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Iron-Catalyzed Preparation of Trifluoromethyl Substituted Vinyl- and Alkynylcyclopropanes

Bill Morandi, Jeremy Cheang, and Erick M. Carreira*

Laboratorium für Organische Chemie, ETH Zürich, CH-8093 Zürich, Switzerland

carreira@org.chem.ethz.ch

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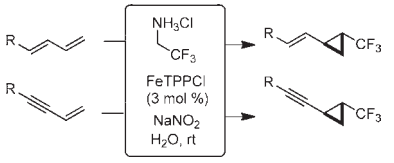
ABSTRACT

A convenient iron-catalyzed procedure to prepare trifluoromethylated vinyl- and alkynylcyclopropanes in a chemo- and diastereoselective manner is presented. The active diazo compound (trifluoromethyl diazomethane) is generated in situ and used in the concomitant cyclopropanation reaction.

Trifluoromethylated compounds have found wide use in medicinal chemistry due to their ability to affect the physical and chemical properties of drug candidates.[1] However, very few synthetic methods have been developed for the preparation of trifluoromethylated cyclopropanes.[2] We recently reported reaction conditions for the cyclopropanation and cyclopropenation of styrene derivatives and alkynes, respectively, with trifluoromethyl diazomethane generated in situ. A range of metal catalysts have been identified to be compatible with the diazotization reaction, allowing a tandem reaction to take place in aqueous media.[3] Herein we disclose a significant development in the method that permits the preparation of trifluoromethyl substituted vinyl- and alkynylcyclopropanes.[4]



Vinyl- and alkynylcyclopropanes have been used in a variety of organic transformations,[5] and their trifluoromethyl substituted analogues would consequently provide entry into a host of complex trifluoromethylated intermediates. The conditions in our previous report prescribed the use of FeTPPCl (TPP = 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine) as a catalyst in degassed water and syringe pump addition of sodium nitrite to an aqueous solution of trifluoroethylamine hydrochloride buffered with H_2SO_4/NaOAc. In extending the scope of the process we have also become interested in further simplifying the execution of the reaction. We were thus pleased to note that the reaction may also be conducted open to air and without recourse to addition employing a syringe pump when the amount of trifluoroethylamine hydrochloride was adjusted to 2 equiv and acid is omitted. We hypothesize that in the absence of

(1) (a) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303. (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

(2) (a) Denton, J. R.; Sukumaran, D.; Davies, H. M. L. *Org. Lett.* **2007**, *9*, 2625. (b) Le Maux, P.; Juillard, S.; Simmoneaux, G. *Synthesis* **2006**, 1701. (c) Mykhailiuk, P. K.; Afonin, S.; Palamarchuk, G. V.; Shishkin, O. V.; Ulrich, A. S.; Komarov, I. V. *Synthesis* **2008**, 1757. (d) Mykhailiuk, P. K.; Afonin, S.; Ulrich, A. S.; Komarov, I. V. *Angew. Chem., Int. Ed.* **2008**, *47*, 5765. (e) Grygorenko, O. O.; Artamonov, O. S.; Komarov, I. V.; Mykhailiuk, P. K. *Tetrahedron* **2011**, *67*, 803.

(3) (a) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 938. (b) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4294. (c) Morandi, B.; Mariampillai, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 1101.

(4) For selected examples of cyclopropanation of dienes and enynes, see: (a) Suematsu, H.; Kanchiku, S.; Uchida, T.; Katsuki, T. *J. Am. Chem. Soc.* **2008**, *130*, 10327. (b) Ichinose, M.; Suematsu, H.; Katsuki, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 3121.

(5) (a) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (b) de Meijere, A.; Kozhushkov, S. I.; Schill, H. *Chem. Rev.* **2006**, *106*, 4926.

