

tion products in good yields.

CH₂CF₃ CH₂CF₃

up to 84% yield

Cobalt-Catalyzed Radical Hydrotrifluoroethylation of Styrenes with Trifluoroethyl Iodide

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F₃-containing compounds have broad applications in / fluorinated agrochemicals, pharmaceuticals, and functional materials because their introduction into an organic compound can significantly improve its activity, lipophilicity, and metabolic stability.1 Thus, synthetic methodologies of CF₃-containing compounds, including the construction of C-CF₃ bonds² and CF₃ introduction via versatile CF₃-containing building blocks,³ have attracted a great deal of attention and have been extensively developed in recent years. Among them, CF₃ introduction via direct trifluoroethylation reactions,^{3b,c} with readily available CF₃CH₂-containing starting materials, such as $CF_{3}CH_{2}I_{4}^{4} CF_{3}CH_{2}N_{2}^{5} CF_{3}CHCl_{2}^{6} CF_{3}CH_{2}SO_{2}CI_{7}^{1}$ $(CF_{3}CH_{2})_{2}Zn_{7}^{8} [ArI(CH_{2}CF_{3})]^{+}(OT_{f})^{-9} CF_{3}COOH_{7}^{10}$ 10 $[Ph_2S(CH_2CF_3)]^+(OTf)^{-,11}$ etc., is highly valuable. Specifically, CF₃CH₂I is an important and popular trifluoroethylation building block due to its inexpensive price and ease of use.

fluoroalkyl halides, generating the corresponding hydrofluoroalkyla-

Radical 1,2-difunctionalization type fluoroalkylation of various unsaturated carbon–carbon bonds for simultaneous and efficient incorporation of one fluoroalkyl group and the other important functional group in one step has been a hot research field.¹² Radical trifluoroethylation of a C=C bond serves as a powerful synthetic strategy for CF₃CH₂-containing compounds. For examples, an elegant photochemical trifluoroethylation of styrene derivatives with CF₃CH₂I has been reported by Carreira, Martin, and co-workers to efficiently provide various trifluoroethylated alkenes (Figure 1a).¹³ The Xiang group disclosed a copper/silver co-mediated oxidative coupling of styrenes with CF₃CH₂I to afford β -CF₃-substituted ketones (Figure 1d).¹⁴ Trifluoroethylstyrenes were efficiently produced by copper-catalyzed decarboxylative trifluoroethylation of cinamic acid derivatives with CF₃CH₂I (Figure 1e).¹⁵

We have long-standing interest in inert C–X bond activation and radical reactions of CF_3CH_2I and its analogues via a singleelectron transfer (SET) process. The reductive cleavage of unactivated carbon–chlorine bond of various fluoroalkyl halides, such as perfluoroalkyl chlorides (R_FCI),¹⁶ 2-chloroPrevious work:



R = H

This work:

$$\begin{array}{c} \mathsf{R} \\ \mathsf{Ar} \end{array} + \mathsf{CF}_{3}\mathsf{CH}_{2}\mathsf{I} \xrightarrow{[\mathsf{Co}], [\mathsf{H}]} \\ \mathsf{Ar} \end{array} \xrightarrow{\mathsf{H}} \mathsf{CH}_{2}\mathsf{CF}_{3} \end{array}$$

Figure 1. Radical trifluoroethylation of styrenes with CF₃CH₂I.

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1,1,1-trifluoroethane (CF₃CH₂Cl),¹⁷ and 1,1-dichloro-2,2,2trifluoroethane (CF_3CHCl_2) ,^{6,18} via a single-electron transfer (SET) process has been achieved. Notably, we have already realized the sulfinatodehalogenation of CF3CH2I to generate the CF₃CH₂ radical and its subsequent reactions with various unactivated alkenes.¹⁹ Moreover, the photocatalytic activation of CF₂CH₂I can efficiently afford the corresponding CF₂CH₂ radical, which can react with styrenes to afford the desired γ trifluoromethyl alcohols in the presence of an oxygen source (Figure 1b),²⁰ or with aryl silvl enol ethers to produce the corresponding β -CF₃-substituted ketones (Figure 1c).²¹ As a continuation of our research interest in the activation and radical reactions of CF₃CH₂I, we have currently investigated the activation of CF₃CH₂I and its subsequent radical reactions with styrenes under a cobalt catalyst. Without the addition of an extra hydrogen source, addition of the generated CF₃CH₂ radical to styrenes proceeded smoothly to produce a new radical intermediate and its self-coupling finished the corresponding trifluoroethylation self-coupling products in high yields. Interestingly, in the presence of both thiophenol and tris(trimethylsilyl)silane as an extra hydrogen source, high yields of the desired hydrotrifluoroethylated products were obtained.

