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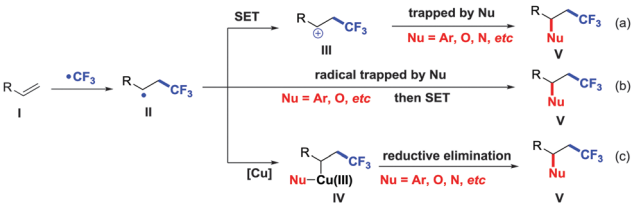
Organic base-catalysed solvent-tuned chemoselective carbotrifluoromethylation and oxytrifluoromethylation of unactivated alkenes†

Ning-Yuan Yang,‡ Zhong-Liang Li,‡ Liu Ye, Bin Tan and Xin-Yuan Liu*

An unprecedented and efficient organic base-catalysed highly chemoselective carbo- and oxytrifluoromethylation of unactivated alkenes with Togni's reagent was developed. The switchable chemoselectivity was tuned by simply changing the organic base catalyst and solvent. Mechanistic studies indicated that a radical cyclization pathway for carbotrifluoromethylation in DMSO and a carbocation pathway for oxytrifluoromethylation in DCE were probably involved.

Controlling the selectivity in radical reactions is a fundamental challenge due to the intrinsically high reactivity and instability of radical intermediates.[1] Although recently developed mild conditions allow for highly stereoselective accumulation of the desired product,[1,2] there is still demand for the development of general strategies to tune the selectivity of radical reactions. The strategy for the realization of reaction chemodivergence in a controlled manner is a long-standing goal and represents a powerful and promising synthetic tool in diversity-oriented synthetic chemistry since it can enable the assembly of various molecules from identical reactants. Thus, tuning the chemoselectivity of a reaction in a facile and predictable manner has been attracting more and more attention.

Over the past decades, owing to the importance of trifluoromethylated compounds in pharmaceutical and agricultural chemistry,[3] installing CF_3 groups into organic molecules has been a hot topic.[4] In this context, the difunctionalization of unactivated alkenes,[5] such as aminotrifluoromethylation,[6,13c,d] carbotrifluoromethylation[7] and oxytrifluoromethylation,[8] represents an appealing strategy to introduce various functional groups into alkenes. With regard to the reaction mechanism, there are three possible pathways commonly presented in the literature (Scheme 1). All of them are initiated by the reaction of a CF_3 radical with alkene **I** to generate an α-CF_3 alkyl radical **II**, followed by the following different pathways: (1) it is firstly oxidized to carbocation **III** and subsequently trapped by nucleophiles to afford product **V** (Scheme 1a);[9] (2) it couples directly with the radical partner, followed by an SET oxidation (Scheme 1b);[7b,f] (3) it forms an alkylcopper(III) species with the corresponding nucleophiles, followed by a reductive elimination (Scheme 1c).[8d] In spite of the blooming developments in the trifluoromethylation of alkenes, the reaction mechanism is still not well-documented. Therefore, a detailed mechanistic study of radical trifluoromethylation-triggered difunctionalizations of alkenes is urgent and will provide instructive insight for switching the reaction selectivity with different nucleophiles *via* simply altering the reaction conditions.



Scheme 1 Proposed reaction mechanisms for radical trifluoromethylation of alkenes.

Compared with the widely-developed transition-metal catalysed radical trifluoromethylation of alkenes, metal-free methods, which have a huge advantage due to the capacity of tolerating many different coordinating functional groups that would otherwise form a strong coordination with the metal catalyst to impede the reaction efficiency,[10] remain widely unexplored.[7l,8b] More recently, our research group has developed an organic base-initiated radical trifluoromethylation of alkenes to trigger remote C–H bond functionalization of amides.[13a,i] In this context, the choice of solvent always has a significant impact on the reaction efficiency in radical trifluoromethylation reactions.[7–11] For example, DMSO, as a polar solvent, is widely studied in radical reactions[12] and supposed to promote radical reactions presumably because the radical intermediate forms a cluster with DMSO, thus stabilizing the radical–solvent adduct *via* delocalization of the radical to further tune the redox potential of the oxidant.[12b,c]

Department of Chemistry, South University of Science and Technology of China, Shenzhen, 518055, China. E-mail: liuxy3@sustc.edu.cn

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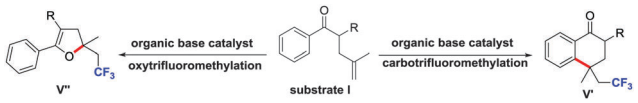
‡ These authors contributed equally to this work.

