Communications

Trifluoromethylation

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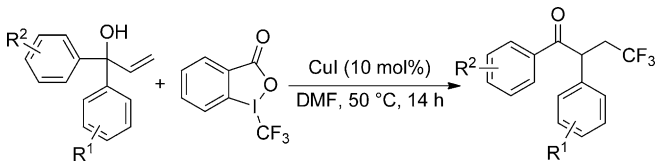
X. Wu* _____ ■■■■–■■■■

Copper-Catalyzed Trifluoromethylation-Initiated Radical 1,2-Aryl Migration in α,α-Diaryl Allylic Alcohols



Not only symmetrical, but also unsymmetrical α,α-diaryl allylic alcohols are employed as substrates in the title reaction. A number of arenes and even heteroarenes underwent radical 1,2-aryl migration ("neophyl rearrangement") to produce α-aryl β-trifluoromethyl ketones. The preferential migration of electron-deficient aryl groups over electron-rich ones in unsymmetrical substrates supports the radical mechanism, which was further confirmed by DFT calculations.

Trifluoromethylation

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Copper-Catalyzed Trifluoromethylation-Initiated Radical 1,2-Aryl Migration in α,α-Diaryl Allylic Alcohols**

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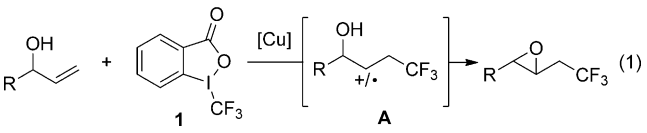
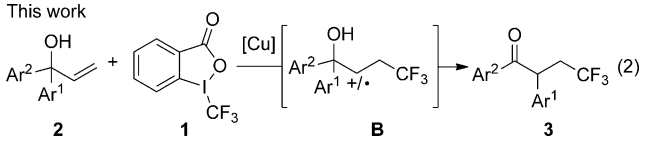
The trifluoromethyl (CF_3) group is an important structural motif in many pharmaceutically relevant molecules because of its unique chemical and metabolic stability, lipophilicity, and binding selectivity.[1] Consequently, much effort has been directed toward the development of efficient methods for the introduction of the trifluoromethyl group into small molecules.[2] While a variety of processes have been reported to generate aromatic $C(sp^2)$–CF_3 bonds,[3] the analogous direct trifluoromethylation of alkenes and their derivatives has received less attention. In 2011, the groups of Buchwald, Liu, and Wang independently reported efficient allylic trifluoromethylation of unactivated alkenes with copper catalysts under mild conditions.[4] The trifluoromethylation of allylsilanes,[5] vinyltrifluoroborates,[6] and enamides[7] has since been disclosed by several groups, allowing the effective formation of compounds with a CF_3 group in an allylic or vinylic position. Furthermore, oxytrifluoromethylation,[7,8] carbotrifluoromethylation,[9] and hydrotrifluoromethylation[10] of alkenes have been achieved with and without transition-metal catalysis. These reactions provide a valuable array of highly regioselective C–CF_3 bond-forming methods under mild conditions. However, the mechanism of these copper-catalyzed trifluoromethylation reactions is not fully understood. Addition of both the trifluoromethyl cation or radical have been suggested as routes to the observed products.

Buchwald reported the efficient formation of CF_3-containing epoxides from secondary allylic alcohols, possibly via intermediate **A** [Eq. (1)].[8b] Thus, we envisioned that the trifluoromethylation of α,α-diaryl allylic alcohols **2** with the Togni reagent (**1**)[11] would lead to the analogous intermediates **B**, which could undergo 1,2-aryl migration to provide β-trifluoromethyl ketones **3** [Eq. (2)]. Importantly, electron-rich aryl groups migrate preferentially in cationic (semi-pinacol) rearrangements,[12] whereas electron-poor aryl groups migrate preferentially in radical ("neophyl") rearrangements.[13,14] Therefore, the structures of the products from unsymmetrical substrates would provide important insight into the reaction mechanism.

