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Highly Enantioselective Aza-Henry Reaction of Ketoimines Catalyzed by Chiral *N,N′*-Dioxide−Copper(I) Complexes

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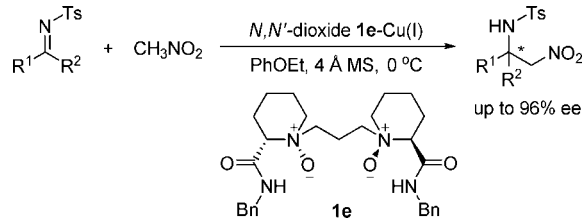
ABSTRACT



The first example of catalytic enantioselective aza-Henry reaction of ketoimines has been realized using a simple chiral *N,N′*-dioxide−Cu(I) complex as catalyst. It performs well over a range of substrates to give the corresponding products in moderate to good yields (up to 83%) with high enantioselectivities (up to 96% ee).

The catalytic asymmetric aza-Henry (or nitro-Mannich) reaction[1] is one of the most powerful and efficient methods for the synthesis of chiral vicinal diamines[2] and α-amino acids[3] through C−C bond formation. Since the pioneering work of Shibasaki[4] and Jørgensen,[5] various catalysts have been developed over the past decade, including both metal complexes[6] and organocatalysts, such as chiral thioureas,[7] chiral proton catalysts,[8] chiral phase transfer catalysts,[9] and so on.[10] However, the substrates are limited to only aldimines. The catalytic enantioselective aza-Henry reaction of ketoimines, which leads to a direct approach for the formation of optically active quarternary carbon centers,[11] is a long-standing problem and has not been achieved so far.

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Even for a racemic or diastereoselective version, only a few examples with limited substrate scope have been reported.[12] The low reactivity and the difficulty in enantio-face differentiation are the two main obstacles that make the development of catalytic asymmetric addition to ketoimines extraordinarily challenging and desirable.[13] Having established a general catalytic racemic aza-Henry reaction of ketoimines,[12c] herein, we wish to report the first enantioselective example using chiral *N*,*N*′-dioxide−Cu(I) complexes as the catalyst.

Initially, the reaction between ketoimine **2a** and nitromethane was selected as the model reaction. Nitromethane was used as solvent considering the low reactivity. Screening of catalysts revealed that the Cu(I) complexes of chiral *N*,*N*′-dioxides[14,15] derived from (*S*)-pipecolic acid[16] and primary amines (Figure 1) are superior for the reaction (Table 1, entries 1−4). While the typical ligand **1a** gave the desired product **3a** in 14% yield and 67% ee (Table 1, entry 4), other known ligands with different amine moieties including both aliphatic and aromatic amines failed to accelerate the reaction (Table 1, entries 5−7). Then the new ligand **1e**, having benzyl groups, was synthesized and tested. The enantioselectivity was dramatically increased to 79% ee with some improvement in yield (Table 1, entry 8). The benzyl substituents in the ligand with appropriate steric hindrance played a key role in this advancement.

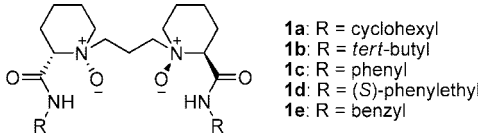
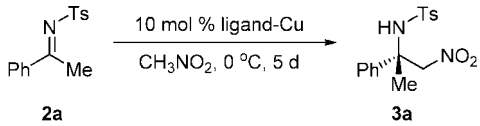


Figure 1. *N*,*N*′-Dioxide ligands evaluated.

