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Copper-Mediated α-Trifluoromethylation of *N*-Phenylcinnamamides Coupled with Dearomatization: Access to Trifluoromethylated 1-Azaspiro[4.5]decanes

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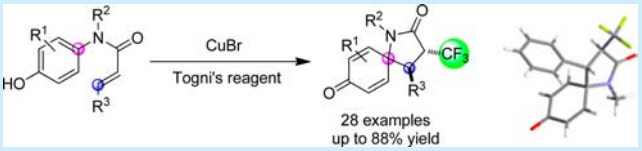
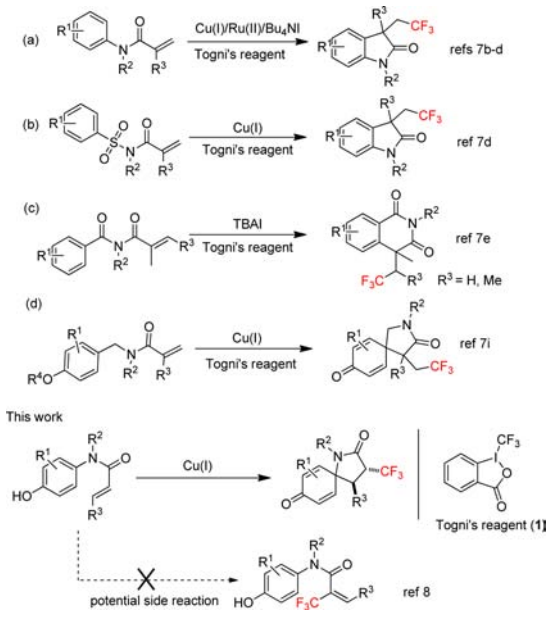
Supporting Information

ABSTRACT: Copper-mediated intramolecular trifluoromethylation of *N*-phenylcinnamamides coupled with cyclization and dearomatization was used to construct various trifluoromethylated 1-azaspiro[4.5]decanes in moderate to high yields and with excellent regioselectivity and diastereoselectivity.



The trifluoromethyl group plays a privileged role in pharmaceuticals and agrochemicals because introducing the group into organic molecules tends to improve their chemical and metabolic stability and increase their lipophilicity, bioavailability, and protein-binding affinity.[1] Consequently, the development of selective, efficient, versatile methods for introducing a trifluoromethyl group has gained increasing attention.[2] Since Togni's reagent (**1**) for trifluoromethylation reactions was first reported in 2006,[3] this versatile reagent has attracted the attention of many research groups worldwide. Transition-metal-mediated direct difunctionalization-type trifluoromethylation of alkenes with Togni's reagent is effective for the construction of polyfunctional molecules. For example, allylic trifluoromethylation of terminal alkenes to form allylic $C(sp^3)-CF_3$ bonds was described independently by Buchwald[4a] and Wang[4b] et al., and the difunctionalization of alkenes by means of simultaneous formation of $C(sp^3)-CF_3$ and C−O, C−N, or C−C bonds has been investigated by many groups.[5−7] Trifluoromethylation/cyclization cascade reactions of *N*-phenylacrylamides with Togni's reagent to yield oxindoles were reported independently by the research groups of Sodeoka, Zhu, and Nevado (Scheme 1a).[7b−d] Meanwhile, Nevado and co-workers reported the trifluoromethylation/cyclization of tosyl acrylamides and benzoyl acrylamides to yield oxindole and isoquinolinedione products (Scheme 1b, 1c).[7d,e] Although significant progress has been made, the trifluoromethylation of acrylamides and allylamines has several major limitations. For example, carbotrifluoromethylation of alkenes is almost exclusively limited to monosubstituted terminal alkenes, and the main cyclic products are exocyclic trifluoromethylated products.[7] Reports of regioselective α-trifluoromethylation of α,β-unsaturated carbonyls are still scarce. Bi et al. recently reported the copper-catalyzed trifluoromethylation of α,β-unsaturated amides using Togni's reagent to afford (*E*)-α-trifluoromethylated amides in moderate yields.[8] Mechanistic studies suggested that a trifluoromethyl cation or a radical species was an intermediate in these reactions, but few other investigators have conducted detailed mechanistic studies.

