Asymmetric Synthesis

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Direct Asymmetric Mannich-Type Reaction of α-Isocyanoacetates with Ketimines using Cinchona Alkaloid/Copper(II) Catalysts**

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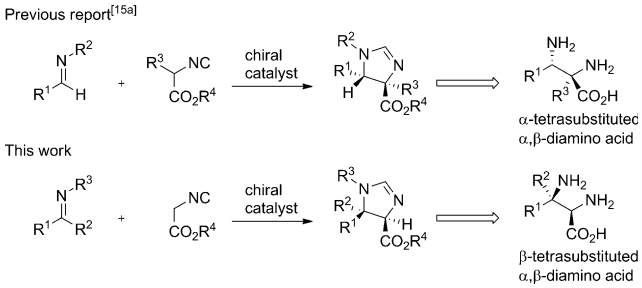
Abstract: *The enantioselective direct Mannich-type reaction of ketimines with α-isocyanoacetates has been developed. Excellent yields and enantioselectivity were observed for the reaction of various ketimines and α-isocyanoacetates using cinchona alkaloid/Cu(OTf)$_2$ and a base. Both enantiomers of the products could be obtained by using pseudoenantiomeric chiral catalysts. This process offers an efficient route for the synthesis of α,β-diamino acids.*

Optically active α,β-diamino acids are key intermediates for the synthesis of biologically active compounds.[1] Their synthetic importance has prompted considerable interest to develop asymmetric syntheses for α,β-diamino acids.[2] One of the most efficient methods for the synthesis of optically active α,β-diamino acids would be the direct asymmetric Mannich-type reaction of α-amino acid equivalents.[3] Specifically, α-isocyanoacetates are attractive compounds as α-amino acid equivalents, as the reaction of α-isocyanoacetates with imines affords imidazoline derivatives[4–6] which can be readily hydrolyzed into chiral α,β-diamino acids. Although excellent methodologies have been developed for the asymmetric reaction of α-isocyanoacetates with various electrophiles such as aldimines,[7] carbonyl compounds,[8] azo compounds,[9] α,β-unsaturated carbonyl compounds,[10] and nitroolefins,[11] there has been no report on the enantioselective reaction with ketimines, probably because of their low reactivity and the difficulty in enantiofacial control.[12] Matsunaga, Shibasaki et al. reported the stereodivergent direct asymmetric Mannich-type reaction of α-isothiocyanato esters with ketimines to give cyclic thioureas, which were converted into chiral imidazoline compounds with high enantioselectivity.[13] During the preparation of this manuscript, Ortín and Dixon reported the *anti*-selective enantioselective reaction of α-isocyanoacetates with ketimines using 20 mol% of a chiral cinchona-alkaloid-derived aminophosphine/Ag_2O catalyst to give products with high enantioselectivity.[14] Although a pioneering study has been made, the development of novel catalyst systems with wide substrate tolerance and acceptable catalytic activity for enantioselective reactions of α-isocyanoacetates with ketimines still remains a major challenge. In contrast, we recently reported the highly enantioselective reaction of α-substituted-α-isocyanoacetates with aldimines using bifunctional organocatalysts to give α-tetrasubstituted chiral imidazolines with high enantioselectivity.[15] We also reported novel cooperative catalysts derived from cinchona alkaloid picolinamides and Lewis acids,[16] and the enantioselective reaction of ketimines with various nucleophiles.[12c,l,17] We herein report the direct asymmetric Mannich-type reaction of α-isocyanoacetates with various ketimines using our original chiral catalysts derived from cinchona alkaloids (Scheme 1).



Scheme 1. Asymmetric synthesis of α,β-diamino acids having a quaternary carbon center by using a Mannich-type reaction of α-isocyanoacetates with ketimines.

