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Desulfonylation-Initiated Distal Alkenyl Migration in Copper-Catalyzed Alkenylation of Unactivated Alkenes

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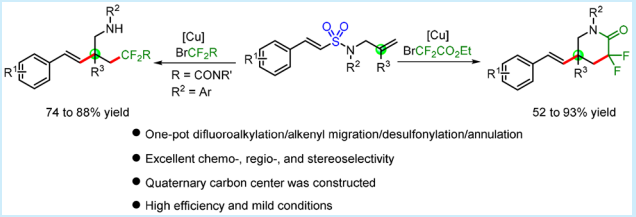
Supporting Information

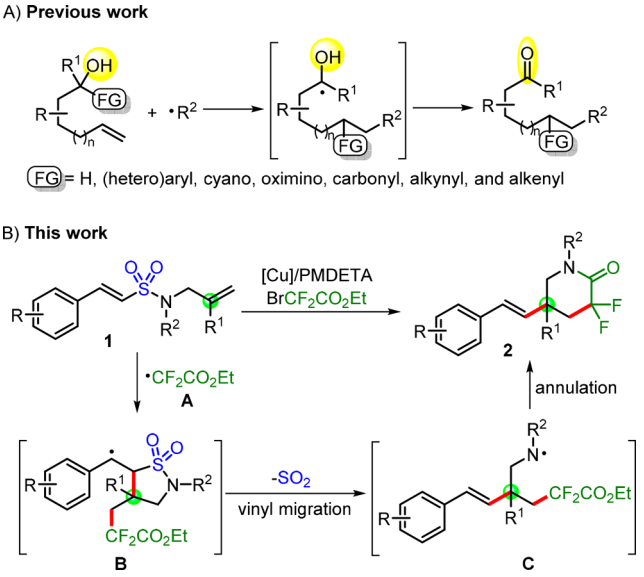
ABSTRACT: A novel and efficient protocol for desulfonylation-initiated distal alkenyl migration and its application to the elusive alkenylation of unactivated alkenes have been presented. This radical cascade process has successfully achieved the vicinal difluoroalkylalkenylation of unactivated alkenes with excellent chemo-, regio-, and stereoselectivity in high efficiency under mild conditions. The reactions afford previously unknown 3,3-difluoro-5-styrylpiperidin-2-one derivatives or β-styryl-γ-difluoroalkyl amines bearing a quaternary stereocenter. This is the first report of difunctionalization of unactivated alkenes through desulfonylation-initiated distal alkenyl migration.



The remote radical migration strategy has attracted much attention recently since it not only offers new synthetic protocols to reconstruct the molecular structures through a modular approach in organic synthesis but also provides an excellent alternative pathway to existing ionic-type rearrangement reactions.[1] During the past several years, a great number of examples of the radical-mediated distal functional group migration have been documented. Vicinal difunctionalization of alkenes through intramolecular functional group migration has been established as a promising synthetic method, in particular, for the unactivated alkenes, and the migration of diverse functional groups, including hydrogen,[2] formyl,[3] (hetero)aryl,[4] cyano,[5] alkynyl,[6] and oximino[7] has been achieved. Although energetically unfavorable compared with other functional groups based on density functional theory calculations,[8] the efficient radical-mediated alkenyl migration has been developed recently and subjected to vicinal fluoroalkylalkenylation of unactivated alkenes by Liu's and Studer's groups, respectively.[9] These excellent works take advantage of the delicate incorporation of hydroxyl moieties that tend to form a low energy neutral ketyl radical, thus facilitating the intramolecular migration of adjacent vinyl group. However, the requirement of a hydroxyl moiety seriously limits the substrate scope to alcohols (Scheme 1A).[10] Therefore, it is highly desirable to develop a novel and efficient strategy to expand the substrate scope of radical-initiated migration into manifold substrates.

