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Efficient trifluoromethylation *via* the cyclopropanation of allenes and subsequent C–C bond cleavage†

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As we know, the incorporation of a trifluoromethyl group into organic molecules may significantly alter their physical and biological properties due to the high electronegativity, lipophilicity, and excellent metabolic stability of the trifluoromethyl substituent. Thus, an efficient method for the introduction of the trifluoromethyl group is of high current interest. On the other hand, vinylic cyclopropanes are a class of strained compounds capable of undergoing ring-opening reaction with other molecules. Here, CF_3-substituted vinylic cyclopropanes have been highly selectively formed by a copper-catalyzed cyclic trifluoromethylation of (4,4-disubstituted-2,3-butadienyl)malonates with Togni's reagent II, in which the trifluoromethyl group was installed at the middle carbon of the allene unit by applying 1,10-phenanthroline as the ligand. Such unique cyclopropanes successfully bring the trifluoromethyl group to other useful organic skeletons by the selective cleavage of C–C bonds with an exclusive diastereoselectivity. Based on the mechanistic studies, an allene radical addition, oxidation, and allylic substitution pathway has been proposed.

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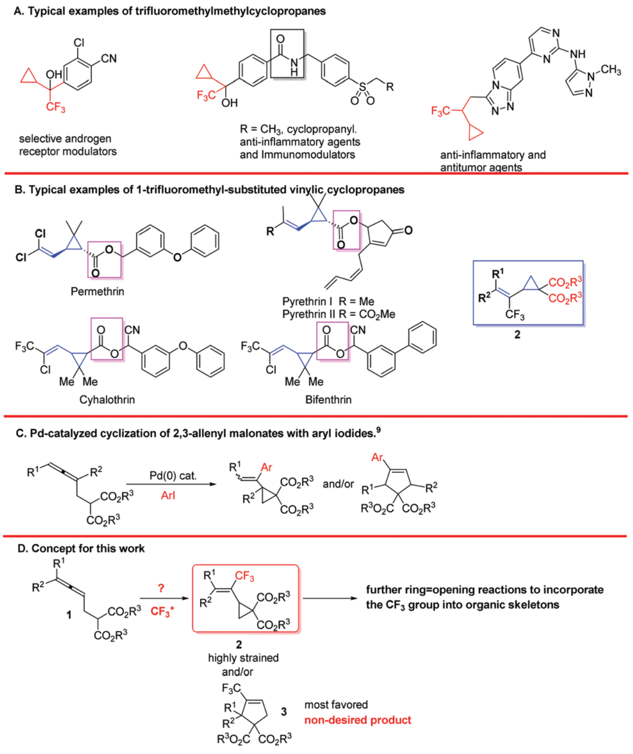
Trifluoromethylated compounds have been widely used in all aspects of chemistry, such as materials, pharmaceuticals, agrochemicals, and fine chemicals due to the high electronegativity, lipophilicity, and excellent metabolic stability of the trifluoromethyl substituent.[1–3] Of particular interest, compounds containing a 2,2,2-trifluoroethylcyclopropane unit have been identified as selective androgen receptor modulators,[4a] anti-inflammatory agents,[4b,c] immuno-modulators,[4b] and anti-tumor agents[4c] (Scheme 1). On the other hand, vinylcyclopropanes are the core structures of various pyrethroids such as pyrethrin,[4d,e] permethrin,[4f,g] cyhalothrin,[4h] and bifenthrin.[4i] Thus, we envisioned the structure of trifluoromethyl-substituted vinylcyclopropanes **2** and have been interested in developing methodologies for the efficient synthesis of this type of compound (Scheme 1). In addition, due to the high



Scheme 1 A and B) Some bioactive cyclopropanes containing a trifluoromethyl group; (C) Pd-catalyzed cyclization of allenyl malonates with organic halides; (D) concept of introducing a trifluoromethyl group *via* transition metal-catalyzed cyclopropanation.

