Radical Mediated Hydroperfluoroalkylation of Unactivated Alkenes

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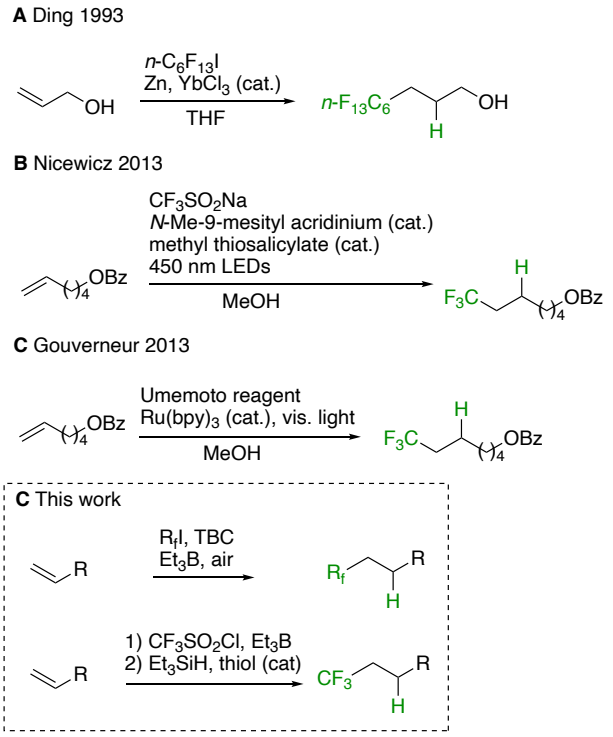
Abstract. The direct hydroperfluoroalkylation of a wide range of unactivated alkenes have been achieved at room temperature with readily available iodoperfluoroalkanes using 4-*tert*-butylcatechol as a source of hydrogen atom and triethylborane. The hydrotrifluoromethylation could also be achieved under these conditions using gaseous trifluoromethyl iodide. An experimentally simple two-step, one-pot hydrotrifluoromethylation process using the easy-to-use trifluoromethanesulfonyl chloride as the source of trifluoromethyl radicals has also been developed. Using these two approaches, a broad range of substrates, including isoprenoid natural products, were efficiently derivatized.

Keywords: radical, hydroalkylation, carbohydrogenation, fluorine, perfluoroalkyl, trifluoromethyl, catechol, triethylborane

Introduction

Fluorinated compounds are of high interest in medicinal, agrochemical, and material chemistry owing to the unique ability of fluorinated residues to modulate the physical (polarity, lipophilicity, solubility) and chemical (metabolic stability) properties of drug candidates.[1–4] Selective, general and efficient methods for the introduction of trifluoromethyl and other perfluoroalkyl groups are still very much needed and have attracted a great deal of attention in the last decades. The hydroperfuoroalkylation of alkenes represents a very attractive method to achieve this goal. The hydroperfluoroalkylation of electron deficient alkenes such as acrylates has been developed under reducing conditions.[5–17] The reaction involving the less reactive unactivated alkenes is more challenging. The reaction can be performed via a two-step procedure using iodine/bromine atom transfer radical addition (ATRA) followed by a dehalogenation process.[18–20] This procedure is however not very practical for the hydrotrifluoromethylation due to the gaseous nature of trifluoromethyl iodide. The hydrotrifluoromethylation has been observed as a side reaction by Davies et al. during the addition of CF_3I to alkenes[21] and by Muller during the electrochemical decarboxylation of trifluoroacetic acid in the presence of alkenes.[22] Ding and co-workers reported hydroperfluoroalkylation of alkenes with perfluoroalkyl iodide promoted by zinc and a catalytic amount of yterbium(III) in THF as solvent and a source of hydrogen atom (Scheme 1, A).[23] A similar reductive process was described by Chen and Long using in situ generated perfluoroalkyl iodides and sodium dithionite.[24] Desulfitative processes have been examined by Langlois and co-workers[25] and by Tommasino et al.[26] In these two reactions, the solvent was also the source of hydrogen atom leading to rather inefficient processes. This approach was nicely extended by Nicewicz and coworkers who developed a photoredox catalyzed trifluoromethylation of styrene and unactivated alkenes using an aromatic thiol as catalytic source of hydrogen atom (Scheme 1, B).[27] Gouverneur and coworkers reported the hydrotrifluoromethylation of unactivated alkenes using Umemoto reagent as the $CF_3\cdot$ source under photoredox catalysis using methanol as source of hydrogen atom (Scheme 1, C).[28] A related photocatalytic hydrotrifuoromethylation reaction was reported by Scaiano and coworkers using Togni reagent II as a source of $CF_3\cdot$, methylene blue as a catalyst and amines such as TMEDA and DBU as source of hydrogen atoms.[29] A flow process was developed by Noël and coworkers using iridium photocatalyzed hydrotrifluroromethylation of styrene derivatives with trifluoromethyl iodide and 4-hydroxythiophenol as a source of hydrogen atom.[30] A similar hydroperfluoroalkylation using sulfilimino iminiums as a source of perfluorinated radicals was proposed by Magnier and wo-workers.[31] The hydroperfluoroalkylation of unactivated alkenes under visible light irradiation of perfluoroalkyl bromide was achieved in the presence of eosin Y as a catalyst under reductive conditions ($Na_2S_2O_3$) or using THF as a source of hydrogen atoms.[32] More recently, the

