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Organocatalytic Asymmetric Fluorination/Semipinacol Rearrangement: An Efficient Approach to Chiral β-Fluoroketones

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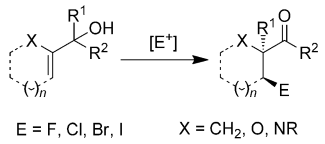
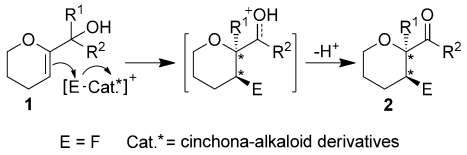
Chiral fluorinated molecules have attractive properties for agricultural, medicinal, and material applications.[1] Therefore, the introduction of carbon–fluorine bonds in an asymmetric manner is of great importance in modern synthetic chemistry, and the development of methodologies that achieve this transformation are in high demand. During the past years, tremendous efforts have been made in developing methods for the asymmetric formation of carbon–fluorine bonds;[2] many of these methods focus on the catalytic asymmetric fluorination of 1,3-dicarbonyl compounds[3] and carbonyl compounds.[4] In contrast, very few methods involving the catalytic asymmetric fluorination of olefins have been described.[5,6] There has been significant progress in the development of addition reactions of olefins involving the heavier halogen atoms (X = Br, Cl, and I), a series of transformations that are some of the most powerful in organic chemistry;[7] the catalytic enantioselective fluorination of olefins remains a challenge. The fluorination/semipinacol rearrangement, which is initiated by fluorination of the double bond,[8] is a straightforward strategy for the preparation of β-fluorocarbonyl compounds, which are potentially useful compounds for fluorine chemistry.[9] Moreover, two adjacent stereocenters, one of which is quaternary, are formed simultaneously through this rearrangement, which uses simple allylic alcohols as starting materials (Scheme 1). In 2005, our research group reported a noncatalytic asymmetric fluorination/semipinacol rearrangement,[10] however, a suitable catalytic method has yet to be reported.



Scheme 1. Halogenation/semipinacol rearrangement reaction.

In the past years, cinchona alkaloids and their derivatives, which are some of the most important organocatalysts, have been extensively studied. Various enantioselective transformations promoted by these catalysts have been achieved.[11] Recently, our research group and that of others have reported some examples of asymmetric bromination/semipinacol rearrangement reactions that are catalyzed by cinchona-alkaloid derivatives.[12] In light of our previous results, combined with our long-standing interest in semipinacol-rearrangement reactions,[13,14] we hypothesized that the fluorination/semipinacol rearrangement reaction could also be catalyzed by cinchona-alkaloid derivatives in an asymmetric manner (Scheme 2). Herein, we present our preliminary results on this reaction.



Scheme 2. A design for a catalytic enantioselective fluorination/semipinacol rearrangement reaction.

We began our investigation using 2-oxa allylic alcohol **1a** as a model substrate. A careful survey of cinchona-alkaloid-derived catalysts was conducted for the fluorination/semipinacol rearrangement reaction (Table 1). Among these catalysts, hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether ($(DHQD)_2PYR$), **3c**) was the most effective catalyst and gave **2a** in 32% yield and with an *ee* value of 50% (Table 1, entries 1–4).[15] Next, using **3c** as the catalyst, various inorganic bases, such as Na_2CO_3, Cs_2CO_3, and K_2CO_3, were investigated as additives (Table 1, entries 5–7). Remarkably, it was found that the use of K_2CO_3 led to a reaction of enhanced enantioselectivity (62% *ee*). More encouragingly, when the reaction temperature was lowered to 0°C, the enantioselectivity increased to value of 72% (Table 1, entry 8). To further improve the yield and the enantioselectivity, we screened the solvent, the nature of which strongly affected both the reactivity and the enantioselectivity. The use of tetrahydrofuran (THF) as a solvent led to no reac-

