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Synthesis of 3-Aryl-2-(trifluoromethyl)indoles via Copper-Catalyzed Hydroarylation and Subsequent Cadogan Cyclization

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Abstract. The Copper-catalyzed hydroarylation of (trifluoromethyl)alkynes with (*o*-nitrophenyl)boronic acids selectively afforded trisubstituted (trifluoromethyl)alkenes bearing an *o*-nitrophenyl group. The obtained hydroarylation products were converted into 3-aryl-2-(trifluoromethyl)indoles in high yields via Molybdenum-catalyzed Cadogan cyclization. Similarly, the hydroarylation product prepared from (*o*-nitrophenyl)(trifluoromethyl)alkyne and (*p*-anisyl)boronic acid also underwent Cadogan cyclization, albeit with a longer reaction time, affording the desired indole product in a high yield.

Keywords: copper; molybdenum; fluorine; alkyne; indole

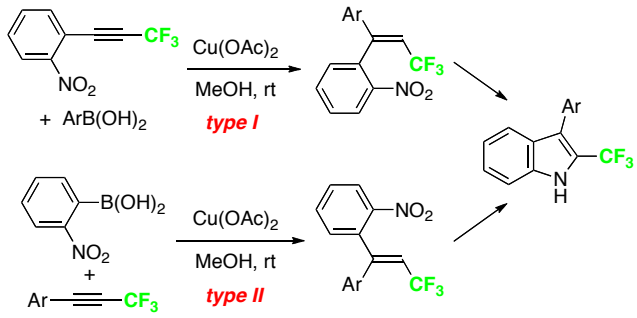
Fluoroalkyl-substituted indoles have received much attention as drug leads.[1] This is because indole is a privileged molecular scaffold for drug discovery[2] and the introduction of a fluoroalkyl substituent to a drug molecule can dramatically improve its pharmaceutical activity.[3] Therefore, various synthetic methods have been developed to access fluoroalkyl-substituted indoles.[1] However, the accessible indole derivatives are still limited. Thus, development of new strategies for the synthesis of fluoroalkyl-substituted indoles is a very important research objective.

We focused on the combination of Cu-catalyzed hydroarylation of (trifluoromethyl)alkynes and Cadogan cyclization, because it should provide a convergent route to 3-aryl-2-(trifluoromethyl)indoles. Among numerous indole-ring construction methods,[4] Cadogan cyclization is particularly useful, because *N*-unprotected indoles can be directly obtained via the deoxygenation of *o*-nitrostyrenes.[5] Therefore, we envisaged that our recently developed Cu-catalyzed hydroarylation of (trifluoromethyl)alkynes can be utilized for the regioselective synthesis of trisubstituted (trifluoromethyl)alkenes bearing an *o*-nitrophenyl group,[6] which can be further transformed to 3-aryl-2-(trifluoromethyl)indoles via Cadogan cyclization. The expected products are interesting as new drug leads, because several biological activities have been reported for the parent 3-phenylindole.[7] To the best of our knowledge, only one example of the synthesis of 5,6-dichloro-2-(trifluoromethyl)indole using Cadogan cyclization has been reported.[8] Thus, the application of Cadogan cyclization to the synthesis of other trifluoromethylated indoles is underdeveloped.

Several precedents have been mentioned in literature for the synthesis of 3-aryl-2-(trifluoromethyl)indoles. Nevertheless, aryl groups at the 3 position have been limited to the parent phenyl and *p*-anisyl groups.[9] ~~Nevertheless,~~ Konno and coworkers reported the cycloaddition of aryl(trifluoromethyl)alkynes and *o*-iodoanilines with a wider scope for the 3-aryl groups; however, 3-aryl-2-(trifluoromethyl)indoles and 2-aryl-3-(trifluoromethyl)indoles were produced with low selectivities.[10] Later, a regioselective method using Fischer indole synthesis was developed, even though the product yields were not always high (most yields were below 70%).[11] Thus, a general and regioselective synthetic method needs be developed.

