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

Yang Tang,‡a Qiong Yu‡b and Shengming Ma*‡a,c

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, CF₃-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.

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. Of particular interest, compounds containing a 2,2,2-trifluoroethylcyclopropane unit have been identified as selective androgen receptor modulators, anti-inflammatory agents, immuno-modulators, and anti-tumor agents (Scheme 1). On the other hand, vinylcyclopropanes are the core structures of various pyrethroids such as pyrethrin, permethrin, cyhalothrin, and bifenthrin. 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

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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.
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 CF₃-substituted vinyl 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).\(^6\) 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).\(^8\) 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-(buto-2,3-dienyl)malonate 1a with Togni’s reagent II in the presence of 5 mol% of PdCl₂ and 2 equiv. of K₂CO₃ 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.\(^9\) This clearly indicated that in this simplest case the trifluoromethyl group was directed to the terminal position of the allene unit in dimethyl 2-(buto-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, CuCl₂, CuF₂·H₂O and Cu(OTf)₂ (Table 2, entries 1–4) did afford the designed trifluoromethylated vinyl 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).

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<th>Entry</th>
<th>Catalyst</th>
<th>Yield of 2b(%)</th>
<th>Recovery of 1b(%)</th>
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<td>1</td>
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<td>28</td>
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<tr>
<td>2</td>
<td>CuCl₂</td>
<td>55</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>CuF₂·H₂O</td>
<td>35</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OTf)₂</td>
<td>47</td>
<td>53</td>
</tr>
<tr>
<td>5</td>
<td>CuOAc</td>
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<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Cu(OAc)₂</td>
<td>65</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OAc)₂</td>
<td>69</td>
<td>16</td>
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<tr>
<td>8</td>
<td>Cu(OAc)₂</td>
<td>63</td>
<td>14</td>
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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-pyrydyl 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
yield is much lower (Table 3, entry 6). Subsequently, we tested

b Determined by 19F NMR and 1H NMR spectroscopy using PhCF3 and

Entry | L | Base | Yield of 2b (%) | Recovery of 1b (%)
--- | --- | --- | --- | ---
1 | L1 | K2CO3 | 69 | 16
2 | L2 | K2CO3 | 77 | 13
3 | L3 | K2CO3 | 12 | 27
4 | L4 | K2CO3 | 42 | 19
5 | L5 | K2CO3 | 27 | 36
6 | — | K2CO3 | 10 | 34
7 | L6 | Na2CO3 | 63 | 17
8 | L7 | Cs2CO3 | 12 | 0
9 | L8 | K2CO3 | 82 | 9
10 | L9 | K2PO4 | 76 | 12
11 | L10 | K2PO4 | 87 | 0
12 | L11 | — | 40 | 31
13 | L12 | K2PO4 | 42 | 0

as 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 CH2Cl2 under an argon atmosphere. b Determined by 19F NMR and 1H NMR spectroscopy using PhCF3 and mesitylene or CH2Br2 as the internal standards. c The reaction was carried out with 2.0 equiv. of Tognii’s reagent II and 3.0 equiv. of Cu(OAc)2 as internal standards. d The reaction was carried out with 2.0 equiv. of Tognii’s reagent II. e The reaction was carried out with 10 mol% of CuOAc instead of Cu(OAc)2.

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-5a12 was formed highly diastereoselectively in 85% yield; with nitro, cis-tetrahydro-1,2-oxazines cis-6a12 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 7a12 in 90% yield (Scheme 2 and Fig. 1).

During the study, we also identified the Tognii’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 CH2Cl2 (Scheme 3B, eqn (1)). When potassium 2-iodobenzoate was exposed under the standard conditions without the allene and K2PO4, 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 trifluoromethylcyclopropylation reaction was completely shut.
down (Scheme 4, eqn (2)). With TEMPO, the reaction didn’t occur and the radical trapping TEMPO-CF<sub>3</sub> adduct 9 was formed in 71% yield (Scheme 4, eqn (3)). With BHT, the trifluoromethylative product 2g was not formed while a BHT-CF<sub>3</sub> 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<sup>13</sup> (Scheme 4, eqn (4)). These results indicated that the reaction may proceed via a radical pathway in the beginning.

A mechanism was then proposed on the basis of the above results (Scheme 5). Initially, the in situ reduction<sup>14</sup> or disproportionation<sup>15</sup> of Cu(OAc)<sub>2</sub> 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<sub>3</sub> 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 α-iodobenzoic acid anion associated with...
the regeneration of the catalytically active Cu(i) species A. The reaction of two molecules of the o-iodobenzoic acid anion with CH₂Cl₂ would generate the isolated by-product B.¹⁶ The unfavorable 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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Notes and references


For X-ray single crystal data for cis-5a, cis-6a, 7a, and 8, see the ESL†


