Quinine/selectfluor combination induced asymmetric semipinacol rearrangement of allylic alcohols: an effective and enantioselective approach to α-quaternary β-fluoro aldehydes†

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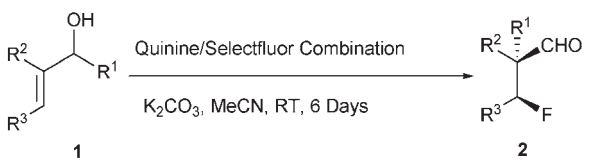
A quinine/Selectfluor combination inducing rearrangement reaction of allylic alcohols was discovered, which involved a moderate yield with good enantioselective construction of α-quaternary carbon center and β-fluoro aldehyde under base condition.

Stereoselective fluorination, especially in asymmetric fashion, is of significant importance in the synthetic fluorine chemistry, because of the uniquely chemical and biological properties of fluorinated molecules, which have attracted a great deal of attention of organic agricultural, medicinal, and material chemists.[1–3] Up to now, selectivity controlled introduction of fluorine has made much progress,[4] in which the enantioselective α-fluorination of carbonyl compounds was widely developed.[5] Despite such progress, however, very few reports on the stereoselective synthesis of β-fluoro carbonyl compounds were revealed.[6] In connection with our continuous interest in the stereoselective construction of 2-quaternary 1,3-diheteroatom units,[7] we have recently discovered an efficient approach to the enantioselective synthesis of α-quaternary β-fluoro aldehydes *via* a quinine/Selectfluor combination mediated asymmetric semipinacol rearrangement of racemic allylic alcohols (Scheme 1). This tandem reaction, to the best of our knowledge, was first discovered in high enantioselectivity to prepare the β-fluorinated carbonyl compounds with two adjacent stereocenters, one being an important chiral quaternary carbon center.[8] In this paper, we present our preliminary experimental results in detail.

Initially the fluorination of **1a** was investigated as the model reaction by the use of cinchonine/Selectfluor combination prepared *in situ* from cinchonine and Selectfluor in MeCN at room temperature.[9,10] However, the expected product **2a** was only

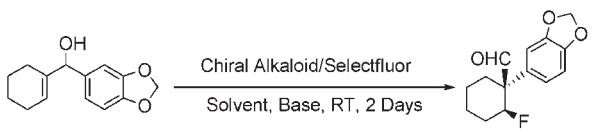


R^1 = aryl; R^2, R^3 = alkyl

Scheme 1

obtained with 15% ee in 15% yield (entry 1 of Table 1). Subsequently, several other cinchona alkaloids were screened under parallel experimental conditions (entries 2–7). Of these alkaloids examined above, quinine as a chiral ligand in MeCN gave the best enantioselectivity of 42% ee (entry 7). At the same time, a crystal of F–QN–BF_4 [11] was also examined and no obvious effects on the improvements of yield and ee were found. Considering the release of stoichiometric amount of acid during this rearrangement reaction of **1a**, some inorganic bases as an additive were employed (entries 8–10). Remarkably, it was found that the use of K_2CO_3 or Cs_2CO_3 could increase the reaction enantioselectivity, wherein K_2CO_3 was the better base to furnish **2a** with ee up to 72% in moderate yield (entry 9). In order to further optimize this reaction condition, different reaction media (entries 11–15) were subjected to this model reaction, however no improvement of the yield and the enantioselectivity was observed.

Table 1 Optimization of reaction conditions for the asymmetric fluorination of **1a**



1a **2a**

Entry	Alkaloid[a]	Solvent	Base[b]	Ee (%)[c]	Yield (%)
1	Cinchonine	MeCN	None	15	15
2	Cinchonidine	MeCN	None	22	17
3	Quinidine	MeCN	None	35	23
4	DHQ	MeCN	None	41	19
5	DHQN	MeCN	None	39	21
6	$(DHQ)_2PHAL$	MeCN	None	32	7
7	Quinine	MeCN	None	42	20
8	Quinine	MeCN	Na_2CO_3	38	24
9	Quinine	MeCN	K_2CO_3	72[d]	30
10	Quinine	MeCN	Cs_2CO_3	70	31
11	Quinine	^{i}PrOH	K_2CO_3	45	10
12	Quinine	DCM	K_2CO_3	67	27
13	Quinine	DMF	K_2CO_3	51	25
14	Quinine	PhH	K_2CO_3	33	6
15	Quinine	Et_2O	K_2CO_3	25	5

[a] The cinchona alkaloid/Selectfluor combination was prepared from cinchona alkaloid (1.4 equiv) and Selectfluor (1.4 equiv) in solvent at room temperature for 30 min. [b] 0.6 equivalent of base was used. [c] Ee values were determined by HPLC analysis using a Chiralpak AS column. [d] The absolute configuration (*2R*, *3S*) was determined by Mosher's Method. For detailed information, see the electronic supplementary information.

