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Synthesis of Trifluoromethyl-Substituted Cyclopropanes via Sequential Kharasch–Dehalogenation Reactions

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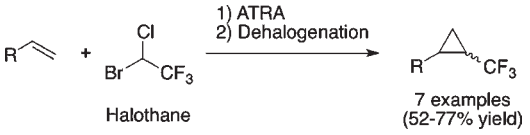
ABSTRACT



A two-step process for the synthesis of trifluoromethyl-substituted cyclopropanes is described. Halothane, an anesthetic agent, is added to olefins in a ruthenium-catalyzed Kharasch reaction. The resulting 1,3-dihalides are converted into cyclopropanes by dehalogenation with magnesium. This procedure represents an alternative to metal-catalyzed cyclopropanations involving trifluoromethyl diazomethane.

The trifluoromethyl group is a popular functionality in medicinal and bioorganic chemistry, and numerous methods for introducing trifluoromethyl groups have been developed.[1] However, the synthesis of trifluoromethylated cyclopropanes is still challenging. A common method involves the utilization of trifluoromethyl diazomethane, which is activated photochemically or by transition metal catalysts.[2] This procedure suffers from the fact that trifluoromethyl diazomethane is toxic, gaseous at room temperature, and potentially explosive.

An important step toward a safer procedure was recently reported by Carreira and co-workers.[3] They were able to obtain trifluoromethylated cyclopropanes from styrenes and trifluoromethyl diazomethane, which was generated in situ from $F_3CCH_2NH_2 \cdot HCl$ and $H^+/NaNO_2$ (Scheme 1, eq 1). The reactions were carried out in water in the presence of an iron-porphyrin catalyst. A limitation of the method is the substrate scope: only styrene derivatives gave good yields. This limitation can be overcome by using a two-step process: alkynes are first coupled with in situ generated F_3CCHN_2 in the presence of a Rh catalyst. Subsequent hydrogenation gives the desired cyclopropanes (Scheme 1, eq 2).[4] Since then, reactions with in situ generated F_3CCHN_2 were used to synthesize numerous trifluoromethyl-substituted products: cyclopropanes in an enantioselective fashion,[5] vinyl- and alkynylcyclopropanes,[6] aziridines,[7] benzofuranols,[8] and ketones.[9] These procedures represent an important improvement over previous methodologies. However, they still involve the problematic reagent F_3CCHN_2, although its dangers are strongly diminished because it is generated in situ. Below we describe a new process for the preparation of aromatic and aliphatic trifluoromethyl-substituted cyclopropanes. The CF_3 group is introduced via the anesthetic agent halothane ($F_3CCHBrCl$).

(1) Selected reviews: (a) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071–1081. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320–330. (c) Smits, R.; Cadicamo, C. D.; Burger, K.; Koksch, B. *Chem. Soc. Rev.* **2008**, *37*, 1727–1739. (d) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886. (e) Schlosser, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5432–5446. (f) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303–319. (g) Zanda, M. *New J. Chem.* **2004**, *28*, 1401–1411.

(2) Grygorenko, O. O.; Artamonov, O. S.; Komarov, I. V.; Mykhailiuk, P. K. *Tetrahedron* **2011**, *67*, 803–823.

(3) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 938–941.

(4) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4294–4296.

(5) Morandi, B.; Mariampillai, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 1101–1104.

(6) Morandi, B.; Cheang, J.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 3080–3081.

(7) Künzi, S. A.; Morandi, B.; Carreira, E. M. *Org. Lett.* **2012**, *14*, 1900–1901.

(8) Morandi, B.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 5984–5985.

(9) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 9085–9088.

