination of (*R*,*R*)-Ph-BPE and [Cu(CH$_3$CN)$_4$]ClO$_4$ was optimum for enantioselectivity, so we turned our attention to enhancing the basicity of the hard Brønsted base. The reaction of **1a** and **2a** proceeded with nearly perfect enantioselectivity at −40 °C under conditions otherwise identical to the previously developed conditions, albeit with lower chemical yield (Table 2, entries 1 and 2). Thus, the subsequent studies were performed at −40 °C to compare the effects of the conditions employed on the reaction efficiency. The fact that Li(OC$_6$H$_4$-*p*-OMe) exhibited the best enantioselectivity prompted us to enhance the basicity of Li(OC$_6$H$_4$-*p*-OMe) with the aid of a hard Lewis base.[31,32] Among the chemical species in the present reaction system, the hard Lewis base was anticipated to preferentially coordinate to the Li cation, leading to an increased negative charge (and therefore stronger

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(28) The catalyst turnover step, namely, protonation of metalated **3aa**, would proceed with HOC$_6$H$_4$-*p*-OMe rather than **1a** on the basis of the much higher (kinetic and thermodynamic) acidity of HOC$_6$H$_4$-*p*-OMe. **1a** would not be involved in the catalyst turnover step.

(29) Coordination in an end-on fashion has been generally proposed for nitriles. See: (a) Michelin, R. A.; Mozzon, M.; Bertani, R. *Coord. Chem. Rev.* **1996**, *147*, 299. (b) Kukushkin, V. Y.; Pombeiro, A. J. L. *Chem. Rev.* **2002**, *102*, 1771.

(30) For selected examples of side-on coordination of nitriles to transition metals, see: (a) Thomas, S.; Young, C. G. *Organometallics* **1998**, *17*, 182. (b) Shin, J. H.; Savage, W.; Murphy, V. J.; Bonanno, J. B.; Churchill, D. G.; Parkin, G. *J. Chem. Soc., Dalton Trans.* **2001**, 1732. (c) Atesin, T. A.; Li, T.; Lachaize, S.; Brennessel, W. W.; García, J. J.; Jones, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 7562. (d) Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874. (e) Ohnishi, Y.; Nakao, Y.; Sato, H.; Nakao, Y.; Hiyama, T.; Sakaki, S. *Organometallics* **2009**, *28*, 2583.

(31) In the previous communication (ref 20a), Li(OC$_6$H$_4$-*o*-OMe) was used to obtain a slight improvement in the chemical yield (the enantioselectivities were identical). The use of Na(OC$_6$H$_4$-*p*-OMe) or K(OC$_6$H$_4$-*p*-OMe) resulted in lower enantioselectivity (76% yield, 96% ee for Na and 87% yield, 85% ee for K under reaction conditions otherwise identical to those for entry 2).

(32) Li(OC$_6$H$_4$-*p*-OMe) is known to form a tetramer (ref 25). The possibility that the enhanced catalytic activity of Li(OC$_6$H$_4$-*p*-OMe) in the presence of a hard Lewis base (entries 3−7) originates from the dissociation of this relatively stable tetramer cannot be ruled out.

(33) For a comprehensive review of Lewis base catalysis, see: (a) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560, and references cited thereinFor selected examples of Lewis base activation of Brønsted bases, see: (b) McGrath, M. J.; O'Brien, P. *J. Am. Chem. Soc.* **2005**, *127*, 16378. (c) Saito, S.; Tsubogo, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2007**, *129*, 5364. (d) Morimoto, H.; Yoshino, T.; Yukawa, T.; Lu, G.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 9125.

(34) Enhanced Lewis basicity of LiOPh was observed by using bidentate bis(phosphine oxide) **4** in Mukaiyama aldol reactions. X-ray crystallographic analysis proved the coordination of **4** to the Li cation in a bidentate fashion. See: Hatano, M.; Takagi, E.; Ishihara, K. *Org. Lett.* **2007**, *9*, 4527.

(35) Lewis basic additive **4** was less efficient in the reactions using Na(OC$_6$H$_4$-*p*-OMe) and K(OC$_6$H$_4$-*p*-OMe) as the Brønsted base (63% yield, 98% ee for Na and 57% yield, 98% ee for K under reaction conditions otherwise identical to those of entry 6).

