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Development of a CuCl/phosphine system to catalyze phenylation and methylation of \(N\)-tosyl aldimines with phenylboronic and methylboronic acids

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Abstract. The addition of phenylboronic and methylboronic acids to activated aromatic aldimines was demonstrated in the presence of copper(I)-phosphine complexes. The desired products were obtained using copper chloride/phosphine, and potassium fluoride in under toluene reflux, in moderate-to-good yield and a suitable reaction time.

Keywords. Phenylation reaction, Methylation reaction, Copper catalysis, Boron reagent, Phenylboronic acid.

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1. Introduction

In many essential chemical or biological reactions, various amines containing phenyl or methyl groups are utilized as precursors for preparing drugs and biological compounds as well as ligands in organic synthesis [1,2]. Among the many findings in the formation of a new carbon–carbon bond, the addition of an aryl or an alkyl group to a \(\text{C}=\text{N}\) bond using organometallic reagents, producing amine products, is known to be a significant pathway. These additions are widely catalyzed in the presence of different transition metal complexes of Rh(\(\text{I}/\text{II}\)) \([3]\), Pd(\(\text{II}\)) \([4]\), Ni(\(\text{0}\)/\(\text{II}\)) \([5]\), Ru(\(\text{II}\)) \([6]\), Co(\(\text{II}\)), Fe(\(\text{III}\)), and Cu(\(\text{I}/\text{II}\)).

The use of air-stable organoboron reagents is preferred compared to zinc, tin \([7,8]\), silane \([9]\), and titanium \([10]\), which are toxic and difficult to manage. Consequently, as a result of the work by Hayashi \([11]\), Miyaura \([12]\), Lin \([13]\), Xu \([14]\), Zhang \([15]\), Manolikakes \([16]\), and others, the addition of organoboron reagents using noble metal catalysts has increased considerably. However, most
of these additions were carried out by means of rare and costly rhodium and palladium catalysts [17–19]. Currently, there is a growing trend toward the use of copper. Copper is an earth-abundant transition metal with a magnificently diverse chemistry and coordination ability with respect to heteroatoms or pi bonds when used as a catalyst in various organic reactions [20]. Despite many successful copper-catalyzed additions on N-protected aldimines using stannane and silane reagents, there have been few reports on the use of aryl or alkyl boron reagents in the literature [21]. Schaus and co-workers reported the efficient addition of aryl boron reagents to active α-iminoesters using chiral 1,1′-biphenols and thiourea [22]. Hu and co-workers reported the addition of CuCl/bipyridine-catalyzed arylboroxines to N-Ts-aldimines using microwave energy, achieving a conversion rate up to 84% [23]. Zhou and co-workers reported the asymmetric arylation of N-azaaryl aldimines with arylboroxines in the presence of copper–monodentate phosphoramidite complexes [24]. Highlighting the importance of cost-effective first-row transition metals in direct 1,2-addition, in this work, phenylation of aldimines along with methylation is developed by utilizing cheap copper salts and air-stable organoboron reagents (Scheme 1).

Initially, the addition of phenylboronic acid (2a) to aldimine was investigated in the presence of a copper complex of common monodentate and bidentate phosphine ligands (Table 1). The reaction did not proceed with dpdm, dppp, dppf, and dppb. Dppe, PMe$_3$, and P(OMe)$_3$ produced a low yield of the desired product, while PPh$_3$ generated approximately 55%. When different copper salts were used, the addition of 2a to N-(4-chlorobenzylidene)-4-methylbenzenesulfonamide did not proceed well. The use of copper(II) chloride resulted in the formation of chloride 4-chloro-N-tosylbenzamide as a by-product (4; 85% for 10 h) most probably through the phenylation of sulfonamide from aldimine hydrolysis (Scheme 2, Equation (1)) [25–28]. Replacing the copper salt by copper(II) acetate produced 4-chloro-N-tosylbenzamide (5; 95% for 30 min) (Scheme 2, Equation (2)) [29–32]. In such side reactions, the presence of copper(II) salts prevents the formation of active copper species and the occurrence of a catalytic cycle (Table 2, entries 1–5). Although the reaction is run with some copper(I) salts, catalyzation by copper(I) chloride is the most efficient for a time of 24 h with a much higher yield (entries 6–10, Table 2). Using 5 mol% of copper(I) chloride with 10 mol% PPh$_3$ results in the desired product 3a with a 65% yield (entry 12, Table 2). Surprisingly, when the reaction is conducted using 2.5 mol% CuCl with 5 mol% PPh$_3$ at 110 °C, the yield of the favored product 3a reaches 83% with no observation of by-products 4 and 5 (entry
Table 1. Effect of various phosphine ligands

