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One-pot Construction of Difluorinated Pyrrolizidine and Indolizidine Scaffolds via Copper-Catalyzed Radical Cascade Annulation

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Abstract. A convenient approach to the synthesis of diverse difluorinated nitrogen-containing polycycles via a copper-catalyzed radical cascade annulation of amine-containing olefins and ethyl bromodifluoroacetate was developed. Three new bonds, including a C_{sp3}-CF_2 and two C-N bonds, are forged simultaneously in this strategy. Through this strategy, a series of difluorinated pyrrolizidine and indolizidine derivatives have been conveniently synthesized in good yields.

Keywords: annulation; difluorinated; copper-catalyzed; pyrrolizidine; indolizidine

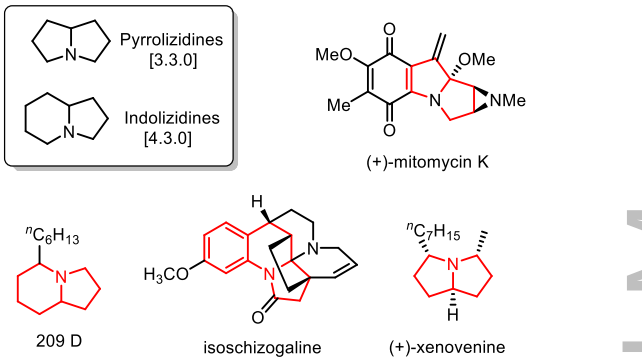

Figure 1. Representative biologyically active izidine alkaloids.

Nitrogen-containing polycycles are commonly found in a vast class of biologically active molecules and natural products. The izidine alkaloids, which are of diverse biological activities, constitute nearly 30% of all known natural alkaloids. Among them, pyrrolizidines and indolizidines are particular interesting examples and prevalent in pharmacologically active natural compounds (Figure 1).[1] So, it is of great interest to develop general protocols for the synthesis of these skeletons. However, only a few limited examples have been reported to form both the pyrrolizilines and indolizidines cores.[2] Transition metal catalyzed reactions, such as the palladium-catalyzed cyclization reaction, have been successfully applied to the construction of nitrogen-containing polycycles.[3] The ruthenium- and rhodium-catalyzed methods were also reported.[4]

Incorporation of fluorine atoms or fluorine-containing groups into organic motifs can significantly influence the lipophilicity, metabolic stability, and bioavailability of organic molecules.[5] As a bioisostere of hydroxyl, thiol, and carbonyl groups, the difluoromethylene group (CF_2) is a valuable structural motif in organic synthesis,[6] and the exploration of practical methodologies for the introduction of CF_2 in organic molecules is in high demand. Recently, transition metal-catalyzed difluoroalkylation of arylborons,[7] organohalides,[8] unsaturated carboxylic,[9] and C-H bond of alkenes and (hetero)arenes[10] have been developed. The aminodifluoroalkylations of alkenes catalyzed by palladium, copper, and photoredox catalyst were also reported,[11] which provide an efficient access to difluoro-γ-lactams and 3,3-difluoro-2-oxindoles. However, the substrates in these reports[12] are limited to aromatic amines with aliphatic amines failing to result annulation products. Therefore, methods for the synthesis of various difluorinated heterocyclic are still limited,[13] especially methods for the synthesis of difluorinated pyrrolizidines and indolizidines. Until now, only a few examples for the multi-step synthesis of difluorinated pyrrolizidines

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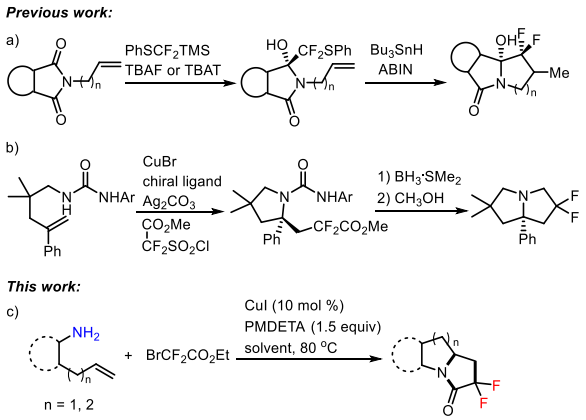
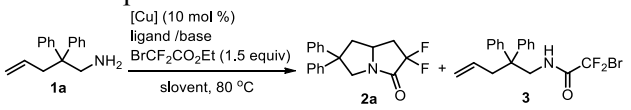


