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Direct Catalytic Asymmetric Addition of Allyl Cyanide to Ketones

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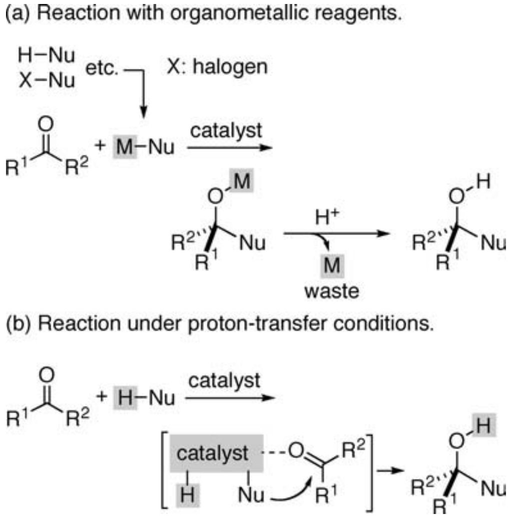
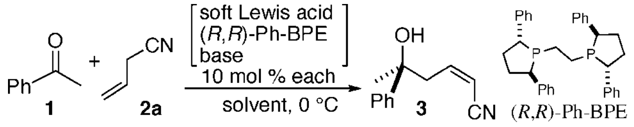
Catalytic asymmetric construction of optically active tertiary alcohols remains a challenging task.[1] Asymmetric addition to ketones is the simplest and most efficient approach to this important class of compounds. In contrast to a number of reported examples of asymmetric additions to aldehydes, relatively few exist for the ketone counterpart because of its attenuated reactivity and lesser steric dissimilarity of the substituents at the prochiral carbonyl group.[2] Recent advances in this field allow for a catalytic asymmetric addition of organometallics (Zn,[3] B,[4] Si,[5] Sn[6]) and enol silyl ethers[7] to ketones, affording enantioenriched tertiary alcohols in moderate to high enantioselectivity.[8]The inevitable formation of more than stoichiometric amounts of waste to compensate for the use of an active nucleophile remains a major drawback in these reactions (Scheme 1a). Moreover, tedious pregeneration of organometallic species decreases the overall efficiency. The catalytic generation of active nucleophiles under proton-transfer conditions and integration into the following C−C bond-forming process is obviously a more advantageous methodology (Scheme 1b), but the retro-reaction is usually dominant (e.g., aldol reactions) in equilibrium except for in special cases such as HCN.[9] We previously documented allylic cyanides as viable pronucleophiles for the construction of chiral tetrasubtituted carbons in the reaction with ketoimines.[10,11] The favorable properties of allylic cyanides are (1) suitable pK_a for deprotonative activation; (2) small steric demand; and (3) prospective divergent transformation of nitrile functionality in product elaboration. Herein, we report a direct catalytic asymmetric addition of allyl cyanide to ketones under proton-transfer conditions, affording enantioenriched tertiary alcohols bearing a *Z*-configured α,*β*-unsaturated nitrile.

Scheme 1. Approaches to Enantioenriched Tertiary Alcohols by Asymmetric Addition Reactions to Ketones



A catalytic system comprising [Cu(CH_3CN)$_4$]ClO_4, (*R*,*R*)-Ph-BPE, and Li(OC_6H_4-*p*-OMe), which is effective for a direct catalytic asymmetric addition of allylic cyanides to ketoimines,[10] emerged as an effective catalyst in a reaction of acetophenone (**1a**) and 10 equiv of allyl cyanide (**2a**)[12] (Table 1). In this catalytic system, **2a** was chemoselectively activated by a soft Lewis acid through nitrile functionality and subsequently deprotonated by the hard base to generate the active nucleophile. With a catalyst loading of 10 mol %, exclusive *γ*-addition to **1a** was observed at 0 °C in THF, affording *Z*-configured α,*β*-unsaturated nitrile (**3aa**) in 95% ee (entry 1). Whereas the reaction in nonpolar solvents was sluggish, enantioselectivity was uniformly high, implying that yield was linked to the efficiency of the deprotonation process (entries 3−7). A decrease in yield when 5 equiv of **2a** were used is consistent with this assumption (entry 8). The use of Li(OC_6H_4-*o*-OMe) and degassed solvent increased the catalyst lifetime, possibly due to bidentate coordination of *o*-methoxyphenoxide to Cu^+, which enhanced the stability of the catalyst complex (entry 9).[13]

