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Photocatalytic Synthesis of Allylic Trifluoromethyl Substituted Styrene Derivatives in Batch and Flow

Lukas M. Kreis,[†] Simon Krautwald,[†] Nicole Pfeiffer,[†] Rainer E. Martin,*[,‡] and Erick M. Carreira*[,†]

Laboratory of Organic Chemistry, ETH-Zürich, HCI H335, Wolfgang-Pauli-Strasse 10, 8093 Zürich, Switzerland, and F. Hoffmann-La Roche AG, pRED, Pharma Research & Early Development, Small Molecule Research, Medicinal Chemistry; Grenzacherstrasse 124, 4070 Basel, Switzerland

carreira@org.chem.ethz.ch; rainer_e.martin@roche.com

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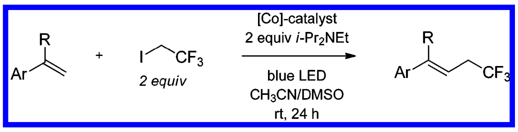
ABSTRACT



A cobalt-catalyzed photochemical synthesis of allylic trifluoromethanes from styrene derivatives using 2,2,2-trifluoroethyl iodide is described. The method complements existing approaches, providing an alternative bond construction strategy to access these compounds. The process may be conducted in continuous mode in a novel photochemical flow reactor, resulting in a notable productivity increase.

The trifluoromethyl group has found widespread application in the pharmaceutical and agrochemical sciences as a consequence of its effect on the physicochemical properties of underlying scaffolds. Trifluoromethyls can, for instance, lead to lead compounds in drug discovery with increased metabolic stability and lipophilicity.[1] Consequently, efficient and mild methods for the introduction of trifluoromethyls are in demand. Herein, we disclose a cobalt-catalyzed synthesis of allylic trifluoromethanes from styrene derivatives using 2,2,2-trifluoroethyl iodide (**1**) (Scheme 1). In addition, we document how the process may be conducted in continuous mode in a novel photochemical flow reactor. To the best of our knowledge, the work we delineate represents the first example of a Heck-type coupling reaction using 2,2,2-trifluoroethyl iodide.[2]

Until recently there were rather few practical methods for the preparation of allylic trifluoromethanes.[3−5] Over the past year, several reports describing the coupling of trifluoromethyl and allyl groups have been disclosed. Buchwald,[6] Wang,[7] and Liu[8] independently documented

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[†] ETH-Zürich.

[‡] F. Hoffmann-La Roche AG.

(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) For selected recent reports on other reactions involving 2,2,2-trifluoroethyl iodide, see: (a) Liang, A.-P.; Li, X.-J.; Liu, D.-F.; Li, J.-Y.; Zou, D.-P.; Wu, Y.-J.; Wu, Y.-S. *Chem. Commun.* **2012**, *48*, 8273. (b) Zhao, Y.-C.; Hu, J.-B. *Angew. Chem., Int. Ed.* **2012**, *51*, 1033. (c) Feng, Y.-S.; Xie, C.-Q.; Qiao, W.-L.; Xu, H.-J. *Org. Lett.* **2013**, *15*, 936.

(3) The single example of Stille coupling of *E*- and *Z*-styryl stannane with 2,2,2-trifluoroethyl iodide proceeds in 35−38% yield; see: Matsubara, M.; Mitani, M.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 5857.

(4) For the synthesis of allylic trifluoromethyl groups via substitution of allylic bromide using stoichiometric copper reagents, see: (a) Su, D.-B.; Duan, J.-X.; Chen, Q.-Y. *Tetrahedron Lett.* **1991**, *32*, 7689. (b) Chen, Q.-Y.; Duan, J.-X. *J. Chem. Soc., Chem. Commun.* **1993**, 1389. (c) Duan, J.-X.; Su, D.-B.; Chen, Q.-Y. *J. Fluorine Chem.* **1993**, *61*, 279. (d) Kim, J.; Shreeve, J. M. *Org. Biomol. Chem.* **2004**, *2*, 2728. For a recent Cu-catalyzed substitution of allylic bromides using TMSCF$_3$, see: (e) Miyake, Y.; Ota, S.-I.; Nishibayashi, Y. *Chem.—Eur. J.* **2012**, *early view*. For recent Cu-catalyzed trifluoromethylations of allyl silanes, see: (f) Shimizu, R.; Egami, H.; Hamashima, Y.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4577. (g) Mizuta, S.; Galicia-López, O.; Engle, K. M.; Verhoog, S.; Wheelhouse, K.; Rassias, G.; Gouverneur, V. *Chem.—Eur. J.* **2012**, *18*, 8583. For a recent review on radical trifluoromethylation reactions, see: (h) Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950.

