## Electrophilic Trifluoromethylation by Copper-Catalyzed Addition of CF<sub>3</sub>-Transfer Reagents to Alkenes and Alkynes

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Regio- and stereoselective Cu-catalyzed addition of the above hypervalent iodine reagent to alkynes and alkenes was achieved. In the presence of Cul, the reaction is suitable to perform trifluoromethyl-benzoyloxylation and trifluoromethyl-halogenation of alkenes and alkynes. Electron-donating substituents accelerate the process, and alkenes react faster than alkynes emphasizing the electrophilic character of the addition reaction.

Trifluoromethylated compounds have highly desirable physical, physiological, and pharmacokinetic properties, which renders them important synthetic targets in pharmaceutical and agrochemical industries.<sup>1</sup> A high demand for structurally diverse trifluoromethylated compounds requires development of new synthetic methods for selective formation of C–CF<sub>3</sub> bonds in organic substrates.<sup>1a,2</sup>



Figure 1. Electrophilic CF<sub>3</sub> transfer reagents.

The appearance of highly reactive yet easily handleable trifluoromethylating reagents inspired the development of many new procedures. Togni and co-workers<sup>2n-r,u</sup> developed the synthesis and use of easily accessible hypervalent iodine reagents **1a** and **1b** (Figure 1), which are efficient electrophilic CF<sub>3</sub> transfer reagents.<sup>2j-l,n-r,u</sup>

Reagents **1a**–**b** together with **1c** have been extensively used in C-H functionalization based trifluoromethylation reactions.<sup>2h-1</sup> Commonly used strategies for introduction of a CF<sub>3</sub> group are based on substitution reactions (including C–H functionalization); $^{2d,f-q}$  however there are a few examples of addition reactions as well (Scheme 1).<sup>2t,v,3a-3c</sup> It was shown<sup>3a</sup> that CuI and CF<sub>3</sub>I, in the presence of Zn powder, undergo addition to alkynes, which after hydrolysis gives vinyl-CF3 derivatives. Kumadaki and co-workers2t,v,3b have shown that  $\alpha,\beta$ -unsaturated ketones react with CF<sub>3</sub>I in the presence of Et<sub>2</sub>Zn and catalytic amounts of RhCl(PPh<sub>3</sub>)<sub>3</sub> (Scheme 1), which can be employed for  $\alpha$ trifluoromethylation of keto groups. Furthermore, S-trifluoromethyl xanthates efficiently add to alkenes without metal catalysis in a radical process.<sup>3c</sup> There are also several examples for introduction of polyfluoroalkyl<sup>3d,e</sup> and trifluormethylphosphate<sup>3f</sup> groups to C–C multiple bonds.

We have now found that hypervalent iodine 1a undergoes an addition reaction with both alkynes (2) and alkenes (3) in the presence of a CuI catalyst affording vinyl-CF<sub>3</sub> (4) and alkyl-CF<sub>3</sub> products (5–6) respectively. The reaction proceeds with excellent regio- (4–5) and stereoselectivity (4). An advantage of this approach is that use of gaseous and rather costly reagent CF<sub>3</sub>I could be replaced by 1a and that not only a trifluoromethyl but also another functionality could be introduced to the substrates. Furthermore, this addition reaction represents one of the most atom

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<sup>(1) (</sup>a) Pacheco, M. C.; Purser, S.; Gouverneur, V. Chem. Rev. 2008, 108, 1943. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Chem. Soc. Rev. 2008, 37, 320. (c) Müller, K.; Faeh, C.; Diederich, F. Science 2007, 317, 1881.

