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Copper-Catalyzed β-Trifluoromethylation of Conjugated Hydrazones

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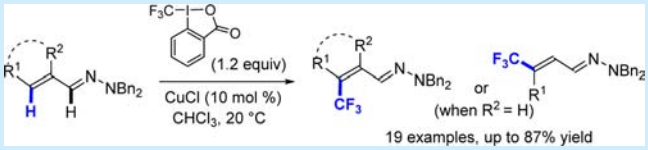
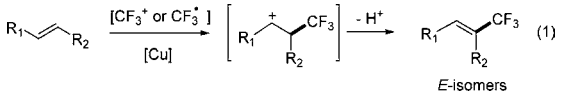
Supporting Information

ABSTRACT: The Cu-catalyzed direct β-trifluoromethylation of α,β-unsaturated aldehyde *N,N*-dibenzylhydrazones with Togni hypervalent iodine reagent is described. The reaction yields stereodefined CF_3-alkenyl derivatives under mild conditions and is proposed to proceed via a radical process.

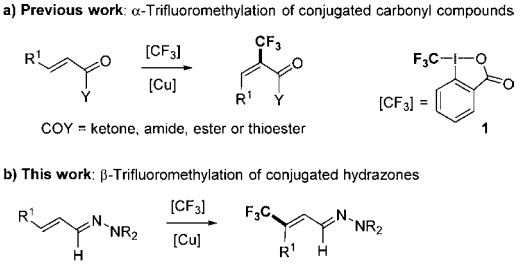


The trifluoromethyl (CF_3) group has gained tremendous importance in various areas of medicinal and agrochemical chemistry owing to its unique functional properties. It is lipophilic, strongly electron-withdrawing, and bulky and can mimic various groups as an isostere.[1] On this basis, the search for new efficient methods for the incorporation of this group into target molecules is highly desirable and has been the subject of intense renewed activity in recent years.[2] CF_3-substituted olefins are especially attractive compounds. For instance, 2-trifluoromethyl-1-alkenes are valuable building blocks for organic syntheses.[3] In addition, trifluoromethyl alkene isosteres have found applications as peptide-bond surrogates.[4] The development of selective and direct methods for the formation of sp^2-CF_3 bonds by replacement of an alkenyl C−H moiety, i.e. without prefunctionalization of the olefin, is being actively pursued, and most achievements in this area have benefited from newly designed electrophilic CF_3-transfer reagents often requiring catalysis, notably by Cu salts. It is proposed that these reactions follow addition−elimination pathways involving the intermediacy of a carbocation that generates the corresponding alkene with (*E*)-configuration predominantly after deprotonation [eq 1].



In 2012, the groups of Sodeoka[5] and Loh[6] investigated the Cu-catalyzed trifluoromethylation of styrene derivatives[7] and α-substituted enamides, respectively, which led to the corresponding β-trifluoromethyl alkenes. More recently, Bi et al.[8] examined the Cu-catalyzed C−H trifluoromethylation of electron-deficient alkenes, including enones as well as α,β-unsaturated amides, esters, and thioesters which resulted in the regioselective incorporation of the CF_3 moiety at the α-position of the enones (Scheme 1a).[9] The reactivity of α,β-unsaturated amides having an occupied α-position had been previously examined by Loh[10] and by Besset and Cahard.[11] The reactions afforded β-trifluoromethylated acrylamides and exhibited excellent stereoselectivities, albeit in favor of (*Z*)-isomers. It is thought that, in these particular cases, the amide moiety is directing the introduction of the CF_3 group to the same side of the double bond. As a complement to these works, we report herein the regioselective β-trifluoromethylation of α,β-unsaturated aldehyde *N,N*-dialkyl hydrazones giving rise to stereodefined (*E*)-trifluoromethylalkenyl hydrazones preferentially (Scheme 1b).