eosinY photocatalyzed was coupled with the use of ascorbic acid as a reducing agent.[33]



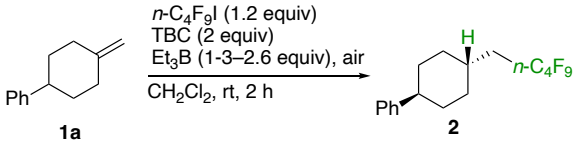
Scheme 1. Hydroperfluoroalkylation of unactivated alkenes

Recently, we have developed an efficient radical mediated chain reaction for the hydroalkylation of unactivated and electron rich alkenes employing 4-*tert*-butylcatechol (TBC) as a source of hydrogen atoms and triethylborane as a chain transfer reagent.[34–37] This process proved to be efficient with a broad range of electrophilic radicals and its efficiency was attributed to very favourable polar effects and an unprecedented repair mechanism.[38,34] Considering the simplicity and efficiency of the method, we envisaged that it could be extended to the hydroperfluoroalkylation of unactivated alkenes (Scheme 1, D). We also report a practical method for the hydrotrifluoromethylation of alkenes that does not rely on the use of gaseous CF_3I or expensive radical precursors such as Togni or Uemoto reagents.[39]

Results and Discussion

Hydroperfluoroalkylation with perfluoroalkyl iodides

The hydroperfluoroalkylation of 4-phenyl-1-methylenecyclohexene **1a** with commercially available nonafluoro-1-iodobutane was investigated first (Scheme 2). Reactions were performed with 4-*tert*-butylcatechol (TBC, 2 equivalents) as a source of hydrogen atoms and triethylborane as a chain transfer reagent. To make the reaction more attractive, the excess of the perfluorroalkyl iodide was limited to 1.2 equivalents relative to the alkene. Reagents were mixed under inert atmosphere and the reaction vessel was then open to air to initiate the radical process. The first run with 2 equivalents TBC and 1.3 equivalents Et_3B added at once at the beginning of the reaction provided the desired product **2** in 80% yield together with traces of the iodine ATRA product. Portion-wise addition of TBC (2 × 1 equiv) and triethylborane (2 × 1.3 equiv) provided **2** in 88% yield without traces of the iodine ATRA product.