Our study commenced by using 4-vinylbiphenyl (1a) as the model substrate, CF_3CH_2I as the trifluoroethyl source, and zinc powder as the reductant at room temperature for 6 h in acetone. Initially, we investigated the influence of different metal salts as a catalyst with the assistance of PPh₃ as the ligand (see Table S1 for details). However, instead of the desired hydrotrifluoroethylation product, trifluoroethylation self-coupling product **2a** was obtained. We tested the effect of CF_3CH_2I loading, various catalysts, and their loadings and found that 0.6 equiv of $CoCl_2$ combined with 1.5 equiv of CF_3CH_2I afforded the best yield of **2a**.

With the optimal conditions for product 2 in hand, several styrenes were subjected to the cobalt-mediated trifluoroethylation self-coupling reactions. As shown in Figure 2, utilization



Figure 2. Trifluoroethylation self-coupling reactions of various styrenes. Reaction conditions: 1 (0.5 mmol, 1.0 equiv), CF_3CH_2I (0.75 mmol, 1.5 equiv), Zn (1.0 mmol, 2.0 equiv), $CoCl_2$ (0.3 mmol, 0.6 equiv), PPh₃ (1.2 mmol, 2.4 equiv), acetone (5 mL), rt, 12 h, Ar atmosphere. Isolated yields are shown. "The yield was determined by ¹⁹F NMR spectroscopy with trifluorotoluene as an internal standard and ¹H NMR spectroscopy using dibromomethane as an internal standard.

of 4-vinylbiphenyl (1a) as the substrate resulted in a good yield of 2a of 82%, which is a 1:1 mixture of two diastereomers. After repeat flash column chromatography and preparative thin layer chromatography on silica gel, they can be successfully separated and diastereomer 2a'' was unambiguously assigned by X-ray crystallographic analysis.²² Other substrates containing various groups, including methyl, methoxy, and fluorine, on the aromatic ring are all applicable to the reactions, affording the target products in nice yields.

Aiming at hydrotrifluoroethylation of vinylbiphenyl 1a, we continued to examine screening conditions by adding an extra hydrogen source (see Tables S4-S7 for details). Notably, CoBr₂ and PPh₃ stood out as the best catalyst combination and were used in the radical hydrotrifluoroethylation reactions (see Tables S2 and S3 for details), and the first choice of an extra hydrogen source that came to our mind was thiol because it is known that an alkyl radical can readily abstract a hydrogen from thiol.²³ After examining various thiols, we found thiophenol (PhSH) performed best and the desired hydrotrifluoroethylation product 3a was successfully obtained (see Table S4 for details). To our delight, the use of 1.0 equiv of thiophenol efficiently suppressed the formation of self-coupling product 2a, but another byproduct 4 was generated obviously due to the combination of benzyl radical and phenylthio radical generated in the reaction system (Figure 5). A further increase in thiophenol loading resulted in more byproduct 4, and the same yield of desired product 3a was observed (see Tables S5 and S6 for details). Additionally, it is worth mentioning that the direct reaction of the CF₃CH₂ radical with PhSH to give PhSCH₂CF₃ in the reaction mixture was observed by ¹⁹F NMR spectroscopy.

Next, we considered adding a second extra hydrogen source to transfer the phenylthio radical back to thiophenol to suppress the formation of side product 4. We chose tris(trimethylsilyl)silane [(Me₃Si)₃SiH] because the alkyl radical generated from addition of the CF₃CH₂ radical with styrene is not prone to abstracting the hydrogen from (Me₃Si)₃SiH, while the phenylthio radical can readily abstract the hydrogen of (Me₃Si)₃SiH. We then investigated the influence of its loading (see Table S7 for details). Fortunately, it was observed that (Me₃Si)₃SiH did effectively suppress the production of 4. The more (Me₃Si)₃SiH we used, the less byproduct 4 we obtained. Although utilization of 1.0 equiv of (Me₃Si)₃SiH almost completely eliminated byproduct 4, it was found that some starting styrene was still not consumed. To improve the yield of desired product 3a, we further investigated the loading of CF₃CH₂I and Zn powder used (see Table S7 for details). We found that 1.5 equiv of Zn powder and 3.0 equiv of CF₃CH₂I afforded the best yield of 88%. On the basis of all of the screening results mentioned above, the optimized conditions for the cobalt-catalyzed radical trifluoroethylation of styrenes were set as follows: styrene (1.0 equiv), CF_3CH_2I (3.0 equiv), $CoBr_2$ (0.2 equiv), PPh_3 (0.8 equiv), Zn (1.5 equiv), PhSH (1.0 equiv), (Me₃Si)₃SiH (1.0 equiv), acetone, Ar atmosphere, room temperature, 12 h.

