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Fluorination **Hot Paper**

Regio- and Enantioselective Intermolecular Aminofluorination of Alkenes via Iodine(I)/Iodine(III) Catalysis**

*Michael Schäfer, Timo Stünkel, Constantin G. Daniliuc, and Ryan Gilmour**

Dedicated to Professor Alois Fürstner on the occasion of his 60th birthday

Abstract: The regio- and enantio-selective, intermolecular *vicinal* fluoroamination of α-trifluoromethyl styrenes has been achieved by enantioselective I^I/I^{III} catalysis. Leveraging C_2-symmetric resorcinol-based aryl iodide catalysts, it has been possible to intercept the transient iodonium intermediate using simple nitriles, which function as both the solvent and nucleophile. In situ Ritter reaction provides direct access to the corresponding amides (up to 89 % yield, *e.r.* 93:7). This main group catalysis paradigm inverts the intrinsic regioselectivity of the uncatalyzed process, thereby providing facile access to tertiary, benzylic stereocenters bearing both CF_3 and F groups. Privileged phenethylamine pharmacophores can be generated in which there is complete local partial charge inversion ($CF_3^{\delta-}/F^{\delta-}$ versus $CH_3^{\delta+}/H^{\delta+}$). Crystallographic analyses of representative β-fluoroamide products reveal highly pre-organized conformations that manifest the stereoelectronic *gauche* effect.

Introduction

Of the plenum of structural editing strategies commonly leveraged in functional small molecule discovery, fluorination enjoys a privileged role in the vanguard.[1,2] This is reflected by ever-increasing incursions into unchartered 3D organofluorine chemical space[3] to address the urgent demand for next generation pharmacophores. Sustaining innovation is, however, conditional on the conception of enabling technologies to access new motifs with unprecedented physicochemical signatures.[4] The prominence of stereochemically rich, fluorinated motifs in contemporary medicinal chemistry is a compelling manifestation of this synergy,[5,6] which provides an opportunity for creative endeavor in the field of stereoselective catalysis.[7] Alkene fluorofunctionalization has a venerable history in this regard, enabling chiral antipodes to be generated *ad arbitrium* from readily accessible precursors.[8] Motivated by the prevalence of $F–C_\beta–C_\alpha–N$ motifs across the pharmaceutical, agrochemical and catalysis spectrum,[9] *vicinal* fluoroamination has been particularly important in this evolution. Successfully addressing the regio- and stereo-selectivity challenges associated with this direct approach allows the physicochemical advantages conferred by fluorination to be harnessed: these effects are inextricably linked to the conformational behavior of β-fluoroamine derivatives, where stabilizing hyperconjugative interactions manifest themselves in the venerable stereoelectronic *gauche* effect (**1**) (Scheme 1A).[10] Seminal studies by O'Hagan and co-workers have established that acyclic β-fluoroamides (**2**) adopt *syn-clinal* conformations which are favored by ca. 1.8 kcal mol^{-1}.[11] This is further amplified in charged species (**3**), where reinforcing stereoelectronic and electrostatic contributions favor the (fluorine-ammonium ion) *gauche* conformation by 5.8 kcal mol^{-1}.[12]

A striking example of the translational potential of the fluorine-amide *gauche* effect in modulating biomolecule behavior is the report of hyperstability in fluorinated collagen (**4**) by Raines and co-workers.[13] The biomedical importance of β-fluoroamine derivatives is also noteworthy (e.g. phenethylamines such as adrenaline) and has led to the achiral fluoroamination of styrenes, using nitriles as latent amines, having been intensively pursued (Scheme 1B). Seminal contributions from Zupan,[14] Shreeve,[15] Chandrakanth[16] and Wang[17] have established strategies to favor the α-fluorinated regioisomer. In contrast, Nevado and co-workers have shown that the β-fluorinated isomer can be generated by using a stoichiometric hypervalent iodine species in the presence of a limiting external amine.[18] In the ensuing decade, advances in main group reagent- and catalysis-based fluorination have afforded opportunities for creative endeavor in developing effective fluorocyclization processes to access coveted β-fluoroamines.[19–22] Most recently, chiral I^I/I^{III} catalysis has been leveraged by Jacobsen and co-workers to enable a highly stereoselective fluoroaziridination of cinnamyl amine derivatives,[23] and by Szabó and co-workers in the development of an efficient fluorocyclization route to generate nosyl-protected pyrrolidines.[24]

