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Asymmetric Reductive Mannich Reaction to Ketimines Catalyzed by a Cu(I) Complex

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β-Amino acids are important building blocks for a wide variety of natural products, pharmaceutical agents, and mimics of protein structural motifs.[1] The substitution pattern and stereochemistry at the C-2 and/or C-3 positions strongly influence the structural, chemical, and biologic characteristics of β-amino acids and their oligomers (β-peptides). A particularly intriguing, but not well-evaluated class of β-amino acids is the densely substituted amino acids, including β,β-disubstituted ($\beta^{3,3}$) and α,β,β-trisubstituted ($\beta^{2,3,3}$) amino acids. Asymmetric synthesis of these β-amino acids is extremely challenging,[2] which hampers the use of these amino acids as components of functional molecules.

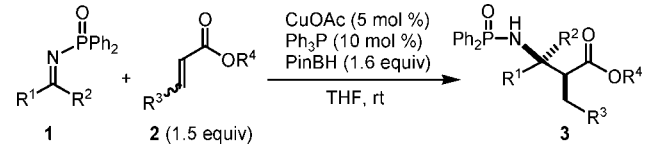
The catalytic asymmetric Mannich-type reaction of ketimines is one of the most straightforward methods for accessing β,β-disubstituted amino acids.[3−6] We developed a catalytic enantioselective Mannich-type reaction between nonactivated ketimines and an acetate-derived silyl enolate using chiral Cu(I) complexes.[7] This reaction is the first example that can catalytically overcome the low reactivity of ketimines (relative to aldimines, aldehydes, and ketones) in enolate addition.[8] The high catalyst performance is attributed to the generation of reactive copper enolates through transmetalation from silicon enolates.[9] This method, however, is limited to acetate-derived enolates as donors (i.e., no reaction using propionate-derived enolates). Therefore, a new method is required to achieve catalytic asymmetric synthesis of $\beta^{2,3,3}$-amino acids containing a substituent at the α-position. In this communication, we describe the development of a catalytic asymmetric reductive Mannich reaction of ketimines, which greatly expands the previous scope of catalytic asymmetric β,β-disubstituted amino acid synthesis.

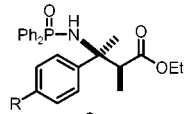
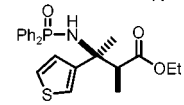
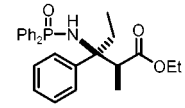
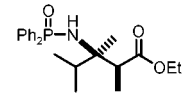
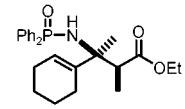
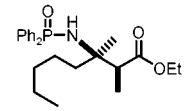
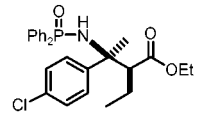
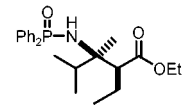
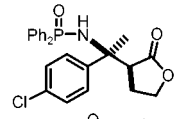
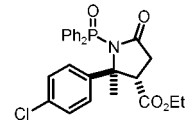
We first established the catalytic conditions to realize Mannich-type addition of a propionate-derived enolate to ketimines in a racemic system. After several unsuccessful attempts to increase the reactivity of copper enolate, which was generated through transmetalation, with soft Lewis base additives or cuprate formation, we focused on an alternative approach to increase the concentration of active copper enolate.[10] The conjugate addition of Cu-based nucleophiles to α,β-unsaturated esters was an attractive candidate for this purpose.[11,12]

The reductive Mannich coupling between ketimine **1b** and ethyl acrylate (**2a**) in the presence of CuOAc−PPh_3 catalyst (5 mol %) was selected as a model reaction for optimization of the conditions.[13] Although the yield and diastereoselectivity were not satisfactory (yield ≈ 60%, dr ≈ 3:1) when using $(EtO)_3SiH$ as a stoichiometric reducing reagent in the presence or absence of previously identified additive accelerators ($(EtO)_3SiF$[7] or LiO^iPr[14]), the reaction proceeded smoothly using pinacolborane (PinBH), affording the product (**3ba**) in excellent yield and diastereoselectivity (92% yield, dr = 50:1, Table 1, entry 2).[15] Other Cu sources, such as CuF and CuH, produced less satisfactory results.

We then studied the substrate scope of this highly diastereoselective reductive Mannich reaction of ketimines under the optimized conditions (Table 1). Except for one entry using a linear aliphatic

Table 1. Catalytic Diastereoselective Reductive Mannich Reaction of Ketimines



entry	product		time (h)	yield[a]	dr[b]
1		R = H (**3aa**)	5	89	18/1
2		R = Cl (**3ba**)	4	92	50/1
3		R = MeO (**3ca**)	5	94	16/1
4		**3da**	4	84	99/1
5		**3ea**	18	75	36/1
6[c]		**3fa**	48	85	17/1
7		**3ga**	18	97	6/1
8		**3ha**	42	77	2/1
9		**3bb**	4	73	13/1
10		**3fb**	18	85	29/1
11		**3bc**	4	86	4/1
12		**4bd**	4	90	99/1

[a] Combined yield of diastereomers. [b] Diastereomer ratio determined by ^1H NMR spectroscopy. [c] $MePPh_2$ was used instead of Ph_3P.