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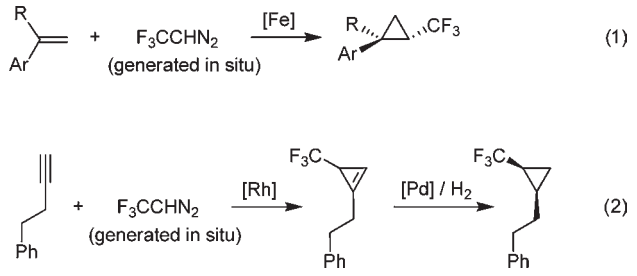
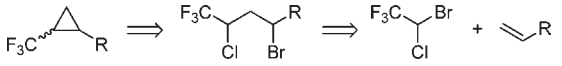
Scheme 1. Syntheses of Trifluoromethyl-Substituted Cyclopropanes with in Situ Generated F_3CCHN_2 as Described by Carreira and Co-workers[3,4]



Recently, we have reported a one-pot-two-step procedure for the synthesis of substituted cyclopropanes.[10] 1,1-Dichlorides were added to olefins in the presence of $Cp^*RuCl_2(PPh_3)$ (Cp^* = pentamethylcyclopentadienyl) in a ruthenium-catalyzed Kharasch reaction.[11] The resulting 1,3-dichlorides were then cyclized to give cyclopropanes by reductive coupling with Mg. The method was expanded by the use of Mn instead of Mg for the synthesis of cyclopropanes from highly activated chlorides such as ethyl trichloroacetate or diethyl 2,2-dichloromalonate.[12] These results prompted us to explore the possibility of synthesizing trifluoromethyl-substituted cyclopropanes via a Kharasch/dehalogenation pathway. 2-Bromo-2-chloro-1,1,1-trifluoroethane (halothane) appeared to be a potentially well-suited CF_3 source for this purpose. Halothane is commercially available and a liquid at ambient conditions (bp 50 °C). It has been used widely as an inhalational general anesthetic, and its toxicity is thus low. The C−Br bond of halothane is activated by the adjacent Cl and CF_3 groups. A radical process involving homolytic cleavage of the C−Br bond should thus be possible. In fact, the addition of halothane to olefins was reported to occur with sodium dithionite $Na_2S_2O_4$ as radical initiator. The reaction proceeds with enol ethers of cyclic ketones,[13] β-pinene,[14] and different allyl-benzene derivatives but failed with conjugated olefins such as styrene.[15] The retrosynthetic pathway for the synthesis of trifluoromethyl-substituted cyclopropanes via a Kharasch reaction of halothane and a terminal olefin, followed by dehalogenation, is outlined in Scheme 2.[16]

Scheme 2. Retrosynthetic Pathway for the Synthesis of Trifluoromethyl-Substituted Cyclopropanes from $CF_3CHBrCl$



As a test reaction, we investigated the atom transfer radical addition of halothane to styrene (Scheme 3). The air stable Ru^{III} complex $Cp^*RuCl_2(PPh_3)$ (**1**) in combination with the reducing agent Mg was used to catalyze the reaction.[17] The role of the reducing agent is the generation and regeneration of the catalytically active Ru^{II} complex.[18]

Scheme 3. Ruthenium-Catalyzed Kharasch Reaction of Styrene and $F_3CCHBrCl$ in the Presence of Mg

For the coupling reaction between styrene and $F_3CCHBrCl$, an excess of Mg (30 equiv with respect to styrene) and 1 mol % of the Ru catalyst **1** were found to provide excellent results when the reaction was performed in neat halothane ([olefin] = 0.5 M). Styrene was completely consumed after 2 h, and the desired product was formed as a mixture of two diastereoisomers in high yield (>95%) according to GC-MS and NMR spectroscopic analyses. Reducing the Mg amount led to lower yields. As a side product, the dichlorinated (1,3-dichloro-3-trifluoromethyl-propyl)-benzene was observed in small quantities (<5%). The amount of this side product can be reduced if the bromo complex $Cp^*RuBr_2(PPh_3)$ is used as a catalyst precursor. However, we found that the 1,3-dichloro side product is also converted into cyclopropanes, and further attempts to reduce the amount of the side product were thus not made. Reactions in toluene with a smaller excess of halothane with respect to styrene (6:1) were also successful, but the yields were lower, even if the reaction time was prolonged to 24 h. The activated C−Br bond of halothane was found to be crucial for the success of the reaction. Attempts to perform Ru-catalyzed Kharasch reactions with the inhalational anesthetics 2-chloro-2-(difluoromethoxy)-1,1,1-trifluoroethane (isoflurane) and 2-chloro-1,1,2-trifluoro-1-difluoromethoxyethane (enflurane) did not give 1,3-addition products.

