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Asymmetric Addition Reaction of Organozinc Reagents to Nitrones Using a Catalytic Amount of External Chiral Auxiliary

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Abstract: Catalytic asymmetric addition reactions of dialkylzinc to nitrones are realized; *i.e.*, in the presence of a catalytic amount of bromomagnesium (*2S,3R*)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butoxide, dialkylzincs were reacted with 3,4-dihydroisoquinoline *N*-oxide derivatives to give the corresponding 1-alkylated hydroxylamines enantioselectively. In order to achieve higher stereoselection, addition of bromomagnesium triphenylmethoxide was crucial.

Recently the enantioselective addition reactions of dialkylzinc and Grignard reagents to a nitrone, 3,4-dihydroisoquinoline *N*-oxide, utilizing bromomagnesium (*2S,3R*)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butoxide as a chiral auxiliary was developed to give each enantiomer of the corresponding hydroxylamines, respectively.[1] With these results in hand, we were interested in a catalytic asymmetric addition of organometallics to carbon-nitrogen double bond. In contrast to many successes in the catalytic asymmetric addition of organometallic reagents to carbonyl compounds,[2] examples of the catalytic asymmetric addition of organometallics to the imine function are still limited.[3] Herein, we would like to report our studies on the catalytic asymmetric addition reaction of dialkylzinc to nitrones possessing dihydroisoquinoline skeleton.[4]

The reaction of 2.2 molar amounts of diethylzinc with 3,4-dihydroisoquinoline *N*-oxide **1A**[5] in the presence of 1.1 molar amounts of bromomagnesium (*2S,3R*)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butoxide **2**, prepared from Chirald®[6] and Grignard reagent[7] *in situ*, in THF at 25 °C gave the corresponding hydroxylamine **3a** in 65% ee (Entry 1 in Table 1).[8] In the reaction using 0.2 molar amounts of magnesium alkoxide **2**, however, optical yield of the hydroxylamine disappointingly lowered to 33% ee (Entry 2). After several attempts, it was found that addition of another magnesium alkoxide generated from the corresponding alcohol and Grignard reagent[7] *in situ* was effective. That is, addition of 0.2 molar amounts of bromomagnesium butoxide improved the enantioselectivity up to 45% ee (Entry 3). Among alkoxides derived from several alcohols, bromomagnesium triphenylmethoxide **4** was revealed to be the most effective for

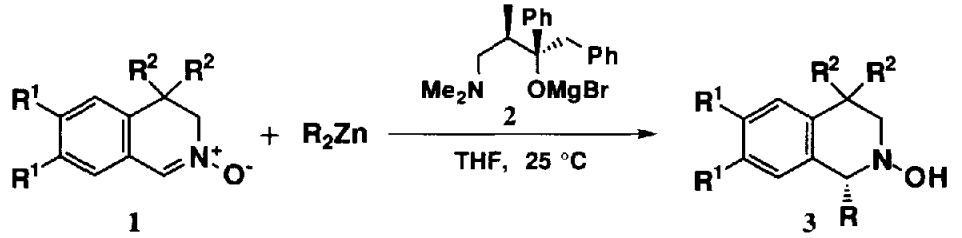
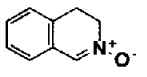
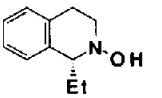
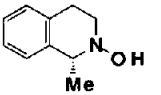
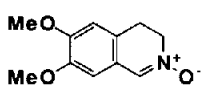
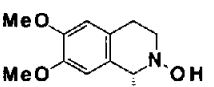
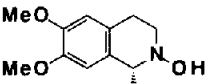
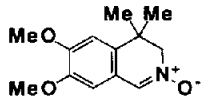
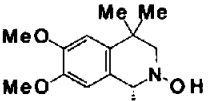


Table 1. The asymmetric addition reaction of dialkylzinc to nitrones 1 using catalytic amount of 2

Entry	Nitrones 1	Molar amounts of 2	Additive (molar amounts)	R_2Zn[a]	Time /h	Products 3	Yield /%	ee[b] /%
1	 1A	1.1	---	Et_2Zn	13	 3a	78	65
2		0.2	---	Et_2Zn	16		80	33
3		0.2	*n*BuOMgBr (0.2)	Et_2Zn	17		84	45
4		0.2	*i*PrOMgBr (0.2)	Et_2Zn	17		84	47
5		0.2	*t*BuOMgBr (0.2)	Et_2Zn	17		86	43
6		0.2	$Ph_3COMgBr$ (4) (0.2)	Et_2Zn	17		82	56
7		0.2	$Ph_3COMgBr$ (4) (0.3)	Et_2Zn	14		91	62
8		0.2	$Ph_3COMgBr$ (4) (0.4)	Et_2Zn	24		87	56
9		1.1	---	Me_2Zn	17	 3b	88	66
10	1A	0.2	---	Me_2Zn	17		77	21
11		0.2	$Ph_3COMgBr$ (4) (0.3)	Me_2Zn	17		93	58
12	 1B	1.1	---	Et_2Zn	18	 3c	87	58
13		0.2	---	Et_2Zn	16		60	18
14		0.2	$Ph_3COMgBr$ (4) (0.3)	Et_2Zn	16		97	70
15		1.1	---	Me_2Zn	17	 3d	96	50
16	1B	0.2	---	Me_2Zn	19		91	57
17		0.2	$Ph_3COMgBr$ (4) (0.3)	Me_2Zn	16		84	63
18	 1C	1.1	---	Et_2Zn	15	 3e	96	57[c]
19		0.2	---	Et_2Zn	19		80	28[c]
20		0.2	$Ph_3COMgBr$ (4) (0.3)	Et_2Zn	18		89	78[c]

