A highly enantioselective addition reaction of a chiral allylsilane to an activated *N*-acylisoquinolinium ion

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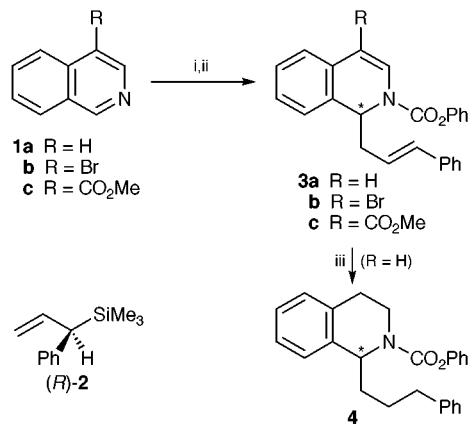
The addition reactions of a chiral allylsilane to activated *N*-acylisoquinolinium ions proceeded in a highly enantioselective manner (more than 90%) to afford homochiral 1-allyl-1,2-dihydroisoquinolines in good yields.

Considerable efforts have been made for the stereoselective introduction of carbon substituents into isoquinoline systems.[1] Although many diastereo- and enantio-selective methods have been available for the stereoselective addition of carbon nucleophiles to 3,4-dihydroquinolines systems (cyclic imines and imine *N*-oxides),[2,3] few reactions have been reported for stereoselective additions to isoquinoline itself and all of them have exploited the diastereoselective additions of achiral organometallic reagents to isoquinolines with chiral auxiliaries in the activating groups.[4] The enantioselective addition reaction of a chiral organometallic reagent to achiral isoquinoline has not been reported. We have recently reported that quinolines and isoquinolines are activated by $ClCO_2Ph$ and AgOTf such that these *N*-acylated aza-aromatic ions can readily react with allylsilanes and alkynylsilanes to afford allylated and alkynylated products chemo- and regio-selectively in good yields.[5] We disclose here the fact that the addition reaction of a chiral allylsilane to the activated *N*-acylisoquinolinium ion proceeded in a highly enantioselective manner to give homochiral 1-allyl-1,2-dihydroisoquinoline. To the best of our knowledge, this is the first example of the addition reaction of a chiral organometallic reagent to an achiral nitrogen heteroaromatic ion with high enantioselectivity.

Isoquinoline **1a** was activated by treatment with $ClCO_2Ph$ (1.2 equiv.) and a catalytic amount of AgOTf (0.1 equiv.) in MeCN, and then a chiral allylsilane, (*R*)-3-phenyl-3-trimethylsilylpropene **2**[6] (81% ee determined by a chiral GLC analysis), was added to the mixture under ice-cooling. The reaction mixture was stirred at room temperature for 24 h to yield a single 1-allylated 1,2-dihydroisoquinoline adduct **3a** in 54% yield (Scheme 1).† The ^{1}H NMR coupling constant (J = 16 Hz) of the olefinic protons indicates that the stereochemistry of the allylic double bond was *E*. These results suggest that the present allylic silicon substitution reactions proceed in an *anti* S_E2' manner (*vide infra*). Since **3a** could not be separated by chiral HPLC. **3a** was hydrogenated to give tetrahydroisoquinoline derivative **4**, the ee of which was determined to be 77% by chiral HPLC analysis. Thus, it is apparent that the chirality transfer of the present reaction is as high as 95%. Similarly, the reactions of functionalized isoquinolines with (*R*)-**2** proceeded in good yields with a high degree of enantioselectivity (more than 90%) as well. The results are summarized in Table 1.