(5) For the synthesis of an allylic trifluoromethyl group via a Wittig reaction using the Wittig salt prepared from 3,3,3-trifluoropropyl iodide and triphenylphosphine, see: Liou, Z.; Kumar, K. *Synthesis* **2010**, 1905.

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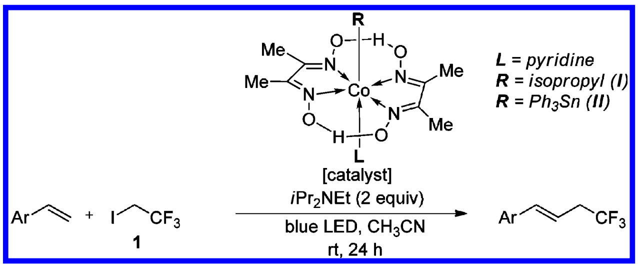
the Cu-catalyzed trifluoromethylation of allyl groups with Togni's (**2**) or Umemoto's reagent (**3**). Qing subsequently developed a copper-catalyzed method employing Ruppert's reagent (Me_3SiCF_3) and $PhI(OAc)_2$.[9]

Scheme 1. Cobalt-Catalyzed Trifluoroethylation of Styrenes



We have reported an alkyl Heck-type coupling reaction catalyzed by simple cobalt-complexes[10,11] and, thus, became interested in examining the coupling of olefins with the readily available 2,2,2-trifluoroethyl iodide (**1**). Such a method would complement the existing approaches of Buchwald, Liu, Wang, and Qing, providing an alternative bond construction strategy to access allylic trifluoromethanes.[5−8] Thus, while published methods require allylic starting materials and lead to the formation of allylic C−C bonds (Scheme 2a), a method involving a Co-catalyzed C=C bond addition with trifluoroethyl iodide would commence with vinyl-substituted starting materials (Scheme 2b).

At the outset of our studies, we were concerned with the potential complication that the necessary intermediate cobalt species in the catalytic cycle would be enthalpically and entropically susceptible to elimination, giving a cobalt fluoride salt (Co−F BDE ~430 kJ/mol)[12] and 1,1-difluoroethylene, thereby shutting down the desired reaction process (Scheme 2b).

Initial screening experiments with 4-*tert*-butylstyrene **5a** and trifluoroethyl iodide using isopropyl catalyst **I** (Scheme 1) in the presence of *i*-Pr_2NEt and under irradiation with blue LED light (λ_{max} = 465 nm) did not afford product (Table 1, entry 1). This stands in contrast to what we had previously observed with **I** in intramolecular alkyl Heck type cyclizations of alkyl iodides and enones.[10] However, triphenyltin-catalyst **II** enabled the desired transformation, giving product **6a** in 45% yield (entry 2) as a single diastereomer. The olefin configuration was assigned as *trans* on the basis of the large vicinal coupling of the olefinic protons (J = 15.8 Hz).

Scheme 2. Complementary Bond Disconnections in Cu- and Co-Catalyzed Synthesis of Allylic Trifluoromethanes

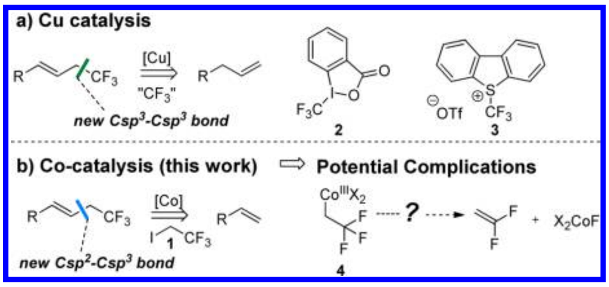
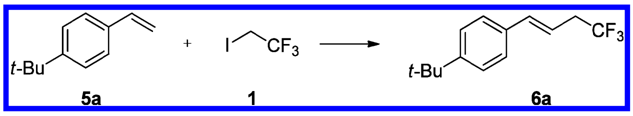