Scheme 1. Methods for the synthesis of difluorinated pyrrolizidines and indolizidines

and indolizidines have been developed (Scheme 1, a and b).[11d, 14] Herein, we disclosed a novel and convenient approach to the synthesis of diverse difluorinated *N*-containing polycycles via a copper-catalyzed radical cascade annulation of amine-containing olefins and ethyl bromodifluoroacetate (Scheme 1, c). Both aliphatic amines and aromatic amines can cyclize smoothly through the new developed method and a series of difluorinated pyrrolizidine and indolizidine derivatives have been synthesized in high efficiency.

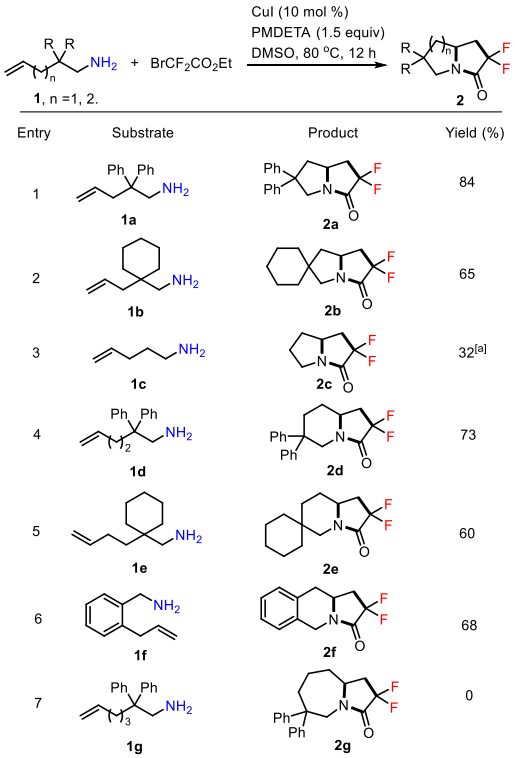
Table 1. Optimization of the reaction conditions.[a]



Entry	[Cu]	Ligand/Base	Solvent	Yield (%) [b]	
				2a	**3**
1[c]	CuI	Phen/K_2CO_3	DMSO	16	35
2[c]	CuI	Bpy/K_2CO_3	DMSO	<5	38
3[c]	CuI	PMDETA /K_2CO_3	DMSO	32	25
4[c]	CuI	PMDETA /K_2CO_3	DMSO	40	33
5[d]	CuI	PMDETA	DMSO	90 (84)	<5
6[d]	CuI	PMDETA	DMF	46	23
7[d]	CuI	PMDETA	CH_3CN	36	45
8[d]	CuI	PMDETA	toluene	<5	78
9[d]	CuI	PMDETA	dioxane	14	53
10[d]	CuCN	PMDETA	DMSO	48	20
11[d]	CuBr	PMDETA	DMSO	88	<5
12[d]	$Cu(OTf)_2$	PMDETA	DMSO	<5	70
13[d]	$CuBr_2$	PMDETA	DMSO	6	72
14[d]	-	PMDETA	DMSO	-	81
15[d,e]	CuI	PMDETA	DMSO	34	6
16[d,f]	CuI	PMDETA	DMSO	67	<5

[a] Reaction conditions: Unless otherwise noted, all reactions were performed with **1a** (0.3 mmol, 1.0 equiv), $BrCF_2CO_2Et$ (0.45 mmol, 1.5 equiv), and [Cu] (10 mol %), in DMSO (3 mL) at 80 °C under Ar for 8 h. [b] Determined by GC with dodecane as internal standard. The value in parentheses is the isolated yield. [c] Ligand (0.2 equiv), base (1.5 equiv). [d] PMDETA (1.5 equiv). [e] 30 °C. [f] 50 °C.

