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Regio- and stereoselective α-allylation of quinolines activated by chloroformate and triflate ion by means of chiral allylsilane: a synthesis of chiral 2-substituted 1,2-dihydroquinolines

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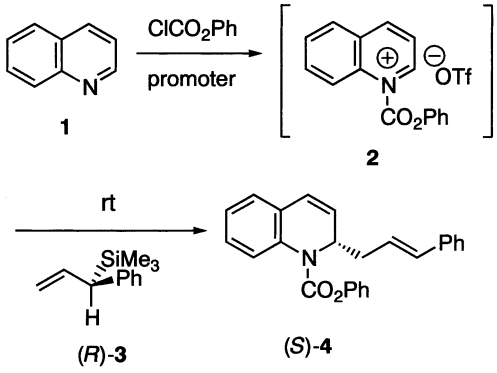
Abstract—Addition reactions of a chiral allylsilane to a variety of quinolines activated by phenyl chloroformate and triflate ion proceed with high regio- and stereoselectivities to afford various chiral 2-allylated 1,2-dihydroquinolines in good yields.

Hydroquinoline derivatives have attracted great attention as biological active nitrogen compounds,[1] and regio- and/or stereoselective nucleophilic addition of organometallic reagents to quinolinium ion have been widely investigated.[2,3] All of the methods so far reported have exploited diastereoselective additions of achiral organometallic reagents to quinolinium ion with a chiral auxiliary in the activating group or on the quinoline ring. Stereoselective addition reaction of chiral organometallic reagent to an achiral quinolinium ion has been rarely reported.[4] In view of great interest in allylation reactions,[5] we have recently revealed that allylsilanes, which are less toxic but less reactive than allyltins, can readily react with quinolines and isoquinolines activated by phenyl chloroformate and triflate ion to give allylated products.[6,7] We have also reported stereoselective addition of a chiral allylsilane to isoquinolines.[8] We wish to disclose here that a chiral allylsilane can differentiated the ring-face of *N*-acylated quinolinium ion to afford chiral 2-allylated 1,2-dihydroquinolines in highly regio- and stereoselective manners.

When quinoline (**1**) was activated by phenyl chloroformate (1.2 equiv.) and AgOTf (1.2 equiv.) in CH_3CN to generate a quinolinium ion **2** and, then, reacted with (*R*)-3-phenyl-3-trimethylsilyl-1-propene (**3**)[9] (83% ee by a chiral GLC analysis) at room temperature, the 2-allylated 1,2-dihydroquinoline adduct **4**[10] was obtained regioselectively in 94% yield (Scheme 1). No formation of the 1,4-adduct was observed by NMR. The exclusive formation of *E* geometry ($J=16$ Hz) of the allylic double bond was observed, supposing the high anti-S_E2' manner of the present allylation reaction.[5] The chiral HPLC analysis showed 77% ee of **4**, indicating 93% of the stereoselectivity (Table 1, entry 1). The results of the reactions using other triflate ions are summarized in Table 1.

As shown in Table 1, the stereoselectivity of the present reactions is as high as 90%. $Zn(OTf)_2$ gave the very high selectivity (96%), although the yield was very low



Scheme 1.

Keywords: *N*-acylquinolinium ion; regio- and stereoselective allylation; chiral allylsilane; chiral 2-substituted 1,2-dihydroquinoline.

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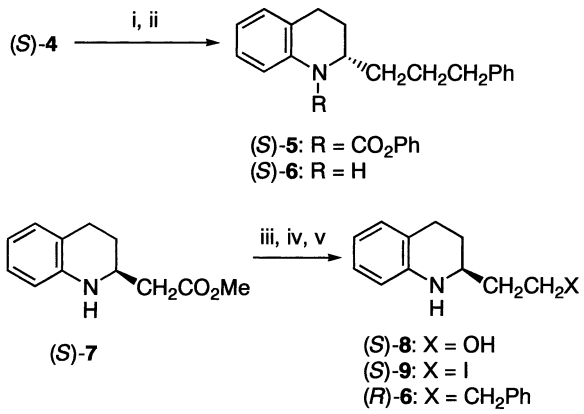
Table 1. Additions of (*R*)-**3** to quinoline activated with $ClCO_2Ph$ and promoter

Entry	Promoter (equiv.)	Time (h)	Yield of **4** (%)[a]	ee of **3** (%)[b]	ee of **4** (%)[c]	Select. (%)[d]
1	AgOTf (1.2)	5	94	83	77	93
2	$Zn(OTf)_2$ (1.0)	5	24	83	80	96
3	TMSOTf (1.0)	5	72	76	69	90
4	AgOTf (0.1)	24	65	76	68	89

[a] Isolated yield.
[b] Determined by a chiral GLC (Chiral-DEX CB) analysis.
[c] Determined by a chiral HPLC (SUMICHIRAL OA-2000) analysis.
[d] Stereoselectivity.