economical<sup>4</sup> applications of reagent **1a**. The addition reaction of 1a to alkynes 2a-e requires relatively high temperatures (typically 80-100 °C) and usually catalytic amounts (10 mol %) of CuI. The isolated yield for the reaction of phenyl acetylene 2a is about the same with catalytic (entry 1) and stoichiometric amounts (entry 2) of CuI. However, in the case of anisyl derivative 2b the yield dropped substantially when the reaction was conducted with 10 mol % CuI (entry 3) instead of a stoichiometric amount (entry 4). Because of the limited thermostability of 1a, heating of the reaction mixture for extended times decreased the yield. Therefore, using microwave conditions was found to be beneficial in several cases (e.g., entries 5 and 7). The reactions usually proceed cleaner and with better yields, when the substrates have electron supplying substituents. For example, we obtained a better yield with anisyl derivative 2b and methoxy naphthyl substrate 2d than with nitro phenyl acetylene 2c.

Furthermore, silyl acetylene 2e could easily be functionalized to give 4e, probably due to the presence of the electron donating silyl functionality. In this case microwave conditions gave the best yields. When the reaction was conducted by traditional heating for extended times, the yield dropped due to the decomposition of product 4e. The addition reactions proved to be highly regio- and stereoselective. The presented trifluoromethyl styrene derivatives 4a - e are isolated as single isomers. Although, the crude mixture contained some

(3) (a) Kitazume, T.; Ishikawa, N. J. Am. Chem. Soc. 1985, 107, 5186.
(b) Sato, K.; Omote, M.; Ando, A.; Kumadaki, I. Org. Synth. 2009, Coll. Vol. 11, 336. (c) Bertrand, F.; Pevere, V.; Quiclet-Sire, B.; Zard, S. Z. Org. Lett. 2001, 3, 1069. (d) Fuchikami, T.; Ojima, I. Tetrahedron Lett. 1984, 25, 303. (e) Uneyama, K.; Kitagawa, K. Tetrahedron Lett. 1991, 32, 3385. (f) Yang, Z. Y.; Burton, D. J. J. Org. Chem. 1992, 57, 4676.

(4) Trost, B. M. Angew. Chem., Int. Ed. Engl. 1995, 34, 259.

Scheme 1. Examples for Trifluoromethylation by Addition to Carbon–carbon Double and Triple Bonds (Ar = 2-Iodophenyl)



unidentified byproducts, we could not find any evidence for the formation of other regio- or stereoisomers. Authentic synthesis (see Supporting Information) of **4b** has shown that the addition of **1a** across the triple bond occurs with trans selectivity.

Alkenes, such as  $3\mathbf{a}-\mathbf{e}$ , also undergo smooth addition reactions with  $1\mathbf{a}$  using copper catalysis. In these reactions the corresponding trifluoromethyl alkanes  $5\mathbf{a}-\mathbf{e}$  are formed with high regioselectivity. Similarly to alkynes the reaction proceeds with higher yield and more cleanly for electronrich styrenes. The addition reaction is relatively tolerant of steric effects, as both para methoxy (**3a**) and ortho methoxy styrene (**3b**) could be efficiently functionalized.

However, the reaction is faster for 3a than for 3b (see below). Disubstituted alkene 3e also undergoes trifluoromethyl-benzoyloxylation reaction to give tertiary alcohol derivative 5e. This process is more sluggish than the reaction of the analog styrene derivatives and requires microwave heating to proceed with high yield (Table 1, entry 13). Not only styrene derivatives but also vinyl sulfide (3d) and silane (3f) substrates undergo addition reactions. Vinyl sulfide 3d reacted similarly to styrenes 3a-c and 3e to give the expected trifluoromethyl benzoate product 5d. However, vinyl silane 3f showed a surprising reactivity. At elevated temperatures 3f and 1a with a catalytic or stoichiometric amount of CuI gave a complex mixture of products. On the other hand, when the reaction was conducted at 20 °C with a stoichiometric amount of CuI, compound 6a was formed in high yield and selectivity. In this reaction an iodide functionality was introduced instead of an iodobenzoate. Furthermore, when CuI was replaced by CuBr a bromination of the silvlated carbon occurred (entry 14) affording 6b. Thus, in the presence of a silyl substituent the trifluoromethyl-benzoyloxylation reaction of alkenes can be switched to a trifluoromethylhalogenation process further extending the synthetic potential of the above methodology.