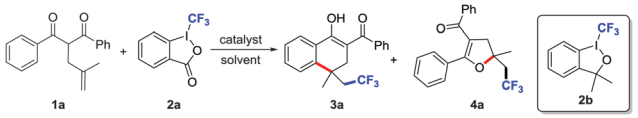


Scheme 2 Substrate design and chemodivergent transformation.

Considering the possibility of control of the radical selectivity through solvent-binding effects,[12] and in our continued efforts to develop the trifluoromethylation of alkenes,[13] we envisioned that substrates **I** bearing both a carbon reactive center and an oxygen reactive center might chemoselectively undergo carbotrifluoromethylation *via* a radical pathway or oxytrifluoromethylation *via* a carbocation pathway, by simply tuning the catalyst and solvent system (Scheme 2). Herein, we disclose an unprecedented solvent-tuned chemodivergent carbo- and oxy-trifluoromethylation of unactivated alkenes catalysed by organic base to afford trifluoromethylated tetralins and 4,5-dihydrofurans in a predictable and mechanistically controlled manner. These structural motifs are promising components of various biologically active medicinal compounds.[3] Also reported here are our mechanistic studies of such organic base-catalysed trifluoromethylations of alkenes employing control experiments, KIE studies and the Hammett experiment.

To validate our hypothesis, substrate **1a** bearing a diphenylketone group was selected as the model substrate with Togni's reagent **2a**[14] as the CF_3 radical source to optimize the reaction conditions for the carbotrifluoromethylation of alkenes (Table 1). Several reported protocols, with Cu(I) salts[7l] or *n*-Bu_4NI[15] as the catalysts to initiate **2a** or with $PhI(OAc)_2$ as the oxidant to initiate $TMSCF_3$[13a] were firstly screened. To our disappointment, the results were not satisfactory and both carbotrifluoromethylation product **3a** and oxytrifluoromethylation product **4a** were obtained with poor selectivity or yield (entries 1–3). Inspired by the success of our recently developed organic base-catalysed radical trifluoromethylation of alkenes,[13i] we next focused on the organic base-catalysed trifluoromethylation of alkenes. Several types of bases including secondary and tertiary amines with ethyl acetate (EtOAc) as the solvent at 80 °C were tested, and all of them favoured the formation of **4a** resulting from oxytrifluoromethylation, and the desired product **3a** was obtained as the minor product (entries 4–7). To our surprise, DMSO, which is believed to stabilize radical intermediates well,[12c] reversed the product distribution completely, implying that the choice of solvent can significantly control the chemoselectivity of the reaction (entry 11). Other solvents, such as THF, dioxane and chloroform, proved no better than DMSO (entries 8–10). Lowering the temperature to 50 °C enhanced the yield of **3a** to 79% and meanwhile **4a** was obtained in only 1% yield determined by ^{19}F NMR spectroscopy (entry 12). Replacing **2a** with **2b** or reducing the catalytic amount of DBN did not give a better result (entries 13–15). Finally we identified the optimal conditions as follows: reaction of **1a** (1.0 equiv.) and **2a** (2.0 equiv.) catalysed by DBN (20 mol%) with DMSO as solvent for 10 h (entry 12) delivered carbotrifluoromethylation product **3a** in 79% NMR yield.