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† Electronic supplementary information (ESI) available: Preparation and characterisation data as well as ^1H and ^{13}C NMR spectra of all compounds. CCDC 1012501, 1012706, 1012812 and 1012813. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7qo00419b

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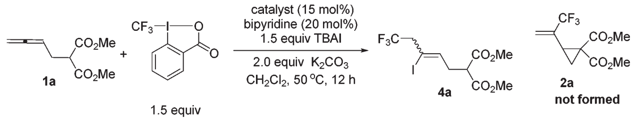
reactivity of the three-membered ring, such cyclopropanes **2** may also bring the trifluoromethyl group to other useful organic skeletons *via* the C–C bond cleavage reactions.[5] To the best of our knowledge, there is no method for the construction of such CF_3-substituted vinylic cyclopropanes and no report on their related reactivity study. We proposed a trifluoromethylative cyclization of allenes containing a malonate unit for the efficient synthesis of **2**-type of compound (Scheme 1D).[6–8] The challenge here would be the regioselectivity affording either the non-favored highly strained 3-membered products **2** or the most favored 5-membered products **3** as observed in the Pd-catalyzed cyclization of allenylmalonates with organic halides (Scheme 1C).[9] Herein, we report our recent observation on the highly regioselective copper-catalyzed trifluoromethylation of (2,3-butadienyl)malonates using a hypervalent trifluoromethyl iodonium reagent, which allows for the exclusive formation of strained trifluoromethylated vinyl cyclopropanes **2**.

Our initial investigation started with the reaction of dimethyl 2-(buta-2,3-dienyl)malonate **1a** with Togni's reagent II in the presence of 5 mol% of $PdCl_2$ and 2 equiv. of K_2CO_3 in DCM at 50 °C, however, no trifluoromethylation product **2a** was observed (Table 1, entry 1). Instead, a highly regioselective iodo-trifluoromethylation product **3a** was detected albeit as a pair of *Z*/*E* stereoisomers.[10] This clearly indicated that in this simplest case the trifluoromethyl group was directed to the terminal position of the allene unit in dimethyl 2-(buta-2,3-dien-1-yl)malonate **1a**, excluding the possibility of forming the expected cyclized product **2a**. Cu(I) or Cu(II) catalysts exhibited similar results, still affording low yields of **4a** while the formation of **2a** was not detected (Table 1, entries 2–4).

Thus, we envisioned to increase the steric hindrance of the terminal position of the allene unit in **1** for the possible direction of the trifluoromethyl group to the allene middle carbon atom to form a π-allylic metal species, which would be followed by nucleophilic substitution to possibly afford the cyclized products **2** or **3**. When dimethyl 2-(buta-2,3-dien-1-yl) malonate **1a** was replaced with dimethyl 2-(4-methyl-2,3-pentadienyl)malonate **1b**, the reaction under the catalysis of $Cu(OAc)_2$, $CuCl_2$, $CuF_2·H_2O$ and $Cu(OTf)_2$ (Table 2, entries 1–4) did afford the designed trifluoromethylated vinylic cyclopropane **2b** exclusively in moderate yields and the formation of the 5-membered ring **3b** was not observed. $Cu(OAc)_2$ gave the best results, affording **2b** in 65% yield with 28% recovery of **1b** (Table 2, entry 1). CuOAc could also catalyse the reaction with a slightly decreased yield (Table 2, entry 5). The reaction was even better with just 1.0 equiv. of TBAI (Table 2, entry 6). Rather unexpectedly, reducing the catalyst loading of $Cu(OAc)_2$ from 15 mol% to 10 mol% improved the yield of **2b** from 65% to 69% (Table 2, entry 7). When we further reduced the loadings of the catalyst and ligand, the yield dropped to 63% (Table 2, entry 8). By comparison, only 11% of product **2b** was obtained in the absence of the copper complex (Table 2, entry 9).

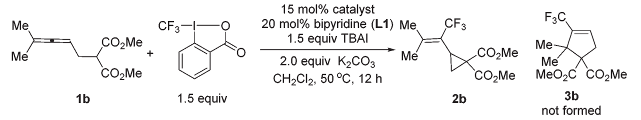
Table 1 Effect of catalysts on iodo-trifluoromethylation of allene **1a**[a]



Entry	Catalyst	Yield of **4a** (%) (*Z*/*E*)[b]	Recovery of **1a**[b] (%)
1	$PdCl_2$ [c]	3 (2 : 1)	48
2	CuBr	13 (1.5 : 1)	26
3	$[Cu(CH_3CN)_4]PF_6$	20 (1.5 : 1)	16
4	$Cu(OAc)_2$ [d]	33 (2.3 : 1)	0

