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Electrochemically-Driven 1,4-Aryl Migration via Radical Fluoromethylation of N-allylbenzamides: a Straightforward Access to Functionalized β -Arylethylamines

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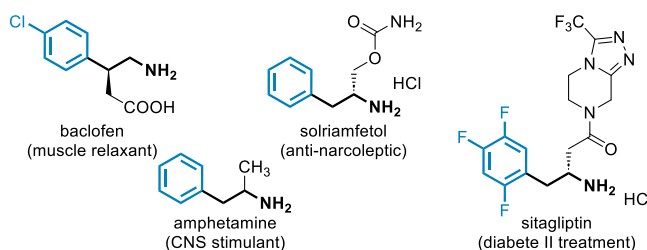
Abstract: An electrochemical radical Truce Smiles rearrangement of N-allylbenzamides is documented herein. The selective 1,4-aryl migration was triggered by the radical fluoromethylation of the alkene providing a direct route to fluoro derivatives of the highly privileged β -arylethylamine pharmacophore. This practical transformation utilizes readily available starting materials and employs an electrical current to drive the oxidative process under mild reaction conditions. It accommodates a variety of migratory aryl groups with different electronic properties and substitution patterns. Careful selection of the protecting group on the nitrogen atom of the N-allylbenzamide is crucial to outcompete the undesired 6-*endo* cyclization and achieve high level of selectivity towards the 1,4-aryl migration. DFT calculations support the reaction mechanism and unveil the origin of selectivity between the two competitive pathways.

Introduction

The radical Truce-Smiles rearrangement is a powerful transformation involving the migration of an aromatic ring to a carbon centered radical.^[1] An aryl group can therefore be regioselectively installed at a position that would be difficult to achieve under more classical approaches.^[2] The radical desulfonylative rearrangement of arylsulfonamides represents a particularly valuable application as it gives rise to the β -arylethylamine motif, a privileged pharmacophore prevalent in endogenous neurotransmitters and in several drugs treating the central nervous system disorders (antidepressants, psychostimulants, myorelaxants, antidiabetics... Figure 1a).^[3-4] Such a reaction initiates with the selective generation of a β -amino radical, triggering the aryl migration through a spirocyclic intermediate and the breaking of the C-S bound. Subsequent spontaneous SO₂ extrusion completes irreversibly the process (Figure 1b). Since the pioneering work of Speckamp *et al.*,^[5] various elegant methods have recently been developed to generate the crucial β -amino radical, usually under mild reaction conditions.^[6] Among them, we can cite a few recent examples of photocatalytic desulfonylative Truce-Smiles rearrangements of sulfonamides designed for the synthesis of β -arylethylamines. For

instance, Stephenson and co-workers harnessed visible light SET oxidation of electron rich styrene derivatives and subsequent addition of sulfonamide nitrogen atom for the production of various 1,1-diarylethylamines.^[6c-d] Greaney *et al.* introduced an elegant decarboxylation of β -sulfonamido ethanoic acids through visible-light energy transfer.^[6e] The same group documented a photocatalytic ring opening of N-cyclobutylsulfonamides via the β -scission of iminyl radicals.^[6f]

(a) Examples of the arylethylamine motif in drugs



(b) Arylethylamine access via radical Truce-Smiles rearrangement

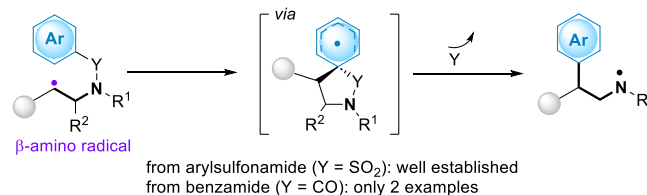


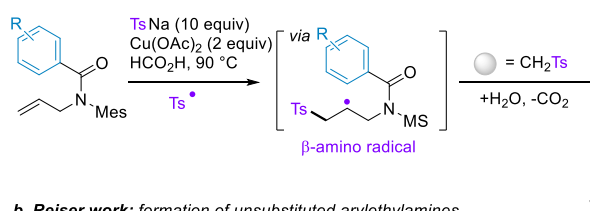
Figure 1. The radical Truce-Smiles rearrangement for the synthesis of arylethylamines.