| Ligand          | dppf (trace) | dppm (trace)a |
|-----------------|--------------|---------------|
| P(Ph3)3 (40)    |              |               |
| PMe3 (12)       |              |               |
| P(OMe)3 (<10)   |              |               |

Reaction conditions: p-chlorobenzaldimine (0.1 mmol), 2a (0.2 mmol), copper salt (10 mol%), ligand (20 mol%), and toluene (0.5 mL) for 24 h under reflux in Ar atmosphere. aIsolated yield (%).

Table 2. Optimization of condition

| Entry | Copper salt   | Base         | Yielda |
|-------|---------------|--------------|--------|
| 1     | Cu(OTf)2     | KF           | 20     |
| 2     | KF            | CuSO4       | Trace  |
| 3     | KF            | Cu(NO3)2·6H2O| Trace  |
| 4     | KF            | CuCl2       | Trace  |
| 5     | KF            | Cu(OAc)2    | Trace  |
| 6     | KF            | CuCl        | 55     |
| 7     | KF            | Cu(OTf)     | 28     |
| 8     | KF            | CuF         | 25     |
| 9     | KF            | CuBr        | 15     |
| 10    | KF            | CuI         | 20     |
| 11b   | KF            | CuCl        | -      |
| 12c   | KF            | CuCl        | 65     |
| 13d   | KF            | CuCl        | 83     |
| 14    | Et3N         | CuCl        | -      |
| 15    | K2CO3        | CuCl        | 20     |
| 16e   | K2CO3        | CuCl        | 50     |
| 17f   | KF            | CuCl        | 45     |
| 18f   | KF            | CuCl        | 40     |

Reaction conditions: p-chlorobenzaldimine (0.1 mmol), 2a (0.2 mmol), KF (0.3 mmol), and toluene (0.5 mL) for 24 h under reflux in Ar atmosphere. aIsolated yield (%). bNo ligand was used. cCopper salt (5 mol%) and PPh3 (10 mol%). dCopper salt (2.5 mol%) and PPh3 (5 mol%). eEt3N used as additive. f2b (0.1 mmol) was used after 48 h.
Table 3. Scope of phenylation

| Entry | X  | Yielda | mp (°C) | mp (°C)b |
|-------|----|--------|---------|----------|
| 1     | p-Cl| 83     | 114.5–115| 114–115  |
| 2     | o-Cl| 72     | 170–173  | 172–173.2 [33] |
| 3     | m-Cl| 75     | 132–133  | 135–136 [16] |
| 4     | p-F | 80     | 122–124  | 120–121  |
| 5     | p-NO2| 75    | 124–126  | 121–123 [34] |
| 6     | p-CF3| 80    | 145–146  | 142–144  |
| 7     | p-BR| 78     | 120–121  | 121–123  |
| 8     | p-OMe| 65    | 139–140  | 139–141 [35] |
| 9     | o-OMe| 45    | 124–125  | 126.6–127.8 [33] |
| 10    | p-CH3| 51    | 133–136  | 132–134 [36] |
| 11    | –H  | 60     | 155–156  | 157–159  |

Reaction conditions: p-chlorobenzaldimine (0.1 mmol), 2a (0.2 mmol), CuCl (2.5 mol%), PPh3 (5 mol%), KF (0.3 mmol), and toluene (0.5 mL) for 24 h under reflux in Ar atmosphere. a Isolated yield (%). b Reported melting point.