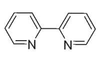
[a] Reaction conditions: Unless otherwise specified, the reaction was carried out using **1a** (0.2 mmol), Togni's reagent II (0.3 mmol), TBAI (0.3 mmol), K_2CO_3 (0.4 mmol), copper catalyst (0.03 mmol), and 2,2′-bipyridine (**L1**) (0.04 mmol) in 2 mL of CH_2Cl_2 under an argon atmosphere. [b] Determined by ^{19}F NMR and ^{1}H NMR spectroscopy using $PhCF_3$ and CH_2Br_2 as the internal standards, respectively. [c] The reaction was carried out without bipyridine and TBAI. [d] The reaction was conducted on a 1 mmol scale of **1a** with 2 equiv. of Togni's reagent II, K_3PO_4 (2 mmol) as the base, $Cu(OAc)_2$ (10 mol%), and 1,10-phenanthroline (**L2**) (0.2 mmol) as the ligand; reaction time was 22 h.

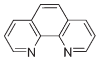
Table 2 Effect of catalysts on trifluoromethylcyclopropanation of allene **1b**[a]

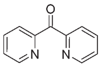


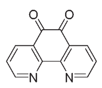
Entry	Catalyst	Yield of **2b**[b] (%)	Recovery of **1b**[b] (%)
1	$Cu(OAc)_2$	65	28
2	$CuCl_2$	55	25
3	$CuF_2·H_2O$	35	24
4	$Cu(OTf)_2$	47	53
5	CuOAc	42	0
6	$Cu(OAc)_2$ [c]	65	15
7	$Cu(OAc)_2$ [c,d]	69	16
8	$Cu(OAc)_2$ [c,e]	63	14
9	—	11	51

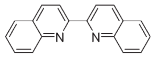
[a] Reaction conditions: Unless otherwise specified, the reaction was carried out using **1b** (0.2 mmol), Togni's reagent II (0.3 mmol), TBAI (0.3 mmol), K_2CO_3 (0.4 mmol), copper catalyst (0.03 mmol), and 2,2′-bipyridine (**L1**) (0.04 mmol) in 2 mL of CH_2Cl_2 under an argon atmosphere. [b] Determined by ^{19}F NMR and ^{1}H NMR spectroscopy using $PhCF_3$ and mesitylene or CH_2Br_2 as the internal standards. [c] The reaction was carried out using 1.0 equiv. of TBAI. [d] The reaction was carried out using 10 mol% of $Cu(OAc)_2$. [e] The reaction was carried out with 5 mol% of $Cu(OAc)_2$ and 10 mol% of **L1**.


L1


L2

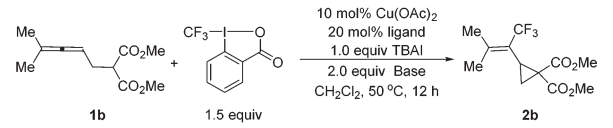

L3


L4


L5

To further improve the yield, we applied the ligand effect by evaluating a series of bidentate ligands (Table 3): when 1,10-phenanthroline (**L2**) was used, the yield was further improved to 77% (Table 3, entry 2); the use of 1,10-phenanthroline-5,6-dione (**L4**) afforded the product in 42% yield; it is observed that the use of a di-2-pyridyl ketone (**L3**) or 2,2′-biquinoline (**L5**) afforded **2b** in 12% and 27% yields, respectively (Table 3, entries 3 and 5). By contrast, in the absence of any ligands, the

Table 3 Effect of ligands and bases on the reaction of trifluoromethylcyclopropanation[a]



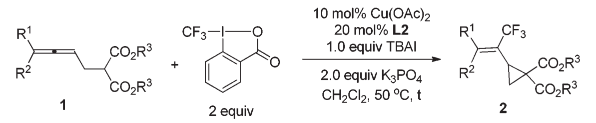
Entry	L	Base	Yield of **2b**[b] (%)	Recovery of **1b**[b] (%)
1	**L1**	K_2CO_3	69	16
2	**L2**	K_2CO_3	77	13
3	**L3**	K_2CO_3	12	27
4	**L4**	K_2CO_3	42	19
5	**L5**	K_2CO_3	27	26
6	—	K_2CO_3	10	34
7	**L2**	Na_2CO_3	63	17
8	**L2**	Cs_2CO_3	12	0
9	**L2**	K_3PO_4	82	9
10	**L2**	K_3PO_4 [c]	76	12
11[d]	**L2**	$\mathbf{K_3PO_4}$	**87**	**0**
12	**L2**	—	40	31
13[d,e]	**L2**	K_3PO_4	42	0

