Synthetic Methods

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Enantioselective Organocatalytic Fluorination-Induced Wagner–Meerwein Rearrangement**

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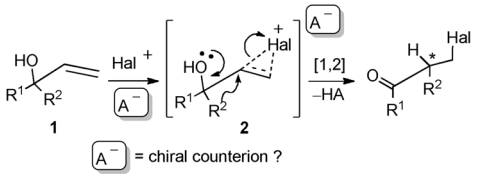
Despite the fact that only 21 fluorinated molecules are known to be biosynthesized,[1] it is notable that about 20–25% of all modern pharmaceuticals and agrochemicals incorporate at least one fluorine atom.[2] Nevertheless, the practice of introducing fluorine atoms into bioactive compounds is rather recent, as the first synthetic fluorinated drug, namely 5-fluorouracil, was synthesized as late as in 1957.[3] Ever since, the research aimed at incorporating fluorine atoms into small organic molecules has attracted and intrigued synthetic organic chemists.[4] Yet, despite the importance of fluorine, carbon–fluorine bond formation remains a challenge.[5] Performing this task in concert with bringing chirality into the target molecule, and doing so with only a catalytic quantity of the enantioinducing reagent is of even greater practical importance.[6]

Halocyclization of olefins is an important class of organic transformations. Among these reactions, halolactonizations have been studied extensively and applied in the synthesis of many bioactive molecules.[7] Very recently, catalytic enantioselective versions of the aforementioned transformation were also reported.[8] Far less studied is the related halogenation/semipinacol rearrangement cascade.[9] In this last reaction, an allylic alcohol (**1**) undergoes a Wagner–Meerwein alkyl migration, which is initiated by the formation of the halonium ion intermediate **2** (Scheme 1). Whereas the chlorination- and bromination-induced Wagner–Meerwein rearrangements of electron-rich cyclic enol ethers were recently shown to be amenable to asymmetric catalysis,[10,11] the development of a truly enantioselective catalytic fluorination-induced variant remains underexplored.[12] This is partly related to the inherently high reactivity of most electrophilic fluorinating reagents, and leaves little room for the introduction of a chiral catalyst.[13]



Scheme 1. The concept of halonium-ion-promoted Wagner–Meerwein transposition of allylic alcohols, and the idea of inducing chirality by means of a chiral counterion. Hal = F, Cl, Br, or I.

In the course of the last ten years, it has been extensively demonstrated that ionic catalysts incorporating at least one chiral ion are able to render enantioselective those transformations which proceed through reaction intermediates bearing an opposite electrostatic charge.[14,15] Specifically in the field of asymmetric-counteranion-directed catalysis, binol-derived phosphoric acids have been disclosed as privileged precursors of chiral anions.[16,17] Reasoning that our postulated halonium ion intermediate **2** bears a net positive charge, we were interested to see if a chiral anion could induce asymmetry into the Wagner–Meerwein rearrangement. Among the four possible halogen atoms, we were particularly attracted by fluorine as initiator for the Wagner–Meerwein transposition. Furthermore, to the best of our knowledge, chiral-binol-derived phosphoric acids have only been used to promote semipinacol rearrangements of electron-rich cyclic enol ethers.[18] The transposition of simple allylic alcohols remains a great challenge because it cannot be initiated by a proton alone. Nevertheless, such a reaction could be of great synthetic interest, as it would lead to the formation of valuable all-carbon quaternary stereogenic centres. Herein, we report some of our recent results on this subject. Our catalytic system was inspired from the one recently reported for related fluorocyclization reactions.[19]

Optimization studies were carried out with the strained allylic alcohol **A1**, Selectfluor as the fluorinating reagent, and a set of synthetic axially chiral phosphoric acids (**L**), derived from (R_a)-binol (Table 1).