Initially, olefin **1a** and widely available ethyl bromodifluoroacetate ($BrCF_2CO_2Et$) were chosen as the model substrate for the optimization of reaction conditions. The challenge of this transformation is to avoid the generation of the byproduct **3** because of the nucleophilic ability of primary amines. When the reaction was conducted in dimethyl sulfoxide (DMSO) with CuI (10 mol %) as a catalyst, 1,10-phenanthroline as ligand, and K_2CO_3 as a base at 80 °C, it is encouraging to find that the desired product **2a** was obtained in 16% yield even though the byproduct **3** was also obtained in 35% yield (entry 1). When 2,2'-bipyridine (bpy) was employed as ligand, only trace amount of **2a** was generated (entry 2). Inversely, the use of PMDETA (pentamethyldiethylenetriamine) as ligand led to **2a** in a higher yield (32%) (entry 3). Employing triethylamine instead of K_2CO_3 as base further improved the yield of **2a** to 40% (entry 4). To our delight, the desired product **2a** could be generated in excellent yield when PMDETA was employed as both a ligand and a base (entry 5). It is well known that alkyl radical could be efficiently generated from corresponding alkyl halides in the presence of a copper complex with multidentate amine ligands.[15] Several solvents including *N*,*N*-dimethyl formamide,

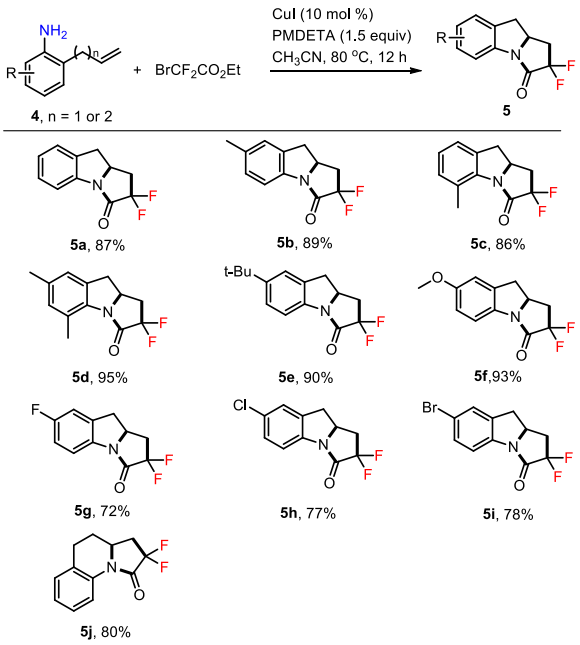


Scheme 2. Substrate Scope of Primary Amine-Containing Olefins. *Reaction conditions:* **1** (0.5 mmol, 1.0 equiv), bromodifluoroacetate (0.75 mmol, 1.5 equiv), PMDETA (0.75 mmol, 1.5 equiv), CuI (10 mol %), DMSO (3.0 mL), under Ar at 80 °C for 12 h. [a] **2c** was purified by silica gel chromatography followed by preparative TLC.

acetonitrile, toluene, 1,4-dioxane, and dimethyl sulfoxide have been screened and dimethyl sulfoxide

proved to be the optimal choice (entries 5-9). Other copper salts were screened (entries 10-13). In the presence of CuCN, $CuBr_2$, and $Cu(OTf)_2$, the yield of **2a** decreased dramatically, accompanied by increasing formation of byproduct **3**. When CuBr was applied, similar yield was resulted. In the absence of Cu catalyst, **2a** can't be obtained and **3** was generated in high yield (entry 14). When the reaction was conducted at lower temperature (entries 15 and 16), the conversion rate of **1a** decreased. Consequently, CuI as catalyst, PMDETA as both ligand and base, dimethyl sulfoxide as solvent were chosen as the optimized conditions.

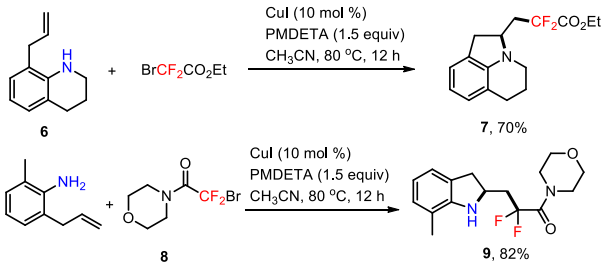
With the optimized reaction conditions in hand, a variety of aliphatic primary amine-containing olefins were investigated to demonstrate the substrate scope. The linear aliphatic amino olefins with geminal disubstitutions could afford the desired difluorinated pyrrolizidine products in good yields (**2a** and **2b**). Without geminal substitutions, **2c** was obtained with a much lower yield. The reason for low cyclized yield of **1c** compared with other substrates might be due to Thorpe-Ingold effect,[16] where increasing the size of two substituents on a tetrahedral center facilitate the cyclized reactions of the other two substituents. Notably, difluorinated indolizidine derivatives could also be obtained in high efficiency through this method (**2d** and **2e**). Importantly, difluorinated tetrahydroisoquinoline derivative **2f** with aza-[4,3,0] bicyclic skeleton was also obtained in 71% yield. Unfortunately, the aza-[5,3,0] bicyclic skeleton **2g** couldn't be obtained through this method. It is noteworthy that, in fact, only a few successful transition metal-catalyzed methods for the annulation of aliphatic primary amine-containing olefins to construct nitrogen-containing heterocycles have been reported.[17]



