N-Heterocyclic Carbene Ligands in Copper-Catalyzed Addition of Diethylzinc to *N*-Sulfonylimines

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***N*-Heterocyclic carbenes (NHCs) were generated *in-situ* from imidazolium and imidazolinium salts by deprotonation of C-2 hydrogen and were used as ligands in the copper-catalyzed addition of diethylzinc to *N*-sulfonylimines. The copper–NHC complexes were shown to possess an efficient ligand acceleration effect (LAE).**

Key words *N*-heterocyclic carbene ligand; *N*-sulfonylimine; diethylzinc; copper-catalyzed addition

N-Heterocyclic carbenes (NHCs) are strong σ-donating species, showing coordination properties similar to those of phosphines.[1,2] Initially, the widespread use of catalysts containing carbene ligands was limited due to their relatively difficult preparation. Since the discovery of stable carbenes by Arduengo[3] in 1991, interest in the use of *N*-heterocyclic carbene–metal complexes have increased, and it has been demonstrated that they are efficient catalysts in important chemical transformations such as Pd-catalyzed coupling reactions,[4] Ru-catalyzed olefin metathesis,[5] and Rh-catalyzed hydrosilylations.[6—8] NHCs have also attracted great attention as organocatalysts in several reactions (*e.g.*, benzoin condensation,[9—14] Stetter reaction,[15—17] transesterification/acylation reactions,[18,19] and nucleophilic substitution reactions).[20—22] Recently, our research group as well as other groups have reported the cyanosilylation of aldehydes catalyzed by NHCs.[23—26]

In the course of our studies on the use of NHCs in organic synthesis, we have found that copper–NHC complexes exhibit the ligand acceleration effect (LAE) in the addition of diethylzinc to *N*-sulfonylimines. The LAE of copper–NHC complexes was first reported in the addition of diethylzinc to cyclohexenone,[27] and later the asymmetric version of these conjugate addition reactions was accomplished by using chiral NHC ligands.[28,29] In this study, we report our results on the addition of diethylzinc to *N*-sulfonylimines by using catalytic amounts of copper–NHC complexes.

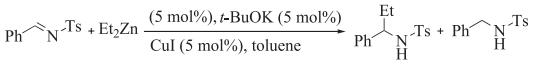
Results and Discussion

In order to examine the catalytic abilities of the copper–NHC complexes, an addition reaction of diethylzinc to *N*-(benzylidene)-*p*-methylbenzenesulfonamide (*N*-sulfonylimine) **1a**[30] was carried out in the presence of 5 mol% of imidazolium salt **2a** as a ligand source, 5 mol% of CuI, and 5 mol% of *t*-BuOK in toluene (Table 1). After reacting at room temperature for 1.5 h, the addition product **3a** (50%) and the reduction product **4a** (28%) were obtained (Table 1, entry 1). The formation of **4a** could be due to the transfer of the β-hydrogen of the ethyl functionality to the C=N bond of the *N*-sulfonylimine **1a**. In the absence of **2a**, the reaction afforded the desired product **3a** in only 15% yield and afforded **4a** as the major product (entry 2). The reaction without CuI at room temperature for 6 h afforded **3a** and **4a** in 31% and 22% yields, respectively (entry 3). These results indicate that the LAE of NHC is involved in the addition reaction. To increase the yield of **3a** and to suppress the byproduct formation, the reaction was carried out at 0 °C. It was observed that though the yield of **3a** was increased to 65%, byproduct **4a** (12%) was still obtained. Further lowering of the reaction temperature to −5 °C led to the exclusive formation of **3a** (entry 5).

