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Catalytic enantioselective intermolecular reductive aldol reaction to ketones

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Abstract—We describe the first example of a catalytic enantioselective intermolecular reductive aldol reaction. Three types of reactions were studied: (1) reactions between acetophenone and methyl acrylate; (2) reactions between symmetric ketones and β-substituted α,β-unsaturated esters; and (3) reactions between acetophenone derivatives and an allenic ester. Although only moderate enantioselectivity was obtained in the first reaction type, high to excellent enantioselectivity was realized in the enantio-induction at the α-position in the second reaction type and at the δ-position in the third reaction type. Specifically, the third reaction type afforded the corresponding tertiary alcohols with up to 99% ee. Pre-activation of the nucleophile by silyl enolate formation is not necessary in these one-pot catalytic enantioselective reductive aldol reactions.

The development of catalytic enantioselective carbon–carbon bond-forming reactions using simple ketones as substrates has been intensively studied.[1–4] This type of reaction produces optically active tertiary alcohols, which are important building blocks in many biologically active naturally occurring compounds and artificial pharmaceuticals. Synthetically useful catalytic enantioselective reactions that can target ketones, however, are limited due to both the attenuated reactivity of ketones and the difficulty in differentiating subtle changes between the two substituents on a ketone carbonyl group. Among these types of reactions, the catalytic enantioselective aldol reaction to ketones is the least well established. Denmark reported the pioneering reaction in this category.[4a,b] Due to its unsatisfactory enantioselectivity (8–86% ee), low substrate generality, and required use of sensitive trichlorosilyl enolate, this approach requires further improvement. Recently, Campagne reported a catalytic asymmetric vinylogous aldol reaction using silyl dienolate as the nucleophile.[4c] In this reaction, the chemical yield of the desired δ-lactone is not necessarily high (17–81% yield). To broaden the scope of this field, the development of a catalytic reaction that can overcome the low reactivity of ketones is necessary, and such studies should allow for further development of catalytic enantioselective tertiary alcohol synthesis using a novel approach. In this letter, we describe the first catalytic enantioselective intermolecular reductive aldol reaction to ketones using a chiral CuF catalyst.[5]

We previously reported a general method for the catalytic aldol reaction of ketene trimethylsilyl acetals to simple ketones using CuF as a catalyst.[6,7] In this method, the addition of a stoichiometric amount of $(EtO)_3SiF$ was critical. Mechanistic studies suggested that a copper enolate generated through transmetalation between silicon and copper atoms is the actual nucleophile, and $(EtO)_3SiF$ facilitates the rate-determining copper enolate formation via the generation of triethoxysilyl enolates from trimethylsilyl enolates. This method almost completely overcame the reactivity problem of ketones in the aldol reaction, producing a high chemical yield and reaction rate from a wide range of ketones and silyl enolates. Moreover, this reaction was recently extended to a catalytic enantioselective aldol reaction to ketones.[8] By developing new chiral diphosphine ligands, ketone aldol products were produced with up to 66% ee.

In parallel with our development of the CuF-catalyzed aldol reaction to ketones, the Buchwald and Lipshutz groups independently reported a catalytic enantioselective conjugate reduction of α,β-unsaturated carbonyl