Scheme 1 *Reagents and conditions*: i, $ClCO_2Ph$ (1.2 equiv.), AgOTf (0.1 equiv.), MeCN; ii, (*R*)-**2** (1.0 equiv.), room temp., 24 h; iii, H_2, Pd-C, MeOH. Spectral data for **3b**,**c**, **4**, **6** and **7** are available from the RSC web site, see http://www.rsc.org/suppdata/cc/1999/2213/

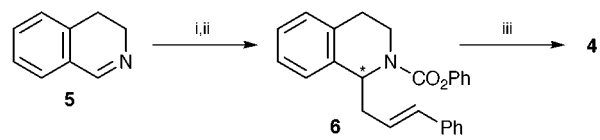
Table 1 Enantioselective additions of (*R*)-**2** to activated *N*-acylisoquinolinium ions

Entry	**1**	R	Yield of **3** (%)[a]	Ee of **2** (%)[b]	Ee of **3** (%)	Enantioselectivity (%)
1	**a**	H	54	81	77[c]	95
2	**b**	Br	86	83	78[d]	94
3	**c**	CO_2Me	78	83	77[d]	93

[a] Isolated yield. [b] Determined by a chiral GLC (Chiral-DEX CB) analysis. [c] Determined by a chiral HPLC (SUMICHIRAL OA-2000) analysis of the hydrogenated product **4**. [d] Determined by a chiral HPLC (CHIROSE C1) analysis.

In contrast with the above results, the similar reaction of 3,4-dihydroisoquinoline **5** with (*R*)-**2** showed a moderate degree of enantioselectivity (Scheme 2). The results are summarized in Table 2. Thus, 76% enantioselectivity was obtained in the reaction even at −15 °C. These results could indicate that the planarity of *N*-acyliminium salts is critical to obtain a high degree of the enantioselectivity (*vide infra*).

The absolute configuration of **4** was determined as follows (Scheme 3): **4** (55% ee) was deprotected[7] to give 1-(3-phenylpropyl)-1,2,3,4-tetrahydroisoquinoline **7**, the optical rotation of

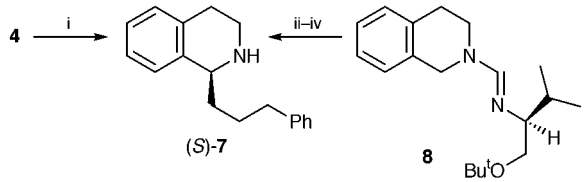


Scheme 2 *Reagents and conditions*: i, $ClCO_2Ph$ (1.2 equiv.), additive (0.1 equiv.), MeCN; ii, (*R*)-**2** (1.0 equiv.), 24 h; iii, H_2, Pd-C, MeOH.

Table 2 Enantioselective additions of (*R*)-**2** (81% ee) to *N*-acyl-3,4-dihydroisoquinolinium ion

Entry	Additive	*T*/°C	Yield of **6** (%)[a]	Ee of **4** (%)[b]	Enantioselectivity (%)
1	AgOTf	0	83	59	73
2	$AgClO_4$	0	67	61	75
3	AgOTf	−15	53	62	76

[a] Isolated yield. [b] Determined by a chiral HPLC (SUMICHIRAL OA-2000) analysis.



Scheme 3 *Reagents and conditions*: i, KOH, Pr^iOH–H_2O, reflux, 3 d; ii, LDA, THF, −78 °C; iii, $PhCH_2CH_2CH_2Br$, −90 °C; iv, NH_2NH_2, AcOH, EtOH.

which was determined to be levorotatory ($[\alpha]_D^{20}$ −28). Since authentic (*S*)-**7** was prepared from **8** according to Meyers' procedures[8] and the optical rotation of (*S*)-**7** is levorotatory ($[\alpha]_D^{20}$ −43), the absolute configuration of **4** should be *S*. Thus, it is apparent that the reactions of isoquinolines with (*R*)-**2** afford (*S*)-1-[(*E*)-3-phenylprop-2-enyl]-1,2-dihydroisoquinolines in a highly enantioselective manner.

It has been generally proposed[9] that the electophilic addition reactions of chiral, acyclic allylsilanes take place in an *anti*-S_E2' manner to form the allylic *E* double bond. Thus, it is highly probable that the present addition reactions proceed through a highly selective *anti*-S_E2' mode. It has also been suggested that two transition models, *i.e.* antiperiplanar and synclinal, are possible in non-chelation transition states. In the present reactions of isoquinolinium ions with (*R*)-**2**, the antiperiplanar *anti*-S_E2' transition state **A** is expected to produce the (*S*)-adduct, while the synclinal *anti*-S_E2' transition state **B** would produce the (*R*)-adduct. Since the (*S*)-adduct is obtained as mentioned above, it is evident that the reactions proceed through the antiperiplanar *anti*-S_E2' transition state **A** (Fig. 1).