Table 1. Initial Screening[a]



entry	soft Lewis acid	base	solvent	time (h)	yield[b] (%)	ee (%)
1	[Cu(CH_3CN)$_4$]ClO_4	Li(OC_6H_4-*p*-OMe)	THF	18	83	95
2	[Cu(CH_3CN)$_4$]PF_6	Li(OC_6H_4-*p*-OMe)	THF	18	68	95
3	[Cu(CH_3CN)$_4$]ClO_4	Li(OC_6H_4-*p*-OMe)	toluene	18	37	97
4	[Cu(CH_3CN)$_4$]ClO_4	Li(OC_6H_4-*p*-OMe)	CH_2Cl_2	18	20	98
5	[Cu(CH_3CN)$_4$]ClO_4	Li(OC_6H_4-*p*-OMe)	$CF_3C_6H_5$	18	21	95
6	[Cu(CH_3CN)$_4$]ClO_4	Li(OC_6H_4-*p*-OMe)	ether	18	62	83
7	[Cu(CH_3CN)$_4$]ClO_4	Li(OC_6H_4-*p*-OMe)	EtOAc	18	79	96
8[c]	[Cu(CH_3CN)$_4$]ClO_4	Li(OC_6H_4-*p*-OMe)	THF	18	36	82
9[d]	[Cu(CH_3CN)$_4$]ClO_4	Li(OC_6H_4-*o*-OMe)	THF	40	91	95

[a] **1**: 0.2 mmol, **2a**: 2.0 mmol. [b] Determined by ^{1}H NMR analysis with Bn_2O as an internal standard. [c] 5 equiv (1.0 mmol) of **2a** was used. [d] Degassed solvent was used.

The substrate scope of the direct catalytic asymmetric addition of allyl cyanide (**2a**) to ketones **1** is summarized in Table 2.[14] Excellent enantioselectivity and complete *Z*-selectivity were observed with aryl methyl ketones including heteroaromatic substrates (entries 1−3, 6, 8), whereas a ketone with a 2-furyl group **2e** exhibited slightly lower enantioselectivity (entry 7). High enantioselectivity was maintained in the reaction under reduced catalyst loading or a lower equivalent of **2a**, albeit in moderate chemical yield (entries 4, 5). The reaction with ketones bearing ethyl or *n*-propyl substituents required a stronger base (LiO^{t}Bu instead of Li(OC_6H_4-*o*-OMe)), likely because the higher concentration of deprotonated **2a** partly compensated for the low reactivity (entries

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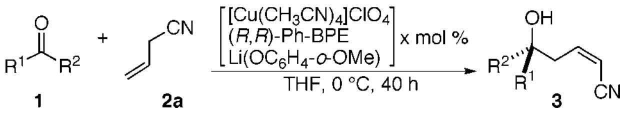
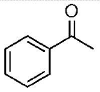
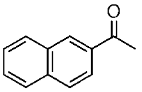
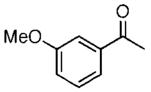
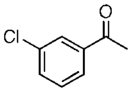
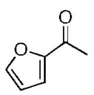
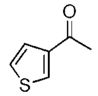
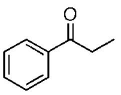
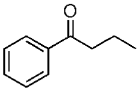
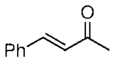
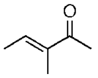
Table 2. Catalytic Asymmetric Addition of Allyl Cyanide (**2a**) to Ketones under Proton-Transfer Conditions[a]



entry	ketone		x	product	yield[b] (%)	ee (%)
1		**1a**	10	**3aa**	81	97
2		**1b**	10	**3ba**	88	96
3		**1c**	10	**3ca**	92	94
4[c]		**1c**	5	**3ca**	68	93
5[c,d]		**1c**	10	**3ca**	53	93
6		**1d**	10	**3da**	76	95
7		**1e**	10	**3ea**	80	84
8		**1f**	10	**3fa**	73	94
9[e]		**1g**	10	**3ga**	48	87
10[e]		**1h**	10	**3ha**	41	77
11		**1i**	10	**3ia**	79	78
12[e]		**1j**	10	**3ja**	54	88