Scheme 1. Trifluoromethylation of Acrylamides with Togni's Reagent



Oxidative dearomatization of phenols is a powerful strategy for the synthesis of the bicyclic scaffolds of natural products from readily available aromatic compounds.[9] Research on the construction of spirocyclic frameworks, which are found in a wide variety of biologically active natural products and pharmaceuticals, is ongoing in our laboratory. In continuation of our work on copper-mediated difunctionalization-type trifluoromethylation of acrylamides (Scheme 1d),[7i] we herein

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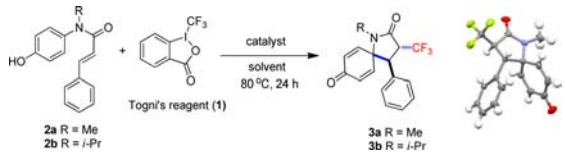
report the use of Togni's reagent for regioselective α-trifluoromethylation of *N*-phenylcinnamamides coupled with cyclization and dearomatization to afford 1-azaspiro[4.5]-decanes, which are important structural motifs in several biologically active alkaloids.[10] The incorporation of fluorine into 1-azaspiro[4.5]decanes may provide unprecedented benefits for drug discovery and may find valuable applications in medicinal chemistry.

Successful α-trifluoromethylation of acrylamides requires that competitive β-trifluoromethylation must be prevented. To achieve this goal, we designed and used **2a** as a test substrate to screen various reaction conditions.[11] Selected results are shown in Table 1. We initially examined the reaction of **2a** with

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	solvent[b]	yield[c] (%)
1	$[Cu(MeCN)_4]PF_6$	$CHCl_3$	20
2	CuCl	$CHCl_3$	36
3	CuBr	$CHCl_3$	56
4	CuI	$CHCl_3$	40
5	CuTc	$CHCl_3$	40
6	CuCN	$CHCl_3$	52
7	Cu_2O	$CHCl_3$	40
8	CuBr	DCE	63
9[d]	CuBr	DCE	70
10[d,e]	CuBr	DCE	74
11[d,e,f]	CuBr	DCE	80 (76)[g]

[a]Reaction conditions: **2a** (0.2 mmol), **1** (0.4 mmol), catalyst (0.1 mmol), solvent (3 mL), 80 °C, 24 h, under N_2 (unless otherwise noted). [b]Reaction temperature in $CHCl_3$ was 60 °C. [c]Determined by ^{19}F NMR analysis with (trifluoromethyl)benzene as an internal standard. [d]Substrate **2b** was used. [e]100 mol % Cu catalyst was used. [f]4 Å molecular sieves were added. [g]Value in parentheses is the isolated yield.

Togni's reagent (**1**) as the source of CF_3 and $Cu(CH_3CN)_4PF_6$ as the catalyst and were delighted to find that the reaction afforded desired trifluoromethylated product 1-azaspiro[4.5]-decane **3a** in 20% yield (as determined by ^{19}F NMR spectroscopy, entry 1). Encouraged by this result, we turned our attention to investigating various copper catalysts. With CuBr as the catalyst, the yield increased to 56%, and other Cu(I) compounds such as CuCl and CuCN also mediated the reaction, albeit in slightly lower yields (entries 2–7). Evaluation of various solvents (see the Supporting Information) revealed that the reaction was highly solvent dependent: DCE gave a good yield (entry 8), whereas in EtOH, none of the desired product was detected. With CuBr as the catalyst and DCE as the solvent, we next examined various ligands such as 2,2′-bipyridine, 1,10-phenanthroline, and 2,2′-biquinoline, which is reportedly effective for copper-catalyzed trifluoromethylation.[7] Unfortunately, none of the ligands facilitated the transformation (see the Supporting Information).

Analysis of the reaction byproducts showed that **2a** decomposed into fragments that did not bear a trifluoromethyl group. Therefore, the methyl substituent on the nitrogen atom of **2a** was replaced with an isopropyl group (**2b**) to minimize the decomposition of the substrate, and reaction of **2b** afforded the desired product in an improved of 70% (entry 9). Increasing the loading of the CuBr catalyst to 100 mol % raised the yield to 74% (entry 10), and adding 4 Å molecular sieves resulted in the best yield (80%, entry 11). Moreover, all the reactions of both substrates showed excellent regioselectivity and diastereoselectivity: only one product was observed. The structure of **3a** was unambiguously established by X-ray crystallography, which showed the trifluoromethyl and the phenyl groups to be in the trans configuration.[12]