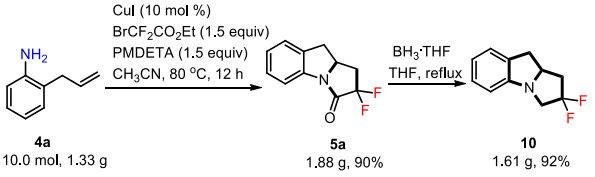
Scheme 3. Substrate Scope of Aromatic Amines. *Reaction conditions:* **4** (1.0 mmol, 1.0 equiv), bromodifluoroacetate (1.5 mmol, 1.5 equiv), PMDETA (1.5 mmol, 1.5 equiv), CuI (10 mol %), CH_3CN (2.0 mL), under Ar at 80 °C for 12 h.

Next, a series of *o*-allylaniline derivatives was tested. However, the optimized conditions described above were not productive. Gratefully, with acetonitrile as solvent instead of dimethyl sulfoxide, a variety of difluorinated benzopyrrolizidine derivatives could be obtained in good to excellent yields (**5a**–**5i**). A variety of substituents, including electron-donating (Me, ^{t}Bu, OMe) and electron-withdrawing substituents (F, Cl and Br), were all well-tolerated. Notably, the present method could be applied to the synthesis of difluorinated benzoindolizidine derivative **5j** in high efficiency.

Inspired by the above results and previous work,[11a,b] we envisioned that difluoroalkylated indoline derivatives could be obtained when the primary amine was replaced by secondary amine. As expected, secondary amine substrate **6** was effectively converted into the difluoroalkylated indoline derivative **7** under the standard conditions. Similarly, when ethyl bromodifluoroacetate ($BrCF_2CO_2Et$) was replaced by *α*-bromodifluoroacetamide **8**, the difluoroalkylated indoline derivative **9** could be obtained in excellent yield (Scheme 4). It should be noted that multigram-scale experiment has been conducted using **4a** as a model substrate, and the yield of the desired product **5a** was maintained under the standard conditions. Remarkably, the difluorinated benzopyrrolizidine derivative **5a** could be converted to difluorinated benzopyrrolizidine **10** in high efficiency through a simple step (Scheme 5). These results indicate this efficient and convenient approach may provide practical access to scale-up synthesis of difluorinated pyrrolizidines and indolizines.