Scheme 2. *Reagents and conditions*: (i) H_2, Pd–C, 92%; (ii) KOH, *i*-PrOH–H_2O, 92%; (iii) $LiAlH_4$, 94%; (iv) I_2, PPh_3, imidazole, 91%; (v) $PhCH_2MgCl$, CuI (cat.), 46%.

(entry 2). TMSOTf gave the high selectivity and the moderate yield (entry 3). Among the promoters, AgOTf seems preferable in views of the yield and selectivity. The use of catalytic amount (0.1 equiv.) of AgOTf worked as well (entry 4), though the yield was lower.

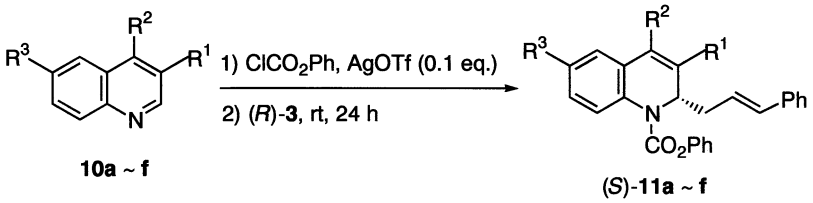
The absolute configuration of **4** was determined to be *S* by the following experiments (Scheme 2). The adduct **4** (70% ee) was hydrogenated and deprotected[11] to give 2-(3-phenylpropyl)-1,2,3,4-tetrahydroquinoline (**6**), which showed a levorotatory optical rotation ($[\alpha]_D = -46$). On the other hand, (*R*)-**6** (95% ee) was prepared from (*S*)-**7**[12] through the three step operations (Scheme 2) and showed a dextorotatory optical rotation ($[\alpha]_D = +65$). Thus, it is evident that the present addition reaction afforded the (*S*)-adduct **4**.

We next examined the stereoselective addition reaction of (*R*)-**3** to various functionalized quinolines activated by $ClCO_2Ph$ and a catalytic amount (0.1 equiv.) of AgOTf (Scheme 3). The results are summarized in Table 2.

As is shown in Table 2, the present reaction tolerates a variety of functional groups. The stereoselectivities are also higher than 90%, except for 3-methoxycarbonylquinoline (entry 3). The best result (96% yield, 96% stereoselectivity) was obtained in the reaction of 6-nitroquinoline (entry 6). The absolute configurations of the adducts **11** are deduced to be *S*, because all of them show levorotatory optical rotations.

In order to clarify the origin of the high stereoselectivity of the present reactions, it is inevitable to know the conformation of the reactive intermediate, *N*-phenoxycarbonylquinolinium triflate (**2**). Then, we have been able to prepare **2** by reaction of **1** with equimolar amounts of $ClCO_2Ph$ and AgOTf as moisture sensitive solids. A single crystal of **2** could be obtained by recrystallization from CH_2Cl_2 and a X-ray structure of **2** is shown in Fig. 1.[13,14] It is apparent that the carbonyl group directs to the inside of the aromatic ring and that the dihedral angle between the carbonyl and the aromatic planes is about 36 degrees probably due to reducing the steric repulsion between them. This slightly twisted conformation is contrasted with the almost coplanar conformations observed for *N*-acylpyridinium[15] and -isoquinolinium ions.[16]

As mentioned above, it is highly likely that the present addition reaction proceeds via the generally proposed anti-S_E2' mode, in which antiperiplanar and synclinal non-chelation transition states are possible.[5] Considering the conformation of the intermediate **2** revealed by the X-ray analysis, three possible transition state (A, B, and C) in the present reaction are depicted in Fig. 2. The transition states A and B are antiperplanar and the transition state B is synclinal. It is apparent that, among the two antiperplanar transition states, B is more congested than A. It is also probable that the



Scheme 3.

Table 2. Additions of (*R*)-**3** to a variety of quinolines activated with $ClCO_2Ph$ and a catalytic amount of AgOTf

Entry	R^1	R^2	R^3	Product	Yield (%)[a]	Select. (%)[b,c]
1	Br	H	H	**11a**	76	96
2	Me	H	H	**11b**	71	90
3	CO_2Me	H	H	**11c**	64	84
4	H	CO_2Me	H	**11d**	58	97
5	H	H	OMe	**11e**	62	96
6	H	H	NO_2	**11f**	96	96

[a] Isolated yield.
[b] Stereoselectivity.
[c] Calculated on the basis of enantiomeric purities of (*R*)-**3** and the products **11a**–**11f**.

