Copper−Amidophosphine Catalyst in Asymmetric Addition of Organozinc to Imines

Hidetaka Fujihara, Kazushige Nagai, and Kiyoshi Tomioka*

Graduate School of Pharmaceutical Sciences
Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

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The discovery and development of new catalytic reactions that lead to C−C bond formation by addition of organometallic reagents to C═N of imines are of fundamental importance in the continuing development of efficient processes for chemical synthesis. Of greater importance, the catalytic generation of reactive organometal-chiral ligand complexes from the corresponding less reactive organometallic reagents in situ under mild conditions would provide comfortable avenues for the development of new, efficient asymmetric processes leading to C−C bond formation.[1] Reactive organolithium reagents have been activated by a chiral amino ether ligand and applied into a catalytic asymmetric addition to C═N of imines.[2,3] Since then, considerably energetic approaches toward catalytic asymmetric addition of organometallic reagents to C═N of imines have appeared.[4] Among these, zinc triflate-chiral amino alcohol-catalyzed acetylide addition,[5] chiral π-allylpalladium-catalyzed allylation with allylstannane or allylsilane,[6] and rhodium-MOP-based phosphine-catalyzed arylation with arylstannanes[7] showed impressive success.[8] However, the catalytic asymmetric addition of simple alkylmetals that satisfies high catalytic performance in chemical yield and enantioselectivity has not yet been achieved.[9] This is in great contrast to the chiral amino alcohol-catalyzed asymmetric alkylation of aldehydes with organozinc reagents, which becomes a very effective and general method.[10] We document our observations involving the addition of diethylzinc to C═N of a broad range of *N*-sulfonylimines in the presence of catalytic (1 mol %) copper(II) triflate and a chiral amidophosphine in toluene under mild conditions (0 °C).

At the outset of our study, we examined a reaction of diethylzinc with *N*-tosylimine **1a** (R^1 = Tol), which is highly reactive[11] and readily accessible by condensation of benzaldehyde with *p*-toluenesulfonamide in the presence of tetraethoxysilane.[12] Contrary to our expectation, the reaction of **1a** in toluene was sluggish and after 4 h at 0 °C gave the corresponding reduction product **3a**, the desired ethylation product **2a** (R^1 = Tol) and starting **1a** in 40, 10, and 50% yields, respectively. Copper(II) triflate (20 mol %) was beneficial in accelerating ethylation to afford **2a**, **3a**, and **1a** in 46, 32, and 18% yields after 12 h at room temperature. Upon further addition of 40 mol % of tributylphosphine, the reaction was accelerated to afford, after 4 h at 0 °C, **2a**, **3a**, and **1a** in 57, 15, and 22% yields. Encouraged by the catalyzing effects of copper(II)−phosphine, some chiral phosphines were applied into diethylzinc reaction. However, it was very disappointing to learn that a representative chiral bisphosphine, (*R*)-(+)-BINAP **4** (20 mol %), was not endowed with good catalyzing attitude to afford, after 24 h at 0 °C, **2a** and **3a** in 52 and 16% yields, respectively. The enantiomeric excess of **2a** was determined to be only 2% by HPLC analysis with a chiral stationary phase column (Daicel Chiralcel OD-H, hexane/*i*-PrOH (10/1), 254 nm, 0.6 mL/min). (−)-DIOP **5** (20 mol %) was a slightly better ligand to afford, after 24 h at 0 °C, (*R*)-**2a** in 60% yield and 27% ee.[13]

Dramatic improvement in catalytic activity, reaction-type selectivity, and enantioselectivity was realized using an amidophosphine (*S*)-(−)-**6**[14] as a ligand for copper. The reaction of 3 equiv of diethylzinc (hexane solution) was conducted in toluene in the presence of 8 mol % of copper(II) triflate and 10 mol % of **6** at 0 °C for 1 h to afford (*S*)-**2a** in 98% yield and 93% ee. It is also surprisingly delightful to learn that only 1.3 mol % of **6** and 1 mol % of copper (II) triflate were enough to catalyze the addition of 2 equiv of diethylzinc for 2 h at 0 °C, giving **2a** in 94% yield and 90% ee (Table 1, entry 1).

The performance of copper-**6** catalyst in reactivity, reaction-type selectivity, and enantioselectivity is tunable by variation of *N*-sulfonyl groups of imines **1**. 4-Methoxyphenylsulfonylimine **1b** was a good acceptor to provide the same level of high catalytic performance as tosylimine **1a** (entry 2). However, 4-nitrophenylsulfonyl group **1c** was less efficient in providing nosylamide **2c** in 67% yield and 65% ee after 6 h at 0 °C (entry 3). Pentafluorophenylsulfonylimine **1d** was a highly nonreactive substrate providing **2d** in only 22% yield and 6% ee after 24 h (entry 4). Steric bulkiness is another influential factor shown by 2,4,6-trimethylphenylsulfonylimine **1e**, affording **2e** in 26% yield and 5% ee after 24 h (entry 5). Alkylsulfonylimines are good acceptors allowing high catalytic performance (entries 6, 7). Methanesulfonyl (Ms) group **1f** showed the highest performance providing mesylamide in 97% yield and 94% ee after 4 h. 2-Trimethylsilylethanesulfonyl (SES) group **1g** also showed a high performance providing the SES-amide in 94% yield and 89% ee after 12 h.

