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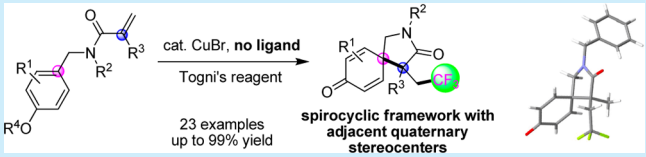
Copper-Catalyzed Intramolecular Trifluoromethylation of *N*-Benzylacrylamides Coupled with Dearomatization: Access to CF_3-Containing 2-Azaspiro[4.5]decanes

Guifang Han, Yuxiu Liu, and Qingmin Wang*

State Key Laboratory of Elemento-Organic Chemistry, Research Institute of Elemento-Organic Chemistry, Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Nankai University, Tianjin 300071, China

Supporting Information

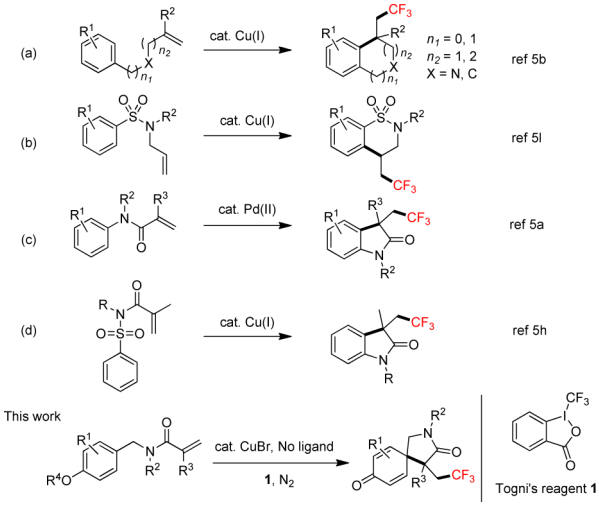
ABSTRACT: Copper-catalyzed intramolecular trifluoromethylation of *N*-benzylacrylamides coupled with dearomatization was achieved and used to regiospecifically construct a variety of trifluoromethylated 2-azaspiro[4.5]decanes bearing adjacent quaternary stereocenters under mild conditions in moderate to excellent yields.



The trifluoromethyl group is of interest in pharmaceutical chemistry, agrochemistry, and materials science because introducing a trifluoromethyl group to small organic molecules can dramatically enhance chemical and metabolic stability, as well as lipophilicity.[1] Thus, the development of efficient methods for selectively introducing a trifluoromethyl group into organic molecules is a hot topic in modern organic chemistry.[2] Transition-metal-mediated direct difunctionalization of alkenes involving the simultaneous formation of C−CF_3 and C−O, C−N, or C−C bonds was recently reported to be effective for the construction of polyfunctional molecules.[3−5] For example, catalytic electrophilic allylic trifluoromethylation of terminal alkenes has been reported,[6] and an intramolecular oxytrifluoromethylation that yields trifluoromethylated epoxides, cyclic ethers, and lactones has been elaborated.[3d,4b] The Wu,[5d] Sodeoka,[5g] and Tu[5e] research groups independently demonstrated that Cu(I) and Fe(II) catalyze carbotrifluoromethylation of α,α-diaryl allylic alcohols via trifluoromethylation coupled with 1,2-aryl migration to afford β-trifluoromethyl ketones. Cu/Pd-catalyzed aryltrifluoromethylation of terminal alkenes with Togni's reagent as the CF_3 source yields compounds with conjugated rings as the main product.[5] Meanwhile, the Nevado group reported the metal-free catalytic aryltrifluoromethylation of activated alkenes to achieve trifluoromethylated isoquinolinediones, spirobicycles, oxindoles, and α-aryl-β-trifluoromethylamides with high regioselectivity.[5k] The trifluoromethyl cation or a radical species has been suggested as an intermediate, but the detailed mechanisms of these reactions have not been elucidated.