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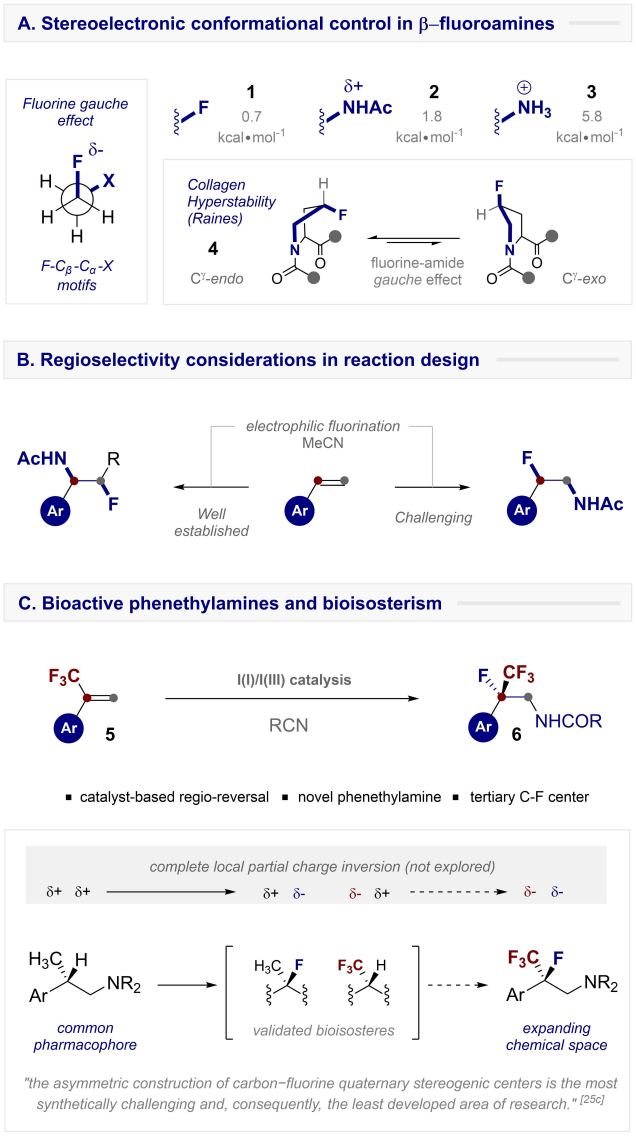
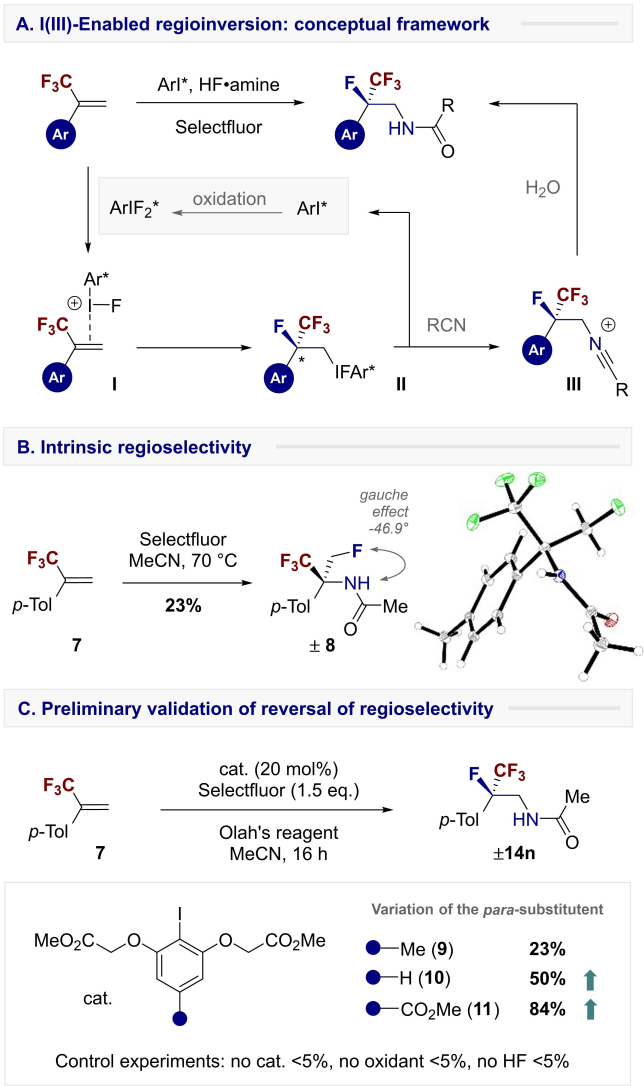


Scheme 1. The conformational behavior and synthesis routes to β-fluoroamine derivatives.