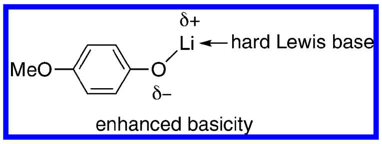

Figure 3. Enhancement of the basicity of the lithium aryloxide by the hard Lewis base.

Brønsted basicity) on the aryloxide anions (Figure 3).[33] Indeed, the addition of $Ph_3P{=}O$ as a Lewis base substantially facilitated the reaction at −40 °C to afford **3aa** in 91% yield and 99% ee (entry 3). An equimolar amount of $Ph_3P{=}O$ relative to $Li(OC_6H_4$-*p*-OMe) was sufficient to boost the reaction (entries 3 and 4). The reaction could be performed with 1 mol % catalyst loading and 2 equiv of **1a** without any loss of enantioselectivity, albeit with moderate yield (entry 5). Bidentate bis(phosphine oxide) **4** exhibited better performance, giving **3aa** in 69% yield and 99% ee after 16 h with 1 mol % catalyst (entry 6), and the elongation of the reaction time to 40 h afforded satisfactory results (entry 7).[34,35]

The use of the hard Lewis base allowed us to successfully reduce the catalyst loading as well as the amount of **1a**, culminating in nearly ideal reaction conditions in terms of atom economy:[2] 1 mol % catalyst with 2 equiv of **1a** (Table 2, entry 7). The beneficial effect of hard Lewis base **4** was evaluated through ^{31}P NMR and ESI-MS analyses. As shown in Figure 4a−c, the downfield shift and line broadening of the ^{31}P signal for **4** in THF-d_8 was detected upon addition of $Li(OC_6H_4$-*p*-OMe) or $LiClO_4$, indicating coordination of **4** to Li cations.[34] In the absence of Li cations, the signal derived from [Cu/(*R*,*R*)-Ph-BPE]ClO_4 was upfield-shifted upon addition of **4**, with a concomitant downfield shift of the signal derived from **4** (Figure 4d,e), suggesting that **4** was coordinated to Cu cations to form [Cu/(*R*,*R*)-Ph-BPE/**4**]ClO_4, as confirmed by ESI-MS (Figure 5).[36] In the presence of Li cations, the intensity of the signal derived from [Cu/(*R*,*R*)-Ph-BPE/**4**]ClO_4 decreased, and the signal corresponding to [Cu/(*R*,*R*)-Ph-BPE]ClO_4 was restored (Figure 4f). The appearance of the peak derived from $LiClO_4$/**4** suggested that **4** is predominantly coordinated to Li cations in the catalyst solution, possibly because the hard−hard interaction ($P{=}O\cdots Li^+$) is more favorable than the hard−soft interaction ($P{=}O\cdots Cu^+$).

On the basis of the observations described above, a plausible catalytic cycle involving the soft Lewis acid/hard Brønsted base/hard Lewis base catalytic system comprising $[Cu(CH_3CN)_4]ClO_4$, (*R*,*R*)-Ph-BPE, $Li(OC_6H_4$-*p*-OMe), and bis(phosphine oxide) **4** is illustrated in Figure 6. Mixing $[Cu(CH_3CN)_4]ClO_4$, (*R*,*R*)-Ph-BPE, and **4** would generates the cationic complex [Cu/(*R*,*R*)-Ph-BPE/**4**]ClO_4, and the subsequent addition of $Li(OC_6H_4$-*p*-OMe) would lead to the formation of an equilibrium between {$Cu(OC_6H_4$-*p*-OMe)/(*R*,*R*)-Ph-BPE + $LiClO_4$/**4**} and {[Cu/(*R*,*R*)-Ph-BPE]ClO_4 + $Li(OC_6H_4$-*p*-OMe)/**4**}. [Cu/(*R*,*R*)-Ph-BPE]ClO_4 would activate **1a** as a soft Lewis acid, while $Li(OC_6H_4$-*p*-OMe)/**4** would serve as a hard Brønsted base to deprotonate the α-proton of **1a** and generate the α-*C*-copper active nucleophile α-**5a**, with the hard Lewis base **4** enhancing the basicity of $Li(OC_6H_4$-*p*-OMe) through coordination to the Li cation. The substantial acceleration of this step in the presence of **4** would be the basis for the significant improvement of the reaction efficiency: 1 mol % catalyst loading and 2 equiv of **1a**. The initially formed α-**5a** would be interconverted to the γ-*C*-copper nucleophile γ-**5a**, which should provide an *E*,*Z* mixture of the γ-addition product in the following 1,2-addition to the ketone.[37] The exclusive formation of a *Z*-configured olefin would be indicative of the involvement of a six-membered cyclic transition state. The proposed transi-

