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Catalytic Enantioselective Aldol Reaction to Ketones

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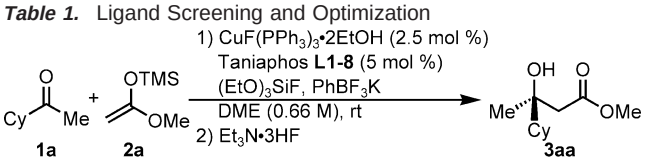
Chiral tertiary alcohols are important building blocks and ubiquitous subunits present in many biologically active compounds and medicinal leads. They are difficult to produce, however, using current synthetic methods.[1] Catalytic enantioselective carbon-nucleophile addition to simple ketones[1d] is a fundamental methodology, constructing the new tetrasubstituted stereogenic carbon center concomitant with carbon−carbon bond formation. Catalytic enantioselective aldol reactions to simple ketones are among the most synthetically useful reactions in this category. The following inherent features of this type of reaction make its development extremely challenging, compared to the catalytic enantioselective aldol reaction to aldehydes:[2,3] (1) attenuated reactivity of ketones usually leads to low conversion; (2) retro-reaction is generally rapid; and (3) enantioface discrimination is difficult due to the similar electronic/steric nature between the two substituents of the ketone carbonyl carbon. Therefore, catalysts that promote enantioselective aldol reaction to ketones need to be highly active and discriminate subtle differences between the two substituents on a prochiral carbon.

Because of these difficulties, there are currently only a few reports of catalytic enantioselective aldol reaction to ketones,[4] including two from our group.[5,6] All of these reactions have a narrow substrate scope, however, especially on the nucleophile side, which hampers practical utilization of these reactions. In this Communication, we report a general enantioselective catalytic aldol reaction to ketones.

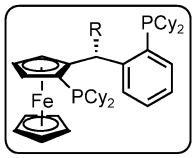
We previously reported a general and mild aldol reaction between ketones and ketene trimethylsilyl acetals catalyzed by a copper(I) fluoride-phosphine complex.[5a] Mechanistic studies indicated that a copper enolate generated through transmetalation is the actual nucleophile, and the addition of a stoichiometric amount of $(EtO)_3SiF$ to facilitate the rate-determining catalyst turnover is essential. More recently, we demonstrated promising results toward enantioselective extension.[5b] A deep chiral environment around Cu constructed by a chiral diphosphine ligand was determined to be necessary to efficiently shield one enantioface of the ketone.

On the basis of this knowledge, we rescreened diphosphine ligands. Taniaphos **L1**[7] was found to be a promising lead for our aldol reaction between ketone **1a** and ketene silyl acetal **2a** (Table 1, entry 1). To maximize efficiency, we tuned the ligand structure. We mainly focused on tuning the amine moiety because molecular modeling studies indicated that bulky amine substituents could fix the position of the cyclohexyl groups, which is an essential requirement for effective enantioselection. Indeed, enlargement of the amine moiety improved the enantioselectivity; however, the reactivity decreased dramatically (entry 2). In addition, the silyl enol ether derived from **1a** was produced (ca. 10%) as a side product. The undesired side reaction is likely promoted by an intermediate copper aldolate (see **C** in Scheme 1) working as a strong Brönsted base. To improve the yield, various additives were screened. The addition of 10 mol % of $PhBF_3K$ significantly improved the yield without affecting the enantioselectivity (entry 3). Increasing the amount of $(EtO)_3SiF$ and decreasing the amount of **2a** further improved the yield (entry 4). The ligand was further tuned using these conditions (entries 5−10). Finally, we identified di-*n*-butylamine-type Taniaphos **L4** as the optimum ligand. Using