The enantioselective reaction of the ketimine **1a** with methyl isocyanoacetate (**2**; 1.5 equiv) was carried out in the presence of 10 mol% of the picolinamide ligands **3**, derived from cinchona alkaloids (Table 1). The reaction of **1a** with **2** using *N*-picolynoyl-9-amino-9-deoxy-*epi*-cinchonine (**3a**) gave *anti*-**4a** as a racemic compound in high yield (entry 1). In contrast, the combined catalyst of **3a** and Et_2Zn gave *syn*-**4a** in high yield with moderate diastereo- and enantioselectivity (entry 2). The reaction using $Cu(OAc)_2$ improved the enantioselectivity of the product *syn*-**4a** albeit in low yield (entry 3). The addition of Cs_2CO_3 was effective for promoting the reaction (entry 4). After an optimization experiment for Lewis acids, the reaction using **3a**/$Cu(OTf)_2$ afforded *syn*-**4a** in high yield with high stereoselectivity (entries 5–7). To improve the diastereoselectivity, we added the substituent at

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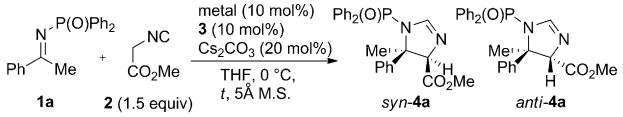
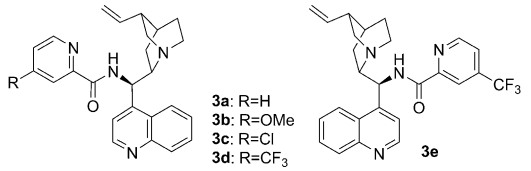
Table 1: Asymmetric Mannich-type reaction of **2** with the ketimines **1a** using various chiral ligands and metal species.[a]

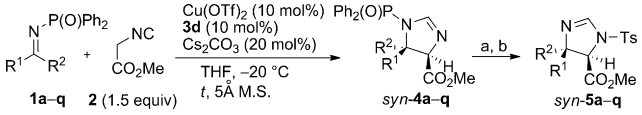




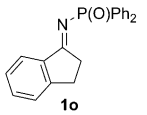
Entry	Metal species	3	t [h]	Conv. [%][b]	*syn*/*anti*[b]	*ee* [%][c]
1	–	**3a**	6	87	14:86	0
2[d]	Et_2Zn	**3a**	12	95	78:22	82
3[e]	$Cu(OAc)_2$	**3a**	18	30	78:22	93
4	$Cu(OAc)_2$	**3a**	3	100	55:45	24
5	$Cu(OTf)_2$	**3a**	1.5	100	78:22	98
6	$Zn(OTf)_2$	**3a**	18	29	73:27	78
7	$Ni(OTf)_2$	**3a**	18	100	94:6	21
8	$Cu(OTf)_2$	**3b**	2	100	82:18	98
9	$Cu(OTf)_2$	**3c**	2	100	84:16	99
10	$Cu(OTf)_2$	**3d**	1.5	100	91:9	98
11[f]	$Cu(OTf)_2$	**3d**	7	100	92:8	99
12[f,g]	$Cu(OTf)_2$	**3d**	15	100	90:10	99
13[f]	$Cu(OTf)_2$	**3e**	60	57	77:23	97[h]

[a] Reaction conditions: ketimine **1a** (0.1 mmol), **2** (1.5 equiv), metal species (10 mol%), **3** (10 mol%), Cs_2CO_3 (20 mol%), and 5 Å M.S. (20 mg) in THF (0.1 M). [b] Conversion and diastereomeric ratio were determined by NMR analysis of the crude reaction mixtures. [c] The *ee* value (for major diastereomer, *syn*) was determined by HPLC analysis using a chiral stationary phase. [d] Without Cs_2CO_3 and 5 Å M.S. [e] Without Cs_2CO_3. [f] At −20 °C. [g] Used 5 mol% of **3d**/$Cu(OTf)_2$ and 10 mol% of Cs_2CO_3. [h] Enantiomer was obtained. M.S. = molecular sieves, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

