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Catalytic Enantioselective Mannich-type Reactions of Ketoimines

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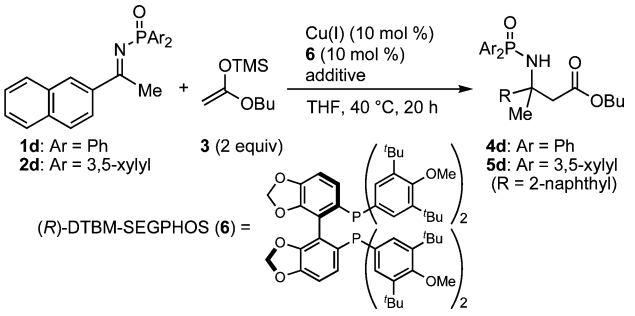
Chiral β-amino acids are important building blocks for a wide variety of natural products, pharmaceutical agents, and mimics of protein structural motifs.[1] The catalytic asymmetric Mannich reaction is one of the most powerful and direct methods for accessing such chiral building blocks through C−C bond formation.[2] This method, however, is currently limited to using aldimines or iminoesters[3] as substrates. The catalytic asymmetric Mannich reaction to simple ketoimines produces direct precursors of β,β-disubstituted amino acids, which are not easily accessible by the current synthetic methods.[4] The low reactivity of ketoimines, the rapid isomerization of an electrophilic ketoimine to an unreactive enamine under basic conditions, and the difficulty in differentiating the two substituents on the prochiral ketoimine carbon are the three main obstacles that make the development of a catalytic asymmetric Mannich reaction of simple ketoimines formidably challenging. To date, a non-stereocontrolled catalytic Mannich reaction of simple ketoimines has yet to be reported. In this communication, we describe the first catalytic enantioselective Mannich reaction of simple ketoimines.

We recently reported that the CuF−Taniaphos complex catalyzes an asymmetric aldol reaction between simple ketones and ketene silyl acetals.[5] In this reaction, a highly nucleophilic copper enolate, generated through transmetalation from the corresponding silyl enolate,[6] functions as the nucleophile. The catalyst regeneration step from the intermediate copper aldolate (formed via the addition of a copper enolate to a substrate ketone) is the turnover-limiting step. Combining a stoichiometric amount of $(EtO)_3SiF$ and a catalytic amount of $PhBF_3K$ as additives was essential to facilitate this step. Together, these additives generated a small amount of highly electrophilic polyfluorosilicon species [$(EtO)_{4-n}SiF_n$, $n \geq 2$] in situ, which can quickly trap the copper aldolate and regenerate the catalytically active copper fluorosilicate.

We began developing a catalytic enantioselective Mannich reaction of simple ketoimines by applying the optimized conditions for the ketone aldol reaction.[5] Initial screening of the chiral ligands and protecting groups of the ketoimine nitrogen atom led to the identification of DTBM−SEGPHOS (**6**) and *N*-phosphinoyl imines (**1**) as a promising ligand and substrates, respectively; using a CuF·3PPh$_3$·2EtOH−**6** complex (10 mol %), the reaction between ketoimine **1d** and silyl enolate **3** produced **4d** in 60% yield with 60% ee (Table 1, entry 1).[7] To improve the results, a copper source was then screened, and CuOAc was found to be superior with regard to reaction enantioselectivity (entry 2). The enantioselectivity was further improved to 94% ee in the absence of $PhBF_3K$ (entry 3).

To improve the yield, we planned to accelerate the presumable turnover-limiting catalyst regeneration step from the intermediate copper amide (generated via the addition of a copper enolate to the imine) by using a more electrophilic silicon species than $(EtO)_3SiF$ as a trapping reagent.[8] As expected, the addition of 1 equiv of $(MeO)_2SiF_2$,[9] instead of $(EtO)_3SiF$, significantly enhanced the reactivity; product **4d** was obtained in 85% yield with no decrease in the enantioselectivity (Table 1, entry 4). The synthesis

Table 1. Optimization of Catalytic Enantioselective Mannich Reaction to Aromatic Ketoimine



entry	ketoimine	Cu source	additive[a]	yield[b] (%)	ee[c] (%)
1	**1d**	CuF[d]	$(EtO)_3SiF + PhBF_3K$	60	60
2	**1d**	CuOAc	$(EtO)_3SiF + PhBF_3K$	58	85
3	**1d**	CuOAc	$(EtO)_3SiF$	54	94
4	**1d**	CuOAc	$(MeO)_2SiF_2$	85	93
5	**1d**	CuOAc	$Me_2Si(OAc)_2$	68	78
6	**1d**	CuOAc	$EtSi(OAc)_3$	60	80
7	**1d**	CuOAc	$(EtO)_2Si(OAc)_2$	82	92
8	**2d**	CuOAc	$(EtO)_2Si(OAc)_2$	74	96