At −5 °C, the addition reactions of diethylzinc to **1a** were carried out by using imidazolium and imidazolinium salts **2b—d** as ligand precursors, and the addition products **3a** were isolated in good yields (66—72%, Table 2, entries 1—3). The use of imidazolium and imidazolinium compounds

Table 1. Addition of Diethylzinc to *N*-Sulfonylimine **1a** Catalyzed by Copper–NHC Complex from **2a**

2a

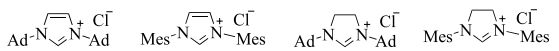


1a **3a** **4a**

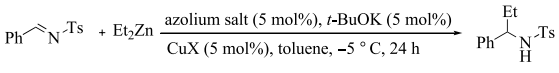
Entry	Condition	Yield (%) **3a**[a]	**4a**[b]	Recovery (%)[a]
1	rt, 1.5 h	50	28	10
2[c]	rt, 2 h	15	46	30
3[d]	rt, 6 h	31	22	46
4	0 °C, 24 h	65	12	12
5	−5 °C, 24 h	63	0	28

a, *b*) Isolated yields. *c*) Without imidazolium salt **2a**. *d*) Without copper iodide.

Table 2. Diethylzinc Addition to **1a** Catalyzed by Copper–NHCs **2a—d**



2a **2b** **2c** **2d**



1a **3a**

Entry	CuX	Azolium salt	Yield (%)[a]	Recovery (%)[a]
1	CuI	**2b**	69	23
2	CuI	**2c**	72	13
3	CuI	**2d**	66	30
4	$Cu(OTf)_2$	**2a**	71	12
5	$Cu(OTf)_2$	**2b**	66	22
6	$Cu(OTf)_2$	**2c**	69	15
7	$Cu(OTf)_2$	**2d**	64	23

a) Isolated yield.

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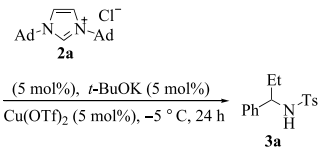
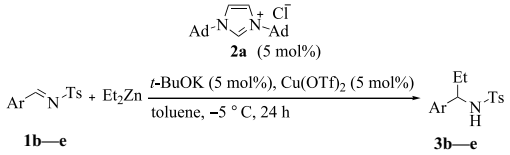
Table 3. Diethylzinc Addition to **1a** in Various Solvents



Entry	Solvent	Yield (%)[a]	Recovery (%)[a]
1	Toluene	71	12
2	THF	22	68
3	Ether	18	73
4	CH_2Cl_2	21	75

a) Isolated yield.

Table 4. Diethylzinc Addition to *N*-Sulfonylimines **1b**—**e** Catalyzed by Copper–NHCs



Entry	Ar	Yield (%)[a]	Recovery (%)[a]
1	 **b**	87	7
2	 **c**	81	9
3	 **d**	69	15
4	 **e**	45	44

a) Isolated yield.

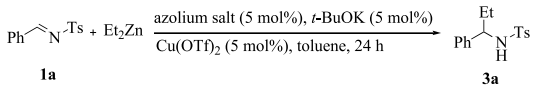
resulted in comparable yields of the addition product.

It has been reported that copper sources and solvents influences the efficiency of the diethylzinc addition reaction.[31] Therefore, the reactions were carried out by using $Cu(OTf)_2$ instead of CuI. However, no significant change in the yields of **3a** was observed (Table 2, entries 4—7). The addition reactions were carried out in various solvents such as toluene, THF, ether, and dichloromethane; toluene was found to be the solvent of choice (Table 3).

The reaction of diethylzinc under the catalysis of copper–NHC in toluene was successfully applied to the ethylation of *N*-sulfonylimines **1b**—**e** that were derived from 4-chlorobenzaldehyde, 2-chlorobenzaldehyde, 4-methylbenzaldehyde, and 2-methoxy benzaldehyde, affording the corresponding addition products **3b**—**e** in moderate to high yields (Table 4).