Dearomatization reactions provide a powerful strategy for the synthesis of ring systems from readily available aromatic compounds.[7] The dearomatization of phenols to cyclohexadienones is of particular interest, and numerous such dearomatizations have been used in complex total syntheses.[8] For example, Pettus[9] reported the first total synthesis of (+)-rishirilide B by dearomatization of resorcinol derivatives, and Nicolaou[10] synthesized (−)-platensimycin through oxidative dearomatization of a phenolic substrate with concomitant C−C bond formation. Research on the synthesis of spirocyclic frameworks, which are found in a wide variety of biologically active natural products and pharmaceuticals, is ongoing in our laboratory, and the spirocyclic framework could be obtained by trifluoromethylation of a benzyl-substituted alkene coupled with C−C bond formation when a hydroxyl group or methoxy group was present at the para position of the aromatic ring,[5k] despite the existence of a pathway to afford the conjugated ring product or other byproducts.[11] Herein, we describe copper-catalyzed intramolecular trifluoromethylation of *N*-benzylacrylamides coupled with dearomatization in the presence of Togni's reagent (Scheme 1).

Scheme 1. Metal-Catalyzed Trifluoromethylation of Alkenes



We optimized the reaction conditions using *N*-(4-hydroxy)-benzylacrylamide (**2a**)[12] as a model substrate (Table 1). We

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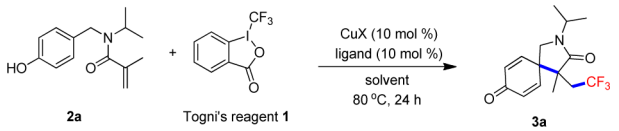
Table 1. Optimization of Reaction Conditions[a]



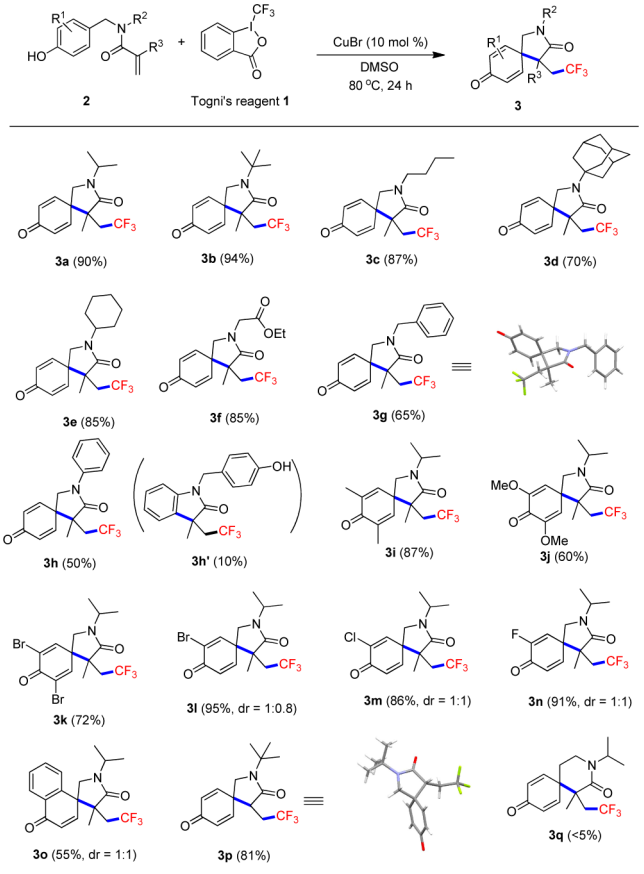
entry	catalyst	ligand	solvent	yield[b] (%)
1	CuI		1,4-dioxane	20
2	CuI	Bipy	CH_3CN	65
3		Bipy	CH_3CN	0
4	CuCl	Bipy	CH_3CN	52
5	$[Cu(MeCN)_4]PF_6$	Bipy	CH_3CN	75
6	$Cu(OAc)_2$	Bipy	CH_3CN	61
7	CuBr	Bipy	CH_3CN	92 (85)[c]
8	CuBr		CH_3CN	93
9	CuBr		1,4-dioxane	72
10	CuBr		DCE	91
11	CuBr		$CHCl_3$[d]	87
12	CuBr		DMF	72
13	CuBr		EtOH	95
14	CuBr		DMSO	99