Table 1. Screening of Metal Sources and Ligands[a]

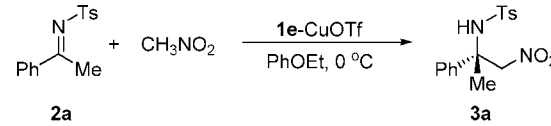


entry	ligand	metal[b]	yield (%)[c]	ee (%)[d]
1	**1a**	$Cu(OAc)_2$	10	10
2	**1a**	$Cu(acac)_2$	13	0
3	**1a**	$Cu(OTf)_2$	nr[e]	
4	**1a**	CuOTf	14	67
5	**1b**	CuOTf	trace	nd[f]
6	**1c**	CuOTf	trace	nd[f]
7	**1d**	CuOTf	trace	nd[f]
8	**1e**	CuOTf	19	79

[a] Reactions were carried out with ligand (10 mol %), metal (10 mol %) and **2a** (0.1 mmol) in CH_3NO_2 (0.5 mL) at 0 °C for 5 days. [b] $Cu(OAc)_2{\cdot}H_2O$, $Cu(acac)_2{\cdot}H_2O$, $Cu(OTf)_2$, and $(CuOTf)_2{\cdot}C_7H_8$ were used as metal sources. [c] Isolated yield. [d] Determined by HPLC using chiral OD-H column. [e] No reaction occurred. [f] Not determined.

The enantioselectivity was further increased to 83% ee when phenyl ethyl ether was used as solvent; meanwhile the amount of nitromethane could be reduced (Table 2, entry 1). Excess nitromethane was essential to obtain the product. After a screen of additives, it was found that the addition of 4 Å molecular sieves could improve both the yield and enantioselectivity (22% yield and 88% ee; Table 2, entry 2).[17] The use of amines as additives was also investigated. However, the enantioselectivity was decreased obviously without remarkable enhancement of the reactivity (Table 2, entries 3 and 4). Further investigation showed that using higher catalyst loading and prolonging the reaction time could give good yield without decrease in enantioselectivity (64% yield and 88% ee; Table 2, entries 5 and 6). No side reaction was observed and unreacted ketoimine could be recovered by flash column chromatography. Although extension of the reaction time was indispensable to obtain higher yield due to the awfully poor reactivity of ketoimines,[18] the result was significant in view of the enormous challenge and difficulty of this reaction.

Table 2. Selected Results for the Optimization of Reaction Conditions[a]



entry	catalyst (mol %)	time (d)	yield (%)[b]	ee (%)[c]
1	10	5	16	83
2[d]	10	5	22	88
3[d,e]	10	5	25	81
4[d,f]	10	5	29	79
5[d]	20	5	39	88
6[d]	20	10	64	88

[a] Unless otherwise noted, reactions were carried out with **1e** (10 mol %), $(CuOTf)_2{\cdot}C_7H_8$ (5 mol %), **2a** (0.1 mmol) and CH_3NO_2 (0.1 mL) in PhOEt (0.5 mL) at 0 °C. [b] Isolated yield. [c] Determined by HPLC using chiral OD-H column. [d] 4 Å MS (20 mg) was added. [e] *i*-Pr_2NEt (10 mol %) was added. [f] Et_3N (10 mol %) was added.

Having optimized the reaction conditions, substrate scope was investigated and the results are summarized in Table 3. High enantioselectivities were obtained with a series of aromatic ketoimines bearing either electron-withdrawing

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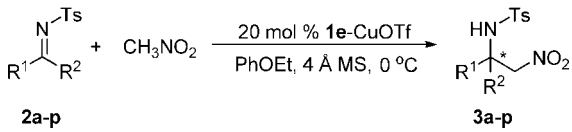
Table 3. Substrate Scope for the Catalytic Enantioselective Aza-Henry Reaction of Ketoimines[a]