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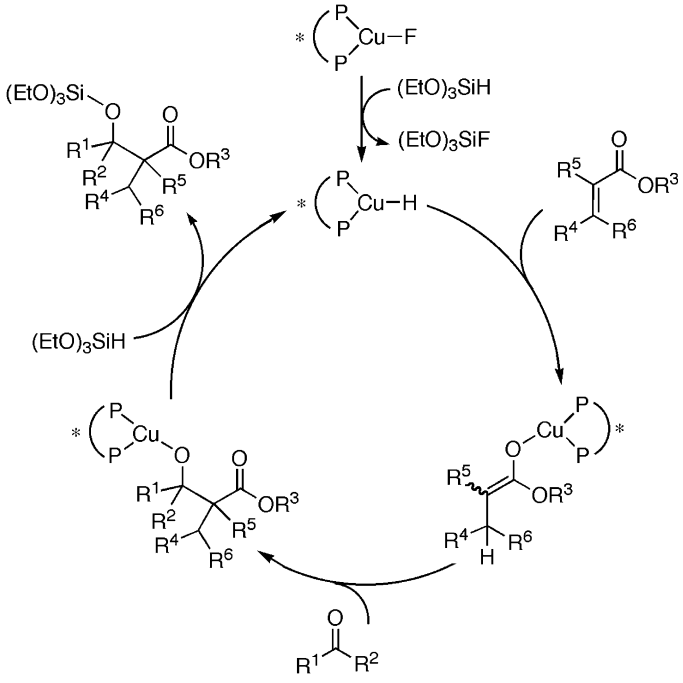
compounds using chiral Cu(I) catalysts.[9–11] These asymmetric reactions are based on the findings by Mori et al.[12] and Hosomi et al.[13] that conjugate reduction of enones and α,β-unsaturated esters proceeds using hydrosilane and Cu(I) salts (20–200 mol %). The intermediate of the asymmetric conjugate reduction should be a chiral copper enolate, therefore we thought it would be possible to use this intermediate as a nucleophile in an aldol reaction to ketones in the second step of a one-pot sequential reductive aldol reaction (Scheme 1). An advantage of this methodology compared to the previous catalytic enantioselective aldol reactions to ketones using silyl enolates is that pre-activation of the nucleophile by silyl enolate formation is not necessary. Thus, we planned to investigate a catalytic enantioselective reductive aldol reaction to ketones using a chiral CuF catalyst. A catalytic enantioselective intermolecular reductive aldol reaction between aldehydes and acrylate esters was initially developed by Morken using Rh–chiral bisphosphine or Ir–pybox complex as a catalyst and Et_2MeSiH as the reducing reagent.[14,15] *Syn*-aldol products were obtained using Morken's reaction. Recently, Nishiyama reported an *anti*-selective enantioselective reductive aldol reaction of aldehydes using a chiral Rh-complex with an N–C–N ligand.[16,17] In contrast, a catalytic enantioselective intermolecular reductive aldol reaction to ketones has not yet been reported. The previously reported reductive aldol reaction to ketones is restricted to only an intramolecular version.[5,18]

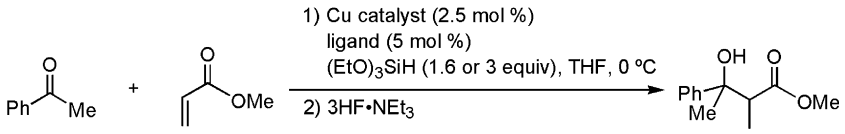
To determine the reaction conditions, a reductive aldol reaction between methyl acrylate (**2a**) and acetophenone (**1a**) was first studied using (*R*)-tol-BINAP (5 mol %) as a ligand (Table 1). $(EtO)_3SiH$ was selected as a reducing reagent under the assumption that the second aldolization step would proceed even if the reductively generated copper enolate was trapped by the triethoxysilyl group in the first step.[19] When CuO^{t}Bu (prepared in situ from CuCl and NaO^{t}Bu), a catalyst in the Buchwald and Lipshutz conjugate reduction, was applied to the catalytic reductive aldol reaction (entry 1), the desired product **3aa** was obtained in only 37% yield. The major product was 1-phenylethanol, generated through a 1,2-reduction of **1a**. The yield of **3aa** was improved to 47% when CuF·3PPh$_3$·2EtOH was used as a catalyst (entry 2). The 1,2-reduction of **1a**, however, was still a problematic side reaction pathway. To more efficiently differentiate between the desired conjugate reduction of **2a** and the undesired 1,2-reduction of **1a**, we tried a slow addition of $(EtO)_3SiH$. When $(EtO)_3SiH$ was added slowly to a mixture of the catalyst, **1a**, and **2a** over 8 h, the desired reductive aldol product was obtained in quantitative yield (entry 3). Although the diastereoselectivity (1.2:1) and enantioselectivity (up to 29% ee) were low in this case,[20] we determined the reaction conditions for the intermolecular reductive aldol reaction to ketones. Pinacolborane could also be used instead of $(EtO)_3SiH$ to promote this reductive aldol reaction (entry 4). Comparable results were obtained between these two reducing reagents, which suggested that a copper enolate is the actual nucleophile. The reductive aldol reaction between **1a** and **2a** did not proceed at all with other catalysts, such as $[Rh(COD)Cl]_2$ (the catalyst for reductive aldol reaction to aldehydes reported by Morken[14]), AgF, NiF_2, $Co_2(CO)_8$,[21] $Fe_2(CO)_9$,[21] or $In(OAc)_3$.[17a] Preliminary screening of the chiral bisphosphines (entries 5 and 6) slightly improved the diastereoselectivity (entry 6 using ^{i}Pr-DUPHOS); however, the enantioselectivity and total chemical yield decreased.

Substrate generality in terms of both nucleophile precursors and ketones was then investigated under the optimized reaction conditions. Because meaningful enantio- and diastereoselectivity was not produced from



Scheme 1. Mechanistic speculation for reductive aldol reaction to ketones.