Previous work (Buchwald)



This work



β-Trifluoromethyl ketones such as **3** are difficult to prepare. Nucleophilic trifluoromethylating reagents typically undergo 1,2-addition to enones, affording trifluoromethyl allylic alcohols rather than β-trifluoromethyl ketones by 1,4-addition.[15] Only a few cyclic β-trifluoromethyl ketones have been prepared by 1,4-addition of a nucleophilic CF_3 group to cyclic enones.[16] The use of radical or electrophilic CF_3 reagents for this challenging task has been rarely described.[17]

Consequently, we wanted to develop new $C(sp^3)$–CF_3 bond-forming reactions[18] to prepare β-trifluoromethyl ketones, and to probe the mechanism of the copper-catalyzed trifluoromethylation of alkenes as discussed above. We report herein an unprecedented trifluoromethylation-initiated radical 1,2-aryl migration("neophyl rearrangement")[19] in α,α-diaryl allylic alcohols utilizing **1**, leading to a wide variety of acyclic β-trifluoromethyl α-aryl ketones **3**.

We commenced our study with the reaction of **2a** with the Togni reagent (**1**) and $[(MeCN)_4Cu]PF_6$ as catalyst (Table 1). To our delight, the reaction in methanol at 50 °C for 14 h afforded the desired rearranged product **3a** in 27% yield (entry 1). It also provided 48% of compound **4a**, which was probably derived by trapping of the allylic cation of **2a** by MeOH. Complex product mixtures were obtained when the reaction was performed in the less nucleophilic alcohols trifluoroethanol or hexafluoroisopropanol (HFIP; entries 2 and 3, respectively). In acetonitrile and dichloromethane, mixtures of the desired ketone **3a** (22% and 9%, respectively) and substitution product **4b** (23% and 76%, respectively, entries 4 and 5) were formed. In DMSO, the yield of **3a** increased to 51%, but the conversion was not complete (entry 6). In DMF, the yield of **3a** increased further to 69%

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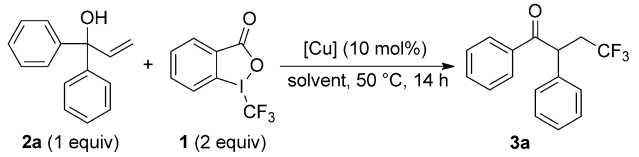
Table 1: Selected optimization studies.[a]



2a (1 equiv) **1** (2 equiv) **3a**

Entry	[Cu]	Solvent	Yield of **3a** [%][b]
1	$[(MeCN)_4Cu]PF_6$	MeOH	27
2	$[(MeCN)_4Cu]PF_6$	CF_3CH_2OH	trace
3	$[(MeCN)_4Cu]PF_6$	HFIP	trace
4[c]	$[(MeCN)_4Cu]PF_6$	MeCN	22
5	$[(MeCN)_4Cu]PF_6$	CH_2Cl_2	9
6[c]	$[(MeCN)_4Cu]PF_6$	DMSO	51
7	$[(MeCN)_4Cu]PF_6$	DMF	69
8	CuI	DMF	76
9	CuCl	DMF	71
10	$Cu(OAc)_2$	DMF	68
11[c]	$CuCl_2$	DMF	31

[a] Reaction conditions: **2a** (0.2 mmol), **1** (0.4 mmol), [Cu] (10 mol%), solvent (1 mL), 50°C, 14 h. [b] Determined by ^{19}F NMR spectroscopy using α,α,α-trifluorotoluene as an internal standard. [c] Incomplete conversion.

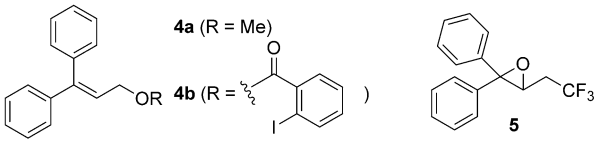


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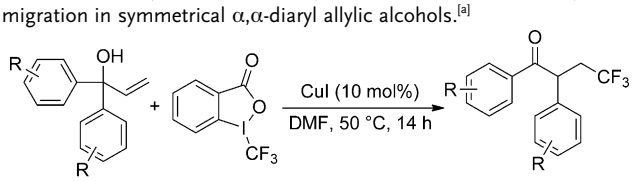
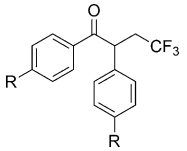
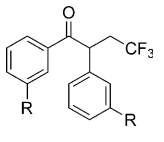
Table 2: Cu-catalyzed trifluoromethylation-initiated radical 1,2-aryl migration in symmetrical α,α-diaryl allylic alcohols.[a]