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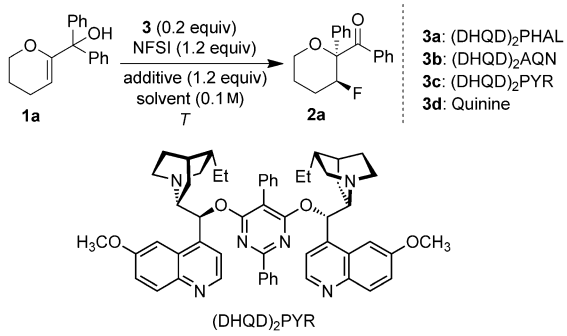
Table 1. Optimization of the asymmetric reaction.[a]



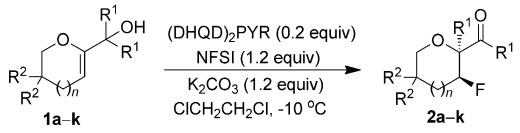
Entry	Cat.	T [°C]	Solvent	Additive	Yield [%][b]	*ee* [%][c]
1	**3a**	RT	CH_3CN	–	27	17
2	**3b**	RT	CH_3CN	–	25	10
3	**3c**	RT	CH_3CN	–	32	50
4	**3d**	RT	CH_3CN	–	20	16[f]
5	**3c**	RT	CH_3CN	Na_2CO_3	30	54
6	**3c**	RT	CH_3CN	Cs_2CO_3	35	54
7	**3c**	RT	CH_3CN	K_2CO_3	36	62
8	**3c**	0	CH_3CN	K_2CO_3	44	72
9	**3c**	0	THF	K_2CO_3	–	–
10	**3c**	0	$CHCl_3$	K_2CO_3	28	81
11	**3c**	0	DCE	K_2CO_3	48	86
12	**3c**	-10	DCE	K_2CO_3	52	90
13[d]	**3c**	-10	DCE	K_2CO_3	56	93
14[e]	**3c**	-10	DCE	K_2CO_3	54	93

[a] All reactions, unless otherwise noted, were performed with 0.1 mmol of **1a** in 1 mL of solvent. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] 1.2 equiv of NFSI was added in six portions. [e] Using 6.0 equiv of K_2CO_3. [f] the sense of asymmetric induction was opposite that observed in reactions associated with other entries in this table.

tion, whereas the use of the chlorinated solvent, 1,2-dichloroethane (DCE), led to much improved enantioselectivity, 86% *ee* (Table 1, entries 9–11). To our delight, when the reaction temperature was further lowered to −10°C, the enantioselectivity increased further (90% *ee*; Table 1, entry 12). Considering that a background reaction might be influencing the result, we added *N*-fluorobenzenesulfonimide (NFSI) portionwise, a condition that further improved the enantioselectivity (93% *ee*; Table 1, entry 13). In addition, no improvement in enantioselectivity and yield was observed when a large excess of K_2CO_3 was used (Table 1, entry 14).

With optimized reaction conditions established, various 2-oxa allylic alcohols (**1b–k**) were subjected to the fluorination/semipinacol rearrangement reaction. All substrates afforded the desired chiral β-fluoroketone derivatives in moderate to good yields with moderate to excellent levels of enantioselectivity (Table 2). In comparison to the reaction of model substrate **1a**, the reaction of a substrate bearing a halogen substituent at the *para* position of the phenyl moiety showed lower levels of enantioselectivity (Table 2, entries 3–5). When 4-fluorophenyl-substituted allylic alcohol **1b** was used, a similarly high level of enantioselectivity was observed (Table 2, entry 3). However, substrates containing either 4-chlorophenyl or 4-bromophenyl substituents gave

Table 2. Asymmetric fluorination reaction using catalyst $(DHQD)_2PYR$.[a]



