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Copper(II) Fluoride a New Efficient Promoter of Chan-Lam-Evans Coupling

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RESEARCH ARTICLE

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Abstract

The Chan-Lam-Evans coupling is the copper(II) acetate promoted reaction of phenols and boronic acids producing diaryl ethers. In this paper a modification of the original reaction is reported using copper(II) fluoride reagent which gives higher yields than copper(II) acetate. The most significant increase in yield was observed in formation of sterically hindered phenols. We hypothesize that fluoride ions help to cleave the boron-carbon bond. The novel method is suitable for selective, efficient and economical synthesis of diaryl ether compounds under mild conditions.

Keywords

cross coupling, copper(II) fluoride, boronic acid, diaryl ether

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1 Introduction

Several natural and biologically active substances are diaryl ethers, therefore the development of efficient methods for their preparation is an actively studied topic. [1] Diaryl ethers may be synthesized by *Ullmann* ether synthesis [2] or *Hartwig-Buchwald* coupling [3], however both require vigorous reaction conditions. The copper(II) acetate promoted coupling of arylboronic acids and phenols under mild conditions was reported independently by *Evans* [4] and *Chan* [5]. Several copper salts were tested and copper(II) acetate proved to be most efficient. However, some other promoters including $Cu(OTf)_2$ and Cu_2O were also described [6,7]. In most cases the promoter is used in equimolar quantity and also oxygen from air is necessary.

Fluoride ions are known to assist the *Suzuki* [8], *Stille* [9] and *Hiyama* [10] cross-coupling reactions, by cleaving the carbon-heteroatom bond in the transmetallation step of the reactions. In this article we report the application of copper(II) fluoride reagent in the *Chan-Lam-Evans* coupling.

2 Results and Discussion

The transmetallation step of the hypothesized reaction mechanism of *Chan-Lam-Evans* coupling is shown on Fig. 1. In our experiments, pyridine served both as ligand and as base. It could be assumed that boronic acid reacted with the copper(II) complex through a cyclic transition state (Fig. 1a). The cleavage of the boron-carbon bond might be assisted by the acetate ligand of the complex, by forming a neutral leaving species. Because fluoride ion proved to be efficient in other coupling reactions [8,9,10] we performed the transmetallation step with copper(II) fluoride (Fig. 1b). According to the proposed mechanism, the reductive elimination step is indifferent to the counter anion of copper.

In the fluoride assisted coupling reactions, fluoride ion usually stems from cesium fluoride. In the case of the copper salt promoted reactions, however, use of the cesium salt is not necessary since copper(II) fluoride is commercially available. CuF_2 was applied as catalyst in oxidation of aldehydes, [11] stereoselective reduction of ketones [12] and *N*-arylations. [13]

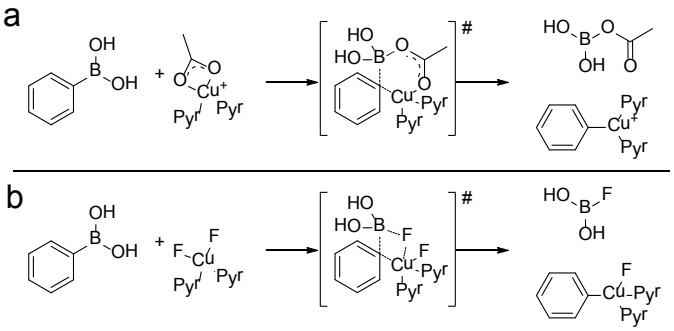


Fig. 1 Proposed mechanism for transmetallation of phenylboronic acid with copper(II) acetate (**a**) and copper(II) fluoride (**b**).

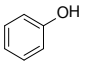
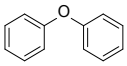
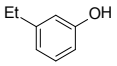
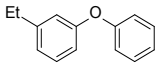
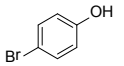
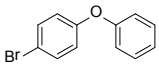
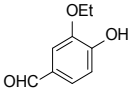
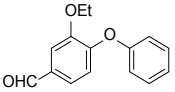
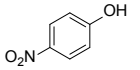
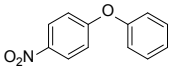
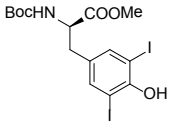
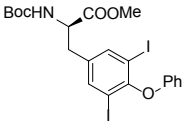
In our study, we applied the reaction conditions published originally by *Chan* [5]. During the reaction, copper(II) fluoride dissolved completely, and no precipitate was formed. The pyridine complex of copper(II) acetate is deep brownish blue, whereas the copper(II) fluoride complex is light yellow. The copper reagents were not soluble in dichloromethane and no reaction occurred without pyridine as ligand. Both promoters, in equimolar quantity, gave almost quantitative yield in the reaction of phenol with phenylboronic acid. In case of copper(II) fluoride and phenol, it was possible to reduce the quantity of the promoter without significant decrease of the yield. Unfortunately substituted phenols gave lower yields when less than equimolar promoter was used.