[a]Reaction conditions: **2a** (0.2 mmol), **1** (0.4 mmol), catalyst (0.02 mmol), ligand (0.02 mmol), solvent (2 mL), 80 °C, 24 h, under N_2. [b]Determined by ^{19}F NMR analysis with (trifluoromethyl)benzene as an internal standard. [c]The value in parentheses was isolated yield. [d]Reaction temperature, 60 °C. Bipy = 2,2′-bipyridyl.

initially examined the reaction of **2a** with Togni's reagent (**1**) as the source of CF_3 and CuI as the catalyst and found that reaction in 1,4-dioxane at 80 °C afforded the desired trifluoromethyl-containing product, 2-azaspiro[4.5]decane **3a**, in 20% yield as determined by ^{19}F NMR spectroscopy (entry 1). Encouraged by this result, we investigated whether the yield could be improved by addition of a ligand; fortunately, we found that the addition of 2,2′-bipyridyl and the use of CH_3CN as the solvent increased the yield to 65% (entry 2). The copper catalyst was essential; no reaction occurred in the absence of CuI (compare entries 2 and 3). Various copper catalysts were then evaluated. The use of CuCl, $[Cu(MeCN)_4]PF_6$, or $Cu(OAc)_2$ lowered the yield (entries 4–6), whereas CuBr gave **3a** in 92% yield as indicated by ^{19}F NMR (isolated yield, 85%; entry 7). With the ideal copper catalyst in hand, we discovered that a ligand was unnecessary for the high yield (entry 8). We then screened various organic solvents in reactions without a ligand and found that the solvent did not strongly influence the yield: reactions in 1,4-dioxane, DCE, $CHCl_3$, DMF, and EtOH all gave satisfactory yields (entries 9–13). When the reaction was conducted in DMSO, the starting material was completely converted after 24 h at 80 °C, and the yield of the desired product was nearly quantitative (entry 14).

Using the optimized reaction conditions (Table 1, entry 14), we investigated the substrate scope with a wide range of substituted *N*-benzylacrylamides (Scheme 2). First we focused on the N-substituent (R^2). Substrates with *n*-butyl and cyclohexyl substituents, more bulky isopropyl and *tert*-butyl substituents, and even a 1-adamantanyl substituent, all afforded the corresponding 2-azaspiro[4.5]decanes **3a–e** in excellent yields. Substrate **2f**, which was substituted with the methyl ester of glycine, cyclized efficiently to give **3f** in 85% yield. When R^2 was a benzyl group, there were two aromatic rings in the substrate; we nevertheless obtained **3g** exclusively, which indicates that the phenolic hydroxyl group is essential for the spiro cyclization. The structure of **3g** could be unequivocally assigned by X-ray

Scheme 2. Substrate Scope of Copper-Catalyzed Trifluoromethylation/Dearomatization[a]



[a]Reactions were carried out with CuBr (10 mol %) and **1** (2 equiv) in degassed DMSO at 80 °C under N_2. Isolated yields are provided.

diffraction analysis.[13] When R^2 was a phenyl group, desired product **3h** was obtained in 50% yield, along with a 10% yield of conjugated-ring byproduct **3h′**; this result provided some insight into the reaction mechanism. Next, we turned our attention to the substituents on the aromatic ring (R^1). Substrates with electron-donating CH_3 and OMe groups or electron-withdrawing F, Cl, or Br atoms afforded desired products **3i–n** in good to excellent yields. When the substituents were axisymmetric with respect to the phenolic hydroxyl group, corresponding 2-azaspiro[4.5]decanes **3i–k** were obtained exclusively; nonaxisymmetric substrates gave pairs of diastereomers in an approximately 1:1 ratio. When the phenol was replaced with a naphthol, the desired product **3o** was also obtained as two diastereomers in 55% yield. Finally, we investigated the reaction of a monosubstituted olefin (R^3 = H), which was previously reported not to undergo reaction leading to the conjugated-ring product;[5] however, we obtained desired product **3p** in 81% yield, and its structure was unequivocally determined by X-ray diffraction analysis.[13] Expecting carbotrifluoromethylation and subsequent formation of a six-membered ring, we subjected **2q** to the standard reaction conditions, but unfortunately, the expected product **3q** was not detected by ^{19}F NMR.