Table 1 Screening of reaction conditions for carbotrifluoromethylation[a]

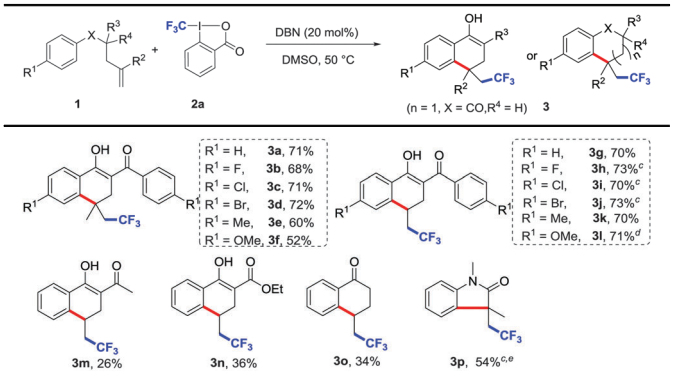


Entry	Cat. (*X* equiv.)	Solvent	*T* (°C)	*Y* (%) of **3a** (**4a**)[b]
1	CuI (0.1)	Dioxane	80	13 (69)
2	*n*-Bu_4NI (0.3)	CH_3CN	80	23 (24)
3[c]	$PhI(OAc)_2$ (2.0)	EtOAc	50	Trace
4	Pyrrolidine (0.2)	EtOAc	80	15 (61)
5	DIPEA (0.2)	EtOAc	80	7 (70)
6	DMAP (0.2)	EtOAc	80	20 (78)
7	DBN (0.2)	EtOAc	80	28 (46)
8	DBN (0.2)	THF	80	29 (33)
9	DBN (0.2)	Dioxane	80	17 (80)
10	DBN (0.2)	$CHCl_3$	80	18 (40)
11	DBN (0.2)	DMSO	80	41 (5)
12	**DBN (0.2)**	**DMSO**	**50**	**79 (1)**
13[d]	DBN (0.2)	DMSO	50	28 (8)
14[e]	DBN (0.15)	DMSO	50	78 (7)
15[f]	DBN (0.10)	DMSO	50	58 (5)

[a] Unless otherwise noted, the reaction was conducted with **1a** (0.1 mmol), Togni's ester **2a** (0.2 mmol), and base (0.02 mmol) in 1.0 mL solvent for 10 h. [b] Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. [c] $TMSCF_3$ (4.0 equiv.) as the source of CF_3, $PhI(OAc)_2$ as the oxidant, KF (4.0 equiv.) was added. [d] **2b** (0.2 mmol) was used and reaction time is 36 h. [e] Reaction time is 24 h. [f] Reaction time is 36 h. DIPEA: diisopropylethylamine. DMAP: *N*,*N*-dimethylaniline. DBN: 1,5-diazabicyclo-[4.3.0]non-5-ene.

With the optimized reaction conditions in hand, we next turned our attention to the generality of the protocol (Table 2). Substrates containing electron-withdrawing groups or electron-donating groups on the *para* position of the phenyl ring underwent the carbotrifluoromethylation smoothly to afford the desired products **3b–3f** in moderate to good yields (52–72%). Notably, for monosubstituted alkenes **1g–1o**, the reaction showed good compatibility. Substrates with several substituents on the *para* position of the phenyl ring gave **3g–3l** in good yields (70–73%). In addition to symmetric diketone substrates, the reaction of unsymmetric substrates, as exemplified by 1,3-diketone substrate (**1m**) and β-keto ester (**1n**), worked under the standard conditions albeit with a lower yield (26% and 36%, respectively). The desired product can be accessed from other types of substrates.

Table 2 Substrate scope with carbotrifluoromethylation reaction[a,b]



[a] Reaction conditions: **1** (0.20 mmol), **2a** (0.40 mmol), DBN (0.04 mmol), DMSO (2 mL) at 50 °C for 10 h. [b] Isolated yield based on **1**. [c] EtOAc as solvent. [d] At 80 °C. [e] At 100 °C.

For example, linear ketone substrate **1o** delivered the desired product in 34% yield and the previously reported trifluoromethylated oxindole skeleton **3p**[13a] can also be generated from the corresponding substrate in 54% yield.

