

Cu-Pd Dual Catalyst System for Amide Styrylation Reaction from Potassium Styryltrifluoroborates and Amides

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Abstract

An interesting reaction procedure for the cross-coupling of potassium styryltrifluoroborates and amides has been developed by using PdCl₂(d'bpf)-CuI dual catalyst system. By applying this method, good numbers of amide styrylation products are formed in 85% - 92% yields.

Keywords

Amide Styrylation Reaction, Dual Catalyst, Microwave

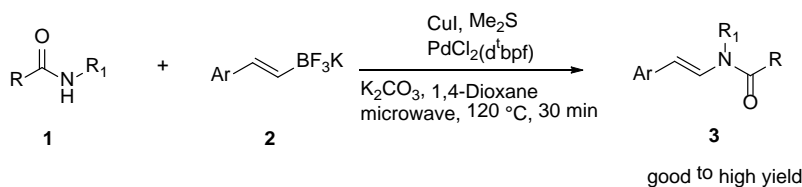
1. Introduction

Nitrogen containing compounds are important because of their presence in natural products, their presence in synthetic organic products, and they display wide-range of functionalities. The formation of the C-N bond is important as it opens avenues for introducing nitrogen in organic molecules. Buchwald and Hartwig have separately developed successful metal complexes and ligands for the construction of C-N bonds using transition metal-catalyst [1]-[7]. Although significant progress has occurred in this field, the formation of C-N bond through amide styrylation reaction has not been animated by many chemists. The pioneering work by Buchwald's group on palladium-catalyzed intermolecular amidation of aryl halides and effective use of Xantphos as ligand is promising [8]. In another development, Buchwald showed the copper-catalyzed amidation of vinyl halides and the effective use of N,N'-dimethyl ethylene diamine ligand [9]. Hartwig also reported the ligand effect of P(^tBu)₃ and Pd-catalyzed intermolecular cross-coupling of aryl bromides and chlorides with *tert*-butyl carbamate [10]. Other groups also reported palladium-catalyzed amide arylation reactions

[11] [12] [13]. In our ongoing process in making C-N bond formation reactions by cross-coupling of styryltrifluoroborates and sodium nitrite as well as from aryltrifluoroborates and bismuth nitrate [14] [15] [16], we tried to explore amide styrylation reaction by introducing potassium styryltrifluoroborates and various amides. In this work, we have originated copper-palladium dual catalyst system for the successful amide styrylation reaction between styryltrifluoroborates and amides (**Scheme 1**).

2. Results and Discussion

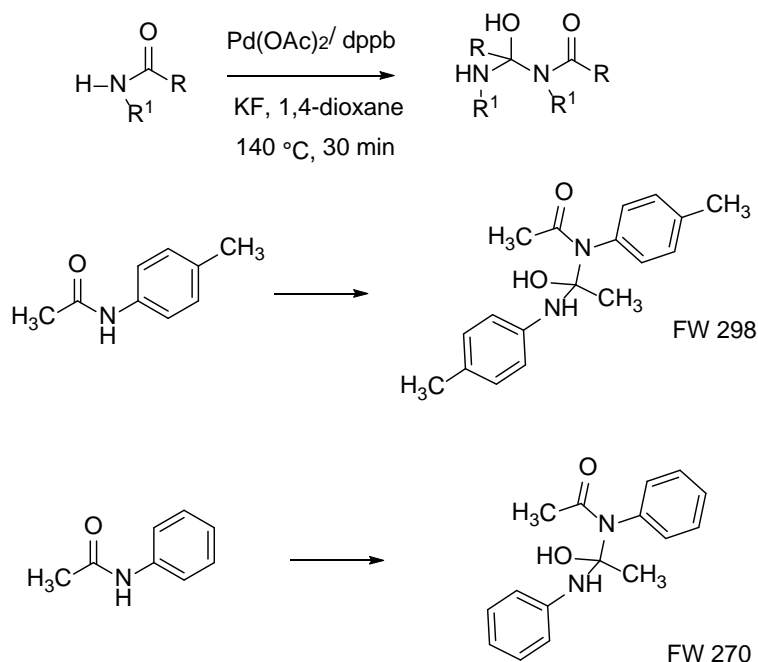
Various aromatic and aliphatic amides were used as N-H source because of the tendency of N-H bond to leave proton due to the electronegativity difference between nitrogen and hydrogen. We employed many palladium complexes as catalysts and solvent system in single catalyst method to find an effective catalyst system. Also, various ratios of amides and potassium styryltrifluoroborates were applied while the base system and number of bases were varied simultaneously. Due to the encouraging catalytic effect of $\text{PdCl}_2(\text{d}^t\text{ppf})$ complex in cross-coupling reaction, we concentrated on dppf coordinated palladium complexes for amide styrylation along with other palladium complexes. None of them worked amidation, but the dppf complexes showed the formation of aldol type products from amides instead of new C-N bonded amide styrylation product. Some of the aldol type observations are shown in (**Figure 1**). Formations of aldol product were observed in GC-MS and NMR analysis (**Scheme 2**).