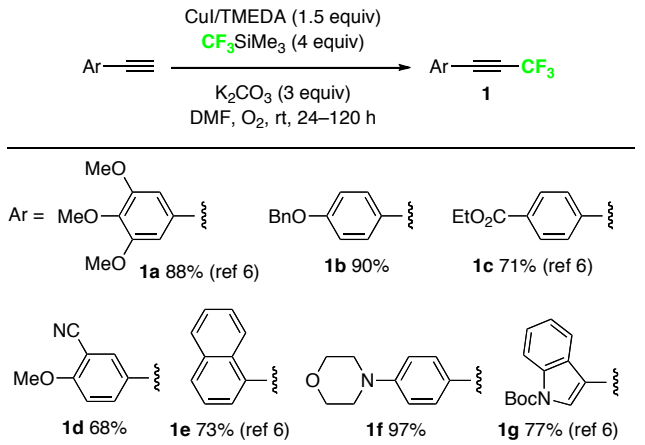
Our study started by investigating the Cu-catalyzed hydroarylation of (trifluoromethyl)alkynes with arylboronic acids to synthesize *o*-nitrophenyl-substituted (trifluoromethyl)alkenes as the Cadogan cyclization precursors (Scheme 1). Two hydroarylation routes were envisaged: (i) the hydroarylation of (*o*-nitrophenyl)(trifluoromethyl)alkyne with arylboronic acids (type I) and (ii) the hydroarylation of (trifluoromethyl)alkynes with (*o*-nitrophenyl)boronic acid (type II). Although these two methods produce mutually opposite stereoisomers, subsequent Cadogan cyclization is expected to afford the desired indole products irrespective of the stereochemistry of the precursors. Type I route seemed to be promising because we previously reported that the Cu-catalyzed hydroarylation of 3-(*o*-nitrophenyl)propiolates with

arylboronic acids and subsequent Cadogan cyclization of the resultant 3,3-diarylacrylate products afforded 3-arylindole-2-carboxylates.[12] However, the synthetic method for (*o*-nitrophenyl)(trifluoromethyl)alkyne is strictly limited,[13] even though various efficient methods have been developed for the synthesis of (trifluoromethyl)alkynes.[14] Thus, we commenced our study by investigating type II protocol.



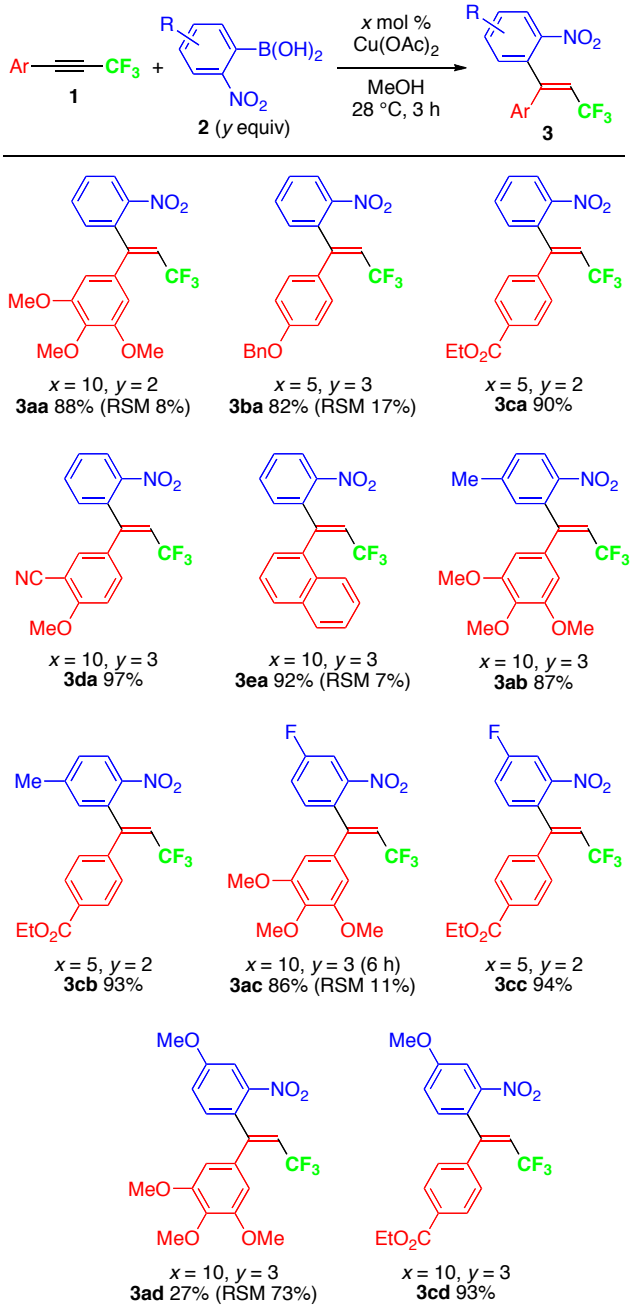
Scheme 1. Two possible routes to Cadogan cyclization precursors using Cu-catalyzed hydroarylations of (trifluoromethyl)alkynes.