We next focused on the optimization of the reaction conditions for oxytrifluoromethylation. As mentioned before, the best ratio of **4a**/**3a** was observed in EtOAc with DIPEA as catalyst. Encouraged by this result, we further screened the solvent effect, the ratio of **2a** as well as the CF_3 source, and finally identified the following protocol as optimal: reaction of **1a** and **2a** with a molar ratio of 1.0 : 2.0 in the presence of DIPEA (20 mol%) with DCE as the solvent at 80 °C for 10 h, **4a** was obtained in 85% yield (see Table S1 in ESI†).

To expand the application of this methodology, the substrate scope was further examined employing the optimal conditions for oxytrifluoromethylation (Table 3). Firstly, the electronic effect on the phenyl ring was investigated and the result showed that substrates bearing both *para*-electron-withdrawing and electron-donating groups afforded the 4,5-dihydrofurans **4b–4f** in good yields (68–82%) with excellent chemoselectivity. Notably, geminal-substituted substrates **1q** and **1r** also generated products **4q** and **4r** with 75% and 76% yields and excellent regioselectivity (>20 : 1). The phenyl substituents (**1s–1x**) can also be tolerated to provide the desired products in moderate to good yields (38–73%).

To gain insight into the reaction mechanism, control experiments were performed. Treatment of **1a** and **2a** under standard conditions for carbo- and oxytrifluoromethylation was completely inhibited upon addition of 2 equiv. of 1,4-dinitrobenzene, suggesting that a radical pathway is likely involved under the current system (Scheme S1 in ESI†, eqn (1) and (2)). Furthermore, an intermolecular KIE experiment was conducted, and the small k_H/k_D (1.15 : 1) indicated that C–H bond cleavage was not involved in the rate-determining step of the carbotrifluoromethylation (Scheme S1 in ESI†, eqn (3)).[7b]

To further demonstrate the role of solvent in tuning the reaction pathway, the electronic effect of substituents on phenyl ring of substrates was investigated under the standard reaction conditions (Fig. 1). For DMSO-tuned carbotrifluoromethylation to generate **3**, substrates **1h**, **1i** and **1j** with electron-withdrawing groups exhibited a much faster reaction rate than **1k** and **1l** with electron-donating groups, presenting a large positive σ value (2.73) (Fig. 1A).[16] The result argued against the involvement of the carbocation intermediate in the carbotrifluoromethylation and thus demonstrated that a radical cyclization pathway might be involved for the carbotrifluoromethylation in DMSO.[16] In sharp contrast, substrate **1b**, **1c** and **1d** with electron-withdrawing groups reacted slightly slower than **1e** and **1f** with electron-donating groups in DCE, generating a negative σ value (−0.94) (Fig. 1B), which implied that an oxygen-centred nucleophilic attack to the carbocation center might occur in the cyclization step and thus a carbocation intermediate might be involved before the cyclization step of the oxytrifluoromethylation.[16b]

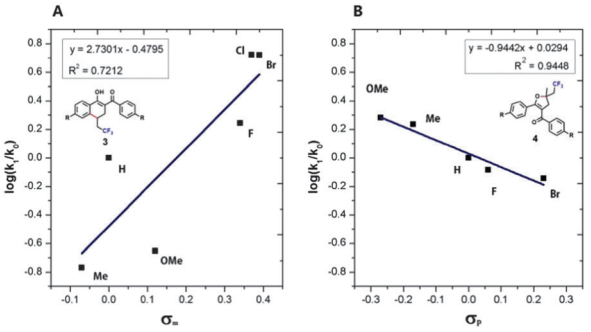
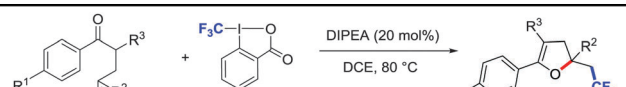
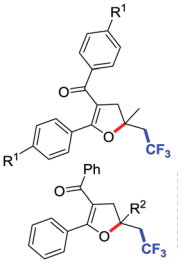


Fig. 1 Hammett study (A) using σ_m for carbotrifluoromethylation in DMSO; (B) using σ_p for oxytrifluoromethylation in DCE.