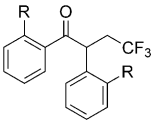
2 (1 equiv) **1** (2 equiv) **3**



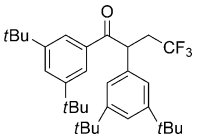
3b (R = Me, 66%)[b]
3c (R = Br, 67%)
3d (R = Cl, 65%)
3e (R = OPh, 50%)



3f (R = Me, 68%)[b]
3g (R = CF_3, 82%)
3h (R = Cl, 62%)



3i (R = Cl, 64%)
3j (R = OMe, 61%)



3k (62%)

[a] Reaction conditions: **2** (0.2 mmol), **1** (0.4 mmol), CuI (10 mol%), DMF (1 mL), 50°C, 14 h; yields of isolated products (average of two runs). [b] A by-product with a CF_3 group on the migrated aryl ring was isolated and characterized (see the Supporting Information).

and the formation of **4b** was completely suppressed (entry 7). These results demonstrate that the solvent has a dramatic effect on the reaction. The best catalyst, CuI, was slightly more effective than CuCl or $Cu(OAc)_2$ and much better than $CuCl_2$ (entries 8–11). Of note, epoxide **5**, which was analogous to those reported by Buchwald and co-workers, was detected in no more than 12% yield under any of these conditions. However, careful analysis of the reaction mixtures showed the formation of small amounts of by-products with aromatic CF_3 groups (see the Supporting Information).

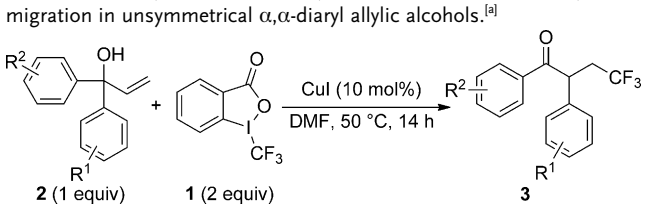
We then explored the scope of the rearrangement reactions using the optimized conditions (Table 1, entry 8) with various symmetric α,α-diaryl allylic alcohols (Table 2). A range of allylic alcohols containing electron-deficient or electron-rich aryl groups were found to undergo rearrangement, affording the corresponding α-aryl β-trifluoromethyl ketones (**3b**–**3k**) in moderate to good yields. Substituents in *ortho*, *meta*, or *para* position of the aryl groups were all well tolerated.

To expand the scope of this novel transformation and investigate the selectivity of the aryl migration, we turned our attention to unsymmetrical α,α-diaryl allylic alcohols. Gratifyingly, all rearrangements proceeded chemoselectively (Table 3). The copper-catalyzed trifluoromethylation-initiated rearrangement is compatible with cyano and pyridyl groups (**3q** and **3r**). For substrates **2l**–**2q** with *meta* and *para* substituents and **2r** with a pyridyl ring, the more electron-deficient aryl group migrated preferentially to give β-trifluoromethyl ketones **3l**–**3r**. Ketones such as **3l′**, which arise from migration of the more electron-rich aryl group, were detected as minor products. This selectivity is that expected for a radical ("neophyl") rearrangement,[13] but is in striking contrast to that expected for a cationic (semipinacol) rearrangement, in which the more electron-rich aryl group migrates preferentially, because it is better able to stabilize the positive charge in the resulting cationic transition state or intermediate.[12] On the other hand, *ortho*-substituted aryl rings migrated less effectively, regardless of whether the substituent was electron-donating or electron-withdrawing (**3s**–**3w**).

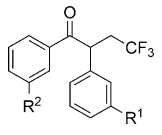
To investigate whether our rearrangement proceeds via an iodonium intermediate analogous to that reported by Feng and Loh,[7] we treated **2m** with iodine and AgOAc using the conditions described by Ciganek (Scheme 1).[20] An iodonium ion **6m** was formed and an aryl group migrated to give a mixture of unstable β-iodo ketones **7**. Elimination occurred during preparative TLC, affording 51% of enone **8m′**, which resulted from migration of the phenyl group, and only 7% of enone **8m**, which resulted from migration of the *para*-trifluoromethylphenyl group. In contrast, trifluoromethylation of **2m** gave predominately **3m**, resulting from migration of the *para*-trifluoromethylphenyl group.

