

A Domino Approach of Heck Coupling for the Synthesis of β -Trifluoromethylstyrenes

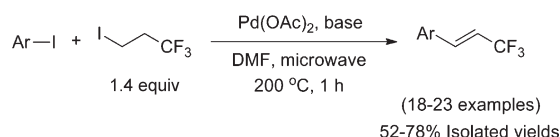
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ABSTRACT



A domino approach of Heck coupling was used to synthesize β -trifluoromethylstyrene derivatives from iodoarenes and 1-iodo-3,3,3-trifluoropropane in moderate to good yields. This method avoids the use of low-boiling, gaseous reagents such as 3,3,3-trifluoropropene, and additives and phosphines in the catalytic system.

The trifluoromethyl group is known for its ability to alter the lipophilicity, metabolic activity, and bioavailability of host compounds.¹ The electron-withdrawing nature of the trifluoromethyl group is also an added advantage for further chemical transformations as the electron density around the adjacent carbon center is altered. Specifically, the 3,3,3-trifluoropropenyl ($\text{CF}_3\text{CH}=\text{CH}-$) group has found important implications in medicinal chemistry and agricultural chemistry (insecticides) and has been found to impart volatility to aliphatic compounds.² Conjugated aromatic systems with trifluoromethyl groups such as β -trifluoromethylstyrene derivatives have found wide use in Organic Light Emitting Diodes (OLEDs) and in other material chemistry applications.³

The synthesis of β -trifluoromethylstyrene derivatives has been explored mainly by two different pathways.

One is by transition metal catalyzed trifluoromethylation of β -halostyrenes using various trifluoromethylating reagents (Figure 1, disconnection 1).⁴ The second approach involves both the traditional Horner reaction and reverse Wittig reaction (Figure 1, disconnection 2).^{2,5} The former approach requires access to β -halostyrenes and, in some cases, synthesis of the trifluoromethylating reagent as an added step. Latter approaches involve the synthesis of corresponding ylides, which can be cumbersome and require aldehydes as one of the starting components. In 1981, Fuchikami et al. reported the palladium catalyzed coupling of aromatic halides and 3,3,3-trifluoropropene to synthesize β -trifluoromethylstyrenes in high yields (Figure 1, disconnection 3).⁶ Unfortunately, the latter method requires the use of gaseous 3,3,3-trifluoropropene as a reaction component in an autoclave and the substrate scope is limited. In 2005, Vogel et al. reported⁷ another palladium catalyzed cross-coupling reaction between styrene (5 equiv) and trifluoromethanesulfonyl chloride to synthesize β -trifluoromethylstyrene

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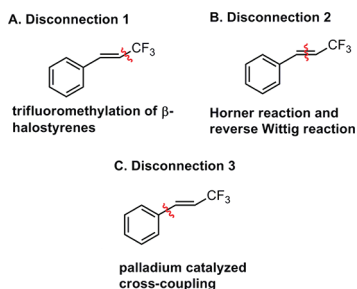


Figure 1. Previous approaches toward the synthesis of β -trifluoromethylstyrenes.

derivatives albeit in 50% yield, again with limited substrate scope.

We decided to synthesize β -trifluoromethylstyrenes using our recently reported⁸ domino Heck chemistry approach. This approach involves a palladium catalyzed Heck reaction between aryl halides and commercially accessible 1-iodo-3,3,3-trifluoropropane under highly basic conditions (>3 equiv). Under such conditions, 1-iodo-3,3,3-trifluoropropane undergoes dehydrohalogenation to produce 3,3,3-trifluoropropene (vinyl- CF_3) *in situ*, which would react with aryl halides with palladium(II) acetate as a catalyst to yield the desired β -trifluoromethylstyrenes.

