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

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SUMMARY

The development of azide migration reactions is a formidable challenge because of 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, and DFT calculations suggest 1,2-azide migration occurs via a three-membered azacyclic transition state. By 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 because of 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 because of their superior ability to participate in a variety of C–N bond forming reactions.[4–12] Among their many applications,[13,14] 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),[15–18] or as a 1,3-dipole (e.g., click reactions).[12,15] 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,[19–24] which is limited in utility because of the generation of mixtures of allylic azide products (Figure 1A). The development of new azide migration reactions would therefore be of great value, not only because 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 favorable loss of N_2.[13,14]

β-difluoroalkylamines are key structural motifs in a variety of medicinally important compounds such as anticancer, anticholinergic, and anti-inflammatory therapeutic agents (Figure 1B);[25–31] however, current synthetic approaches require tedious multi-step operations.[25] We questioned whether the readily available α-vinyl azides—a class of structurally unique functionalized alkene that displays a rich reactivity profile[6]—could offer a much more rapid entry to β-difluoroalkylamines

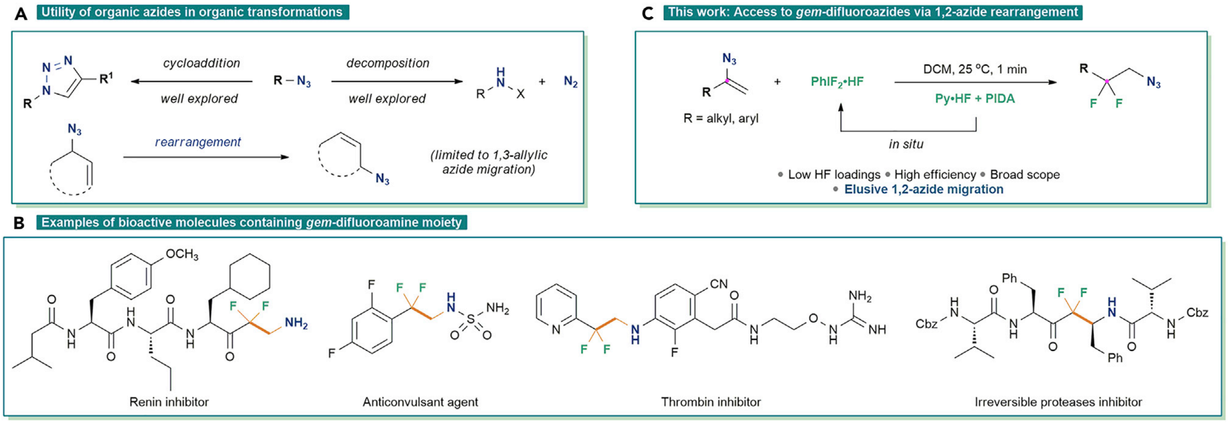

Figure 1. Development of 1,2-Azide Migration Reactions

(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 $PhIF_2$•HF via an unprecedented 1,2-azide migration process (this work).

via a *gem*-difluorination and 1,2-azide migration (Figure 1C). The related *gem*-difluorination and 1,2-aryl migration of styrenes, recently been described by Jacobsen[32,33] and others,[34–38] provides an efficient and powerful means to access the *gem*-difluoroalkyl motif, a useful bioisostere of common polar functional groups.[39] However, with the exception of isolated examples involving benzyl ether (OBn) and sulfonamide (NHTs) groups,[40] these rearrangements proceed almost exclusively via arene migration. Under similar oxidative fluorination conditions (pyridine•HF and hypervalent iodine),[36] we report herein a conceptually novel 1,2-azide migration, which enable the efficient synthesis of a wide range of *gem*-difluorinated alkyl azides (Figure 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 versus arene migration). Further, the product *gem*-difluoroalkylazides can be readily converted to the corresponding biologically relevant *gem*-difluoroalkylamines.[41,42]

RESULTS AND DISCUSSION

We first sought to establish conditions for the *gem*-difluorination and 1,2-azide migration reaction by using vinyl azide **1aa** as a model substrate (Table 1). Subjection of **1aa** to oxidative fluorination conditions employed for *gem*-difluorination and 1,2-aryl migration of styrenes[36] (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), whereas other potential fluorine sources (e.g., AgF,[43] CsF,[44] Et_3N•HF[45]) led to no reaction (entries 3–5). Changing the oxidant to the more potent *bis*(trifluoroacetoxy)iodobenzene (PIFA)[34] resulted in a significantly reduced yield of **2aa** (30%, entry 6), whereas use of PhIO[44] 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°C or −78°C led to reduced yields (entries 10 and 11).