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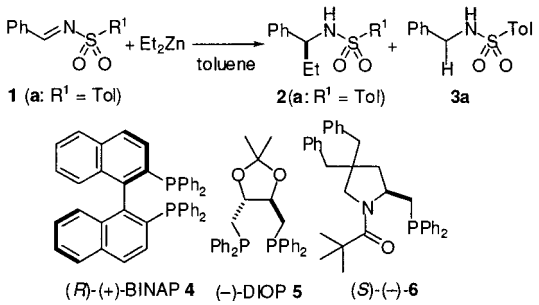
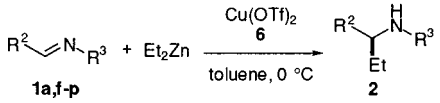
Table 1. Catalytic Asymmetric Addition of Et_2Zn (2 equiv) to *N*-Sulfonylimines **1** Catalyzed by 1 mol % of $Cu(OTf)_2$ and 1.3 mol % of **6** in Toluene at 0 °C



entry	**1**	R^1	time/h	yield/%	ee/%
1	**a**	4-MeC_6H_4	2	94	90
2[a]	**b**	4-$MeOC_6H_4$	3	97	90
3[a]	**c**	4-$NO_2C_6H_4$	6	67	65
4	**d**	C_6F_5	24	22	6
5	**e**	2,4,6-$Me_3C_6H_2$	24	26	5
6	**f**	Me	4	97	94
7[a]	**g**	$Me_3Si(CH_2)_2$	12	94	89

[a] The reaction was conducted in the presence of 3 mol % of $Cu(OTf)_2$ and 3.9 mol % of **6**.

Table 2. Catalytic Asymmetric Addition of Et_2Zn to *N*-Sulfonylimines **1**



entry	**1**	R^2	R^3	Cu-**6**/mol %	time/h	yield/%	ee[a]/%
1	**a**	Ph	Ts	8	1	98	93
2	**f**	Ph	Ms	1	4	97	94
3	**g**	Ph	SES	8	2	98	90
4	**h**	1-naphthyl	Ms	5	16	79	92
5	**i**	2-naphthyl	Ms	1	8	94	93
6	**j**	4-$MeOC_6H_4$	Ms	5	24	83	92
7	**k**	4-ClC_6H_4	Ms	1	8	95	94
8	**l**	4-ClC_6H_4	SES	8	2	99	93
9	**m**	3-ClC_6H_4	Ms	1	3	95	90
10	**n**	2-ClC_6H_4	Ms	5	1	95	92
11	**o**	2-Furyl	Ms	1	3	98	93
12	**p**	2-Furyl	SES	8	1	98	93

[a] The ee's of mesylamides were determined by NMR in the presence of $Eu(hfc)_3$ judged by the integration of methyl groups. The ee's of SES amides were determined by HPLC.

When a solution of *N*-mesyl and SES-imines (1 mmol) derived from arylaldehydes and furfural is treated with 2 equiv of diethylzinc (1 M hexane solution) and 1−8 mol % of copper(II) triflate-**6** (**6**/Cu = 1.3) in toluene (8 mL) at 0 °C for 0.5−24 h, ethyl *N*-sulfonamides are isolated in excellent % ee's (up to 94% ee) and yields (up to 99%) (Table 2). In general, *N*-sulfonylimines derived from arylaldehydes bearing an electron-withdrawing substituent are more reactive than the corresponding parent counterpart (entry 6). It is advantageous that imines **1o**,**p** derived from furfural can be converted to adducts in 98% yields and 93% ees (entries 11, 12), which are useful intermediates for synthesis of biologically active compounds.[15]

The mechanistic details of the asymmetric process are currently under scrutiny to determine the nature of the reactive species and reaction mode involved. Our current hypothesis is that a zinc cuprate−phosphine complex is formed in situ, analogous to the well-studied chemistry of organocuprates.[16] The observation that a bulky mesitylenesulfonyl group **1e** retarded the addition reaction implies coordination of zinc or copper with a sulfonyl oxygen followed by 1,4-addition-type alkylation. Poor reactivity exhibited unexpectedly by an electron-withdrawing nosyl and pentafluorophenylsulfonyl groups **1c**,**d** also suggests the above scenario, considering the decreasing coordinating ability of a sulfonyl oxygen.[17]

Additional studies demonstrated that the total process is extended to asymmetric amine synthesis. The *N*-sulfonyl groups used in this study can be removed by the established methods to provide the corresponding amines. For example, although reduction of mesylamide **2f** with Red-Al[18] in refluxing benzene for 12 h gave (*S*)-1-phenylpropylamine[19] in 87% yield with slight racemization, *N*-tosylamide **2a** was treated with SmI_2[20] in a mixture of THF and HMPA under reflux for 5 h gave (*S*)-amine in 84% yield without any racemization. The corresponding *N*-SESamide **2g** was treated with CsF[21] in DMF at 95 °C for 40 h gave (*S*)-amine in 84% yield without any racemization.

In summary, we have reported a novel copper(II)−chiral amidophosphine **6**-catalyzed asymmetric process for the addition of diethylzinc to *N*-sulfonylimines. The asymmetric addition process affords *N*-sulfonylamides in excellent ee's and yields in toluene under mild conditions. In our working model, we postulate that the process proceeds through the intermediacy of a zinc cuprate in a 1,4-conjugate addition manner.

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Supporting Information Available: General procedure and spectroscopic and analytical data for the products **2** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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