High 1,3-Asymmetric Induction in Addition of Allylic Tin Reagents to Chiral 3-Substituted 3,4-Dihydroisoquinolines Activated by Acyl Chlorides

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Nucleophilic addition reactions of allylic tin reagents to chiral 3-substituted 3,4-dihydroisoquinolines activated by acyl chlorides afford anti 1,3-disubstituted 1,2,3,4-tetrahydroisoquinolines stereoselectively through high 1,3-asymmetric induction.

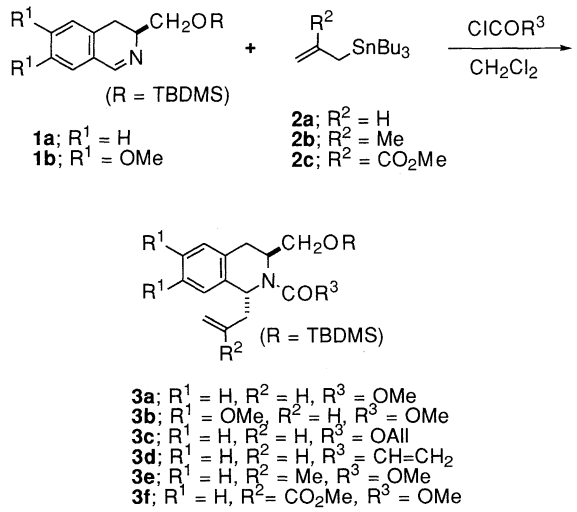
Stereoselective introduction of functional carbon substituents into the 1-position of isoquinoline system is important for synthesizing various isoquinoline alkaloids and analogues; both electrophilic and nucleophilic alkylation methods have been widely studied.[1,2] Although the highly stereoselective electrophilic alkylations of chiral 3-substituted tetrahydroisoquinolines have been reported,[3] there have been few reports on the stereoselective nucleophilic alkylation of chiral 3-substituted 3,4-dihydroisoquinolines.[4] We have found that allylic tin reagents readily react with cyclic C=N double bonds activated by various acyl chlorides in highly chemo- and regioselective manners, providing an effective method for introducing functionalized carbon groups into nitrogen heterocycles.[5] Considering significant roles of allylic metal reagents in organic synthesis,[6] we wish to report here that allylic tin reagents add to chiral 3-substituted 3,4-dihydroisoquinolines activated by acyl chlorides to afford anti 1,3-disubstituted 1,2,3,4-tetrahydroisoquinolines stereoselectively through high 1,3-asymmetric induction.[7,8]

The chiral 3-substituted 3,4-dihydroisoquinolines can be readily prepared from phenylalanine.[4,7] When methyl chloroformate was added to a solution of (*S*)-3-*tert*-butyldimethylsiloxymethyl-3,4-dihydroisoquinoline (**1a**) and allyltributyltin (**2a**) in dichloromethane at 0 °C, *N*-acylation of **1a** followed by the nucleophilic attack with **2a** proceeded very smoothly and 1,3-anti adduct **3a**[9] was predominantly produced in 93% yield and 88% *de* (Scheme 1). Similarly, the high chemical yield and diastereoselectivity have been obtained with other allylic tin reagents in the presence of acyl chlorides.[10] The results are summarized in Table 1.

Table 1. Stereoselective allylations of chiral 3-substituted 3,4-dihydroisoquinolines

Run	Temp /°C	Time /h	Product	Yield /%[a]	*de* /%[b]
1	0	1.5	**3a**	93	88
2	-15	4	**3a**	86	88
3	-15	4	**3b**	96	90
4	0	2	**3c**	91	89
5	0	3	**3d**	78	95
6	-15	4	**3e**	86	94
7	-15	8	**3f**	67	94

[a]Isolated yield. [b]Determined by ^{1}H NMR (500 MHz).



Scheme 1.

Lowering the reaction temperature from 0 °C to -15 °C does not appear to affect the stereoselectivity (runs 1 and 2), indicating that the high 1,3-asymmetric induction occurs effectively even at 0 °C. 7,8-Dimethoxy-3,4-dihydroisoquinoline derivative **1b** was also allylated in high chemical yield with high stereoselectivity (run 3). When unsaturated acyl chloride was used as the activating agent, the very high 1,3-asymmetric induction (95% *de*) was observed (run 5). The bulky 2-substituted allylic tin reagents also produced the adducts in highly stereoselective manner (runs 6 and 7). It should be noted that a Michael acceptor group can be readily introduced into the isoquinoline system (run 7).

On the other hand, Lewis acid (BF_3·Et_2O) promoted reaction of **1a** with **2a** was sluggish (yield = ca. 10%) and the diastereoselectivity was not good (ca. 78% *de*). Furthermore, the reaction of allyl Grignard reagents with **1a** activated by methyl chloroformate at -78 °C resulted in the decreased chemical yield (74%) and diastereoselectivity (53% *de*). These two findings clearly indicate that the presence of *N*-acyl group and the use of tin reagents are essential to obtain the high chemical yield and the high stereoselectivity.