[a] In entries 1 and 2, 1 equiv of $(EtO)_3SiF$ and 10 mol % of $PhBF_3K$ were used. In other entries, 1 equiv of additive was used. [b] Isolated yield. [c] Determined by chiral HPLC. [d] CuF·3PPh$_3$·2EtOH.

of $(MeO)_2SiF_2$, however, was troublesome. Therefore, more readily available electrophilic silicon species were screened. Although reactions using alkyl-substituted silyl acetates as an additive produced less satisfactory results (entries 5 and 6), $(EtO)_2Si(OAc)_2$[10] produced comparable reactivity and enantioselectivity to $(MeO)_2SiF_2$ (entry 7). In addition, the enantioselectivity was improved to 96% ee using di(3,5-xylyl)phosphinoyl imine **2d** as a substrate (entry 8).[11]

The behavior of the aliphatic ketoimine **2h** was different from that of the aromatic substrate (Table 2). Although high enantioselectivity (87% ee) was obtained under the optimized conditions for aromatic ketoimine **2d**, the yield of **5h** was only 29% (Table 2, entry 1). We attribute the low yield in the case of the aliphatic ketoimine to isomerization of the imine to the corresponding enamine form under the reaction conditions. This undesired reaction pathway was effectively suppressed using $(EtO)_3SiF$ as a trapping reagent and DuPHOS derivatives as the chiral ligand (entries 3 and 4). Specifically, DuPHOS **8**, which contains bulky 4-trans-^{t}Bu-substituted cyclohexyl groups, produced the optimum results (entry 4).

Under the optimized conditions, we investigated substrate generality (Table 3). From aromatic ketoimines, including heteroaromatic (**2e** and **2f**) and ethyl-substituted (**2g**) ketoimines, excellent enantioselectivity was produced under condition A using CuOAc−DTBM−SEGPHOS (**6**) as a catalyst and $(EtO)_2Si(OAc)_2$ as a trapping reagent (entries 1−7). When the aliphatic ketoimines

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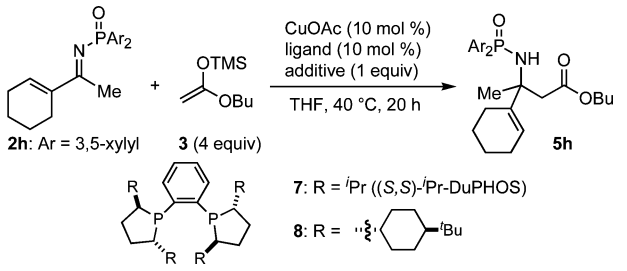
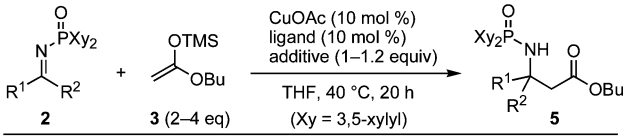
Table 2. Optimization of Catalytic Enantioselective Mannich Reaction to Aliphatic Ketoimine

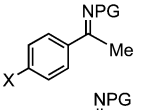
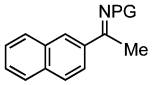
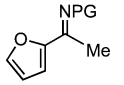
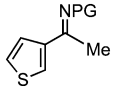
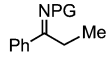
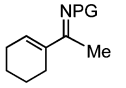
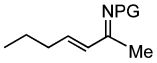
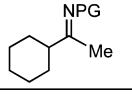


entry	ligand	additive	yield[a] (%)	ee[b] (%)
1	**6**	$(EtO)_2Si(OAc)_2$	29	87
2	**6**	$(EtO)_3SiF$	58	86
3	**7**	$(EtO)_3SiF$	90	75
4	**8**	$(EtO)_3SiF$	99	81

[a] Isolated yield. [b] Determined by chiral HPLC.