The decarbonylative radical Truce-Smiles rearrangement of benzamides constitutes an attractive alternative to the traditional desulfonylative methods since the critical benzamides can be easily prepared from readily available benzoic acids. While very appealing, such a variant has been under-explored, with only two examples described so far.^[7] The first one, outlined by the Chuang group, involves the radical tosylation of N-allylbenzamides under harsh reaction conditions requiring a considerable excess of reagents and oxidants which limit synthetic applications (Scheme

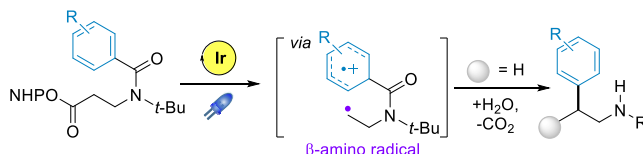
1a).^[7a] In contrast, the most recent one, disclosed by the Reiser group, utilizes mild conditions through the photocatalytic decarboxylation of designed N-acyloxyphthalimides but only produces unsubstituted arylethylamines (Scheme 1b).^[7b] Despite these achievements, there is still a significant need for the development of novel radical Smiles rearrangement, mild, and atom-economical procedure with a broader scope.

In this context, building on our previous works on radical electrochemical trifluoromethylation of allylic amines for constructing CF₃-containing azacycles,^[8] we envisioned the selective generation of the β-amino radical through the electrochemical trifluoromethylation^[9] of readily available N-allylbenzamides **1** with the Langlois reagent **2a**. This strategy would harness the electrons as safe and atom economic reagents to drive the oxidative radical process under mild reaction conditions.^[10] Moreover, it would provide an innovative and straightforward method for synthesising unprecedented fluoro-containing β-arylethylamines, which could have notable relevance considering the significance of both the fluorine atom^[11] and the β-arylethylamine motif in pharmaceutical compounds. However, several pitfalls must be avoided for a successful transformation. First, the addition of the β-amino radical to the aromatic ring has to be fast enough to prevent overoxidation on the anode surface. Secondly, although Chuang *et al.* reported the unique example of using N-allylbenzamides for 1,4-aryl migration, these substrates have mainly been explored for constructing dihydroisoquinolinone derivatives via radical 6-endo cyclization.^[12] For instance, Wang and Li *et al.* devised the photocatalytic oxidative radical cyclization of N-allyl benzamides with **2a** for the assembly of trifluoromethylated dihydroisoquinolinones.^[12b] Therefore, we questioned whether meticulous examinations of reaction parameters would allow to identify an efficient electrochemical system capable of selectively favour the 5-exo cyclization of the β-amino radical over the competitive 6-endo cyclization to promote the desired 1,4-aryl migration (Scheme 1c). Herein, we wish to report the development of an electrochemical trifluoromethylation and chlorodifluoromethylation of N-allylbenzamide derivatives triggering the selective migration of the aromatic ring to form relevant CF₂X-containing β-arylethylamines.

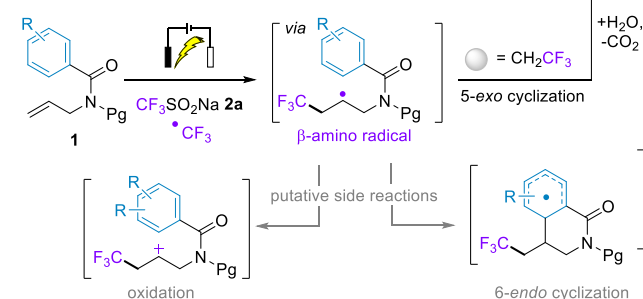
a. Chuang work: harsh reaction conditions



b. Reiser work: formation of unsubstituted arylethylamines



c. Our plan: mild and oxidant-free electrochemical approach formation of functionalized arylethylamines



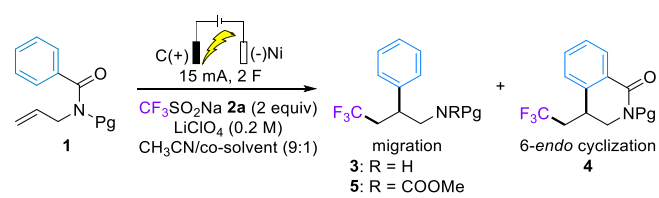
Scheme 1. Selective generation of a β-amino radical on benzamide for decarbonylative Truce-Smiles rearrangement. NHP: N-hydroxyphthalimide.