Sulfur dioxide extrusion has been successfully applied to Smiles rearrangement to promote transfer of the aryl group.[11] Enlightened by this, we hypothesized that incorporating a sulfonyl group into the substrates bearing two alkenyl groups could trigger alternative reaction pathways. Based on our recent progress of the radical reaction of alkenes with ethyl bromodifluoroacetate ($BrCF_2CO_2Et$),[12] the substrate **1** was designed which might undergo vinyl migration to afford skeletal reorganization products. In this scenario, the radical **B** might be formed by difluoroalkylation of terminal alkene followed by 5-exo cyclization in the substrate **1**. Subsequent

Scheme 1. Vicinal Difunctionalization of Unactiviated Olefins via Remote Radical Functional Migration



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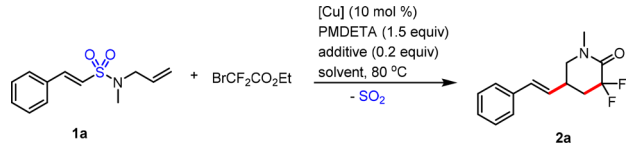
kinetically favored β-scission of the sulfonyl group followed by desulfonylation could afford the intramolecular 1,4-alkenyl migration product **C**. (*E*)-3,3-Difluoro-5-styrylpiperidin-2-one **2** would then be obtained upon annulation of the *N*-centered radical **C** (Scheme 1B). Herein, we present a novel and efficient protocol for desulfonylation-initiated distal alkenyl migration and its application to the elusive alkenylation of unactivated alkenes.

We initiated this study with (*E*)-*N*-allyl-*N*-methyl-2-phenylethenesulfonamide **1a** as a model substrate and commercially available ethyl bromodifluoroacetate ($BrCF_2CO_2Et$) as a CF_2 radical source[13] for the optimization of reaction conditions (Table 1). To our delight, the desired product 3,3-difluoro-1-methyl-5-styrylpiperidin-2-one **2a** was obtained in 31% yield with excellent *E*/*Z* selectivity via a vinyl migration and desulfonylation process in the presence of CuI (10 mol %) and PMDETA (pentamethyldiethylenetriamine, 1.5 equiv) at 80 °C for 12 h (entry 1). The yield decreased to 27% when *N*,*N*-dimethylformamide (DMF) was used as the solvent (entry 2) but increased to 50% when dimethyl sulfoxide (DMSO) was used (entry 3). When the amount of CuI was increased to 1.1 equiv, the desired product **2a** can be obtained in 61% yield (entry 4). Then different copper salts were screened, including CuCl, CuCN, $Cu(OTf)_2$, $Cu(MeCN)_4PF_6$, and Cu_2O (entries 5−9). For this cascade difluoroalkylation/5-exo cyclization/desulfonylation and annulation reaction, Cu_2O proved to be the optimized catalyst and provided the desired product **2a** in 59% yield (entry 9). Encouraged by this result, we used sodium pyrosulfite ($Na_2S_2O_5$) as the reducing reagent for the regeneration of Cu(I) catalyst, and the yield of the desired product **2a** was improved to 72% with 10 mol % of Cu_2O (entry 10). Replacing $Na_2S_2O_5$ with other reducing reagents, such as sodium thiosulfate ($Na_2S_2O_3$), hydroquinone, and copper powder, led to inferior results (entries 11−13). When the dosage of PMDETA was decreased to 30 mol % (entry 14), the yield of **2a** decreased dramatically to 32%, so PMDETA is not only a ligand but also a base in the catalytic system.[14]

With the optimal reaction conditions established, the scope of the reaction was next investigated. First, the migrating styryl group was systematically investigated (Scheme 2). A variety of substrates bearing electron-donating or electron-withdrawing groups at the *para* position in the aryl afforded the desired products **2a**−**f** in 63−72% yields, so the electronic effects of the *para* position of the aryl moiety are not pronounced. The