[a] Reaction conditions: Unless otherwise specified, the reaction was carried out using **1b** (0.2 mmol), Togni's reagent II (0.3 mmol), TBAI (0.2 mmol), base (0.4 mmol), $Cu(OAc)_2$ (0.02 mmol), and ligand (0.04 mmol) in 2 mL of CH_2Cl_2 under an argon atmosphere. [b] Determined by ^{19}F NMR and ^1H NMR spectroscopy using $PhCF_3$ and mesitylene or CH_2Br_2 as the internal standards. [c] The reaction was carried out with 2.5 equiv. of K_3PO_4. [d] The reaction was carried out with 2.0 equiv. of Togni's reagent II. [e] The reaction was carried out with 10 mol% of CuOAc instead of $Cu(OAc)_2$.

yield is much lower (Table 3, entry 6). Subsequently, we tested some bases with K_3PO_4 being the best (Table 3, entry 9). Further increasing the amount of K_3PO_4 led to a lower yield (Table 3, entry 10). To our delight, 2 equiv. of Togni's II reagent led to the full consumption of **1b**, affording **2b** in 87% yield (Table 3, entry 11). In the absence of a base, the reaction was poor (Table 3, entry 12). It should be noted that the yield dropped to 42% with the full consumption of **1b** when the catalyst was replaced by CuOAc (Table 3, entry 13).

With the optimized protocol in hand, we next turned to demonstrate the generality of this reaction. The results summarized in Table 4 show that this reaction indeed provides a straightforward entry to a series of trifluoromethylated vinyl cyclopropanes in moderate to good yields. Different substitutions at the terminal position of allene, such as methyl, ethyl, butyl, cyclobutyl, cyclopentyl and cyclohexyl could be compatible in this reaction, affording the corresponding trifluoromethylated vinyl cyclopropanes **2b–2j** in moderate to good yields (Table 4, entries 1–9); the substrate with a sterically bulky isopropyl substituent also furnishes the corresponding product **2k** in a moderate yield (Table 4, entry 10). Moreover, phenyl- and methyl-substituted malonate **1l** afforded the corresponding product **2l** in 66% yield with a ratio of 1 : 3 for the corresponding stereoisomers (Table 4, entry 11). To further demonstrate the potential of this reaction, we carried out this reaction on a gram scale under the standard conditions: when 1.0604 g of **1b** was used, 1.1061 g of **2b** was obtained in 79% yield.

Table 4 Copper-catalyzed trifluoromethylcyclopropanation of (2,3-butadienyl)malonates[a]

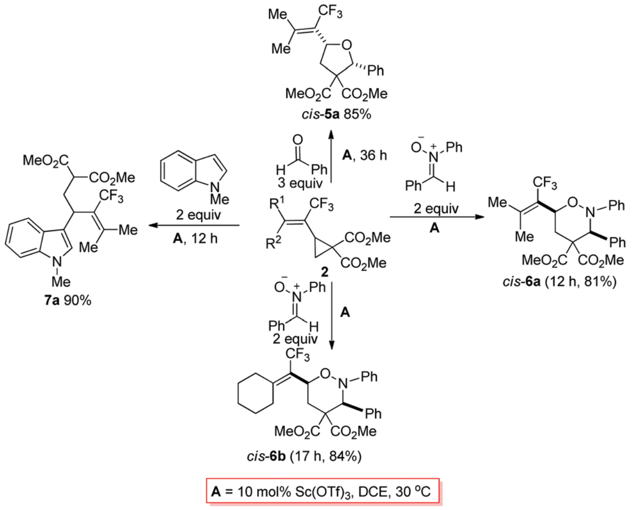


Entry	R^1, R^2	R^3	*t* (h)	Yield of **2**[b] (%)
1	Me, Me	Me (**1b**)	12	86 (79[c])(**2b**)
2	$-(CH_2)_5-$	Me (**1c**)	24	84 (**2c**)
3	Me, Me	Et (**1d**)	13.5	82 (**2d**)
4	Me, Me	Bn (**1e**)	12	74 (**2e**)
5	Et, Et	Et (**1f**)	24	70 (**2f**)
6	*n*-Bu, *n*-Bu	Et (**1g**)	24	79 (**2g**)
7	$-(CH_2)_3-$	Et (**1h**)	17	64 (**2h**)
8	$-(CH_2)_4-$	Et (**1i**)	15	60 (**2i**)
9	$-(CH_2)_5-$	Et (**1j**)	13	74 (**2j**)
10[d]	*i*-Pr, *i*-Pr	Et (**1k**)	24	51 (**2k**)
11	Ph, Me	Me (**1l**)	12	66[e] (**2l**)