Table 4. Scope of methylation

| Entry | X  | Yielda | mp (°C) | mp (°C)b |
|-------|----|--------|---------|----------|
| 1     | p-Cl| 65     | 127–130  | 128–130  |
| 2     | o-Cl| 30     | Oily product | - |
| 3     | m-Cl| 43     | 64–65    | 66.7–67.8 |
| 4     | p-F | 72     | 112–114  | 115–116  |
| 5     | p-NO2| 75    | 156–150  | 156–159 [37] |
| 6     | p-CH3| 50    | 113–115  | 114–116  |
| 7     | p-Br| 59     | 136–140  | 139–141  |
| 8     | o-OMe| 21    | 101–104  | 105–108  |
| 9     | p-OMe| 25    | 85–88    | 88–89    |
| 10    | p-CF3| 78    | 119–121  | 122–123  |
| 11    | –H  | 55     | 80–83    | 82–84 [38] |
| 12    | β-naphthyl| 65   | 144–146  | 146–148  |
| 13    | α-naphthyl| 51   | 121–123  | 122.5–123.5 |

Reaction conditions: p-chlorobenzaldimine (0.1 mmol), 2b (0.2 mmol), CuCl (2.5 mol%), PPh3 (5 mol%), KF (0.3 mmol), and toluene (0.5 mL) for 48 h under reflux in Ar atmosphere. a Isolated yield (%). b Reported melting point.

Based on observations, a catalytic cycle is proposed for the reaction (Scheme 3). In toluene (S), the starting point of the catalytic cycle is the solvated complex [Cu(PPh3)2S2]Cl, abbreviated to [Cu(PPh3)2]+ (A), having a copper atom in tetrahedral coordination. The oxidative addition of the phenyl group to copper(I) complex A gives copper(III) phenyl complex B. Insertion of imine into the resulting boron–copper bond of B yields an α-boroxyalkycopper phenyl intermediate D, which then is converted to the boron ether of a sec-alcohol by reductive elimination [39,40].

In summary, the addition of aryl and alkyl boron reagents to N-Ts-aldimines was performed in the presence of copper/phosphine catalysts. The coordination of copper(I) chloride with PPh3 was determined as the most efficient combination for this addition, delivering the desired products in moderate-to-good yield. The potential of direct synthesis of the N–C amino bond along with the broad scope of the reaction has implications for the fields of organic chemistry and medicine. Despite the lower yield of this catalytic system in comparison to that of rhodium and palladium, the use of economical and available copper salt is the main highlight of this protocol. Further studies, including an investigation into the enantioselective procedure, are being actively pursued by our research group.

All the chemicals were procured from Sigma-Aldrich and Merck Chemicals. Et2O and 1,4-dioxane were distilled from benzophenone/sodium under nitrogen atmosphere prior to use. Aldimines, phenylboronic acids, and methylboronic acids, triphenylboroxine and trimethylboroxine were prepared according to reported procedures [41,42]. The 1H NMR spectra were recorded on Bruker Avance III HD 500 MHz using TMS as the internal standard.
Scheme 3. Proposed mechanism: solvated complex [Cu(PPh$_3$)$_2$]$^+$ (A), copper(III) phenyl complex (B), and α-boroxylalkylcopper phenyl intermediate (D).

2. General procedure

Under argon atmosphere, triphenylphosphine (0.01 mmol, 2.6 mg) was placed in a flame-dried Schlenk tube. CuCl (0.005 mmol, 0.5 mg) and toluene (0.5 mL) were added. The contents of the Schlenk tube were stirred at room temperature for 30 min, and aldimine 1 (0.1 mmol) and 2a (0.2 mmol) and potassium fluoride (0.3 mmol, 17.4 mg) were added sequentially. The Schlenk tube was placed in an oil bath at 110 °C. Then, the mixture was stirred for 24 h, cooled to room temperature, and filtered through a short silica gel column with Et$_2$O (5 mL) as the eluent. The mixture was concentrated via evaporation, and the residue was purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate 10:1) to obtain the corresponding product (3).

N-((4-chlorophenyl)(phenyl)methyl)-4-methylbenzenesulfonamide (3a)
Yield: 30.80 mg (83%); white solid; mp 114.5–115 °C.
$^1$H NMR (500 MHz, CDCl$_3$): δ 2.39 (s, 3H), 5.16 (d, J = 7.0 Hz, 1H), 5.54 (d, J = 7.1 Hz, 1H), 6.92–6.96 (m, 4H), 7.02–7.07 (m, 4H), 7.17–7.21 (m, 3H), 7.55 (d, J = 8.3 Hz, 2H) [34].

