

Synthesis of β -Difluoroalkyl Azides via Elusive 1,2-Azide Migration

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Abstract

The development of azide migration reactions is a formidable challenge, due to the potential competition of side processes driven by the release of molecular nitrogen. Here we report a conceptually novel 1,2-azide migration in an unprecedented *gem*-difluorination of the readily available α -vinyl azides, a transformation that enables the synthesis of a range of novel β -difluorinated alkyl azides. The practicality of the method is demonstrated by broad substrate scope, excellent functional group compatibility, and high yields. The migrating group selectivity can be tuned through electronic effects, with DFT calculations suggesting 1,2-azide migration occur via a three-membered azacyclic transition state. Using routine protocols, the β -difluorinated alkyl azide products can be easily transformed to biologically relevant β -difluorinated amines – common structural motifs in pharmaceuticals, thus demonstrating the utility of these fluorinated organic azides for pharmaceutical synthesis as well as other synthetically useful derivatives.

Introduction

The construction of carbon-nitrogen (C–N) bonds is one of the most important transformations in organic chemistry, owing to the prevalence of nitrogen-containing compounds in pharmaceuticals, natural products, and organic materials.^{1–3} Organic azides are widely recognized as convenient tools in such processes, due to their superior ability to participate in a variety of C–N bond forming reactions.^{4–11} Among their many applications,^{12,13} organic azides are easily transformed into amines, and readily undergo C–N bond formation via nitrogen-centered reactive intermediates (e.g. nitrenoid chemistry, driven by the release of molecular nitrogen),^{14–17} or as a 1,3-dipole (e.g. click reactions).^{11,14} In contrast, transformations in which the azide functionality remains intact in the final product are almost unknown, the sole exception being a pericyclic 1,3-allylic azide rearrangement,^{18–23} which is limited in utility due to the generation of mixtures of allylic azide products (Fig. 1A). The development of new azide migration reactions would therefore be of great value, not only as they would provide an ideal approach to organic azides inaccessible by existing methods, but also due to the conceptual challenge of avoiding the highly entropically favourable loss of N₂.^{12,13}

β -Difluoroalkylamines are key structural motifs in a variety of medicinally important compounds such as anticancer, anticholinergic, and anti-inflammatory therapeutic agents (Fig. 1B),^{24–30} however, current synthetic approaches require tedious multi-step operations.²⁴ We questioned whether the readily available α -vinyl azides – a class of structurally unique functionalized alkene that displays a rich reactivity profile⁶ – could offer a much more rapid entry to β -difluoroalkylamines via a *gem*-difluorination / 1,2-azide migration (Fig. 1C). The related *gem*-difluorination / 1,2-aryl migration of styrenes, recently been described by Jacobsen^{31,32} and others,^{33–37} provides an efficient and powerful means to access the *gem*-difluoroalkyl motif, a useful bioisostere of common polar functional groups.³⁸ However, with the exception of isolated examples involving benzyl ether (OBn) and sulfonamide (NHTs) groups,³⁹ these rearrangements proceed almost exclusively via arene migration. Under

similar oxidative fluorination conditions (pyridine•HF and hypervalent iodine),³⁵ we report herein a conceptually novel 1,2-azide migration, which enable the efficient synthesis of a wide range of *gem*-difluorinated alkyl azides (Fig. 1C). The migratory preference can be tuned through electronic effects, enabling a product switch in the reactions of α -aryl vinyl azides (i.e. azide migration vs arene migration). Further, the product *gem*-difluoroalkylazides can be readily converted to the corresponding biologically-relevant *gem*-difluoroalkylamines.^{40,41}