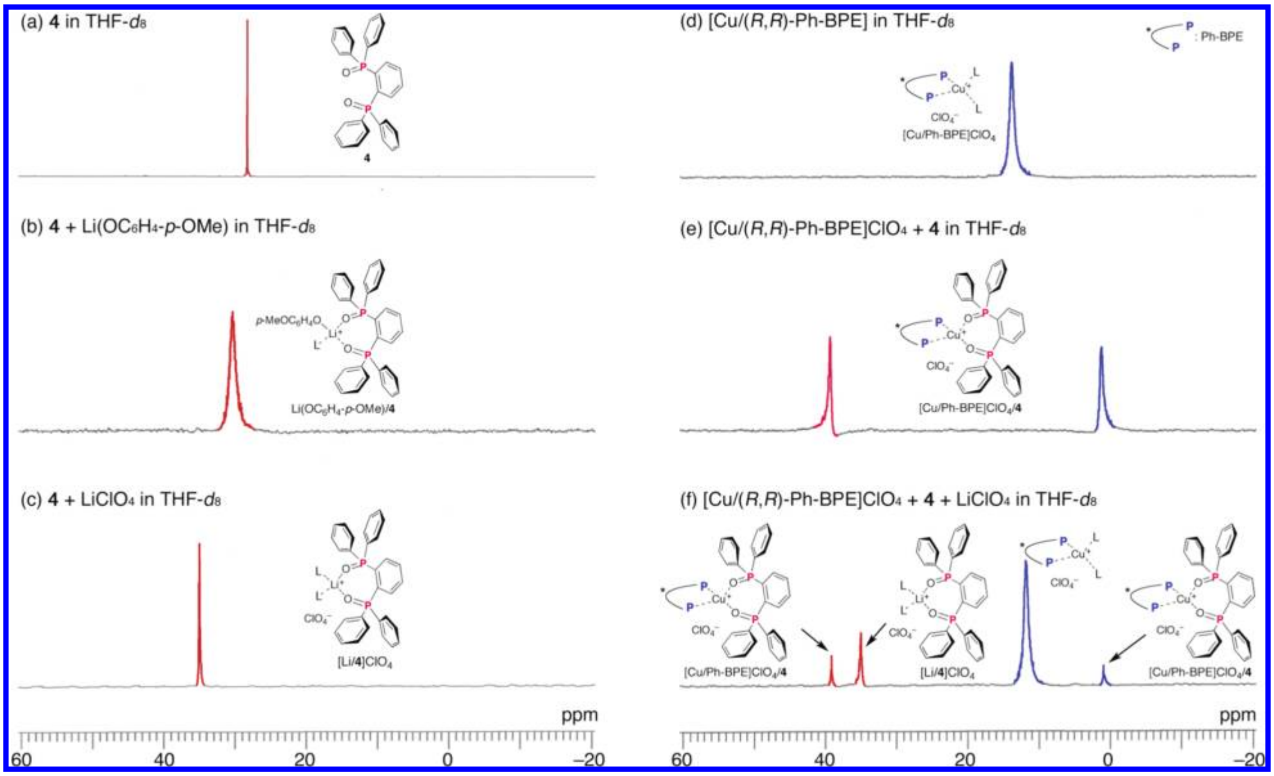

Figure 4. ^{31}P NMR spectra of **4** and (*R*,*R*)-Ph-BPE under various conditions: (a) **4** in THF-d_8; (b) **4** and $Li(OC_6H_4$-*p*-OMe) (1:1) in THF-d_8; (c) **4** and $LiClO_4$ (1:1) in THF-d_8; (d) [Cu/(*R*,*R*)-Ph-BPE]ClO_4 in THF-d_8; (e) [Cu/(*R*,*R*)-Ph-BPE]ClO_4 and **4** (1:1) in THF-d_8; (f) [Cu/(*R*,*R*)-Ph-BPE]ClO_4, $LiClO_4$, and **4** (1:1:1) in THF-d_8. "L" represents the solvent molecule (THF-d_8 or CH_3CN).