Table 1. Optimization Studies of the Trifluoroethylation[a]



entry	1	catalyst	conv[b]
1	1 equiv	15 mol % **I**	–
2	1 equiv	15 mol % **II**	45%[c]
3	3.5 equiv	15 mol % **II**	54%
4	10 equiv	15 mol % **II**	64%
5[d]	2 equiv	20 mol % **II**	full

[a] Conditions: catalyst, 1 equiv **5a**, 2 equiv *i*-Pr_2NEt, blue LED, CH_3CN, rt, 24 h. [b] Conversion of **5a** determined by ^1H NMR analysis of the crude reaction mixture. [c] Isolated yield of **6a**. [d] Reaction run in a 1:1 CH_3CN/DMSO solvent mixture.

Increasing the amount of **1** to 3.5 and 10 equiv led to the improved conversion of *tert*-butylstyrene (**5a**) (54% and 64%, respectively, as shown in entries 3 and 4). We noticed over the course of the reaction the formation of a solid byproduct, whose identity remains to be established. We surmised that the ensuing suspension prevented the efficient absorption of light, resulting in incomplete conversion. Further optimization trials rapidly revealed, however, that conducting the reaction in a mixture of CH_3CN/DMSO (1:1) prevented the formation of the suspension and led to full conversion (entry 5).

With a protocol in hand, the scope of the reaction was examined (Table 2). Although aliphatic olefins did not undergo trifluoroethylation, a large collection of styrenes participated in the reaction in useful yields. The mild conditions of the reaction (rt, MeCN, *i*-$PrNEt_2$) allow a wide range of functional groups to be tolerated including amines, aldehydes, thioethers, alcohols, and pyridines. Sterically more demanding 1,2-disubstituted styrene derivatives are also suitable substrates. Analysis by ^1H NMR of the unpurified product from the reaction mixture revealed that only *trans* olefins were formed.

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(9) Chu, L.; Qing, F.-L. *Org. Lett.* **2012**, *14*, 2106.

(10) (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. (d) Morandi, B.; Cheang, J.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 3080. (e) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 9085. (f) Morandi, B.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 5984. (g) Künzi, S. A.; Morandi, B.; Carreira, E. M. *Org. Lett.* **2012**, *14*, 1900.

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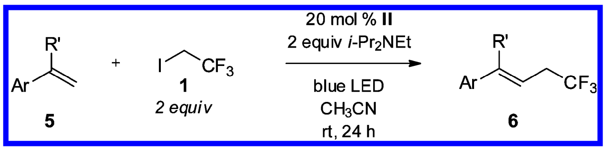
(12) Luo, Y. R. *Comprehensive Handbook of Chemical Bond Energies*; CRC Press: Boca Raton, FL, 2007.

Table 2. Scope of the Trifluoroethylation



entry	product	yield[a]
1	**6a**: *p*-*tert*-Bu-C_6H_4-	83%[b]
2	**6b**: *p*-MeO-C_6H_4-	76%
3	**6c**: *p*-AcO-C_6H_4	68%
4	**6d**: *p*-(CbzNH)-C_6H_4	65%[b]
5	**6e**: *p*-Me_2N-C_6H_4	74%
6	**6f**: *p*-MeO_2C-C_6H_4	68%
7	**6g**: *p*-OHC-C_6H_4	73%[b]
8	**6h**: 2-Naphthyl	56%[b]
9	**6i**: *p*-$HOCH_2$-C_6H_4	53%[b]
10	**6j**: *p*-MeS-C_6H_4	59%[b,c]
11	**6k**: 2-pyr-	64%
12	**6l**: Ar, R′ = Ph	51%
13	**6m**: Ar, R′ = *p*-Br-Ph	56%

[a] Yield of the isolated product. [b] Reaction run in a 1:1 MeCN/DMSO mixture. [c] Product contaminated with 10% starting material according to ^{1}H NMR analysis.

Photochemical reactions conducted with standard laboratory batch equipment can have several shortcomings. Most notably, the reactive irradiation volume is limited as light penetration through a medium decreases exponentially with increasing path length (Beer−Lambert law). Consequently, photochemical reactions in batch mode occur most efficiently in the vessel region nearest the light source. This aspect can limit the application of photochemical processes in preparative chemical synthesis.