With the optimized conditions in hand (Table 1, entry 11), we evaluated the substrate scope of the reaction (Scheme 2). The substituent on the nitrogen (R^2) dramatically influenced the yield. Substrates with a Me, *i*-Pr, Bn, or CH_2COOEt group afforded the corresponding 1-azaspiro[4.5]decanes (**3a**–**3e**) in good yields whereas a phenyl substituent gave a lower yield (**3c**), and none of desired product **3f** was obtained when R^2 was a Tos group. Note that Boc-containing substrate **2g** gave not desired product **3g** but deprotected product **3g′**. Cinnamamides bearing an electron-withdrawing (**2j**–**p**) or electron-donating group (**2h** and **2i**) on the aromatic ring were also suitable substrates, affording the corresponding spirocyclic products in good yields. However, substrates with an electron-withdrawing group generally gave higher yields than those with an electron-donating group. Specifically, substrates **2h** and **2i**, each bearing an aryl ring with an electron-donating substituent, were efficiently transformed into 1-azaspiro[4.5]decanes **3h** and **3i** in 65% and 67% yields, respectively. Substrates with a chloro or bromo group in the ortho, meta, or para position (**2j**–**m**) afforded the expected spirocyclic products (**3j**–**m**), and the chloro and bromo substituents allowed further derivatization by means of metal-catalyzed organic reactions. Reactions of substrates with a F group, a CF_3 group, or even a NO_2 group proceeded smoothly to generate **3n**, **3o**, and **3p**, respectively, in good yields.

Cinnamamides bearing an electron-rich furan or thiophene moiety were also suitable substrates and produced **3q** and **3r** in moderate yields. Note that compared with benzene, these electron-rich heterocycles gave slightly lower yields because the electron-rich aromatic ring in the spirocyclic product could undergo competitive trifluoromethylation of the aromatic ring, and the resulting byproduct was hard to separate from the desired product.[13] Reaction of a substrate bearing a pyridine (**2s**) afforded <5% of the desired product (**3s**). Remarkably, when $\alpha,\beta,\gamma,\delta$-unsaturated amide substrate **2u** was subjected to the standard reaction conditions, α,β-difunctionalization product **3u** was formed regioselectively in 48% yield.[12]

Further investigation revealed that the reaction was insensitive to the electronic effects of substituents on the aniline ring (R^1). Substrates with either electron-donating groups (CH_3 and OMe) or electron-withdrawing groups (halogen or ester) afforded the desired products (**3v**–**z**, **3aa**, and **3ab**) in good yields. Generally, when the substituent was axisymmetric with respect to the phenolic hydroxyl group (substrates **2a**–**v**), one pair of corresponding enantiomers (**3a**–**v**) was obtained exclusively; substrates with nonaxisymmetric substituents gave two pairs of diastereomers in different ratios.

To illustrate the synthetic utility of the method, we point out that trifluoromethylated compounds **3** can be converted into various CF_3-containing heterocycles and valuable synthons by means of conventional organic reactions (Scheme 3). 2,5-Cyclohexadienones are versatile class of building blocks that

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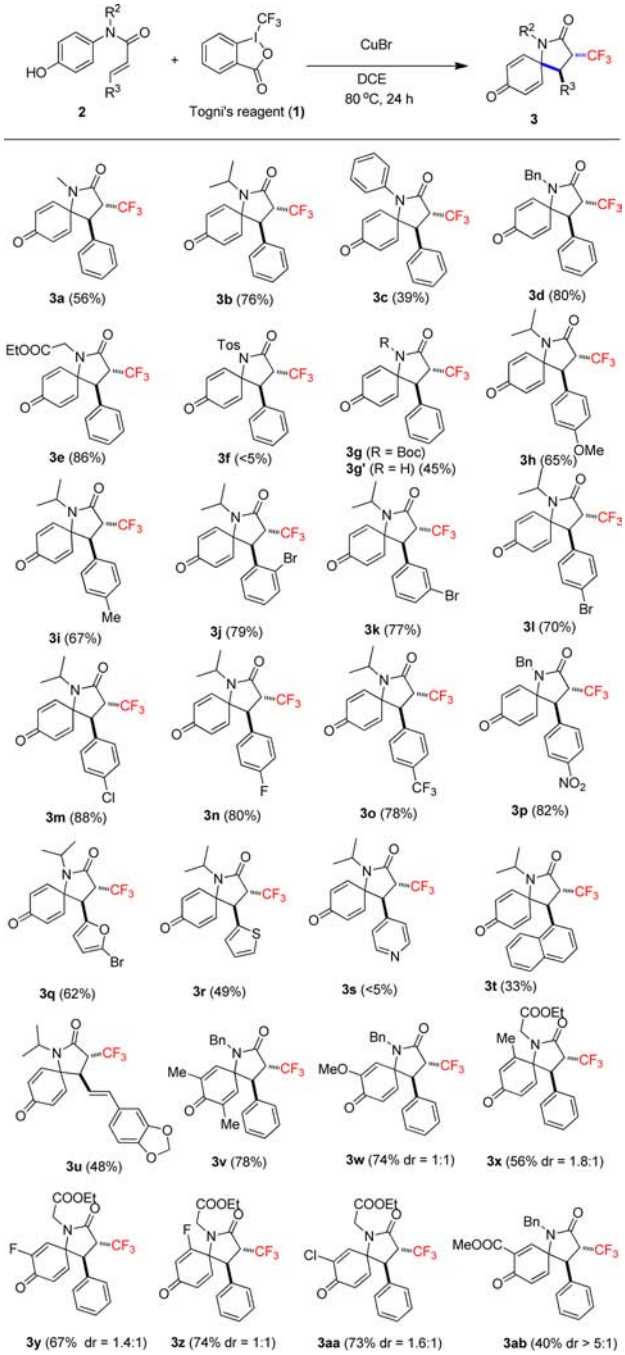
Scheme 2. Substrate Scope of Copper-Mediated Trifluoromethylation/Dearomatization.[a]

