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Trifluoromethylation of Secondary Nitroalkanes

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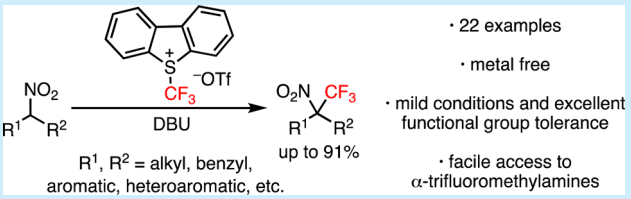
Supporting Information

ABSTRACT: Using a commercially available Umemoto's reagent, the metal-free trifluoromethylation of nitroalkanes is now possible. This method provides a general, high-yielding synthesis of α-(trifluoromethyl)nitroalkanes. The quaternary α-(trifluoromethyl)nitroalkanes obtained from this transformation can be elaborated to a variety of complex nitrogen-containing molecules, including α-(trifluoromethyl)amines.



Organofluorine compounds play a vital role in the chemical enterprise, including in pharmaceuticals, agrochemicals, liquid crystals, dyes, and polymers.[1] Trifluoromethyl groups, in particular, have been shown to impart unique physiological properties, including modulation of binding affinity, metabolic stability, lipophilicity, and bioavailability when introduced into small molecules.[2] For example, the introduction of a trifluoromethyl group α to nitrogen has been shown to modulate the biological properties of numerous small molecules compared to their nonfluorinated analogues.[3]

A potentially efficient entry into such α-(trifluoromethyl)-amino compounds would involve the trifluoromethylation of a nitroalkane.[4] In 2007, Togni reported that α-nitroesters can be trifluoromethylated in reasonable yields under copper catalysis (Figure 1, top).[5] Unfortunately, this method is not applicable to nitroalkanes lacking the adjacent activating ester group. A general protocol for the trifluoromethylation of nitroalkanes has not yet been described.[6]

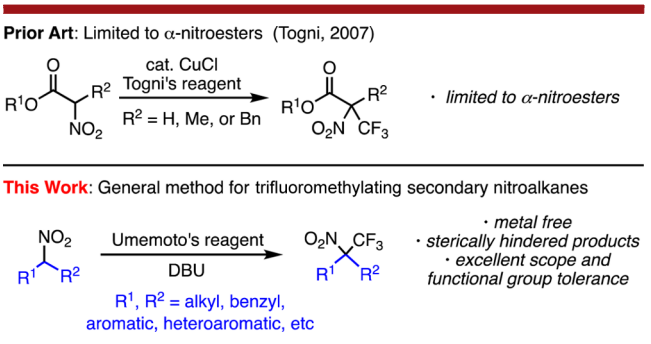
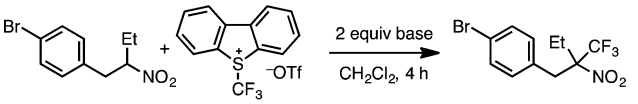


Figure 1. Trifluoromethylation of nitroalkanes.

Recent studies from our group have demonstrated a variety of reactions for the alkylation of nitroalkanes using copper catalysis and radical-stabilizing alkyl halide electrophiles.[7] Given the variety of recent examples of transformations involving trifluoromethyl radicals[8] and the broad utility of nitroalkanes,[9] we were inspired to investigate the trifluoromethylation of nitroalkanes as a potential entry into α-(trifluoromethyl)amino compounds. Herein we report simple, transition-metal-free conditions for trifluoromethylation of secondary nitroalkanes. These conditions provide high-yielding access to fully substituted α-(trifluoromethyl)nitroalkanes, which can be readily converted into the corresponding α-(trifluoromethyl)-amines.

In analogy to our prior studies, our initial efforts focused on the use of copper catalysts in combination with a variety of reagents known to generate trifluoromethyl radicals.[10] Using nitroalkane **1** as a model substrate, we were initially pleased to find that the combination of catalytic CuBr and a diketiminate ligand with Umemoto's reagent (**2**) and base led to detectable levels of the desired product **3** (Table 1, entry 1).[11] Control experiments, however, quickly revealed that the reaction did not require the catalytic additives (entry 2). Switching the base from sodium trimethylsilanolate to DBU increased the yield to 52% (entry 3). The reaction proved most efficient when conducted in methylene chloride.[10] Finally, lowering the temperature from +40 to −25 °C afforded optimal amounts of the desired product **3** (entries 3−5).