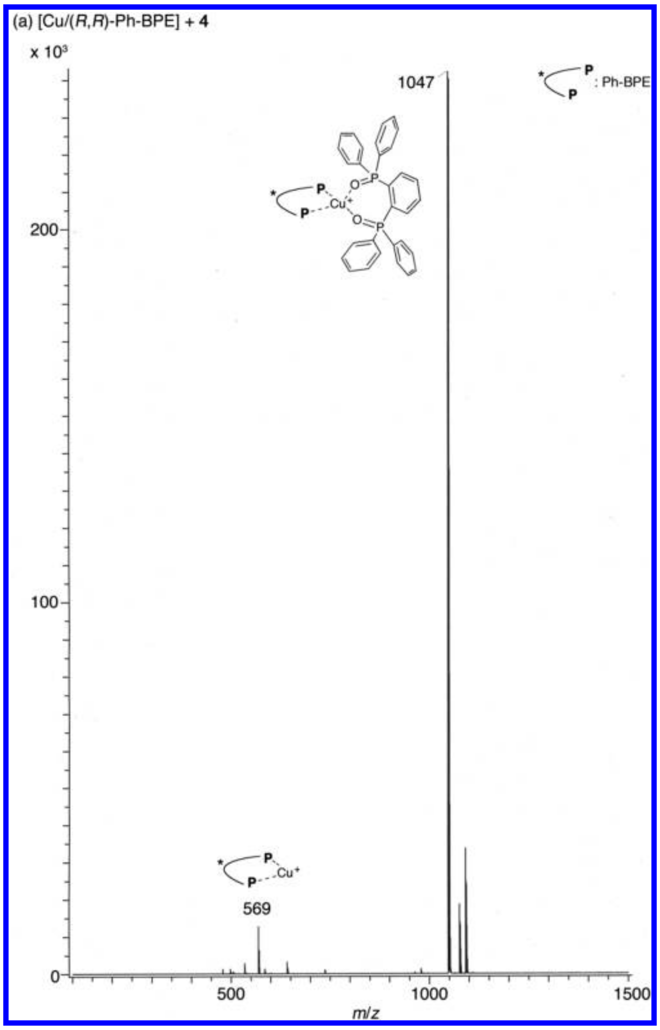

Figure 5. ESI-MS analysis of the solution containing [Cu(CH$_3$CN)$_4$]ClO$_4$, (*R*,*R*)-Ph-BPE, and **4** (1:1:1).

tion-state model is depicted as **6**, in which the reaction would proceed through the α-**5a** intermediate with the nitrile group occupying the pseudoaxial position to avoid steric repulsion with the phenyl group of (*R*,*R*)-Ph-BPE, affording the (*S*)-*Z*-adduct **3aa**. The molecular architecture of Cu/(*R*,*R*)-Ph-BPE was drawn on the basis of the X-ray crystal structure of the [CuCl/(*R*,*R*)-Ph-BPE]$_2$ dimer complex prepared from CuCl and (*R*,*R*)-Ph-BPE (Figure 7).[38] The linear relationship between the enantiopurity of Ph-BPE and the enantioselectivity of the product (Figure 8) is consistent with the assumption that the monomeric Cu complex is involved in the enantiodiscrimination step.[39,40]

Scope of the Catalytic Asymmetric Addition of 1a to Ketones via Soft Lewis Acid/Hard Brønsted Base/Hard Lewis Base Catalysis. Having significantly improved the reaction conditions, we proceeded to investigate the reaction with a diverse set of ketones (Table 3).[41] The newly developed conditions achieved higher enantioselectivities and comparable or higher chemical yields than obtained under the previously developed conditions, despite using one-tenth and one-fifth the amounts of the catalyst and **1a**, respectively (entries 1−5, 8−11, 16, and 17). Excellent enantioselectivity (99% ee) was observed with as little as 0.5 mol % catalyst loading (entry 2). The substrate scope was expanded to other α,β-unsaturated ketones and cyclic ketones, although a stronger base, LiO^{t}Bu, was required instead of Li(OC$_6$H$_4$-*p*-OMe) (entries 12−15). A beneficial effect of **4** was also observed for LiO^{t}Bu, possibly because the reaction is driven by the same mechanism. Reaction with 1-cyclohexenyl methyl ketone (**2k**) gave product **3ak** with 99% ee, but the reaction was sluggish even with 5 mol % catalyst loading (entry 12). Tetralone (**2m**) and indanone (**2n**) were converted to the desired products **3am** and **3an** in a highly enantioselective manner, albeit with moderate yields, presumably because the partial deprotonation of **2m** and **2n** retarded the addition of the active nucleophile (entries 14 and 15). Reactions with ketones bearing ethyl and *n*-propyl substituents exhibited lower reactivities, but both the yield and enantioselectivity were improved relative to the those obtained under previously developed conditions (entries 16 and 17). More sterically demanding ketone **2q** afforded the desired product **3aq** with excellent enantioselectivity using 5 mol % catalyst (entry 18). The reaction was sluggish with an aliphatic ketone, 3-phenyl-2-butanone (**2r**), and the product was obtained in moderate yield with insufficient enantiocontrol (entry 19).

