Asymmetric Fluorination

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Enantioselective Fluoroamination: 1,4-Addition to Conjugated Dienes Using Anionic Phase-Transfer Catalysis**

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The halogen-promoted cyclization reactions of alkenes is an invaluable method for synthetic chemistry, generating carbon–heteroatom bonds and providing access to a wide range of products from relatively simple starting materials.[1] Recently, the development of enantioselective versions of these reactions has become a topic of considerable interest for the synthetic community,[2] as these reactions allow for the generation of vicinal stereocenters.[3] Extension of this reactivity to enantioselective 1,4-halofunctionalization of 1,3-dienes requires controlling regio- (1,2- vs. 1,4-functionalization) and diastereoselectivity (*syn* vs. *anti*; Figure 1). While

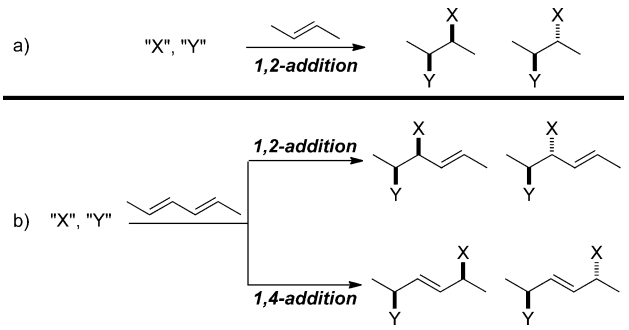

Figure 1. Possible diastereomers resulting from 1,2- or 1,4-addition to an acyclic olefin (a) or diene (b).

enantioselective oxidative 1,4-difunctionlization reactions of conjugated dienes have been reported,[4] enantioselective 1,4-halofunctionalization reactions of 1,3-dienes have yet to be developed.[5]

Previous examples of 1,4-halofunctionalization reactions have mainly utilized chlorine, bromine, or iodine electrophiles in the presence of oxygen or nitrogen nucleophiles.[6] Due to their unique biological activity, the synthesis of fluorine containing small molecules has recently received a significant amount of interest.[7] Aminofluorination, owing to the ubiquity of amines as bioactive motifs, has been an especially desirable transformation. While electrophilic fluorination of olefins with oxygen nucleophiles has been well-precedented,[8,9] reports using nitrogen nucleophiles have been rare.[10–12] Previous examples of enantioselective aminofluorination reactions of isolated olefins have been disclosed, but to the best of our knowledge the analogous transformation utilizing 1,3-dienes is unknown. Herein we report the first catalytic asymmetric 1,4-aminofluorination of conjugated dienes using chiral-anion phase-transfer catalysis.[13]

Substrates of type **1** (Table 1) were chosen for this investigation in the hope of achieving the desired fluoroamination reaction. If successful, the 6-*endo*-trig fluoroamination of diene substrate **1a** would produce an allylic fluoride, an important scaffold in many areas of chemistry.[14] Additionally, these products are fluorinated analogues of pharmacologically relevant benz[*f*]isoquinolines,[15] and because of the unique pharmacological effect of substituting a fluorine for a hydrogen atom, products of this reaction could be quite interesting for biological studies.

With substrate **1a** in hand, phase-transfer fluorination was attempted using Selectfluor (**3a**), Na_2CO_3, and (*R*)-TRIP (10 mol%) in fluorobenzene (Table 1, entry 3) without special precautions to exclude air or water. To our delight, the desired 1,4-fluoroamination product was formed, albeit with poor selectivity (37% *ee*). After this encouraging result, additional BINOL-derivatives were examined as phase-transfer catalysts in hopes of enhancing the solubility and selectivity of the fluorinating reagent without compromising reactivity. The (*R*)-TCYP (entry 2) emerged as the optimal catalyst, producing **2a** in the highest enantiomeric excess.