Reaction of phenols containing electron withdrawing groups or large substituents are reported to have low yields [4, 5]. To demonstrate the positive impact of the fluoride ion in the copper(II) salt promoted phenolic coupling reactions, we investigated these types of phenol derivatives in our study as summarized in Table 1.

The original $Cu(OAc)_2$ promoter gave low yields for the 4-bromophenol, 3-ethoxy-4-hydroxybenzaldehyde and 4-nitrophenol. In contrast, use of CuF_2 almost doubled the yield of the reaction with 4-bromophenol and also increased the yield of the reactions with 3-ethoxy-4-hydroxybenzaldehyde and 4-nitrophenol. The *Chan-Lam-Evans* coupling of the benzaldehyde compound was reported with low yield and long reaction time. [14] The high reaction rate with copper(II) fluoride enabled rapid reaction with 3-ethoxy-4-hydroxybenzaldehyde, thus oxidation of the aldehyde in the presence of air could be minimized. As a result, a dramatic improvement of yield (89%) was achieved compared to the one of the $Cu(OAc)_2$ promoted coupling (30%).

Iodinated tyrosine derivatives have great medicinal importance [15]. *Chan et al.* reported synthesis of thyroxin, with copper(II) acetate promoted coupling and noted that the two iodine atoms adversely affected the reactivity of the phenolic hydroxyl group. [5] Thus, longer reaction time and 3 equivalents of boronic acid reagent were necessary to perform the reaction with good yield. In contrast, the reaction of methyl (*S*)-2-(*tert*-butoxycarbonylamino)-3-(4-hydroxy-3,5-diiodophenyl)propanoate and phenylboronic acid with copper(II) fluoride gave 30% higher yield. The reaction time was reduced from 72 hours to 18 hours and only 2 equivalent of boronic acid was used.

Table 1

Substrate	Product	Isolated yield (%)	
		$Cu(OAc)_2$	CuF_2
		96	98
		61	77
		20	38
		30	89
		31	34
		50	80

There is only one drawback of copper(II) fluoride as new reagent in diaryl ether formation. Presence of the fluoride ion is not compatible with silyl protecting groups which are cleaved by the fluoride ions. In these cases, use of the classical copper(II) acetate remains a better choice.

3 Conclusion

In this study, a modification of the *Chan-Lam-Evans* coupling is reported. Copper(II) fluoride, as a novel promoter, gave higher yields and shorter reaction times for all compounds studied. In case of a protected diiodotyrosine and 3-ethoxy-4-hydroxybenzaldehyde, the improvement in yield is tremendous. Thus, the copper(II) fluoride promoted *Chan-Lam-Evans* coupling is suitable for selective, efficient and economical synthesis of diaryl-ether compounds under mild conditions.

4 Experimental Section

TLC was carried out using Kieselgel 60 F_{254} (Merck) sheets. Spots were visualized under UV light (254 nm and 365 nm) or by treatment with 5% ethanolic phosphomolybdic acid solution and heating of the dried plates. The NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-300 spectrometer operating at 300 MHz for ^1H and 75 MHz for ^{13}C, and signals are given in ppm on the δ scale. Infrared spectra were recorded on a Bruker ALPHA FT-IR spectrometer and wavenumbers of bands are listed in cm^{-1}.

General procedure for the synthesis of diaryl ethers: Phenol (1 mmol) and phenylboronic acid (1.5-2 mmol) were dissolved in dichloromethane (10 ml), then pyridine (5 mmol) and the appropriate copper(II) salt (1 mmol) were added to the solution. The mixture was stirred at room temperature for 18 hours. After evaporation off the solvent in vacuum, ethyl acetate (50 ml) was added and the organic phase was washed with 1M HCl solution (10 ml), 1M NaOH solution (10 ml) and brine (10 ml). After drying the organic phase over Na_2SO_4, it was concentrated in vacuum. The residue was purified with flash chromatography on silica gel with mixture of n-hexane and ethyl acetate as eluent.