To further explore the applications of this reaction system, we extended it to stable, easy-to-prepare substrates with various substituents (R^4) on the phenol O atom (Table 2). As expected, even when the phenol O atom was masked with a methyl group

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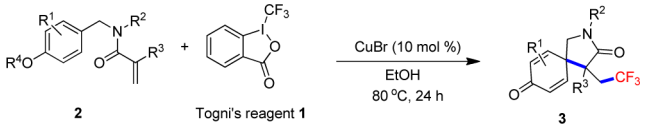
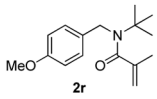
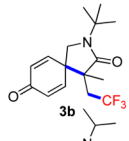
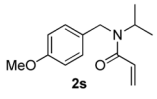
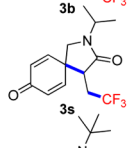
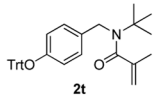
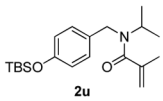
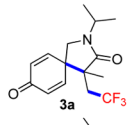
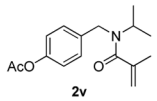
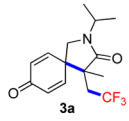
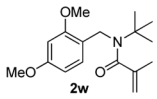
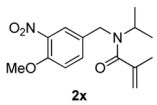
Table 2. Copper-Catalyzed Trifluoromethylation/ Dearomatization of Substrates with Masked Phenol Groups[a]



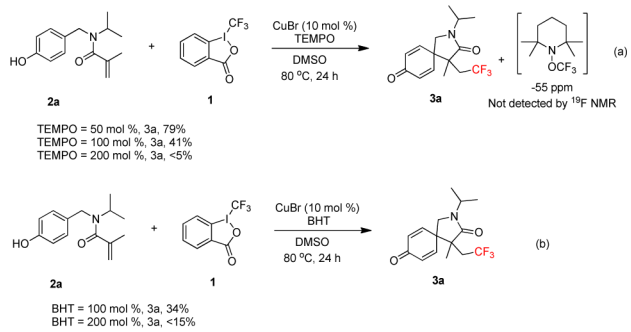
entry	substrate	product	yield/%[b]
1	 2r	 3b	63
2	 2s	 3s	64
3	 2t	 3b	88
4	 2u	 3a	74
5	 2v	 3a	53
6	 2w	 3w	75 (dr = 1:2)
7	 2x	 3x	trace

[a]Reactions were carried out with CuBr (10 mol %) and **1** (2 equiv) in degassed EtOH at 80 °C under N_2. Isolated yields are provided.

(substrate **2r**), the tandem cyclization occurred and afforded spirocyclic product **3b** in 63% yield rather than the conjugated-ring product (isoquinolinone, entry 1). Note that the reaction was carried out in EtOH rather than DMSO because complete conversion took longer in DMSO. Even monosubstituted olefin **2s** (R^3 = H) furnished corresponding product **3s** in moderate yield (entry 2). Substrates **2t**, **2u**, and **2v**, which bear triphenylmethyl, *tert*-butyldimethylsilyl, and acetyl protecting groups respectively, were good substrates, affording spirocyclic compounds in moderate to excellent yields (entries 3−5). Substrate **2w**, which bears an electron-donating OMe group at the ortho position of the aromatic ring, afforded **3w** in 75% yield as a 1:2 mixture of diastereomers (entry 6). However, **2x** which has an electron-withdrawing nitro group, gave unsatisfactory results (entry 7).