Table 1. Optimization of Reaction Conditions



1 2 3

entry	base	additive	temp (°C)	yield 3[a] (%)
1	$NaOSiMe_3$	20 mol % Cu/L[b]	40	22
2	$NaOSiMe_3$	none	40	24
3	DBU	none	40	52
4	DBU	none	rt	58
5	DBU	none	−25	90

[a]1.3 equiv of **2**; yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]20 mol % of CuBr, 20 mol % of bis-*N*,*N*′-(2,6-dimethylphenyl)-2,4-diiminopentane added to reaction.

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With optimized conditions in hand, the scope of the transformation was investigated (Scheme 1). The reaction is general for a broad range of secondary nitroalkanes. The model substrate was isolated in 83% yield (**3**).[7a] Other homobenzylic nitroalkanes (**4**) led to similar results. Both benzylic substrates (**5**–**8**)[12] and Michael reaction adducts (e.g., **9**–**12**) were also well tolerated. Sterically demanding substrates could also be used. For example, even neopentylic substrates led to appreciable yields of products (**14**) containing vicinal fully substituted centers. In contrast to secondary substrates, primary nitroalkanes provide very little reactivity. For example, only traces of **13** were observed. Further studies will be directed at expanding the scope of the reaction to primary nitroalkanes.

Significantly, nitroalkanes bearing a tertiary stereocenter β to the nitro group proved to be excellent substrates.[7b] In these cases, good to excellent levels of diastereoselection were observed. For example, amide **15** was formed with greater than >95:5 selectivity favoring the diastereomer shown.[13] Similar selectivity was observed for the Weinreb amides (**16**). Related ester products could also be prepared (**17**–**19**), albeit with slightly lower levels of diastereoselection. These results mirror the selectivities previously observed in Michael additions of β-nitrocarbonyls.[14] Henry reaction products (**20**),[9a] as well as those from conjugate addition of nitroalkenes (**21**),[15] could both be trifluoromethylated with good to excellent levels of diastereoselectivity. In the latter case, stereoselectivity is consistent with addition of the CF_3 group away from the large aromatic ring.

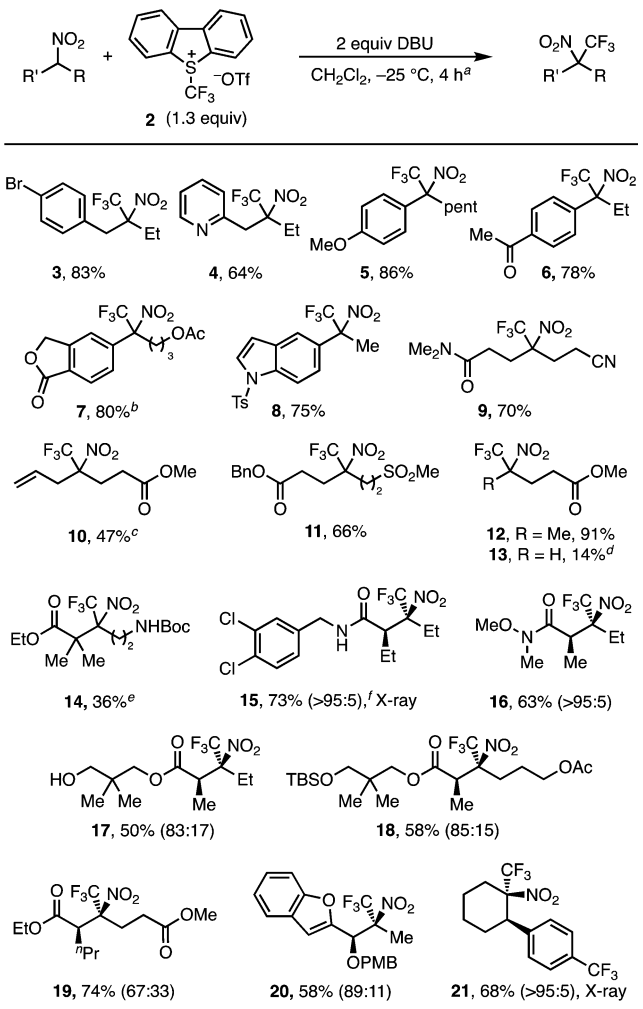
The functional group tolerance of the reaction is very high. In addition to those already mentioned, tolerated functional groups include aryl halides (**3** and **15**), heterocycles (**4**, **7**, **8**, and **20**), alkenes (**10**), aryl ethers (**5**), nitriles (**9**), ketones (**6**), protected and free alcohols (**7**, **17**, **18**, and **20**), sulfones (**11**), and protic nitrogen functional groups (**14** and **15**).