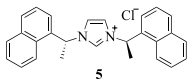
Recently, Tomioka K. and co-workers[32] and Wang M. *et al.*[33] have reported the asymmetric alkylation of *N*-sulfonylimines catalyzed by copper–chiral amidophosphine complexes. We have also examined the asymmetric alkylation of *N*-sulfonylimines by using copper–chiral NHC complexes. The reaction using C_2-symmetric imidazolium salt **5**[34] was carried out at −5 °C and −78 °C for 24 h to afford **3a** in 83% (1% ee) and 50% yields (1% ee), respectively

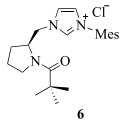
Table 5. Asymmetric Diethylzinc Addition to **1a** Catalyzed by Copper–Chiral NHCs



Entry	Azolium salt	Temperature	Yield **3a** (%)[a]	Recovery (%)[a]	ee (%)[b]
1	**5**	−5 °C	83	12	1
2	**5**	−78 °C	50	40	1
3	**6**	−78 °C	50	46	7

a) Isolated yield. *b*) ee was determined by chiralcel OD.





(Table 5, entries 1, 2). We envisioned that the enantioselectivity could increase by using bidentate-type *N*-heterocyclic carbenes. As a bidentate ligand precursor, we synthesized the chiral pyrrolidinylmethyl imidazolium compound **6**. The addition reaction was carried out by using copper–chiral NHC generated from imidazolium salt **6** at −78 °C for 24 h. Compound **3a** was isolated in 50% yield with a slightly increased enantioselectivity of 7% ee (Table 5, entry 3).

Conclusion

In conclusion, we have demonstrated the LAE of NHCs in the addition of diethylzinc to *N*-sulfonylimines. The copper–NHC complexes accelerate the formation of the adducts. To the best of our knowledge, this is the first example of the addition of diethylzinc to *N*-sulfonylimines using copper–NHC complexes. Further investigations are in progress in our laboratory to elucidate the mechanistic details of the catalytic system and to develop an asymmetric version of the addition reaction.

Experimental

General The melting points were determined using a Yazawa micro melting point apparatus (without correction). The ^{1}H-NMR (500 MHz) and ^{13}C-NMR (126 MHz) spectra were recorded on a JEOL ECA-500 NMR spectrometer. The IR spectra were recorded on a Shimadzu IRPrestige-21 spectrophotometer. The FAB-MS spectra were recorded on a JEOL MStation JMS-700 mass spectrometer using *m*-nitrobenzyl alcohol as a matrix. (*S*)-2-(Chloromethyl)pyrrolidine hydrochloride was prepared from (*S*)-(+)-2-(hydroxymethyl)pyrrolidine, according to the literature,[35] and was used without purification. Column chromatography was performed with silica gel 60N (spherical, neutral; Kanto Chemical Co., Inc).

General Procedure for the Copper–NHCs Catalyzed Addition of Diethylzinc to *N*-Sulfonylimine Under an argon atmosphere, to a suspension of azolium or azolinium salt (0.0125 mmol), the copper salt (0.0125 mmol) in the solvent (1 ml), 1 M *t*-BuOK/THF (0.0125 mmol) was added at room temperature and the mixture was stirred for 30 min. Then, the suspension was maintained at −5 °C for 30 min with stirring, and then Et_2Zn (0.375 ml, 0.375 mmol, 1 M solution in hexane) was added dropwise. After stirring for 5 min, a solution of **1a**—**e** (0.25 mmol) in toluene (1 ml) was added dropwise. The resulting mixture was stirred for 24 h at the same temperature. The reaction was quenched with 3 N HCl (1 ml) and stirred at room temperature for another 0.5 h. The products were extracted with diethyl ether. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (*n*-hexane : ethyl acetate=3 : 1) to afford the addition products **3a**—**e** and reduction product **4a**.