Results and Discussion

To assess the feasibility of the proposal, the electrochemical trifluoromethylation reaction of benzamides **1** was initially carried out in an undivided cell using the Langlois reagent **2a** as the trifluoromethyl source in a mixture of CH₃CN/H₂O. Different protecting groups on the N-atom of the benzamide were evaluated (Table 1, entries 1-4). The mesitylsulfonyl (Mes),^[7a] the *tert*-butoxycarbonyl (Boc) and the methoxy group proved unsuitable. A positive outcome was observed with the tosyl group (Ts), furnishing the desired phenylethylamine derivative **3b** in a 26% NMR yield, although in a 1:1 mixture with the dihydroisoquinolinone **4b**. Intriguingly, only the decarbonylative Truce-Smiles rearrangement took place, with no observed desulfonylative version.^[13] This encouraging result confirmed the high ability of benzamides to undergo aryl migration. To further improve the selectivity of the process toward the phenylethylamine formation, we decided to test the *tert*-butyl protecting group.^[7b] However, in case of success, this transformation would lead to the secondary dialkyl amine **3e** which could both undergo over-oxidation during the electrolysis^[14] and be difficult to isolate from the reaction mixture. To overcome these impediments, we envisaged the use of methanol as co-solvent instead of water with the aim to isolate the β-phenylethylamine derivatives under the form of the methylcarbamates **5**.^[15, 7b] This hypothesis was firstly validated with the N-tosyl protected benzamide **1b** which indeed afforded the methylcarbamate **5b** in 25% NMR yield. The latter was again

obtained in a 1:1 mixture with the dihydroisoquinolinone **4b** indicating that the co-solvent does not have any influence on the 5-*exo*/6-*endo* selectivity of the process. Gratefully, the *N*-*tert*-butyl protected benzamide **1e** gave rise exclusively to the corresponding methylcarbamate **5e**, indicating the significant influence of the protecting group.

Table 1. Evaluation of various *N*-protecting groups^[a]

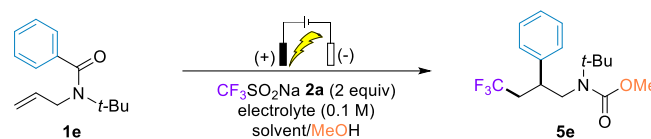


Entry	Co-solvent	Pg	Migration ^[b]	6- <i>endo</i> ^[b]
1	H ₂ O	1a : Mes	3a : 0%	4a : 0%
2	H ₂ O	1b : Ts	3b : 26%	4b : 26%
3	H ₂ O	1c : Boc	3c : 0%	4c : 0%
4	H ₂ O	1d : OMe	3d : 0%	4d : 10%
5	MeOH	1b : Ts	5b : 27%	4b : 24%
6	MeOH	1e : <i>t</i> -Bu	5e : 63%	4e : 0%

[a] Reaction conditions: undivided cell, C(+)|Ni(-), **1** (0.2 mmol), **2a** (0.4 mmol), CH₃CN/co-solvent (9:1, 3 mL), LiClO₄ (0.2 M), CCE (15 mA), 2 F (2h03), RT. [b] NMR yield using 1,3,5-trimethoxybenzene as an internal standard.

Having identified the *tert*-butyl as the optimal protecting group for the trifluoromethylation/aryl migration sequence, a systematic optimization of the reaction parameters was performed, and our key findings are depicted in Table 2.^[16] A solvent survey revealed that dichloroethane (DCE) was optimal providing **5b** in 68% yield (entries 1-4). Interestingly, a lower current (5 mA instead of 15 mA, entry 5) improved the yield. Screening various electrolytes led to 81% yield with *n*-Bu₄NClO₄ (entries 6-7). Increasing the concentration of the reaction mixture had a positive impact on the reaction efficiency delivering **5e** in 90% yield (entry 8). Evaluating different electrode materials showed a slightly decreased yield with stainless steel (SS) or nickel foam instead of a nickel plate, but a high yield was maintained by replacing the carbon graphite anode with inexpensive carbon felt (entries 9-11). Finally, fine-tuning the DCE/MeOH ratio to 95:5 furnished **5e** in 92% NMR yield (77% isolated yield).