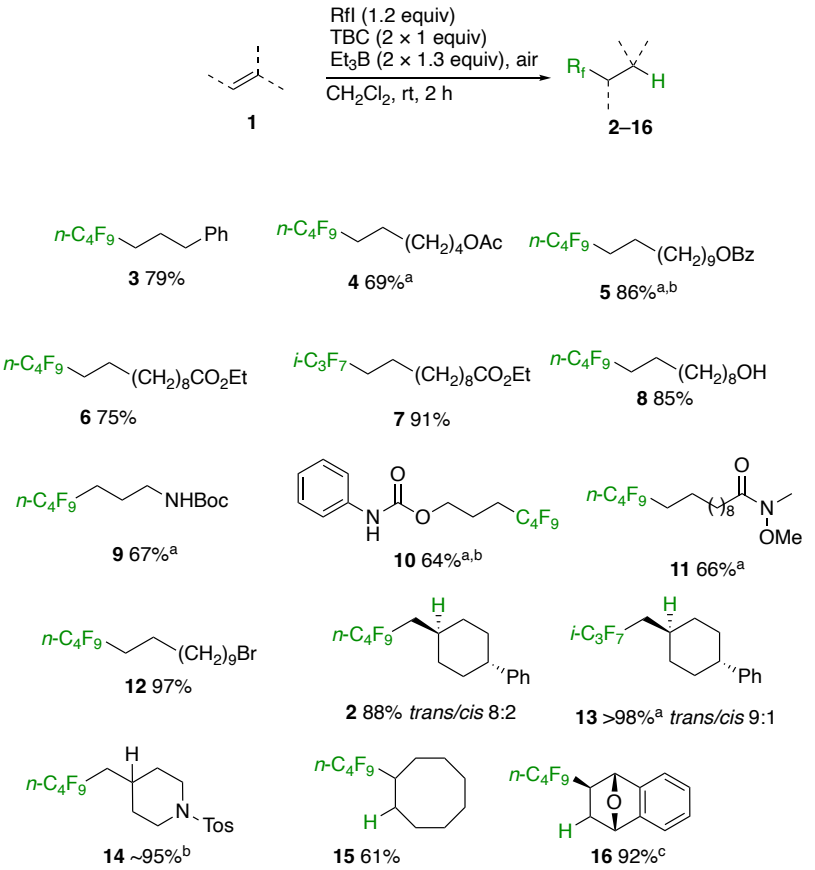


TBC (2 equiv) Et_3B (1.3 equiv)	**2** 80% (*trans/cis* 8:2) traces of ATRA product)
TBC (2 × 1 equiv) Et_3B (2 × 1.3 equiv)	**2** 88% (*trans/cis* 8:2)

Scheme 2. Optimized conditions for the hydroperfluoroalkylation of **1a**.

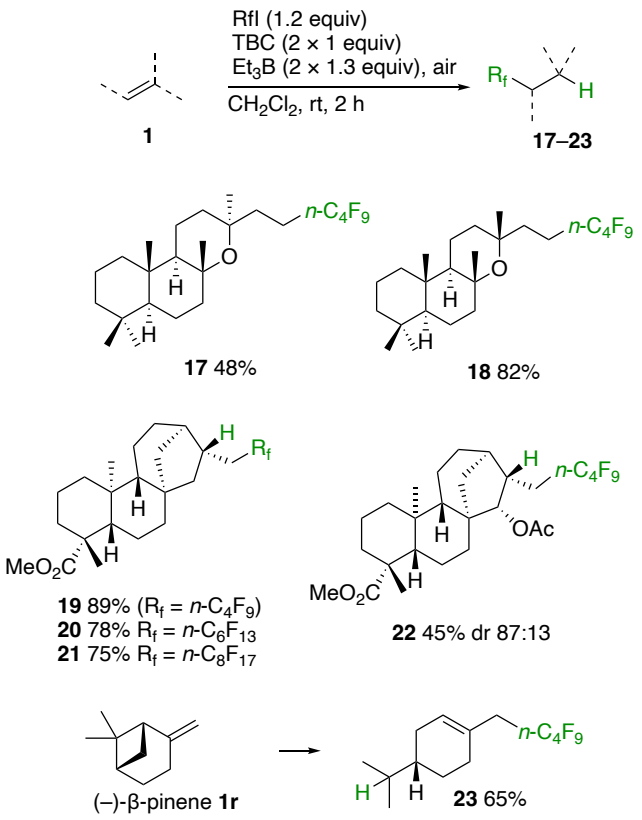
These optimized reaction conditions were employed to investigate the scope of the process with a wide range of alkenes (Scheme 3). Terminal monosubstituted alkenes were investigated first. Reaction with allylbenzene **1b** gave **3** in 79% yield. Ester containing alkenes **1c**–**1e** gave products **4**–**6** in good yield. The preparation of **5** from the benzoate ester **1d** worked more efficiently when 10 mol% of K_2CO_3 was added to minimize the formation of unsaturated side-products arising from the decomposition of the intermediate iodine ATRA product. The reaction of the ω-unsaturated ethyl ester alkene **1e** with perfluoroisopropyl iodide gave **7** in 91% yield. In this case, a small amount of the iodine atom transfer product (6%) was also isolated and characterized. Perfluoroalkalkylation of alkenes containing a free hydroxy group (**1f**), carbamates (**1g** and **1h**), a Weinreb amide (**1i**) and a bromide (**1j**) were efficiently hydroperfluoroalkalted to **8**–**12** demonstrating further the good functional group compatibility of the reaction. Reactions with 2,2-disubstituted alkenes was investigated next (Scheme 2, B). The hydroperfluoroalkylation of 4-phenyl-1-methylenecyclohexene **1a** was performed with perfluoro-*n*-butyl iodide and perfluoro-*i*-propyl iodide providing **2** and **13** in high yields. The hydroperfluoroalkylated product **14** was also obtained in high yield (95%) from 1-*p*-toluenesulfonyl-4-methylenepiperidine **1k**. Finally, the reaction was attempted with the more challenging non-terminal alkenes. The reaction with cyclooctene **1l** afforded the desired perfluoroalkylated cyclooctane **15** in 61% yield when the reaction was run with 3 equivalents of TBC. The reaction with naphthalene-1,2-oxide **1m** proved to be more problematic. Under our standard conditions, only the product of iodine atom transfer was obtained indicating that the TBC-mediated