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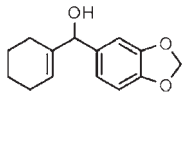
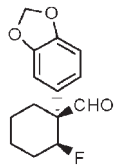
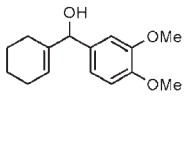
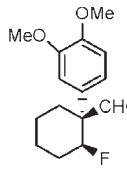
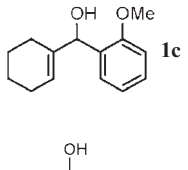
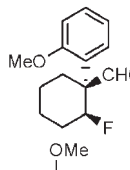
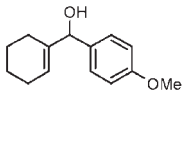
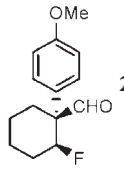
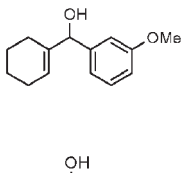
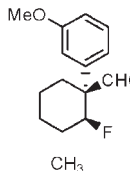
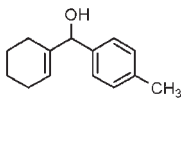
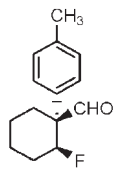
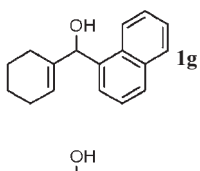
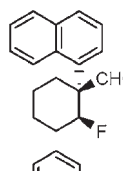
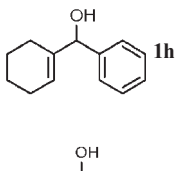
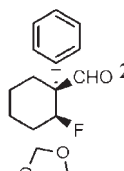
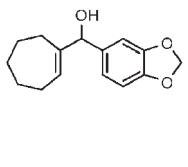
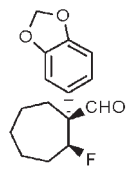
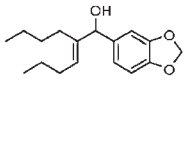
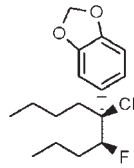
On the basis of the preliminary results mentioned above, a series of allylic alcohols were prepared to test the generality of this asymmetric semipinacol rearrangement reaction. As can be seen in Table 2, cyclic allylic alcohols with six-membered rings **1b–1h** gave the expected corresponding α-quaternary β-fluoro aldehydes **2b–2h** with good yield and fair ee (entries 2–8). For example, allylic alcohols **1b–d** (entries 2–4) and **1f** (entry 6), which contain the electron-donating groups (EDG) at *ortho*- or *para*-position of the migrating aryl group, gave 70–76% ee (*e.g.* from 70 to 93% ee after recrystallization, entry 6). When the substrate without any substituent on the migrating aryl group (entry 8) or only with one *meta*-electron-donating group on the migrating one (entry 5) was employed, however, lower enantiomeric excess was observed. In contrast, allylic alcohol **1g** containing the migrating 1-naphthyl group (entry 7) gave the highest ee of 82%. These results indicated that the property of the migrating group in substrates, to some extent, has influence on the enantioselectivity of this rearrangement reaction. In addition, when the substrate bearing the seven-membered ring (entry 9) instead of the six-membered one was subjected to this reaction, the corresponding fluorinated product **2i** could also be obtained with 65% ee. To further expand the substrate scope, we examined one acyclic substrate **1j** (entry 10). This reaction proceeded smoothly to afford the expected product **2j** with 61% ee when exposed to the standard condition. Unexpectedly, the tertiary allylic alcohol (*e.g.* 1-(1′-cyclohexenyl)-1-phenylethanol) as a substrate was found to be ineffective in this rearrangement reaction, and it is possibly due to the spatial bulkiness of the substitute bearing the tertiary hydroxyl group and the less electrophilic reactivity of the fluorinating reagent F–QN–BF_4.