In recent years, flow chemistry has received considerable attention because of its advantages compared to batch mode.[13] Particularly noteworthy among these benefits is the potential of continuous flow reactors to overcome the traditional drawbacks of photochemistry.[14] We thus anticipated that the intermolecular trifluoroethylation reaction might be significantly accelerated due to the enhanced light penetration in the small channels of a flow reactor.

We decided to examine the photocatalytic addition of trifluoroethyl iodide to styrenes in continuous mode employing the setup depicted in Figure 1.

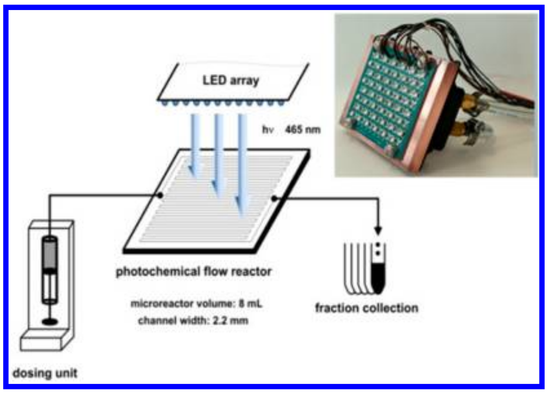


Figure 1. Flow photoreactor setup. The small insert shows the LED array used as a light source consisting of 48 high-power LEDs (λ_{max} = 465 nm) mounted on a water-cooled copper block for efficient heat dissipation.

The self-made flow reactor photobox consists of a single-channel syringe pump, a water-cooled array of 48 high-power light-emitting diodes (LEDs), and a mesoscale glass microreactor with integrated tempering.[15] The LED assembly has a total radiant flux of approximately 37 W and is placed 5 mm above the glass chip. These two components are encased in a protective box lined with silver glass mirrors for optimal reflectivity.

In an initial experiment, irradiation of a solution of *p*-methoxy-styrene in the flow reactor with residence time t_R = 30 min (flow rate = 0.267 mL min^{-1}) led to 65% conversion, and the product was isolated in 47% yield (66% brsm, Figure 2). Several reaction parameters were varied, including residence time, light intensity, and concentration, as well as catalyst loading and the amount of **1**. However, conversions > 65% could not be achieved, leading to the recovery of starting material along with the desired product in all cases. Significantly, a salient feature of the flow experiments is that they required residence times of only 30 min as compared to a reaction time of 24 h in batch mode, illustrating the significant acceleration enabled by the photobox system.

Encouraged by these promising results, we decided to revisit the intramolecular cobalt-catalyzed alkyl-Heck cyclizations previously reported[10] (Table 3). To our delight, the cyclizations were as efficient in flow as in batch mode and nearly identical isolated yields were

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(13) For recent reviews on microreactors and flow chemistry, see: (a) Yoshida, J.; Kim, H.; Nagaki, A. *ChemSusChem* **2011**, *4*, 331. (b) Wiles, C.; Watts, P. *Chem. Commun.* **2011**, *47*, 6512. (c) Wegner, J.; Ceylan, S.; Kirschning, A. *Chem. Commun.* **2011**, *47*, 4583. (d) Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, *1*, 675. For an essay on the merits of homogeneous reactions in continuous flow reactors, see: (e) Valera, F. E.; Quaranta, M.; Moran, A.; Blacker, J.; Armstrong, A.; Cabral, J. T.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2010**, *49*, 2478. (f) Kopach, M. E.; Murray, M. M.; Braden, T. M.; Kobierski, M. E.; Williams, O. L. *Org. Process Res. Dev.* **2009**, *13*, 152–160. For two recent examples of the use of flow reactors in chemical synthesis involving hazardous chemicals, see: (g) Gutmann, B.; Roduit, J.-P.; Roberge, D.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2010**, *49*, 7101–7105. (h) Palde, P. B.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 3525–3528.