deiodination was in this case inefficient. Gratifyingly, the desired product of hydroperfluoroalkylation **16** could be obtained in good yield via a two-step procedure involving and our recently developed di-*tert*-butylhyponitrite (DTBHN) mediated iodine ATRA reaction,[40] followed by deiodination with hypophosphorous acid according to Barton's procedure.[41,42]



Scheme 3.Hydroperfluoroalkylation of alkenes. a) With 3 equivalents TBC. b) With 10 mol% K_2CO_3. c) Using a two-step procedure.

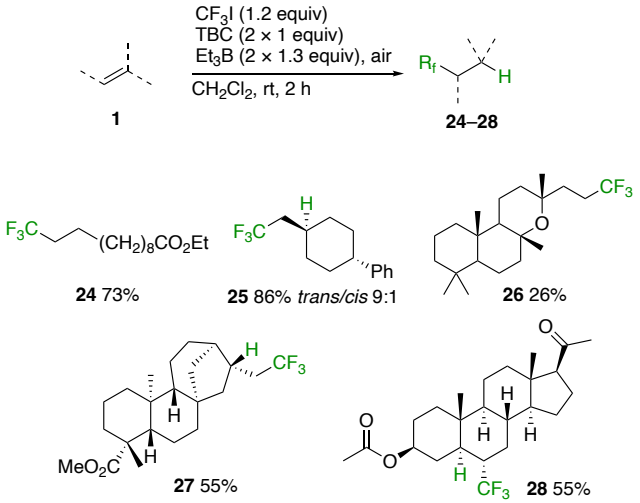
The hydroperfluoroalkylation of terpenoids was investigated next and results are presented in Scheme 4. Treatment of *epi*-manoyl oxide **1n** under the standard reaction conditions gave **17** in 48%. The same reaction using manoyl oxide **1o** provided the hydroperfluoroalkylated product **18** in high yield (82%). Finally, the hydroperfluoroalkylation of methyl *ent*-kaurenoate **1p** was investigated with different perfluoroalkyl iodides. The desired product **19**–**21** were obtained in 75–89% yield as a single diastereomers. The hydroperfluoroalkylation of methyl 15α-acetoxy-*ent*-kaurenoate **1q** was attempted. It provided the desired product **22** in 45% yield as a 83:13 mixture of diastereomers. Finally, the reaction of (–)-β-pinene **1r** was examined. The reaction afforded, as anticipated for a radical process, the ring-opened product **23** in 65% yield. Overall, these examples demonstrate the utility of our hydroperfluoroalkylation process for the modification of terpenic natural products.



Scheme 4.Hydroperfluoroalkylation of terpenoids.