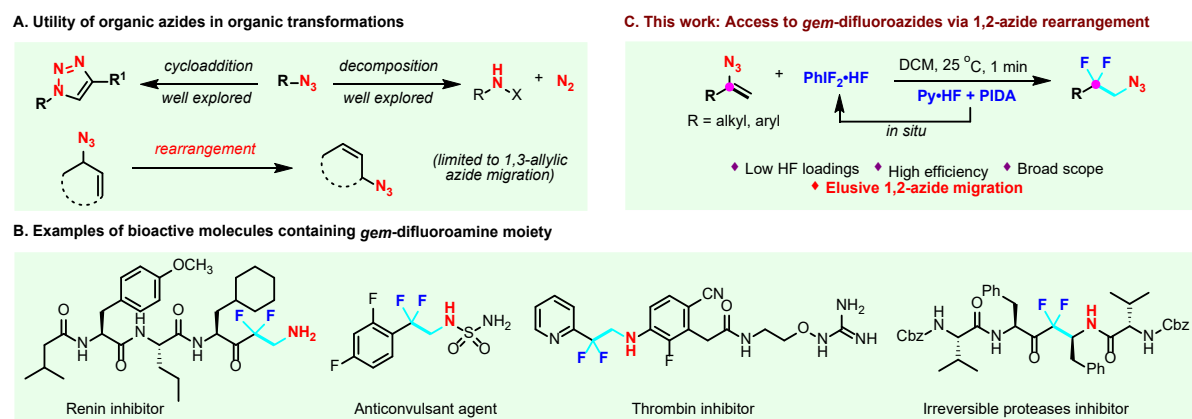


Fig. 1 (A) Applications of organic azides in organic synthesis. (B) Examples of bioactive molecules containing a *gem*-difluoroalkylamine motif. (C) Planned *gem*-difluorination of vinyl azides with *in situ*-generated PhIF₂•HF via an unprecedented 1,2-azide migration process (*this work*).

Results and Discussion

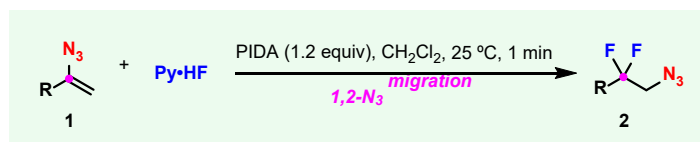
Table 1. Optimization of the reaction conditions^a

Entry	Oxidant	Fluorinating agent	Solvent	<i>T</i> (°C)	Yield (%) ^b
1	PIDA	Py•HF	CH ₂ Cl ₂	25	92
2	none	Py•HF	CH ₂ Cl ₂	25	0
3	PIDA	AgF	CH ₂ Cl ₂	25	0
4	PIDA	CsF	CH ₂ Cl ₂	25	0
5	PIDA	Et ₃ N•HF	CH ₂ Cl ₂	25	0
6	PIFA	Py•HF	CH ₂ Cl ₂	25	30
7	PhIO	Py•HF	CH ₂ Cl ₂	25	90
8	PIDA	Py•HF	CH ₃ CN	25	47
9	PIDA	Py•HF	DMSO	25	0
10	PIDA	Py•HF	CH ₂ Cl ₂	-40	60
11	PIDA	Py•HF	CH ₂ Cl ₂	-78	30

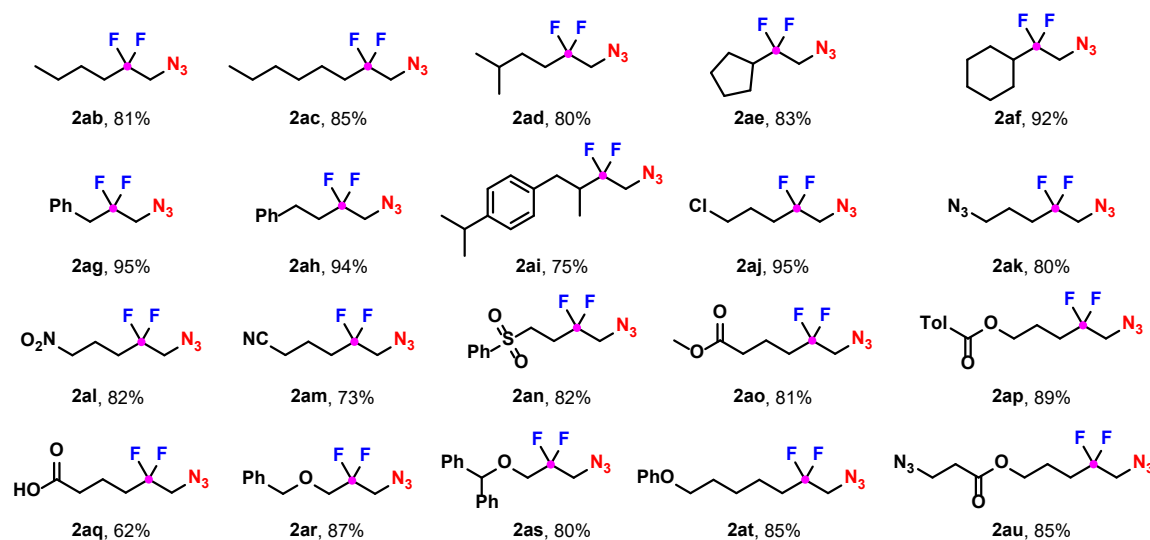
^a Reaction conditions: **1aa** (0.5 mmol), PIDA (0.6 mmol), and Py•HF (2.5 mmol) in CH₂Cl₂ (5 mL) at 25 °C for 1 min. ^b Isolated yield.