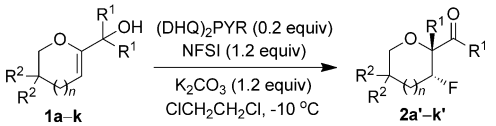
Entry	Substrate	Yield [%][b]	*ee* [%][c]
1	**1a**: $n=1$, $R^1=C_6H_5$, $R^2=H$	56	93
2[d]	**1a**: $n=1$, $R^1=C_6H_5$, $R^2=H$	53	92
3	**1b**: $n=1$, $R^1=$4-F-C_6H_4, $R^2=H$	41	92
4[e]	**1c**: $n=1$, $R^1=$4-Cl-C_6H_4, $R^2=H$	34	79
5[e]	**1d**: $n=1$, $R^1=$4-Br-C_6H_4, $R^2=H$	39	71
6[e]	**1e**: $n=1$, $R^1=$3-F-C_6H_4, $R^2=H$	41	93
7[e]	**1f**: $n=1$, $R^1=3,5$-$(CH_3)_2C_6H_3$, $R^2=H$	76	66
8	**1g**: $n=1$, $R^1=$2-naphthyl, $R^2=H$	54	71
9[e]	**1h**: $n=1$, $R^1=$2-thienyl, $R^2=H$	76	38
10	**1i**: $n=1$, $R^1=C_6H_5$, $R^2=Me$	47	86
11	**1j**: $n=0$, $R^1=C_6H_5$, $R^2=H$	66	85
12	**1k**: $n=0$, $R^1=$4-F-C_6H_4, $R^2=H$	48	81

[a] All reactions, unless noted otherwise, were performed with 0.1 mmol of **1**, 0.12 mmol of K_2CO_3, and 0.02 mmol of $(DHQD)_2PYR$ in 1 mL of 1,2-dichloroethane at −10°C. NFSI (0.12 mmol) was added in six portions. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Using 0.1 equiv of $(DHQD)_2PYR$. [e] The reaction was carried out at 0°C.

products with lower *ee* values (Table 2, entries 4 and 5). The use of 3-fluorophenyl-substituted allylic alcohol **1e** led to enantioselectivity that was similar to that of the-4-fluorophenyl substituted substrate (Table 2, entry 6). It was found that the presence of more than one substituent on the phenyl group adversely affected the enantioselectivity (Table 2, entry 7). Additionally, the sterically demanding 2-naphthyl-substituted substrate also gave moderate enantioselectivity (Table 2, entry 8). Unfortunately, heterocycle-substituted allylic alcohols were not good substrates for the catalytic asymmetric reaction (Table 2, entry 9). To further expand the substrate scope, a substrate with a *gem*-dimethyl substituted C5 position within the dihydropyranyl ring was also examined and when used in the reaction it led to the corresponding product in moderate yield with a high *ee* value (Table 2, entry 10). Finally, the reaction of two substrates containing dihydrofuranyl moieties also gave the desired products with high *ee* values (Table 2, entries 11 and 12). Notably, the absolute configuration of the product **2a** was determined by X-ray crystallography analysis of its derivative, **4a** (see the Supporting Information for further details).[16]

Because enantiomers generally have disparate biological activities, convenient access to both enantiomers is distinctly important in asymmetric catalysis. To our delight, the reaction of **1a** with 20 mol% hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether ($(DHQ)_2PYR$) and NFSI in the presence of K_2CO_3 in 1,2-dichloroethane at −10°C gave **2a′** (*ent*-**2a**) in 46% yield with 89% *ee* (Table 3, entry 1). Next, the same substrates that were used above with $(DHQD)_2PYR$ (**3c**) as the catalyst were subjected to the standard reaction conditions using $(DHQ)_2PYR$, thus giving the products **2a′–k′**,

Table 3. Asymmetric fluorination reaction using catalyst $(DHQ)_2PYR$.[a]