Drastic effects on reactivity and selectivity were observed depending on the identity and stoichiometry of the base employed. Initial studies performed using sodium carbonate (Na_2CO_3) as an insoluble base suffered from poor conversion (Table 1, entries 1–6). Other insoluble bases were then evaluated to alleviate this problem. Various sodium salts were chosen with basicities similar to Na_2CO_3. Sodium sulfite (entry 7) did not perform as well as sodium carbonate, while the use of dibasic sodium phosphate did not afford any of the desired product (entry 8). However, tribasic sodium phosphate (Na_3PO_4) resulted in 100% conversion of the starting material (entry 9), forming the product in 82% *ee*. By lowering the stoichiometry of the base in the reaction, the enantioselectivity could be further improved to 89% *ee* with full conversion of the starting material in fluorobenzene (entry 10). Subsequent solvent and concentration screening revealed that α,α,α-trifluorotoluene ($PhCF_3$) was the ideal solvent for the transformation (entries 11–14), affording **2a** in 96% *ee* with complete conversion of the starting material (entry 13).

The configuration and absolute stereochemistry of the major diastereomer was determined unambiguously by X-ray

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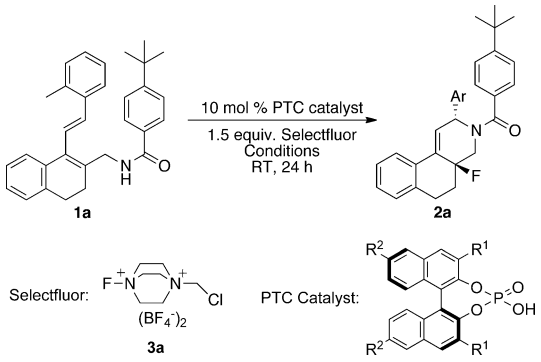
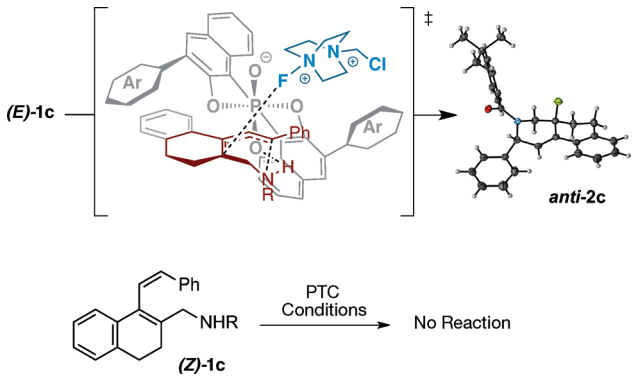
Table 1: Optimization of reaction conditions.



Entry	R^1	R^2	Base (Equiv)	Solvent, [M]	Conversion [%][a]	*ee* [%][b]
1	3,5-$(CF_3)_2C_6H_3$	H	Na_2CO_3 (1.5)	PhF, [0.05]	30	46
2	2,4,6-$(Cy)_3C_6H_2$	H	Na_2CO_3 (1.5)	PhF, [0.05]	50	92
3	2,4,6-$(iPr)_3C_6H_2$	H	Na_2CO_3 (1.5)	PhF, [0.05]	50	37
4	2,4,6-$(iPr)_3C_6H_2$	H	Na_2CO_3 (1.5)	PhF, [0.05]	80	50
5	2,4,6-$(Cy)_3C_6H_2$	C_8H_{17}	Na_2CO_3 (1.5)	PhF, [0.05]	70	88
6	Ph_3Si	C_8H_{17}	Na_2CO_3 (1.5)	PhF, [0.05]	100	16
7	2,4,6-$(Cy)_3C_6H_2$	$C_{12}H_{25}$	Na_2SO_4 (1.5)	PhF, [0.05]	33	80
8	2,4,6-$(Cy)_3C_6H_2$	H	Na_2HPO_4 (1.5)	PhF, [0.05]	0	–
9	2,4,6-$(Cy)_3C_6H_2$	H	Na_3PO_4 (1.5)	PhF, [0.05]	100	82
10	2,4,6-$(Cy)_3C_6H_2$	H	Na_3PO_4 (1.25)	PhF, [0.05]	100	89
11	2,4,6-$(Cy)_3C_6H_2$	H	Na_3PO_4 (1.25)	$PhCF_3$, [0.05]	50	93
12	2,4,6-$(Cy)_3C_6H_2$	H	Na_3PO_4 (1.1)	$PhCF_3$, [0.05]	73	91
13	2,4,6-$(Cy)_3C_6H_2$	H	Na_3PO_4 (1.1)	$PhCF_3$, [0.10]	100	96
14	2,4,6-$(Cy)_3C_6H_2$	H	Na_3PO_4 (1.0)	$PhCF_3$, [0.10]	56	97