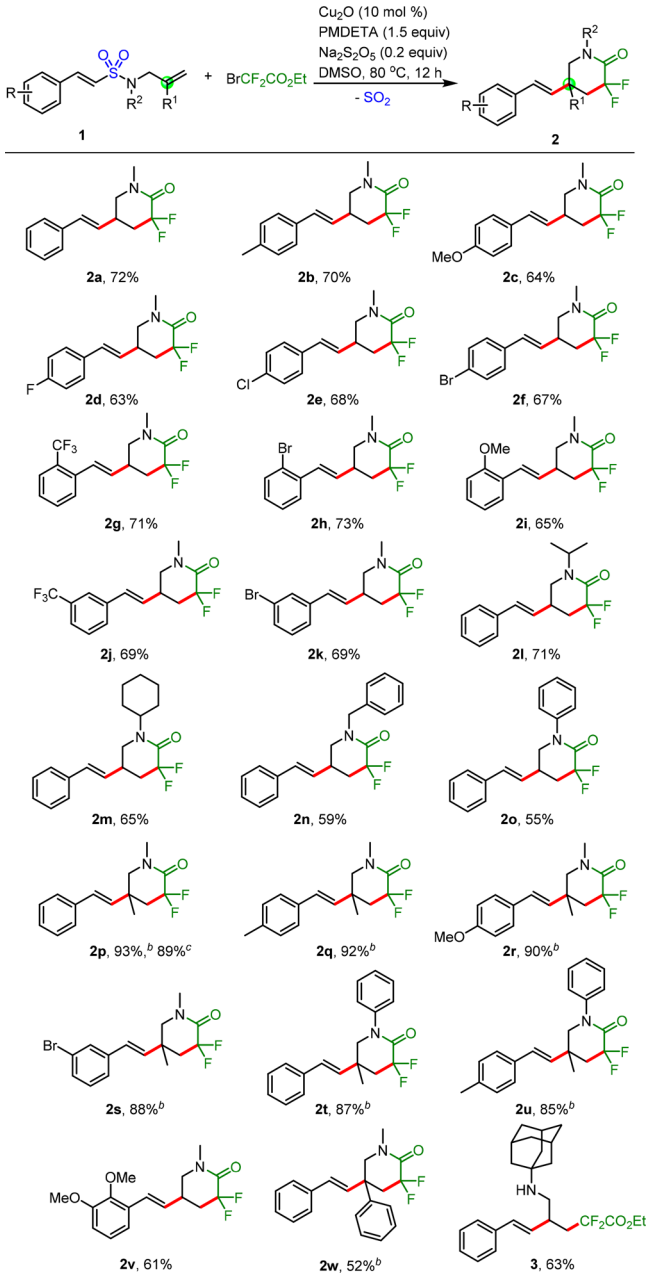
Table 1. Optimization of Reaction Conditions[a]



entry	[Cu]	solvent	additive	yield[b](%)
1	CuI	CH_3CN		31
2	CuI	DMF		27
3	CuI	DMSO		50
4[c]	CuI	DMSO		61
5	CuCl	DMSO		33
6	CuCN	DMSO		43
7	$Cu(OTf)_2$	DMSO		31
8	$Cu(MeCN)_4PF_6$	DMSO		36
9	Cu_2O	DMSO		59
10	**Cu_2O**	**DMSO**	**$Na_2S_2O_5$**	**72**
11	Cu_2O	DMSO	$Na_2S_2O_3$	58
12	Cu_2O	DMSO	quinol	53
13	Cu_2O	DMSO	Cu	63
14[d]	Cu_2O	DMSO	$Na_2S_2O_5$	32

[a]Reaction conditions: Unless otherwise noted, all reactions were performed with **1a** (0.4 mmol), $BrCF_2CO_2Et$ (0.6 mmol), PMDETA (0.6 mmol), and [Cu] (10 mol %) in solvent (1 mL) at 80 °C under Ar for 12 h. [b]Isolated yield. [c]CuI (1.1 equiv) was used. [d]PMDETA (0.12 mmol, 30 mol %).