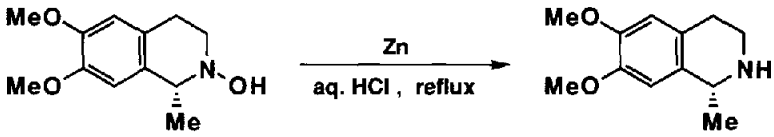
a) 2.2 Molar amounts of dialkylzinc were used. b) Enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel OD-H). c) Enantiomeric excess was determined by ^1H NMR analysis of the corresponding (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) ester derivatives.

the stereoselection and gave the hydroxylamine **3a** in 56% ee (Entries 3-6). Furthermore, the addition of 0.3 molar amounts of **4** improved the stereoselectivity up to 62% ee (Entries 6-8). The reaction of dimethylzinc with the nitrone **1A** was also examined and the similar tendency in stereochemical course was observed (Entries 9-11).

Next, asymmetric addition reaction of dialkylzinc to 6,7-dimethoxy-3,4-dihydroisoquinoline *N*-oxide **1B** was examined. Stoichiometric reaction with diethylzinc afforded the corresponding hydroxylamine **3c** in 58% ee (Entry 12), while the catalytic reaction gave **3c** with rather low stereoselectivity (Entry 13). In

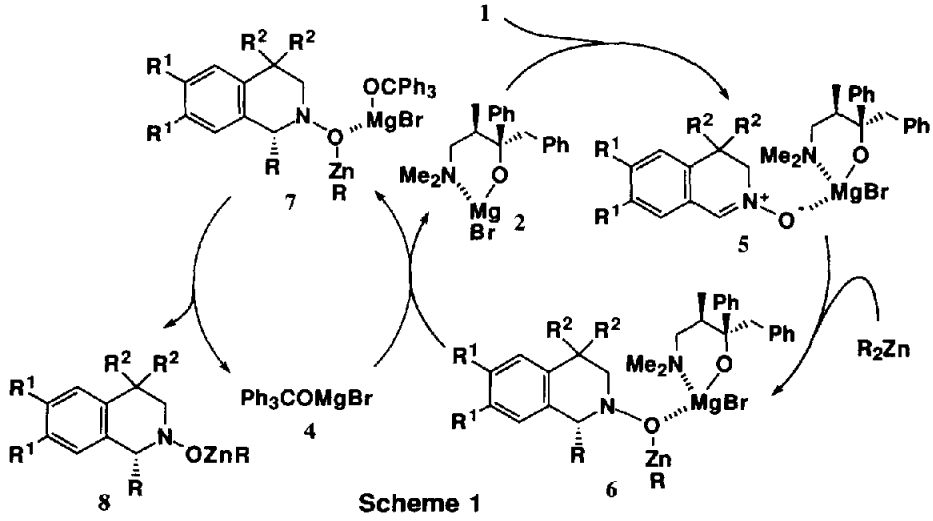
contrast, addition of 0.3 molar amounts of triphenylmethoxide **4** realized higher stereoselectivity than that in the stoichiometric reaction (Entry 14). The reaction of dimethylzinc with **1B** afforded the methylated product **3d** in 63% ee (Entry 17). In the case of the nitrone **1C**, the dramatic effect of the additive **4** was also observed (Entries 18-20) and the hydroxylamine **3e** was obtained in 78% ee (Entry 20). These results are summarized in Table 1.

The stereochemistry of the newly formed chiral center in **3d** was determined by conversion to salsolidine;[4b,9] *i.e.*, reduction[5] of the hydroxylamine **3d** (50% ee) obtained by the reaction of **1B** with Me_2Zn gave salsolidine ($[\alpha]_D^{25}$ +31 (c 1.89, EtOH)) in 92% yield, whose configuration was confirmed to be *R* by the comparison of its specific rotation with that reported for (*R*)-salsolidine ($[\alpha]_D^{22}$ +62.8 (c 0.1, EtOH)).[9e] The stereochemistry of the stereogenic center in **3b** had been already determined to be *R*.[1]



3d **(*R*)-salsolidine**

Although the precise mechanism of the present reaction is still an open question, the role of bromomagnesium triphenylmethoxide **4** might be explained as follows: Dialkylzinc would react with the nitrone coordinated to magnesium alkoxide of Chirald® (depicted as **5**) from the less hindered *re*-face to afford **6**.[1] In the catalytic system, **2** should be regenerated accompanied with the production of **8**. Without triphenylmethoxide **4**, the rate of regeneration of **2** might be slow and dialkylzinc would react with nitrone uncoordinated to **2** without stereoselection. In the presence of **4**, the alkylated adduct **6** would react with alkoxide **4** to give **7** and chiral auxiliary **2** would be smoothly regenerated (Scheme 1). Furthermore, it is also probable that magnesium in triphenylmethoxide **4** might be also coordinated by oxygen of nitrone to produce the complex **9**. The *si*-face of nitrone **9** would be effectively shielded and alkylation would proceed from *re*-face stereoselectively (Fig. 1 shows the complex **9** corresponding to **1A**) and the adduct immediately dissociates into **2** and **7** followed by reproduction of **9**.