[a] Conversion determined by integration of ^{1}H NMR spectra with internal standard. [b] % *ee* determined by chiral-phase HPLC. Cy = cyclohexyl, *i*Pr = 2-propyl, Ph = phenyl.

crystallography of derivative **2c** and shows that the aryl group and the fluorine atom are *anti* on the newly formed heterocycle (Scheme 1). The transition-state model in Scheme 1 accounts for the observed stereochemistry of the fluorine stereocenter and is consistent with our previously established model for enantioselective fluorination.[13d,e] We hypothesized that the diastereoselectivity could either arise from selective *anti*-1,4-addition to the diene or through a stepwise process that generates an equilibrating allyl cation in which one isomer reacts preferentially. To distinguish these possibilities (*Z*)-**1c** was subjected to the optimized reaction conditions and showed no reactivity. This observation is most consistent with a concerted process that is prevented by the increased $A^{1,3}$ strain in the transition state for cyclization of (*Z*)-**1c**.



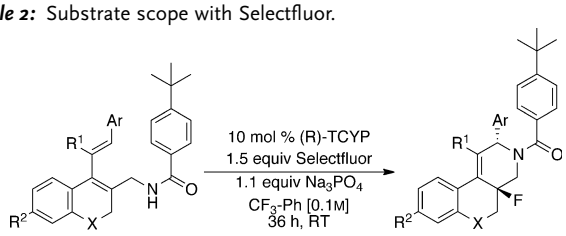
Scheme 1. Suggested origin of diastereo- and regioselectivity.

Having achieved an optimized set of conditions, the scope of the fluoroamination was examined for various 1,3-dienes. Substitution at various positions on the aryl ring of the styrenyl fragment was well-tolerated (Table 2). A methyl group at the *ortho* position displays the highest selectivity of 96% *ee* with >20:1 d.r. (Table 2, entry 1). However, a methyl group at the *meta* position (entry 2) or an unsubstituted phenyl ring (entry 3) gives slightly lower selectivity but with no loss in yield. Furthermore, without the *ortho* substitution, the diastereoselectivity for the products **2b** and **2c** drops to 5.9:1 and 6.9:1, respectively. Dienes containing both electron-rich and electron-poor aryl groups are viable substrates in the fluoroamination reaction (entries 6 and 7) exhibiting excellent enantiomeric excesses and increases in diastereoselectivity relative to an electronically neutral phenyl ring.

An electron-rich tetralone derivative (entry 4) exhibited excellent selectivity and reactivity (93% *ee*, 90% yield); however a slight reduction in selectivity and yield is observed for a chromanone-based substrate (entry 5). The reaction also proved to be amenable towards a trisubstituted styrene derivative (entry 8), forming compound **2h** in excellent selectivity (94% *ee*, >20:1 d.r.).

Substrates **1d** and **1e** highlight the mildness of the reaction conditions. These electron-rich substrates decom-

Table 2: Substrate scope with Selectfluor.



