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The enantioselective diethylzinc addition to imines catalyzed by chiral Cu(II)–oxazoline complexes

Xin Li, Lin-Feng Cun, Liu-Zhu Gong,* Ai-Qiao Mi* and Yao-Zhong Jiang

Key Laboratory for Asymmetric Synthesis and Chirotechnology of Sichuan Province, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, China

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Abstract—A series of copper complexes of chiral bisoxazolines has been applied in the catalytic diethylzinc addition to *N*-sulfonyl imines. It has been found that the tridentate ligands **3**–**5** provided higher enantioselectivity than bidentate ones. Addition of 4 Å molecular sieves to the reaction system benefits the enantioselectivity. The optimal procedure for diethylzinc addition to different imines resulted in moderate yields and enantioselectivities of up to 82% ee.

The important synthetic utility of chiral amines has stimulated great interest in developing methods for the asymmetric preparation of such molecules.[1] Enantioselective dialkylzinc addition to imines is one of the most efficient approaches to chiral amines. Many chiral β-amino alcohols have been designed to promote the dialkylzinc addition with high enantioselectivity, but stoichiometric amounts of ligands are required.[2] Recent studies in this area have revealed that several chiral complexes, including copper-amidophosphine,[3] chiral Zr(IV) complexes,[4] zinc complexes of [2,2]-paracyclophane-*N*,*O*-ligands,[5] copper-Me-DuPhos[6] etc. catalyze the dialkylzinc addition to imines bearing different protected groups with high enantioselectivity. Li et al. have used the copper(I) pybox complex to catalyze the direct-addition of terminal alkynes to imines with excellent results.[7] On the basis of this observation and successful applications of copper–phosphine complexes in diethylzinc additions to imines,[3,6] we envisioned that the chiral copper–oxazoline complexes should work as catalysts to promote the dialkylzinc addition to imines enantioselectively. To the best of our knowledge, the evaluation of chiral copper–oxazoline complexes in diethylzinc additions to imines has not been reported. Herein, we present our preliminary results on this area (Fig. 1).

Initially, to find out an optimal procedure, the diethylzinc addition to **6a** was carried out under different conditions with **3a** as the chiral ligand. The results were summarized in Table 1.

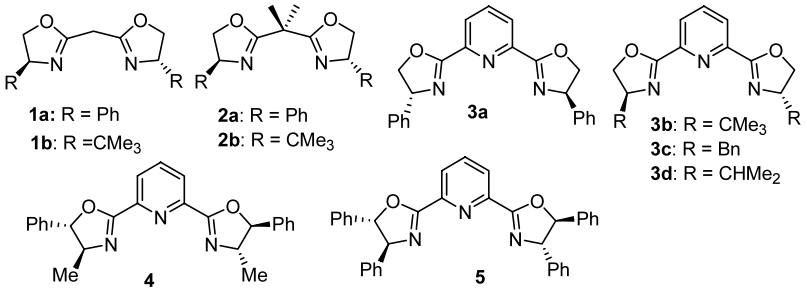

Figure 1. The chiral oxazolines used for this study.

* Corresponding authors. Fax: +86-28-85223978; e-mail: gonglz@cioc.ac.cn

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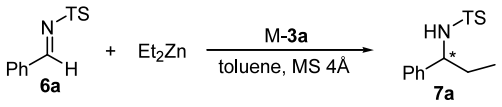
Table 1. The enantioselective diethylzinc addition to **6a** catalyzed by complexes of **3a**[a]



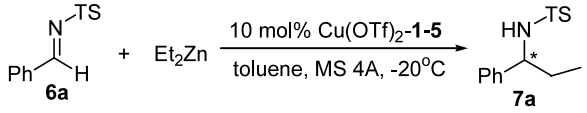
Entry	M	Mol% M	Mol% **3a**	Temp. (°C)	Time (h)	Yield (%)[c]	Ee (%)[d]
1	$Cu(OTf)_2$	10	10	25	9	26	24[b]
2	$Cu(OTf)_2$	10	10	25	9	21	42
3	$Cu(OTf)_2$	10	10	0	20	62	29[b]
4	$Cu(OTf)_2$	10	10	0	20	55	65
5	$Cu(OTf)_2$	10	10	–20	31	71	32[b]
6	$Cu(OTf)_2$	10	10	–20	30	60	76
7	$Cu(OTf)_2$	10	12	–20	31	58	77
8	$Cu(OTf)_2$	12	10	–20	31	62	75
9	CuOTf	10	10	–20	31	60	78
10	$Cu(acac)_2$	10	10	–20	31	41	10
11	$Zn(OTf)_2$	10	10	–20	31	25	0

[a] The concentration of imine is 0.05 mol/L, and the ratio of Et_2Zn to imine is 4.
[b] Without MS 4 Å.
[c] Isolated yield.
[d] The ee was determined with HPLC, and the absolute configuration of **7a** was assigned as *S* by comparing retention time of HPLC with the literature value.[3a]