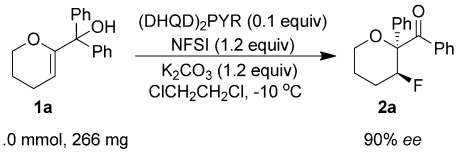
Entry	Substrate	Yield [%][b]	*ee* [%][c]
1	**1a**: $n=1$, $R^1=C_6H_5$, $R^2=H$	46	89
2[d]	**1a**: $n=1$, $R^1=C_6H_5$, $R^2=H$	46	90
3[e]	**1a**: $n=1$, $R^1=C_6H_5$, $R^2=H$	42	90
4	**1b**: $n=1$, $R^1=4$-F-C_6H_4, $R^2=H$	38	86
5[f]	**1c**: $n=1$, $R^1=4$-Cl-C_6H_4, $R^2=H$	31	77
6[f]	**1d**: $n=1$, $R^1=4$-Br-C_6H_4, $R^2=H$	29	70
7[f]	**1e**: $n=1$, $R^1=3$-F-C_6H_4, $R^2=H$	35	87
8[f]	**1f**: $n=1$, $R^1=3,5$-$(CH_3)_2$-C_6H_3, $R^2=H$	73	63
9	**1g**: $n=1$, $R^1=2$-naphthyl, $R^2=H$	44	68
10[f]	**1h**: $n=1$, $R^1=2$-thienyl, $R^2=H$	58	36
11	**1i**: $n=1$, $R^1=C_6H_5$, $R^2=Me$	42	77
12	**1j**: $n=0$, $R^1=C_6H_5$, $R^2=H$	54	86
13	**1k**: $n=0$, $R^1=4$-F-C_6H_4, $R^2=H$	33	84

[a] All reactions, unless noted otherwise, were performed with 0.1 mmol of **1**, 0.12 mmol of K_2CO_3, and 0.02 mmol of $(DHQ)_2PYR$ in 1 mL of 1,2-dichloroethane at −10 °C. NFSI (0.12 mmol) was added in six portions. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Cs_2CO_3 was added instead of K_2CO_3. [e] Using 0.1 equiv of $(DHQ)_2PYR$. [f] The reaction was carried out at 0 °C.

which are the enantiomers of **2a–k**, in moderate yields and with moderate to high levels of enantioselectivity. In comparison to the products **2a–i**, the products **2a′–i′** were obtained with slightly lower *ee* values (Table 3, entries 1–11), although, two substrates containing dihydrofuranyl moieties were obtained with slightly higher *ee* values (Table 3, entries 12 and 13). In addition, we also examined the effect of Cs_2CO_3 as an additive (instead of K_2CO_3), which was also examined in our initial optimization studies, and found that the enantioselectivity was slightly higher in the reaction of **1a** (90% *ee*; Table 3, entry 2). However, the use of Cs_2CO_3 instead of K_2CO_3 had a negative effect on the enantioselectivity for other substrates.

Chiral β-fluoroketones are potentially useful synthons for fluorine chemistry, and therefore, the investigation of a large-scale reaction would be necessary to evaluate the synthetic utility of the reaction. Accordingly, the rearrangement of substrate **1a** was carried out on a 1 mmol scale with catalyst loading of 10 mol% and the desired product **2a** was obtained in 43% yield with an *ee* value of 90% (Scheme 3).

In summary, a novel asymmetric fluorination/semipinacol rearrangement reaction that is catalyzed by cinchona-alkaloid derivatives was developed. This reaction is valuable because a series of chiral β-fluoroketones, which contain various substituents and oxygen-containing rings of various size, can be prepared from simple allylic alcohols. Moreover, both enantiomers of the products were readily obtained with moderate to excellent *ee* values. Further investigations are underway to determine the mechanism.



Scheme 3. Asymmetric fluorination reaction on a 1 mmol scale.

Experimental Section

General procedure: A mixture of $(DHQD)_2PYR$ (20 mol%) or $(DHQ)_2PYR$ (20 mol%) and NFSI (0.02 mmol) in 1,2-dichloroethane (0.5 mL) was stirred under argon at RT for 10 min. K_2CO_3 (0.12 mmol) was then added to the solution, and the reaction mixture was stirred for 10 min at −10 °C. A solution of the 2-oxa allylic alcohol **1a** (0.1 mmol) in 1,2-dichloroethane (0.5 mL) was added to the mixture and the resulting mixture was stirred at the same temperature. NFSI (0.1 mmol) was added in five portions (0.02 mmol every 8 h). After the substrate was completely consumed (as detected using thin-layer chromatography), the reaction mixture was directly subjected to column chromatography using silica gel as the stationary phase and petroleum ether/ethyl acetate (125:1) as the eluent to give the desired product.

Acknowledgements

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Keywords: asymmetric catalysis · cinchona alkaloids · fluorination · organocatalysis · rearrangement

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[16] CCDC 881661 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www. ccdc.cam. ac.uk/data request/cif.

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