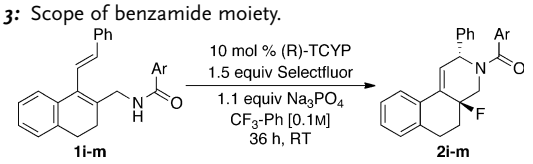
Entry	Product	Ar	R^1	R^2	R^2	Yield [%][a]	ee [%][b]	d.r.[c]
1	**2a**	2-MeC_6H_4	H	H	-CH_2-	91	96	>20:1
2	**2b**	3-MeC_6H_4	H	H	-CH_2-	92	92	5.9:1
3	**2c**	C_6H_5	H	H	-CH_2-	90	92	6.9:1
4	**2d**	C_6H_5	H	OMe	-CH_2-	90	93	6.9:1
5	**2e**	C_6H_5	H	H	O	85	91	5.5:1
6	**2f**	4-$CF_3C_6H_4$	H	H	-CH_2-	94	95	10:1
7	**2g**	4-$MeOC_6H_4$	H	H	-CH_2-	89	93	7.5:1
8[d]	**2h**	C_6H_5	*n*Bu	H	-CH_2-	85	94	>20:1

[a] Yield given after purification as a combination of both diastereomers. [b] % *ee* determined by chiral-phase HPLC. [c] d.r. calculated by integration of ^{1}H NMR spectra. [d] Reaction run in benzene.

pose in a homogeneous acetonitrile solution of Selectfluor. However, the phase-transfer conditions allow for clean fluoroaminations in high yields with no observable decomposition products.

Although far from the reactive center, substitution on the benzamide arene exerts a surprisingly strong influence on selectivity. The results in Table 3 highlight the advantage of

Table 3: Scope of benzamide moiety.



1i-m **2i-m**

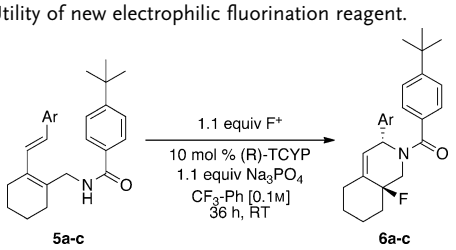
Entry	Product	Ar	Yield [%][a]	*ee* [%][b]	d.r.[c]
1	**2i**	C_6H_5	95	86	6.3:1
2	**2j**	4-BrC_6H_4	96	92	8.7:1
3	**2k**	3,5-$(MeO)_2C_6H_3$	97	90	7.5:1
4	**2l**	3,5-$(CF_3)_2C_6H_3$	82	88	8.8:1
5	**2m**	2,4,6-$(Me)_3C_6H_2$	0	–	–

[a] Yield given after purification as a combination of both diastereomers. [b] % *ee* determined by chiral-phase HPLC. [c] d.r. calculated by integration of ^{1}H NMR spectra.

using the 4-*tert*-butylbenzamide as the nucleophile. For example, removal of all substitution on the benzamide aryl ring afforded the product in 86% *ee* (Table 3, entry 1). Selectivity is increased to 88–90% *ee* as substituents are added to the *meta* positions of the benzamide (entries 3 and 4), with a further enhancement to 92% *ee* when it is *para*-substituted (Table 3, entry 2). Conversely, the benzamide **2m** (Table 3, entry 5) containing methyl groups at both *ortho* positions of the phenyl ring is unreactive under the reaction conditions, as this substitution pattern twists the aryl ring out of the amide plane.[16]

Our attention then focused on the fluorocyclization of a less-reactive diene of type **5** (Table 4). When subjected to the optimized reaction conditions using Selectfluor as the electrophilic fluorine source, diene **5a** reacted sluggishly, affording racemic product with very low conversion (Table 4, entry 1). We hypothesized that the electrophilicity of the fluorine source could be increased by attaching an electron-poor aryl group, which is more electron-deficient than the chlorine atom on Selectfluor. Previous syntheses of Selectfluor and its derivatives required the use of elemental fluorine to install the fluorine atom onto dabconium intermediates.[17] To avoid the use of elemental fluorine, we developed a facile method for preparation of novel Selectfluor-type derivatives. By treating the known tetrafluoroborate salts **4** with XeF_2, different Selectfluor derivatives were synthesized in decent yields (Scheme 2). Whereas Selectfluor was not synthetically useful in the fluoroamination reaction with diene **5a**, we were pleased to find that reagent **3b** outperformed Selectfluor and derivative **3c**, affording the octahydroisoquinoline product **6a** in good yield with 76% enantiomeric excess (Table 4, entry 2). Substrate **6b**, containing an *ortho*-methyl substituent on the tethered phenyl ring, also underwent the desired

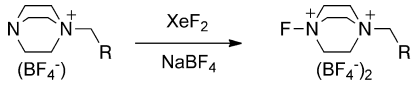
Table 4: Utility of new electrophilic fluorination reagent.