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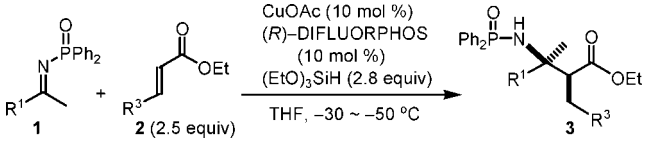
ketimine (entry 8), products containing contiguous tetra- and trisubstituted carbons were produced from a wide range of ketimines with excellent chemical yield and diastereoselectivity.[16] The generality of the donor α,β-unsaturated esters was also broad (entries 9−12). When using ethyl fumarate (**2d**) as the donor, the synthetically attractive γ-lactam **4bd** was produced in one-pot with complete diastereoselectivity (entry 12).

Table 2. Catalytic Asymmetric Reductive Mannich Reaction of Ketimines

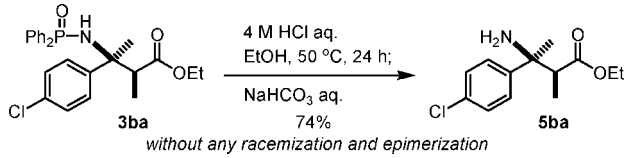


entry	product	temp (°C)	time (h)	yield[a] (dr[b])	ee[c]
1	**3aa**	−50	41	95 (9/1)	85
2	**3ba**	−50	42	90 (6/1)	91
3	**3ia**: R^1 = 2-naphthyl, R^3 = H	−50	41	88 (3/1)	86
4	**3ga**	−30	36	90 (9/1)	91
5	**3bb**	−30	48	86 (5/1)	82
6	**3bd**: R^1 = 4-Cl-C_6H_4, R^3 = CO_2Et	−40	65	65 (17/1)	90
7	**3gd**: R^1 = 1-cyclohexenyl, R^3 = CO_2Et	−50	36	47 (30/1)	93

[a] Combined yield of diastereomers. [b] Diastereomer ratio determined by ^{1}H NMR spectroscopy. [c] Enantiomeric excess of the major isomer determined by chiral HPLC.

This platform reaction was then extended to catalytic asymmetric variants using chiral phosphines. No appreciable enantio-induction was produced, however, even after intensive screening of the chiral ligands. In sharp contrast, enantioselectivity was markedly higher when using silanes instead of PinBH as the reducing reagent.[17] Although the reactions were slower when using silanes, compared to using PinBH, product yield was significantly improved when sterically less crowded bis-arylphosphines were used as ligands and the reactions were performed at lower temperature. The optimized conditions for the catalytic asymmetric reductive Mannich reaction were identified: CuOAc−DIFLUORPHOS[18] complex as a catalyst and $(EtO)_3SiH$ as a reducing reagent at −30 °C or lower (Table 2).[15] The substrate scope covers both aromatic and α,β-unsaturated ketimines as acceptors, affording α-methyl-, ethyl-, and ethoxycarbonylmethyl-substituted products[19] with high enantio- and diastereoselectivities. The products were converted to enantiomerically enriched $\beta^{2,3,3}$-amino acid derivatives in high yield without any racemization and epimerization through cleavage of the diphenylphosphinoyl group under acidic conditions (Scheme 1).[20]

Scheme 1. Conversion to $\beta^{2,3,3}$-Amino Acid Derivative



In conclusion, we developed the first catalytic asymmetric reductive Mannich reaction to ketimines. Products containing contiguous tetra- and trisubstituted stereocenters were produced with high enantio- and diastereoselectivities.[21] This methodology is the first entry to the catalytic asymmetric synthesis of $\beta^{2,3,3}$-amino acid derivatives. Studies to improve the catalyst turnover and expand the substrate generality are in progress.

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Supporting Information Available: 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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(13) For the initial stage optimization, see Table S-1 in Supporting Information (SI). *N*-Phosphinoyl ketimines produced more promising results than *N*-benzyl and *N*-toluenesulfonyl ketimines.
(14) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687.
(15) For determination of the relative and absolute configuration of the products, see SI.
(16) There was no simple and general catalytic method for diastereoselective synthesis of $\beta^{2,3,3}$-amino acid derivatives, even in a racemic system.
(17) For example, a CuOAc−tol-BINAP catalyst produced **3ba** with only 25% ee using PinBH, but with 68% ee using $(EtO)_3SiH$ (0 °C). This sharp difference might be due to switching of the reactive nucleophile (achiral boron enolate vs. chiral copper enolate) depending on the reducing reagents (see SI). The fact that enantiomeric excess of **3ba** improved to 56% ee in the presence of pyridine (1.8 equiv: possible deactivator of boron enolate) using PinBH supports this consideration.
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(19) In Table 2, entries 6 and 7, no cyclized products such as **4bd** were observed.
(20) See SI for more examples of product conversion.
(21) Reviews of Cu-catalyzed asymmetric tetrasubstituted carbon construction, see: (a) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853. (b) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873.

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