Scheme 1

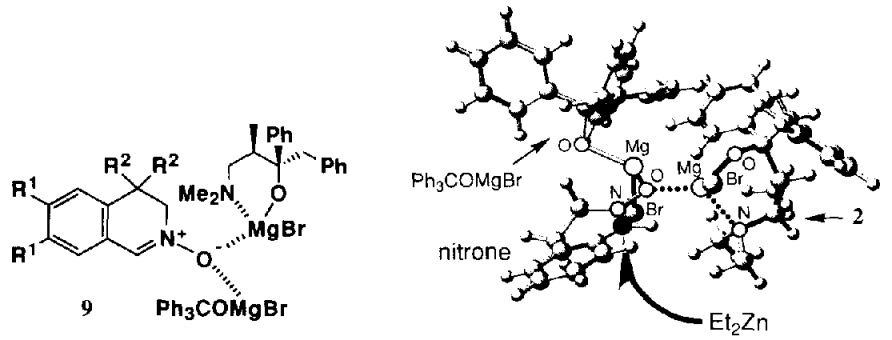


Fig. 1

In summary, we have demonstrated the catalytic asymmetric addition reaction of dialkylzinc to carbon-nitrogen double bond and the present reaction provided a facile method for the synthesis optically active 1-alkyltetrahydroisoquinoline alkaloids such as (*R*)-salsolidine.

References and Notes

1) Y. Ukaji, T. Hatanaka, A. Ahmed, and K. Inomata, *Chem. Lett.*, **1993**, 1313.

2) K. Tomioka, *Synthesis*, **1990**, 541; R. Noyori and M. Kitamura, *Angew. Chem., Int. Ed. Engl.*, **30**, 49 (1991); K. Soai and S. Niwa, *Chem. Rev.*, **92**, 833 (1992) and references cited therein.

3) I. Inoue, M. Shindo, K. Koga, and K. Tomioka, *Tetrahedron*, **50**, 4429 (1994); K. Soai, T. Suzuki, and T. Shono, *J. Chem. Soc., Chem. Commun.*, **1994**, 317; S. E. Denmark, N. Nakajima, and O. J.-C. Nicaise, *J. Am. Chem. Soc.*, **116**, 8797 (1994) and references cited therein.

4) Recent reports on asymmetric synthesis using nitrones: a) S.-I. Murahashi, Y. Imada, M. Kohno, and T. Kawanami, *Synlett*, **1993**, 395; b) S.-I. Murahashi, J. Sun, and T. Tsuda, *Tetrahedron Lett.*, **34**, 2645 (1993); c) S.-I. Murahashi, S. Watanabe, and T. Shiota, *J. Chem. Soc., Chem. Commun.*, **1994**, 725.

5) Nitrones **1** were prepared from the corresponding tetrahydroisoquinolines: S.-I. Murahashi, H. Mitsui, T. Shiota, T. Tsuda, and S. Watanabe, *J. Org. Chem.*, **55**, 1736 (1990).

6) Catalytic asymmetric addition reaction of organozinc reagents to aldehydes using Chirald® was reported: G. Muchow, Y. Vannoorenberghe, and G. Buono, *Tetrahedron Lett.*, **28**, 6163 (1987); E. Laloë and M. Srebnik, *ibid.*, **35**, 5587 (1994).

7) Butylmagnesium bromide or phenylmagnesium bromide was used.

8) Previously we reported that the reaction of diethylzinc with **1A** in the presence of **2** gave **3a** in 57% ee.[1] After further experiments, the use of fairly purified crystalline **1A** was found to realize higher selection.

9) Recent reports on the asymmetric synthesis of salsolidine: a) R. Noyori, M. Ohta, Y. Hsiao, M. Kitamura, T. Ohta, and H. Takaya, *J. Am. Chem. Soc.*, **108**, 7117 (1986); b) R. E. Gawley, G. Hart, M. Goicoechea-Pappas, and A. L. Smith, *J. Org. Chem.*, **51**, 3076 (1986); c) A. I. Meyers, D. A. Dickman, and M. Boes, *Tetrahedron*, **43**, 5095 (1987); d) R. P. Polniaszek and C. R. Kaufman, *J. Am. Chem. Soc*, **111**, 4859 (1989); e) M. Yamato, K. Hashigaki, N. Qais, and S. Ishikawa, *Tetrahedron*, **46**, 5909 (1990); f) C. A. Willoughby and S. L. Buchwald, *J. Am. Chem. Soc.*, **116**, 11703 (1994).

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