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Dramatic Ligand Effect in Catalytic Asymmetric Reductive Aldol Reaction of Allenic Esters to Ketones

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Chiral tertiary alcohols are important building blocks in many biologically active naturally occurring compounds and artificial pharmaceuticals.[1] Catalytic enantioselective addition reactions of carbon nucleophiles targeting ketones produce enantiomerically enriched tertiary alcohols through carbon−carbon bond formation. Among recent intensive studies to develop such reactions, the catalytic enantioselective aldol reaction to simple ketones has just begun to be explored.[2] After the pioneering report by the Denmark group using trichlorosilyl enolate as a nucleophile,[3a,b] Campagne's vinylogous aldol reaction of trimethylsilyl dienolate[3c] and our aldol reaction using trimethylsilyl enolates[3d−f] were developed. Preactivation of nucleophiles is essential in those three reactions. On the other hand, a catalytic enantioselective reductive aldol reaction to ketones via in situ generation of metal enolates is an attractive alternative. The first example of this reaction type was demonstrated by Lam's group, but it was restricted to an intramolecular version.[4a] Our group[4b] and the Riant group[4c] independently developed catalytic enantioselective intermolecular reductive aldol reactions to simple ketones using either an allenic ester or an acrylate ester as the prenucleophile. These reactions should be improved, however, especially in terms of substrate generality. In this communication, we report a general catalytic asymmetric reductive aldol reaction of allenic esters to ketones. Specifically, two different constitutional isomers (α- and γ-aldol products) were selectively synthesized from the same starting materials, depending on the conditions.

Successful catalytic asymmetric reductive aldol reactions of allenic esters to ketones depend on the control of various types of selectivities, namely, chemo- (ketone vs allenic ester in the initial reduction step), regio- (α- vs γ-addition in the vinylogous aldol reaction step), stereo- (cis vs trans of γ-adducts), diastereo- (syn vs anti of α-adducts), and enantioselectivity.[5] In our previous report, there was only moderate γ/α regioselectivity (**3a**+**4**/**5a**+**6**) of the reaction between acetophenone (**1a**) and allenic ester (**2b**) using CuF·3PPh$_3$·2EtOH−(*R*)-DTBM-SEGPHOS as the catalyst, although the cis/trans selectivity (**3a**/**4**) and enantioselectivity of the major γ-cis-product (**3a**) were promising (Table 1, entry 1).[4b]

To improve regioselectivity, effects of copper salt and an additive were investigated. The representative results are summarized in Table 1. When a chiral Cu complex was reductively generated in situ from CuF$_2$·2H$_2$O and excess (*R*)-DTBM-SEGPHOS,[6] a very small amount of the desired γ-product was produced (entry 2). These contrasting results directed our attention to the effect of the achiral phosphine (PPh$_3$). A similar tendency was observed with higher γ-selectivity when CuOAc was used as the Cu salt (entries 3 and 4); PPh$_3$-free CuOAc produced moderate γ/α regioselectivity (entry 3), whereas the combination of CuOAc/(*R*)-DTBM-SEGPHOS/PPh$_3$ (1:2:3) significantly improved the γ/α regioselectivity to 10:1 without any loss of the enantioselectivity of **3a** (entry 4). Moreover, generation of the γ-trans-product (**4**) was completely eliminated in the presence of the achiral phosphine additive. The chemical yield of **3a** was further improved when PCy$_3$ was used instead of PPh$_3$ (entry 5). Finally, the best result was obtained when CuOAc/(*R*)-DTBM-SEGPHOS/PCy$_3$ (1:2:2) was used as the catalyst (entry 6); the γ-cis-adduct (**3a**) was produced predominantly in 96% yield with excellent γ/α regioselectivity (25:1) and enantioselectivity (99% ee).

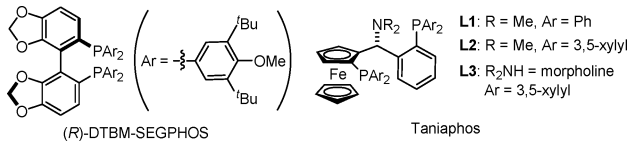
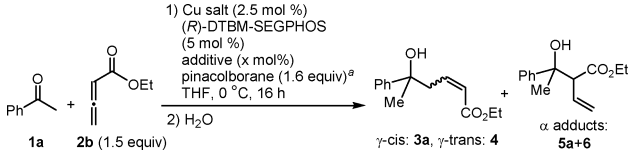


Figure 1. Chiral phosphine ligands used in our system.