2a-p 3a-p

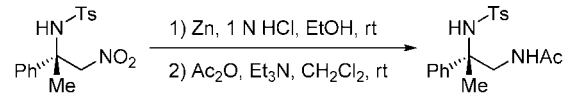
entry	R^1	R^2	time (d)	yield of **3** (%)[b]	ee (%)[c]
1	Ph (**2a**)	Me	5	39 (64)	88 (88)[d]
2	2-FC_6H_4 (**2b**)	Me	5	50 (80)	91 (90)
3	4-FC_6H_4 (**2c**)	Me	5	48 (75)	92 (91)
4	4-ClC_6H_4 (**2d**)	Me	5	58 (81)	93 (92)
5	3-ClC_6H_4 (**2e**)	Me	5	70 (80)	96 (96)
6	4-BrC_6H_4 (**2f**)	Me	5	61 (83)	92 (92)
7	4-MeC_6H_4 (**2g**)	Me	5	21 (42)	90 (90)
8	4-$MeOC_6H_4$ (**2h**)	Me	10	30	88
9	2-$MeOC_6H_4$ (**2i**)	Me	10	44	87
10	3-$MeOC_6H_4$ (**2j**)	Me	10	49	85
11	Ph (**2k**)	Et	10	36	92
12	2-naphthyl (**2l**)	Me	10	47	88
13	2-furyl (**2m**)	Me	5	51 (82)	91 (91)
14	2-thienyl (**2n**)	Me	10	43	78
15	$Ph(CH_2)_2$ (**2o**)	Me	5	47 (76)	71 (71)
16	cyclohexyl (**2p**)	Me	10	35	83
17[e]	Ph (**2a**)	Me	5	33	87

[a] Unless otherwise noted, reactions were carried out with **1e** (0.02 mmol), $(CuOTf)_2{\cdot}C_7H_8$ (0.01 mmol), 4 Å MS (20 mg), **2** (0.1 mmol) and CH_3NO_2 (0.1 mL) in PhOEt (0.5 mL) at 0 °C. [b] Isolated yield. The reaction time for the data in parentheses was 10 days. [c] Determined by HPLC using commercial chiral columns. The reaction time for the data in parentheses was 10 days. [d] The absolute configuration was determined to be *S*. See Supporting Information for details. [e] Reaction was carried out on 1 mmol scale.

or electron-donating substitutents (85−96% ee; Table 3, entries 1−10), while substrates with electron-donating groups provided lower reactivity and extended reaction time was needed (Table 3, entries 7−10). The more sterically hindered substrates such as **2k** and **2l** could also gave the corresponding products in moderate yields with high enantioselectivities (Table 3, entries 11 and 12). In the cases of heteroaromatic ketoimines **2m** and **2n**, the reaction was obviously affected by the heteroatom of the heteroaromatic ring, and **2m** afforded much better result than **2n** (Table 3, entry 13 vs 14). The reaction was also applicable to primary alkyl-substituted ketoimine **2o** and aliphatic ketoimine **2p** (Table 3, entries 15 and 16). In addition, preliminary investigation showed that the reaction could be carried out on 1 mmol scale without decrease in enantioselectivity (Table 3, entry 17). Other nitroalkanes including nitroethane and nitropropane were also tested under the optimized conditions, but only trace of products could be detected.

The synthetic potential of this catalytic approach is due to the formation of useful chiral building blocks,[19] for example, vicinal diamines.[20] The optically active product such as **3a** was readily converted into the corresponding *N*-protected 1,2-diamine **4a** in good yield by zinc-mediated reduction[21] without loss of enantioselectivity (Scheme 1).

Scheme 1. Conversion of the Product to 1,2-Diamine



3a (88% ee) 97% yield **4a** (90% ee)

This method leads to a simple procedure for the synthesis of a new class of optically active vicinal diamines with a quaternary stereogenic center.

In conclusion, the first catalytic enantioselective aza-Henry reaction of ketoimines has been realized using a simple chiral *N*,*N*′-dioxide−Cu(I) complex as catalyst. It performed well over a range of substrates to give the desired products in moderate to good yields (up to 83%) with high enantioselectivities (up to 96% ee). The optically active products can be easily converted into chiral vicinal diamines with a quaternary stereogenic center. Further studies of the reaction mechanism as well as improvement of the reaction efficiency are in progress.

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(16) Ligands derived from other chiral amino acids such as L-proline and (*S*)-ramipril acid gave very poor results (less than 20% ee).

(17) The role of 4 Å molecular sieves in the reaction has not yet been established. Using other additives, including 3 Å and 5 Å molecular sieves, was less efficient.

(18) Imines with other *N*-protecting groups, such as *N*-phenyl and *N*-diphenylphosphinoyl ketoimines, were also tested, but no reaction occurred.

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Supporting Information Available: Experimental procedures, spectral and analytical data for the products, and determination of the absolute configuration of **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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