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Copper-Catalyzed One-Pot Trifluoromethylation/Aryl Migration/Desulfonylation and C(sp^2)−N Bond Formation of Conjugated Tosyl Amides

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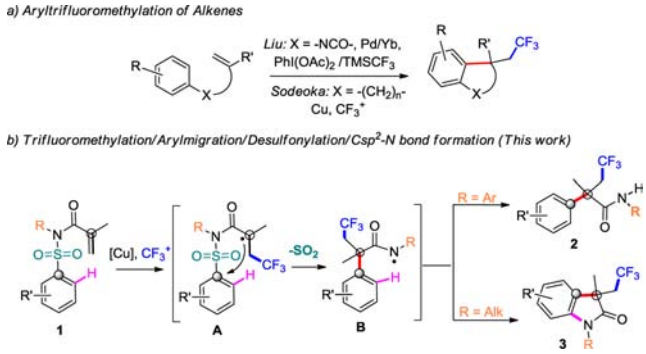
Supporting Information

ABSTRACT: A novel copper-catalyzed one-pot trifluoromethylation/aryl migration/desulfonylation and C(sp^2)−N bond formation with conjugated tosyl amides as starting materials is presented here. The reaction affords α-aryl-β-trifluoromethyl amides bearing a quaternary stereocenter or trifluoromethylated oxindoles in a regioselective manner.

The increasing presence of trifluoromethyl groups in agrochemicals, pharmaceuticals, and molecular materials stems from its unique ability to dramatically change the physical properties of these molecules due to both the high electronegativity as well as the metabolic stability of the C−fluorine bonds.[1,2] Transition-metal-mediated trifluoromethylation reactions have received increasing attention due to the mild reaction conditions they can offer in comparison to the analogous metal-free processes. Copper- and palladium-catalyzed C−CF_3 bond formation from C(sp^2)−H bonds,[3] aryl halides,[4] boronic acids,[5] and alkynes[6] have been recently developed. In addition, copper-catalyzed trifluoromethylations of nonactivated olefins,[7] allyl halides,[8] allylsilanes,[9] and α,β-unsaturated carboxylic acids[10] have also been described. In this context, the copper-mediated oxidative difunctionalization of alkenes involving the simultaneous formation of C−CF_3 and C−O bonds has aroused as a highly attractive strategy to create structural complexity, enabling an streamlined access to building blocks such as CF_3-containing lactones, cyclic ethers, epoxides, and benzylic alcohols among others.[11] Combining C−C and C−CF_3 bond formation in a single operation has also been recently explored (Scheme 1a). In 2012, Liu's group reported an efficient intramolecular Pd/Yb-catalyzed aryltrifluoromethylation of activated alkenes in which a Pd^{IV}−CF_3 intermediate generated in the presence of $PhI(OAc)_2$ and $TMSCF_3$ delivers a new C(sp^3)−CF_3 bond via reductive elimination.[12] A complementary copper-catalyzed aryltrifluoromethylation of unactivated alkenes has also been recently reported by Sodeoka and co-workers.[13] Most copper-catalyzed olefin trifluoromethylations are proposed to proceed through either cationic or radical pathways, although an in-depth mechanistic understanding of these transformations is still missing.[7−11,13] Due to our ongoing interest in the development of selective oxidative difunctionalization of alkenes,[14] we hypothesized that the presence of a sulfonyl group in the arene-ene substrates could trigger alternative reaction pathways (Scheme 1b). If an α-CF_3-alkyl radical **A** were to be formed upon alkene trifluoromethylation in tosyl amide **1**, an intramolecular

Scheme 1. Transition-Metal-Catalyzed Aryltrifluoromethylation of Alkenes



1,4-aryl migration[15] via 5-*ipso* cyclization/desulfonylation could yield amidyl radical **B**. α-Aryl-β-trifluoromethyl amides **2** would then be obtained upon H abstraction or alternatively, trifluoromethylated oxindoles **3** could be produced upon cyclization, with both processes occurring in a regioselective manner. Herein we report the successful implementation of this concept with a novel copper-catalyzed one-pot trifluoromethylation/aryl migration/desulfonylation/C(sp^2)−N bond formation from conjugated tosyl amides.