To demonstrate the utility of this method, we treated allylic alcohol **2x** with the Togni reagent (**1**) under the standard reaction conditions, which afforded **3x** in 41% yield (Scheme 2). In three steps, ketone **3x** can be converted to **9**, which shows antiestrogenic activity with an IC_{50} of 9 nM.[21] Our formal synthesis of **9** utilizes the shelf-stable trifluoromethylating reagent **1** to install the CF_3-containing side chain rather than using volatile CF_3CH_2Br, as described in the

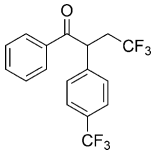
Table 3: Cu-catalyzed trifluoromethylation-initiated radical 1,2-aryl migration in unsymmetrical α,α-diaryl allylic alcohols.[a]



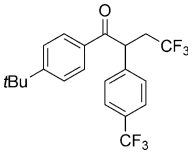
2 (1 equiv) **1** (2 equiv) **3**



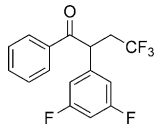
3l (51%, R^1=CF_3, R^2=H)
3l' (13%, R^1=H, R^2=CF_3)



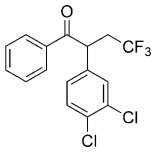
3m (72%)[b] (20:1)[c]



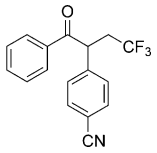
3n (83%)[b] (20:1)[c]



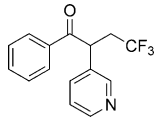
3o (67%)[b] (6.7:1)[c]



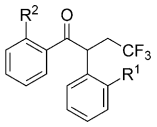
3p (70%)[b] (6.7:1)[c]



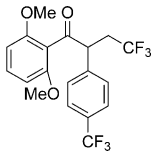
3q (78%)[b] (>20:1)[c]



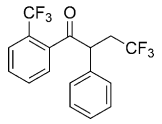
3r (43%)[b] (3.7:1)[c]



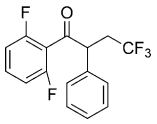
3s (55%, R^1=H, R^2=OMe)
3s' (18%, R^1=OMe, R^2=H)



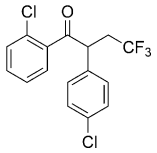
3t (78%)[b] (>20:1)[c]



3u (61%)[b] (5.6:1)[c]



3v (75%)[b] (>30:1)[c]

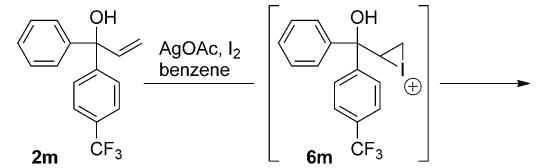


3w (52%)[b] (16.7:1)[c]

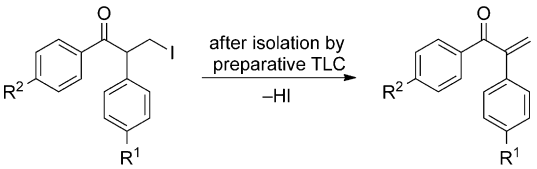
[a] Reaction conditions: **2** (0.2 mmol), **1** (0.4 mmol), CuI (10 mol%), DMF (1 mL), 50°C, 14 h; yields of isolated products (average of two runs). [b] The yield is reported for major product as shown. [c] The ratio of **3** to its isomer was determined by ^{1}H NMR analysis of the crude product.

literature. Therefore, similar sequences could be easily used to prepare antiestrogenic analogues of **9**.