We first sought to establish conditions for the *gem*-difluorination / 1,2-azide migration reaction using vinyl azide **1aa** as a model substrate (Table 1). Subjection of **1aa** to oxidative fluorination conditions employed for *gem*-difluorination / 1,2-aryl migration of styrenes³⁵ (pyridine•HF as fluorine source, *bis*(acetoxy)iodobenzene

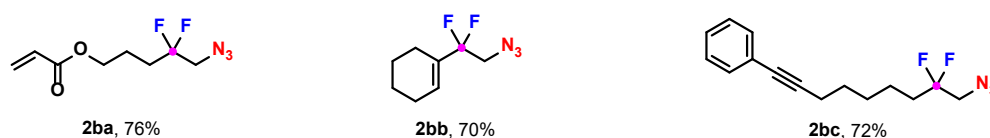
(PIDA) as oxidant in CH_2Cl_2 at 25 °C) afforded the 1,2-azide migration product **2aa** in excellent yield (entry 1). An oxidant was essential (entry 2), while other potential fluorine sources (e.g. AgF ,⁴² CsF ,⁴³ $\text{Et}_3\text{N}\cdot\text{HF}$,⁴⁴) led to no reaction (entries 3-5). Changing the oxidant to the more potent *bis*(trifluoroacetoxy)iodobenzene (PIFA)³³ resulted in a significantly reduced yield of **2aa** (30%, entry 6), while use of PhIO ⁴³ offered no advantage (entry 7). A brief survey of other solvents revealed poor or no conversion in acetonitrile and DMSO (entries 8 and 9); similarly, lowering the reaction temperature to -40 or -78 °C led to reduced yields (entries 10 and 11).



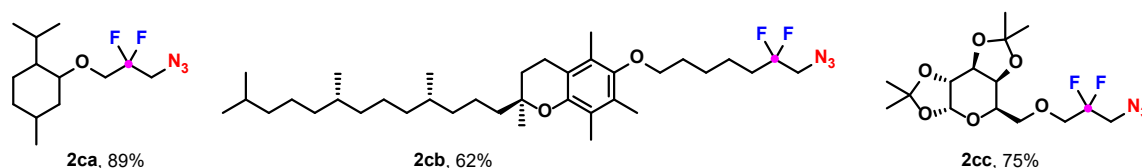
A. 1,2-Azide migratory *gem*-difluorination of alkyl-substituted vinyl azides



B. Selective 1,2-azide migratory *gem*-difluorination of vinyl azides bearing an unsaturated group



C. 1,2-Azide migratory *gem*-difluorination of natural product derivatives



D. 1,2-Azide migratory *gem*-fluorination of dimeric and tetrameric vinyl azides

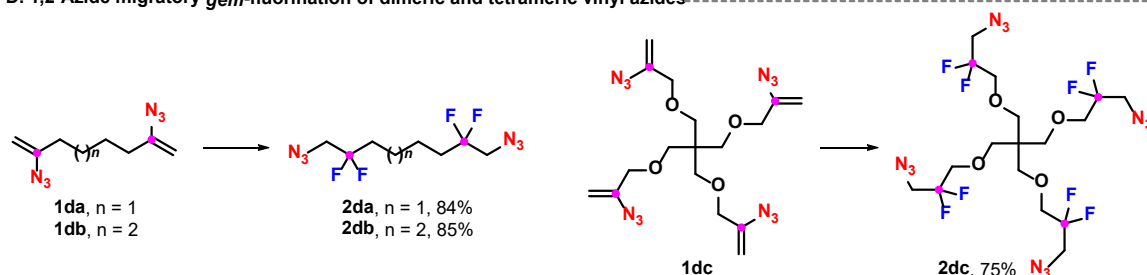


Fig. 2 Scope of 1,2-azide migratory *gem*-difluorinations. (A) Varying the α -alkyl group. (B) Unsaturated substrates. (C) Natural product derivatives bearing a vinyl azide moiety. (D) Polyazide substrates.

Having identified optimal conditions (Table 1, entry 1), the scope of this *gem*-difluorination / 1,2-azide migration was first explored with a range of α -alkyl vinyl azides (Fig. 2). As shown in Fig. 2A, vinyl azides with primary alkyl (**1ab**, **1ac**, and **1ah**), secondary alkyl (**1ad**, **1ae**, **1af**, and **1ai**), or benzyl (**1ag**) groups were smoothly converted to products **2ab–2ai** in 75–95% yield. α -Alkyl vinyl azides featuring a variety of functionalities on the terminal carbon of the alkyl chain (e.g. chloro, nitro, cyano, sulfonyl, ester, carboxylic acid and ether groups) also proved suitable substrates, giving products **2aj–2au** in 62–95% yield. This included tolerance of other potentially reactive azides on the alkyl chains (substrates **1ak** and **1au**), which afforded the rearrangement products **2ak** and **2au** in 80 and 85% yield, respectively. Substrates with α -substituents such as acrylic ester (**1ba**), cyclohexenyl (**1bb**), and internal alkynyl (**1bc**) moieties (Fig. 2B), also selectively delivered the corresponding *gem*-difluorination / 1,2-azide migration products (**2ba–2bc**) in good yield, without detrimental fluorination of the other unsaturated functionality of the α -substituents. These intriguing results clearly reveal the higher reactivity of olefins bearing an azide group compared to other unsaturated functionalities.