Table 2. Optimization of the trifluoromethylation/aryl migration sequence of *N*-allylbenzamide **1e**.^[a]



Entry ^[b]	Solvent	Electrolyte	Electrodes	Yield (%) ^[b]
1	CH ₃ CN	<i>n</i> -Bu ₄ NPF ₆	C _{gr} (+) Ni(-)	67
2	DCE	<i>n</i> -Bu ₄ NPF ₆	C _{gr} (+) Ni(-)	68
3	DMSO	<i>n</i> -Bu ₄ NPF ₆	C _{gr} (+) Ni(-)	traces
4	1,4-dioxane	<i>n</i> -Bu ₄ NPF ₆	C _{gr} (+) Ni(-)	traces
5 ^[c]	DCE	<i>n</i> -Bu ₄ NPF ₆	C _{gr} (+) Ni(-)	77
6 ^[c]	DCE	<i>n</i> -Bu ₄ NClO ₄	C _{gr} (+) Ni(-)	81
7 ^[c]	DCE	<i>n</i> -Bu ₄ BF ₄	C _{gr} (+) Ni(-)	50
8 ^[c,d]	DCE	<i>n</i> -Bu ₄ NClO ₄	C _{gr} (+) Ni(-)	90
9 ^[c,d]	DCE	<i>n</i> -Bu ₄ NClO ₄	C _{gr} (+) SS(-)	84
10 ^[c,d]	DCE	<i>n</i> -Bu ₄ NClO ₄	C _{gr} (+) Ni _{foam} (-)	74
11 ^[c,d]	DCE	<i>n</i> -Bu ₄ NClO ₄	C _{felt} (+) Ni(-)	90
12 ^[c,d,e]	DCE	<i>n</i> -Bu ₄ NClO ₄	C _{gr} (+) Ni(-)	61
13 ^[c,d,f]	DCE	<i>n</i> -Bu ₄ NClO ₄	C _{gr} (+) Ni(-)	92 (77)
14 ^[c,d,f,g]	DCE	<i>n</i> -Bu ₄ NClO ₄	C _{gr} (+) Ni(-)	0

[a] Reaction conditions: undivided cell, **1e** (0.15 mmol), **2a** (0.3 mmol), CH₃CN/MeOH (9:1, 3 mL), electrolyte (0.1 M), CCE (15 mA), 3 F, RT. [b] NMR yield using 1,3,5-trimethoxybenzene as an internal standard; isolated yield is written between parentheses. [c] 5 mA instead of 15 mA. [d] **1e** (0.25 mmol). [e] DCE/MeOH (8:2, 3 mL). [f] DCE/MeOH (95:5, 3 mL), [g] No electricity.

With the best reaction conditions in hand, we started to examine the substrate scope with respect to the migrating aromatic ring (Scheme 2). Notably, the transformation exhibited complete regioselectivity, precluding the formation of dihydroisoquinolinone by-products. Various substituents with different electronic properties were well tolerated at the *para*-position producing the corresponding methyl carbamates **5e-14** in moderate to high yields (41-78%). Aromatic rings with one or two substituents at the *meta* position underwent smooth translocation furnishing the corresponding products **15-16** in high yields (74 and 80%, respectively). Gratifyingly, *ortho*-substituted aromatic rings (**17-19**) were also compatible with our reaction conditions. Furthermore, other primary as well as secondary alcohols could effectively replace methanol as co-solvent allowing the access to the corresponding carbamates (**20-23**) in decent to good yields. We then turned our attention to the access to CF₂-containing β-arylethylamine derivatives by evaluating other sulfinate salts.