N-(1-Phenylpropyl)-4-methylbenzenesulfonamide[32] (**3a**): Colorless needles (recrystallized from *n*-hexane/CH_2Cl_2), mp 104—106 °C; IR (ATR) cm^{-1}: 3271, 1599, 1317. ^{1}H-NMR ($CDCl_3$) δ: 0.78 (3H, t, J=7.5 Hz),

1.67—1.83 (2H, m), 2.35 (3H, s), 4.17 (1H, q, J=7.5 Hz), 4.82 (1H, d, J=7.5 Hz), 6.98—7.01 (2H, m), 7.10 (2H, d, J=8.6 Hz), 7.13—7.17 (3H, m), 7.52 (2H, d, J=8.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 10.5, 21.6, 30.7, 59.9, 126.6, 127.1, 127.4, 128.5, 129.4, 137.5, 140.7, 143.1. MS (FAB) m/z 290 (M+1). The enantiomeric excesses of **3a** obtained by chiral ligands **5** and **6** were determined before recrystallization. HPLC condition: Daicel Chiralcel OD, hexane/*i*PrOH=10/1, 0.7 ml/min, 254 nm, minor 14.1 min and major 15.9 min.

N-[1-(4-Chlorophenyl)propyl]-4-methylbenzenesulfonamide[32] (**3b**): Colorless needles (recrystallized from *n*-hexane/CH_2Cl_2), 136—139 °C; IR (ATR) cm^{-1}: 3244, 1317, 1165. ^{1}H-NMR ($CDCl_3$) δ: 0.77 (3H, t, J=7.5 Hz), 1.63—1.79 (2H, m), 2.37 (3H, s), 4.16 (1H, q, J=7.5 Hz), 4.84 (1H, bs), 6.93 (2H, d, J=8.6 Hz), 7.09—7.13 (4H, m), 7.49 (2H, d, J=8.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 10.5, 21.6, 30.6, 59.2, 127.1, 128.1, 128.6, 129.4, 133.3, 137.5, 139.2, 143.4. MS (FAB) m/z 324 (M+1).

N-[1-(2-Chlorophenyl)propyl]-4-methylbenzenesulfonamide (**3c**): Colorless needles (recrystallized from *n*-hexane/CH_2Cl_2), mp 130—132 °C; IR (ATR) cm^{-1}: 3269, 1319, 1155. ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, t, J=7.5 Hz), 1.72—1.78 (2H, m), 2.32 (3H, s), 4.64 (1H, q, J=7.5 Hz), 5.32 (1H, d, J=7.5 Hz), 7.03—7.15 (6H, m), 7.55 (2H, d, J=8.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 10.5, 21.5, 29.6, 57.0, 126.9, 127.1, 128.3, 128.5, 129.3, 129.7, 132.4, 137.2, 138.3, 143.1. FAB-MS m/z: 324.0840 (M+1) (Calcd for $C_{16}H_{19}NO_2S$: 324.0825).

N-[1-(4-Methylphenyl)propyl]-4-methylbenzenesulfonamide[32] (**3d**): Colorless needles (recrystallized from *n*-hexane/CH_2Cl_2), mp 114—116 °C; IR (ATR) cm^{-1}: 3261, 1315, 1157. ^{1}H-NMR ($CDCl_3$) δ: 0.76 (3H, t, J=7.5 Hz), 1.66—1.82 (2H, m), 2.26 (3H, s), 2.36 (3H, s), 4.12 (1H, q, J=6.9 Hz), 4.80 (1H, d, J=6.9 Hz), 6.88 (2H, d, J=8.0 Hz), 6.95 (2H, d, J=8.0 Hz), 7.11 (2H, d, J=8.0 Hz), 7.53 (2H, d, J=8.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 10.6, 21.1, 21.6, 30.6, 59.7, 126.6, 127.2, 129.1, 129.4, 131.6, 137.2, 137.7, 143.0. MS (FAB) m/z 304 (M+1).