Hydrotrifluoromethylation with trifluoromethyl iodide and trifluoromethanesulfonyl chloride

The good results obtained with perfluoroalkyl iodides incited us to extend the reaction to the hydrotrifluoromethylation of alkenes using trifluoromethyl iodide. The gaseous nature of this reagent made the reaction experimentally more demanding. However, a practical procedure was developed by using a Schlenk flask of a defined total volume (25 mL = 1.2 mmol, 10 mL = 0.5 mmol) which was filled at room temperature and atmospheric pressure with gaseous CF_3I (see supplementary material for details). The closed Schlenk flask was cooled down with liquid nitrogen to condense CF_3I and the system was set under inert N_2 atmosphere and placed in dry ice ethanol bath at –78 °C. A solution of the alkene and TBC in dichloromethane was added followed by Et_3B. After placing the reaction mixture at –20 °C, air was added via a syringe the mixture was stirred at this temperature for 1 h, allowed to warm up to room temperature and further stirred open to air until completion of the reaction. Using this procedure, the monosubstituted alkene **1e** was hydrotrifluoromethylated to **24** in 73% yield (Scheme 5). Similar results were obtained with the *exo*-methylene cyclohexane derivative **1a** affording **25** in 86% yield as a *trans/cis* 9:1 mixture. The terpenoids manoyl oxide **1o** and methyl *ent*-kaurenoate **1p** afforded **26** and **27** in 26% and 55% yields, respectively. Hydrotrifluoromethylation of the more challenging non-terminal alkene *O*-acetyl pregnelonone **1s** afforded the desired product **28** in 55% yield. In several reactions, small amounts of alkenes resulting presumably from HI elimination of the intermediate iodine ATRA products are observed.

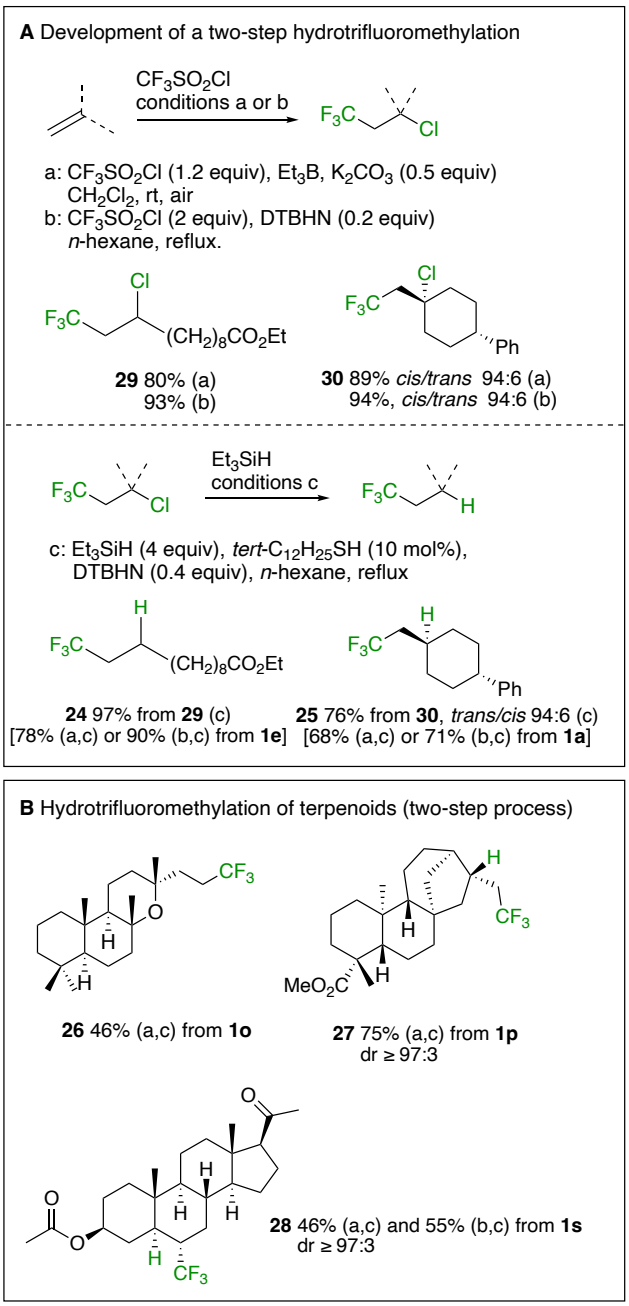


Scheme 5. Hydrotrifluoromethylation with CF_3I.