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 (Figure 2). As shown in Figure 2A, vinyl azides with primary alkyl (**1ab, 1ac**, and **1ah**), secondary alkyl (**1ad**, **1ae**, **1af**, and **1ai**), or benzyl (**1ag**) groups were

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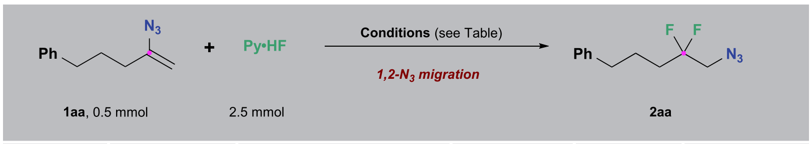
Table 1. Optimization of the Reaction Conditions



Entry	Oxidant	Fluorinating Agent	Solvent	T (°C)	Yield (%)[a]
1	PIDA	Py•HF	CH_2Cl_2	25	92
2	none	Py•HF	CH_2Cl_2	25	0
3	PIDA	AgF	CH_2Cl_2	25	0
4	PIDA	CsF	CH_2Cl_2	25	0
5	PIDA	Et_3N•HF	CH_2Cl_2	25	0
6	PIFA	Py•HF	CH_2Cl_2	25	30
7	PhIO	Py•HF	CH_2Cl_2	25	90
8	PIDA	Py•HF	CH_3CN	25	47
9	PIDA	Py•HF	DMSO	25	0
10	PIDA	Py•HF	CH_2Cl_2	−40	60
11	PIDA	Py•HF	CH_2Cl_2	−78	30

Reaction conditions: **1aa** (0.5 mmol), PIDA (0.6 mmol), and Py•HF (2.5 mmol) in CH_2Cl_2 (5 mL) at 25°C for 1 min.

[a] Isolated yield.

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 to be 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% yields, respectively. Substrates with α-substituents such as acrylic ester (**1ba**), cyclohexenyl (**1bb**), and internal alkynyl (**1bc**) moieties (Figure 2B) also selectively delivered the corresponding *gem*-difluorination and 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 that if the compound contains two unsaturated groups, olefins bearing an azide group have higher reactivity than free unsaturated groups.

We applied this methodology to the late-stage modification of natural product derivatives bearing a vinyl azide (Figure 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 Figure 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.[46–48]