Scheme 1. Cu-Pd dual catalyst system for amide styrylation reaction.

Solvents	Catalyst	Base	Temperature	Cross-coupling
THF-H ₂ O	$\text{PdCl}_2(\text{dppf})\text{CH}_2\text{Cl}_2$	K_2CO_3	120 °C	None
ⁱ PrOH-H ₂ O	$\text{Pd}(\text{dba})_3\cdot\text{CHCl}_3/\text{dppf}$	K_2CO_3	140 °C	None
ⁱ PrOH-H ₂ O	$\text{PdCl}_2(\text{d}^t\text{ppf})$	NaO^iBu	100 °C	None
Toluene	$\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$	NaO^iBu	120 °C	None
1,4-Dioxane	$\text{Pd}(\text{OAc})_2/\text{dppf}$	Hunig's Base	140 °C	None
Toluene	$\text{Pd}(\text{OAc})_2/\text{Xantphos}$	NaO^iBu	120 °C	None
1,4-Dioxane	$\text{PdCl}_2(\text{d}^t\text{ppf})$	NaO^iBu	140 °C	None
1,4-Dioxane	$\text{PdCl}_2(\text{d}^t\text{ppf})$	K_2CO_3	140 °C	None

Figure 1. Some examples of single catalyst method for amide styrylation.



Scheme 2. Aldol type product.

In the course of these studies, we struggled to establish single catalyst system for amide styrylation reaction, consequently we screened dual catalyst system [17]. The palladium chloride complex $[\text{PdCl}_2(\text{d'bpf})]$ is a useful palladium complexes which has been successfully applied as a catalyst in recent years in various organic transformations involving potassium organotrifluoroborates [18] [19] [20] [21]. The higher bite angle of P-Pd-P in $\text{PdCl}_2(\text{d'bpf})$ improves its effectiveness to be used as catalyst [22] [23] [24]. Among other available complexes, this palladium complex illustrates better catalytic effect for C-N bond formation with styryltrifluoroborates. Copper iodide is another catalyst we chose for our dual catalyst system because of its low cost and effective catalytic activity on cross-coupling. The N-H bond of amide first activated with Cu-catalyst to form Cu-species and C-BF₃K bond of styryltrifluoroborates activated separately with Pd-catalyst to get Pd-species in the presence of a proper amount of solvent and base. Then Cu-species was transferred into Pd-species and the resulting mixture was microwaved (300 W) at 120°C for 30 minutes. The successful results for this new process for amide styrylation reaction are summarized in **Figure 2**.

The solid product was isolated in good yields. This isolated product was pure enough to use for analysis without further purification. The cross-coupled conjugated amide products with new C-N bond seemed to be very reactive. When the reaction products were subjected to silica gel chromatography for purification TLC and NMR clearly showed decomposition. Even when the reaction product was subjected to neutral alumina chromatography instead of silica gel, no significant improvement for the product purification was observed. In two cases (**Figure 2**, Entries 7, 8), we were able to collect products by column chromatography.