We applied this methodology to the late-stage modification of natural product derivatives bearing a vinyl azide (Fig. 2C). Substrates derived from menthol (**1ca**), vitamin E (**1cb**) and diacetone-D-galactose (**1cc**) afforded the desired products **2ca–2cc** in 62–89% yields. These examples highlight the potential utility of this method in the straightforward derivatization of bioactive molecules. This difluoroazidation methodology can also be used to build polyfunctionalized products; as depicted in Fig. 2D, 2,7-diazidoocta-1,7-diene (**1da**) and 2,8-diazidonona-1,8-diene (**1db**) provided the bis-difluoroazides **2da** and **2db** in 84% and 85% yield, respectively. Even a substrate containing four vinyl azide units (**1dc**) was converted to the desired product (**2dc**) in good yield (75%). Such azides are potentially useful building blocks for the synthesis of linear and poly(triazole) dendrimers via click chemistry, opening up applications in material science and medicinal chemistry.^{45–47}

Spurred on by the positive results obtained with α -alkyl vinyl azides, and with previous reports on styrene *gem*-difluorination / 1,2-aryl migration in mind,^{31–37} we next interrogated the reactivity of α -aryl vinyl azides **3**. As shown in Fig. 3, these substrates exhibited migration selectivity that could be turned by the electronic nature of the arene substituent: specifically, difluorination was accompanied by 1,2-migration of either the azide or aryl group, leading to β -difluoroalkylazides **4** or α -difluoroalkylazides **5**, respectively (Fig. 3A). Azides with strongly electron-withdrawing groups (EWGs) on the aryl moiety (**3aa–3ad**) underwent the expected *gem*-difluorination / 1,2-azide migration at 40 °C to afford the corresponding products **4aa–4ad** in moderate to good yields (62–82%, Fig. 3B; inferior yields were obtained at 25 °C). Certain disubstituted aryl vinyl azides, including 3,5-bis-trifluoromethyl- (**3ae**) and 3,5-difluoroarenes (**3af**), also afforded the azide migration products (**4ae** and **4af**), while substrates bearing formyl, acetyl, or ester groups at the *p*- or *m*-positions of the aryl ring (**3ag–3aj**) afforded mixtures of competing 1,2-azide and 1,2-aryl migrations, in favour of the former (**4ag–4aj** vs **4ag'–4aj'**). The structure of the product of the 1,2-azide migration **4ah** was unambiguously confirmed by single-crystal X-ray crystallography. Realizing that the electronic nature of the arene could be used to control the chemoselectivity of the migration, other substituted arenes were tested. A *meta*-chloro substituent (**3ak**) again gave rise to a mixture of the products of the 1,2-migration (**4ak** and **4ak'**); however chloro, bromo and fluoro substituents at the *p*-position of the aryl ring all exclusively delivered the *gem*-difluorinated products of 1,2-aryl migration (**4al–4an**, 72–79%). Despite the inductive electron-withdrawing nature of these substituents, this selectivity likely arises from mesomeric stabilization of developing positive charge at the *para* position during arene migration. This switch in product selection allowed us to prepare a variety of previously inaccessible α -difluoroalkylazides **5**, thus providing an entry to novel α -difluoroalkylamines.