Diphenyl ether

Yellowish oil; ^{1}H NMR: 7.37 (4H, dd, J = 7.9 Hz), 7.13 (2H, t, J = 7.4 Hz), 7.04 (4H, d, J = 7.7 Hz); ^{13}C NMR: 157.47, 129.95, 123.43, 119.10; IR: 3039, 1582, 1484, 1455, 1284, 1228, 1197, 1162, 1071, 1023.

1-Ethyl-3-phenoxybenzene

Yellowish oil;^{1}H NMR: 7.33 (2H, dd, J = 7.9 Hz), 7.24 (1H, dd, J = 7.8 Hz), 7.10 (1H, t, J = 7.4 Hz), 7.02 (2H, d, J = 8.5 Hz), 6.95 (1H, d, J = 7.6 Hz), 6.89 (1H, s), 6.82 (1H, d, J = 8.1 Hz), 2.64 (2H, q, J = 7.6 Hz), 1.23 (3H, t, J = 7.6 Hz); ^{13}C NMR: 157.62, 157.41, 146.58, 129.89, 129.71, 123.24, 123.07, 118.99, 118.69, 116.31, 28.97, 15.64; IR: 2964, 2929, 1582, 1485, 1234, 1213, 1162, 918, 750, 690.

1-Bromo-4-phenoxybenzene

Yellowish oil; ^{1}H NMR: 7.45 (2H, d, J = 8.6 Hz), 7.37 (2H, dd, J = 7.8 Hz), 7.15 (1H, t, J = 7.5 Hz,), 7.02 (2H, d, J = 8.0 Hz), 6.91 (2H, d, J = 8.6 Hz); ^{13}C NMR: 156.93, 156.78, 132.88, 130.09, 123.93, 120.64, 119.24, 115.81; IR (KBr): 2922, 1577, 1480, 1230, 1163, 1068, 1008, 751, 690, 486.

3-Ethoxy-4-phenoxybenzaldehyde

White solid; Mp.: 91-92°C; ^{1}H NMR: 9.91 (1H, s), 7.53 (1H, s), 7.38 (3H, m, J = 7.9 Hz), 7.18 (1H, t, J = 7.3 Hz), 7.06 (2H, d, J = 7.9 Hz,), 6.98 (1H, d, J = 8.1 Hz), 4.19 (2H, q, J = 6.9 Hz), 1.42 (3H, t, J = 6.9 Hz); ^{13}C NMR: 190.99, 156.28, 152.32 , 150.52, 132.41, 129.85, 125.51, 124.10, 119.21, 118.54, 112.15, 64.74, 14.59; IR: 3056; 1984; 2817; 1700; 1677; 1585; 1507; 1488; 1278; 1131.

1-Nitro-4-phenoxybenzene

Yellowish oil; ^{1}H NMR: 8.22 (2H, d, J = 9.0 Hz), 7.46 (2H, dd, J = 7.5 Hz), 7.28 (1H, t, J = 7.1 Hz), 7.11 (2H, d, J = 7.8 Hz), 7.03 (2H, d, J = 8.6 Hz); ^{13}C NMR: 163.42, 154.77, 142.70, 130.37, 125.98, 125.45, 120.58, 117.14; IR: 3078, 2846, 1581, 1513, 1483, 1340, 1238, 1110, 748, 687.

Methyl (*S*)-2-(*tert*-butoxycarbonylamino)-3-(4-hydroxy-3,5-diiodo-4-phenoxyphenyl)propanoate

White solid; Mp.: 128°C; ^{1}H NMR: 7.66 (2H, s), 7.32 (2H, dd, J = 7,8 Hz), 7.07 (1H, t, J = 7,3 Hz), 6,79 (2H, d, J = 8,3 Hz), 5,12 (1H, br), 4.57 (1H, m), 3.79 (3H, s), 3.13 (1H, dd, J = 13,3, 5,3 Hz), 2.95 (1H, dd, J = 13.5, 6.2 Hz), 1.47 (9H, s); ^{13}C NMR (DMSO-d_6): 172.01, 171.14, 156.43, 152.90, 141.58, 137.80, 129.88, 122.71, 116.42, 91.26, 80.52, 54.54, 52.73, 37.12, 28.70; IR (KBr): 3365, 1734, 1682, 1599, 1593, 1522, 1490, 1457, 1438, 1391.

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