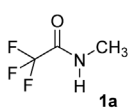
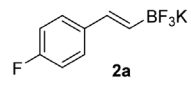
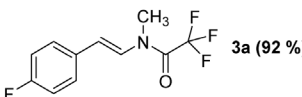
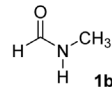
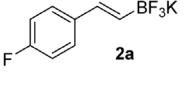
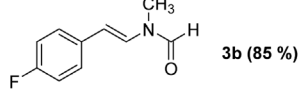
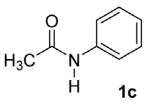
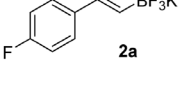
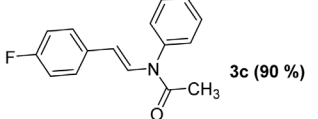
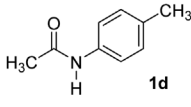
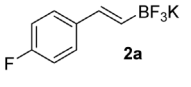
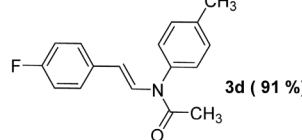
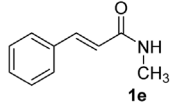
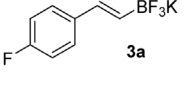
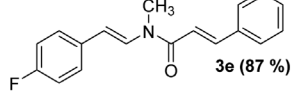
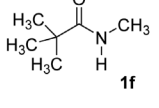
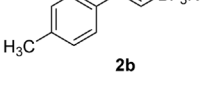
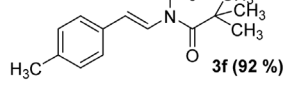
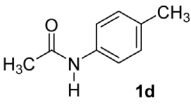
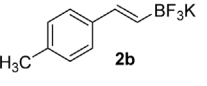
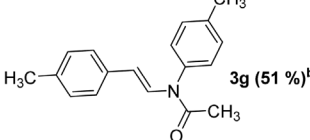
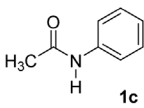
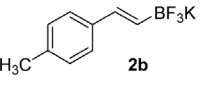
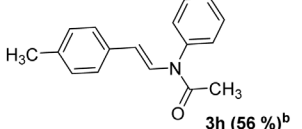
Obs	Amides	StyrylBF ₃ K	Cross-coupling product ^a
1	 1a	 2a	 3a (92 %)
2	 1b	 2a	 3b (85 %)
3	 1c	 2a	 3c (90 %)
4	 1d	 2a	 3d (91 %)
5	 1e	 3a	 3e (87 %)
6	 1f	 2b	 3f (92 %)
7	 1d	 2b	 3g (51 %)^b
8	 1c	 2b	 3h (56 %)^b

Figure 2. Cu-dual catalyst system for amide styrylation reaction^a. ^aThe reaction products were collected after filtered through celite pad twice and dried under vacou over night Column Chromatography attempts were unsuccessful. ^bThe products **3g** and **3h** are separated by silica get chromatography.