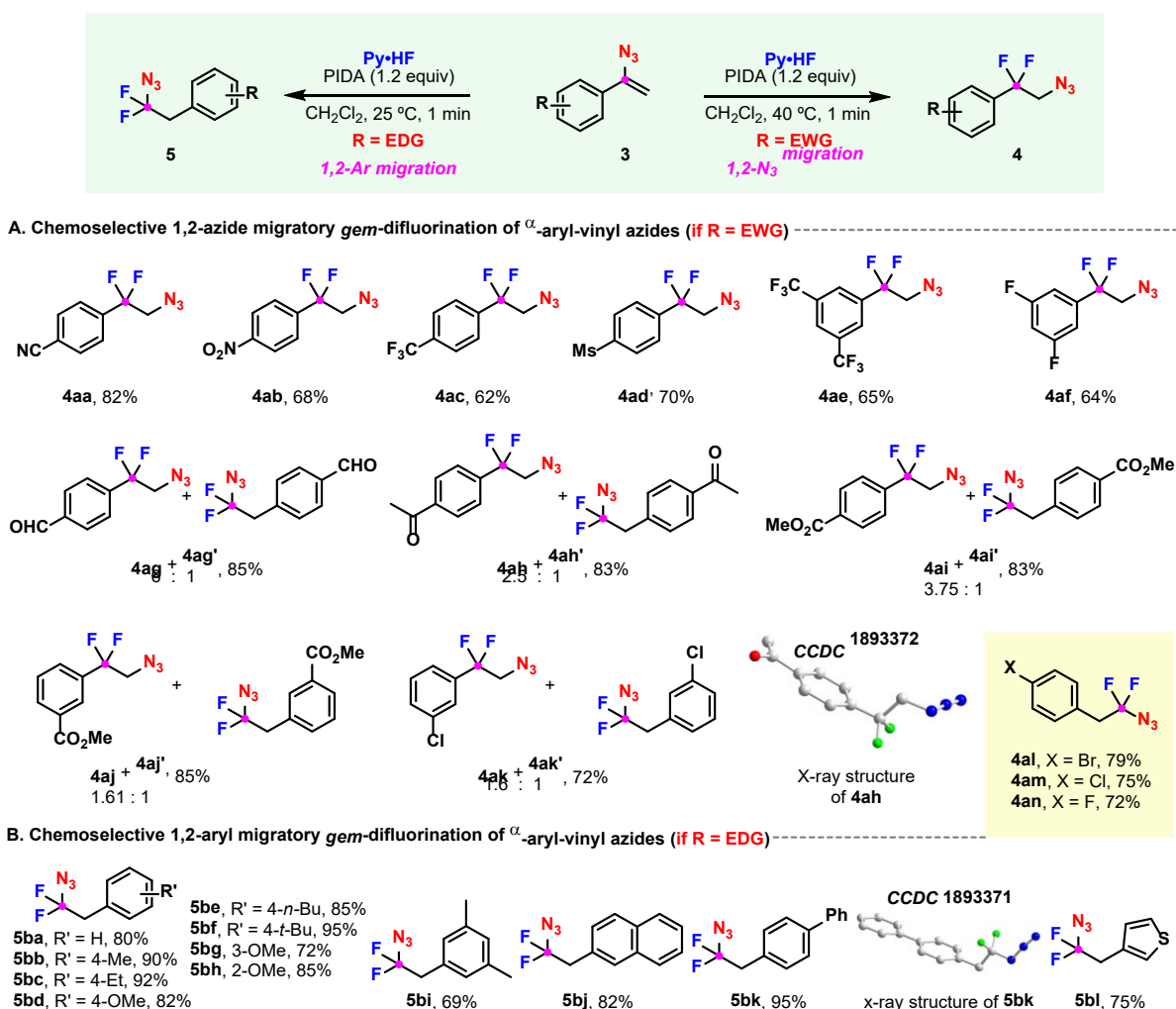
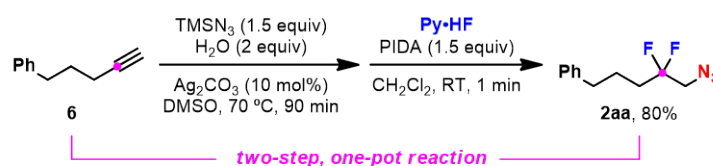


Fig. 3 Divergent migration pathways in the *gem*-difluorination of α -aryl vinyl azides.

This switch in selectivity was conveniently extended to a range of α -aryl vinyl azides equipped with electron-donating substituents (EDGs) on the aryl moiety (Fig. 3B). α -Aryl vinyl azides featuring alkyl and alkoxy groups at any position on the aryl ring (**3ba–3bi**) were efficiently transformed into the corresponding 1,2-aryl migration products (α -difluoroalkylazides **5ba–5bi**) in good to excellent yields, with no 1,2-azide migration products being observed. Substrates with additional sp^2 substituents (2-naphthyl, phenyl, and 3-thienyl; **3bj–bl**) were also smoothly converted to equivalent products (**5bj–5bl**) in high yields, with the structure of **5bk** confirmed by single crystal X-ray crystallography. Overall, these results illustrate the connection between migratory aptitude and the arene substituent (EWG vs EDG).

The vinyl azides employed in this chemistry are readily derived by hydroazidation of the corresponding terminal alkynes,⁴⁸ and many tandem hydroazidation reactions of terminal alkynes have been established.^{49,50} Accordingly, we questioned whether it would be possible to access the difluoroalkylazide products directly from alkynes in a two-step, one-pot process consisting of hydroazidation, followed by *gem*-difluorination / 1,2-azide migration. Using alkyne **6** as substrate, both steps indeed proceeded efficiently, giving *gem*-difluorinated alkyl azide **2aa** in 80% yield (Fig. 4A). This sequenced approach offers a step economic and operationally simple method for the synthesis of *gem*-difluorinated alkyl azides.