(Trifluoromethyl)alkynes **1** used for type II hydroarylation were prepared from the corresponding terminal alkynes using the modified Evano–Blanchard procedure (Scheme 2).[6.15] New (trifluoromethyl)alkynes **1d** and **1f** were obtained in 68% and 97% yields, respectively.



Scheme 2. Preparation of (trifluoromethyl)alkynes used for type II hydroarylation.

Similar to our previous study, several aryl(trifluoromethyl)alkynes **1** reacted with 2–3 equiv of (*o*-nitrophenyl)boronic acid (**2a**, R = H) in the presence of 5–10 mol % $Cu(OAc)_2$ in methanol at room temperature for 3 h (Scheme 3). The reactions of alkyne substrates **1a** bearing an electron-donating 3,4,5-trimethoxyphenyl substituent afforded hydroarylation product **3aa** in 88% yield, even though a 10 mol % catalyst loading was required. The hydroarylation of **1b** bearing a less electron-donating *p*-benzyloxyphenyl terminal effectively proceeded with a decreased catalyst loading of 5 mol %, affording **3ba** in 82% yield. In this case, an increased catalyst loading (10 mol %) led to a lower conversion.

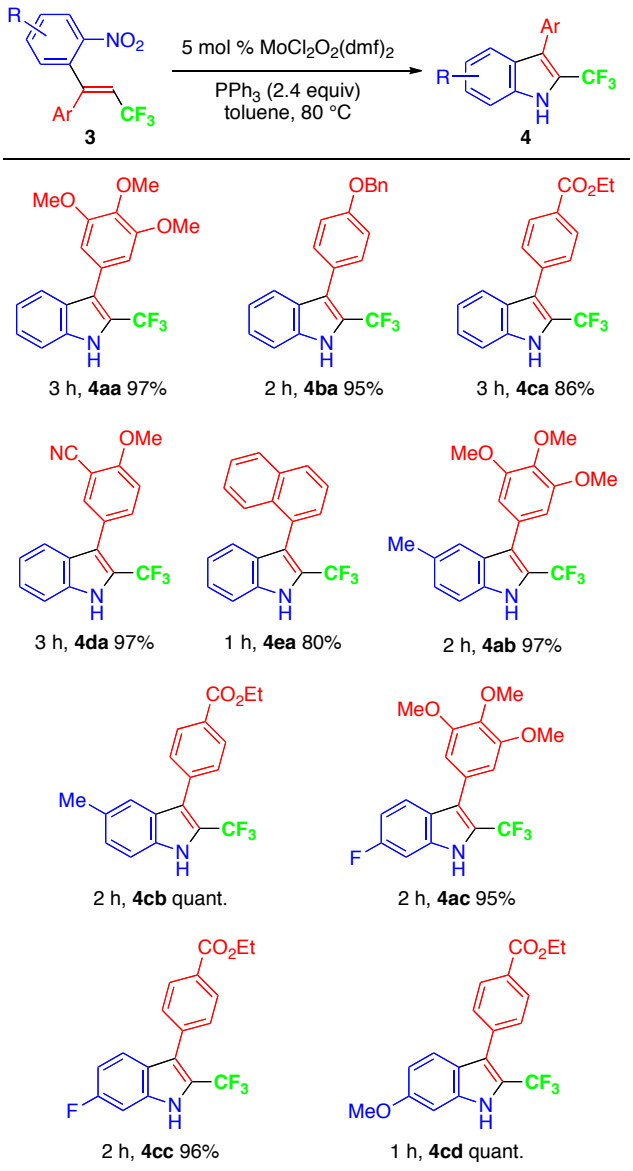


Scheme 3. Cu-catalyzed hydroarylations of aryl(trifluoromethyl)alkynes **1** with *o*-nitrophenylboronic acids **2**.

The reaction of alkyne **1c** bearing an electron-withdrawing ethoxycarbonyl group on the phenyl terminal afforded **3ca** in 90% yield, even though the amount of **2a** was reduced to 2 equiv. Moreover, hydroarylation products **3da** and **3ea** bearing 3-cyano-4-methoxyphenyl and 1-naphthyl groups,

respectively, were also obtained in high yields. In striking contrast, alkyne substrates **1f** and **1g** bearing a morpholine and 3-indolyl moiety, respectively, hardly produced the corresponding hydroarylation products. Thus, a highly electron-donating aryl terminal is detrimental for the Cu-catalyzed hydroarylation.