To elucidate the enantioselectivity of this asymmetric semipinacol rearrangement reaction of racemic allylic alcohols, the chiral HPLC analysis of the recovered substrate **1** (*e.g.* **1a**, **1c** and **1h** of Table 2) was carefully conducted during the whole reaction. Interestingly, the recovered allylic alcohol **1** was still racemic and its kinetic resolution was not observed in the current reaction. Importantly, this unusual analytical result means that both enantiomers of the racemic starting materials converge on the same single enantiomer of the product. It should be highly noteworthy that this new asymmetric reaction model with more potential synthetic values is significantly different from the common situation of one enantiomer reacting and one being relatively unaffected in the classic kinetic resolution. On the basis of the experimental results mentioned above and the previously reported literature sources,[9a,12] we proposed a possible reaction mechanism in Fig. 1. There could be four dominating transition states, **TS-1**, **TS-2**, **TS-3** and **TS-4**, in this asymmetric transformation. Due to the steric hindrance between the quinoline moiety in the fluorinating reagent and the substituent incorporating the secondary hydroxy group in the substrate, **TS-1** and **TS-2** that generated the expected product (*2R*, *3S*)-**2** are more favorable than **TS-3** and **TS-4**, wherein the bulky aryl migrating group should be anti-periplanar to the π-orbital of the double bond, with the fluorine being delivered from the opposite face. Additonally, the above experimental fact that the remaining substrate was still racemic revealed that **TS-1** and **TS-2** might have the semblable energy barrier in this enantioselective semipinacol rearrangement reaction.

Table 2 Enantioselective synthesis of α-quaternary β-fluoro aldehydes

Entry	Substrates (**1**)	Products (**2**)	Yield (%)	Ee (%)[b]
1	 **1a**	 **2a**	39	74
2	 **1b**	 **2b**	42	73
3	 **1c**	 **2c**	50	71
4	 **1d**	 **2d**	41	76
5	 **1e**	 **2e**	48	54
6	 **1f**	 **2f**	35	70 (93)[c]
7	 **1g**	 **2g**	45	82
8	 **1h**	 **2h**	33	67
9	 **1i**	 **2i**	34	65
10	 **1j**	 **2j**	37	61

[a] The fluorination of **1** with quinine/Selectfluor combination (1 : 1, 1.4 equiv) and K_2CO_3 (0.6 equiv) in MeCN at room temperature for 6 d. [b] Determined by HPLC analysis using a Chiralpak AS column. [c] Ee was determined after recrystallization.

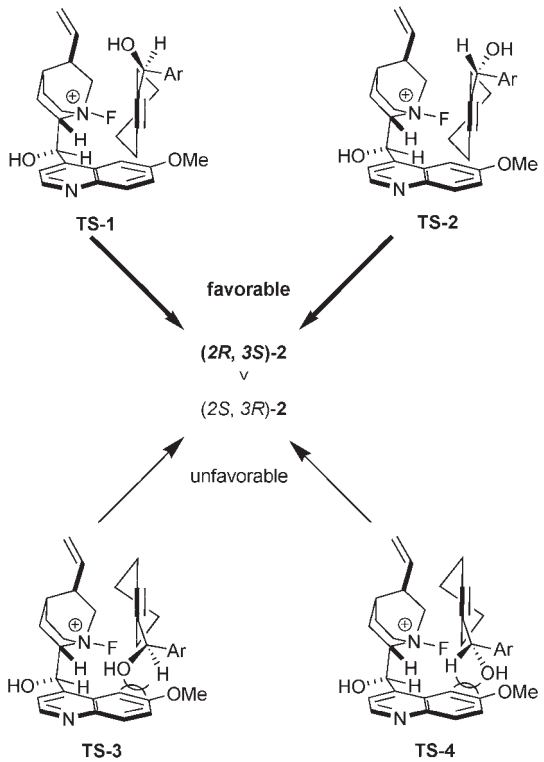


Fig. 1 Proposed transition-state assemblies.

In summary, we have successfully developed a new stereoselective method for the synthesis of chiral α-quaternary β-fluoro aldehydes, with ee up to 82%, in which an optical pure product could be obtained from a racemic substrate once a quinine/Selectfluor combination was employed in the process of rearrangement. Further investigation on exploring other effective asymmetric fluorinating reagents to improve their enantioselectivity and chemical yield is ongoing in our group.‡

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Notes and references

‡ A typical experimental procedure is as follows: A solution of **1** (0.20 mmol) in CH_3CN (1 ml) and K_2CO_3 (16.6 mg, 0.12 mmlol) were added to quinine/Selectfluor combination [prepared *in situ* from quinine (90.7 mg, 0.28 mmol) and Selectfluor (95%, 99.1 mg, 0.28 mmol) in CH_3CN (2 ml) at room temperature for 30 min] in sequence at room temperature under Ar atmosphere. After stirring for 6 d, water was added to the reaction mixture and extracted with AcOEt. The organic phase was washed with sat. NH_4Cl, sat. $NaHCO_3$, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a crude oil, which was purified by preparative TLC on silica-gel to give **2**.

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