A. 1,2-azide migratory *gem*-difluorination starting from terminal alkynes



B. Gram scale synthesis and further reactions of the β -difluoroazides to medicinal chemistry intermediates

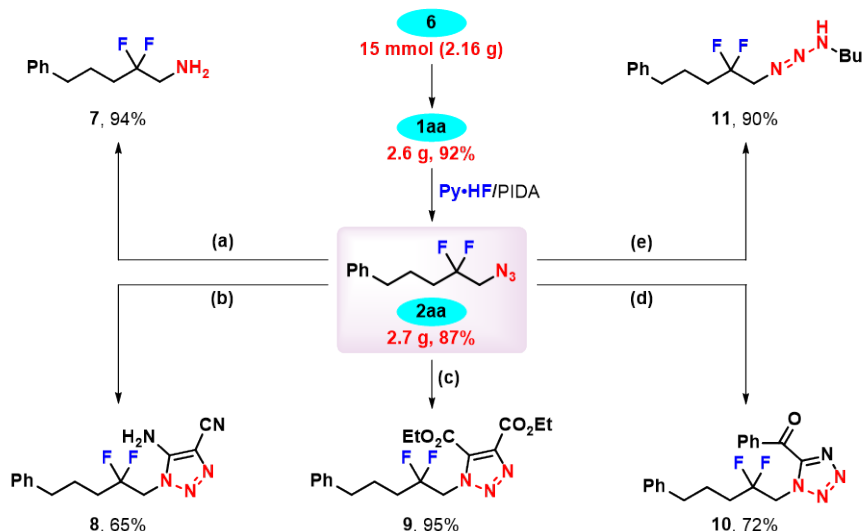


Fig. 4 Tandem hydroazidation / difluorination, gram scale synthesis, and further product transformations. (A) *gem*-Difluorination / 1,2-azide migration of terminal alkynes. Reaction conditions: **6** (0.5 mmol), TMSN_3 (1.0 mmol), Ag_2CO_3 (10% mol), in DMSO (2.0 ml) and H_2O (2.0 equiv) at 80 °C for 90 min; then DCM (2 mL), $\text{Py}\cdot\text{HF}$ (2.5 mmol), PIDA (1.0 mmol), 25 °C. PIDA = (Diacetoxyiodo)benzene; Py = Pyridyl. (B) Gram scale synthesis and further reactions of the β -difluoroalkylazides to access products relevant to medicinal chemistry applications. Reaction conditions: (a) **2aa** (0.5 mmol), PPh_3 (1.0 mmol), H_2O (200 μL) in THF (2.0 ml) at 50 °C for 3 h. (b) **2aa** (0.5 mmol), malononitrile (0.6 mmol), K_2CO_3 (1.0 mmol) in DMSO at 45 °C. (c) **2aa** (0.5 mmol), dimethyl acetylenedicarboxylate (DMAD) (0.6 mmol) in water (8 mL) at 70 °C. (d) **2aa** (0.5 mmol) and benzoyl cyanide (1.2 mmol) at 120 °C under Ar. (e) **2aa** (0.5 mmol), *n*-BuLi (0.6 mmol) in THF at -78 °C under Ar. THF = Tetrahydrofuran.

The practicality of the process was readily tested by conducting a multigram scale synthesis of **2aa** (Fig. 4B, 15 mmol scale, 2.7 g, 87%). **2aa** can be used to synthesize various previously unknown *gem*-difluorinated compounds of potential interest as useful building blocks in medicinal chemistry: for instance, reduction of the azide group produced β -difluoroalkylamine **7** in excellent yield,⁴¹ while base-mediated 1,3-dipolar cycloaddition of **2aa** with malononitrile⁵¹ or dimethyl acetylenedicarboxylate (DMAD)⁵² gave the trisubstituted 1,2,3-triazole derivatives **8** and **9** in 65% and 95% yields, respectively. 1,3-Dipolar cycloaddition of **2aa** with benzoyl cyanide afforded 1,5-disubstituted tetrazole **10** in good yield,⁵³ while addition of an alkyl lithium afforded triazene **11** in 90% yield.⁵⁴ The efficiency of these cycloadditions could enable further applications in bioconjugation processes.⁵⁵ These results clearly illustrate the potential of β -difluorinated alkyl azides to access nitrogen-containing β -difluorinated products, which could influence physical and biological properties such as conformation, lipophilicity, and metabolic stability.⁵⁶⁻⁵⁸ Positron emission tomography (PET) and single photon emission computed tomography (SPECT) are important fields of nuclear imaging in medicine.^{59, 60} Fluorine-18 (^{18}F , $t_{1/2} = 109.7$ min) is the most widely used nuclide for positron emission tomography (PET); as our methodology proceeds in a short reaction time (even within one minute), this difluorination chemistry could be well-suited for the efficient and rapid ^{18}F -radiolabeling of organic molecules.⁶¹