Scheme 1. Cu-Catalyzed Trifluoromethylation of Functionalized Alkenes



We previously reported the copper chloride catalyzed trifluoromethylation of aldehyde *N,N*-dialkyl hydrazones which was shown to occur at the azomethine carbon using Togni hypervalent iodine reagent **1**. The reaction is believed to occur by a CF_3 radical transfer mechanism.[12] Given the known propensity of α,β-unsaturated hydazones to undergo conjugative attack of electrophiles at the terminal olefinic carbon by virtue of the umpolung caused by the electron-releasing amino component, it was reasonable to expect that trifluoromethylation would occur preferentially at the olefinic β-carbon.[13,14]

With this in mind, we applied our previously established protocol (1.2 equiv of Togni reagent **1**, 10 mol % CuCl, $CHCl_3$, 25 °C) to cinnamaldehyde *N,N*-dimethylhydrazone (**2a**) as a model substrate (Table 1, entry 1). Gratifyingly, after 24 h the reaction led to the formation of the desired trifluoromethylated product **3a** in acceptable yield and excellent (*E*)-stereoselectivity in the C=C double bond formation, as determined by $^{19}F-^{1}H$ HOESY NMR experiments. However, the reaction produced also the regioisomeric compound **4a** resulting from incorporation of the CF_3 group at the azomethine carbon. As previously

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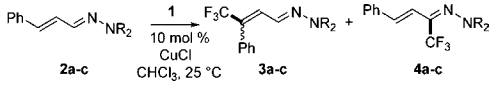
Table 1. Screening of Cinnamaldehyde *N,N*-Dialkyl Hydrazones[a]



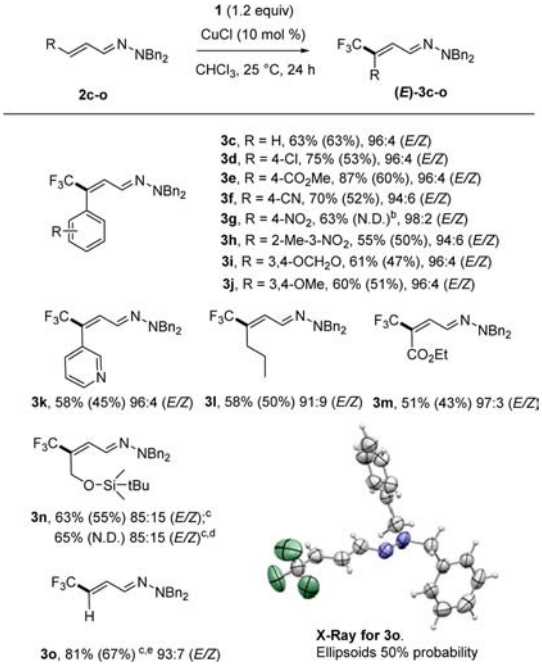
entry	NR_2 =	global yield **3** + **4** (%)	*E*/*Z* for **3**	ratio **3**/**4**
1	NMe_2, **2a**	55	91:9, **3a**	2:1
2	1-piperidinyl, **2b**	57	93:7, **3b**	3:1
3	NBn_2, **2c**	73	96:4, **3c**	11:1

[a]Reaction conditions: **2** (0.5 mmol), **1** (0.6 mmol), and CuCl (0.05 mmol) in 3 mL of $CHCl_3$ at 25 °C for 24 h. Yields and ratios were determined by ^{19}F NMR spectroscopy of the crude reaction mixture using trifluorotoluene as an internal standard.

observed, the geometry of the C═N bond of **4a** was determined to be exclusively *Z* by $^{19}F-^{1}H$ HOESY NMR experiments. Although the reaction did indeed favor the desired regioisomer, the **3a**/**4a** ratio (2:1) was unsatisfactory. This prompted us to examine other cinnamaldehyde dialkylhydrazones expecting that the nature of the amino group would affect the regioselectivity, with bulkier *N*-alkyl substituents probably disfavoring azomethine trifluoromethylation. The corresponding piperidinyl- and dibenzylhydrazones (**2b,c**) were thus selected as new candidates, our choice being guided by the ready availability of the hydrazine precursors. Thus, while the piperidinyl derivative led to little improvement, the dibenzylhydrazone afforded a satisfactory 11:1 ratio of regioisomers **3c**/**4c** (Table 1, entry 3), with increased yield and stereoselectivity. Hydrazone **2c** was thus used as a model substrate to further screen catalysts and reaction conditions, but no significant improvement was obtained. Note that only traces of products were detected in the absence of any catalyst.[15]