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,[32–38] we next

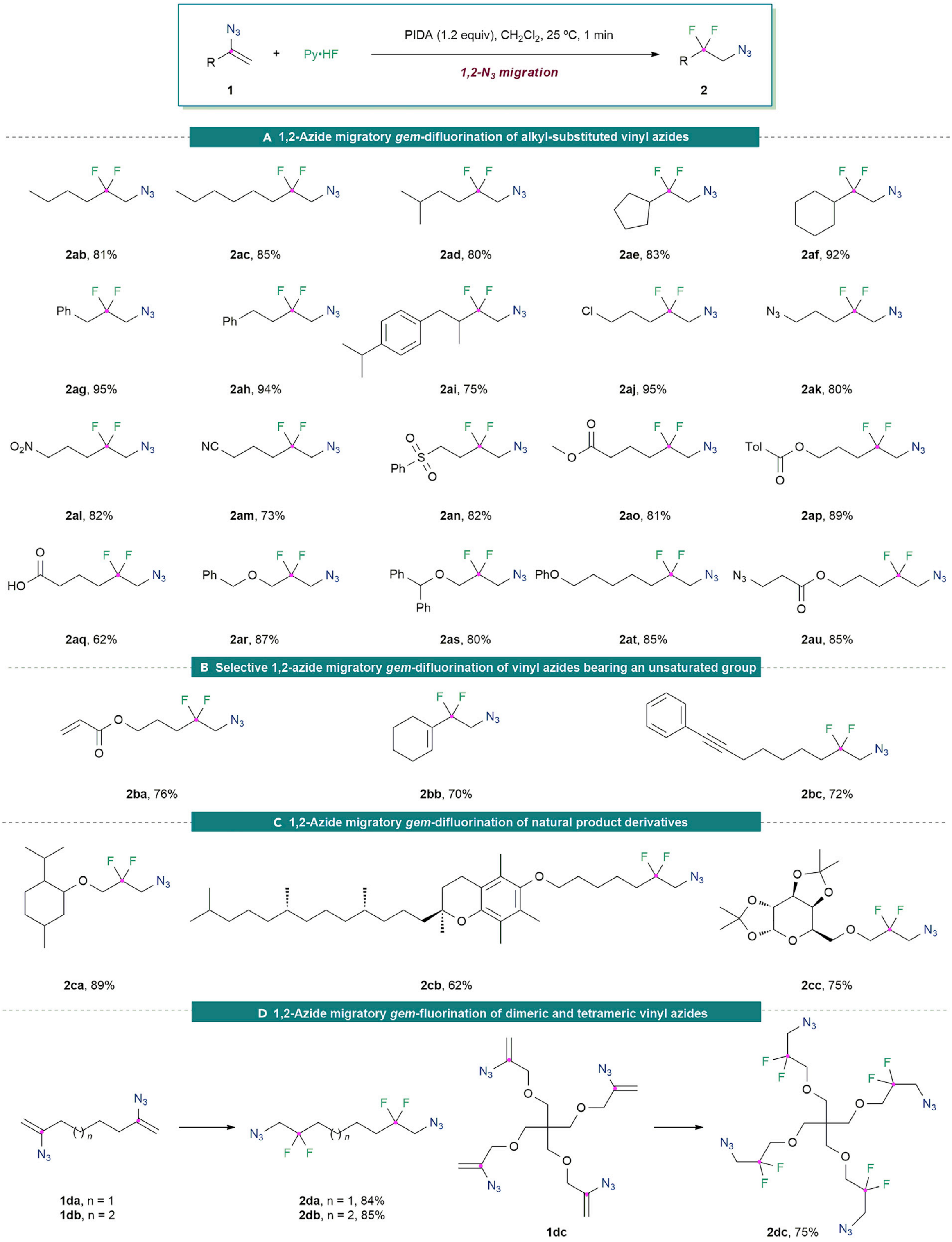
N$_3$
R
1
+
Py•HF
PIDA (1.2 equiv), CH$_2$Cl$_2$, 25 ºC, 1 min
1,2-N$_3$ migration
F F
R
N$_3$
2
A 1,2-Azide migratory gem-difluorination of alkyl-substituted vinyl azides
2ab, 81%
2ac, 85%
2ad, 80%
2ae, 83%
2af, 92%
2ag, 95%
2ah, 94%
2ai, 75%
2aj, 95%
2ak, 80%
2al, 82%
2am, 73%
2an, 82%
2ao, 81%
2ap, 89%
2aq, 62%
2ar, 87%
2as, 80%
2at, 85%
2au, 85%
B Selective 1,2-azide migratory gem-difluorination of vinyl azides bearing an unsaturated group
2ba, 76%
2bb, 70%
2bc, 72%
C 1,2-Azide migratory gem-difluorination of natural product derivatives
2ca, 89%
2cb, 62%
2cc, 75%
D 1,2-Azide migratory gem-fluorination of dimeric and tetrameric vinyl azides
1da, n = 1
1db, n = 2
2da, n = 1, 84%
2db, n = 2, 85%
1dc
2dc, 75%

Figure 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.

interrogated the reactivity of α-aryl vinyl azides **3**. As shown in Figure 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 (Figure 3A). Azides with strong electron-withdrawing groups (EWGs) on the aryl moiety (**3aa–3ad**) underwent the expected *gem*-difluorination and 1,2-azide migration at 40°C to afford the corresponding products **4aa–4ad** in moderate to good yields (62%–82%, Figure 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**), whereas 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 favor of the former (**4ag–4aj** versus **4ag′–4aj′**), and the structure of azide migration product **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-difluoroalkylamins.

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 (Figure 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, and no 1,2-azide migration products were 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, and the structure of **5bk** was confirmed by single-crystal X-ray crystallography. Overall, these results illustrate the connection between migratory aptitude and the arene substituent (EWG versus EDG).