Table 2: Mannich-type reaction of **2** with the ketimines **1a–q** using **3d**/$Cu(OTf)_2$.[a]



1a: $R^1 = C_6H_5$, R^2 = Me
1b: R^1 = 4-MeC_6H_4, R^2 = Me
1c: R^1 = 4-$MeOC_6H_4$, R^2 = Me
1d: R^1 = 4-FC_6H_4, R^2 = Me
1e: R^1 = 3-ClC_6H_4, R^2 = Me
1f: R^1 = 4-ClC_6H_4, R^2 = Me
1g: R^1 = 3-BrC_6H_4, R^2 = Me
1h: R^1 = 4-BrC_6H_4, R^2 = Me
1i: R^1 = 4-$NO_2C_6H_4$, R^2 = Me
1j: R^1 = 2-naphthyl, R^2 = Me
1k: R^1 = 2-thienyl, R^2 = Me
1l: R^1 = 3-thienyl, R^2 = Me
1m: R^1 = 2-furyl, R^2 = Me
1n: $R^1 = C_6H_5$, R^2 = Et
1p: $R^1 = PhCH_2CH_2$, R^2 = Me
1q: R^1 = *i*Bu, R^2 = Me

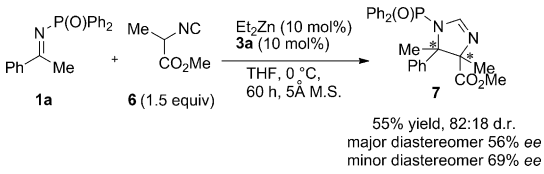


Entry	1	5	t [h]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1	**1a**	**5a**	5	62	92:8	99
2	**1b**	**5b**	48	48	88:12	99
3	**1c**	**5c**	12	68	88:12	98
4	**1d**	**5d**	24	55	86:14	99
5	**1e**	**5e**	12	47	86:14	96
6	**1f**	**5f**	4	62	83:17	96
7	**1g**	**5g**	10	62	83:17	98
8	**1h**	**5h**	4	46	81:19	95
9	**1i**	**5i**	3	51	86:14	97
10[e]	**1j**	**5j**	24	59	84:16	99
11	**1k**	**5k**	8	45	83:17	99
12	**1l**	**5l**	8	55	88:12	98
13	**1m**	**5m**	12	52	92:8	93
14	**1n**	**5n**	7	67	89:11	91
15[f]	**1o**	**5o**	24	44	91:9	98
16	**1p**	**5p**	12	54[g]	28:72	93 (72)
17	**1q**	**5q**	18	78[g]	40:60	95 (89)

[a] Reaction conditions: ketimine **1** (0.1 mmol), **2** (1.5 equiv), $Cu(OTf)_2$ (10 mol%), **3d** (10 mol%), and Cs_2CO_3 (20 mol%) in THF were used. Reaction conditions for conversion of **4** into **5**: a) 4M HCl/ 1,4-dioxane, b) TsCl, Et_3N. [b] Yield is that of the isolated *syn*-**5** after three steps. [c] The diastereomeric ratio was determined by NMR spectra of the crude reaction mixture of **4**. [d] The *ee* value for the *syn*-**5**. The *ee* value for *anti*-**5** is provided within parentheses. [e] At −30 °C. [f] In THF and CH_2Cl_2 (1:1). [g] Yield for the isolated *syn* and *anti* isomer. Ts = 4-toluenesulfonyl.

the 4-position of the pyridine ring in the picolinamide ligand. The diastereoselectivity was improved by using 4-substituented cinchona alkaloid picolinamide ligands, and as a result the 4-trifluoromethyl group was the most suitable substituent (entries 8–10). Finally, lowering the reaction temperature to −20 °C provided *syn*-**4a** with high diastereoselectivity and excellent enantioselectivity (entry 11). The catalyst loading of **3d**/$Cu(OTf)_2$ was successfully reduced to 5 mol% without loss of enantioselectivity (entry 12). The enantiomer of *syn*-**4a** was obtained, by the reaction using **3e** derived from 9-amino-9-deoxy-*epi*-cinchonidine, in moderate yield with good diastereo- and enantioselectivity (entry 13).[18]