[a] Reaction conditions: Unless otherwise specified, the reaction was carried out using **1** (1 mmol), Togni's reagent II (2.0 mmol), TBAI (1 mmol), K_3PO_4 (2 mmol), $Cu(OAc)_2$ (0.10 mmol) and **L2** (0.20 mmol) in 7 mL of CH_2Cl_2 under an argon atmosphere. [b] Isolated yield. [c] The reaction was carried out using **1b** (5 mmol, 1.0604 g), Togni's reagent II (10.0 mmol), TBAI (5 mmol), and $Cu(OAc)_2$ (0.5 mmol) and **L2** (1.0 mmol) in 35 mL of CH_2Cl_2 under an argon atmosphere. [d] The reaction was carried out using 3 equiv. of K_3PO_4 and 3 equiv. of Togni's reagent II. [e] The reaction gave a pair of *Z*/*E* stereoisomers with a ratio of 1 : 3.

As stated in the introduction, one unique character of the strained three-membered ring is the selective cleavage of C–C bonds in cyclopropanes with an easy incorporation of other molecules to afford a series of complex molecules bearing the trifluoromethyl group. After some screening of the reported Lewis acid catalysts for such transformations,[5,11] we observed that reactions catalyzed by 10 mol% of $Sc(OTf)_3$ in DCE afforded the ring-opening products under very milder conditions: when trifluoromethylated vinylic cyclopropane **2b** was exposed to benzaldehyde, a highly substituted tetrahydrofuran product *cis*-**5a**[12] was formed highly diastereoselectively in 85% yield; with nitrone, *cis*-tetrahydro-1,2-oxazines *cis*-**6a**[12] and *cis*-**6b** were formed in 81% and 84% yields from **2b** and **2c**, respectively; the reaction of **2b** with *N*-methylindole afforded the ring-opened functionalized indole product **7a**[12] in 90% yield (Scheme 2 and Fig. 1).

During the study, we also identified the Togni's reagent II-based by-product by the X-ray diffraction study unambiguously as methylene bis(2-iodobenzoate) **8** (Scheme 3A).[12] Control experiments showed that in the absence of the copper complex, potassium 2-iodobenzoate didn't react with CH_2Cl_2 (Scheme 3B, eqn (1)). When potassium 2-iodobenzoate was exposed under the standard conditions without the allene and K_3PO_4, compound **8** was formed in 31% yield. In order to further study the mechanism, radical scavengers were added under the standard reaction conditions (Scheme 4). With 1,4-dinitrobenzene, the reaction was somewhat suppressed to yield 21% of **2g** (Scheme 4, eqn (1)). With benzoquinone, the trifluoromethylative cyclization reaction was completely shut



Scheme 2 Sc(OTf)$_3$-catalyzed reactions of **2**.

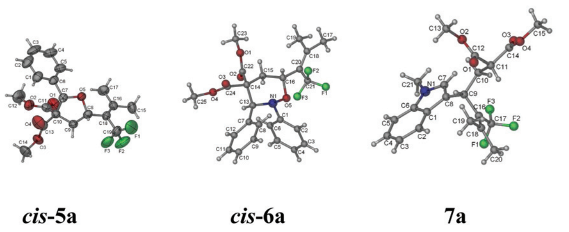
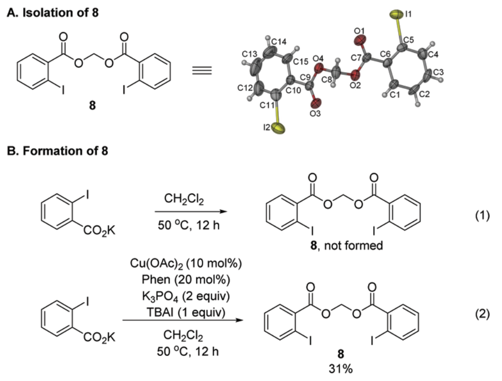
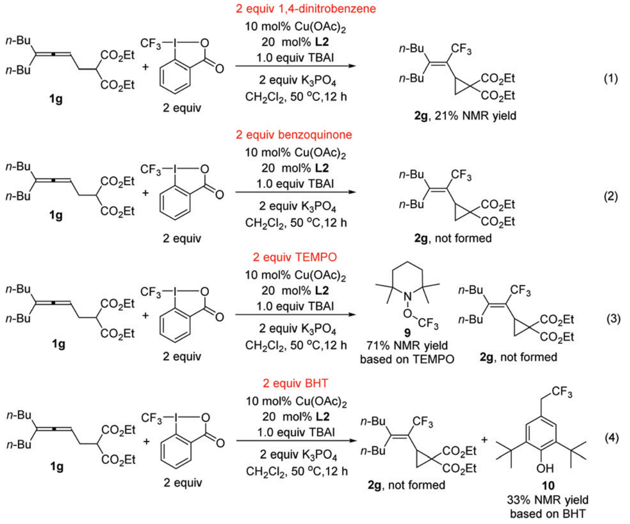