To complement these fluorocyclization strategies, and further expand organofluorine chemical space to target an unprecedented motif, an intermolecular aminofluorination of α-trifluoromethyl styrenes was investigated (Scheme 1C). This would provide a platform to complete the $H^{\delta+}/CH_3^{\delta+}$, $F^{\delta-}/CH_3^{\delta+}$, $H^{\delta+}/CF_3^{\delta-}$, $F^{\delta-}/CF_3^{\delta-}$ continuum in phenethylamine pharmacophores (Scheme 1C, **5**→**6**) and address the pressing issues of regiocontrol and the enantiocontrolled construction of tertiary C(sp^3)–F centers.[25] Although α-trifluoromethyl styrenes are electronically deactivated, it was envisaged that iodine(III) activation would facilitate regiocontrolled fluorination,[26] with an external nitrile serving as both solvent and nucleophile. Moreover, the presence of the α–CF_3 group would mitigate phenonium ion rearrangement that would ultimately generate the *geminal* difluoride product.[26k,m] This strategy would circumvent the reactivity constraints imposed when using amines in I^I/I^{III}-based oxidative fluorination reactions, and mitigate fragmentation risks that are often observed in carbanionic manipulations.[27]

The conceptual framework for the title transformation centered upon in situ generation of a chiral $ArIF_2$ species[28] to engage the alkene and orchestrate an enantiodetermining C(sp^3)–F bond forming event (Scheme 2A. **I**→**II**): this would override the anticipated substrate-based regiocontrol (see Schemes 1B and 2B). Judicious choice of nitrile solvent or additive would then enable a subsequent Ritter reaction (**III**)[29] to close the catalytic cycle and install a protected amine, which would be amenable to downstream functionalization.



Scheme 2. Conceptual framework and exploration of reactivity and selectivity. Reaction conditions for the conversion of **7**→**8**: Alkene (1 mmol), MeCN (15 mL), Selectfluor® (1.1 mmol), 70 °C, 4 d. General conditions for catalyst optimization: alkene **7** (0.2 mmol), catalyst **9**–**11** (20 mol%), Olah's reagent (0.5 mL), MeCN (0.5 mL) and Selectfluor® (0.3 mmol), CCDC (**8**) 2155710.[31] Yield and conversion were determined by ^{19}F NMR using trifluorotoluene as internal standard.

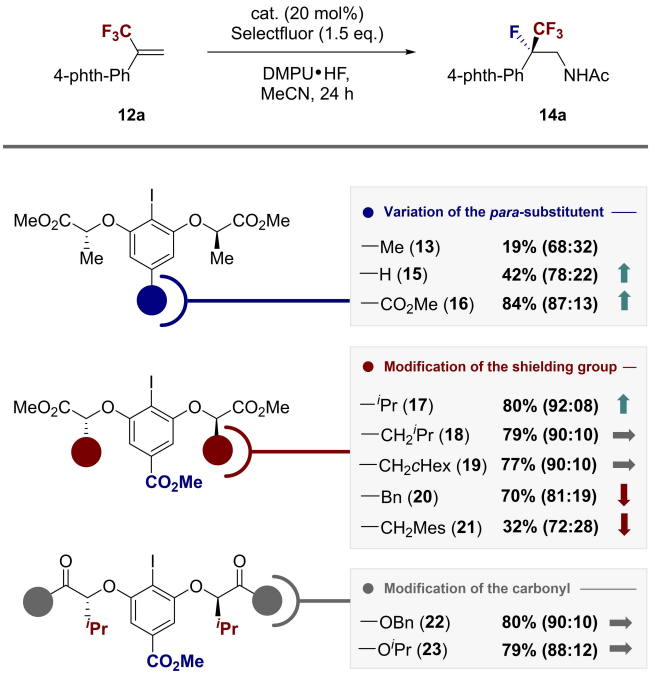
Results and Discussion

To enable a comparison of the regiochemical course of the catalyzed and uncatalyzed aminofluorination of α-trifluoromethylstyrenes, substrate **7** was initially exposed to Selectfluor® in MeCN at 70 °C. This led to exclusive formation of the undesired product **8**, which is in full agreement with the regioselectivity in the fluorofunctionalization of styrenes with Selectfluor® as reported by Lal.[30] It was possible to isolate crystals of **8** that were suitable for X-ray analysis, thus unequivocally establishing the molecular connectivity (Scheme 2B, right, CCDC 2155710).[31] A pertinent feature of the structure is a −46.9° dihedral angle of F–C_β–C_α–N motif, which is consistent with the stereoelectronic *gauche* effect.