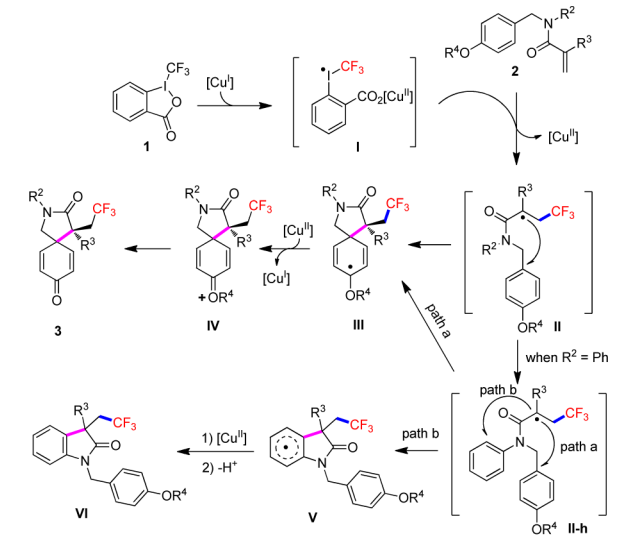
To gain insight into the reaction mechanism, we performed several control experiments. The trifluoromethylation reaction of **1** and **2a** was conducted under the standard conditions in the presence of various amounts of a radical scavenger, either 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT). In the presence of 50 mol % of TEMPO, the yield of **3a** dropped to 79% as determined by ^{19}F NMR. In the presence of 100 mol % of TEMPO, the yield decreased further to 41%, and the reaction was almost completely shut down by the addition of 200 mol % of TEMPO (Scheme 3a). Similar results were obtained with BHT (Scheme 3b). These results clearly point toward a radical mechanism. However, when the reaction in the presence of TEMPO was followed by ^{19}F NMR, the corresponding TEMPO−CF_3 adduct was not detected, which suggests that some species other than CF_3 radical might form at the outset of the process. In addition, when R^2 was Ph (Scheme 2), the reaction gaves pirocyclic product **3h** and the conjugated-ring product **3h′**, which suggests that the two products maybe form from the same intermediate during the initial stage of the reaction.

Scheme 3. Mechanistic Investigation



On the basis of these results and previously reported results,[3−5] we propose the mechanism illustrated in Scheme 4.

Scheme 4. Proposed Reaction Mechanism



In the first step, Cu(I) reacts with **1** to generate highly reactive CF_3Cu(II)-containing radical **I**, which reacts with **2** to form a radical species with a C(sp_3)−CF_3 bond (**II**). The carbon-centered radical undergoes thermodynamically controlled 5-*exo* cyclization onto the phenol ring to give spiro intermediate **III**,[5k] rather than a 6-*endo* cyclization leading to the isoquinolinone.[14] Radical **III** is then oxidized by Cu(II) to oxonium ion **IV** or the corresponding protonated species. Oxonium ion **IV** is transformed into **3** either in the reaction medium or during workup, and Cu(I) is released to participate in the next reaction cycle. When R^2 is Ph, there is an alternative pathway: radical **II-h** may undergo 5-*endo* cyclization, oxidation, and deprotonation to give oxindole **VI** (e.g., **3h′**). The possibility of the mechanism to proceed via a nucleophilic attack of electron-rich aryl ring to

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acrylamide involved carbocation intermediate to afford **3h′** cannot be excluded.[5b,c,k]

In summary, we developed a copper-catalyzed cascade reaction involving trifluoromethylation of substituted *N*-benzylacrylamides, 5-*exo* cyclization, and dearomatization. This reaction allows regiospecific construction of trifluoromethylated spirocyclohexadienones bearing adjacent quaternary stereocenters under mild conditions in good to excellent yields. Because of the wide substrate scope and operational simplicity, this reaction should be useful for medicinal chemistry and other applications. We are working on developing an asymmetric variant in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, copies of ^{1}H ^{13}C and ^{19}F NMR spectra for compounds **2a−x**, **3a−q**, **3h′**, **3s**, and **3w**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wangqm@nankai.edu.cn, wang98@263.net.

Notes

The authors declare no competing financial interest.

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