The vinyl azides employed in this chemistry are readily derived by hydroazidation of the corresponding terminal alkynes,[49] and many tandem hydroazidation reactions of terminal alkynes have been established.[50,51] 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 (Figure 4A). This sequenced approach offers a step economic and operationally simple method for the synthesis of *gem*-difluorinated alkyl azides.

The practicality of the process was readily tested by conducting a multigram scale synthesis of **2aa** (Figure 4B, 15 mmol scale, 2.7 g, 87%). **2aa** can be used to

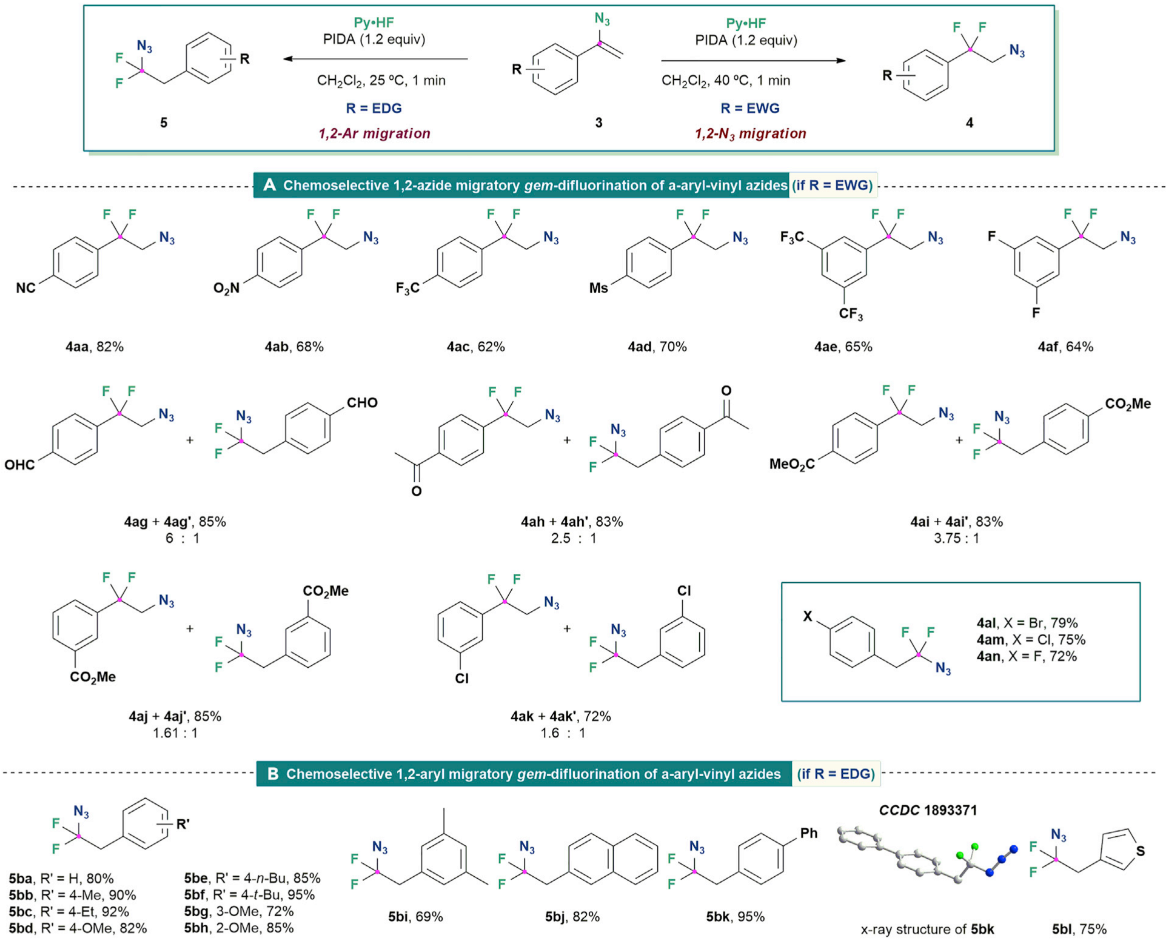
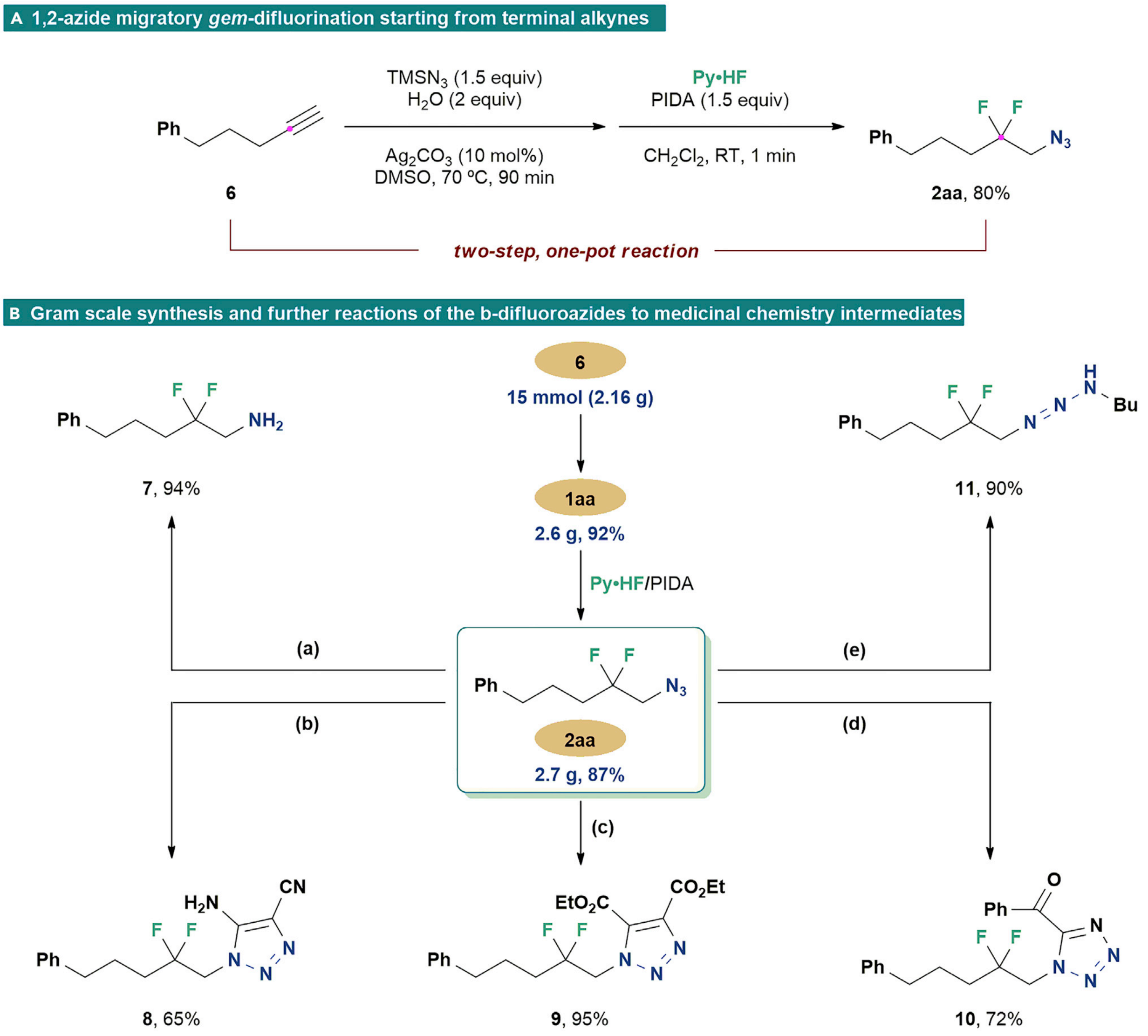


Figure 3. Divergent Migration Pathways in the *gem*-difluorination of α-Aryl Vinyl Azides