Next, the scope of various substrates bearing acyclic disubstituted alkenes was explored. Gratifyingly, the results in Scheme 2 demonstrate an excellent degree of tolerance of alkene substitution. Good results were first obtained for a series of aryl-substituted alkenes regardless of electron-donating or -withdrawing properties of functional groups on the phenyl ring (**3c**–**3j**). Various substituents/functional groups were tolerated, including cyano, ester, nitro, and halide. Even sterically demanding ortho-substituents were tolerated without significant effect on the regioselectivity of CF_3-addition. An heteroaromatic substrate such as a pyridinylalkenyl hydrazone delivered the desired compound (**3k**) in acceptable yield. In addition, different nonaromatic substituents such as alkyl (**3l**), as well as carboxylic ester (**3m**), and silyloxymethyl (**3n**) were well tolerated thus offering opportunities for further diversification. The unsubstituted acrolein dibenzylhydrazone also proceeded efficiently, albeit requiring a higher temperature and prolonged reaction time, to afford the target compound (**3o**) in good yield, with the structure confirmed by X-ray analysis. Finally, the robustness of this transformation was further demonstrated by performing the synthesis of **3o** on a semipreparative 2 mmol scale without any decrease in yield. Remarkably, all substrates yielded mainly (*E*)-alkenyl products, which is in accordance with the intermediacy of a cationic species [see eq 1]. As an additional experiment, it was shown that **3n** could also be accessed in a stereoconvergent fashion from a mixture of *E* and *Z* isomers (*E*/*Z* = 20:80) of the starting alkenyl hydrazone in identical yield (65%) and stereoselectivity (*E*/*Z* = 85:15) with respect to the same reaction performed on the geometrically pure *E*-isomer.

Scheme 2. Substrate Scope for (*E*)-*β*-Substituted Alkenyl Hydrazones[a]



[a]Reaction conditions: **2** (0.5 mmol), **1** (0.6 mmol), and CuCl (0.05 mmol) in 3 mL of $CHCl_3$ at 25 °C for 24 h. Yields and *E*/*Z* ratios for **3** (major isomers are drawn) were determined by ^{19}F NMR of the crude mixtures. In all cases, trace to small amounts (<15%) of a trifluoromethylated byproduct which we assumed to be the regioisomer **4** have also been detected. Isolated yields of **3** are given in brackets. *E*/*Z* configurations were determined by $^{19}F-^{1}H$ HOESY NMR experiments on products **3c**, **3l**, and **3n**. [b] N.D. = not determined; an inseparable mixture of regioisomers was obtained in this case. [c] Reaction performed at 50 °C. [d] Reaction conducted on a 80:20 mixture of *Z* and *E* isomers of the starting alkenyl hydrazone. [e] 48 h reaction time. The reaction was also performed on a 2 mmol scale without a significant change in the yield (83%).

The next stage of the work consisted of examining the effect of substitution at the *α*-position of the double bond on the reactivity and reaction outcome. Notably, alkyl-substitution would offer another possible position for the terminating H-elimination step, and hence it was reasonable to expect the formation of isomers which differ in the position of the double bond. Thus, a series of *α*-substituted conjugated hydrazones were prepared and subjected to our standard reaction conditions (Table 2).

The behavior of *α*-methyl cinnamaldehyde hydrazone **2p** was first investigated. Interestingly, the reaction proved very effective, producing the expected *β*-trifluoromethyl alkenyl product **3p** in a slightly better yield (67%) and shorter amount of time (2 h) compared with the parent unsubstituted cinnamaldehyde derivative **2c** (24 h). In this case the geometry of the C═C double bond of the major isomer was determined to be *Z* by $^{19}F-^{1}H$ HOESY NMR experiments (*E*/*Z* = 21:79). The methacrolein hydrazone **2q** lacking substitution at the *β*-position was next examined. The compound behaved similarly furnishing the desired product **3q** in an identical yield (67%) but with lower stereoselectivity (*E*/*Z* = 28:72). Not unexpectedly, **3q** was accompanied by the allylic trifluoromethyl derivative **3q′** as a minor isomeric byproduct (17%) which is likely to be the result of competitive H-elimination of the putative cationic intermediate species at the methyl group rather than at the *α*-position