Scheme 2. Copper-Catalyzed Difluoroalkylation/5-Exo Cyclization/Desulfonylation and Annulation[a]



[a]Reaction conditions: **1** (0.4 mmol, 1.0 equiv), $BrCF_2CO_2Et$ (0.6 mmol, 1.5 equiv), PMDETA (0.6 mmol, 1.5 equiv), Cu_2O (10 mol %), DMSO (1.0 mL), under Ar at 80 °C for 12 h. Isolated yield was based on **1**. [b]50 °C. [c]5 mmol scale.

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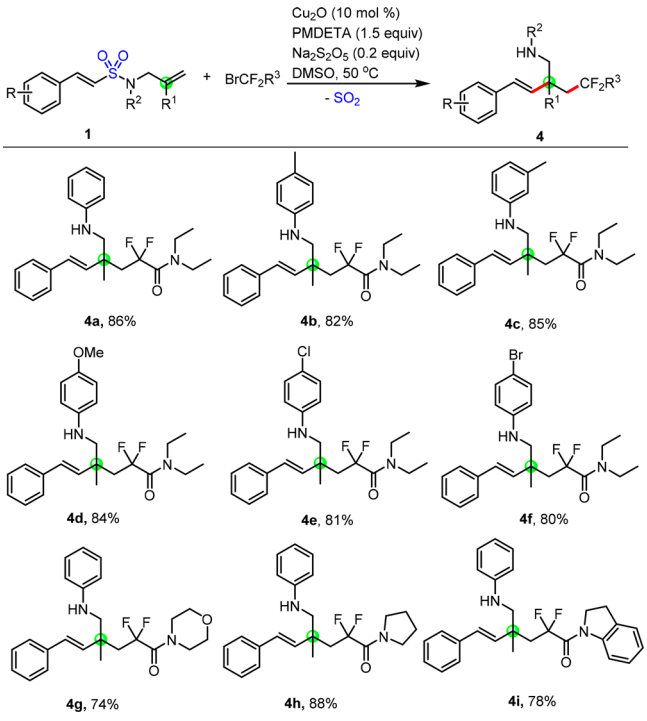
ortho-substituted substrates generated the targeted products **2g−i** in 65−73% yields; the *meta*-substituted substrates also worked well, and both **2j** and **2k** were isolated in 69% yields. Substrates bearing a disubstituted styryl group afforded the corresponding product **2v** in 61% yield. Next, we focused on the substrates bearing different substituents at the N atom. Isopropyl, cyclohexyl, benzyl, and phenyl were tolerated, affording the desired products **2l−o** in good yields. Notably, the geminal-disubstituted alkenes also underwent this transformation and furnished the desired products **2p−u** bearing a quaternary carbon center on the ring of piperidin-2-ones in excellent yields even under lower reaction temperature (50 °C), indicating that alkenyl migration also works for tertiary alkyl radical. The substituents both on the benzene ring of the migrating styryl and at the N atom do not play a major role. An aromatic group could also be incorporated at the 2-position of the terminal alkene, and the corresponding product **2w** was obtained in moderate yield. However, when the more sterically demanding adamantyl directly bound to N atom was used, the annulation was hindered and the noncyclic product **3** was isolated in 63% yield.

In order to afford the noncyclized product, the ethyl bromodifluoroacetate with labile ester group was replaced by *β*-bromodifluoroacetamides with robust amide group, thus the annulation through ester exchange would be hindered (Scheme 3). As expected, the desired product *β*-styryl-*γ*-difluoroalkyl amine **4a** bearing a quaternary carbon center was isolated in 86% yield. The influence of the substituents on the aryl group directly bonded to the N atom was investigated first, and *p*- and *m*-methyl were efficiently transformed into the corresponding products **4b** and **4c**. Both electron-donating and electron-withdrawing substituents at the *para* position had no effect and the corresponding products **4d** to **4f** were formed in good yields. We then investigated a variety of other bromodifluoroacetamides, and the corresponding products **4g** to **4i** were obtained in good yields, respectively. However, when *β*-bromodifluoroacetamides derived from pyrrole or alkyl/benzyl amine were subjected to above condition, the reaction became messy and no desired products can be isolated (see the Supporting Information).