Table 3. Catalytic Enantioselective Mannich Reaction of Ketoimines

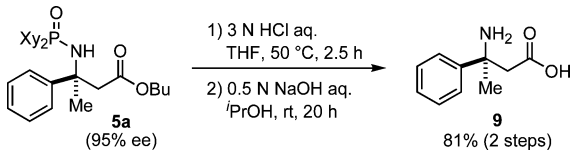


entry	substrate		conditions[a]	yield (%)[b]	ee (%)[c]
1		X = H (**2a**)	A	81	95[g]
2		X = Cl (**2b**)	A	82	97
3[d]		X = OMe (**2c**)	A	87	97
4		**2d**	A	74	96
5[d]		**2e**	A	74	96
6		**2f**	A	92	97
7[d]		**2g**	A	61	91
8[e]		**2h**	B	99	75
9[f]			B	99	81
10[e]		**2i**	B	74	58
11[f]			B	65	77
12[e]		**2j**	B	81	75
13[f]			B	45	80

[a] Condition A: **3** = 2 equiv, ligand = **6**, additive = $(EtO)_2Si(OAc)_2$ (1 equiv). Condition B: **2** = 4 equiv, ligand = DuPHOS (**7** or **8**), additive = $(EtO)_3SiF$ (1.2 equiv). [b] Isolated yield. [c] Determined by chiral HPLC. [d] 4 equiv of **3** were used. [e] Ligand = **7**. [f] Ligand = **8**. [g] Absolute configuration was determined to be (*S*).

(**2h**, **2i**, and **2j**) were used, the enantioselectivity was not completely satisfactory, even under optimized condition B using CuOAc−DuPHOS **8** as the catalyst and $(EtO)_3SiF$ as the trapping reagent (entries 9, 11, and 13). Considering the unprecedented features of this type of reaction, however, the enantioselectivity is in a synthetically appreciable range. Enantioselectivity was consistently higher when using new DuPHOS **8** rather than **7** (entries 8, 10, and 12), which suggests that the enantioselectivity of the aliphatic ketoimines can be improved with future intensive ligand optimization.

Scheme 1. Conversion to β,β-Disubstituted Amino Acid



The Mannich product **5a** was successfully converted to a β,β-disubstituted amino acid **9** in high yield through removal of the phosphinoyl group under acidic conditions followed by hydrolysis of the ester with aqueous NaOH (Scheme 1).

In conclusion, we have developed a Cu(I)-catalyzed enantioselective Mannich reaction of simple ketoimines. The reaction is a platform for the synthesis of optically active β,β-disubstituted amino acids, which are important building blocks in many fields. Further studies to improve the reaction efficacy and substrate generality are in progress.

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Supporting Information Available: Results of optimization process, proposed catalytic cycle, experimental procedures, and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(1) (a) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991. (b) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1. (c) Fulop, F. *Chem. Rev.* **2001**, *101*, 2181. (d) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173.

(2) For reviews of asymmetric Mannich reactions, see: (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (b) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10. (c) Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 348.

(3) To date, two examples of tetrasubstituted carbon-forming catalytic enantioselective Mannich reactions of special ketoiminoesters have been reported. See: (a) Saaby, S.; Nakama, K.; Lie, M. A.; Hazell, R. G.; Jørgensen, K. A. *Chem.—Eur. J.* **2003**, *9*, 6145. (b) Zhuang, W.; Saaby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4476.

(4) Mapp recently reported a general β,β-disubstituted amino acid synthesis utilizing diastereoselective nitrile oxide [3 + 2] cycloaddition as a key step. See: (a) Minter, A. R.; Fuller, A. A.; Mapp, A. K. *J. Am. Chem. Soc.* **2003**, *125*, 6846. (b) Fuller, A. A.; Chen, B.; Minter, A. R.; Mapp, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 5376.

(5) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7164.

(6) For pioneering studies on transmetalation from a silyl enoate to a copper enolate, see: Pagenkopf, B. L.; Krüger, J.; Stojanovic, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3124.

(7) The trimethylsilyl enolate derived from methyl acetate produced comparable results; however, in this case, isolation of the product from **1d** was difficult.

(8) Slow addition of a protic additive (such as tBuOH) did not improve the yield in this case. On the other hand, a protic additive facilitated the catalyst turnover in Cu-catalyzed enantioselective allylation of ketoimines: Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687.

(9) August, J. M. *J. Org. Chem.* **1988**, *53*, 3364.

(10) $(EtO)_2Si(OAc)_2$ can be easily synthesized in a multi-gram scale. See Supporting Information.

(11) The yield was slightly lower when using **2d** rather than **1d** as a substrate. In many substrates shown in Table 3, however, both yield and enantioselectivity were improved using a *N*-di(3,5-xylyl)phosphinoyl protecting group rather than a simple *N*-diphenylphosphinoyl group.

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