Our study commenced[16] with the reaction between tosyl amide (**1a**) and Togni's reagent (**4**)[17] in the presence of catalytic amounts of different copper complexes (Table 1). Cu(MeCN)$_4$PF$_6$ (20 mol %) gave no reaction (Table 1, entry 1), whereas the addition of 2,2′-bipyridine afforded 50% conversion of the starting material so that **2a** could be isolated in 40% yield (Table 1, entry 2). Interestingly, a more coordinating solvent such as DMF helped to improve the conversion of the starting material (Table 1, entry 3), whereas the addition of *N*-methylacetamide increased substrate conversion, producing **2a** in 45% yield (Table 1, entry 4). Less expensive copper sources were also evaluated (Table 1, entry 5). To our delight, the use of 40 mol % Cu_2O gave a clean reaction mixture, providing the desired product **2a** in 68% yield. Although the addition of *N*-methylacetamide under these conditions produced almost complete conversion of the starting material, the crude mixture showed formation of side products so that amide **2a** was isolated in 71% yield (Table 1, entry 6). The structure of **2a** could be unequivocally assigned by X-ray diffraction analysis.[18]

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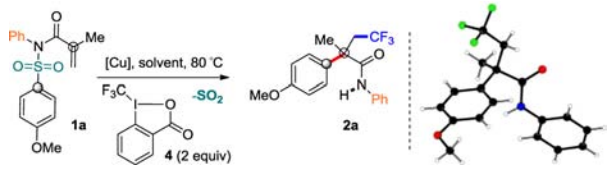
Table 1. Optimization of the Reaction Conditions

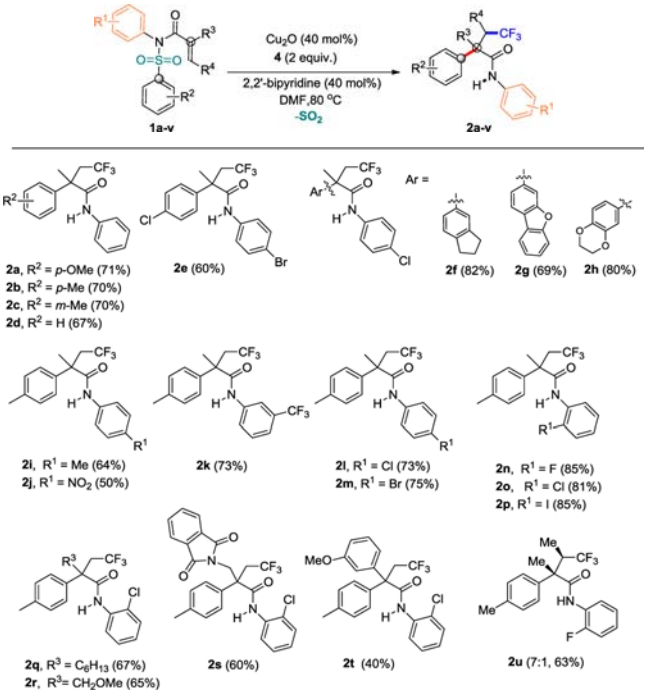


entry	reaction conditions[a]	1a:2a (2a yield, %)[b,c]
1	$Cu(MeCN)_4PF_6$ (20 mol %), CH_3CN	
2	$Cu(MeCN)_4PF_6$ (20 mol %), CH_3CN, 2,2′-bipyridine (40 mol %)	1:1 (40)
3	$Cu(MeCN)_4PF_6$ (20 mol %), DMF, 2,2′-bipyridine (40 mol %)	1:2.5
4	$Cu(MeCN)_4PF_6$ (20 mol %), DMF/*N*-methylacetamide (10:1) 2,2′-bipyridine (40 mol %),	1:8 (45)
5	**Cu_2O (40 mol %), DMF, 2,2′-bipyridine (40 mol %)**	**1:5 (68)**
6	Cu_2O (40 mol %), DMF/*N*-methylacetamide (10:1), 2,2′-bipyridine (40 mol %)	1:8 (71)

[a]Reaction conditions: **1a** (0.1 mmol), **4** (2 equiv) in 1.0 mL of solvent at 80 °C for 14 h. [b]Compound ratio determined by ^{1}H NMR. [c]The value in parentheses reports the isolated yield after column chromatography in silica gel.