To access the desired, antipodal regioisomer,[32] and to demonstrate the feasibility of a catalytic process, simple aryl iodides (**9**–**11**) were explored as organocatalysts (Scheme 2C). In contrast to the elevated temperatures required for the uncatalyzed process, these reactions were conducted at ambient temperature using Selectfluor® as an oxidant and Olah's reagent as the fluoride source and Brønsted acid activator.[33] MeCN was employed as both the reaction medium and masked, aprotic amine source. Gratifyingly, a steady improvement in catalyst performance was observed in the order **9** (23 %) < **10** (50 %) < **11** (84 %). Control reactions where the catalyst, oxidant and HF were systematically removed were unproductive (< 5 %) thereby supporting the involvement of an I^I/I^{III} cycle.

This preliminary validation of catalysis was then advanced to explore the feasibility of an asymmetric variant and establish the scope and limitations of the approach (Scheme 3). For this purpose, the phthalimide substrate **12a** was used to provide a *bis*-*N*-protected linchpin that would be amenable to downstream functionalization. Exploratory reactions (**12a**→**14a**) using Olah's reagent prompted us to explore the more Brønsted acidic DMPU·HF as a fluoride source.[34] A process of catalyst editing was initiated using the lactate-based scaffolds **13**, **15**, **16**. This revealed a similar trend to Scheme 2c both in terms of efficiency and enantioselectivity. Modification of the pendant lactate chain was then conducted starting from the core structure **16** (84 %, 87:13 *e.r.*). Increasing the bulk of the group had a positive effect on catalysis (**17**, 80 % yield, 92:08 *e.r.*). Comparable performances were noted for catalysts **18** and **19** (90:10 *e.r.*). Installing aromatic groups proved to be unsuccessful and led to drops in both yield and selectivity (catalysts **20** and **21**). In the final phase of editing, the impact of modifying the ester substituent in **17** was examined (catalysts **22** and **23**). This had little effect on the catalysis and thus catalyst **17** was utilized for the remainder of this study.

A series of control experiments were then conducted to explore the impact of several key variables (Scheme 3, Table). Switching the oxidant to *m*-CPBA led to a ca. 10 % reduction in efficiency (entry 1). The transformation was found to be sensitive to changes in the HF source (i.e. Brønsted acidity) (entry 2). Attempts to enhance the enantioselectivity through temperature regulation led to