In the course of the preliminary catalyst screening, the employment of highly sterically congested phosphoric acids (**L4**–**L8**), which are related to the known (R_a)-TRIP scaffold,[20] turned out to be crucial for accessing practical enantioselectivities of the product β-fluoro spiroketone **B1** (Table 1, entries 4–6). Interestingly, acids bearing isopropyl (**L4**) and cyclopentyl (**L6**) substituents at positions X and Y outperformed the acid **L5** which bears cyclohexyl groups at these same positions. Among the numerous solvents tested, highly hydrophobic, yet strongly solubilizing solvents (toluene, fluorobenzene, and diisopropylether) were better than hydrophobic solvents of lower solubilizing ability (cyclohexane). Since nonpolar solvents favor ion pairing, the present reaction is an example of anionic phase-transfer catalysis (PTC), where a lipophilic chiral anion extracts the insoluble

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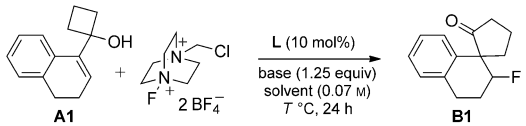
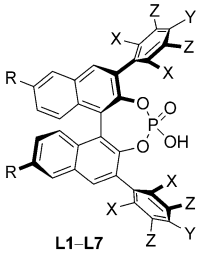
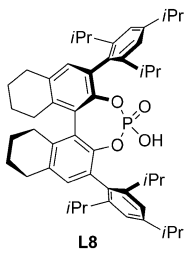
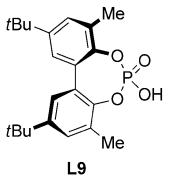
Table 1: Selected optimization studies.[a]





L1 R = X = Y = Z = H
L2 R = H, X = Y = Z = F
L3 R = H, X = Z = H, Y = *t*Bu
L4 R = H, X = Y = *i*Pr, Z = H
L5 R = H, X = Y = *c*-C_6H_{12}, Z = H
L6 R = H, X = Y = *c*-C_5H_{10}, Z = H
L7 R = *n*-C_8H_{17}, X = Y = *i*Pr, Z = H