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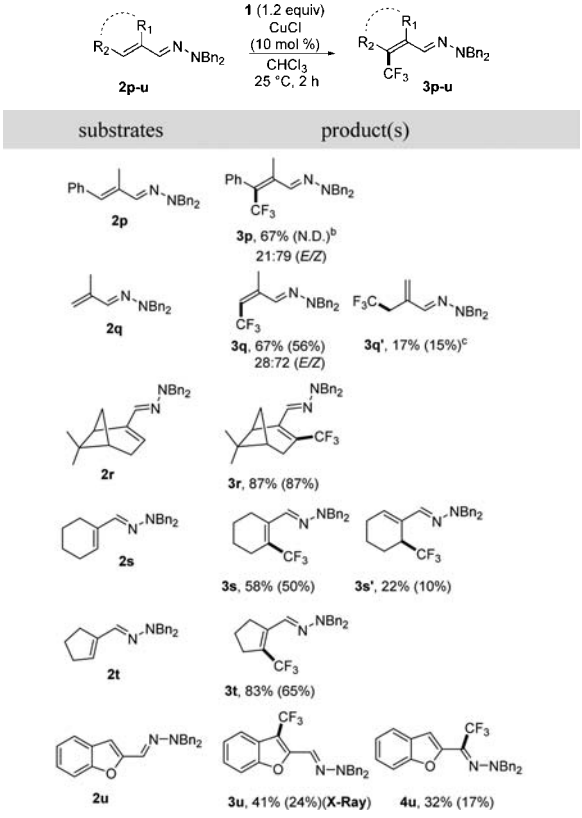
Table 2. Substrate Scope for α-Substituted Alkenylhydrazones[a]

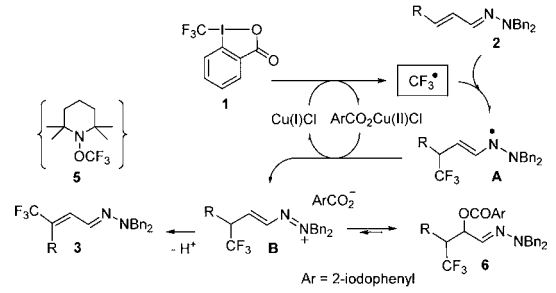


[a]Reaction conditions: **2** (0.5 mmol), **1** (0.6 mmol), and CuCl (0.05 mmol) in 3 mL of $CHCl_3$ for 2 h at 25 °C. Yields and *E*/*Z* ratios for **3** (major isomers are drawn) were determined by ^{19}F NMR of the crude mixtures. In all cases, trace to small amounts (<15% except for **2u**) of a trifluoromethylated byproduct which we assumed to be the regioisomer **4** have also been detected. Isolated yields of **3** are given in brackets. *E*/*Z* configurations of **3p** and **3q** were determined by $^{19}F-^{1}H$ HOESY NMR experiments. [b]N.D. = not determined; an inseparable mixture of regioisomers was obtained in this case. [c]A small amount of a bistrifluoromethylated compound, supposedly a product of CF_3 addition to this newly formed conjugated system, has also been formed; see Supporting Information.

to the trifluoromethyl group.[16] This was less favorable in the case of **2p** owing to the additional stability provided by the conjugating phenyl system. Next, our effort focused on expanding further the substrate scope of this transformation to cycloalkenyl hydrazones. (−)-Myrtenal dibenzylhydrazone (**2r**), having a single location available for the double bond, worked nicely affording the desired product (**3r**) in a very good 87% isolated yield. To our satisfaction, other cycloalkenes (**2s,t**) also exhibited good reactivity, with a loss of selectivity being only observed in the case of the 6-membered ring system. Finally, we sought to include aromatic substrates as possible candidates for this transformation. As illustrated with the benzofuryl derivative **2u**, although the expected β-trifluoromethylation product (**3u**) was formed, the regioselectivity became an issue since the main byproduct resulted from CF_3-addition at the azomethine carbon atom.