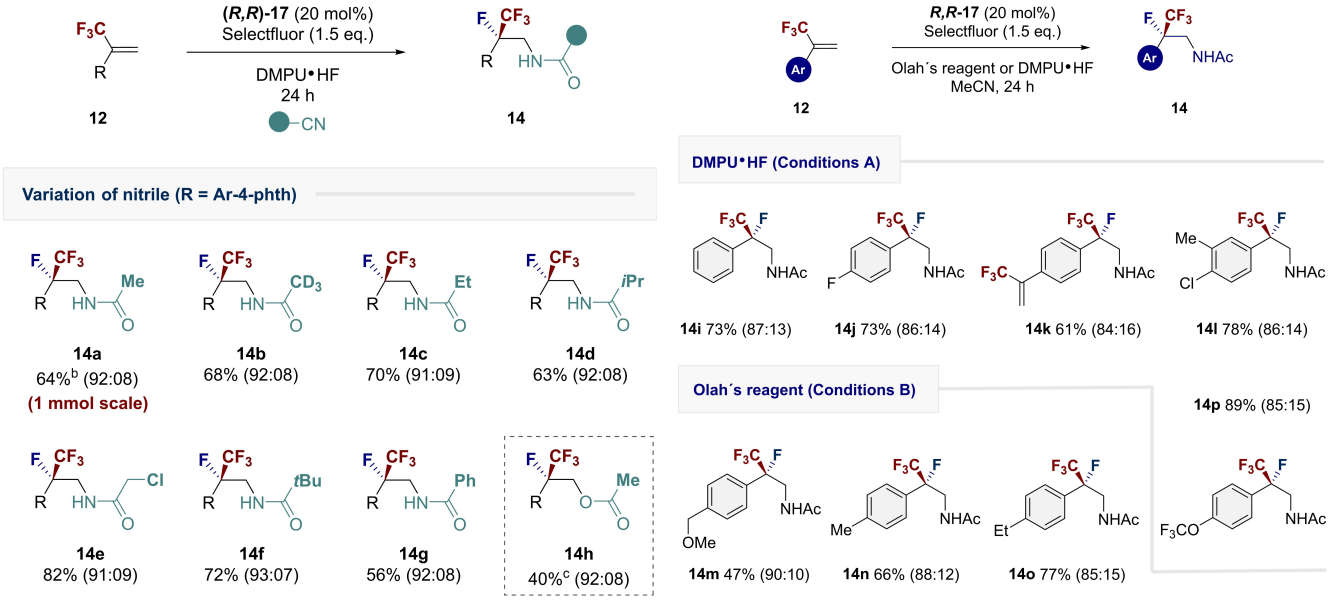


Entry	Modified conditions	Yield (Conv.)[a]	*e.r.*
1	*m*-CPBA as oxidant	64% (>95%)	91:09
2	Olah's reagent	72% (93%)	91:09
3[b]	Reaction at 0 °C	29% (32%)	93:07
4[c]	Reaction at −10 °C	15% (30%)	94:06
5	Reaction with 10 mol% **17**	81% (>95%)	88:12

Scheme 3. Catalyst and reaction optimization for the intermolecular, enantioselective aminofluorination. Standard conditions: alkene (0.2 mmol), Cat. ArI (20 mol %), HF-source (0.5 mL), MeCN (0.5 mL) and Selectfluor® (0.3 mmol). [a] Yield and conversion were determined by ^{19}F NMR using trifluorotoluene as the internal standard, and *e.r.* (in parentheses) was determined by chiral HPLC. [b] Reaction time increased to 48 h. [c] Reaction time increased to 72 h. The enantiomer of **14a** shown was arbitrarily chosen.

modest improvements (entries 3 and 4, up to 94:06 *e.r.*), but lower yields and long reaction times were required. Finally, it was possible to lower the catalyst loading to 10 mol % without significantly impacting efficiency (entry 5).

With optimized conditions in hand, the effect of the nitrile reaction partner was explored with a view to generating structurally diverse amides (Scheme 4). A high degree of tolerance was observed in this regard as is evident from products **14a**–**h** (up to 93:07 *e.r.*). Alkyl nitriles proved to be highly competent partners in this aminofluorination, enabling products **14b** (CD_3), **14c** (Et) and **14d** (*i*Pr) to be generated with comparable efficiency as **14a**. The inclusion of the α-Cl substituent (**14e**, 91:09 *e.r.*) provides a handle for further derivatization and demonstrates the compatibility of the process with sensitive groups. The addition of pivalonitrile enabled the generation of **14f** with an enantiomeric ratio of 93:07 and the benzonitrile-derived product **14g** was formed with appreciable levels of selectivity (92:08 *e.r.*). In a final twist of fate, replacing acetonitrile with acetic



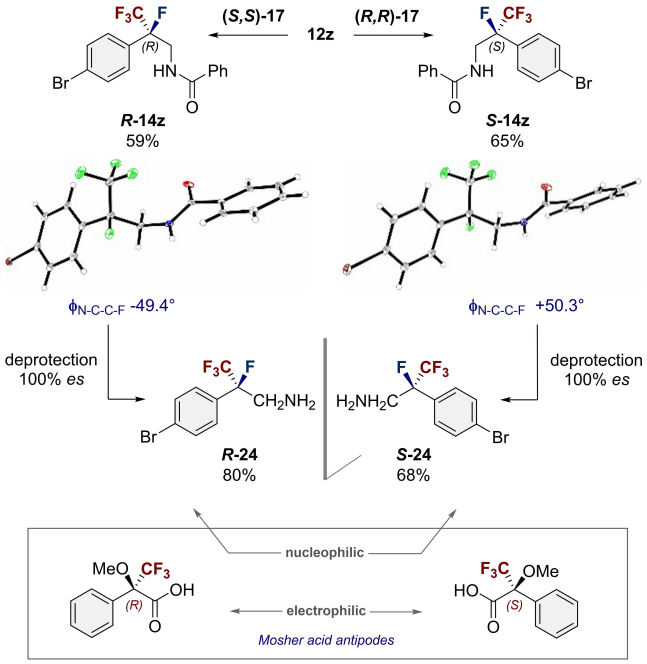
Scheme 4. Exploring the impact of the nitrile on the enantioselective aminofluorination of α-CF_3 styrenes. General catalysis conditions: Alkene (0.2 mmol), **17** (20 mol%), DMPU·HF (0.5 mL), RCN (0.5 mL) and Selectfluor® (0.3 mmol). Yield refers to isolated yields. Enantioselectivity was determined by chiral HPLC. [b] 1 mmol scale. [c] AcOH (0.5 mL) was used instead of RCN and Olah's reagent was used instead of DMPU·HF.