Having established the reaction conditions, the Mannich-type reaction of a series of ketimines (**1a–q**) with **2** was examined using **3d**/$Cu(OTf)_2$ and Cs_2CO_3 as the catalyst (Table 2). Some imidazoline products showed low thermal stability, therefore the diphenylphosphinoyl imidazolines **4** were converted into the corresponding tosyl imidazolines **5** in two steps. The yields in Table 2 are those for the isolated *syn*-isomer of **5** after the three-step reaction sequence. The reaction of the ketimines **1b,c** bearing electron-donating groups such as methyl or methoxy groups in the *para* position gave the corresponding products **5b,c** in moderate yield with good diastereoselectivity and excellent enantioselectivity (entries 2 and 3). The reaction of the electron-deficient ketimines **1d–i**, having fluoro, chloro, bromo, or nitro groups, were tolerated under these reaction conditions and gave the corresponding products **5d–i** with good stereoselectivity (entries 4–9). The ketimines **1j–m**, having 2-naphthyl or a heteroaryl group such as 2- or 3-thienyl, and 2-furyl groups, also afforded the corresponding products **5j–m** in 45–59% yield with 93–98 *ee* (entries 10–13). These reaction conditions were also applicable to the more sterically hindered ketimines **1n,o** derived from propiophenone and 1-indanone, respectively, to give **5n,o** (entries 14 and 15). In contrast, ketimines derived from dialkyl ketones (**1p,q**) were also tolerated under the reaction conditions, and the products **5p,q** were obtained in excellent yield with good diastereoselectivity and high enantioselectivity (entries 16 and 17). These results are the first example for *syn*-selective enantioselective reaction of ketimines with α-isocyanides.

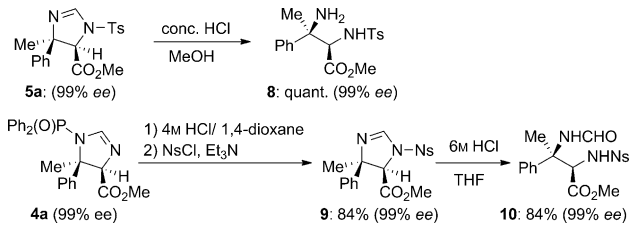


Scheme 2. Asymmetric synthesis of imidazoline having two consecutive tetrasubstituted carbon stereocenters by using a Mannich-type reaction of methyl 2-isocyanopropanoate with the ketimine **1a**.

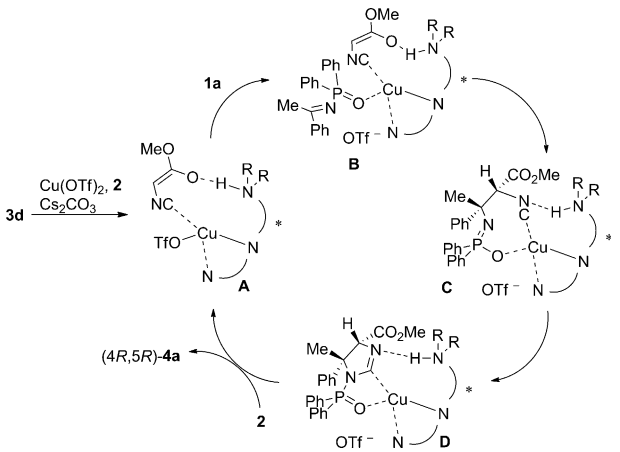
We also examined that the reaction of **1a** with methyl 2-isocyanopropanoate (**6**) to give the imidazoline **7**, having consecutive tetrasubstituted carbon stereocenters, with moderate enantioselectivity (Scheme 2).