[a] **1**: 0.2 mmol, **2a**: 2.0 mmol. [b] Isolated yield. [c] Reaction time was 60 h. [d] 5 equiv (1.0 mmol) of **2a** were used. [e] LiO^{t}Bu was used instead of Li(OC$_6$H$_4$-*o*-OMe).

9, 10). Exclusive 1,2-addition was observed with enones bearing either an aromatic or aliphatic substituent (**1i**, **1j**) with marginally decreased enantioselectivity (entries 11, 12).

Particularly noteworthy in the present catalytic system was the exclusive *γ*-addition of **2a** to ketones, in contrast to the α-addition to ketoimines in a similar catalytic system.[10] In addition, a reversal in enantioselectivity was observed in the present system, suggesting that a different transition state architecture would be attained. The combination of (*R*,*R*)-Ph-BPE and [Cu(CH$_3$CN)$_4$]ClO$_4$ furnished a monomeric (*R*,*R*)-Ph-BPE/Cu complex,[15] which would give (*R*,*R*)-Ph-BPE/Cu(OC$_6$H$_4$-*o*-OMe) and LiClO$_4$ upon anion exchange with Li(OC$_6$H$_4$-*o*-OMe).[16] **2a** was chemoselectively activated by Cu$^+$ through a soft−soft interaction and deprotonated by a neighboring Brønsted base to give an α-*C*-copper active nucleophile. The initially formed α-*C*-copper species would interconvert to a *γ*-*C*-copper nucleophile, which should provide an *E*,*Z*-mixture of the *γ*-addition product in the following 1,2-addition to ketones (Figure 1).[17] The exclusive formation of a *Z*-olefin would be indicative of the involvement of a six-membered cyclic transition state. The proposed transition state model is depicted in Figure 1, where the reaction proceeded through an α-*C*-copper species with the nitrile group occupying the pseudoaxial position to avoid steric repulsion with the phenyl group of Ph-BPE, affording an (*S*)-*Z*-adduct. This assumption is consistent with the observed moderate enantioselectivity and *E*/*Z* selectivity in the reaction with pyruvate **1k** and allyl cyanide (**2a**) (eq 1) where **1k** disrupts the cyclic transition state of the α-*C*-copper nucleophile through bidentate coordination of the α-dicarbonyl moiety in pyruvate to Cu$^+$, resulting in lower *E*,*Z* and enantioselectivity. The reaction through *γ*-*C*-copper nucleophile would be partly involved. Hydrogenation of the obtained *E*,*Z*-mixture **3ka** afforded saturated product **4ka** with 61% ee. In an attempted reaction of ketone **1c** using an α-methyl-substituted allylic cyanide **2b** as a pronucleophile, almost racemic product **3cb** was obtained as a mixture of *E*/*Z* geometrical isomers, with *E* predominating (*E*/*Z* = 84/16) (eq 2). This result is attributed to a six-membered cyclic transition state that is compromised due to the steric demand imposed by the methyl group of **2b**. A different transition state would be operating to give the *E*-product in low enantioselectivity.