Scheme 5. Exploring the effect of the aryl group on the enantioselective aminofluorination of α-CF_3 styrenes. General catalysis conditions: Alkene **12** (0.2 mmol), **17** (20 mol%), DMPU·HF or Olah's reagent (0.5 mL), MeCN (0.5 mL) and Selectfluor® (0.3 mmol). Yield refers to isolated yields. Enantioselectivity was determined by chiral HPLC.

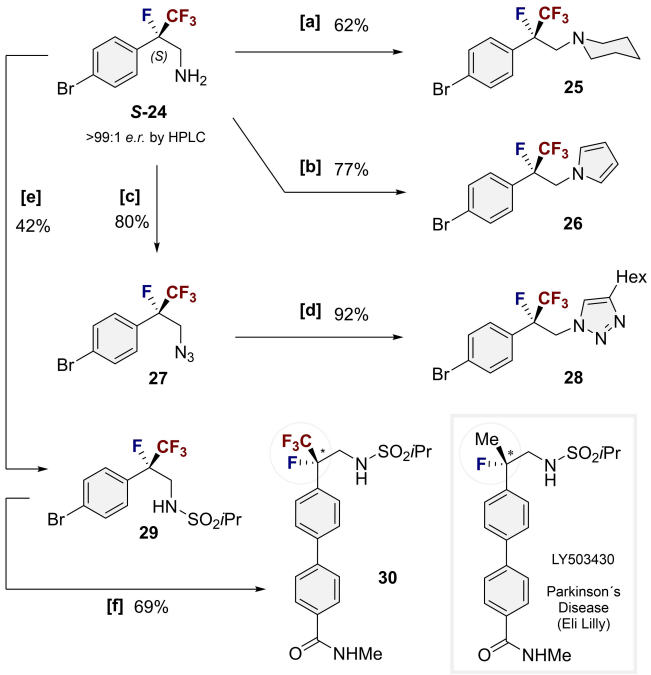
acid enabled a *vicinal* oxyfluorination (**14h**, 92:08 *e.r.*) further underscoring the utility of alkene fluorofunctionalization under the auspices of I^I/I^{III} catalysis.

The competency of catalyst **17** in enabling the *vicinal* fluoroamination of various α-trifluoromethylstyrenes was then investigated using MeCN as the nucleophilic partner (Scheme 5). During this study, two sets of conditions were developed using either DMPU·HF or Olah's reagent as the fluoride source (Conditions A and B, respectively). Under conditions A, the parent scaffold **12i** (Ar = Ph) was smoothly converted to the corresponding amide (**14i**). This was also the case for the *p*-F system (**14j**) and for the selective monofunctionalization of the symmetric 1,4-*bis*(trifluoromethyl)styrene (**14k**). The introduction of a disubstituted aryl ring was equally well tolerated (**14l**) and comparable levels of efficiency and selectivity were noted. Tempering the Brønsted acidity (Conditions B) allowed the scope of *p*-substituents to be further expanded to include the benzyl alcohol derivative **14m** and the Me and Et products **14n** and **14o** (up to 77% yield and 90:10 *e.r.*). It was also possible to generate the OCF_3 derivative using conditions A (**14p**). Extending the scope to 3,5-disubstituted styrenes was also unproblematic enabling products **14q** and **14r** to be generated with up to 91:09 *e.r.* The *m*-Me species **14s** and the estrone derivative **14t** could also be formed using this catalysis platform. Finally, inspired by the importance of fluorinated biphenyls in liquid crystal research,[35] a series of common motifs were examined. Gratifyingly, the products **14u**–**14y** could be forged with synthetically useful levels of efficiency (up to 72%) and selectivity (up to 90:10 *e.r.*).