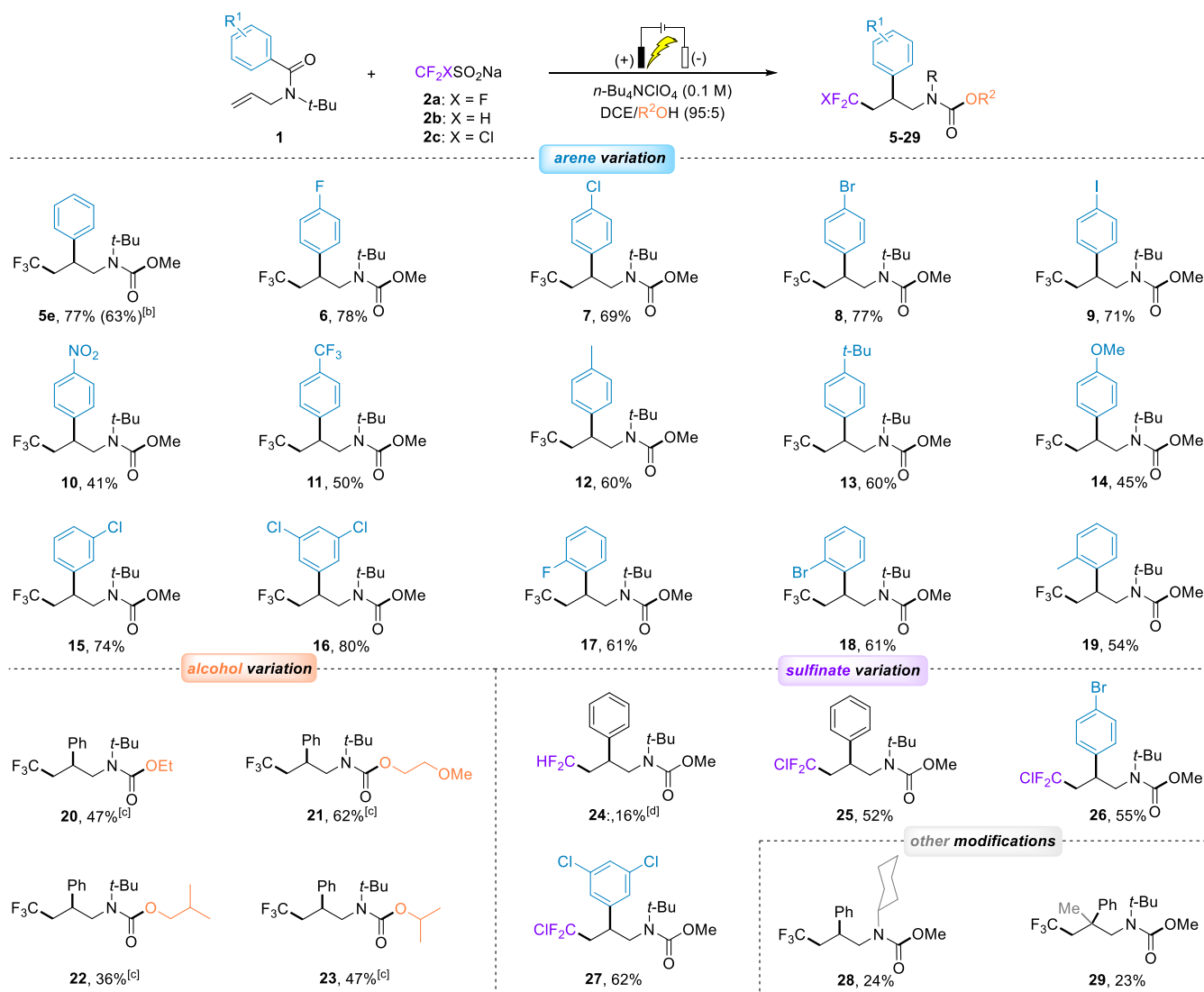
While the addition of CF₂H radical was poorly efficient, we were pleased to find that the more electrophilic CF₂Cl radical,^[17] readily generated from the corresponding chlorodifluoromethyl sulfinate **2c**,^[18] smoothly promoted the aryl translocation affording the CF₂Cl adducts **25–27** in good yields (52–62%). To the best of our knowledge, it is the first example of the electrochemical generation of the CF₂Cl radical. Modification on the benzamide showed that the *tert*-butyl group could be replaced by a cyclohexyl group delivering the cyclohexylamine derivative **28** in modest yield (24%). Worthy of note, the challenging construction of an all-carbon quaternary center was achieved, albeit in lower yield (23%). Unfortunately, N-homoallyl benzamide was unreactive. Finally, a 1 mmol scale experiment of **1e** provided **5e** in 63% yield.