<sup>(2) (</sup>a) Gouverneur, V. Science 2009, 325, 1630. (b) Grushin, V. V. Acc. Chem. Res. 2009, 43, 160. (c) Sato, K.; Tarui, A.; Omote, M.; Ando, A.; Kumadaki, I. Synthesis 2010, 1865. (d) Nagib, D. A.; MacMillan, D. W. C. Nature 2011, 480, 224. (e) Parsons, A. T.; Buchwald, S. L. Nature 2011, 480, 184. (f) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661. (g) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. Science 2010, 328, 1679. (h) Wang, X.; Truesdale, L.; Yu, J.-Q. J. Am. Chem. Soc. 2010, 132, 3648. (i) Xu, J.; Fu, Y.; Luo, D.-F.; Jiang, Y.-Y.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.; Liu, L. J. Am. Chem. Soc. 2011, 133, 15300. (j) Wang, X.; Ye, Y.; Zhang, S.; Feng, J.; Xu, Y.; Zhang, Y.; Wang, J. J. Am. Chem. Soc. 2011, 133, 16410. (k) Parsons, A. T.; Buchwald, S. L. Angew. Chem., Int. Ed. 2011, 50, 9120. (1) Allen, A. E.; MacMillan, D. W. C. J. Am. Chem. Soc. 2010, 132, 4986. (m) Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. Proc. Natl. Acad. Sci. U.S.A. 2011, 108, 14411. (n) Kieltsch, I.; Eisenberger, P.; Togni, A. Angew. Chem., Int. Ed. 2007, 46, 754. (o) Koller, R.; Stanek, K.; Stolz, D.; Aardoom, R.; Niedermann, K.; Togni, A. Angew. Chem., Int. Ed. 2009, 48, 4332. (p) Niedermann, K.; Früh, N.; Vinogradova, E.; Wiehn, M. S.; Moreno, A.; Togni, A. Angew. Chem., Int. Ed. 2011, 50, 1059. (q) Tomashenko, O. A .; Escudero-Adán, E. C.; Martínez Belmonte, M.; Grushin, V. V. Angew. Chem., Int. Ed. 2011, 50, 7655. (r) Zanardi, A.; Novikov, M. A.; Martin, E.; Benet-Buchholz, J.; Grushin, V. V. J. Am. Chem. Soc. 2011, 133, 20901. (s) Prakash, G. K. S.; Krishnan, H. S.; Jog, P. V.; Iyer, A. P.; Olah, G. A. Org. Lett. 2012, 14, 1146. (t) Sato, K.; Omote, M.; Ando, A.; Kumadaki, I. Org. Lett. 2004, 6, 4359. (u) Matoušek, V.; Togni, A.; Bizet, V.; Cahard, D. Org. Lett. 2011, 13, 5762. (v) Sato, K.; Yuki, T.; Yamaguchi, R.; Hamano, T.; Tarui, A.; Omote, M.; Kumadaki, I.; Ando, A. *J. Org. Chem.* **2009**, *74*, 3815. (w) Weng, Z.; Li, H.; He, W.; Yao, L.-F.; Tan, J.; Chen, J.; Yuan, Y.; Huang, K.-W. *Tetrahedron* **2012**, 68, 2527. (x) Chu, L.; Qing, F.-L. Org. Lett. 2012, 14, 2106. (y) Parsons, A. T.; Senecal, T. D.; Buchwald, S. L. Angew. Chem., Int. Ed. 2012, 51, 2947



Table 1. Electrophilic Trifluoromethylation of Alkynes and

<sup>*a*</sup> Unless otherwise stated copper(I) iodide (0.01 mmol, 10 mol %), **1a** (47.4 mg, 0.15 mmol, 1.5 equiv), and substrate **2** or **3** (0.10 mmol) were reacted in chloroform (0.5 mL) for the indicated times and temperatures. <sup>*b*</sup> Reaction conditions: temperature/time = °C/h. <sup>*c*</sup> Ar = 2-iodo-phenyl. <sup>*d*</sup> Isolated yield (%). <sup>*e*</sup> Stoichiometric amount (0.10 mmol) of CuI was used. <sup>*J*</sup> The reaction was conducted under microwave irradiation. <sup>*g*</sup> 0.10 mmol of CuBr was used.