There are many advantages with this approach. First, 1-iodo-3,3,3-trifluoropropane is a liquid at room temperature and hence can be easily handled. Second, the reaction setup does not require an autoclave or any other sophisticated equipment. Another advantage is that this reaction can be performed under microwave irradiation conditions, which reduces the reaction time drastically compared to other methods such as the one reported by Fuchikami et al. (14–97 h depending on substrate vs 1 h reported here). As will be seen later, the substrate scope of this reaction is broad, which increases its applicability in synthesizing various trifluoromethylated styrenes as potential monomers in polymer and material synthesis. Based on Fuchikami's report,⁶ we began our study of the optimization of the reaction conditions with methanol/water (1:1) as the solvent. As the Heck reaction usually requires high temperatures and long reaction times, we decided to carry out the reactions using a microwave reactor to try and reduce the reaction times. However, the reaction of 2-iodoanisole with 1-iodo-3,3,3-trifluoropropane in this solvent system with different bases (Li_2CO_3 , Na_2CO_3 , K_2CO_3 , and Cs_2CO_3) under microwave reaction conditions (150 °C, 1 h) yielded only up to 40% of the desired trifluoromethylated styrene. The poor yields could be a result of the steric bulk of the methoxy group. Accordingly, 3-iodotoluene was chosen as the substrate of choice for further optimization of reaction conditions.

To our delight, the reaction between 3-iodotoluene and 1-iodo-3,3,3-trifluoropropane using DMF as an aprotic, high dielectric constant solvent with K_2CO_3 (3.5 equiv) as base and $\text{Pd}(\text{OAc})_2$ (2 mol %) as catalyst in a microwave reactor at 200 °C for 1 h yielded the desired product in 83% conversion based on ^{19}F NMR analysis. Different palladium catalysts such as $\text{Pd}_2(\text{dba})_3$ and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ were also tested for their efficacy with no observed improvement in yields. Analysis of the results of various reactions yielded the optimized conditions for the title reaction, which were applied to a variety of substituted iodobenzenes. The results are shown in Table 1. Bromobenzene and chlorobenzene were also subjected to the same reaction under identical conditions. As expected, bromobenzene yielded the desired β -trifluoromethylstyrene product, albeit in 10% yield, and chlorobenzene did not give any of the desired product as evidenced by ^{19}F NMR analysis.

Iodobenzene gave the corresponding trifluoromethylstyrene in 76% isolated yield. Both electron-withdrawing and -donating substituents are well tolerated by this method; however electron-donating substituents tend to give slightly better yields than electron-withdrawing substituents. Steric effects also do not seem to affect the overall yield much (Table 1, entry 5 vs 6). 2-Aminoiodobenzene, which is generally known to poison palladium catalysts, possibly due to the lone pairs on the nitrogen atom (a Lewis base), surprisingly gave a 52% isolated yield of the corresponding trifluoromethylstyrene. However, 3-hydroxy and 2-carboxyl iodobenzene failed to give any of the desired product, which could be due to catalyst poisoning under the chosen reaction conditions.

In addition, heterocyclic iodoarenes also gave the desired trifluoromethylated styrenes in low to moderate yields (Figure 2). Previously unknown (*E*)-5-(3,3,3-trifluoroprop-1-en-1-yl)-1*H*-indole (**17**) could be an interesting compound for biological studies. 3-Iodopyridine gave moderate yield of the desired Heck-coupled product, but both 2-iodopyridine and 2-iodopyrazine did not show any reaction under the identical reaction conditions. Diiodoarenes gave the corresponding bis-(trifluoromethyl) styrene derivatives in moderate to good isolated yields (Figure 2), with the exception of 2,3,5,6-tetrafluoro-1,4-diiodobenzene, which did not show any reaction.

In all cases, isolated yields tend to be less than the NMR conversions due to either low boiling points of the products or difficulties in purification of crude products using column chromatography.