Table 1. Copper Salt and Additive Effects on γ-Selective Reductive Aldol Reaction of **2b** to **1a**



entry	copper salt	additive (*x* mol %)	Yield/%[b] **3a** (ee/%)[c]	**4**	**5a** + **6**
1	CuF·3PPh$_3$·2EtOH		46 (99)	<4	22
2[d]	CuF$_2$·2H$_2$O		trace	trace	31
3	CuOAc		32 (99)	<3	18
4	CuOAc	PPh$_3$ (7.5)	60 (99)		6
5	CuOAc	PCy$_3$ (7.5)	90 (99)		9
6	CuOAc	PCy$_3$ (5.0)	96 (99)		4
7	CuOAc	PCy$_3$ (2.5)	78 (99)		8

[a] Slow addition of pinacolborane for 4 h. [b] Yield was determined by ^{1}H NMR of the crude mixture. [c] Enantiomeric excess was determined by HPLC after isolation of pure **3a**. [d] Catalyst was prepared in refluxing methanol for 2 h.

Substrate generality was investigated under the optimized conditions of the γ-cis-selective reductive aldol reaction (Table 2). Both aromatic (entries 1−4) and aliphatic (entries 5−9) ketones were converted to γ-cis-products **3**, generally in high yield and excellent enantioselectivity. It is noteworthy that our system is applicable to unsaturated ketones such as **1e** and **1g** via chemoselective reductive enolate formation from the allenic ester. The products **3** are versatile chiral building blocks in organic synthesis. For example, **3a** was converted to the corresponding α,β-unsaturated δ-lactone in greater than 99% yield through heating in AcOH under reflux without any loss of enantiopurity.

During the course of our optimization, regioselectivity was switched to be exclusively α-selective when Taniaphos-type ligands[7] were used (Table 3). The initial trials were performed with **1a** and **2b** using commercially available **L1** as the chiral ligand. As a result, α-products were produced exclusively without the concomitant generation of trace amounts of γ-products (entry 1). The diastereoselectivity of the α-products was high (**5a**/**6** = 6/1), and the major isomer (**5a**) was obtained in 66% ee. Optimization of the allenic

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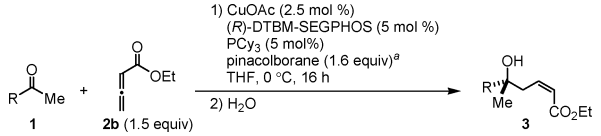
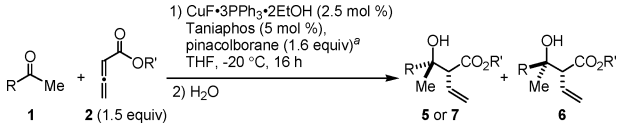
Table 2. γ-cis-Selective Reductive Aldol Reaction to Ketones



entry	ketone (R)	γ/α ratio[b]	product	yield/%[c]	ee/%[d]
1	**1a** (phenyl)	25/1	**3a**	96	99[e]
2	**1b** (*p*-Cl phenyl)	13/1	**3b**	93	98
3	**1c** (*p*-Me phenyl)	9/1	**3c**	90	97
4	**1d** (*m*-Cl phenyl)	9/1	**3d**	90	99
5[f]	**1e** (cinnamyl)	30/1	**3e**	97	84
6[f]	**1f** (phenylethyl)	3/1	**3f**	70	96
7	**1g** (homoallyl)	>8/1[g]	**3g**	86	89
8	**1h** (*n*-butyl)	>6/1[g]	**3h**	86	88
9[h]	**1i** (isopropyl)	>8/1[g]	**3i**	80	98

[a] To a mixture of catalyst, **1**, and **2b**, pinacolborane was added slowly over 4 h. [b] The γ/α ratio was determined by ^{1}H NMR of the crude mixture. [c] Yield was determined by ^{1}H NMR of the crude mixture using an internal standard. Deviation from the isolated yield was generally <10%. [d] Enantiomeric excess was determined by HPLC. [e] The absolute configuration was determined to be (*R*). [f] Reaction was conducted at −20 °C. [g] NMR peaks were overlapping. [h] 5 mol % of catalyst was used.