Table 1. Ligand Screening and Optimization



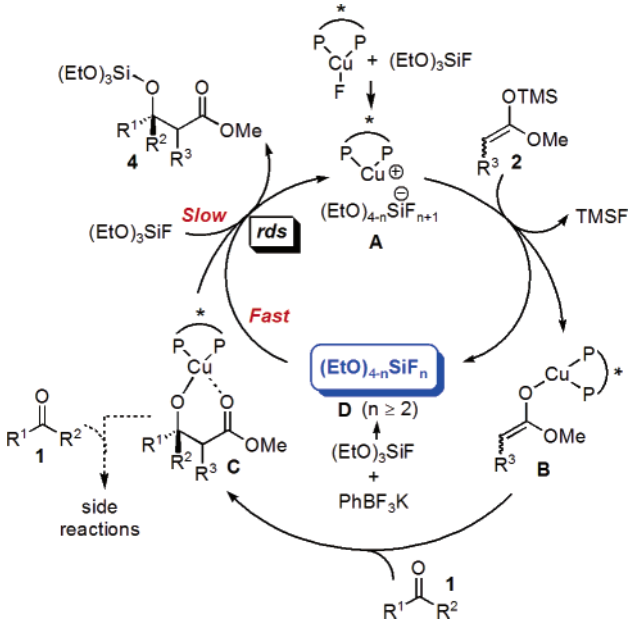
entry	ligand	**2a** (mol %)	$(EtO)_3SiF$ (mol %)	$PhBF_3K$ (mol %)	time (h)	yield (%)	ee (%)
1	**L1**	200	120	–	43	46	48
2	**L2**	200	120	–	31	11	68
3	**L2**	200	120	10	31	43	66
4	**L2**	150	200	10	24	80	67
5	**L3**	150	200	10	24	61	65
6	**L4**	150	200	10	24	84	73
7	**L5**	150	200	10	32	30	71
8	**L6**	150	200	10	24	77	61
9	**L7**	150	200	10	24	48	65
10	**L8**	150	200	10	24	23	0
11[a]	**L4**	150	200	10	32	89	77



L1 (R = NMe_2)
L2 (R = NEt_2)
L3 (R = NBn_2)
L4 (R = N^nBu_2)
L5 (R = N^nDecyl_2)
L6 (R = N^iBu_2)
L7 (R = N^iPrEt)
L8 (R = Me)

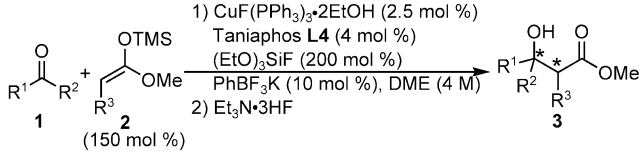
[a] Reaction was conducted with 4 mol % of **L4** under 4 M DME at 0 °C.

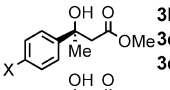
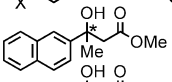
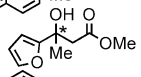
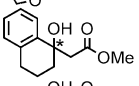
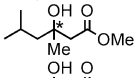
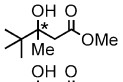
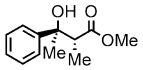
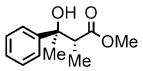
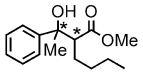
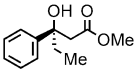
Scheme 1. Plausible Catalytic Cycle and Effect of $PhBF_3K$



10.1021/ja061815w CCC: $33.50

Table 2. Catalytic Enantioselective Aldol Reaction to Ketones[a]



entry	ketone + silyl acetal	product		temp. (°C)	time (h)	yield (%) [dr]	ee (%)
1	**1b** + **2a**		**3ba** (X=H)	–20	19	93	92[d]
2	**1c** + **2a**		**3ca** (X=OMe)	–20	42	95	91
3	**1d** + **2a**		**3da** (X=Cl)	–20	38	85	87
4	**1e** + **2a**		**3ea**	–20	19	92	90
5	**1f** + **2a**		**3fa**	–20	40	88	83
6[c]	**1g** + **2a**		**3ga**	–20	42	92	90
7	**1h** + **2a**		**3ha**	–20	42	73	84
8[b]	**1i** + **2a**		**3ia**	rt	37	93	79
9	**1b** + *E*-**2b** (*E*/*Z* = 5.5/1)		**3bb**	rt	37	96 [80[e]/20[f]]	91[e,g] 75[f]
10	**1b** + *Z*-**2b** (*E*/*Z* = 1/3)		**3bb**	rt	62	58 [86[e]/14[f]]	94[e,g] 78[f]
11	**1b** + *E*-**2c** (*E*/*Z* = >20/1)		**3bc**	rt	35	97 [81[e]/19[f]]	91[e] 82[f]
12[b]	**1j** + **2a**		**3ja**	rt	17	89	78[d]

[a] The detailed procedure is described in the Supporting Information. [b] 5 mol % of CuF and 8 mol % of **L4** were used. [c] 20 mol % of $PhBF_3K$ was used. [d] Absolute configuration was determined to be *S*. [e] More polar isomer. [f] Less polar isomer. [g] Absolute configuration was determined to be (2*R*, 3*S*).

this ligand, both yield and enantioselectivity improved under higher concentrations (4 M) at 0 °C (entry 11).