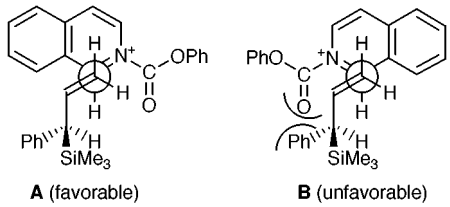


Fig. 1 Possible transition states of the enantioselective *anti*-S_E2' addition reactions of (*R*)-**2** to *N*-acylisoquinolinium ions.

The recent X-ray crystal analysis of an *N*-acylisoquinolinium ion proves that the aromatic rings are coplanar with the carbonyl groups.[10] This conformation is also preferred for maximum overlap of the C=N and C=O bonds, which could make the isoquinolinium ions more electrophilic. Thus, the synclinal *anti*-S_E2' transition state **B** should be unfavorable because of steric repulsion between the carbonyl and the phenyl groups.

In summary, we have demonstrated the highly enantioselective addition reactions of a chiral allylsilane to achiral isoquinolinium ions. A high degree of enantioselectivity (more than 90%) can be obtained in these reactions even at room temperature. Further studies on the reactions of other nitrogen aromatics as well as applications to alkaloids synthesis are underway.

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Notes and references

† *Typical procedure*: To a solution of **1** (1.0 mmol) in MeCN (3.0 ml) was added $ClCO_2Ph$ (0.15 ml, 1.2 mmol, 1.2 equiv.) and AgOTf (0.10 mmol, 0.10 equiv.) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. Then, to the reaction mixture was added **2** (1.0 mmol, 1.0 equiv.) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 24 h. Et_2O (5.0 ml), aqueous $NaHCO_3$ (3.0 ml) and aqueous Na_2CO_3 (3.0 ml) were added, and the organic layer was separated. The aqueous layer was extracted with Et_2O (5 × 5.0 ml). The combined organic layer was washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by flash column chromatography (eluent: hexane–EtOAc) to give the product. The yields and ees are shown in Table 1. All new compounds gave satisfactory analytical and spectral data. *Selected data* for (*S*)-**3a**: mp 117–119 °C; $[\alpha]_D^{25}$ +266 (*c* 0.075, $CHCl_3$) (77% ee); ν_{max}(KBr)/cm^{-1} 1722, 1633, 1215, 756; δ_H(500 MHz, $CDCl_3$, 55 °C, TMS, a mixture of rotamers) 7.12–7.37 (m, 13H), 7.07 (d, *J* 7, 1H), 7.00 (d, *J* 8.0, 1H), 6.39 (d, *J* 16, 1H), 6.24 (dt, *J* 16, 8, 1H), 6.08, 5.99 (d, *J* 7, 1H), 5.57–5.65 (br m, 1H), 2.58–2.82 (m, 2H); δ_C(125.7 MHz, $CDCl_3$, 55 °C, TMS, a mixture of rotamers) 151.1, 150.9 (C), 137.6, 137.3 (C), 133.5 133.0 (CH), 132.4 (C), 130.4, 130.0 (C), 129.2 (CH), 128.5 (CH), 127.9, 127.8 (CH), 127.3, 127.1 (CH), 127.1, 127.0 (CH), 126.4, 126.3 (CH), 126.3 (CH), 125.8, 125.5 (CH), 125.3, 125.1 (CH), 124.9 (CH), 124.2 (CH), 121.5 (CH), 110.1, 109.5 (CH), 56.9, 55.9 (CH), 39.5, 39.4 (CH_2) (calc. for $C_{25}H_{21}NO_2$: C, 81.72; H, 5.76. Found: C, 81.92; H, 5.86%).

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