The method does show some limitations with respect to nitroalkanes bearing acidic and sterically accessible β-protons. In such cases, elimination of an equivalent of nitrous acid from the trifluoromethylated product can be observed. For example, under standard conditions using DBU as base, reaction of **22** did not lead to the trifluoromethyl nitroalkane **23** (Scheme 2, top). Instead, the trifluormethyl alkene **24** was observed in moderate yield. In some cases, the use of the bulkier base, tetramethylguanidine (TMG), enabled access to the desired product without significant elimination, albeit with less than ideal conversion and yield. In other cases, such as with ester **25**, elimination could not be avoided regardless of the base used (Scheme 2, bottom).

Interestingly, the (trifluoromethyl)alkenes described in Scheme 2 all formed with significant selectivity for the *E*-isomer (as determined by $^1H-^{19}F$ HOSEY NMR).[10] We attribute this selectivity to the larger steric size of the CF_3 group compared to an *n*-alkyl group.[2f] Recognizing the possible utility of this process for preparing (trifluoromethyl)alkenes,[16] we investigated if this base-promoted process can be triggered in less acidic products. Using substrate **3** as a model system, we found that exposure to KO^{t}Bu at 40 °C led to a nearly quantitative yield of the corresponding vinyl (trifluoromethyl)-alkene **28** with modest *E*/*Z* selectivity (eq 1). This method potentially provides a mild, high-yielding, two-step synthesis of vinyl (trifluoromethyl)alkenes from a variety of complex nitroalkanes.

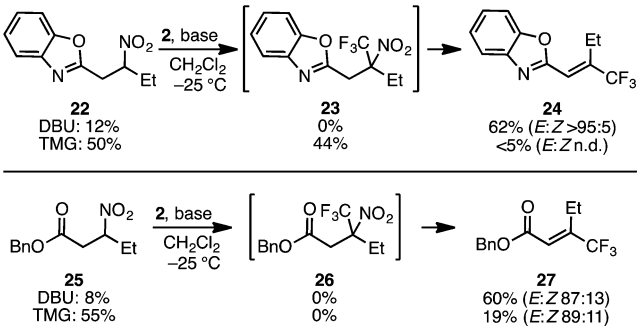
(Trifluoromethyl)nitroalkanes are readily reduced to α-(trifluoromethyl)amines. As shown in Scheme 3 (top and middle), both Zn/AcOH reduction and hydrogenolysis can be effective. However, we note that with α-aryl nitroalkanes, which are prone to denitration,[17] hydrogenolysis is the preferred method for reduction (Scheme 3, bottom).

Scheme 1. Scope of the Trifluoromethylation of Secondary Nitroalkanes



[a]Isolated yields unless otherwise noted. Diastereomeric ratios (dr) determined by ^1H NMR analysis of crude reaction. [b]1.5 equiv of **2** used. [c]18 h. [d]Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [e]48 h. [f]24 h.

Scheme 2. Competitive Alkene Formation and Role of Base



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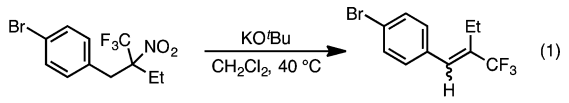
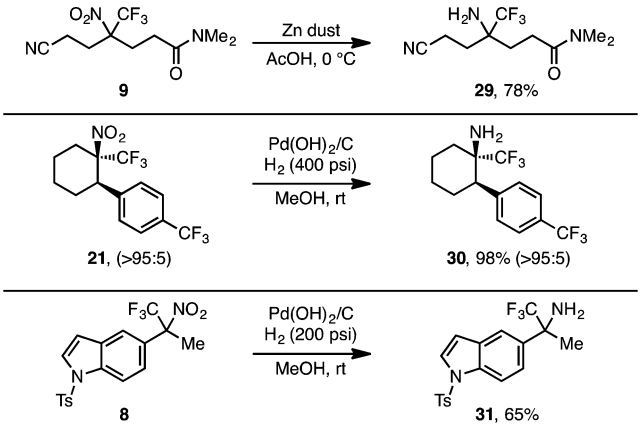
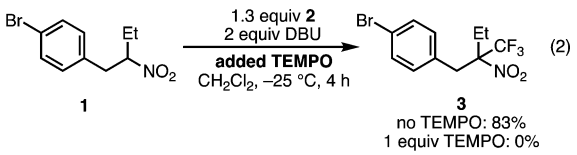