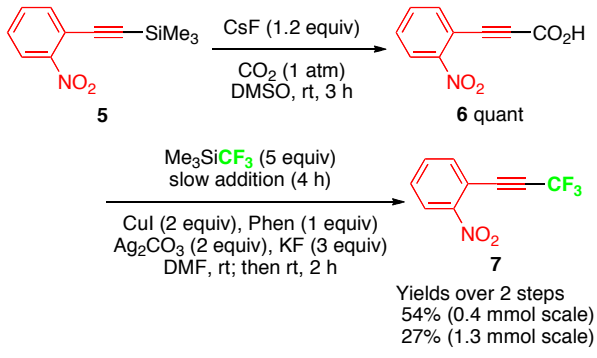
The Cadogan cyclization of type-II hydroarylation products was investigated (Scheme 4). In the original Cadogan cyclization, $P(OEt)_3$ was used as both the deoxygenation reagent and solvent under harsh reaction conditions.[5a,b] Later, modified reaction conditions using PPh_3 as the stoichiometric deoxygenation reagent were reported.[5d] Moreover, the development of a Mo-catalyzed method enabled to perform the Cadogan cyclization at a lower reaction temperature.[5e] We previously synthesized 3-arylindole-2-carboxylates under modified Cadogan conditions using $P(^nBu)_3$ or the molybdenum catalyst with PPh_3; the latter conditions gave better yields.[12] Therefore, the Mo-catalyzed Cadogan cyclization was applied to the trifluoromethyl-substituted hydroarylation products.



Scheme 4. Mo-catalyzed Cadogan cyclization of type-A hydroarylation products **3** leading to 3-aryl-2-(trifluoromethyl)indoles **4**.

In the presence of $MoCl_2O_2(dmf)_2$ (5 mol %) and PPh_3 (2.4 equiv), hydroarylation products **3aa–3ea** were heated in toluene at 80 °C for 1–3 h, affording the corresponding 3-aryl-2-(trifluoromethyl)indoles **4aa–4ea** in 80–97% yields. Thus, the Cadogan cyclization step tolerates both electron-donating and electron-withdrawing substituents, and reactive ester and cyano groups. Moreover, the presence of substituents on the nitrophenyl ring did not affect the Cadogan cyclization; hydroarylation products **3ab**, **3cb**, **3ac**, **3cc**, and **3cd** were also transformed to the corresponding indole products in excellent yields over 95%.

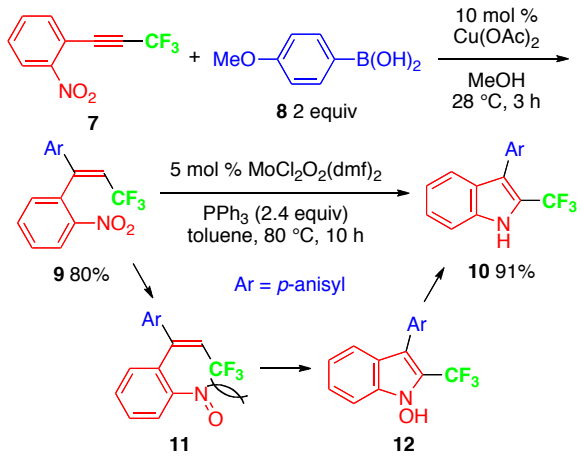
Next, type I route was investigated to synthesize 3-aryl-2-(trifluoromethyl)indoles. However, the required substrate, 1-nitro-2-(3,3,3-trifluoroprop-1-ynyl)benzene (**7**), could not be obtained from the corresponding terminal alkyne using the same preparation method for other (trifluoromethyl)alkynes **1a–g**.[16] According to the previous reports, **7** can be prepared by condensation of *o*-nitrobenzaldehyde with CX_3CF_3 followed by dehydrohalogenation,[13a] or by the Cu/Ag-mediated decarboxylative trifluoromethylation of propiolate **6**.[13b] Because the former requires harmful reagents such as freons and hydrazine hydrate), the feasibility of the latter method was investigated (Scheme 5). Precursor **6** was quantitatively obtained via the carboxylation of silylalkyne **5** following the Kondo's procedure.[17] The obtained carboxylic acid was directly used in the next trifluoromethylation step without purification. Consequently, the desired **7** was obtained in 54% yield at the 0.4-mmol scale. Although the yield could be reproduced at this scale, the same procedure repeated at the 1.3-mmol scale afforded **7** in a much lower 27% yield.



Scheme 5. Preparation of (trifluoromethyl)alkyne **7**.