In order to reason the above high stereoselectivity, we have looked at the relative stability of conformers of 3-methyl-3,4-dihydroisoquinoline (**4**) and its *N*-methoxycarbonyl iminium ion (**5**)[11,12] as model compounds (Figure 1). With the free imine **4**, the equatorial conformer **4e** is expected to be more stable than the axial one **4a**: according to MM2 calculations, **4e** is 0.5 Kcal/mol more stable than **4a**. With the *N*-acyliminium ions **5**, on the contrary, the axial conformers **5a** and **5a'** are expected to be more stable than the equatorial ones **5e** and **5e'**,

respectively, due to a large steric hindrance between the methyl and *N*-acyl groups. Indeed, **5a** and **5a'** are calculated to be 3.3 and 3.5 Kcal/mol more stable than **5e** and **5e'**, respectively. Consequently, the substituent at the 3-position stands up to the axial direction to block the upper side of the iminium ion. The steric effect may be much larger with the more bulky *tert*-butyldimethylsiloxymethyl group. Thus, it is highly probable that the *N*-acylation of **1** may induce the conformational change which should be essential to obtain the high diastereoselectivity.

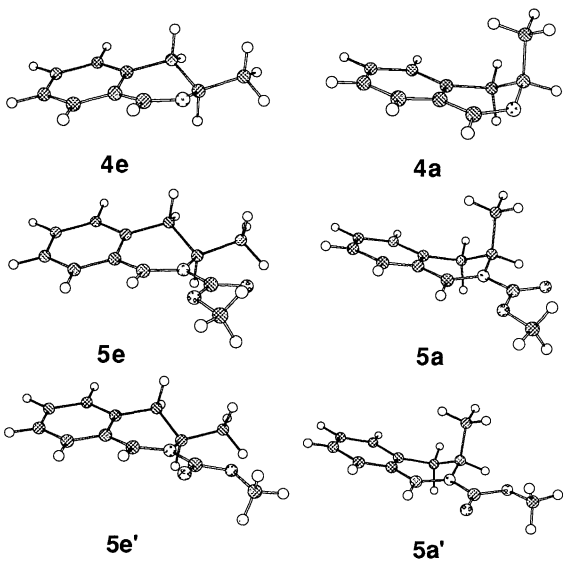


Figure 1. Representative conformers of **4** and **5**.

A typical experimental procedure is as follows. To a solution of **1a** (252 mg, 0.92 mmol) and **2a** (356 mg, 1.1 mmol) in CH_2Cl_2 (5 mL) was added methyl chloroformate (0.1 mL) under ice-cooling. The reaction was complete after 1.5 h. The solvent was evaporated and the residue was analyzed by ^1H NMR and then chromatographed on silica gel. Elution with hexane—CH_2Cl_2 gave **3a** (320 mg, 93%): IR (neat) 1705 cm^{-1}; ^1H NMR [$CDCl_3$, 25 °C, a mixture of rotamers (6 : 4)] δ 7.10—7.24 (m, 3H), 6.92—7.06 (m, 1H), 5.60 (m, 1H), 4.88—4.95 (m, 2H), 4.80 4.70 (m, 1H), 4.32 4.20 (m, 2H), 3.78 3.76 (br s, 3H), 3.60 3.44 (m, 1H), 3.00—3.20 (m, 2H), 2.56—2.82 (m, 2H), 2.36 (m, 2H), 0.93 (s, 9H), -0.03 -0.05 (br, 3H), -0.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 25 °C) δ 156.1 (C), 136.5 (C), 135.4 134.4 (CH), 133.2 133.8 (C), 129.2 129.0 (CH), 127.3 127.2 (CH), 127.1 (CH), 126.0 (CH), 117.6 (CH_2), 62.0 61.0 (CH_2), 57.0 (CH), 53.6 53.2 (CH), 52.4 (CH_3), 42.4 41.3 (CH_2), 29.0 28.7 (CH_2), 25.9 (CH_3), 18.1 (C), -5.4 -5.5 -5.6 (CH_3); Analysis Calcd for $C_{21}H_{33}NO_3Si$: C, 67.16; H, 8.86; Found: C, 67.06; H, 9.04.

In summary, we have demonstrated the high 1,3-asymmetric induction in addition of allylic tin reagents to chiral 3-substituted 3,4-dihydroisoquinolines activated by acyl groups, providing the new methods to synthesize the anti 1,3-disubstituted 1,2,3,4-tetrahydroisoquinolines which may be valuable synthetic intermediates for isoquinoline alkaloids and analogues.

References and Notes

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6 For a recent review on allylic metal reagents, see Y. Yamamoto and N. Asao, *Chem. Rev.*,**93**, 2207 (1193).

7 For our work on a diastereoselective bicycloannulation, see R. Yamaguchi, T. Hamasaki, T. Sasaki, T. Ohta, K. Utimoto, S. Kozima, and H. Takaya, *J. Org. Chem.*, **58**, 1136 (1993).

8 For a diastereoselective synthesis of 1,4-dialkyl-1,2,3,4-tetrahydroisoquinolines, see Ref. 2d.

9 1,3-Anti stereochemistry was determined by the observed NOE (2%) between H1 and the methylene proton of tert-butyldimethylsiloxymethyl group in ^1H NMR (500 MHz). See also Ref. 6.

10 All new compounds gave satisfactory elemental analyses and spectral data.

11 We have assumed that the C=N bond is coplanar with the carbonyl group since it has been also reported that the isoquinoline ring is coplanar with the carbonyl group in the single X-ray crystal structure of *N*-acyl isoquinolinium salt.[12]

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