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Chiral NHC ligands bearing a pyridine moiety in copper-catalyzed addition of diethylzinc to nitroalkenes

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ABSTRACT

Chiral *N*-heterocyclic carbenes, derived from amino acids containing a pyridine ring, are effective ligands in the enantioselective copper-catalyzed addition of diethylzinc to β-nitroalkenes, which provides access to chiral nitroalkanes. The advantages of this process include high yields, broad and complementary substrate scope, and good to high enantioselectivities.

1. Introduction

Chiral *N*-heterocyclic carbenes (NHCs) are popular ligands in organometallic chemistry, and many complexes incorporating NHCs have been used in syntheses, including cross coupling and metathesis reactions [1]. Recently, applications of chiral NHCs to catalytic asymmetric reactions have been reported, with good to excellent stereoselectivity. In 2001, Woodward reported the first copper-catalyzed conjugate addition of diethylzinc [2], and Alexakis expanded this method to allow asymmetric synthesis using chiral NHC precursors derived from C2 symmetric diamines [3]. Subsequently, dramatic improvements in the method were reported by Hoveyda, who developed a chiral bidentate alkoxy-NHC precursor derived from axial symmetric amino hydroxynaphthalene, which achieved high enantioselectivity in copper-catalyzed reactions [4]. These breakthroughs have led to continued interest in chiral multidentate NHC chemistry [5]. For example, Katsuki [6], Sakaguchi [7], Williams [8], Hayashi [9], and Tomioka [10] independently developed chiral multidentate NHC precursors for copper-catalyzed asymmetric reactions that resulted in high enantioselectivity. Our reports have described the synthesis of a series of chiral imidazolium salts, derived from commercially available L-amino acids, each bearing a pyridine moiety; the corresponding NHC generated *in situ* from the salts could act as a ligand for copper catalyzed asymmetric reaction of *N*-sulfonylimines with dialkylzinc reagents [11]. As part of a continuing effort to broaden the scope of copper-chiral-NHC-catalyzed addition of dialkylzinc reagents to imines, the possibility of controlling 1,4-addition to nitroalkenes was explored (Scheme 1). The use of chiral nitroalkanes as intermediates in synthetic reactions is due to the versatile functionality of the nitro group [12]. As excellent Michael acceptors, nitroalkenes reacted with the range of functionalized nucleophiles. Seebach demonstrated enantioselective conjugate additions of diethyl zinc through the use of a stoichiometric amount of titanium TADDOLates [13] as chiral Lewis acids. Another study described a catalytic version [14]. The present study describes 1,4-addition of dialkylzinc reagents to nitroalkenes catalyzed by a combination of CuI and amino acid-based chiral imidazolium salts containing a pyridine ring to give the corresponding chiral nitroalkanes in reasonably high yields with up to 82% ee. (see Fig. 1)

2. Results and discussion

Initially, this study focused on the structure of chiral imidazolium salts **4**–**12**, with an examination of the reaction of nitrostyrene (**1a**) with diethylzinc (**2E**) in the presence of 5.0 mol% copper(II) triflate and the chiral imidazolium salt (6.5 mol%) in toluene at 0 °C. The reaction proceeded smoothly to afford the ethylated product **3aE** with 55% ee in moderate yield in the case of **4** (Table 1, entry 1). To dissolve the imidazolium salts efficiently and form the copper-

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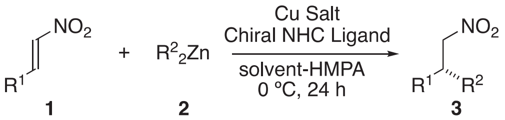


Scheme 1. Enantioselective alkylation of nitroalkenes.

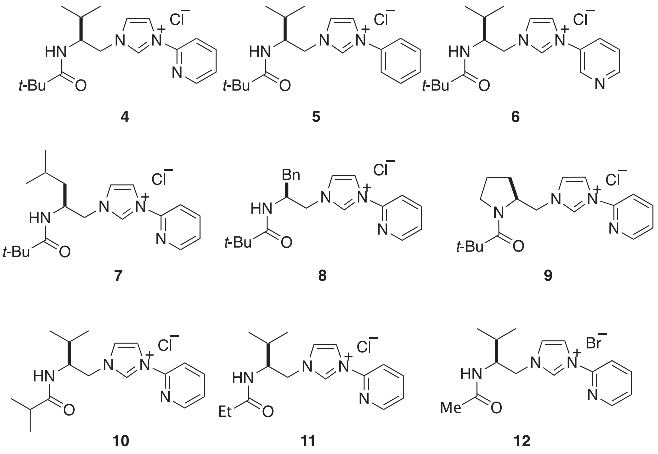
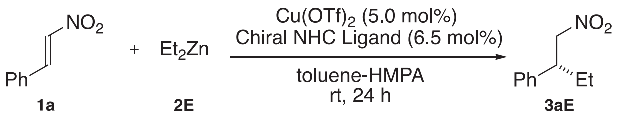


Fig. 1. Chiral imidazolium salts derived from amino acids containing a pyridine ring and phenyl ring.