(10) Thommes, K.; Kiefer, G.; Scopelliti, R.; Severin, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 8115–8119.

(11) For reviews, see: (a) Muñoz-Molina, J. M.; Belderrain, T. R.; Pérez, P. J. *Eur. J. Inorg. Chem.* **2011**, 3155–3164. (b) Severin, K. *Curr. Org. Chem.* **2006**, *10*, 217–224. (c) Delaude, L.; Demonceau, A.; Noels, A. F. *Top. Organomet. Chem.* **2004**, *11*, 155–171. (d) Nagashima, H. *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; WILEY-VCH: Weinheim, 2004, pp 333−343.

(12) Fernández-Zúmel, M. A.; Buron, C.; Severin, K. *Eur. J. Org. Chem.* **2011**, 2272–2277.

(13) Dmowski, W.; Ignatowska, J. *J. Fluorine Chem.* **2003**, *123*, 37–42.

(14) Dmowski, W.; Ignatowska, J.; Piasecka-Maciejewska, K. *J. Fluorine Chem.* **2004**, *125*, 1147–1151.

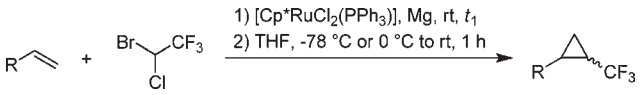
(15) Ignatowska, J.; Dmowski, W. *J. Fluorine Chem.* **2006**, *127*, 720–729.

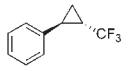
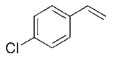
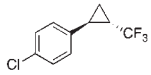
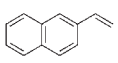
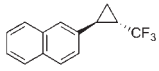
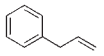
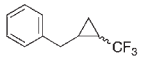
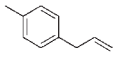
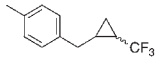
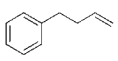
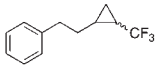
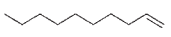
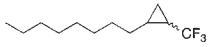
(16) For the synthesis of chlorinated cyclopropanes via carbenes derived from halothane, see: (a) Saxena, A. K.; Bisaria, C. S. *Indian J. Chem.* **1997**, *36B*, 653–655. (b) Saxena, A. K.; Bisaria, C. S.; Saini, S. K.; Pande, L. M. *Synth. React. Inorg. Met. Org. Chem.* **1991**, *21*, 401–416.

(17) Thommes, K.; Içli, B.; Scopelliti, R.; Severin, K. *Chem.—Eur. J.* **2007**, *13*, 6899–6907.

(18) (a) Fernández-Zúmel, M. A.; Thommes, K.; Kiefer, G.; Sienkiewicz, A.; Pierzchala, K.; Severin, K. *Chem.—Eur. J.* **2009**, *15*, 11601–11607. (b) Pintauer, T. *Eur. J. Inorg. Chem.* **2010**, 2449–2460.

Table 1. Sequential Kharasch/Dehalogenation Reactions[a]



entry	alkene	product	Ru cat. (mol %)	conversion after t_1 (%)	t_1 [h]	yield (%)[c]	*trans/cis*
1[b]			1	≈100	2	69 (55)	27:1
2[b]			1	≈100	3	77 (70)	28:1
3[b]			2	≈100	4	64 (61)	24:1
4[c]			2	91	48	52 (48)	1.2:1
5[c]			2	92	72	55 (51)	1.2:1
6[c]			2	95	15	56 (50)	1.2:1
7[c,d]			2	96	15	59 (46)	1:1.1

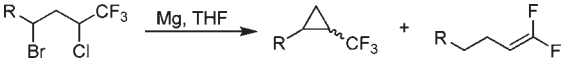
[a] The Kharasch reactions were performed in neat halothane with [olefin] = 0.5 M, [olefin]/[Mg] = 1:30. Mesitylene was used as internal standard (10 mol % relative to the olefin). [b] After the time t_1, the solvent was removed, THF was added at −78 °C, ([product] = 0.05 M), and the reaction was stirred for 1 h at rt. [c] Prior to the dehalogenation step, Mg was activated by DIBAL-H (1 mol % relative to Mg) and LiCl (5 equiv relative to the substrate) as detailed in the Supporting Information. [d] THF was added at 0 °C. [e] Yields as determined by GC-MS; isolated yields in brackets.