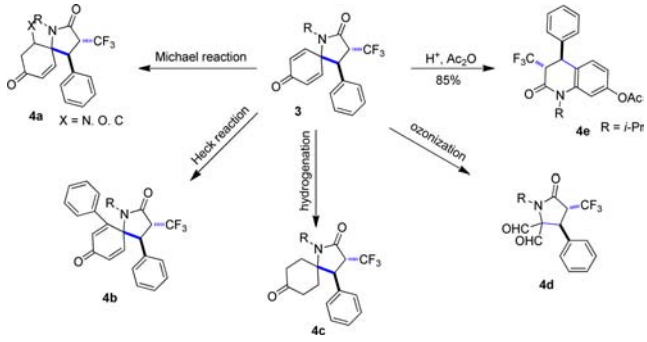


[a]Reactions conditions: **2a** (0.2 mmol), **1** (0.4 mmol), CuBr (0.2 mmol), DCE (3 mL), 80 °C, 24 h, under N_2. Isolated yields are given.

can undergo a large array of transformations:[14] for example, Michael addition reactions afford compounds **4a**,[15] transition metal−catalyzed Heck reactions afford compounds **4b**,[16] hydrogenation reactions give saturated 1-azaspiro[4.5]decanes **4c**,[17] ozonization reactions produce α-trifluoromethylated pyrrolidin-2-ones **4d**,[18] and Lewis acid or Brønsted acid mediated rearrangement reactions afford α-trifluoromethylated 3,4-dihydroquinolin-2(1*H*)-ones **4e**.

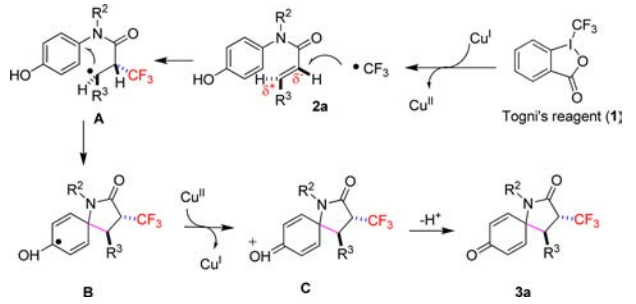
On the basis of literature precedents[5−7] and our previously published results,[7i] we propose the following plausible mechanism for this copper-mediated trifluoromethylation of

Scheme 3. Potential Synthetic Transformations of 1-Azaspiro[4.5]decanes



N-phenylcinnamamides coupled with cyclization and dearomatization (Scheme 4). First, Togni's reagent is reduced by CuBr

Scheme 4. Proposed Reaction Mechanism



to afford a CF_3 radical and Cu(II). Then, the CF_3 radical regioselectively attacks cinnamamide **2** at the α-position, which has slightly higher electron density than the β-position, to generate benzyl carbon−centered radical **A** which is stabilized by the phenyl group (R^3), simultaneously form a C(sp^3)−CF_3 bond. The benzyl radical immediately undergoes thermodynamically controlled 5-*exo* cyclization onto the phenol ring to give spirocyclic intermediate **B**.[19] The steric bulk of the trifluoromethyl and phenyl groups (R^3) favors the trans configuration. Subsequently, **B** is oxidized by Cu(II) to oxonium ion **C**, which is deprotonated to form **3**.

In summary, we developed a copper-mediated cascade reaction involving regioselective α-trifluoromethylation of substituted *N*-phenylcinnamamides, 5-*exo* cyclization, and dearomatization. A diverse array of substrates underwent the cascade reaction to afford the corresponding trifluoromethylated 1-azaspiro[4.5]decanes in moderate to high yields and with excellent regioselectivity and diastereoselectivity, and the products have the potential to be converted to various valuable CF_3-containing heterocycles and synthons by means of conventional organic reactions.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, copies of ^1H ^{13}C and ^{19}F NMR spectra for compounds **2a−ab**, **3a−e**, **3g′**, **3h−r**, **3t−ab**, and **4e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) For detailed experimental procedures and characterization of the starting materials, see the Supporting Information.

(12) CCDC 1024303 (**3a**) and CCDC 1028102 (**3u**) contain supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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