Table 1. Optimization of catalytic enantioselective intermolecular reductive aldol reaction to ketones



1a **2a** **3aa**

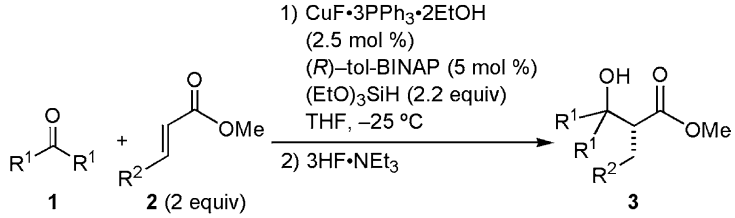
Entry	Cu catalyst	Ligand	Yield (%)[a]	ee (%)[b]
1[c]	CuCl+NaO^{t}Bu	(*R*)-tol-BINAP	37 (57/43)	30/7
2[c]	CuF·3PPh$_3$·2EtOH	(*R*)-tol-BINAP	47 (47/53)	24/5
3[d]	CuF·3PPh$_3$·2EtOH	(*R*)-tol-BINAP	100 (55/45)	29/1
4[e]	CuF·3PPh$_3$·2EtOH	(*R*)-tol-BINAP	100 (47/53)	28/5
5[d]	CuF·3PPh$_3$·2EtOH	(*R*)-DTBM-SEGPHOS	41 (44/56)	15/27
6[d]	CuF·3PPh$_3$·2EtOH	(*S*,*S*)-^{i}Pr-DUPHOS	66 (71/29)	22/7

[a] Isolated yield. Diastereomer ratio (2*S*,3*S*/2*S*,3*R*) is in parenthesis.[20]
[b] Determined by chiral HPLC.
[c] Ratio of **2a**/(EtO)$_3$SiH/**1** = 1.2:3.0:1. (EtO)$_3$SiH was added in one portion. Reaction time = 12 h.
[d] Ratio of **2a**/(EtO)$_3$SiH/**1** = 1.5:1.6:1. (EtO)$_3$SiH was added slowly over 8 h using a syringe pump. Total reaction time = 12 h.
[e] Pinacolborane (1.6 equiv) was used instead of (EtO)$_3$SiH with slow addition for 8 h. Reaction time = 12 h.

ketones with a prochiral carbonyl carbon such as **1a**, we examined asymmetric induction at the α-position using symmetrical ketones, such as 3-pentanone (**1b**) and cyclopentanone (**1c**) (Table 2). A series of β-substituted α,β-unsaturated esters were chosen as pre-nucleophiles. Due to the relatively higher reactivity of aliphatic ketones compared with aromatic ketones, the reaction proceeded at −25 °C. Moderate to high asymmetric induction at the α-position was realized in reactions between ketone **1b** and β-methyl, ethyl, and phenyl substituted α,β-unsaturated esters **2b–d** (Table 2, entries 1–3). Unfortunately, other symmetric ketones such as **1c** produced only low enantioselectivity (30% ee, entry 4). Although the enantioselectivity was still not satisfactory, the fact that a similar level of enantioselectivity was induced in the present reductive aldol reaction compared to the previously developed aldol reaction using silyl enolates[6] (ee values shown in parentheses) further suggested that both of these reactions proceed through the same active nucleophile, a copper enolate. Moreover, the present reaction is more convenient because pre-activation of the nucleophile through silyl enolate formation is not necessary.

Finally, promising results for optically active tertiary alcohol synthesis were obtained using allenic ester **4** as a pre-nucleophile (Table 3).[22] This reaction is significantly more complex than that using α,β-unsaturated esters **2** as the nucleophile. After conjugate reduction of **4**, the aldol reaction of the corresponding copper dienolate[23] would produce α-adducts **5** (diastereomixtures) and γ-adducts (*trans*-**6** and *cis*-**7**). There was a significant difference in reactivity in the reaction between **1a** and **4** when either pinacolborane or (EtO)$_3$SiH was used as the reducing reagent. Although reactions using (EtO)$_3$SiH were very sluggish and the reductive aldol products were obtained in less than 30% yield in most cases, the reaction using pinacolborane proceeded smoothly (Table 3). Thus, using (*R*)-tol-BINAP as a chiral ligand, aldol products were obtained in 82%

Table 2. Asymmetric induction at α-position in reductive aldol reaction to symmetric ketones[a]