As mentioned above the electron-donating groups seem to accelerate the reaction. In order to gain more insight into



Figure 2. Competitive trifluoromethyl-benzoyloxylation experiment to explore the electronic effects on the reactivity.

the substituent effects we performed competitive trifluoromethyl-benzoyloxylation reactions. When a mixture of 2b and 2a was reacted with 1a and a stoichiometric amount of CuI a 1:0.5 mixture of 4b and 4a was formed (Figure 2). This shows that **2b** reacts about twice as fast as **2a**. This acceleration is clearly due to the electron-donating effect of the methoxy substituent in 2b. We have also compared the rates of reaction of 2b and 3a. These experiments showed that alkene 3a undergoes trifluoromethyl-benzoyloxylation four times as fast as alkyne 2b under the same reaction conditions. These simple competitive reactions strongly indicate the electrophilic nature of the copper-catalyzed addition of 1a. A similar competitive experiment was performed to assess the steric effects of the substrates. Competitive trifluoromethyl-benzoyloxylation of 3a and 3b showed that para-substituted substrate 3a reacted about three times as fast as its ortho-substituted counterpart 3b.

We have also studied the effects of the counterions on copper. It was found that CuCl, CuBr, and CuOAc give results similar to those of CuI (except entries 14-15); however the yields are usually higher with CuI. Interestingly, CuPF<sub>6</sub>(MeCN)<sub>4</sub> successfully applied in allylic C-H trifluoromethylation<sup>2k</sup> with **1a** performed very poorly under the above reaction conditions. Chloroform and dichloroethane proved to be the best solvents; however in many reactions chloroform gave cleaner crude products and thus better yields than dichloroethane. It is interesting to note that, in methanol, the preferred solvent in the C-H trifluoromethylation with 1a, 2j, k only traces of the product was formed. Reagents 1b and 1c proved to be much less reactive and selective in the addition reactions. Using 1c with stoichiometric and catalytic amounts of copper gave no products at all. Reagent 1b reacted with 3f; however the reaction mixture was very complex and contained only traces of **6a**. Interestingly, Huang and co-workers<sup>2w</sup> have shown that the copper-catalyzed reaction of 1b with phenyl acetylene derivatives (such as 2) in the presence of base and phenanthroline leads to formation of trifluoromethyl acetylene derivatives. Thus, instead of addition (entries (1-7) C–H trifluoromethylation occurs. The iodobenzoate group can easily be removed from the product by standard hydrolysis (Figure 3). When the benzoate product 5a formed from 3a and 1a (entry 8) was hydrolyzed (without purification) by K<sub>2</sub>CO<sub>3</sub>, alcohol 7 was obtained in 77% overall yield.



Figure 3. Hydrolysis of 5a to  $\beta$ -trifluoromethyl alcohol 7.

The reaction conditions of the above addition process and some of the reported copper-catalyzed allylic C–H trifluoromethylation reactions<sup>2i-k</sup> are rather similar. When substrates with allylic C–H bonds (such as **8**) were reacted with **1a** under the usual catalytic conditions an inseparable mixture of several products were formed. Both allylic trifluoromethylation (**9**) and addition (**10**) products could be detected (by <sup>1</sup>H NMR and MS) as main components in this reaction mixture (Figure 4).



Figure 4. Reaction with substrates containing allylic C-H bond.