The nitrile functionality of the product can serve as an effective handle for further elaboration. The δ-hydroxy amide entity **7aa** was generated by hydrolysis of **3aa** with Na$_2$CO$_3$ and hydrogen peroxide in acetone (Scheme 6). Protection of the tertiary hydroxyl group as the TMS ether **8aa** under neutral conditions[42] followed by reaction with DIBAL provided the corresponding aldehyde **9aa**. Hydride reduction of **8aa** mediated by AlCl$_3$ and LiAlH$_4$ afforded primary amine **10aa**,[43] demonstrating the divergent transformation of the nitrile functionality of the product. The *Z* configuration of the olefin was preserved during these transformations, as confirmed by nuclear Overhauser effect analysis.

Conclusion

A soft Lewis acid/hard Brønsted base/hard Lewis base catalytic system for the direct catalytic asymmetric γ-addition of allyl cyanide (**1a**) to ketones has been developed. The hard Lewis base, bis(phosphine oxide) **4**, substantially accelerates the overall reaction rate by enhancing the Brønsted basicity of Li(OC$_6$H$_4$-*p*-OMe) or LiO^{t}Bu, allowing the reaction to be performed with 0.5−1 mol % catalyst and 2 equiv of **1a** in most cases. The improved reaction conditions are highly

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(36) For an example of a Cu(I) complex coordinated with both phosphine and phosphine oxide, see: Côté, A.; Charette, A. B. *J. Org. Chem.* **2005**, *70*, 10864.

(37) For 1,3-transposition of allylic metal species, see: Sklute, G.; Marek, I. *J. Am. Chem. Soc.* **2006**, *128*, 4642, and references therein.

(38) Details of the X-ray analysis are described in the Supporting Information.

(39) The possibility that oligomeric homochiral and heterochiral complexes exhibit similar reactivity and enantioselectivity to afford the linear relationship cannot be ruled out.

(40) For recent comprehensive reviews of nonlinear effects in asymmetric catalysis, see: (a) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922. (b) Blackmond, D. G. *Acc. Chem. Res.* **2000**, *33*, 402. (c) Satyanarayana, T.; Abraham, S.; Kagan, H. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 456, and references cited therein.

(41) In the reaction with β- or γ-substituted allylic cyanides under the optimized reaction conditions, the desired products were not detected. The steric factor on the allylic cyanide is assumed to be critical in preventing the addition to ketones, possibly because of increased steric demands at the transition state.

(42) Karimi, B.; Golshani, B. *J. Org. Chem.* **2000**, *65*, 7228.

(43) Jaques, B.; Wallace, R. G. *Tetrahedron* **1977**, *33*, 581.