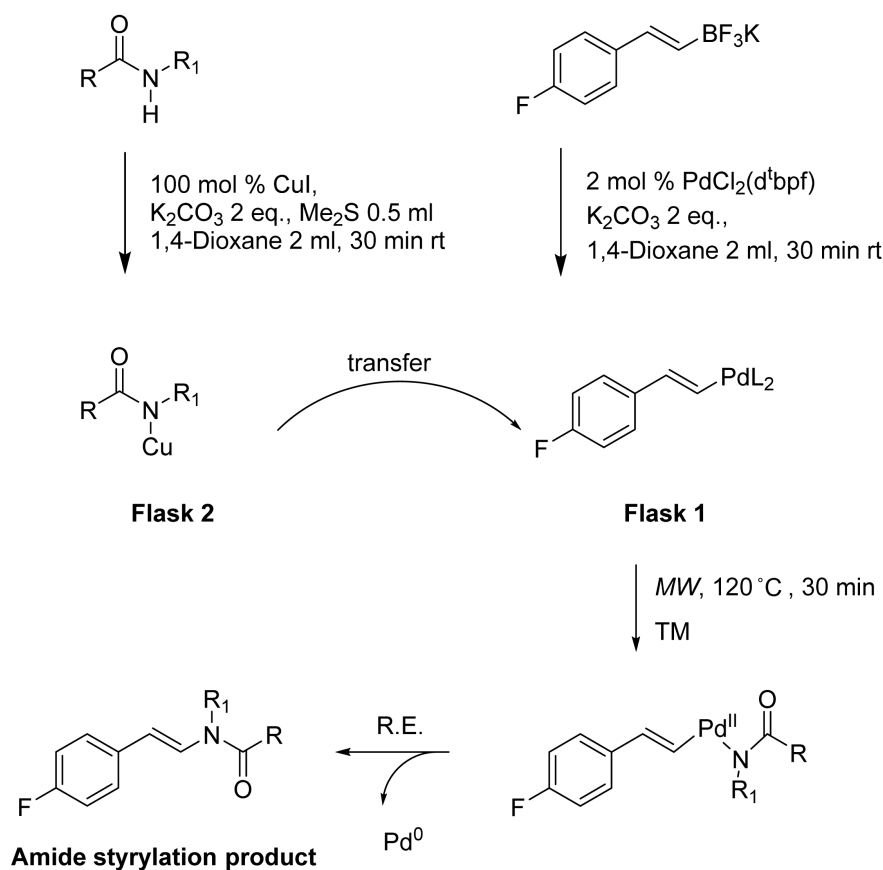
graphy but yields reduced significantly. A combined NMR study of ¹H NMR, ¹³C NMR, and ¹⁹F NMR confirmed the formation of new C-N bonded cross-coupled amides. A series of reactions were run by using various potassium styryltrifluoroborates and amides as an N-H source. **Figure 2** shows the successful series of amide styrylation reaction products from amides and styryl-trifluoroborates.

In ¹H NMR of product **3a**, δ value H_a and H_b are 7.37 ppm and 6.19 ppm re-

spectively but in starting material of 4-fluoro-styryltrifluoroborates, these peaks show at 6.20 and 6.15 ppm. The chemical shift to downfield is an indication that carbon attached to H_a now bonded with more electronegative nitrogen. Also, the ¹⁹F NMR of product **3a** confirmed the presence of 2 (two) fluorine peak (−76.4 ppm for CF₃ and −114.9 ppm for p-F-C₆H₄-). In starting material of 4-fluoro-styryltrifluoroborates, p-F-C₆H₄-appears at −119.5 and BF₃K at −141.8 ppm. [In case of p-F-C₆H₄-BF₃K, Reported ¹⁹F (data are −118.6 and −139.1 by Molander group) [25] [26] Little variation in ppm may be the effect of solvents and styryl moiety.]

Amide styrylation reaction via cross-coupling of potassium styryltrifluoroborates with amides is a new addition to Buchwald's amide arylation reaction from aryl halides and amides. The probable reaction mechanism of this reaction is shown in **Scheme 3**.

Our research employs microwave irradiation to underpin N-H activation of amides and cross-coupling with potassium styryltrifluoroborates forming ena-mides which are building blocks of a vast range of industrial pharmaceuticals, intermediates, agrochemicals, and biological functionalities. This work also demonstrates a novel application of dual catalyst system of PdCl₂(d^tbpf) and CuI for effective cross-coupling of styryltrifluoroborates and amides.



Scheme 3. Dual catalyst for Amide styrylation reaction.