N-[1-(2-Methoxyphenyl)propyl]-4-methylbenzenesulfonamide (**3e**): Colorless crystalline powder (recrystallized from *n*-hexane/CH_2Cl_2), mp 115—118 °C; IR (ATR) cm^{-1}: 3273, 1317, 1155. ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, t, J=7.5 Hz), 1.69—1.90 (2H, m), 2.27 (3H, s), 3.68 (3H, s), 4.18—4.24 (1H, m), 5.57 (1H, d, J=10.3 Hz), 6.56 (1H, d, J=8.0 Hz), 6.68 (1H, t, J=7.5 Hz), 6.80 (1H, dd, J=7.5, 1.7 Hz), 6.96 (2H, d, J=8.6 Hz), 7.05 (1H, ddd, J=8.0, 7.5, 1.7 Hz), 7.42 (2H, d, J=8.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 11.2, 21.5, 29.0, 55.1, 59.4, 110.6, 120.5, 126.9, 127.9, 128.4, 128.9, 129.4, 129.8, 137.7, 142.5. FAB-MS m/z: 320.1304 (M+1) (Calcd for $C_{17}H_{22}NO_3S$: 320.1320).

N-Benzyl-4-methylbenzenesulfonamide[36] (**4a**): Colorless crystalline powder (recrystallized from *n*-hexane/CH_2Cl_2), mp 108—110 °C; IR (ATR) cm^{-1}: 3267, 1321, 1159. ^{1}H-NMR ($CDCl_3$) δ: 2.44 (3H, s), 4.12 (2H, d, J=6.3 Hz), 4.61 (1H, t, J=6.3 Hz), 7.19 (2H, d, J=8.6 Hz), 7.26—7.32 (5H, m), 7.76 (2H, d, J=8.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 21.6, 47.4, 127.3, 128.0, 128.1, 128.8, 129.9, 136.3, 136.9, 143.7. MS (FAB) m/z 262 (M+1).

(*S*)-3-(1-Pivaloylpyrrolidin-2-ylmethyl)-1-(2,4,6-trimethylphenyl)imidazolium Chloride 6 Triethylamine (2.8 ml, 20 mmmol) was added to a solution of (*S*)-2-(chloromethyl)pyrrolidine hydrochloride (10 mmol) in dichloromethane (20 ml) at 0 °C, and subsequently, pivaloyl chloride (1.23 ml, 10 mmol) was added dropwise. The mixture was stirred overnight at room temperature, and then dichloromethane was removed under reduced pressure. The residue was extracted with diethyl ether, washed with 2 N HCl, and dried over $MgSO_4$. The solvent was removed to afford crude (*S*)-2-(chloromethyl)-1-pivaloylpyrrolidine (1.28 g, 63%) as a brown oil, to which chlorobenzene (20 ml) and 1-mesitylimidazole (1.18 g, 6.33 mmol) were added and the mixture was refluxed for 3 d. After the mixture was cooled, the resultant precipitates were collected by filtration to afford imidazolium salt **6** as pale brown scales (1.05 g, 46%). mp 277—278 °C; IR (ATR) cm^{-1}: 1604. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (9H, s, *t*-Bu), 1.84—1.92 (1H, m), 1.94—2.22 (1H, m), 2.08 (6H, s, *o*-CH_3), 2.14—2.20 (1H, m), 2.34 (3H, *p*-CH_3), 2.37—2.47 (1H, m), 3.68 (1H, dt, J=10.3, 7.4 Hz), 3.82 (1H, ddd, J=10.3, 8.0, 4.6 Hz), 4.46—4.50 (1H, m), 4.71 (1H, dd, J=13.2, 4.0 Hz), 5.10 (1H, dd, J=13.2, 7.4 Hz), 7.00 (2H, s), 7.07 (1H, t, J=1.7 Hz), 7.80 (1, t, J=1.7 Hz), 10.9 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 17.7, 17.8, 21.2, 25.3, 26.9, 27.6, 39.3, 48.4, 51.5, 59.7, 122.8, 123.0, 130.0, 130.8, 134.2, 134.2, 139.3, 139.3, 141.4, 178.0. FAB-MS m/z: 354.2559 (Calcd for $C_{22}H_{22}N_3O$: 354.2545). $[\alpha]_D^{24}$ −14.2 (c=1.0, $CHCl_3$).

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