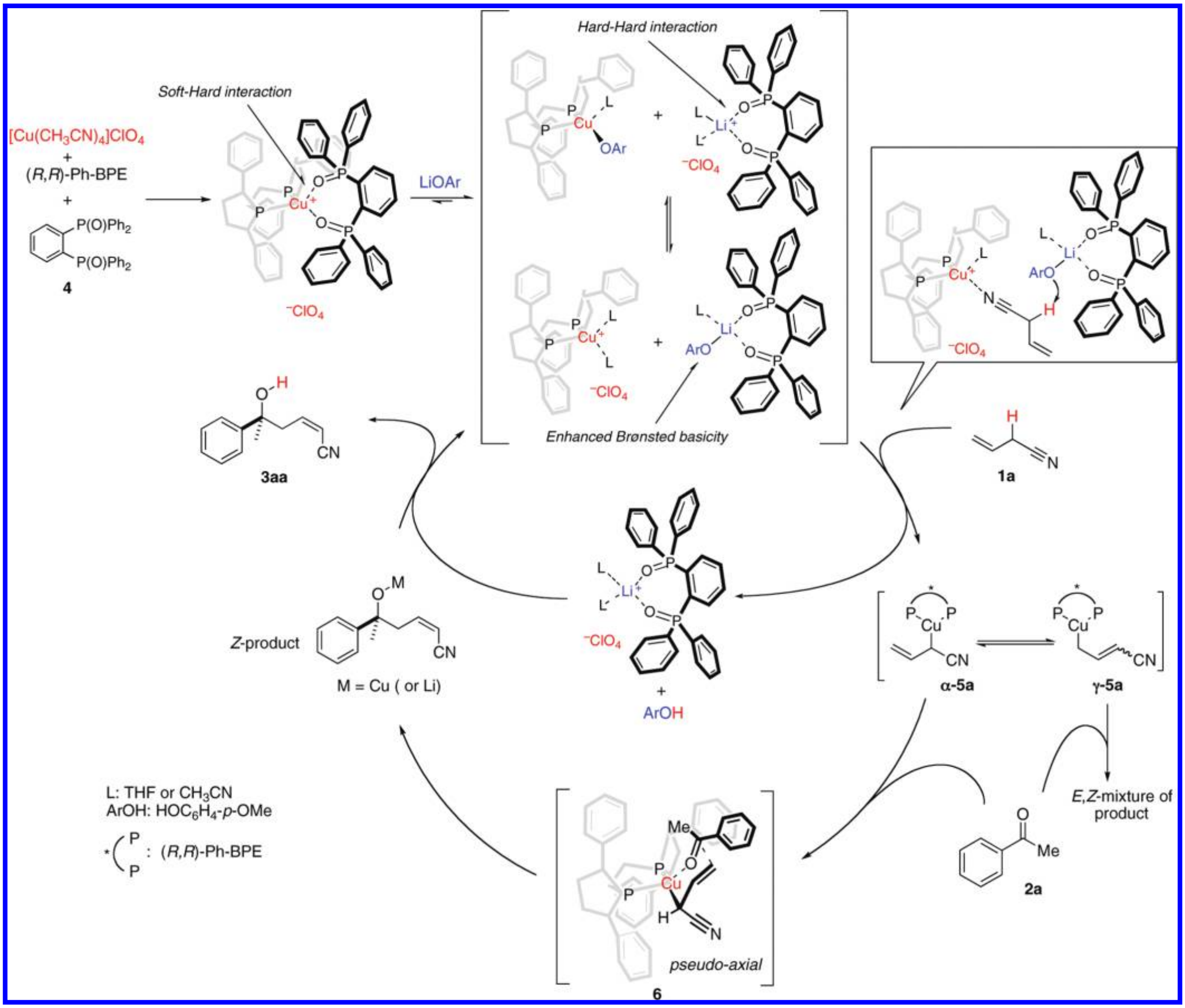


Figure 6. Plausible catalytic cycle.

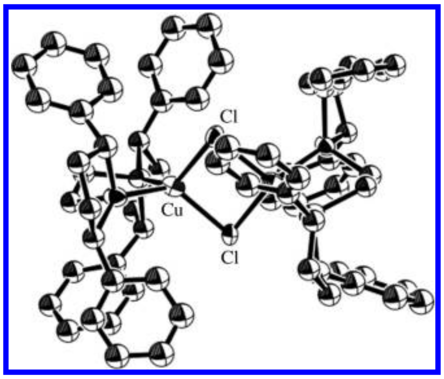


Figure 7. X-ray crystallographic structure of the dimer [CuCl(R,R)-Ph-BPE]$_2$. Hydrogens have been omitted for clarity.

advantageous in terms of atom economy and environmentally benign synthesis, affording enantioenriched tertiary alcohols under proton-transfer conditions from a simple set of substrates. Future efforts will be dedicated to application of