During the purification of **20**, another product **20a** was also isolated (8% yield). This product could be the result of two simultaneous reactions, Heck coupling at one position and aryl–aryl homocoupling (side reaction) occurring at the other position of 1,3-diiodobenzene. During optimization studies with iodobenzene as a substrate, we observed the formation of an interesting product under certain reaction conditions. Unfortunately, we were not able to isolate this product as a pure material. However, GC-MS analysis of the reaction mixture and crude product

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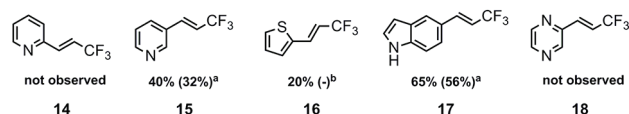
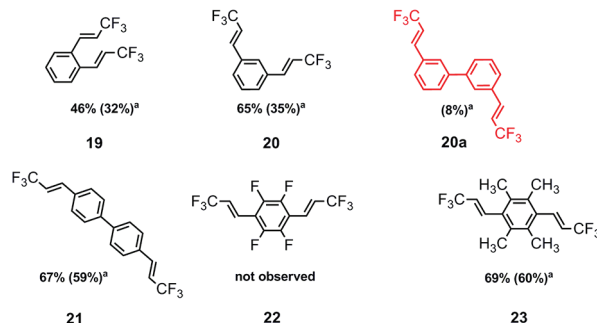
Table 1. Synthesis of β -Trifluoromethylstyrenes

$\text{Ar-I} + \text{I-CH}_2\text{CH}_2\text{CF}_3 \xrightarrow[\text{DMF, MW, 200 } ^\circ\text{C, 1 h}]{\text{2 mol\% Pd(OAc)}_2, \text{3.5 equiv K}_2\text{CO}_3}$ Ar-CH=CH-CF_3			
entry	Ar-I	product	^{19}F NMR conversion (%) ^a
1			83 (76)
2			57 (53)
3			63 (61)
4			0 (0)
5			68 (47)
6			63 (55)
7			73 (54)
8			65 (55)
9			61 (58)
10			61 (52)
11			50 (-) ^b
12			0 (0)
13			82 (78)

^a Isolated yield. ^b The product was formed in a 1:1 ratio along with PhCF₃.

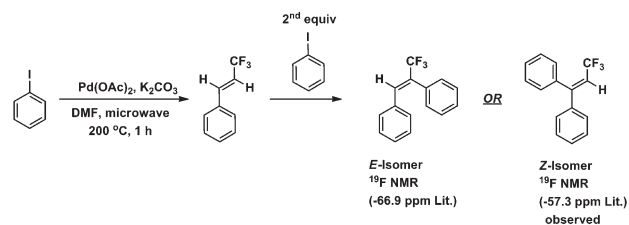
indicated it to be a “double” Heck product, probably resulting via an elimination–Heck–Heck domino reaction

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Heterocyclic compounds - % conversions by ^{19}F NMR**Bis(β -trifluoromethyl)styrenes - % conversions by ^{19}F NMR****Figure 2.** Heterocyclic and bis(β -trifluoromethyl)styrenes. ^aIsolated yield. ^bPure product was not obtained

sequence (Scheme 1).⁹ Crude ^{19}F NMR analysis of the reaction mixture suggested that the probable “double” Heck product could be exclusively the *Z*-isomer. This product was observed only as a minor product, and further studies to obtain this product as a major product under appropriate reaction conditions are underway.

In order to increase the efficacy of the reported method to synthesize β -trifluoromethylstyrenes, a better “contact” time between the gaseous 3,3,3-trifluoromethyl propene generated *in situ* and the palladium catalyst was thought to be necessary. This can be achieved by using an immobilized palladium catalyst, and further efforts are underway for the development of such a catalyst to increase the efficacy of the reported procedure for a scale-up synthesis of β -trifluoromethylstyrenes.

Scheme 1. Elimination–Heck–Heck Domino Reaction Pathway

In conclusion, herein, we report a very easy to perform, efficient, and simple method of synthesizing β -trifluoromethylstyrene derivatives using an elimination/Heck domino reaction sequence. Additionally, the reported method gives us access to some simple, interesting, and previously unknown β -trifluoromethylstyrenes. The method avoids the use of a gaseous 1,1,1-trifluoropropene reagent as one

of the reactants and shows a broader substrate scope than previously reported methods which involve Heck coupling as one of the steps.

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Supporting Information Available. General experimental procedure along with all the spectroscopic characterization of new compounds is included. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.