After the addition of $F_3CCHBrCl$ to styrene, the excess of halothane was removed and THF was added to the reaction mixture at −78 °C. The polar solvent THF was expected to induce the dehalogenation reaction by Mg.[10] Indeed, after the mixture was warmed to room temperature and stirred for 1 h, the desired 2-(trifluoromethyl)-cyclopropyl)benzene was obtained in 69% yield (Table 1, entry 1). The diastereoselectivity of the coupling reaction was found to be very high (*trans*/*cis* = 27:1).

Encouraged by these results, we have investigated reactions with other olefins. The conjugated alkenes 4-chlorostyrene and vinyl-naphthalene were successfully converted into the corresponding trifluoromethyl-substituted cyclopropanes with high *trans* selectivity and in good yields (Table 1, entries 2 and 3). Allyl-benzene, 1-allyl-4-methylbenzene, 4-phenyl-1-butene, and 1-decene were also found to be suitable substrates for the Kharasch/dehalogenation process (Table 1, entries 4−7). However, the Kharasch addition was more sluggish and longer reaction times were required (15−72 h). The dehalogenation step was likewise more difficult, presumably because the Kharasch adducts lack an activated benzylic C−Br bond. Initial attempts using the same conditions as those described for styrene were not successful. It was possible to overcome this lack of reactivity by activating the Mg with DIBAL-H and LiCl[19] prior to the dehalogenation step. This procedure provided the substituted cyclopropanes in isolated yields of ∼50% (overall yield for the two-step process). Contrary to what was observed for the styrene derivatives, the cyclopropanes were obtained as a mixture of *cis* and *trans* isomers in roughly equal amounts.

It is worth noting that the major impurity (∼15%) in the cyclization step for allyl-benzene, 1-ally-4-methylbenzene, 4-phenyl-1-butene, and 1-decene was a difluoroolefin resulting from a reductive elimination process (Scheme 4). It is known that chloro- or bromoalkanes bearing a CF_3 group in the α-position can undergo a metal-induced dehalodefluorination to give difluoroolefins.[20] In our case, an additional bromine atom is eliminated. The 1,1-difluoroolefin was detectable only in traces for the transformations of the styrene derivatives, likely because of the faster cyclization step.

Scheme 4. Difluoroolefins as Side Products



(19) (a) Tistam, U.; Weinmann, H. *Org. Process Res. Dev* **2002**, *6*, 906–907. (b) Piller, F. M.; Metzger, M. A.; Schade, B. A.; Haag, A.; Gavryushin, A.; Knochel, P. *Chem.—Eur. J.* **2009**, *15*, 7192–7202. (c) Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 6802–6806.

(20) Okano, T.; Ito, K.; Ueda, T.; Muramatsu, H. *J. Fluorine Chem.* **1986**, *32*, 377–388.

To summarize, we have successfully achieved the synthesis of trifluoromethyl-substituted cyclopropanes from halothane and different olefins. The coupling of styrene derivatives and halothane can be performed as a one-pot-two-step reaction to give the corresponding cyclopropanes with high *trans* selectivity. The procedure can also be applied to nonconjugated alkenes such as allyl-benzene, 1-allyl-4-methylbenzene, 4-phenyl-1-butene, and 1-decene if slightly more forcing conditions are employed (longer reaction times, activation of Mg). A drawback of our methodology is the utilization of a large excess of Mg and halothane. However, the latter can easily be recovered by distillation after the Kharasch step. A key advantage of our procedure is the fact that it avoids the utilization of the problematic trifluoromethyl diazomethane. Instead, the CF_3 group is introduced by using the commercially available halothane, which is largely nontoxic at low concentrations.

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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.

The authors declare no competing financial interest.