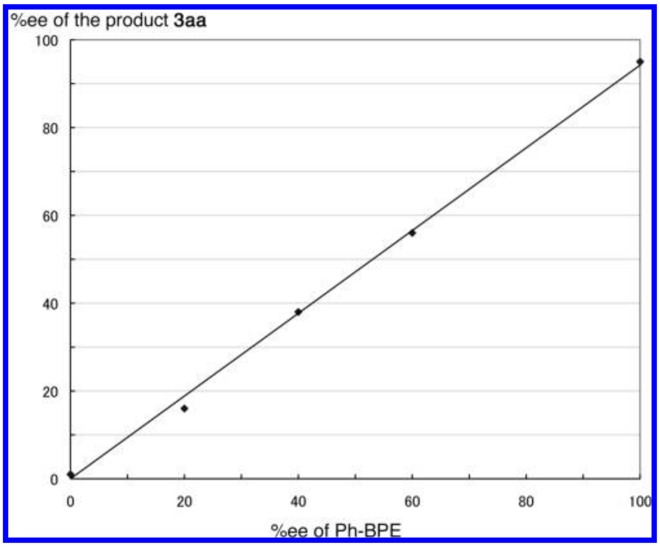
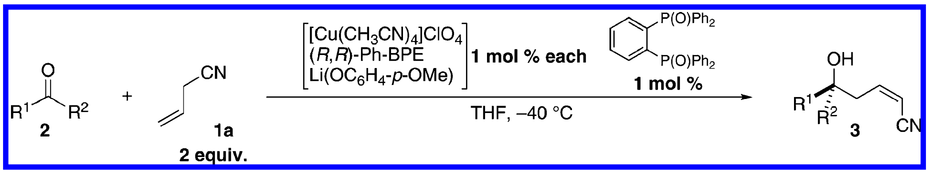
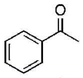
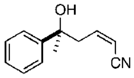
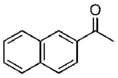
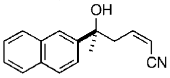
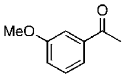
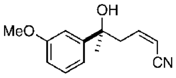
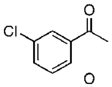
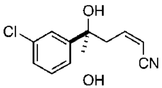
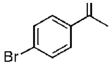
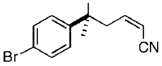
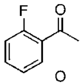
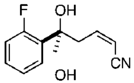
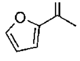
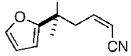
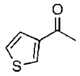
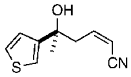
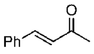
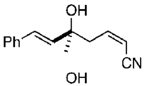
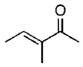
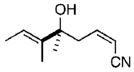
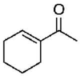
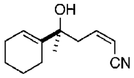
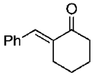
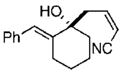
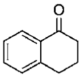
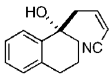
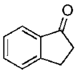
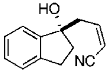
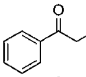
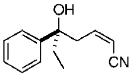
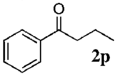
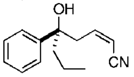
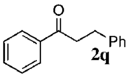
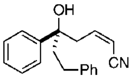
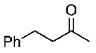
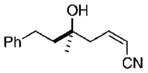


Figure 8. Plot of the enantioselectivity of the product **3aa** vs the enantiopurity of Ph-BPE.

Table 3. Catalytic Asymmetric γ-Addition of Allyl Cyanide (**1a**) to Ketones



entry	ketone	product	previous conditions[a] soft Lewis acid/hard Brønsted base 10 mol % cat., w/o Lewis base 10 equiv. of 1a, 0 °C time (h)	yield[c] (%)	ee (%)	newly developed conditions[b] soft Lewis acid/hard Brønsted base + hard Lewis base cat. (mol %)	time (h)	yield[c] (%)	ee (%)
1	 **2a**	 **3aa**	40	81	97	1	40	86	99
2						0.5	72	74	99
3	 **2b**	 **3ab**	40	88	96	1	40	81	98
4	 **2c**	 **3ac**	40	92	94	1	40	85	98
5	 **2d**	 **3ad**	40	76	95	1	40	90	99
6	 **2e**	 **3ae**	—	—	—	1	40	71	99
7	 **2f**	 **3af**	—	—	—	2	40	66	99
8	 **2g**	 **3ag**	40	80	84	1	40	68	91
9	 **2h**	 **3ah**	40	73	94	1	40	72	99
10	 **2i**	 **3ai**	40	79	78	1	40	62	88
11[d]	 **2j**	 **3aj**	40	54	88	5	40	42	>99
12[d]	 **2k**	 **3ak**	—	—	—	5	72	48	>99
13[d]	 **2l**	 **3al**	—	—	—	5	72	88	97
14[d]	 **2m**	 **3am**	—	—	—	1	72	53	98
15[d]	 **2n**	 **3an**	—	—	—	1	72	67	94
16[d]	 **2o**	 **3ao**	40	48	87	1	72	68	96
17[d]	 **2p**	 **3ap**	40	41	77	1	72	67	96
18	 **2q**	 **3aq**	—	—	—	5	72	55	95
19[d]	 **2r**	 **3ar**	—	—	—	5	72	39	52