To gain further understanding about the migration step, we conducted computational studies using **2m** as a model compound (see details in the Supporting Information). The calculation indicated that the *para*-trifluoromethylphenyl group migrates preferentially over the phenyl group when radical intermediate **B** (R^1 = CF_3, R^2 = H, Scheme 3) is involved, which is in agreement with our experimental result. Moreover, the preferential migratory aptitudes of non-*ortho*-substituted aryl groups over *ortho*-substituted ones

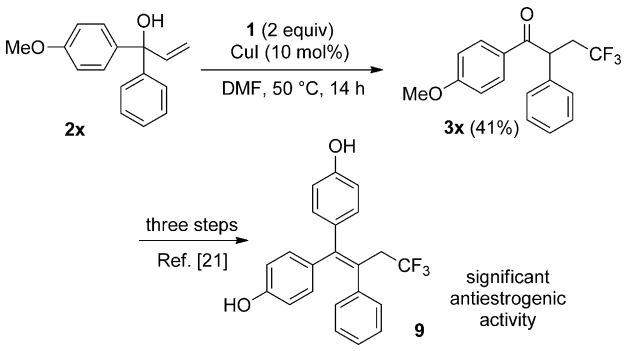


2m **6m**



7m' (R^1 = H, R^2 = CF_3)
7m (R^1 = CF_3, R^2 = H)
8m' (51%, R^1 = H, R^2 = CF_3)
8m (7%, R^1 = CF_3, R^2 = H)

Scheme 1. Opposite chemoselectivity for rearrangement of **2m** under Ciganek's conditions.

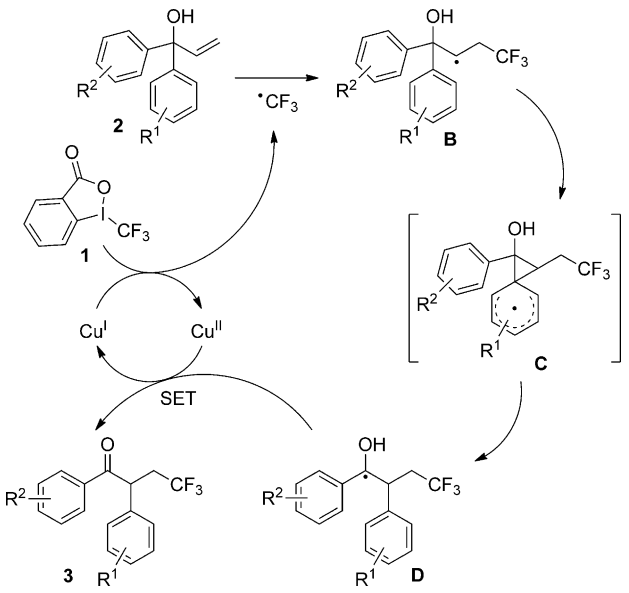


2x **3x** (41%) **9**

Scheme 2. Formal synthesis of antiestrogenic compound **9**.

were also reproduced in our DFT studies, with the migration occurring via radical intermediate **B**. Therefore, a simplified catalytic cycle for the rearrangement is proposed (Scheme 3). A CF_3 radical, presumably arising from the Togni reagent (**1**) and Cu^I, reacts with alkene **2** to generate radical **B**. Subsequent migration of the electron-deficient aryl group via spiro[2,5]octadienyl radical **C** produces intermediate **D**. Single-electron transfer (SET) between Cu^{II} and **D** delivers the desired product **3** with concomitant loss of a proton, and regenerates the active copper(I) species. When *ortho* substituent(s) are present on one of two aryl groups in **2**, the migration of the non-*ortho*-substituted aryl group might be more favorable, generating a sterically less congested radical **C**.

In summary, we have developed a copper-catalyzed trifluoromethylation-initiated radical 1,2-aryl migration ("neophyl rearrangement") in α,α-diaryl allylic alcohols. A wide variety of β-trifluoromethyl α-aryl ketones can be easily prepared under mild conditions. Notably, for *meta*- and *para*-substituted unsymmetrical substrates we found that the more electron-deficient aryl group migrates preferentially over the more electron-rich aryl group. Moreover, *ortho*-substituted groups are reluctant to migrate. These experimental results, in combination with DFT calculations, indicate that this rearrangement occurs through a radical 1,2-aryl migration and that the reaction is initiated by addition of the trifluoromethyl radical to the alkene. Other recently reported copper-



Scheme 3. The proposed mechanism for Cu-catalyzed trifluoromethylation-initiated radical 1,2-aryl migration in α,α-diaryl allylic alcohols.

catalyzed trifluoromethylations and related reactions probably proceed by a similar mechanism. Based on these advances, many novel reactions to form $C(sp^3)$–CF_3 bonds may be expected.

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Keywords: copper · migration · radical reactions · rearrangement · trifluoromethylation

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