In order to gain insight into the possible mechanism of the catalytic reaction (Scheme 3), we performed a radical trapping experiment in the presence of 2,2,6,6-tetramethylpiperidine-*N*-oxy (TEMPO, 1.2 equiv). Under these conditions, trifluoromethylation of **2c** as our model substrate was almost completely inhibited, and the TEMPO−CF_3 adduct (**5**)[12] was formed instead (82% yield as estimated by ^{19}F NMR) suggesting the involvement of a radical mechanism. Another interesting observation was made during our experiments involving cinnamaldehyde-derived dibenzyl hydrazones (Table 1 and Scheme 2). Indeed, ^{19}F and ^{1}H NMR monitoring of the trifluoromethylation reactions showed the total consumption of starting materials at the early stage of reaction (~1.5 h) with concomitant formation of two other trifluoromethylated compounds which then gradually disappeared as the desired β-CF_3 products were being formed, thus prolonging the reaction time to 24 h. In line with literature precedents,[17] we surmised that these could be oxytrifluoromethylated products (**6**) generated as pairs of diastereomers (1:1 ratio) through reversible trapping of the putative cationic intermediate by the 2-iodocarboxylate released from Togni reagent. A kinetic profile for the trifluoromethylation of **2c** is given in Figure 1, which clearly illustrates the intermediacy of a pair of trifluoromethylated compounds, supposedly **6c**, in the formation of **3c**.[18] It was also noted that substitution of the starting alkenyl hydrazones at the α-position of the double bond (Table 2) had a significant effect on the reaction rate. Indeed, the formation of oxytrifluoromethylated species was not observed and, as a consequence, complete conversion to the corresponding β-CF_3 products was achieved in less than 2 h. In these cases the difference in reaction rates may be rationalized in terms of a less reactive carbocation intermediate disfavoring attack of the carboxylate.

Scheme 3. Mechanistic Proposal



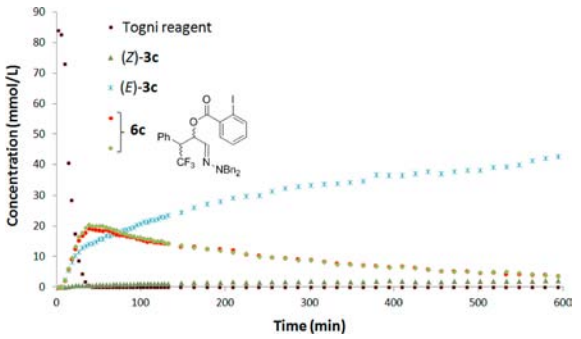


Figure 1. Kinetic profile of the conversion of **2c** to **3c** (^{19}F NMR spectroscopy).

Based on all our experimental results, a plausible mechanism as depicted in Scheme 3 may be proposed. The reaction pathway begins with the activation of Togni reagent by Cu^{I} via single-electron transfer (SET) to generate a Cu(II) species, with concomitant release of a CF_3 radical. Reaction of the latter with

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the conjugated hydrazone produces the trifluoromethylated aminyl radical intermediate **A** stabilized by the lone pair of the adjacent nitrogen atom. Another SET process forms the cationic intermediate **B** and recycles the active Cu(I) catalyst. Reversible trapping of **B** by the 2-iodocarboxylate released from Togni reagent may then occur to form relatively long-lived oxytrifluoromethylated byproducts **6**. Finally, H-elimination restores the conjugated hydrazone. A preferred (*E*)-configuration is observed for α-unsubstituted alkenylhydrazones.

In summary, we have developed a mild, practical procedure for the β-trifluoromethylation of conjugated aldehyde *N*,*N*-dialkylhydrazones based on the use of readily available Togni reagent under simple Cu catalysis. This transformation is believed to proceed by a radical process, following addition−elimination pathways that generate the corresponding alkene with (*E*)-configuration preferentially for the simple α-unsubstituted derivatives.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures including kinetic studies, characterization for all new compounds, NMR spectra for products **3**, and crystallographic data (CIF). 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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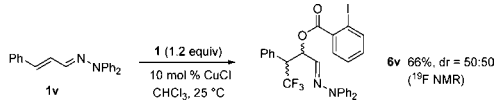
(18) Attempts to isolate these intermediates for characterization failed as they did not withstand chromatographical purification. Pleasingly however, oxytrifluoromethylation of diphenyl hydrazone **1v** produced relatively stable products allowing isolation of a pure sample of **6v** and confirmation of its structure.



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