Fig. 1 ORTEP representation of *cis*-**5a**, *cis*-**6a**, and **7a**.



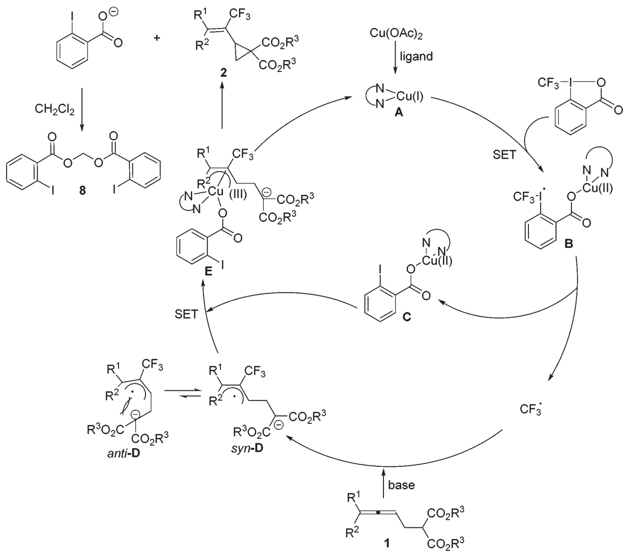
Scheme 3 Formation of by-product **8**: (A) ORTEP representation. (B) Control experiments.

down (Scheme 4, eqn (2)). With TEMPO, the reaction didn't occur and the radical trapping TEMPO-CF$_3$ adduct **9** was formed in 71% yield (Scheme 4, eqn (3)). With BHT, the trifluoromethylative product **2g** was not formed while a BHT-CF$_3$ adduct **10** was observed in 33% yield as judged by the analysis of the crude product comparing the signals with those reported in the literature[13] (Scheme 4, eqn (4)). These results indicated that the reaction may proceed *via* a radical pathway in the beginning.



Scheme 4 Radical trapping experiments.

A mechanism was then proposed on the basis of the above results (Scheme 5). Initially, the *in situ* reduction[14] or disproportionation[15] of Cu(OAc)$_2$ forms the highly reactive Cu(I), which would coordinate with the ligand forming a catalytically active copper(I) species **A**. Then a radical intermediate **B** could be generated by the reaction of **A** with Togni's reagent II, which would further release the CF$_3$ radical and (2-iodobenzoyloxy)copper(II) **C**. Allene **1** would be attacked by the trifluoromethyl radical and its nucleophilic unit would be deprotonated with the base to form the thermodynamically more stable π-allylic radical *syn*-**D**. The intermediate *syn*-**D** would further undergo oxidation with Cu(II) species **C** yielding the π-allylic copper(III) intermediate **E**, which would undergo an intramolecular nucleophilic attack to release the cyclopropane products **2** and the *o*-iodobenzoic acid anion associated with



Scheme 5 Proposed mechanism.

the regeneration of the catalytically active Cu(I) species **A**. The reaction of two molecules of the *o*-iodobenzoic acid anion with CH_2Cl_2 would generate the isolated by-product **8**.[16] The unfavored formation of *anti*-**D** excludes the formation of 3-type of a 5-membered ring. However, it should be noted that the mechanism requires more studies and there may be other possibilities.

In conclusion, we have demonstrated an efficient copper-catalyzed introduction of a trifluoromethyl group into organic skeletons through the cyclization of allenes and C–C bond cleavage-based transformations *via* the formation of the strained trifluoromethylated vinyl cyclopropanes with an excellent regioselectivity under ambient conditions. Further studies in this area are ongoing in our laboratory.

Acknowledgements

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