Since working with gaseous trifluoromethyl iodide is tedious and costly, we looked for an alternative procedure based on the use of a commercially available, affordable, and easy to handle reagent. Recently, we reported that desulfitative processes are particularly efficient to run chloro- and thio- and azidoalkylation of alkenes.[43–46] Trifluoromethanesulfonyl chloride is a very common and commercially available reagent. Its use for the chlorotrifluoromethylation of alkenes[47] was pioneered by Kamigata et al. using metal catalysis,[48–51] a reaction that could also be run under photoredox conditions[52–58] as well as under classical radical initiation.[59] Therefore, we decided to employ it for the development of a two-step alkene hydrotrifluoromethylation process. The first step, a chlorine ATRA process, was investigated first with ethyl-10-undecenoate **1e** and 4-phenyl-1-methylenecyclohexane **1a**. The reaction proved to be efficient upon initiation with triethylborane/air at room temperature in dichloromethane using 1.2 equivalents of trifluoromethanesulfonyl chloride (procedure a). The addition of a of potassium carbonate proved to be beneficial to the reaction by minimizing side product formation, presumably by neutralizing small amounts of triflic acid and HCl generated by hydrolysis of the trifluoromethanesulfonyl chloride. Under these conditions, the products of chlorotrifluromethylation **29** and **30** were isolated in 80% and 89% yield, respectively (Scheme 6, A). Interestingly, by using the procedure we have recently developed for iodine ATRA reaction using di-*tert*-butylhyponitrite (DTBHN) as an initiator,[40] improved yields were obtained and the use of a base was not anymore necessary. The reaction also proved to work efficiently in *n*-hexane as a solvent, a critical aspect for the development of an operationally simple one-pot

procedure (vide infra). Under these conditions (procedure b), chlorides **29** and **30** were obtained in 93% and 94% yields, respectively (Scheme 6, A).

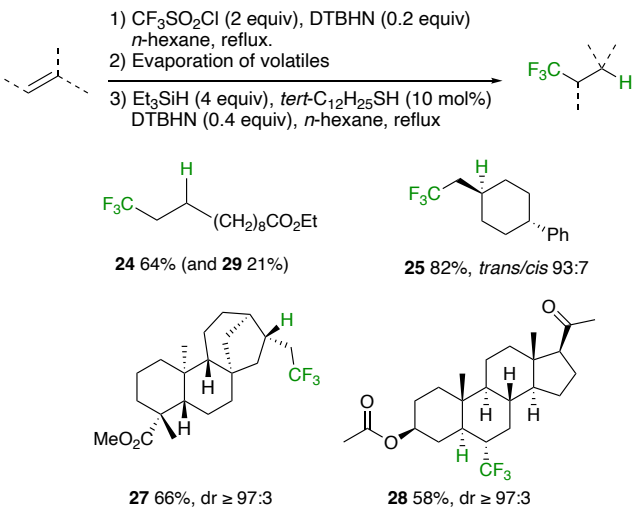
The dechlorination step was investigated next using the mildest possible reaction conditions, i.e. avoiding the use of strong reducing agents such as metals and metal hydrides. For this purpose, the very mild radical mediated method developed by Roberts and co-workers with triethylsilane and *tert*-dodecanethiol was selected.[60,61] By using 4 equivalents of Et_3SiH and 10 mol% of the thiol catalyst under initiation with di-*tert*-butylhyponitrite, the desired hydrotrifluroromethylated products **24** and **25** were obtained in 97% and 76%, respectively (Scheme 6, B). Over this two-step approach using procedures b and c, alkenes **1e** and **1a** were hydrotrifluoromethylated with overall yields of 90% and 71%. These results compare well with the CF_3I mediated process described in Scheme 5. This two-step approach was then applied for the hydrotrifluoromethylation of isoprenoid substrates (Scheme 6, B). Using conditions a (Et_3B initiation) and c, manoyl oxide **1o** and methyl *ent*-kautenoate **1p** afforded **26** and **27** in 46% and 75% yield, respectively. The challenging non-terminal alkene *O*-acetyl pregnelonone **1s** was then examined and it afforded the desired product **28** in 46% (conditions a and c) and 55% (conditions b and c).