Then, the hydroarylation of **7** and subsequent Cadogan cyclization were briefly investigated (Scheme 6). The reaction of **7** with (*p*-anisyl)boronic acid (**8**, 2 equiv) smoothly proceeded in the presence of 10 mol % $Cu(OAc)_2$ in MeOH at room

temperature, affording hydroarylation product **9** in 80% yield.[18] Subsequently, **9** was subjected to the Mo-catalyzed Cadogan cyclization under standard conditions, affording the desired indole product **10** in 91% yield. Notably, the complete conversion of **9** required 10 h, even though the Cadogan cyclization of type II hydroarylation products **3** completed at the most within 3 h. Several mechanisms have been proposed for Cadogan cyclization. Based on previous reports and theoretical calculations, Houk *et al.* suggested that the deoxygenation of the nitro group generates a nitroso intermediate such as **11**, which undergoes 6π electrocyclization.[5c] Subsequent reduction of the resultant *N*-hydroxyindole such as **12** affords the final indole product. For the Cadogan cyclization of **9**, steric and electronic repulsions between the CF_3 substituent and nitroso group hinder the electrocyclization step.



Scheme 6. Type-I hydroarylation of **7** with **8** and subsequent Cadogan cyclization of **9.**

In conclusion, we developed a new method for the synthesis of 3-aryl-2-(trifluoromethyl)indoles from (trifluoromethyl)alkynes and arylboronic acids. To achieve this goal, two types of hydroarylation were investigated: (i) the reaction of (*o*-nitrophenyl)(trifluoromethyl)alkyne with an arylboronic acid (type I) and (ii) the reaction of aryl(trifluoromethyl)alkynes with (*o*-nitrophenyl)boronic acids (type II). Subsequent Cadogan cyclizations of the obtained hydroarylation products afforded the desired 3-aryl-2-(trifluoromethyl)indoles in good overall yields. However, type II method is preferable over type I method because of the availability of (trifluoromethyl)alkyne substrates and the efficiency of Cadogan cyclization.

Experimental Section

General procedure for preparation of (trifluoromethyl)alkynes. Synthesis of 2-methoxy-5-(3,3,3-trifluoroprop-1-ynyl)benzonitrile (1d): CuI (1.15 g, 6.0 mmol), TMEDA (894 μL, 6.0 mmol), and K_2CO_3 (1.66 g, 12.0 mmol) was stirred in dry DMF (18.9 mL) at room temperature under an O_2 atmosphere for 15 min. After the addition of CF_3SiMe_3 (1.25 mL, 8.0 mmol), the mixture was stirred for 1.5 h and was cooled to 0 °C. To this mixture was added a solution of 5-ethynyl-2-methoxybenzonitrile (628 mg, 4.0 mmol) and CF_3SiMe_3 (1.25 mL, 8.0 mmol) in dry DMF (18.9 mL) via a cannula, and the resultant mixture was stirred at 0 °C for 30 min and then at room temperature for 24 h. The reaction was quenched by adding H_2O (50 mL) at 0 °C. The reaction mixture was extracted with Et_2O (2 × 50 mL). The combined organic layer was washed with H_2O (3 × 50 mL) and brine (50 mL) and was dried over $MgSO_4$. The solvents were evaporated in vacuo, and the obtained crude product was purified by silica gel column chromatography (hexane:AcOEt = 100:0~85:15) to afford **1d** (610 mg, 68% yield) as a colorless solid (mp 66.9–68.7 ˚C).

General procedure for hydroarylation. Synthesis of (E)-1,2,3-trimethoxy-5-(3,3,3-trifluoro-1-(2-nitrophenyl)prop-1-enyl)benzene (3aa): A degassed solution of **1a** (130 mg, 0.5 mmol), **2a** (167 mg, 1.0 mmol), and $Cu(OAc)_2$ (9.27 mg, 0.05 mmol) in dry MeOH (1 mL) was stirred at 28 °C under an argon atmosphere for 3 h. The reaction mixture was diluted with AcOEt (3 mL) and filtered through a pad of alumina. The filtrate was concentrated in vacuo and the obtained crude product was purified by silica gel column chromatography (hexane:AcOEt = 100:0~85:15) to afford **3aa** (169 mg, 88% yield) as a light-yellow solid (mp 119.7–121.4 °C).

General procedure for Cadogan cyclization. Synthesis of 2-(trifluoromethyl)-3-(3,4,5-trimethoxyphenyl)-1H-indole (4aa): A solution of **3aa** (115 mg, 0.30 mmol), $MoCl_2O_2(dmf)_2$ (5.18 mg, 0.015 mmol), and PPh_3 (195 mg, 0.72 mmol) in toluene (3.0 mL) was degassed at –78 °C and then was stirred at 80 °C under an argon atmosphere for 3 h. The reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane:AcOEt = 100:0~85:15) to give indole **4aa** (102 mg, 97% yield) as a colorless solid (mp 119.7–120.6 °C).

Acknowledgements

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