On the basis of the above control experiments and mechanistic studies, a proposed mechanism for these reactions is proposed as depicted in Scheme 3. The amine and Togni's reagent **2a** easily form an EDA complex, which provides CF_3 radical and amino radical cation **VI** after electron transfer.[13i,17] The CF_3 radical attacks alkene **1a** to generate a nascent α-CF_3-alkyl radical intermediate **VII**. With DMSO as the solvent, intermediate **VII** could be stabilized through solvation to elongate its lifetime,[12c] allowing the radical cyclization on the aryl ring to give rise to **VIII**, and the subsequent SET process from **2a** and the deprotonation step furnish the final product **3a**.[1d,e] However, in the presence of DCE, intermediate **VII** is readily oxidized to cation **IX** by **2a**, which is prone to be attacked by the enol rather than the aryl ring to deliver product **4a** after deprotonation. Another possibility is that the reductive potential of **2a** differed in different solvents.

Table 3 Substrate scope of the oxytrifluoromethylation reaction[a,b]

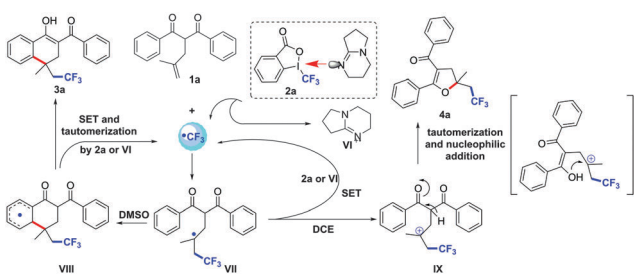




R^1 = H, **4a**, 71% (8.5:1)[c] R^1 = Br, **4d**, 68% (5.1:1)
R^1 = F, **4b**, 71% (6.1:1) R^1 = Me, **4e**, 82% (7.9:1)
R^1 = Cl, **4c**, 73% (8.0:1) R^1 = OMe, **4f**, 50% (10.1:1)

R^2 = Et, **4q**, 75% (>20:1) R^2 = 4-ClC_6H_4, **4u**, 60% (>20:1)
R^2 = *t*-Bu, **4r**, 76% (>20:1) R^2 = 4-BrC_6H_4, **4v**, 62% (>20:1)
R^2 = Ph, **4s**, 90% (>20:1) R^2 = 4-MeC_6H_4, **4w**, 73% (>20:1)
R^2 = 4-FC_6H_4, **4t**, 58% (>20:1) R^2 = 4-$MeOC_6H_4$, **4x**, 38% (>20:1)

[a] Reaction conditions: **1** (0.20 mmol), Togni's reagent **2a** (0.40 mmol), DIPEA (0.04 mmol), DCE (1.0 mL) at 80 °C for 10 h. [b] Isolated yield based on **1**. [c] Ratio of **4a**/**3a** in parenthesis.



Scheme 3 A proposed mechanism for the solvent-tuned trifluoromethylation of alkenes.

In DCE or other solvents it is high enough to oxidize **VII** to **IX**, while in DMSO it fails to oxidize **VII** and the radical pathway is more favourable to afford **3a**.[12b] On the other hand, it cannot be ruled out that amino radical cation **VI** takes part in the SET process instead of Togni's reagent **2a** in both pathways.

In summary, we have successfully developed unprecedented chemodivergent trifluoromethylation transformations of alkenes concurrently bearing different reactive sites under metal free protocol, which allowed for a rapid and diverse accumulation of trifluoromethylated tetralins and 4,5-dihydrofurans, simply by adjusting the catalyst and solvent. Detailed mechanistic studies in selected solvents indicated that a radical pathway in DMSO for carbotrifluoromethylation and a carbocation pathway in DCE for oxytrifluoromethylation might be involved. The high chemoselectivity renders this methodology a powerful tool in radical transformations and is applicable to other radical chemodivergent synthetic methodologies.

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