In the presence of 10 mol% catalyst formed in situ from **3a** and a transition metal complex, the reaction worked enantioselectively to provide the product **7a**. The enantioselectivity was sharply dependent on the reaction conditions. Enantioselectivities ranging from 10 to 78% ee values were observed with different copper complexes (entries 1–10). The promoter generated from $Zn(OTf)_2$ and **3a** gave both poor yield and enantioselectivity for the test reaction (entry 11). The enantioselectivity was highly sensitive to reaction temperature. Lowering the reaction temperature led to a dramatic increase in the enantioselectivity (entries 2, 4, and 6). Addition of 4 Å molecular sieves (MS) benefited the enantioselectivity (entries 1–6), a similar phenomenon had also been observed in copper-pybox catalyzed hetero-Diels–Alder reaction and 1,3-dipolar cycloaddition reactions.[8,9] The ratio of $Cu(OTf)_2$ to **3a** had no obvious influence on either yield or enantioselectivity (entries 6–8). Comparison of results presented in entries 6 and 9 indicated that $Cu(OTf)_2$ had similar reactivity and enantioselectivity to CuOTf. However, the catalyst prepared from $Cu(acac)_2$ and **3a** exhibited much poorer reactivity and stereocontrol to afford **7a** with 41% yield and less than 10% ee (entry 10).

Under the optimal conditions, the Cu(II) complexes of chiral oxazolines **1**–**5** were surveyed to catalyze the diethylzinc addition to **6a**. The results clearly indicated that the enantioselectivity was determined by the structure of the oxazoline. In general, tridentate ligands **3**–**5** (entry 5–10) provided higher enantioselectivity than bidentate oxazolines **1** and **2** (Table 2, entry 1–4). Varying the substituent of the ligand led to an obvious change in the enantioselectivity. The oxazoline **3a** kept the highest level of enantioselectivity among the examined ligands (entry 5).

Table 2. Enantioselective diethylzinc addition to imine **6a** in the presence of 10 mol% $Cu(OTf)_2$ complexes of oxazolines **1**–**5**[a]

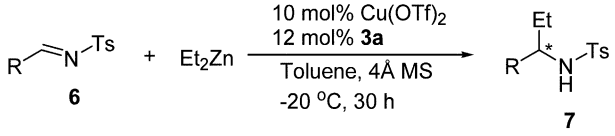


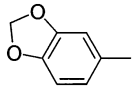
Entry	Oxazoline	Yield (%)[b]	Ee (%)[c]
1	**1a**	41	0
2	**1b**	33	0
3	**2a**	21	9
4	**2b**	41	1
5	**3a**	58	77 (*S*)
6	**3b**	35	23 (*R*)
7	**3c**	32	15 (*R*)
8	**3d**	47	43 (*R*)
9	**4**	32	23 (*S*)
10	**5**	71	50 (*R*)

[a] The ratio of oxazoline to $Cu(OTf)_2$ is 1.2.
[b] Isolated yield.
[c] The ee was determined by HPLC.

The optimal procedure was then examined for the other *N*-sulfonyl imines derived from different aldehydes, and the results are given in Table 3. The reactions of *N*-sulfonyl imines with diethylzinc worked readily to provide chiral sulfonyl amides **7** with moderate yields of 28–62% and enantioselectivities of up to 82% ee. Generally, the absence of substituents containing heteroatoms on the aromatic ring generated the product with higher enantioselectivity (entries 1, 2, 8, and 9) than *N*-sulfonyl imines with heteroatom substituent on the phenyl ring (entries 3–7 and 10). This catalyst system provided poor results for *N*-sulfonyl furyl imine, due to the low reactivity of the substrate.

Table 3. Enantioselective diethylzinc addition to *N*-sulfonylimines



Entry	R	Yield (%)[a]	Ee (%)[b]
1	Ph **6a**	58	77
2	4-MeC_6H_4 **6b**	52	70
3	4-BrC_6H_4 **6c**	60	63
4	4-ClC_6H_4 **6d**	62	64
5	2-ClC_6H_4 **6e**	37	57
6	4-FC_6H_4 **6f**	52	64
7	4-MeOC_6H_4 **6g**	60	61
8	1-Naphthyl **6h**	51	82
9	2-Naphthyl **6I**	40	74
10	 **6j**	58	53
11	2-Furyl **6k**	28	19

[a] Isolated yield.
[b] The ee values were determined on HPLC.

In summary, we have demonstrated that the copper complexes of chiral oxazolines can catalyze the diethylzinc addition to *N*-sulfonyl imines. In the presence of 10 mol% the optimal catalyst in situ generated from $Cu(OTf)_2$ and **3a**, the diethylzinc addition to *N*-sulfonyl imines **6a–k** produced **7a–k** with moderate yields and enantioselectivities of up to 82% ee. Although this catalyst system is not competitive with the known ones at the present stage,[3–6] our results suggest a way to design quite different chiral catalysts from the copper–phosphine system for the organozinc addition to imines.

Acknowledgements

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