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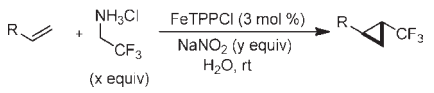
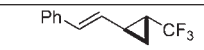
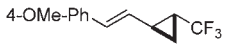
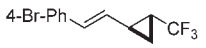
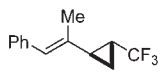
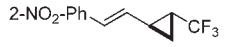
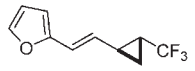
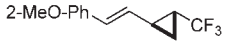
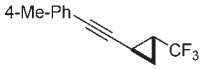
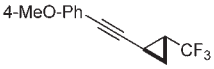
acid buffer the rate of the diazotization process is considerably slowed, resulting in conditions that parallel slow addition with a syringe pump.[6] With the more convenient reaction conditions involving FeTPPCl (3 mol %) on water,[7] we then studied the reaction scope.

Table 1. Reaction Scope[a]



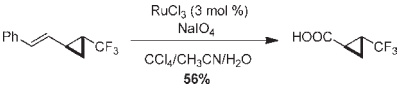
entry	product	x/y	yield[b]
1		2/2.4	74%
2[c]		2/2.4	93%
3[c]		2/2.4	60%
4		2/2.4	83%[d]
5[c]		3/3.6	95%
6		2/2.4	52%
7		2/2.4	93%
8		3.5/4.2	76%
9		4/4.8	81%
10		4/4.8	69%[e]

[a] Reaction conditions: FeTPPCl (3 mol %), $CF_3CH_2NH_3Cl$ (*x* equiv), $NaNO_2$ (*y* equiv), substrate, H_2O, rt. [b] Isolated yield. [c] Toluene used as cosolvent (see Supporting Information for exact conditions). [d] Isolated as a 12:1 mixture of *E*/*Z* isomers. [e] Isolated as an inseparable mixture containing additional starting material (9%).

Both electron-rich and electron-deficient dienes were good substrates for the transformation, affording the products in useful yields as single diastereoisomers. Even a furan-substituted diene (entry 6) formed the trifluoromethyl subtituted cyclopropane, albeit in a lower yield. For solid substrates, a small quantity of toluene was added to the reaction mixture to dissolve the starting material and the catalyst. The method was then extended to enynes to furnish the corresponding alkynylcyclopropanes in good yields, albeit requiring in some cases increased amounts of trifluoroethylamine hydrochloride and sodium nitrite. Overall, the cyclopropanes were formed chemoselectively as single diastereomers and in no case the products of biscyclopropanation were observed. To account for the chemoselective nature of the reaction we subjected *trans*-β-methyl styrene to the standard reaction conditions, but no conversion was observed. The iron catalyst is thus unable to cyclopropanate 1,2-trans substituted double bonds, explaining the observed chemoselectivity with diene substrates. It is important to note that all these products are unprecedented and represent potentially useful fluorinated building blocks.

In order to showcase the utility of the new process we have described, we have employed the product from entry 1 in a Ru-catalyzed oxidative cleavage to form the corresponding carboxylic acid in an unoptimized 56% yield (Scheme 1).[8] This compound has been previously used in the preparation of drug candidates[8b] and insecticides.[9]

Scheme 1. Preparation of Trifluoromethylcyclopropane Carboxylic Acid



In conclusion, we have presented an efficient method for the chemo- and diastereoselective preparation of vinyl- and alkynylcyclopropanes bearing a trifluoromethyl group. The reaction is performed under user-friendly conditions, in an open vial, and with direct addition of all the components. The products are unprecedented and potentially important building blocks for drug discovery. Furthermore these activated cyclopropanes are easily transformed into other compounds, as illustrated by the preparation of trifluoromethylcyclopropane carboxylic acid.

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Supporting Information Available. Full experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

(6) Styrene afforded a 75% yield when performed under the reaction conditions used herein for entry 1 in Table 1. The new procedure thus represents a more practical method for the reaction reported in ref 3a.

(7) For a discussion concerning "on" water reactivity, see: (a) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275. (b) Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725.

(8) For a previous synthesis of this compound, see: (a) Ratier, M.; Pereyre, M.; Davies, A. G.; Surcliffe, K. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1907. (b) WO 2005/011655, 2005.

(9) Mori, T; Ujihara, K.; Matsumoto, O.; Yanagi, K.; Matsuo, N. *J. Fluorine Chem.* **2007**, *128*, 1174.