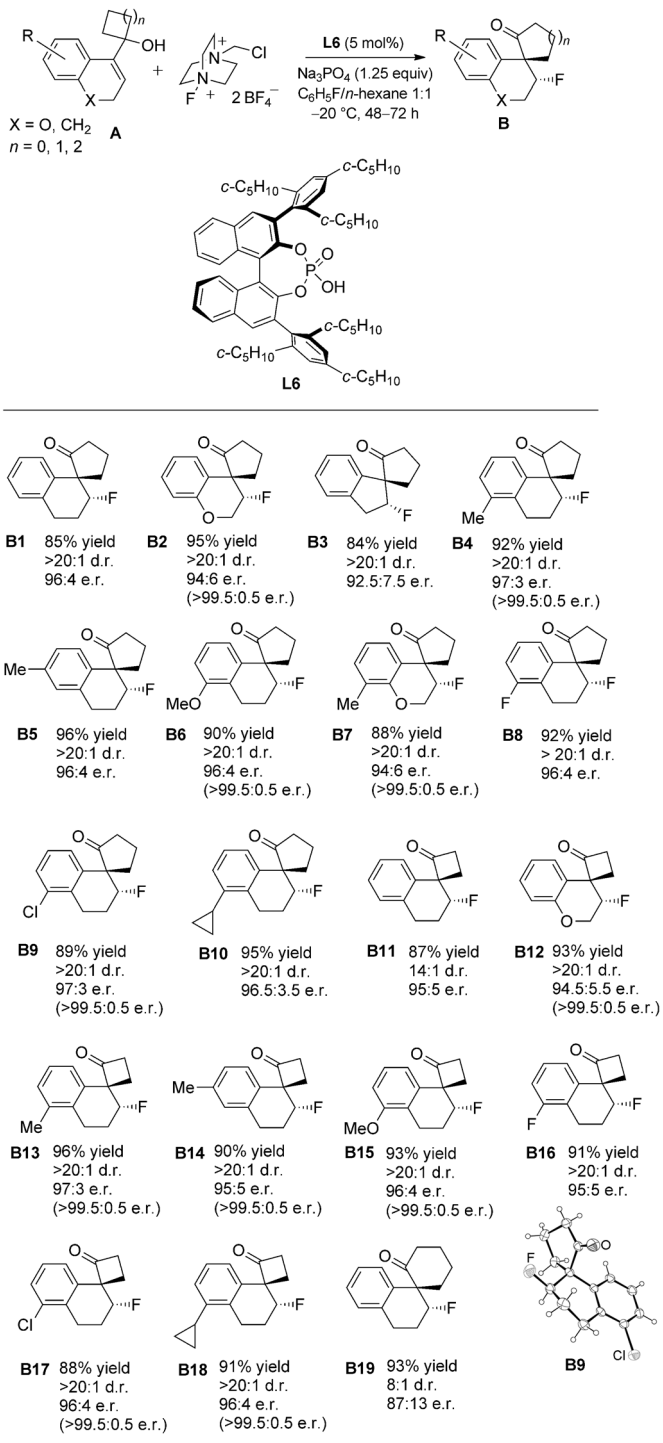
Entry	L	*T* [°C]	Base	Solvent	Yield [%][h]	d.r.[b]	e.r.[c]
1	**L1**	25	Na_2CO_3	toluene	87	20:1	68:32
2	**L2**	25	Na_2CO_3	toluene	35	10:1	57:43
3	**L3**	25	Na_2CO_3	toluene	82	>20:1	63:37
4	**L4**	25	Na_2CO_3	toluene	96	>20:1	86.5:13.5
5	**L5**	25	Na_2CO_3	toluene	74	>20:1	82.5:17.5
6	**L6**	25	Na_2CO_3	toluene	89	>20:1	86.5:13.5
7	**L9**	25	Na_2CO_3	toluene	62	6:1	50:50
8	**L4**	25	–	toluene	19[d]	>20:1	61:39
9	–	25	Na_2CO_3	toluene	trace	n.d.	n.d.
10	–	25	Na_2CO_3	acetonitrile	82	3:2	50:50
11	**L4**	25	Na_2CO_3	PhF	84	>20:1	90:10
12[e]	**L4**	25	Na_2CO_3	PhF	67	>20:1	86.5:13.5
13	**L4**	25	Na_2CO_3	*c*-hexane	56	>20:1	82:18
14	**L4**	25	Na_2CO_3	iPr_2O	78	>20:1	89:11
15	**L4**	0	Na_2CO_3	PhF	75	>99:1	91.5:8.5
16	**L4**	0	Na_2CO_3	PhF/*n*-hexane 1:1	86	>99:1	93:7
17[f]	**L4**	−20	Na_3PO_4	PhF/*n*-hexane 1:1	87	>99:1	95:5
18[f]	**L4**	−20	Cs_2CO_3	PhF/*n*-hexane 1:1	44	>99:1	93:7
19[f]	**L4**	−20	K_3PO_4	PhF/*n*-hexane 1:1	55	>99:1	94:6
20[f,g]	**L6**	−20	Na_3PO_4	PhF/*n*-hexane 1:1	85	>99:1	96:4
21[f,g]	**L7**	−20	Na_3PO_4	PhF/*n*-hexane 1:1	97	>99:1	95:5
22[f,g]	**L8**	−20	Na_3PO_4	PhF/*n*-hexane 1:1	92	>99:1	95:5

[a] Reaction conditions: see the Supporting Information. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC using a chiral stationary phase. [d] ^{1}H NMR conversion. [e] Added 4 Å molecular sieves. [f] Reaction time was extended to 48 h. [g] Used 5 mol% catalyst. [h] Yields of products isolated after flash chromatography. n.d. = not determined.

fluorination reagent into the organic layer, thus rendering it chiral.[19] Accordingly, employing a 1:1 mixture of fluorobenzene and *n*-hexane, coupled with changing of the basic additive from Na_2CO_3 to Na_3PO_4 and lowering of the reaction temperature to −20 °C (entry 17) led to an increase of the enantioselectivity obtained with **L4** to 95:5 e.r. The isolated yield of **B1** could be increased when employing the more-lipophilic phosphoric acids **L6-L8** (entries 20–22). This trend is again in accord with the PTC mechanism, as the more-lipophilic anions derived from **L6-L8** are able to extract the fluorination reagent more readily. In these last three cases, the catalyst loading could be decreased to 5 mol%, albeit at the expense of the reaction time. Since the use of **L6** led to **B1** with the highest level of enantioinduction (96:4 e.r.) and perfect diastereoselectivity (>99:1), this chiral phosphoric acid was selected for further studies.