5a-c **6a-c**

Entry	F^+ Source	Product	Ar	Yield [%][a]	*ee* [%][b]	d.r.[c]
1	**3a**[d]	**6a**	C_6H_5	<10	0	–
2	**3b**	**6a**	C_6H_5	70	76	14:1
3	**3c**	**6a**	C_6H_5	15	5	–
4	**3b**	**6b**	2-MeC_6H_4	65	73	8.3:1
5	**3b**	**6c**	4-$CF_3C_6H_4$	75	89	>20:1

[a] Yield of isolated product given as combination of two diastereomers. [b] *ee* determined by chiral-phase HPLC; given as average of two runs. [c] d.r. calculated by integration of ^{19}F NMR spectra. [d] 1.5 equiv of **3a** used.



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3b: R = 3,5-$(CF_3)_2C_6H_3$ (51 % yield)
3c: R = C_6F_5 (29 % yield)

Scheme 2. Preparation of new electrophilic fluorinating reagents.

transformation with **3b**, albeit with modest yield and enantioselectivity (entry 4). However, the electron-deficient species **5c** produced the cyclized product with the highest levels of enantioselectivity (89% *ee*) for this substrate class (entry 5).

In conclusion, enantioselective 1,4-aminofluorocyclization of 1,3-dienes was developed using lipophilic chiral phosphates as anionic phase-transfer catalysts. The mild reaction conditions allow for the fluorination of substrates that are typically incompatible with homogeneous Selectfluor conditions. Despite the synthetic challenges of 1,4-functionalization of these conjugated dienes, exclusive formation of the 6-*endo*-trig cyclization was observed with varying levels of diastereoselectivity. The resulting benz[*f*]isoquinoline derivatives were formed with high levels of enantiomeric excess, providing the first reported example of a metal-free catalytic asymmetric 1,4-fluoroamination of conjugated dienes. This reaction also expands the scope of competent nucleophiles in our previously published PTC halocylization reactions to nitrogen nucleophiles. Furthermore, a novel method for the fluorination of dabconium salts was utilized to prepare a new Selectfluor type derivative that was shown to have increased reactivity relative to Selectfluor in preparing octahydroisoquinoline derivatives.

Experimental Section

General procedure for PTC reactions: Amide **1a** (0.03 mmol, 11.0 mg), Selectfluor (0.045 mmol, 16.0 mg, 1.5 equiv), Na_3PO_4 (0.033 mmol, 5.4 mg, 1.1 equiv), (*R*)-TCYP catalyst (0.003 mmol, 3.0 mg, 0.1 equiv), and a magnetic stir bar were added to a 3 mL

reaction vial. Trifluoromethylbenzene (0.3 mL) was then added to this mixture and the reaction was stirred vigorously (> 360 rpm) for 36 h. During this time, the vial was periodically shaken to agitate material adhered to the sides of the vial. After 36 h, saturated sodium thiosulfate (1 mL) and water (1 mL) were added to quench the reaction. The mixture was subsequently extracted with CH_2Cl_2 (3 × 3 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude material was then purified by SiO_2 chromatography with hexanes:CH_2Cl_2:Et_2O (60:35:5 to 50:40:10) ($R_f \approx 0.45$ in 50:40:10). Product **2a** was isolated as a white solid in 91% yield as a mixture of two diastereomers (0.025 mmol, 12.0 mg, > 20:1 d.r.).

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