To get a first insight into the reaction mechanism, few control experiments were carried out. First, no reaction occurred in the absence of current indicating that the electricity was essential (Table 2, entry 14). Then, the redox behaviour of the components was examined by cyclic voltammetry analysis (Figure S2). It confirmed that the Langlois reagent was the most likely species to be oxidized under galvanostatic conditions ($E_{2a} = 0.73$ V vs Fc^{+/0} in DCE/MeOH 95:5). Based on these experiments and on previous reports, we propose that the transformation begins by the anodic oxidation of **2a** with concomitant SO₂ extrusion to generate the CF₃[•] radical. The latter undergoes regioselective addition on the alkene to form the β-amino radical **A** (Figure 1a).

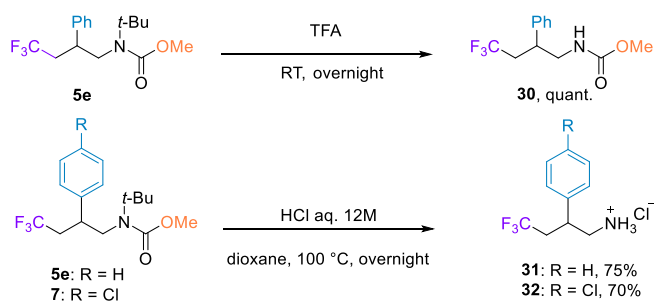
To investigate the following 1,4-aryl migration and especially to rationalize the difference of reactivity between the N-tosyl- and N-*t*-Bu-protected allylbenzamides **1b** and **1e**, density functional theory (DFT) calculations were accomplished using B3LYP-D3/def2-SV(P) level of theory and ascertained with the DLPNO-CCSD(T) method. The latter is used to comment the mechanistic pathway. First, the energy differences between the *s-cis* and *s-trans* conformations of **A** were calculated for the two model substrates (Figure 1b). The *s-trans* isomer of radical **A_{Ts}** is 1.93 kcal.mol⁻¹ more stable than the *s-cis* isomer. In sharp contrast, **A_{t-Bu}** features a clear bias for the *s-cis* isomer due to the bulkiness of the *t*-Bu protecting group ($\Delta E = 3.69$ kcal.mol⁻¹).^[19] Our computational studies revealed that this dissimilarity of geometry between **A_{Ts}** and **A_{t-Bu}** is critical to understand why the subsequent *ipso*-attack is easier with the *t*-Bu group than with the tosyl group (Figure 1c). Indeed, the reactive conformers **B** being *s-cis*, the activation barrier for the formation of **B_{t-Bu}** is much lower