It is important to point out here that both the enantioselectivity as well as the diastereoselectivity of the present transformation are controlled by the catalyst structure. Thus, racemic reactions (carried out with Selectfluor in acetonitrile without any phosphoric acid; Table 1, entry 10) gave quasi 1:1 mixtures of diastereisomers. Additionally, the diastereoselectivity was greatly reduced under PTC conditions as well when employing the lipophilic achiral phosphoric acid **L9** (entry 7). Consequently, the catalyst structure not only controls the initial formation of the fluorinated stereogenic center, but also participates in the second (alkyl migration) step.

With a set of optimal reaction conditions in hand, the substrate scope of the title transformation was studied next. To this end, strained allylic alcohols (**A**) were stirred together with Selectfluor and the chiral phosphoric acid **L6**, under our previously established reaction conditions (Scheme 2). Both three-membered ($n = 0$, products **B11**–**B18**) and four-membered ($n = 1$; products **B1**–**B10**) allylic alcohols were amenable to enantioselective ring expansion, which occurred equally well with scaffolds based on tetralone (X = CH_2, for



Scheme 2. The substrate scope for the fluorination-induced Wagner–Meerwein rearrangement, and the X-ray crystal structure (thermal ellipsoids shown at 50% probability) of **B9**.[21] The values in brackets show enantiomer ratios after recrystallization.

example, **B1**) as well as chromanone (X = O, for example, **B2**) systems. In terms of the substituent tolerance, electron-releasing (alkoxy; products **B6**,**B15**), electron-neutral (alkyl; products **B4**,**B7**,**B10**,**B13**), as well as moderately electron-withdrawing (halogen; products **B8**,**B9**,**B16**,**B17**) groups were equally well tolerated when positioned at C6 of the tetralone/chromanone scaffold. A methyl substituent was also tolerated when placed at C5 of the tetralone scaffold (products **B5**,**B14**). The product β-fluoro spiroketones **B** were isolated in good to excellent yields, and in all cases the products displayed perfect d.r. (> 20:1) and high e.r. (between 94:6 and 97:3) values. In many cases, the recovered β-fluoro spiroketones could be recrystallized from *n*-hexane/Et_2O, thus giving access to enantiomerically pure material. Encouragingly, even **B3**, based on the indanone (X = nothing) scaffold was obtained as a single diastereomer and with an encouraging 92.5:7.5 e.r. value. The sole disappointment came with the spiroketone **B19**, which resulted from expansion of a five-membered ($n = 2$) allylic alcohol. For this last case, the diastereoselectivity decreased to 8:1 and the enantioselectivity decreased to 87:13 e.r.

Unfortunately, at this stage, we were unable to extend our asymmetric methodology to allylic alcohols lacking the aromatic ring. For example, substrates based on dihydropyran or cyclohexene scaffolds furnished the desired β-fluoro spiroketones in good yields but with only moderate stereoselectivities.[23]

Unambiguous assignment of relative and absolute configurations of the products was made possible after carrying out an X-ray diffraction study on a single crystal derived from **B9** (Scheme 2).[21] Based on the model proposed by Simon and Goodman for binol phosphoric acid catalyzed reactions of imines,[22] we present here a rationale for the observed absolute and relative configurations (Figure 1). According to