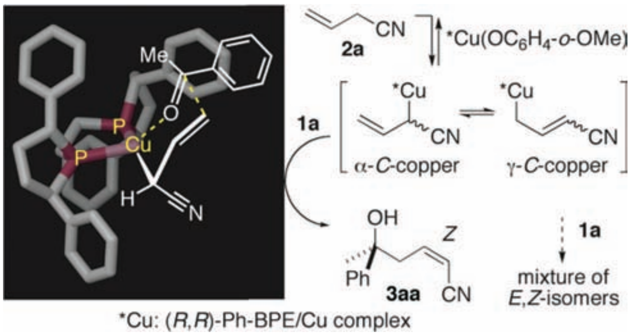
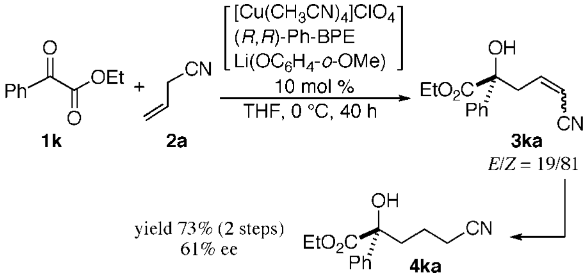
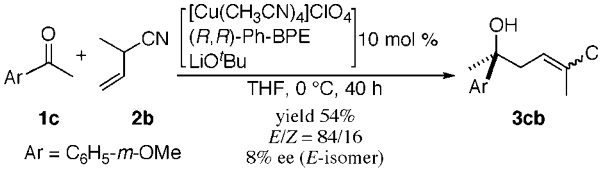


Figure 1. Proposed mechanism for *γ*- and *Z*-selectivity. (*R*,*R*)-Ph-BPE/Cu structure was optimized as Ph-BPE/Cu(OC$_6$H$_4$-*o*-OMe) by DFT calculation at B3LYP/LAV3P+(d,p) level of theory.[13]



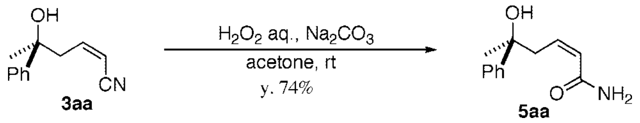
(1)



(2)

The present catalytic system provides an optically active tertiary alcohol bearing a *Z*-configured unsaturated nitrile. The nitrile functionality is valuable from a synthetic point of view as it has a high potential for diversification. The nitrile group of the product **3aa** was transformed into primary amide **5aa**, while maintaining the olefin geometry, in 74% yield using hydrogen peroxide under basic conditions (Scheme 2).

Scheme 2. Transformation of the Product



In conclusion, we developed a direct catalytic asymmetric addition of allyl cyanide to ketones. An obvious advantage over reported precedents of asymmetric addition to ketones is that the reaction proceeded under proton-transfer conditions, harnessing soft Lewis acid/hard Brønsted base bifunctional catalysis. It is worth noting that the obtained enantioenriched tertiary alcohols have a pendant *Z*-configured unsaturated nitrile, which would serve as a useful handle for further elaboration of the product. A comprehensive mechanistic study will be the focus of future investigations.

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Supporting Information Available: Characterization of new compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) An inexpensive C4-pronucleophile. The price is $193.7/500 mL from TCI America as of Dec 2008.

(13) The optimized structure of Ph-BPE/Cu(OC$_6$H$_4$-*o*-OMe) by DFT calculation at the B3LYP/LAV3P+(d,p) level of theory suggested bidentate coordination of *o*-methoxyphenoxide. See Supporting Information for details.

(14) The reaction with enone bearing substituents of similar steric demand at ketone carbonyl gave lower enantioselectivity. Substrate: 3-octen-2-one, catalyst: [Cu(CH$_3$CN)$_4$]ClO$_4$, (*R*,*R*)-Ph-BPE, LiO^{t}Bu 10 mol % each, 0 °C in THF, 40 h, yield <50%, 42% ee. An attempted reaction with benzaldehyde gave the corresponding secondary alcohol bearing *Z*-configured unsaturated nitrile in ca. 80% yield and 80% ee. Crotyl cyanide exhibited very low reactivity in the present catalytic system. The substrate scope on *γ*-substituted allylic cyanides is currently under extensive investigation, and the result will be reported in due course.

(15) The Cu complex obtained from (*R*,*R*)-Ph-BPE and [Cu(CH$_3$CN)$_4$]ClO$_4$ was analyzed by ^{1}H NMR and ESI-MS; see ref 10.

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