than for **B_{Ts}** ($\Delta\Delta E^\ddagger = +8.77$ kcal.mol⁻¹). Consequently, the following *ipso*-attack leading to the spirocyclic intermediate **C_{t-Bu}** occurred with an energy barrier 7.94 kcal.mol⁻¹ lower than for the tosyl substrate (**TS_{BC_{t-Bu}}** and **TS_{BC_{Ts}}** lie at +8.49 and +16.43 kcal.mol⁻¹, respectively). The latter value correlates approximately with the difference in energy between *s-trans*-**A_{Ts}** and *s-cis*-**A_{t-Bu}** ($\Delta\Delta E = 5.62$ kcal.mol⁻¹). To further shed light on the slight additional difference of 2.32 kcal.mol⁻¹ (7.94–5.62 kcal.mol⁻¹), the non-covalent interactions (NCI) plots were obtained for the most stable conformers of **A**. For tosyl-protected β-amino radical **A_{Ts}**, a large green isosurface between the two aromatic rings indicative of attractive NCI (π - π stacking) was clearly identified.^[20] Since these interactions need to be disrupted for the rearrangement to proceed, they can reasonably account for the additional difference of reactivity between the two systems. Last but not least, the overall spirocyclization is more exothermic for the *t*-Bu substrate ($\Delta E = -9.6$ vs -3.8 kcal.mol⁻¹ from **A_{t-Bu}** to **C_{t-Bu}** and **A_{Ts}** to **C_{Ts}**, respectively). In both cases, the ensuing homolytic cleavage of the C–C bond takes place through a moderate barrier of ~16 kcal.mol⁻¹ affording the carbamoyl radical **D**. Subsequently, a second anodic oxidation would generate the corresponding carbamoyl cation **E** which undergoes nucleophilic addition of the methanol to yield the carbamate cation **F** through a barrierless and exothermic process (Figure S6). Also of note, for both protecting groups, the competitive 6-*endo* cyclization (Figure 1c, green line) of **B** generating radical **C'** through **TS_{BC'}** were computed to be less favourable than the 5-*exo* cyclization (*ipso*-attack).^[21] However, the difference between the free energy of activation of **TS_{BC}** and **TS_{BC'}** is more important with the *t*-Bu than with the tosyl (see black arrows on Figure 1c, $\Delta\Delta E^\ddagger = 3.1$ vs 1.6 kcal.mol⁻¹, respectively) which is consistent with our experimental results (Table 1, entries 5–6).

To further demonstrate the practical utility of this transformation, the *t*-Bu group was selectively removed by treating **1a** with trifluoroacetic acid producing the corresponding secondary carbamate **30** in quantitative yield (Scheme 3). Importantly, primary ammonium chloride **31** could be easily obtained directly from **1a** by treatment with aqueous hydrogen chloride under reflux in dioxane. The application of this procedure to compound **7** provided a rapid access to a new analogue **32** of the myorelaxant baclofen^[22] and of the GABA-B receptor antagonists saclofen and phaclofen.^[23]



Scheme 2. Scope of the fluoromethylation/aryl migration sequence of N-allylbenzamide **1**.^[a] [a] Reaction conditions: undivided cell, C(+)|Ni(-), **1** (0.25 mmol), **2** (0.5 mmol), DCE/ROH (95:5, 3 mL), *n*-Bu₄NClO₄ (0.1 M), CCE (5 mA), 3 F (4h05), RT; isolated yields are reported. [b] At 1 mmol scale. [c] 4 F (5h20). [d] in CH₃CN instead of DCE.



Scheme 3. Removal of the protecting groups.

Conclusion

In summary, we have established an easy and straightforward access to valuable tri- and di-fluorocontaining aryethylamine derivatives. The reaction proceeds through the electrochemical fluoromethylation of N-allylbenzamides triggering a radical Truce-

Smiles 1,4-aryl migration under mild reaction conditions and from readily available starting materials. A careful choice of the *N*-*tert*-butyl protecting group on the benzamide was crucial to prevent the competitive 6-*endo* cyclization, ensuring a high level of selectivity toward the *ipso*-substitution. DFT calculations evidenced that this sterically hindered group favors the *s-cis* conformation of the amide, thereby allowing the rearrangement to proceed. Additionally, our computational studies support the mechanism of the overall transformation. The exploration of this process for the construction of new β -arylethylamine derivatives is currently in progress in our laboratory and will be reported in due course.