(14) For a review on recent advances in microflow photochemistry, see: (a) Oelgemöller, M.; Shvydkiv, O. *Molecules* **2011**, *16*, 7522. For selected recent examples of photochemical reactions run in continuous flow mode, see: (b) Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 4144. (c) Nettekoven, M.; Püllmann, B.; Martin, R. E.; Wechsler, D. *Tetrahedron Lett.* **2012**, *53*, 1363. (d) Shen, B.; Bedore, M. W.; Sniady, A.; Jamison, T. F. *Chem. Commun.* **2012**, *48*, 7444. (e) Bou-Hamdan, F. R.; Seeberger, P. H. *Chem. Sci.* **2012**, *3*, 1612. (f) Sugimoto, A.; Fukuyama, T.; Sumino, Y.; Takagi, M.; Ryu, I. *Tetrahedron* **2009**, *65*, 1593. (g) Neumann, M.; Zeitler, K. *Org. Lett.* **2012**, *14*, 2658. (h) Andrews, R. S.; Becker, J. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 4140. For a recent book chapter on microphotochemistry, see: (i) Shvydkiv, O.; Oelgemöller, M. In *CRC Handbook of Organic Photochemistry and Photobiology*, 3rd ed., Vol. 1; Griesbeck, A., Oelgemöller, M., Ghetti, F., Eds.; CRC Press: 2012; pp 49−72.

(15) See the Supporting Information for more details.

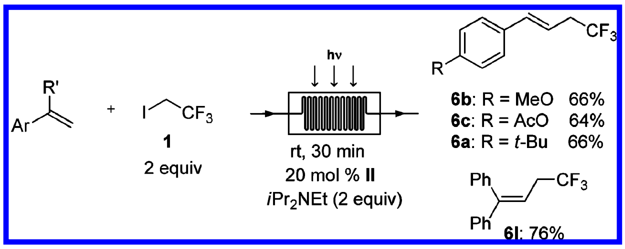
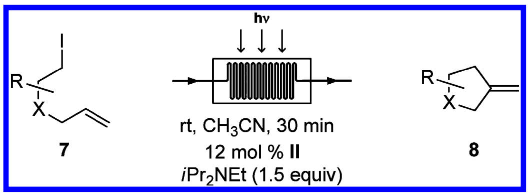
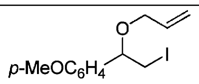
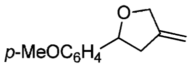
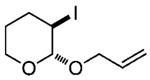
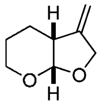
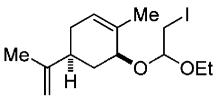
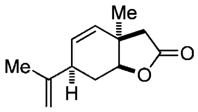


Figure 2. Trifluoroethylation in flow (yields based on recovered starting material).

Table 3. Cobalt-Catalyzed Alkyl-Heck Cyclization in Flow



entry	reactant	product	yield[a],[b]
1	 **7a**	 **8a**	96% (92%)
2	 **7b**	 **8b**	82% (82%)
3	 **7c**	 **8c**	80%[c] (83%)

[a] Yield of the isolated product. [b] Yield of the corresponding batch reaction in parentheses. [c] Isolated after Jones oxidation.

obtained. However, whereas the batch reactions required 24 h to reach completion, full consumption of the starting material required a residence time of only 30 min in the flow reactor.

We have previously run the reaction shown in entry 1 employing batch mode on 1 mmol scale and found that complete conversion was only achieved after 42 h. Conducting the reaction in flow on the same scale required a residence time of only 30 min. This corresponds to an 87-fold increase in productivity in flow as compared to batch (1.92 and 0.022 mmol/h, respectively).

In summary, we have developed a novel strategy for the synthesis of allylic trifluoromethanes from styrene derivatives using 2,2,2-trifluoroethyl iodide (**1**). It constitutes the first report of Co-catalyzed intermolecular trifluoroethylation of olefins using trifluoroethyl iodide. The method allows for direct access to this substrate class and should therefore simplify the evaluation of these compounds in the context of drug discovery. The trifluoroethylation of olefins reported herein provides an approach to the synthesis of allylic trifluoromethanes that is complementary to other existing strategies employing CF$_3$-transfer reagents. In addition, we have designed and assembled an advanced photochemical flow reactor. The use of the high-power LED array mounted on a water-cooled copper block leads to considerable acceleration of the cobalt-catalyzed processes, resulting in the notable productivity increase. Further studies aimed at improving the cobalt-catalyzed trifluoroethylation and alkyl-Heck cyclization in flow, as well as employing the powerful LED light source of the photobox system in a variety of other photochemical reactions, are currently underway in our laboratories and will be reported in due course.

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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.