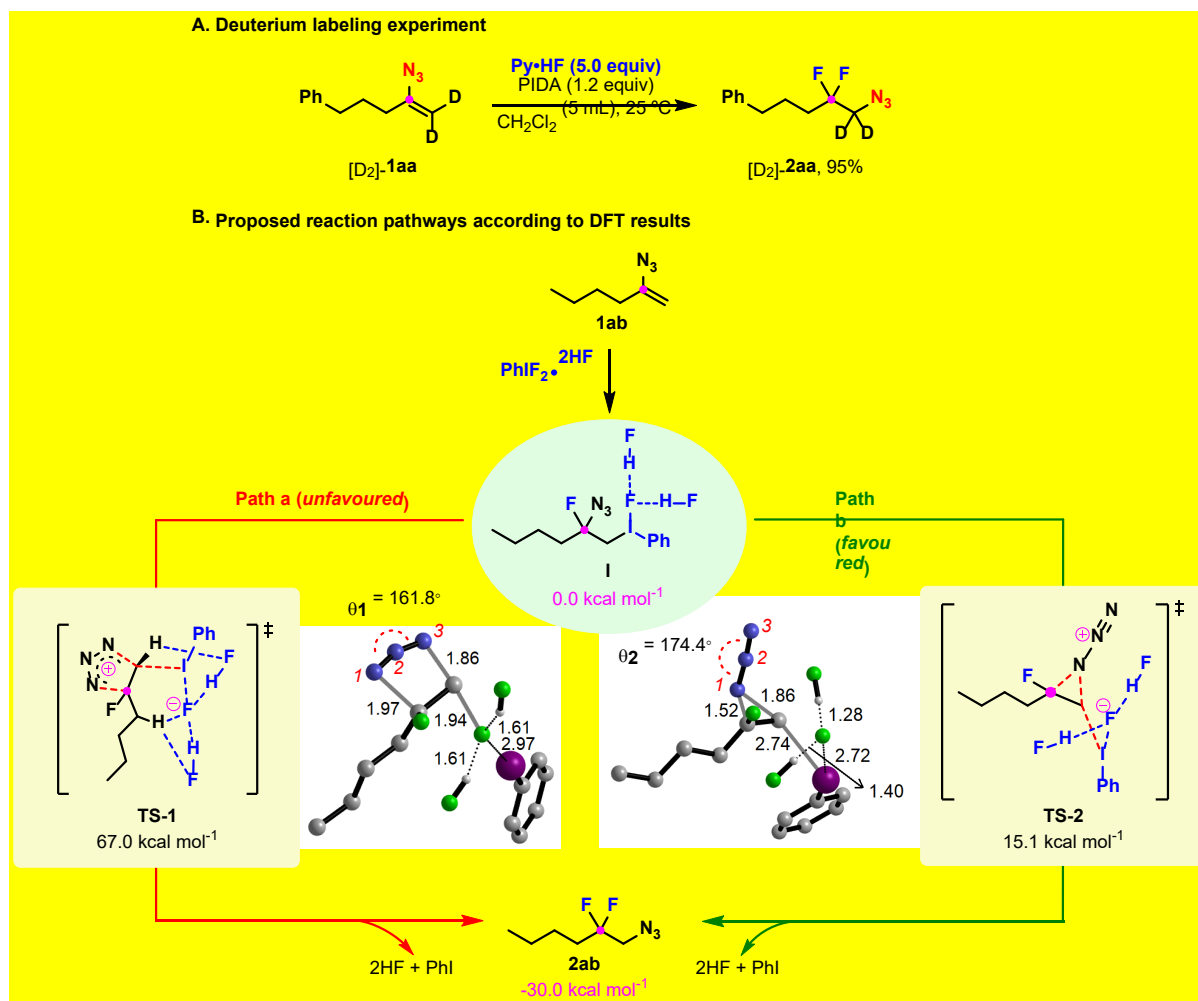


Fig. 5 Mechanistic study and proposal for the *gem*-difluorination/1,2-azide migration of vinyl azides. The energy profile was obtained by DFT calculations at the M062X/6-31G(d, p)/LANL2DZ level.