For completeness, the opposite catalyst antipode **(*S,S*)-21** was prepared to enable facile generation of both product series. Substrate **12z**, bearing a $C(sp^2)$–Br group to enable subsequent derivatization, was then exposed to conditions A in the presence of catalysts **(*S,S*)-17** and **(*R,R*)-17** (Scheme 6). Products ***R*-14z** and ***S*-14z** were generated, respectively, and it was possible to grow crystals of both enantiomers to establish the absolute configuration by X-ray analysis.[36] In both cases, it is pertinent to note that an O'Hagan-type fluorine-amide *gauche* effect is observed.[11] Given the structural similarity of these two chiral antipodes to the venerable Mosher acids,[37] and the presence of two distinct fluorine environments, materials such as ***R*-** and ***S*-24** may find application as nucleophilic derivatizing agents for NMR spectroscopic investigations.



Scheme 6. Determination of the absolute configuration. Conditions: Alkene **12z** (0.2 mmol), catalyst (20 mol%), DMPU·HF (0.5 mL), benzonitrile (0.5 mL) and Selectfluor® (0.3 mmol). Yield refers to isolated yields. Enantioselectivity (86:14 e.r. and 14:86 *e.r.* for ***R*-14z** and ***S*-14z**, respectively) was determined by chiral HPLC. Deprotection: 1,4-dioxane (0.1 M), HCl (conc., 0.1 M), 120 °C. CCDC (***R*-14z**): 2155711, CCDC (***S*-14z**): 2155712.[36]



Scheme 7. Selected applications of the novel fluorinated phenethylamine ***S*-24**. Conditions: [a] 1,5-dibromopentane (1.3 equiv), K_2CO_3 (2.3 equiv), MeCN, 90 °C, 63 h; [b] NaOAc (1.0 equiv), 2,5-dimethoxytetrahydrofuran (1.1 equiv), AcOH:H_2O, 15 h, 80 °C; [c] 2-azido-1,3-dimethylimidazolium hexafluorophosphate (1.2 equiv), diethylamine (5.0 equiv), MeCN, 4 h, rt; [d] $CuSO_4$ (25 mol%), sodium ascorbate (0.5 equiv), 1-octyne (1.2 equiv), *t*BuOH:H_2O, 16 h, rt; [e] 2-propanesulfonyl chloride (1.2 equiv), DMAP (10 mol%), NEt_3 (2.0 equiv), CH_2Cl_2, 21 h, rt; [f] (4-(methylcarbamoyl) phenyl)boronic acid (2.0 equiv), $Pd(PPh_3)_2Cl_2$ (11 mol%), K_2CO_3 (10 equiv), H_2O:THF, 60 °C, 2 h.

To demonstrate the synthetic utility of this new phenethylamine derivative, ***S*-24** was processed to a selection of common heterocycles, including the piperidine **25** and pyrrole **26** (Scheme 7). Formation of the azide **27** proved facile, thereby providing a handle for 1,3-dipolar cycloaddition (**28**). Finally, ***S*-24** was leveraged in the synthesis of a CF_3 analog (**30**) of Eli Lilly's AMPA receptor positive allosteric modulator, LY-503430[38] which is currently being developed to treat Parkinson's Disease. In all cases, the optical purity of the starting material was preserved throughout (100% *es* as determined by HPLC).

Conclusion

In conclusion, a regio- and enantio-selective intermolecular fluoroamination of α–CF_3 styrenes has been achieved via I^I/I^{III} catalysis. This platform not only provides a solution to the enduring challenge of intermolecular fluoroamination,[39] but it also facilitates the generation of unprecedented tertiary CF_3-containing fluorides (up to 89% yield, *e.r.* 93:07). Hypervalent iodine catalysis is crucial to enable the intrinsic, substrate-based regiocontrol of the non-catalyzed process to be inverted, and nitriles are effective non-protic, masked amines under the standard conditions. Efforts to expand the scope and efficiency of the transformation are currently ongoing. Crystallographic analyses of the products revealed highly pre-organized conformations that allow for stabilizing hyperconjugative interactions. In view of the importance of *vicinal* fluoroamines and phenethylamine pharmacophores in contemporary drug discovery, it is envisaged that this addition to the portfolio will find application in expanding chemical space.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Catalysis · Fluorination · Hypervalent Iodine · Phenethylamine · Regioselectivity

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