Base on the above results and the previous works about the radical-mediated difunctionalization of alkenes through distal migration of functional groups, a plausible mechanism is suggested in Scheme 4. The initiation of the catalytic cycle occurs with oxidation of Cu(I) species by $BrCF_2R^3$ through a single-electron transfer process, and an electrophilic fluoroalkyl radical **I** and Cu(II) species are generated concomitantly. Subsequently, fluoroalkyl radical **I** selectively attacks the less sterically hindered terminal alkene to give the transient alkyl radical **II**. The alkyl radical **II** then adds to the internal double bond to furnish a 5-exo cyclization and generate the cyclized radical **III**, which will undergo rapid desulfonylation to form the key *N*-centered radical **IV**, delivering the radical alkenyl migration and the formation of a new $C(sp^2)-C(sp^3)$ bond. Then, hydrogen abstraction of the N-centered radical **IV** from solvent gives the desired products **4** (path a) (see the Supporting Information for the deuterated labeling experiment). An annulation will proceed rapidly if R^3 is CO_2Et and generates the products 3,3-difluoro-5-styrylpiperidin-2-ones (**2**) (path b). Finally, recycling Cu(I) species is completed after the reduction of Cu(II) species by solvent or $Na_2S_2O_5$. Although the reaction can occur without $Na_2S_2O_5$, the yield decreased obviously. Therefore, the major role of $Na_2S_2O_5$ might be accelerating the reduction of Cu(II) species, thus facilitating the regeneration of Cu(I) species. These results are consistent with the results in our previous work.[12e]

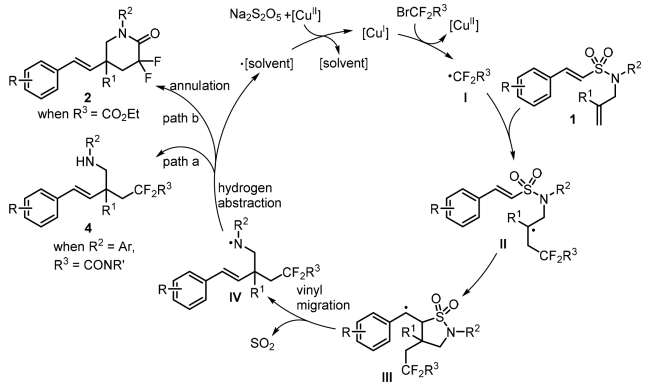
In conclusion, a novel and efficient protocol for desulfonylation-initiated formal distal alkenyl migration and its application to the elusive alkenylation of unactivated alkenes has been presented. The vicinal difluoroalkylalkenylation of unactivated alkenes has been successfully achieved with excellent chemo-, regio-, and stereoslectivity under mild conditions. In particular, this transformation offers a unique and broadly applicable platform to directly access to previous unknown 3,3-difluoro-5-styrylpiperidin-2-ones derivatives. Alternatively, *β*-styryl-*γ*-difluoroalkyl amine bearing a quaternary

Scheme 3. Copper-Catalyzed Difluoroalkylation/5-Exo Cyclization/Desulfonylation[a]



[a]Reaction conditions: **1** (0.4 mmol, 1.0 equiv), $BrCF_2R^3$ (0.6 mmol, 1.5 equiv), PMDETA (0.6 mmol, 1.5 equiv), Cu_2O (10 mol %), DMSO (1.0 mL), under Ar at 50 °C for 12 h. Isolated yield was based on **1**.

Scheme 4. Proposed Mechanism



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stereocenter can be obtained when the annulation is hindered. This is the first report of difunctionalization of unactivated alkenes with desulfonylation-initiated distal alkenyl migration, and detailed mechanistic studies and further expansion of this protocol are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02840.

Experimental procedures, spectral and analytical data, and ^{1}H and ^{13}C NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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