With optimized reaction conditions established, we then investigated the scope of various styrenes for the cobaltcatalyzed radical hydrotrifluoroethylation reactions (Figure 3). We first studied the hydrotrifluoroethylation of substrates 1c-1j bearing electron-donating substituents on the aromatic ring. Compounds bearing methyl, *tert*-butyl, methoxy, hydroxyl, amino, and acetoxy substituents on the benzene core at *meta* or *para* positions afforded the desired products in moderate to



Figure 3. Substrate scope with respect to styrenes for the cobaltcatalyzed radical hydrotrifluoroethylation reactions of styrenes with CF_3CH_2I . Reaction conditions: 1 (0.5 mmol, 1.0 equiv), CF_3CH_2I (1.5 mmol, 3.0 equiv), Zn (0.75 mmol, 1.5 equiv), $CoBr_2$ (0.1 mmol, 0.2 equiv), PPh₃ (0.4 mmol, 0.8 equiv), PhSH (0.5 mmol, 1.0 equiv), (Me₃Si)₃SiH (0.5 mmol, 1.0 equiv), acetone (5 mL), rt, 12 h, Ar atmosphere. Isolated yields are shown.

good yields (49-92%). As for the substrates with electronwithdrawing groups (1k-1p), the transformation was amenable under standard conditions to halogen substitution with fluorine, chlorine, and bromine as well as a cyano substituent. Moreover, vinylnaphthalenes 1s and 1t were suitable substrates for this protocol, resulting in good yields of the corresponding hydrotrifluoroethylation products. 1-Substituted styrenes 1u and 1v were subjected to the standard conditions and delivered good yields of the corresponding products in 76-84% vields. Unfortunately, internal alkenes are not suitable for the transformation, and no desired products are observed, which might be due to their steric hindrance effect. Furthermore, a structurally complicated biologically active steroid derivative 1w was selected as a candidate for this transformation, producing desired product 3w in 70% yield. Gram-scale synthesis of 3f was carried out, and an excellent yield of 90% was achieved, demonstrating the good scalability of the reaction. Notably, the structure of 3a was unambiguously assigned by X-ray crystallographic analysis.²²

To further expand the substrate scope of this transformation, we also decided to explore the substrate scope with respect to various fluoroalkyl halide derivatives, and the results are summarized in Figure 4. A range of fluoroalkyl halides participated in the cobalt-cataylzed hydrofluoroalkylation reactions of styrenes to successfully lead to the corresponding hydrofluoroalkylation products in good yields.

On the basis of the experimental results described above and the literature, 16b,17c we proposed a possible mechanism for the cobalt-catalyzed radical trifluoroethylation of various styrenes (Figure 5). The catalyst CoBr₂ or CoCl₂ is reducted into active catalyst species Co(PPh₃)₄ in the presence of Zn and PPh₃,



Figure 4. Substrate scope with respect to fluoroalkyl halides for the cobalt-catalyzed radical hydrofluoroalkylation of various styrenes with R_FX . Reaction conditions: 1 (0.5 mmol, 1.0 equiv), R_FX (1.5 mmol, 3.0 equiv), Zn (0.75 mmol, 1.5 equiv), $CoBr_2$ (0.1 mmol, 0.2 equiv), PPh₃ (0.4 mmol, 0.8 equiv), PhSH (0.5 mmol, 1.0 equiv), (Me₃Si)₃SiH (0.5 mmol, 1.0 equiv), acetone (5 mL), rt, 12 h, Ar atmosphere. Isolated yields are shown.



Figure 5. Proposed mechanism for the cobalt-catalyzed radical fluoroalkylation of various styrenes.

which can efficiently activate CF3CH2I and generate the CF₃CH₂ radical. Its addition to styrenes results in new alkyl radical species A. In the absence of an extra hydrogen source, self-coupling of intermediate A occurred to produce the corresponding trifluoroethylation self-coupling products. With thiophenol and tris(trimethylsilyl)silane as the extra hydrogen source, subsequent hydrogen abstraction of intermediate A from thiophenol finishes the desired hydrofluoroalkylation products and phenylthio radical. The resulting phenylthio radical abstracts a hydrogen atom from tris(trimethylsilyl)silane to regenerate thiophenol, avoiding the side reaction of alkyl radical species A with phenylthio radical. The radical character of this transformation was further supported by the radical inhibition experiments with a radical scavenger [2,2,6,6tetramethyl-1-piperidinyloxy (TEMPO)] and an electron transfer scavenger (1,4-dinitrobenzene) (see Table S8 for details).

In conclusion, styrenes make up a challenging class of substrates for current radical hydrotrifluoroethylation reactions because of the potentially serious side reactions. We have successfully developed a mild and efficient cobalt-catalyzed radical trifluoroethylation reaction of styrenes with CF_3CH_2I to produce hydrotrifluoroethylated products in the presence of thiophenol and tris(trimethylsilyl)silane, while trifluoroethylation self-coupling products were obtained in their absence.

Notably, a variety of other fluoroalkyl halides is also compatible with a current transformation to afford the corresponding hydrofluoroalkylation products in good yields. Given the overall practicality and scope, this diverse transformation may provide a good route for the introduction of important fluoroalkyl groups, including the CF_3 group, into organic compounds.

ASSOCIATED CONTENT

1 Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02300.

Full experimental details, characterization data, copies of NMR spectra for new compounds, and X-ray crystallog-raphy data (PDF)

Accession Codes

CCDC 1575969–1575970 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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