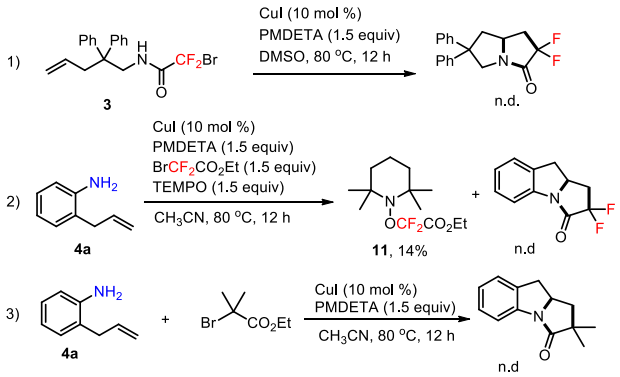


Scheme 4. Synthesis of Difluoroalkylated Indoline Derivatives



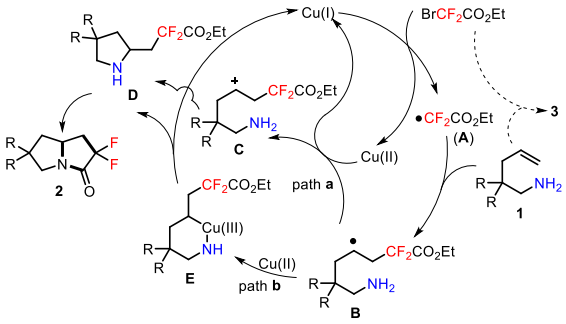
Scheme 5. Multigram-Scale Experiment

Control experiments were carried out to gain some insight into the mechanism of this reaction. Firstly, the treatment of compound **3** under the standard conditions can't afford the desired product, which means that **3** was not an intermediate of this transformation. Secondly, the reaction was completely quenched by the radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 1.5 equiv) and TEMPO-CF_2CO_2Et was observed with 14% yield by ^{19}F NMR spectroscopy, confirming that $\bullet CF_2CO_2Et$ was generated in the catalytic system. In addition, the annulation reaction can't occur when $BrCF_2CO_2Et$ was replaced by ethyl 2-bromo-2-methylpropanoate (Scheme 6).



Scheme 6. Control Experiments

In light of these results and previous reports, plausible mechanism was proposed in Scheme 7. The catalytic cycle was initiated with oxidation of Cu(I) species by $BrCF_2CO_2Et$ through a single-electron transfer (SET) to afford an electrophilic fluoroalkyl radical **A** and Cu(II) species. Subsequently, fluoroalkyl radical **A** reacted with alkenes to form alkyl radical **B**, which underwent oxidation with Cu(II) species to generate the cationic intermediate **C** and recycling Cu(I) species. The cationic intermediate **C** was nucleophilic attacked by the intramolecular nitrogen of the amines and difluoroalkylated pyrrolidine intermediate **D** was produced (path a). Another possible pathway that involves Cu(III) intermediate cannot be ruled out at current stage as shown in path b. The alkyl radical **B** was trapped by Cu(II) and Cu(III) species **E** was generated. Then reductive elimination of **E** led to intermediate **D** and regenerated Cu(I) species. Finally, the desired product was obtained through intramolecular ester-amide exchange.[18]



Scheme 7. Proposed Mechanism.

In conclusion, we disclosed an efficient and novel method for the construction of diverse difluorinated nitrogen-containing polycycles from ethyl bromodifluoroacetate and broadly available primary amines, including aliphatic amines and aniline, through a copper-catalyzed radical cascade annulation. A series of difluorinated pyrrolizidine and indolizidine derivatives has been synthesized in good yields. This method may find broad application in the synthesis of diverse fluorinated alkaloids. Further investigations and applications of this method are underway in our laboratory.

Experimental Section

Synthesis of 2,2-Difluoro-6,6-diphenyltetrahydro-1H-pyrrolizin-3(2H)-one (2a). Representative Procedure I. To a 25 mL of Schlenk tube was added CuI (0.05 mmol, 10 mol%) under air and then evacuated and backfilled with Ar (3 times). Acetonitrile (3 mL), PMDETA (0.75 mmol, 1.5 equiv.), **1a** (0.5 mmol, 1.0 equiv.) and ethyl bromodifluoroacetate (1.5 equiv.) was added subsequently. The reaction mixture was heated to 80 °C (oil bath). After stirring for 12 h, the reaction was allowed to cool down to room temperature and diluted with water (20 mL). The aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. The organic layer was then concentrated under vacuum, and the residue was separated by silica gel column chromatography (Petroleum ether/EtOAc) to give the desired product **2a**. (131 mg) as a yellow solid. Yield 84 %; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.20 (m, 4H), 7.19 – 7.07 (m, 6H), 4.25 (dd, *J* = 12.5, 3.0 Hz, 1H), 3.83 (dd, *J* = 12.3, 2.8 Hz, 2H), 2.82 – 2.48 (m, 2H), 2.25 – 1.94 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.66 (dd, *J* = 33.0, 27.1 Hz), 145.24 (d, *J* = 3.6 Hz), 128.88, 128.85, 127.20, 127.08, 126.72, 126.58, 120.83 (dd, *J* = 257.9, 253.1 Hz), 56.81, 54.04 (d, *J* = 6.6 Hz), 53.17, 44.56, 38.65 (dd, *J* = 25.1, 20.7 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ -102.17 – -103.37 (m, 1F), -105.35 (ddd, *J* = 264.0, 12.4, 1.9 Hz, 1F); HRMS (ESI): *m/z* calcd. for $C_{19}H_{17}F_2NNaO^+$ [M + Na^+]: 336.1170, found: 336.1173.

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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