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,[42] whereas base-mediated 1,3-dipolar cycloaddition of **2aa** with malononitrile[52] or dimethyl acetylenedicarboxylate (DMAD)[53] 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,[54] whereas addition of an alkyllithium afforded triazene **11** in 90% yield,[55] the practical dipolar cycloaddition could further promote their use in bioconjugation.[12,56] 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.[57–59] Otherwise, positron emission tomography (PET) and single photon emission computed tomography (SPECT) are subfields of nuclear imaging that emerged from the combined efforts of national laboratories, academia, and industries.[60,61] Fluorine-18 (^{18}F, $t_{1/2}$ = 109.7 min) is the most widely used nuclide for positron emission tomography (PET). Our methodology has quite a rapid reaction time, even occurring at speeds <1 min. Such a short reaction time should be essential for the efficient introduction of ^{18}F-radiolabel into organic molecules.[62]



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

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

Figure 4. Tandem Hydroazidation/Difluorination, Gram Scale Synthesis, and Further Product Transformations

(A) *gem*-difluorination and 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), Py•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 (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 mechanism of azide group migration is intriguing. To explore this, the *gem*-difluorination/1,2-azide migration was investigated with deuterium-labeled substrate [D_2]-**1aa** (Figure 5A), which under the standard conditions produced difluorinated product [D_2]-**2aa** in 95% yield with exclusive deuteration at the carbon atom bearing the azide group. No indication of deuterium scrambling was observed by ^{1}H 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 $PhIF_2{\cdot}2HF$ (generated *in situ*