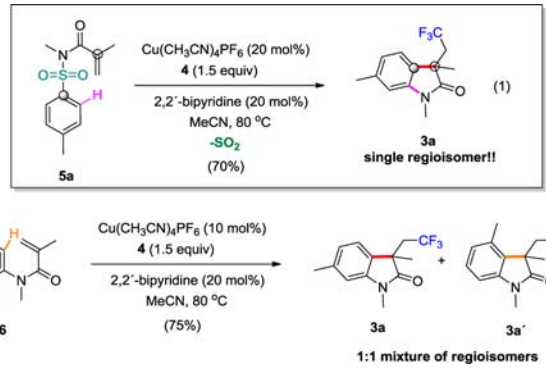
We set out to explore the scope of this transformation (Table 2). First, we studied the substitution pattern on the aromatic ring

Table 2. Cu-Catalyzed Trifluoromethylation/Aryl Migration/Desulfonylation[a,b]



[a]The conditions are the same as in Table 1, entry 5. [b]Isolated yield after column chromatography in silica gel. Except for **1a**, full conversion of the starting material was observed in all cases.

of the sulfonamide group (R^2, head of Table 2). *p*- and *m*-methyl, *p*-chloro-, and phenyl sulfonamide substrates were efficiently transformed into the corresponding *β*-trifluoromethyl amides **2b–e**, respectively. Remarkably, the reaction is completely regioselective, as the 1,4-migration of the aryl group takes place exclusively through the carbon atom bound to the SO_2 group in the starting material. Substrates bearing indane, dibenzofuran, and 1,4-dioxolane sulfonyl moieties (**1f–h**) were transformed into the corresponding trifluoromethylated amides **2f–h** in excellent yields. We also studied the influence of the substituents in the aryl group directly bound to the N atom (R^1, head of Table 2). The introduction of electron-donating groups at the *para* position was well tolerated, as **2i** could be isolated in 64% yield. In contrast, the presence of a nitro group seemed to decrease the reaction's efficiency (**2j**, 50%), although a substrate bearing a CF_3 group at the *meta* position could be transformed into the corresponding aryltrifluoromethylation product **2k** in 73% yield. Products **2l-p** containing halogen atoms *ortho* and *para* to the amide group could be obtained in good yields. Finally, we also investigated different substituents on the alkene. Substrates **1q,r**, bearing *n*-hexyl and methyl methoxy groups at C_2 of the propene moiety, were efficiently transformed into the corresponding amides **2q,r** in 67 and 65% yields, respectively. Nitrogen-containing substituents such as methylphthalimide were also well tolerated (**2s**) at this position. Aromatic groups could also be incorporated at C_2, although the reaction proved to be more complex and amide **2t** could only be isolated in 40% yield. Trisubstituted olefins were also amenable to this transformation, since amide **2u** was isolated in 63% yield as a 7:1 mixture of diastereoisomers. We decided to further evaluate the influence of the N-substitution pattern in the reaction and thus submitted *N*-methyl-*N*-tosyl amide **5a** to the standard reaction conditions.[16] To our surprise, the expected arytrifluoromethylation product was not detected. Instead, a clean transformation of the starting material into oxindole **3a** was observed. This product could be isolated in 70% yield when 20 mol % of $Cu(MeCN)_4PF_6$ and 2,2′-bipyridine were used (eq 1). The formation of **3a** is truly



remarkable, *as upon trifluoromethylation of the alkene, not only has the aryl group undergone a 1,4-migration/desulfonylation but also a new C(sp^2)–N bond in an ortho relative position to the original sufonyl group is formed in a formal 1,3-N migration process, which to the best of our knowledge represents the first example of such a cascade reaction*. It is important to note that this methodology allows us to obtain oxindole **3a** in a regioselective fashion. If one wishes to obtain **3a** from amide **6**, through either the previously reported Cu- or Pd-catalyzed aryltrifluoromethylation methods summarized in Scheme 1a,[12,13] only an inseparable mixture of regioisomers (**3a** and **3a′**) is generated as a result of two possible sites for arylation of the double bond in the corresponding starting materials (eq 2).[16,19] The scope of our study has been summarized in Table 3. First we focused on *N*-tosyl substrates (R^4 = Me, head of Table 3) bearing different substituents at the N atom (R^1). Butyl and more sterically demanding isopropyl groups were tolerated, affording the corresponding oxindoles **3b,c** in moderate yields. The methyl ester derivative of L-alanine