Scheme 6. Two-step hydrotrifluoromethylation with CF_3SO_2Cl.

Since the same initiator (DTBHN) and solvent (*n*-hexane) were used for the desulfitative chlorine ATRA step and for the dechlorination process (Scheme 6, conditions b and c), the possibility of running the hydrotrifluroromethylation as a two-step, one-pot process was envisaged. The hydrotrifluoromethylation of a series of alkenes was attempted without purification of the intermediate chlorides (Scheme 7). The reaction conditions used for the two-step process could be kept unchanged provided that, after the chlorine ATRA process, the excess of the volatile trichloromethyl sulfonyl chloride was evaporated before performing the dechlorination. Using this approach, the alkene **1e** was converted to **24** in 64% yield together with the non-dechlorinated product **29**

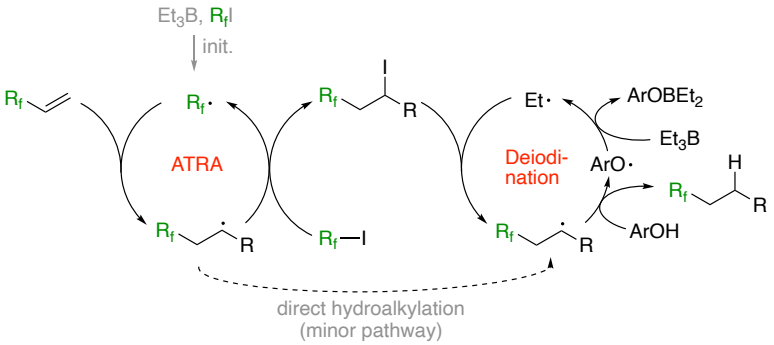
(21%). The reaction of **1a** provided **25** in 82% yield as *trans/cis* 93:7 mixture. The isoprenoids **1p** and **1s** were also subjected to this one-pot process providing **27** and **28** in 66% and 58% as a single detectable diastereomer (dr ≥ 93:7).



Scheme 7. One-pot hydrotrifluoromethylation with CF_3SO_2Cl.

Mechanism

The hydrotrifluoromethylation with perfluorinated alkyl iodides is expected to proceed via the mechanism previously described for α-iodoesters and related compounds.[34] Due to the high rate of iodine atom transfer involving perfluoroalkyl iodides, the major reaction pathway involves presumably a first iodine ATRA reaction, delivering the iodoperfluoroalkylated product, followed by a deiodination process mediated by the system triethylborane/4-*tert*-butylcatechol. As discussed previously, the efficacy of this system relies on a particularly efficient chain reaction due to favourable polar effects and presumably, a chain repair mechanism allowing to overcome chain disrupting processes involving undesired hydrogen atom transfers leading to stabilized allylic radicals. The involvement of this chain repair process has not been probed in this particular case but is nevertheless very likely due to the strong hydrogen atom abstracting character of perfluorinated alkyl radicals.[62]



Scheme 8. Simplified reaction mechanism of the hydroperfluoroalkylation with perfluorinated alkyl iodides.

Conclusion

The direct hydroperfluoroalkylation of unactivated alkenes with perfluoroalkyl iodides, including gaseous trifluoromethyl iodide, has been achieved in good yields under mild conditions using 4-*tert*-butylcatechol as a source of hydrogen atom and triethylborane as a chain transfer agent. The reaction has been shown to work with terminal alkenes as well as di- and trisubstituted internal alkenes including those of complex isoprenoids of natural origin. For the trifluoromethylation reaction, a practical alternative to the use of gaseous and expensive CF_3I has been developed by taking advantage of desulfitative chlorine atom transfer process followed by a thiol catalyzed dechlorination process. This two-step procedure maintains the mildness of reaction conditions and can be performed without purification of the chloride intermediate in a one-pot procedure.