Acknowledgements

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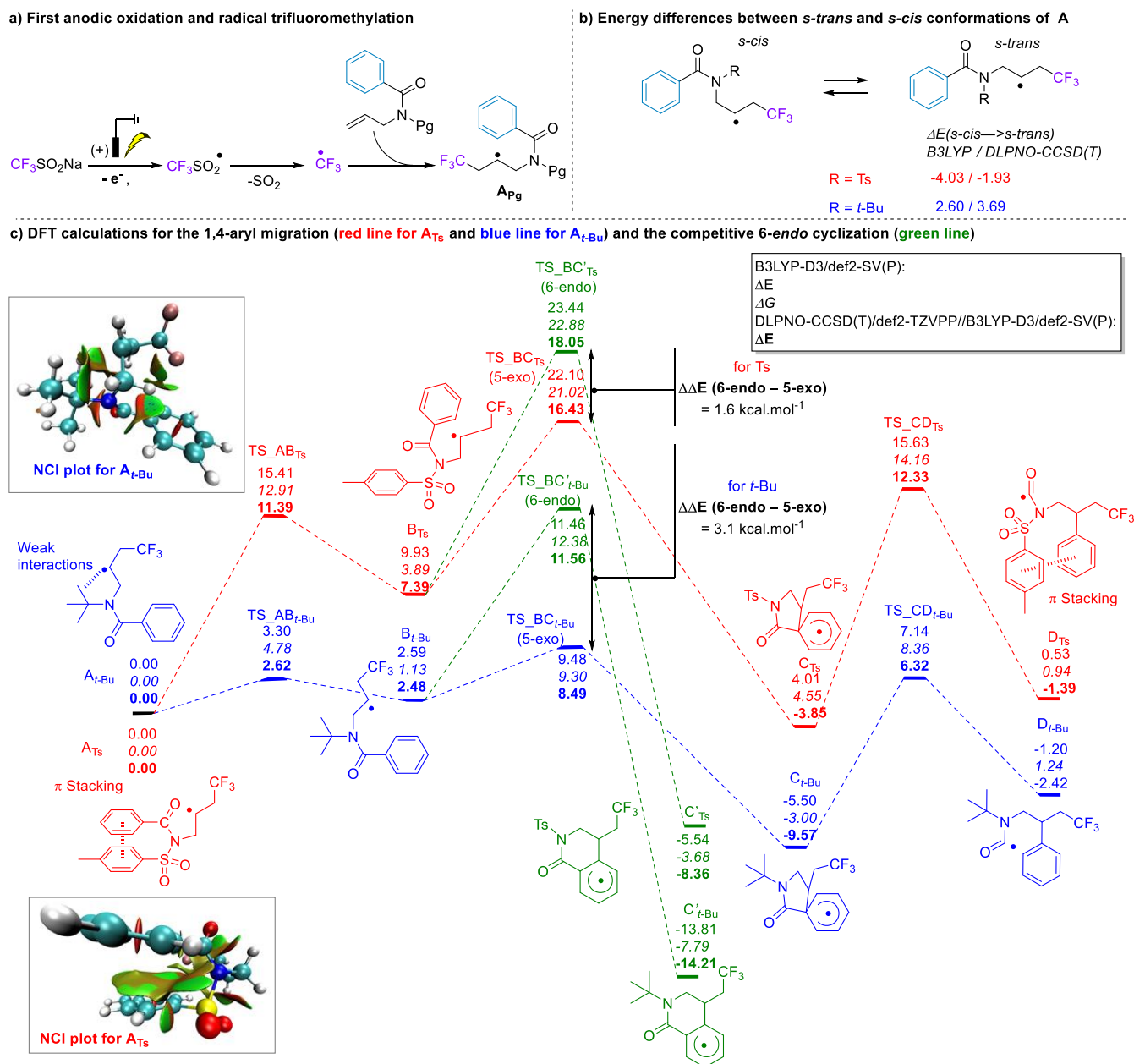


Figure 2. Mechanistic studies.

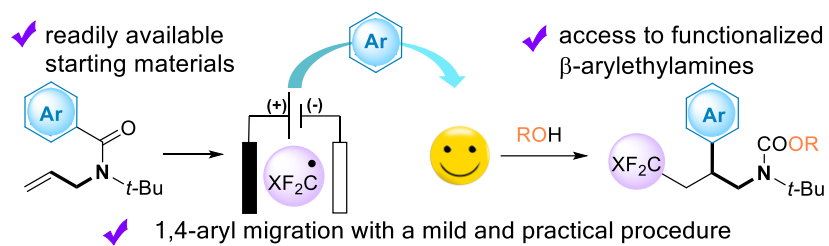
Keywords: arylation • aryloxyamine • electrocatalysis • radical reaction • rearrangement

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An electrochemical difluoro- and trifluoromethylation of N-allylbenzamides triggers the 1,4-migration of the aromatic ring through a radical Truce-Smiles rearrangement. This transformation offers a straightforward access to valuable β -arylethylamine derivatives in good yields and under mild reaction conditions from readily available starting materials.