Table 1
Effects of various chiral imidazolium salts on copper-catalyzed asymmetric ethylation of nitrostyrene.



entry	imidazolium salt	yield/%	ee/%[a]
1	**4**	52	55
2	**5**	64	40
3	**6**	71	24
4	**7**	40	34
5	**8**	80	18
6	**9**	57	52
7	**10**	58	72
8	**11**	59	69
9	**12**	84	9

[a] Absolute configuration of (*R*)-**3aE** was determined by comparison of specific rotation with the reported value [15].

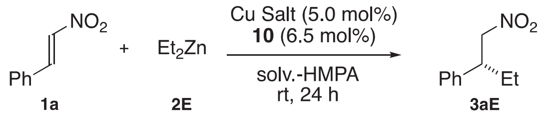
NHC complex, HMPA is important. That is, when we examined the present catalytic asymmetric alkylation of nitrostyrene (**1a**) in the absence of HMPA, a small amount of insoluble material was observed and the ethylated product **3aE** was obtained in 72% yield with 29% ee.

Next, asymmetric ethylation of nitrostyrene (**1a**) with imidazolium salt **5** containing a phenyl ring was investigated. The reaction proceeded more rapidly than that using **4**, but enantioselectivity was decreased to 40% ee (entry 2). These results indicated that the pyridinyl group is critical in realizing the stereoselectivity. Furthermore, introduction of a nitrogen atom onto the C3-position of the aromatic ring (**6**) reduced the enantioselectivity (entry 3). Chiral imidazolium salts prepared from L-leucine (**7**), L-phenylalanine (**8**), and L-proline (**9**) were also examined in the asymmetric reaction (entries 4–6). The reaction proceeded efficiently in all cases, but product enantioselectivities were reduced. The aminocarbonyl group of the imidazolium salt played an important role in the enantioselectivity. Imidazolium salt **10** containing an isopropyl group was the best ligand for the present catalytic asymmetric reaction, affording **3aE** with 72% ee, whereas chiral imidazolium salts **11** and **12** bearing propionamide or acetamide groups resulted in products with low to moderate enantioselectivities (entries 7, 8, and 9).

Since both the solvent and the copper source influenced the reaction efficiency, ethylation of nitrostyrene (**1a**) with diethylzinc (**2E**) was performed using different copper salts and solvents (Table 2). The use of Cu(acac)$_2$ and CuCl$_2$·2H$_2$O resulted in higher enantioselectivities, and chiral nitroalkane **3aE** was obtained with 78% and 77% ee, respectively (entries 2 and 3). In addition, copper(I) salts also were effective in this reaction, affording products with high enantioselectivities in good yields (entries 4–6). Use of the copper halide, copper(I) iodide, was most effective to afford the product with 82% ee (entries 7–9). We examined the addition reaction of diethylzinc to nitrostyrene (**1a**) in the presence of imidazolium salt **10** without copper salts, affording the ethylated product **3aE** in 35% yield with 13% ee. This result suggests that the copper salt plays important roles in terms of chemical yield and enantioselectivity. When employing dichloromethane as the solvent, enantioselectivity was decreased dramatically (entry 10). Interestingly, coordinative solvents such as THF and MeCN were applicable to this reaction, giving **3aE** with good enantioselectivities (entries 11 and 12). Based on these investigations, CuI was selected as the copper salt due to the easy handling compared to that of CuTC.

After applying optimized reaction conditions, the scope of the catalytic asymmetric alkylation was demonstrated using various β-arylnitroalkenes **1** and diethylzinc (**2E**) (Table 3). This catalytic system was applicable to a wide range of β-arylnitroalkenes when used with 5 mol% CuI and 6.5 mol% imidazolium salt **10** in toluene at room temperature. The β-arylnitroalkene **1b**, derived from 2-naphthaldehyde, acted as a good substrate, generating the corresponding product **3bE** in 94% yield and with 76% ee (entry 2). Reactions of **1c**, **1d**, and **1e**, containing 2-, 3-, and 4-methylphenyl groups, gave **3cE**, **3dE**, and **3eE** with 78% ee, 76% ee, and 58% ee, respectively (entries 3–5). Even the relatively deactivated β-arylnitroalkene **1f**, derived from 4-methoxybenzaldehyde, was applicable to this reaction, giving the product **3fE** in 81% yield with 73% ee (entry 6). Substituted β-arylnitroalkenes containing an electron-

Table 2
Copper-catalyzed asymmetric ethylation of nitrostyrene with diethylzinc.



entry	solvents	Cu salts	yield/%	ee/%
1	toluene	Cu(OTf)$_2$	58	72
2	toluene	Cu(acac)$_2$	79	78
3	toluene	CuCl$_2$·2H$_2$O	62	77
4	toluene	CuTC	70	82
5	toluene	(CuOTf)$_2$-PhH	68	73
6	toluene	Cu(MeCN)$_4$BF$_4$	58	57
7	toluene	CuCl	44	39
8	toluene	CuBr	51	9
9	toluene	CuI	70	82
10	CH$_2$Cl$_2$	CuI	74	16
11	THF	CuI	79	78
12	MeCN	CuI	42	73