Next, we investigated the substrate generality under the optimized conditions (Table 2). From various aromatic ketones (entries 1−4, 6, 12), including a heteroaromatic ketone (entry 5), aldol products were obtained in excellent yield with high enantioselectivity. This method produces synthetically useful levels of enantioselection, even with aliphatic ketones, substrates that have previously been poor substrates for enantioselective aldol additions.[4a,b] Remarkably, nucleophiles other than those that are acetate-derived can be used (entries 9−11). The product diastereoselectivity was independent of the *E*/*Z* ratio of silyl acetals (entries 9 and 10). These are the first examples of catalytic enantio- and diastereoselective aldol reactions of ketene silyl acetals to ketones.

NMR experiments were used to gain insight into the unique effect of $PhBF_3K$. When $PhBF_3K$ and $(EtO)_3SiF$ were mixed (3:5 ratio) in THF-d_8 in an NMR tube, new peaks appeared: at −155 ppm in ^{19}F NMR, corresponding to $(EtO)_2SiF_2$; at −158 ppm in ^{19}F NMR, corresponding to $(EtO)SiF_3$; and at 12.2 ppm in ^{11}B NMR, corresponding to $PhB(OEt)_2$.[8] On the other hand, there was no detectable interaction between $PhBF_3K$, and CuF or **2a**.

The NMR studies suggest that the beneficial effect of $PhBF_3K$ is attributable to the generation of highly electrophilic $(EtO)_2SiF_2$ and $(EtO)SiF_3$ (**D** in Scheme 1). In previous kinetic studies, these species were thought to play a key role in the rate-determining catalyst turnover step, even in the absence of $PhBF_3K$.[5a,9] The addition of a catalytic amount of $PhBF_3K$ simply increases the concentration of **D**, intensifying its acceleration effect. In fact, using $(MeO)_2SiF_2$[10] instead of $(EtO)_3SiF$ (in the absence of $PhBF_3K$) under the conditions listed in Table 1, entry 2 significantly improved the yield of **3aa** (22 h, 97% yield, 60% ee).

In conclusion, we developed a general enantioselective Cu(I) fluoride-catalyzed aldol reaction to simple ketones, identifying $PhBF_3K$ as an effective catalytic additive. Remarkably, the robustness of this reaction allowed for the first diastereo- and enantioselective catalytic aldol reaction to ketones using ketene silyl acetals. To achieve the excellent selectivity, steric tuning of the Taniaphos ligand was essential. A unique role of $PhBF_3K$ as a fluoride source to generate the active trapping silyl agent **D** was demonstrated. Further detailed mechanistic studies will be reported elsewhere.

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Supporting Information Available: 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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(8) The assignments are based on the chemical shift of synthesized $(MeO)_2SiF_2$, $(MeO)_3SiF$, $PhBF_2$, and commercial phenylpinacolborane. Alkoxyboron acts as a much less effective trapping reagent according to the control experiment using $B(OMe)_3$ instead of the $(EtO)_3SiF-PhBF_3K$ combination. See Supporting Information for details.

(9) Rate dependencies on [silyl acetal] and [CuF] (−0.8th and 1.5th, respectively) suggested the intervention of the fluoride-rich silicon species **D** in this rate-determining step, even in the absence of $PhBF_3K$ (ref 5a). Other evidence that silyl fluoride is an important species in this reaction is the finding that $CuF-PPh_3$ had higher catalyst activity than $CuO^tBu-PPh_3$ or $CuOAc-PPh_3$.

(10) Tedious fractional distillation is required for the synthesis of $(MeO)_2SiF_2$.

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