This suggests that the allylic C–H trifluoromethylation with hypervalent iodines (1) and the above presented addition reaction take place via similar reaction intermediates. In fact, an addition elimination type mechanism for the Cu-catalyzed allylic C–H functionalization using 1c as the CF<sub>3</sub> source.<sup>2i,k,x</sup> Formation of addition byproducts in allylic C–H trifluoromethylation reactions conducted in the presence of hypervalent iodines was also reported.<sup>2x,y</sup> Currently, the mechanism of the C–H functionalization process is also unclear. Wang and co-workers<sup>2j</sup> studying the mechanism of allylic C–H trifluoromethylation by 1a (cf. Figure 4) have found that the reaction is inhibited by addition of TEMPO, (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl, which is a well-known radical scavenger. Thus, it was suggested that the reaction follow a radical mechanism involving single electron transfer (SET) steps. Several other mechanistic studies on the transfer of the trifluoromethyl group from 1a-c to organic substrates suggest a radical and SET mechanism.<sup>2j,k,x,5a</sup> Our preliminary mechanistic studies also show that TEMPO inhibits the addition of **1a** to C-C multiple bonds, for example to **3a** (entry 9). Furthermore, formation of 4a - e by trans addition of 1a across the triple bond of 2a-e (entries 1-8) suggests a two-step process. All these findings indicate that the allylic C-H functionalization and the presented addition reaction might have a similar mechanism involving trifluoromethyl radical intermediates. Another alternative is that **1a** oxidizes the Cu(I) catalyst to form a  $Cu(III)-CF_3$ complex.<sup>2i,k</sup> Hypervalent iodine reagents are known to easily oxidize transition metals, even Pd(II), to higher oxidation states.<sup>5b-h</sup> Exploration of the mechanistic details of the addition reaction is an ongoing project in our laboratory.

In summary, we have shown that hypervalent iodine **1a** undergoes Cu-catalyzed addition to alkenes and alkynes. The reaction proceeds with high regio- and stereoselectivity. In the case of vinyl silane substrate **3f**, trifluoromethyl-halogenation takes place instead of the expected benzoy-loxylation process (entries 14–15). The addition reaction is accelerated by electron-donating substituents, and alkenes react faster than alkynes under identical reaction conditions. The described reaction is suitable for the synthesis of new trifluoromethyl substances, which are important synthetic targets in pharmaceutical and agrochemical industries<sup>1,6</sup> using inexpensive substrates (**2**–**3**) and easily handleable CF<sub>3</sub> source **1a**.

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**Supporting Information Available.** Detailed experimental procedures and compound characterization data are given. This material is available free of charge via the Internet at http://pubs.acs.org.

<sup>(5) (</sup>a) Macé, Y.; Pradet, C.; Popkin, M.; Blazejewski, J.-C.; Magnier, E. Tetrahedron Lett. **2010**, 51, 5388. (b) Lyons, T. W.; Sanford, M. S. Chem. Rev. **2010**, 110, 1147. (c) Dick, A. R.; Hull, K. L.; Sanford, M. S. J. Am. Chem. Soc. **2004**, 126, 2300. (d) Powers, D. C.; Geibel, M. A. L.; Klein, J. E. M. N.; Ritter, T. J. Am. Chem. Soc. **2009**, 131, 17050. (e) Powers, D. C.; Ritter, T. Nat. Chem. **2009**, 1, 302. (f) Ariafard, A.; Hyland, C. J. T.; Canty, A. J.; Sharma, M.; Brookes, N. J.; Yates, B. F. Inorg. Chem. **2010**, 49, 11249. (g) Pilarski, L. T.; Selander, N.; Böse, D.; Szabó, K. J. Org. Lett. **2009**, 11, 5518. (h) Selander, N.; Willy, B.; Szabó, K. J. Angew. Chem., Int. Ed. **2010**, 49, 4051.

<sup>(6)</sup> Ding, Y.; Huang, X. Heteroatom. Chem. 2003, 14, 304.

The authors declare no competing financial interest.