N-((4-fluorophenyl)(phenyl)methyl)-4-methylbenzenesulfonamide (3d)
Yield: 28.43 mg (80%); white solid; mp 122–124 °C.
$^1$H NMR (500 MHz, CDCl$_3$): δ 2.39 (s, 3H), 5.16 (d, J = 7.0 Hz, 1H), 5.54 (d, J = 7.1 Hz, 1H), 6.92–6.96 (m, 4H), 7.02–7.07 (m, 4H), 7.17–7.21 (m, 3H), 7.55 (d, J = 8.3 Hz, 2H) [34].

N-((4-trifluorophenyl)(phenyl)methyl)-4-methylbenzenesulfonamide (3f)
Yield: 32.43 mg (80%); white solid; mp 145–146 °C.
$^1$H NMR (500 MHz, CDCl$_3$): δ 2.35 (s, 3H), 5.34 (d, J = 7.2 Hz, 1H), 5.59 (d, J = 7.2 Hz, 1H), 7.01–7.05 (m, 2H), 7.10 (d, J = 8.0 Hz, 2H), 7.23 (s, 1H), 7.19–7.23 (m, 3H), 7.58 (d, J = 8.2 Hz, 2H) [34].

N-((4-bromophenyl)(phenyl)methyl)-4-methylbenzenesulfonamide (3g)
Yield: 32.47 mg (78%); white solid; mp 120–121 °C.
$^1$H NMR (500 MHz, CDCl$_3$): δ 2.41 (s, 3H), 5.24 (d, J = 7.1 Hz, 1H), 5.56 (d, J = 7.1 Hz, 1H), 7.04 (d, J = 8.4 Hz, 2H), 7.09–7.15 (m, 4H), 7.16–7.20 (m, 2H), 7.24–7.27 (m, 3H), 7.58 (d, J = 8.3 Hz, 2H) [35].

N-benzhydryl-4-methylbenzenesulfonamide (3k)
Yield: 20.224 mg (60%); yellowish white solid; mp 155–156 °C.
$^1$H NMR (500 MHz, CDCl$_3$): δ 2.38 (s, 3H), 5.32 (d, J = 7.1 Hz, 1H), 5.58 (d, J = 7.2 Hz, 1H), 7.09–7.16 (m, 6H), 7.19–7.24 (m, 6H), 7.57 (d, J = 8.0 Hz, 2H) [38].

4-chloro-N-tosylbenzamide (4)
Yield: 22.25 mg (90%); white solid; mp 170–171 °C.
$^1$H NMR (500 MHz, CDCl$_3$): δ 2.40 (s, 3H), 6.55 (br, 1H), 7.07 (d, J = 7.69, 2H), 7.13 (t, J = 7.5, 1H), 7.2–7.27 (m, 4H), 7.66 (d, J = 8.0 Hz, 2H) [44].

4-chloro-N-tosylbenzamide (5)
Yield: 24.78 mg (80%); white solid; mp 99–101 °C.
$^1$H NMR (500 MHz, CDCl$_3$): δ 2.44 (s, 3H), 7.32 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.6, 2H), 7.75 (d, J = 8.6 Hz, 2H), 7.91 (d, J = 8.4, 2H), 8.38 (br, 1H) [45].

N-(1-(4-chlorophenyl)ethyl)-4-methylbenzenesulfonamide (6a)
Yield: 20.13 mg (65%); white solid; mp 127–130 °C.
$^1$H NMR (600 MHz, CDCl$_3$): δ 1.37 (d, J = 6.9 Hz, 3H), 2.39 (s, 3H), 4.43 (qui, J = 6.9 Hz, 1H), 5.12 (d, J = 6.9 Hz, 1H), 7.02 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H) [46].