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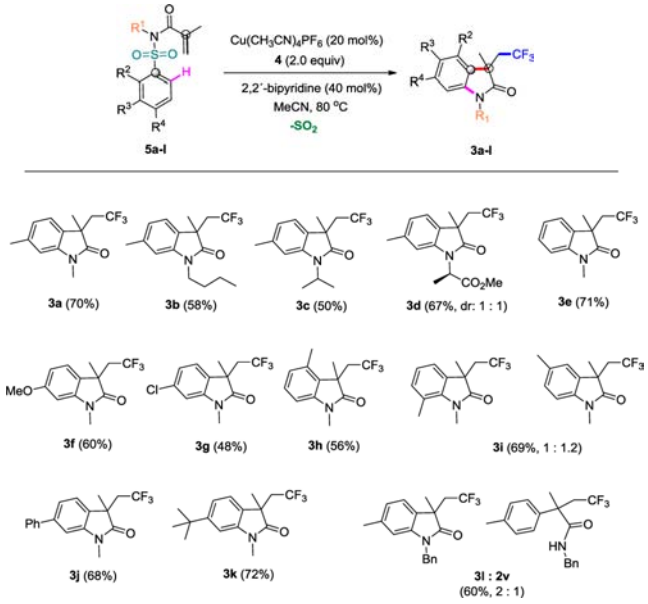
Table 3. Cu-Catalyzed Trifluoromethylation/ Desulfonylation/Aryl Migration/Cyclization[a,b]

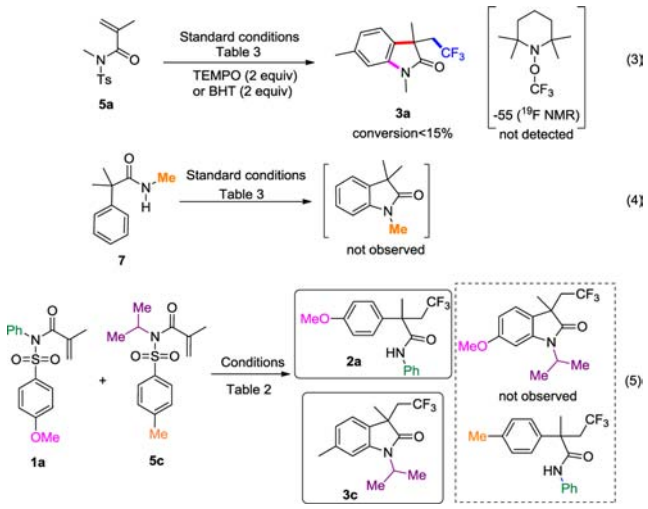


[a]Reaction conditions: **5** (0.1 mmol), **4** (2 equiv), $Cu(MeCN)_4PF_6$ (20 mol %), 2,2′-bipyridine (40 mol %), CH_3CN (1.0 mL) at 80 °C, 17 h. [b]Isolated yield after column chromatography in silica gel.

was also efficiently cyclized giving oxindole **3d**, which was obtained as a 1:1 mixture of diastereoisomers. We then turned our attention to the nature of the sulfonyl group. Benzenesulfonamide substrate **1e** ($R^2 = R^3 = R^4 = H$) was transformed into the corresponding trifluoromethylated oxindole **3e** in 71% yield. *p*-Methoxybenzene sulfonylamide (R^4 = OMe) was efficiently converted into **3f**, whereas less electron rich aromatic rings (R^4 = Cl) proved to be more reluctant to undergo the desired reaction, so that **3g** could only be isolated in 48% yield. Substitution in the *ortho* position of the benzenesulfonyl group could also be accommodated (R^2 = Me), thus confirming the reaction's selectivity, as **3h** was produced as a single regioisomer. Only when the substituent is placed at the *meta* position relative to the sulfonyl group does the reaction affords a ca. 1:1 mixture of regioisomers (**3i**, R^3 = Me). Substrates bearing a phenyl and a *tert*-butyl substituent at the *para* position of the benzenesulfonyl group could also be elaborated into the corresponding oxindoles **3j**,**k** in good yields. Interestingly, the presence of a *N*-benzyl group produced a mixture of the expected oxindole **3l** together with the corresponding *β*-trifluoromethylated amide **2v** in a 1:1 ratio.