3. Procedure

After careful screening reagents (molar ratio, amount of catalyst, solvent, Me₂S for dissolving CuI, temperature, time) used in experiments to optimize the reaction conditions, the best condition found was one equivalent of amides and one equivalent of styryltrifluoroborates. The reaction scale was 0.5 mmol. After purging with argon to remove air, two microwave reaction flasks with magnetic stirrer bar in each were prepared. Flask 1 was loaded with 0.5 mmol of potassium styryltrifluoroborates (90% pure), 2 mol% of PdCl₂(d'bpf), and 2 equiv. of anhydrous K₂CO₃. The mixture was then capped and again purged with argon followed by adding 2 ml of dry 1,4-dioxane under argon atmosphere and allowed to stir for 30 min at room temperature. Flask 2 was similarly loaded with 0.5 mmol of amide, 100 mol% of CuI catalyst, and 2 equiv. of K₂CO₃ as base. Then flask was capped and flushed with argon followed by the addition of 0.5 ml of Me₂S and 2 ml of 1,4-dioxane. The mixture was then allowed to stir for 30 min at room temperature. This 30-min stirring was necessary before transferring the Cu-species into Pd-species. The solution of Cu complex was then added to the Pd complex solution by using cannula. After microwave irradiation, the crude reaction product was subjected to standard extraction with 100 ml of diethyl ether, 50 ml of brine solution, and 25 ml of ammonium chloride. The separated organic layer was dried over anhydrous Na₂SO₄ and again filtered through celite twice to remove unwanted impurities. The filtrate was then evaporated by using rotary evaporator and the concentrated product was allowed to dry for overnight under vacuum pump for the removal of the solvents completely.

Formation of cross-coupling product **3a** is the representative one. **Flask 1** was loaded with 126 mg (0.5 mmol) of potassium trans-2-(4-fluorophenyl)-vinyltrifluoroborates (90% pure), 6.5 mg (2 mol%) of PdCl₂(d'bpf), and 138.21 mg (2 equiv.) of anhydrous K₂CO₃. The mixture was then capped and again purged with argon. Argon flashed flask was then loaded with 2 ml of 1,4-dioxane under inert atmosphere and allowed to stir for 30 min at room temperature. **Flask 2** was similarly loaded with 65.0 mg (0.5 mmol) of N-methyltrifluoroacetamide, 95.22 mg (100 mol%) of CuI catalyst and 138.21 mg (2 equiv.) of K₂CO₃ as base. Then flask was capped and flushed with argon followed by the addition of 0.5 ml of Me₂S and 2 ml of 1,4-dioxane. The mixture then was allowed to stir for 30 min at room temperature. The solution of Cu-complex was then added to the Pd-complex solution by using cannula. The resulting mixture was microwaved at 120°C for 30 min. ¹H NMR (Acetone-d₆, 400 MHz): δ (ppm): **3a**, 7.57 - 7.12 (m, 4H), 7.37 (d, J = 16.0 Hz, 1H), 6.19 (d, J = 16.0 Hz, 1H), 3.60 (s, 3H); **3b**, 7.42 - 6.85 (m, 4H), 7.24 (d, J = 15.0 Hz, 1H), 6.03 (d, J = 16.0 Hz, 1H), 2.92 (s, 3H); **3c**, 7.38 - 6.93 (m, 9H), 7.22 (d, J = 16.0 Hz, 1H), 6.04 (d, J = 16.0 Hz, 1H), 1.93 (s, 3H); **3d**, 7.54 - 7.12 (m, 8H), 7.40 (d, J = 16.0 Hz, 1H), 6.20 (d, J = 16.0 Hz, 1H), 2.27 (s, 3H), 2.10 (s, 3H); **3e**, 7.59 (d, J = 16.0 Hz, 1H), 7.58 - 7.13 (m, 9H), 7.38 (d, J = 16.0 Hz, 1H), 6.77 (d, J = 16.0 Hz, 1H), 6.22 (d, J = 16.0 Hz, 1H), 3.60 (s, 3H); **3f**, 7.41 - 6.99 (m, 4H), 7.19 (J = 16.0 Hz, 1H), 6.19 (d, J = 16.0 Hz), 2.71

(s, 3H), 2.32 (s, 3H), 1.16 (s, 9H); **3g**, 7.53 - 6.92 (m, 9H), 7.40 (d, $J = 16.0$ Hz, 1H), 6.19 (d, $J = 176.0$ Hz, 1H), 2.32 (s, 3H), 2.07 (s, 3H); **3h**, 7.42 - 6.91 (m, 8H), 7.39 (d, $J = 16.0$ Hz, 1H), 6.18 (d, $J = 1$ Hz), 2.33 (s, 2×3 H), 2.07 (s, 3H).

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