The mechanism of azide group migration is intriguing. To explore this, the *gem*-difluorination / 1,2-azide migration was investigated using deuterium-labelled substrate **[D₂]-1aa** (Fig. 5A), which under the standard conditions produced difluorinated product **[D₂]-2aa** in 95% yield with exclusive deuteriation at the carbon atom bearing the azide group. No indication of deuterium scrambling was observed by ¹H NMR spectroscopic analysis, suggesting the involvement of a 1,2-azide migration rather than an elimination process. A mechanism is proposed that involves initial 1,2-iodofluorination of the vinyl azide with PhIF₂•2HF (generated *in situ* from reaction of PIDA with Py•HF), forming intermediate **I** (Fig. 5B). The related activation of different numbers of HF with PhIF₂ has been investigated by Houk *et al.*³², who found that a 'two HF molecule' activation model is the most favoured. Accordingly, we also used this activation model to study the reaction pathways in this work. Subsequently, azide migration (promoted by the leaving group ability of iodobenzene) and concomitant fluorination appears to outcompete processes involving azide decomposition driven by loss of N₂. This 1,2-azide shift in intermediate **I** could occur either via a five-membered ring transition state (**TS-1**, path **a**) or a three-membered ring transition state (**TS-2**, path **b**). These transition states were studied using density functional theory (DFT) calculations at the M062X/6-31G(d, p)/LANL2DZ level. The calculations predict that path **a** (via **TS-1**, Fig. 5B) presents a prohibitively high energy barrier (67.0 kcal/mol) relative to path **b** (**TS-2**, 15.1 kcal/mol). This is potentially due to (1) the torsional strain involved in the migration of the azide group in **TS-1** ($\theta_1 = 161.8^\circ$) which destabilizes its structure more than for **TS-2** ($\theta_2 = 174.4^\circ$); (2) the stronger hydrogen bond

interactions between F^- and H, as well as the stronger electrostatic interactions between F^- and I^+ , are more favoured in **TS-2** than those in **TS-1**; (3) the electrostatic interactions between F^- and N_2^+ on the azide group was also found in **TS-2**, but are absent in **TS-1** (see NCI analysis in **Fig. 6**). As such, path b is proposed to be favoured. The calculations also show that the second fluorination occurs exclusively by nucleophilic attack at the fluorinated carbon, with the azonium ion as the leaving group, completing 1,2-azide migration to β -difluorinated alkyl azide product **2ab**. We speculate that the avoidance of azide decomposition may be explained by the intramolecular delivery of fluoride ion. Finally, in the case of α -aryl vinyl azides, the electronic character of the substituent on the aryl ring plays a pivotal role in the migration selectivity. Whereas electron-poor aromatics undergo equivalent azide migration, the ability of electron-rich arenes to form a phenonium ion outcompetes 1,2-azide migration, and thus delivers α -difluorinated alkyl azides.

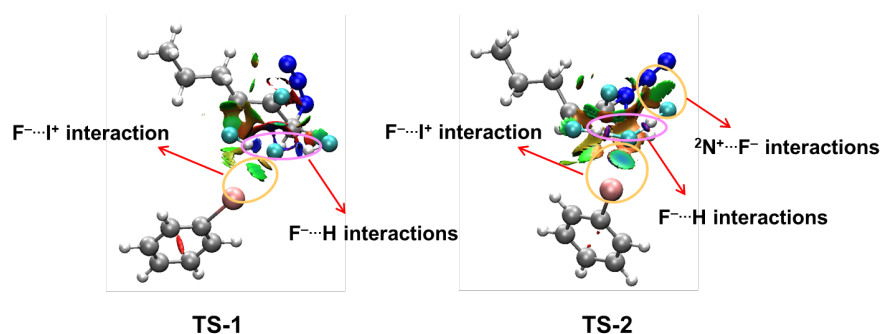


Fig. 6 NCI analysis for the two key transition states (blue, attraction; green, weak interaction; red, steric effect).

Conclusion

An unprecedented 1,2-azide migration has been developed in the *gem*-difluorination of the easily available α -vinyl azides with *in situ*-generated $PhIF_2 \cdot HF$, providing efficient access to a variety of previously inaccessible synthetically useful β -difluorinated azides. The azide functionality in the products can easily undergo further transformations to afford a variety of *gem*-difluorinated nitrogen-containing molecules of potential interest in medicinal chemistry. The azide migration could lead to those organic azides that are inaccessible by conventional methods; therefore, the discovery described here represents a conceptual advance in azide preparation, and has opened up an avenue to the azide migration highly desired by synthetic chemist.

Data availability

The authors declare that all the data supporting the findings of this study are available within the paper and its supplementary information files, or from the corresponding author upon request. The X-ray crystallographic coordinates for structures reported in this article have been deposited at the Cambridge Crystallographic Data Center (**4ah**: 1893372, **5bk**: 1893371). These data could be obtained free of charge from The Cambridge Crystallographic Data Center via <https://www.ccdc.cam.ac.uk/structures/>

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Author contributions

Y.N. and P.S. performed the experiments and the mechanistic studies. Y. N., G.Z., E.A.A. and X.B. conceived the concept, designed the project, analyzed the data, and prepared this manuscript.

Graphical Abstract