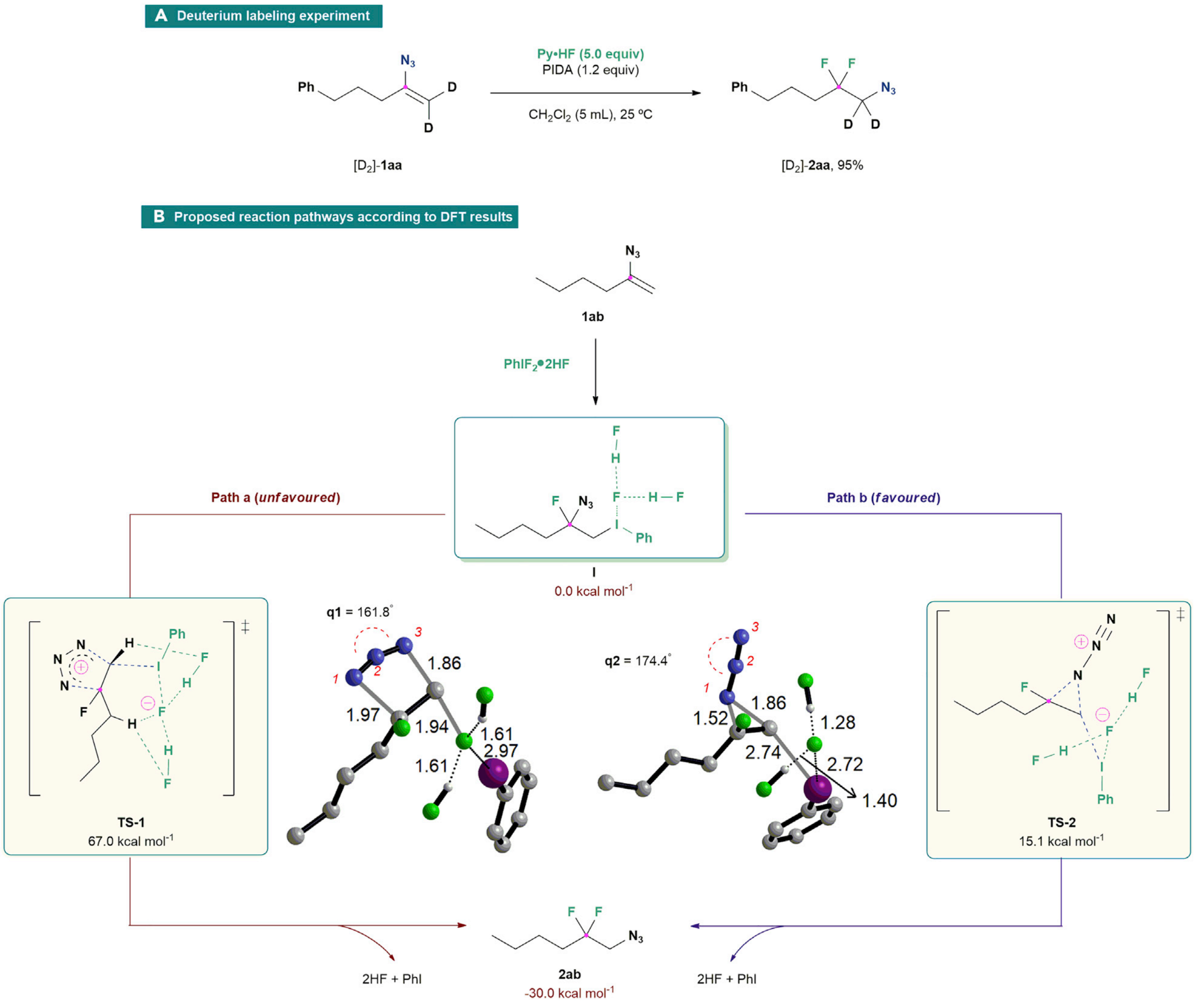


Figure 5. Mechanistic Study and Proposal for the *gem*-difluorination/1,2-Azide Migration of Vinyl Azides

The energy profile was obtained by DFT calculations at the M062X/6-31G(d, p)/LANL2DZ level.

from reaction of PIDA with Py•HF), forming intermediate I (Figure 5B). The similar activation of different molecules of HF to $PhIF_2$ has been investigated by Zhou et al.,[33] and they found that the two-molecule activation model is the most favored. Thus, we directly use this activation model to study the following processes in this work. Subsequently, azide migration (promoted by the leaving group ability of iodobenzene) and concomitant fluorination appear to outcompete processes involving azide decomposition driven by loss of N_2. 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 with density functional theory (DFT) calculations at the M062X/6-31G(d,p)/LANL2DZ level. The calculations predict that path a (via **TS-1**, Figure 5B) presents a prohibitively high energy barrier (67.0 kcal/mol) relative to path b (**TS-2**, 15.1 kcal/mol), potentially because of (1) the torsional strain involved in the migration of the azide group in **TS-1** ($\theta 1$ = 161.8°) makes its structure more destabilized than that of **TS-2** ($\theta 2$ = 174.4°); (2) the stronger hydrogen-bond interactions between F^- and H as

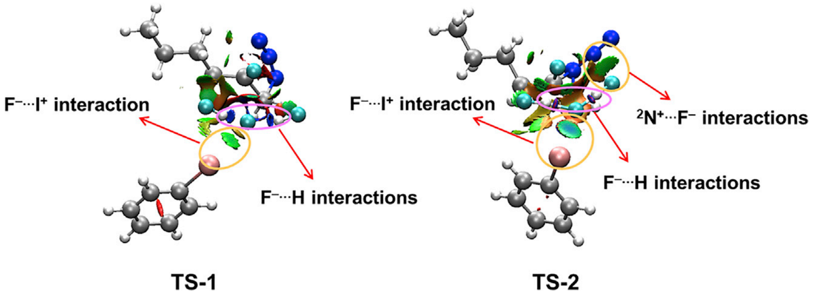


Figure 6. NCI analysis for the two key transition states TS-1 and TS-2

The colors blue, green, and red represent the attraction, weak interaction, and steric effect, respectively, between the atoms.

well as the stronger electrostatic interactions between F^- and I^+ in **TS-2** is more favored than those in **TS-1**, the electrostatic interactions between F^- and N_2^+ on the azide group was also found in **TS-2**, whereas it is absent in **TS-1** (NCI analysis in Figure 6). As such, path b is proposed to be favored. The calculations also show that the second fluorination occurs exclusively by nucleophilic attack at the fluorinated carbon, and the azonium ion is the leaving group, completing 1,2-azide migration to β-difluorinated alkyl azide product **2ab**. We speculate that the avoidance of azide decomposition could be explained by the intramolecular delivery of the 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.

Conclusions

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 chemists.

EXPERIMENTAL PROCEDURES

Full experimental procedures are provided in the Supplemental Information.

DATA AND CODE AVAILABILITY

The X-ray crystallographic coordinates for structures reported in this article have been deposited at the Cambridge Crystallographic Data Center (4ah'': 1960403, 5bk: 1893371). These data could be obtained free of charge from The Cambridge Crystallographic Data Center via https://www.ccdc.cam.ac.uk/structures/.

SUPPLEMENTAL INFORMATION

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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.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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