We next examined the transformation of the product into an α,β-diamino acid (Scheme 3). The product **5a** was hydrolyzed under acidic conditions to give the α,β-diamino acid derivative **8** in quantitative yield. In contrast, hydrolysis of the imidazoline **9** using 6 M hydrogen chloride gave the corresponding *N*-formyl-*N*′-tosyl-α,β-diamino acid derivative **10** in 84% yield. The absolute configuration of **10** was assigned as (2*R*,3*R*) by X-ray crystallographic analysis (see the Supporting Information).

The proposed catalytic cycle for the Mannich-type reaction of **1a** with **2** is shown in Scheme 4. The picolinamide ligand **3d** reacts with $Cu(OTf)_2$ and Cs_2CO_3 to afford the complex **A**, which includes the ketene hemiacetal of **2**.[19]



Scheme 3. Transformation of **4a** and **5a** into the chiral α,β-diamino acids **6** and **8**, respectively. Ns = nosyl.



Scheme 4. Assumed reaction mechanism for the enantioselective reaction of the ketimine **1a** with α-isocyanoacetate (**2**).

After the coordination of the ketimine to **A**, the C–C bond-formation reaction between **2** and the ketimine proceeds within the coordination sphere of copper(II) to give the Mannich-type reaction product (complex **C**). The intramolecular imidazoline formation reaction of complex **C** and the ligand exchange reaction between complex **D** and **2** gives the product (4*R*,5*R*)-**4a** and **A**. To clarify the assumed reaction mechanism, we investigated the ESI-Mass spectra for the reaction mixture of **2**, **3d**, $Cu(OTf)_2$, and Et_3N. The complex **A** could be observed in this reaction mixture (cation mode, calcd for $C_{30}H_{29}N_5O_3F_3Cu$ as complex **A**-OTf^-: 627.1519, found: 627.1525), thus supporting our proposed reaction mechanism.

From the above consideration and absolute stereochemistry of the product, the assumed transition state for the Mannich-type reaction of **1a** with **2** is shown in Figure 1. Two nitrogen atoms from **3d**, one oxygen from ketimine, and isonitrile coordinate to copper (II) in a square-planar manner, and the α-isocyanoacetate attacks the ketimine within the coordination sphere of the copper cation. The *Re*-face of α-isocyanoacetate approaches the *Si*-face of ketamine, thus avoiding the steric repulsion for the diphenylphosphinoyl group. Further studies are required to fully elucidate the mechanistic detail of the reaction.

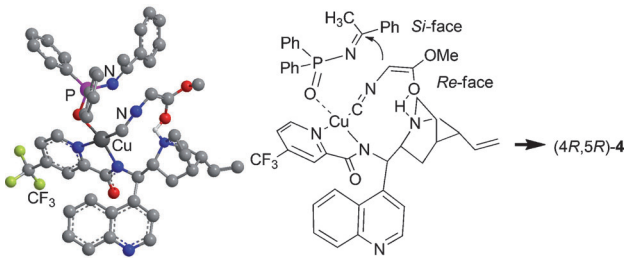


Figure 1. Proposed transition state of the reaction of ketimine **1a** with α-isocyanoacetate (**2**) using **3d**. Hydrogen atoms have been omitted for clarity.

In conclusion, we developed the *syn*-selective enantioselective reaction of ketimines with α-isocyanoacetates. The asymmetric imidazoline formation was screened for a broad range of ketimines and α-isocyanoacetates. This process offers an efficient route for the synthesis of α,β-diamino acids. Products containing contiguous tetra- and trisubstituted stereocenters were produced with high diastereo- and enantioselectivity. The obtained imidazolines can be converted into α,β-diamino acids without the loss of enantiopurity. This process provides stereodivergent access to optically active α,β-diamino acids with tetrasubstituted carbon stereocenters. Additional studies are in progress to study the potential of these catalytic systems to other processes.

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