N-(1-(2-chlorophenyl)ethyl)-4-methylbenzenesulfonamide (6b)
Yield: 9.30 mg (30%). Oily product.
**N-(1-(3-chlorophenyl)ethyl)-4-methylbenzenesulfonamide (6c)**

Yield: 13.32 mg (43%); white solid; mp 64–65 °C.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 1.42 (d, $J = 6.9$ Hz, 3H), 2.34 (s, 3H), 4.89 (m, 1H), 5.13 (d, $J = 7.0$ Hz, 1H), 7.06–7.10 (m, 2H), 7.12 (d, $J = 8.2$ Hz, 2H), 7.16–7.20 (m, 2H), 7.59 (d, $J = 8.3$ Hz, 2H).

**N-(1-(3-fluorophenyl)ethyl)-4-methylbenzenesulfonamide (6d)**

Yield: 21.12 mg (72%); white solid; mp 112–114 °C.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 1.37 (d, $J = 6.9$ Hz, 3H), 2.39 (s, 3H), 4.41 (qui, $J = 6.9$ Hz, 1H), 5.21 (d, $J = 6.9$ Hz, 1H), 7.02 (d, $J = 8.5$ Hz, 2H), 7.12 (d, $J = 8.3$ Hz, 2H), 7.16 (d, $J = 8.2$ Hz, 2H), 7.57 (d, $J = 8.2$ Hz, 2H) [48].

**N-(1-(4-fluorophenyl)ethyl)-4-methylbenzenesulfonamide (6e)**

Yield: 14.47 mg (50%); white solid; mp 113–115 °C.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 1.50 (d, $J = 6.8$ Hz, 3H), 2.23 (s, 3H), 4.63 (q, $J = 6.9$ Hz, 1H), 5.14 (dd, $J = 7.0$, 1H), 7.01 (d, $J = 8.1$ Hz, 2H), 7.21 (d, $J = 8.2$ Hz, 1H), 7.40–7.48 (m, 3H), 7.57 (d, $J = 8.1$ Hz, 2H), 7.65 (d, $J = 8.2$ Hz, 2H), 7.72–7.76 (m, 1H) [49].

**N-(1-(4-bromophenyl)ethyl)benzenesulfonamide (6g)**

Yield: 20.90 mg (59%); white solid; mp 136–140 °C.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 1.37 (d, $J = 6.9$, 3H), 2.39 (s, 3H), 4.43 (q, $J = 6.9$ Hz, 1H), 5.21 (d, $J = 6.9$ Hz, 1H), 7.02 (d, $J = 8.4$ Hz, 2H), 7.12 (d, $J = 8.3$ Hz, 2H), 7.16 (d, $J = 8.1$ Hz, 2H), 7.57 (d, $J = 8.2$ Hz, 2H) [50].

**N-(1-(2-methoxyphenyl)ethyl)-4-methylbenzenesulfonamide (6h)**

Yield: 6.40 mg (21%); white solid; mp 101–104 °C.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 1.44 (d, 6.9 Hz, 3H), 2.30 (s, 3H), 3.69 (s, 3H), 4.51–4.57 (m, 1H), 5.52 (d, $J = 9.3$ Hz, 1H), 6.60 (d, $J = 8.2$ Hz, 1H), 6.73 (t, $J = 7.5$ Hz, 1H), 6.91 (d, $J = 7.5$ Hz, 1H), 7.02 (d, $J = 8.1$ Hz, 2H), 7.06–7.11 (m, 1H), 7.49 (d, $J = 8.2$ Hz, 2H) [47].

**N-(1-(4-methoxyphenyl)ethyl)-4-methylbenzenesulfonamide (6i)**

Yield: 9.16 mg (30%); white solid; mp 85–88 °C.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 1.39 (d, $J = 6.8$ Hz, 3H), 2.38 (s, 3H), 3.74 (s, 3H), 4.40 (qui, $J = 6.8$ Hz, 1H), 4.82–4.97 (br, 1H), 6.71 (d, $J = 8.7$ Hz, 2H), 7.01 (d, $J = 8.7$ Hz, 2H), 7.18 (d, $J = 7.6$ Hz, 2H), 7.61 (d, $J = 8.3$ Hz, 2H) [37].

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Supplementary data

Supporting information for this article is available on the journal’s website under https://doi.org/10.5802/crchem.35 or from the author.

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