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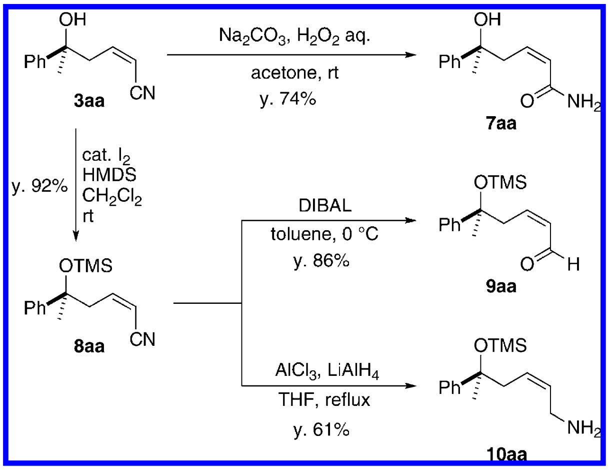
[a] Using (*R*,*R*)-Ph-BPE (10 mol %), [Cu(CH_3CN)$_4$]ClO_4 (10 mol %), Li(OC_6H_4-*o*-OMe) (10 mol %), **2** (0.2 mmol), **1a** (2.0 mmol). [b] Using 0.4 mmol of **2** and 0.8 mmol of **1a**. [c] Isolated yield. [d] LiO^{t}Bu was used instead of Li(OC_6H_4-*p*-OMe).

Scheme 6. Transformation of the Reaction Product



the ternary catalytic system to the deprotonative activation of other pronucleophiles having Lewis basic functionality.

Experimental Section

General Procedure for Direct Catalytic Asymmetric Addition of Allyl Cyanide to Ketones (Table 3, entry 1). A flame-dried 20 mL test tube equipped with a magnetic stirring bar and 3-way glass stopcock was charged with THF (0.4 mL) under an Ar atmosphere and degassed by performing three freeze−pump−thaw cycles. Ar was back-filled into the test tube, after which allyl cyanide (**1a**) (64.4 μL, 0.8 mmol), acetophenone (**2a**) (46.7 μL, 0.4 mmol), and a premixed solution of $[Cu(CH_3CN)_4]ClO_4$, (*R*,*R*)-Ph-BPE, and 1,2-bis(diphenylphosphoryl)benzene (**4**) (80 μL, 0.05 M in THF, 4.0 μmol) were added via a syringe with a stainless-steel needle. The test tube was immersed into an electronically controlled cooling bath containing 2-propanol at −40 °C. Lithium *p*-methoxyphenoxide (40 μL, 0.1 M in THF, 4.0 μmol) was then added at −40 °C. The resulting pale-yellow solution was stirred at the same temperature for 40 h under Ar and quenched with saturated aqueous NH_4Cl. The biphasic mixture was extracted three times with AcOEt, and the combined organic extract was washed successively with saturated aqueous $NaHCO_3$ and brine and then dried over Na_2SO_4. After evaporation of volatiles under reduced pressure, the crude mixture was purified by silica gel column chromatography (2:1 *n*-hexane/ethyl acetate) to give the desired product **3aa** (30.4 mg, 81% yield). The enantioselectivity was determined to be 99% ee by chiral-stationary-phase HPLC analysis [Daicel CHIRALCEL OZ-H, 0.46 cm $\phi \times 25$ cm, detection at 220 nm, 40:1 *n*-hexane/2-propanol, flow rate = 1.0 mL/min, $t_R = 20.3$ min (major), 26.6 min (minor)].

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Supporting Information Available: Detailed experimental procedures, characterization data for new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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