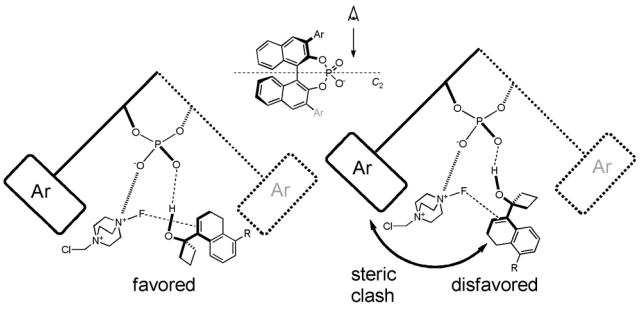


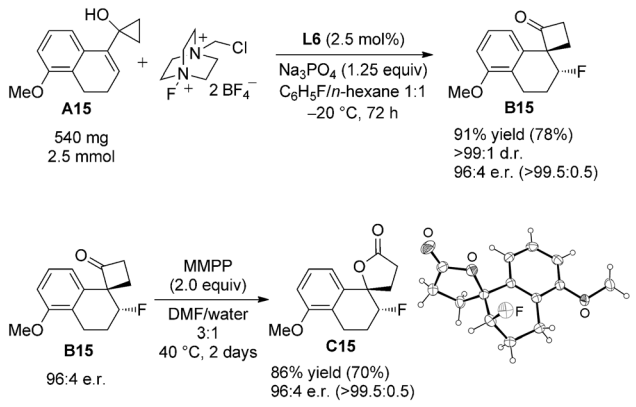
Figure 1. Mechanistic rationale for the observed *Re*-face fluorination with a R_a-configured phosphate anion.

this model, the positively charged Selectfluor reagent occupies the vacant lower-left quadrant of the catalyst, while establishing an ionic bridge with the negatively charged phosphate oxygen atom. Presumably, the allylic cyclobutanol establishes a hydrogen bond with the second phosphate oxygen atom, while fitting the bulk of the tetralone ring into the vacant upper-right quadrant. Consequently, the fluoronium bridge is formed at the *Re* face of the carbon–carbon double bond of the substrate, and migration occurs *anti* relative to the leaving group. From this model, we could speculate that the high tolerance towards substitution at positions C5 and C6 of the tetralone ring observed experimentally is a consequence of these positions ending up in the vacant upper-right quadrant of the catalyst.

It is important to point out that the sense of absolute induction for our transformation is inverted when compared

to the previously reported fluorocyclization of Toste et al. If, in the case of the semipinacol rearrangement, *Re*-face fluorination takes places with an R_a-configured phosphate anion, an identically configured phosphate anion induces *Si*-face fluorination in the case of the fluorocyclization.[19] Clearly, this deviation within the chiral induction is due to an inversion in the preferred binding mode to the catalyst. While the model presented on the left (Figure 1) holds true for our case, it is the model on the right that is preferred when a different substrate is used. Such a switch in the binding preference is presumably caused by a conformational restriction which is present in our substrate. The conformational restriction for tertiary allylic alcohols poised for a Wagner–Meerwein transposition comes from the positioning of the hydroxy group synclinal to the alkene as to ensure the required orthogonality between the migrating C–C bond and the alkene.

Furthermore, the herein disclosed enantioselective fluorination/semipinacol rearrangement cascade was readily amenable to scale-up. In one experiment, the allylic alcohol **A15** (540 mg, 2.5 mmol) was converted into the corresponding β-fluoro spiroketone **B15** with excellent stereoselectivity and as low as 2.5 mol% loading of the catalyst **L6** (Scheme 3).



Scheme 3. A useful synthetic application of the β-fluoro spiroketone **B15**, and the X-ray crystal structure of **C15**.[21] The values in brackets show yields and enantiomer ratios after recrystallization. DMF = *N*,*N*-dimethylformamide, MMPP = magnesium mono(peroxyphthalate).

The desired product could be recovered in diastereo- and enantiomerically pure form with 78% yield after a single recrystallization from *n*-hexane/Et_2O. Subsequently, this strained spiro-cyclobutanone underwent smooth Baeyer–Villiger oxidation to the spiro-γ-lactone **C15** with complete retention of relative and absolute configurations. X-ray diffractometry was employed to confirm the stereochemical course of this transformation.[21]

In conclusion, we present here the first highly enantioselective organocatalytic Wagner–Meerwein rearrangement of strained allylic alcohols initiated by an electrophilic fluorination event. All reactions were catalyzed by our new chiral phosphoric acid **L6**, which is derived from (R_a)-binol. The substrate scope encompasses both allylic cyclobutanols and allylic cyclopropanols based on the tetralone as well as the chromanone scaffolds, with electron-releasing, electron-neutral, and moderately electron-withdrawing substituents at C5 and C6. All stereochemical assignments of products were generously supported by X-ray crystallography.[21] Furthermore, **B15** was amenable to derivatization through a stereospecific Baeyer–Villiger oxidation, thus nicely demonstrating the synthetic relevance of the product β-fluoro spiroketones. Work aimed at extending the scope of the title transformation, in concert with carrying out computational studies to gain insight into the origins of stereoselectivity is currently underway in our laboratory.

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