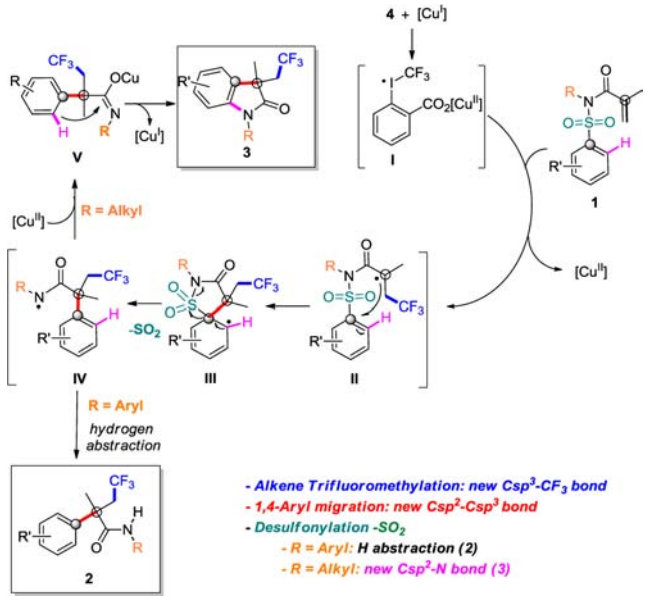
To gain a deeper insight into the mechanism of these transformations, the following control experiments were designed.[16] The reaction of **5a**[20] in the presence of BHT or TEMPO produced the desired products only in marginal yields (eq 3), thus pointing toward a radical mechanism. The reaction in the presence of TEMPO was followed by ^{19}F NMR, but the corresponding TEMPO−CF_3 adduct could not be detected, which suggests that other species rather than $[CF_3]^-$ might be at the outset of these transformations.[7−11,13] In addition, the reaction of amide **7** did not proceed, which suggests that amides **2** are not intermediates in the formation of oxindoles **3** (eq 4).

Finally, to determine whether the aryl migration is an intra- or an intermolecular process, a crossover experiment was designed (eq 5). A 1:1 mixture of **1a** and **5c** was submitted to the standard conditions, producing a 1:1 ratio of both amide **2a** and oxindole



3c. Crossover products were not detected in the reaction mixture, thus suggesting an intramolecular mechanism for these transformations. On the basis of this experimental evidence, the following mechanism is proposed (Scheme 2). In the first step,

Scheme 2. Proposed Mechanism for the Copper-Catalyzed Aryltrifluoromethylation of Conjugated Tosyl Amides



the copper catalyst seems to activate Togni's reagent **4**, generating a highly reactive CF_3-Cu^{II} containing radical **I** which interacts with the activated alkene to give a new $C(sp^3)-CF_3$ bond and *α*-alkyl radical intermediate **II**.[21] A 5-*ipso* cyclization then takes place on the sulfonyl aromatic ring, generating aryl radical **III**, which will undergo rapid desulfonylation to form the key amidyl radical **IV**, delivering a new $C(sp^2)-C(sp^3)$ bond.

Amidyl radical **IV** can undergo hydrogen abstraction from the medium to give trifluoromethylated amides **2**, a process that seems to be favored when the substituent R on the N atom is an aryl group.[22] The presence of *ortho* substituents in the benzenesulfonyl moiety (**2n**−**p** in Table 2) favors the reaction, in line with previously reported radical-mediated aryl migrations proceeding via *ipso*-cyclization/desulfonylation pathways.[23] In contrast, the presence of a more electron donating alkyl moiety

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triggers the oxidation of the radical to give the copper enolate **V**,[24] which is then trapped by the aromatic ring, thus forming oxindoles **3**.

In summary, the first example of a one-pot trifluoromethylation/1,4-aryl migration/desulfonylation/C(sp^2)−N bond formation of conjugated *N*-tosyl amides is presented here. A copper catalyst in the presence of Togni's reagent is able to trifluoromethylate the alkene, producing an amidyl radical intermediate which upon H abstraction delivers previously unknown α-aryl-β-trifluoromethyl amides bearing an α-quaternary stereocenter in a completely regioselective manner. Alternatively, if the amidyl radical can be engaged in a subsequent cyclization to give a new C(sp^2)−N bond, trifluoromethylated oxindoles are obtained in a regioselective fashion.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, figures, and tables giving experimental procedures, additional experiments, and spectroscopic characterization data. 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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(16) For detailed experimental procedures and characterization of starting materials and products, see the Supporting Information.

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(18) CCDC 933951 (**2a**) contains 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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