Table 3. α-Selective Reductive Aldol Reaction to Ketones



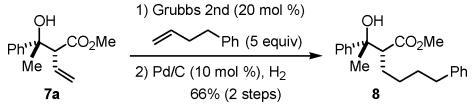
entry	ligand	ketone (R)	allene (R′)	product	**5** or **7**/**6**[b]	yield/%[c]	ee/%[d]
1	**L1**	**1a** (phenyl)	**2b** (Et)	**5a**	6/1	86	66
2	**L1**	**1a** (phenyl)	**2a** (Me)	**7a**	10/1	90	67[e]
3	**L2**	**1a** (phenyl)	**2a** (Me)	**7a**	11/1	90	72[e]
4	**L3**	**1a** (phenyl)	**2a** (Me)	**7a**	10/1	90	84[e]
5	**L3**	**1b** (*p*-Cl phenyl)	**2a** (Me)	**7b**	8/1	89	83
6	**L3**	**1d** (*m*-Cl phenyl)	**2a** (Me)	**7d**	8/1	89	82
7	**L3**	**1j** (*p*-I phenyl)	**2a** (Me)	**7j**	7/1	86	84
8	**L3**	**1k** (2-naphthyl)	**2a** (Me)	**7k**	10/1	91	84
9	**L3**	**1e** (cinnamyl)	**2a** (Me)	**7e**	9/1	87	67

[a] To a mixture of catalyst, **1**, and **2**, pinacolborane was added slowly over 4 h. [b] Ratio was determined by ^{1}H NMR of the crude mixture. [c] Yield of **5** or **7** was determined by ^{1}H NMR of the crude mixture using an internal standard. Deviation from the isolated yield was generally <10%. [d] Enantiomeric excess of **5** or **7** was determined by HPLC after hydrogenation of the terminal olefin. [e] The absolute configuration was determined to be (*R*,*R*).

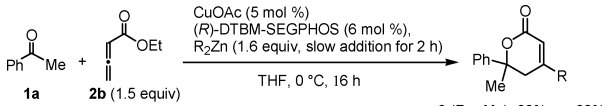
ester structure further improved the diastereoselectivity to 10/1 without affecting the enantioselectivity (67% ee), using methyl ester **2a** (entry 2).[8] Encouraged by this finding, a series of Taniaphos analogues were synthesized and screened (entries 2−4). Taniaphos **L3** containing bulkier di(3,5-xylyl)phosphines and a morpholine unit gave the best results, producing the α-adducts with a 10:1 diastereoselectivity and 84% ee for the major isomer (**7a**; entry 4).

Next, the substrate scope of the α-selective reductive aldol reaction was investigated (entries 4−9). Various aromatic ketones were converted to the corresponding products with high diastereo- and enantioselectivity. The reaction of an enone (**1e**) proceeded chemoselectively with high diastereoselectivity, although the enantioselectivity remained to be improved. The existence of a terminal olefin in **7** allows for further conversion to various α-substituted aldol products using the cross-metathesis reaction.[9] For example, **7a** was converted to **8** containing a longer alkyl chain at the α-position without any epimerization and racemization (Scheme 1). Previously, it was difficult to synthesize such a chiral building block in enantiomerically enriched form.

Scheme 1. Typical Conversion of α-Vinyl Aldol Product



Scheme 2. Preliminary Extension to Catalytic Asymmetric Alkylative Aldol Reaction to Ketones



Finally, the basic reaction pattern (i.e., conjugate addition followed by aldol reaction) can be extended to another catalytic asymmetric multicomponent reaction—an alkylative aldol reaction to ketones initiated by a Cu-catalyzed conjugate addition of dialkylzinc to an allenic ester (Scheme 2). Thus, using CuOAc−DTBM-SEGPHOS complex as a catalyst (5 mol %), β-alkylated δ-lactones (**9** and **10**) were produced in high enantioselectivity from a ketone, an allenic ester, and dialkylzinc reagents. No α-aldol products were isolated in these cases.

In conclusion, we developed an asymmetric reductive aldol reaction between ketones and allenic esters catalyzed by chiral Cu(I) complexes. The product constitution (α- or γ-aldol) can be switched depending on the structure of chiral diphosphine ligands. No preactivation of the substrates is necessary. Clarification of the reaction mechanism and how the two reaction pathways are differentiated depending on the conditions[10] and further improvement of the alkylative aldol reaction are ongoing.

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Supporting Information Available: Results of reaction condition optimizations, experimental procedures, and characterization of the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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