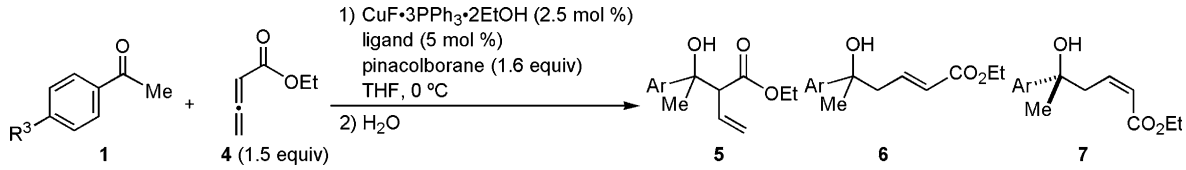


1 **2** (2 equiv) **3**

Entry	R^1	R^2	Yield%[b]	ee (%)[c]
1	Et (**1b**)	Me (**2b**)	93	71 (70)
2	Et (**1b**)	Et (**2c**)	96	76 (72)
3	Et (**1b**)	Ph (**2d**)	52	80 (82)[d]
4	–(CH$_2$)$_4$– (**1c**)	H (**2a**)	60	30 (29)

[a] (EtO)$_3$SiH was added slowly over 8 h using a syringe pump. Total reaction time = 12 h.
[b] Isolated yield.
[c] Determined by chiral HPLC or GC. Ee values in parentheses were obtained in the corresponding aldol reaction using ketene trimethylsilyl acetals (1.2 equiv) in the presence of (EtO)$_3$SiF (1.2 equiv).[6]
[d] Absolute configuration was determined to be *R*.[6]

Table 3. Catalytic asymmetric reductive aldol reaction with allenic ester as nucleophile precursor[a]



1 4 (1.5 equiv) 5 6 7

Entry	Ligand	Ketone (R^3)	Yield (%)[b]		
			5 (diastereo ratio)	**6**	**7** (ee (%)[c])
1	(*R*)-tol-BINAP	**1a** (H)	38 (21/79)	20	24 (98)[d]
2	(*S*,*S*)-^{i}Pr-DUPHOS	**1a** (H)	68 (22/78)	8	23 (87)[d]
3	(*R*)-DTBM-SEGPHOS	**1a** (H)	22 (10/90)	4	46 (99)[d]
4	(*R*)-DTBM-SEGPHOS	**1d** (Cl)	31 (50/50)	3	33 (98)
5	(*R*)-DTBM-SEGPHOS	**1e** (Me)	16 (25/75)	4	47 (99)

[a] Pinacolborane was added slowly over 8 h using a syringe pump. Total reaction time = 16 h.
[b] Calculated from ^{1}H NMR of the crude mixture using an internal standard.
[c] Determined by chiral HPLC.
[d] Absolute configuration was determined to be *R* after conversion to the known δ-lactone.[4c]

combined yield (Table 3, entry 1). The regioselectivity (γ/α selectivity), diastereoselectivity of the α-adducts, and trans/cis selectivity of the γ-adducts were not high. The γ-*cis* adduct **7a**, however, was obtained with extremely high enantiomeric excess (up to 98%). Other products **5a** and **6a** were obtained with less than 30% ee.[24]

After obtaining this preliminary result, chiral ligand effects were screened using other bisphosphine ligands such as ^{i}Pr-DUPHOS and (*R*)-DTBM-SEGPHOS. γ-cis/γ-trans (**7**/**6**) selectivity was improved to 3:1 for ^{i}Pr-DUPHOS, but the yield and enantioselectivity of **7a** decreased (entry 2). On the other hand, the best results were obtained with respect to yield and enantioselectivity of the desired **7a** (46% yield and 99% ee, entry 3) using (*R*)-DTBM-SEGPHOS as a chiral ligand. Although the γ/α selectivity (**6**+**7**/**5**) was still only moderate at the current stage, the cis/trans selectivity (**7**/**6**) of the γ-adducts was satisfactory [with up to 10:1 (entry 3)]. Subsequently, this catalytic system was applied to substituted acetophenone analogues using DTBM-SEGPHOS as the chiral ligand. Excellent enantioselectivity was produced in the γ-*cis* adducts **7b** and **7c** (entries 4 and 5). These results are significant considering that the asymmetric catalyst selectively promotes one specific reaction pathway with enantio-, regio-, chemo-, and cis/trans-selectivities from a number of possible reaction pathways involved in this one-pot multi-component catalytic asymmetric process.[25]

In summary, we developed the first catalytic enantioselective inter-molecular reductive aldol reaction to ketones. This 'one-pot' method produces optically active aldol products containing a tetrasubstituted carbon without a silyl enolate formation step. Excellent enantioselectivity was produced in the reactions using an allenic ester as the pre-nucleophile. Studies toward improving the regioselectivity of this reaction are ongoing. In addition, the current catalyst system will be extended to other multiple-component coupling reactions.

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