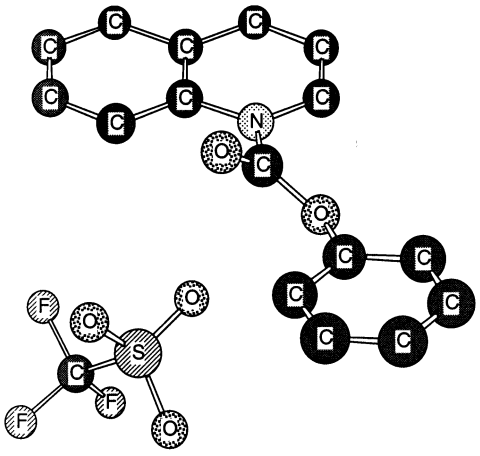


Figure 1. A single-crystal X-ray structure of **2**. The hydrogen atoms are omitted for clarity.

synclinal transition states C leading to (*R*)-**4** would be subjected to the steric repulsion between the allylic moiety and phenoxy group as indicated in Fig. 2 and, therefore, less stable than the transition state A. Thus, the chiral allylsilane could preferably attack to the *si*-face of quinoline ring through the most favorable transition state A to afford the adduct (*S*)-**4** selectively.

In summary, we have demonstrated regio- and stereoselective addition reactions of a chiral allylsilane to quinolines activated with chloroformate and triflate ion to afford chiral 2-allylated 1,2-dihydroquinolines. A variety of functional groups can be tolerated. The present reaction provide a new straightforward method for synthesis of chiral 2-substituted 1,2-dihydroquinolines, which may be valuable synthetic intermediates for alkaloids and related nitrogen heterocyclic compounds.

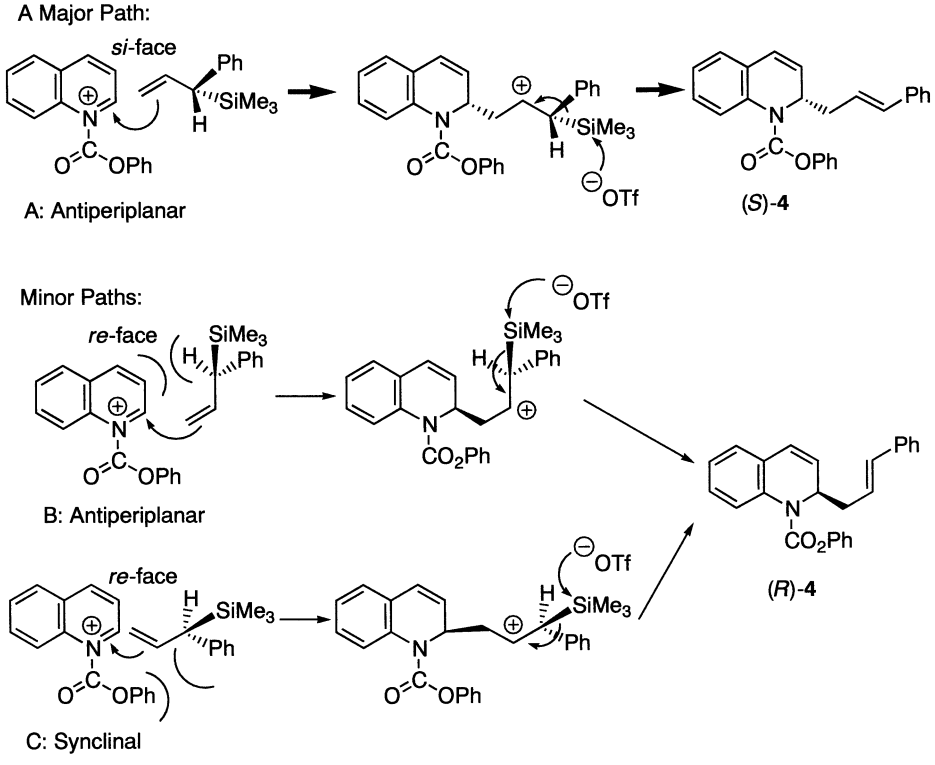


Figure 2. Three possible transition states.

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13. To the best of our knowledge, this is the first example of the single-crystal X-ray structure of *N*-acylquinolinium salt.
14. Crystal data of **2**: $C_{17}H_{12}F_3NO_5S$, $M=399.34$, monoclinic, space group $P21/n$, $a=7.326(4)$, $b=19.920(4)$, $c=12.381(4)$ Å, $\beta=102.02(3)°$, $V=1767(1)$ Å^3, $T=296$ K, $Z=4$, $D_{calcd}=1.501$ g cm^{-3}, 4502 reflections measured ($2\theta<55.0°$), 4191 unique data ($R_{int}=0.081$), 2296 data with $I>2\sigma(I)$, 244 refined parameters. Final $R=0.061$, $R_w=0.057$, GOF = 1.97. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCD 192846.
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