Experimental Section

General procedure for hydroperfluororalkylation with R_fI

To a solution of alkene (1.0 mmol) and 4-*tert*-butylcatechol (TBC) (170 mg, 1.0 mmol) in CH_2Cl_2 (2.8 mL, 0.25 M) was added iodide (1.2 mmol) followed by BEt_3 solution (1.15 M in hexane, 1.13 mL, 1.3 mmol) at rt. The reaction mixture was stirred at rt for 1 h in an open to air flask protected from moisture by $CaCl_2$ tube. Then the second portion of TBC (170 mg, 1.0 mmol) and BEt_3 solution (1.15 M in hexane, 1.13 mL, 1.3 mmol) were added and the solution was stirred for 1 h. The reaction mixture was filtered over short pad of neutral Al_2O_3 eluting with Et_2O or EtOAc in order to remove polar TBC and boron derivatives. The resulting crude filtrate was concentrated under reduced pressure and purified by FC (Et_2O/pentane or EtOAc/heptanes).

General procedure for the hydrotrifluoromethylation with gaseous CF_3I

A 25 mL Schlenk flask was connected to a vacuum/N_2 line and to a CF_3I cylinder via its side

three-way stopcock and to a gas bubbler via the top ground glass joint using a two-way stopcock. The flask was vacuumed, and gaseous CF_3I was carefully introduced. The overpressure was suppressed by opening the two-way stopcock leading to the bubbler. Using this procedure, gaseous CF_3I (25 mL, 1.2 mmol) was introduced in the flask. Then the Schlenk flask was closed and cooled down with liquid N_2 to condense CF_3I as a colorless solid. The cooled system was set under N_2 and the top ground joint was equipped with a septum. The flask was placed in a dry ice-ethanol cooling bath (–78 °C) and a solution of the alkene (1.0 mmol), TBC (339 mg, 2.0 mmol) in CH_2Cl_2 (2.8 mL) was added through syringe followed by a solution of BEt_3 (1.15 M in hexane, 1.13 mL, 1.3 mmol). Air (1–2 mL) was introduced by syringe into the reaction mixture. The cooling bath was then replaced by an ice/water/NaCl bath (–20 °C), and the reaction mixture was stirred at hsi temperature for 1 h. A second portion of TBC (170 mg, 1.0 mmol) and BEt_3 (1.15 M in hexane, 1.13 mL, 1.3 mmol) were added, the cooling bath was removed, the septum was replaced by a $CaCl_2$ tube and stirring open to air was continued at rt. After 2 h, the reaction mixture was filtered over short pad of neutral Al_2O_3 using Et_2O or EtOAc to remove TBC and boron derivatives. The crude filtrate was concentrated under reduced pressure and purified by FC (pentane/Et_2O or heptanes/EtOAc).

General procedure for the two step one-pot hydrotrifluoromethylation with CF_3SO_2Cl

In a 10 mL flask containing *n*-hexane (3 mL), the alkene (1.0 mmol), trifluoromethanesulfonyl chloride (0.22 mL, 2 mmol) and DTBHN (34.8 mg, 0.20 mmol) was heated under reflux for 30 min under Ar. The volatiles (*n*-hexane and excess CF_3SO_2Cl) were removed by evaporation under vacuum at the Schlenk line. *n*-Hexane (3 × 2 mL) was added for efficient co-evaporation of the volatiles. The crude chloride was dissolved in *n*-hexane (1.8 mL) under Ar. Triethylsilane (1.61 mL, 10 mmol), *tert*-dodecanethiol (71.3 µL, 0.3 mmol) and DTBHN (35.2 mg, 0.2 mmol) were added and the reaction mixture was heated under reflux for 1 h. The solution was cooled down and a second portion of *tert*-dodecanethiol (71.3 µL, 0.3 mmol) and DTBHN (35.2 mg, 0.2 mmol) were added and the reaction mixture was further heated under reflux for 1 h. The cooled reaction mixture was washed with aq. sat. $NaHCO_3$ (2 × 10 mL), water and brine. After drying over Na_2SO_4 and concentration under reduced pressure, the crude product was purified by FC (pentane/Et_2O or heptanes/EtOAc) to afford the product of hydrotrifluoromethylation.

Acknowledgements

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Radical Mediated Hydroperfluoroalkylation of Unactivated Alkenes

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