Scheme 3. Preparation of α-(Trifluoromethyl)amines



Consistent with our earlier results,[7] preliminary mechanistic studies suggest that the trifluoromethylation reaction proceeds via a radical mechanism. When the radical inhibitor TEMPO is introduced into the reaction, no desired trifluoromethylated product was observed (eq 2). Further, in situ ^{1}H NMR studies



in CD_2Cl_2 have revealed many of the details of the reaction mechanism. First, combining DBU and nitroalkane **1** at low temperature reveals that a significant equilibrium concentration of nitronate anion **32** is produced and that the deprotonation is relatively slow (it takes about 10 min for a 2:1 mixture of DBU and **1** to reach equilibrium at −25 °C). Second, when DBU and **2** are combined at −25 °C, **2** is instantly consumed and a new complex bearing related aromatic signals is produced. Prior studies have shown that **2** forms electron-donor−acceptor (EDA) complexes with basic amines,[18] and we have tentatively assigned this as the EDA complex **2**·DBU. Third, monitoring the trifluoromethylation reaction by ^{1}H NMR of **1** under slightly modified conditions (−25 °C, half optimal concentration) reveals an initially fast rate of production of **3** that slows considerably as the reaction progresses. Under these conditions, two reactive intermediates are observed. The first, which is maximally present at the first observation point (ca. 2 min) and then decays as the reaction proceeds, has signals that match **2**·DBU. The second builds in early in the reaction and then decays as the reaction progresses. This complex bears ^{1}H NMR signals that are related both to **1** and **2**. We tentatively assign this as the associated ion pair **33**.[19]

Based upon these observations, we propose the following reaction mechanism (Figure 2). Early in the reaction, DBU and **2** form the EDA complex **2**·DBU. As the nitronate anion **32** is formed, **2**·DBU is consumed and the ion pair **33** is formed. The salt complex **33** then undergoes slow decomposition to a nitronate radical **34**, CF_3-radical, and dibenzothiophene via

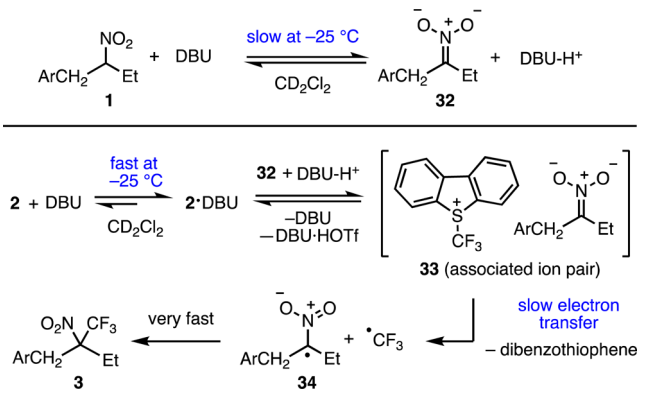


Figure 2. Proposed mechanism for nitroalkane trifluoromethylation.

electron transfer. Rapid recombination of the two radicals results in the formation of the observed product **3**.[20,21]

In conclusion, we have developed mild reaction conditions for the trifluoromethylation of secondary nitroalkanes using a commercially available trifluoromethylating reagent. This procedurally simple protocol allows rapid access to highly complex quaternary α-(trifluoromethyl)nitroalkanes in good yields and diastereoselectivity. The wide functional group tolerance highlights the power of this transformation as a method for late-stage installation of a trifluoromethyl group. In addition, we have demonstrated that these products can be reduced to medicinally interesting α-(trifluoromethyl)amines. Finally, we have also shown that, in at least some cases, base-induced elimination of HNO_2 allows the products to be converted to highly substituted trifluoromethylalkenes with good levels of stereocontrol. Further studies will be aimed at expanding the scope of these transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01196.

X-ray data for compound **21** (CIF)
X-ray data for compound **s12** (CIF)
X-ray data for compound **15** (CIF)
Experimental procedures; crystallographic and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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(19) A similar reaction profile is observed at −25 °C under optimized reaction conditions; however, the reaction is too fast to be adequately observed by NMR over the first half-life and is complicated by initial heterogeneity during the first minutes of the reactions. See the Supporting Information.

(20) Radical substitution mechansims are well precedented for nitro compounds. For an early example, see: Kornblum, N.; Swiger, R. T.; Earl, G. W.; Pinnick, H. W.; Stuchal, F. W. *J. Am. Chem. Soc.* **1970**, *92*, 5513−5514.

(21) We cannot exclude the possibilty of an alternative radical-chain mechanism.

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