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Copper(II) Acetate-Catalyzed Addition of Arylboronic Acids to Aromatic Aldehydes

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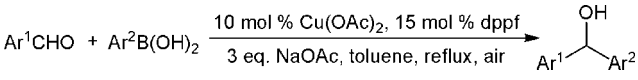

A novel copper-catalyzed protocol for the synthesis of carbinol derivatives has been developed. In the presence of copper(II) acetate and dppf, carbinol derivatives were prepared by the addition of arylboronic acids to aromatic aldehydes in good to excellent yields. Moreover, the rigorous exclusion of air or moisture is not required in these transformations.

Diarylmethanols consist of an important building block in the synthesis of natural products and pharmacological active compounds as well as material science target molecules.[1] General approaches involve the reduction of ketones and addition of organometallic reagents to aldehydes. In recent years, great attention has been paid to the addition of organometallic reagents to aldehydes for the synthesis of diarylmethanols, such as organolithium,[2a,d] organomagnesium,[2e,g] organotin,[2h,i] and organozinc.[2l,m] However, these organometallic reagents are either toxic, have poor functional group compatibility, or are sensitive to air and moisture.

Organboron reagents enjoy great prestige due to their advantages of stability to air or moisture and good functional group tolerance.[3] In 1997, Miyaura and co-workers reported a rhodium-catalyzed addition of aryl- and alkenyl-boronic acids to aldehydes[4] and enones.[5] Since then, various synthetic methods by rhodium-catalyzed[6] and palladium-catalyzed[7] approaches for such transformations have been developed. In our previous report, we have developed a palladium-catalyzed arylation of aldehydes to produce secondary alcohols in good yields.[8] However, palladium is very expensive compared with copper. Furthermore, in our previous report, palladium-catalyzed aldehyde arylations did not tolerate bromo or formyl groups in the substrates. We report herein that diarylmethanols can be prepared successfully by the addition of arylboronic acids to aromatic aldehydes with excellent yields in the presence of copper(II) acetate.

Initially, we chose the addition of phenylboronic acid **2e** to 4-nitrobenzaldehyde **1a** as a model reaction using $Cu(OAc)_2 \cdot H_2O$ as the copper source, NaOAc as the base, and toluene as the solvent. Considering ligands always play important roles in metal-catalyzed chemistry,[9] we first focused on ligand screening (Chart 1). Through screening, we found that the electronic nature and steric demands of the arylphosphine ligands played important roles. For example, use of monodentate phosphine ligands resulted in moderate yields (Table 1, **L6**−**L11**), and the hindrance in the ligands or electron-poor ligands had poor catalytic activity (Table 1,**L12**−**L16**). Bidentate phosphines **L1** and **L2** with smaller bite angle than **L5** stopped the reaction. To our delight, bidentate phosphines with large bite angles such as **L4**, **L5**, and **L6** were effective for this transformation. In addition, we examined the aminophosphine ligands (Table 1,

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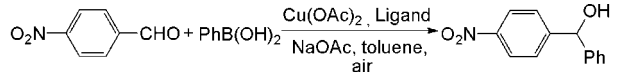
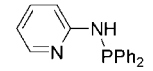
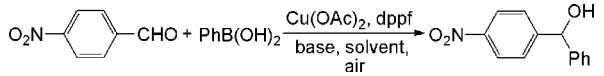
CHART 1. Ligand Screening



dppe	dppp	dppb	(*S*)-binap
L1 <5%	**L2** <5%	**L3** 61%	**L4** 84%
dppf	PPh_3	P(4-MeO-Ph)$_3$	P(2-Nap)$_3$
L5 85%	**L6** 65%	**L7** 53%	**L8** 60%
P(2-Furan)$_3$	P(1-Nap)$_3$	P(3,5-di-Tol)$_3$	P(2-MeO-Ph)$_3$
L9 38%	**L10** 26%	**L11** 46%	**L12** <5%
P(2-Tol)$_3$	P(2,6-di-Tol)$_3$	P(C_6F_5)$_3$	P(4-F-Ph)$_3$
L13 <5%	**L14** <5%	**L15** <5%	**L16** <5%
i-Pr_2NP(2-Tol)$_2$	*i*-Pr_2NPPh_2		
L17 <5%	**L18** 47%	**L19** <5%	**L20** <5%

All reactions were run with 4-nitrobenzaldehyde (30 mg, 0.2 mmol), phenylboronic acid (48.8 mg, 0.4 mmol), $Cu(OAc)_2 \cdot H_2O$ (4.0 mg, 10 mol %), dppf ligand (10 mol %) and NaOAc (32.8 mg, 0.4 mmol) in 3 mL toluene at reflux for 24 h under air atmosphere with isolated yields reported.

TABLE 1. Effects of Bases, Solvents, and the Amounts of Ligand on the Copper(II) Acetate-Catalyzed Addition of Phenylboronic Acid to 4-Nitrobenzaldehyde[a]



entry	base	solvent	yield[b] (%)
1	K_2CO_3	toluene	<5
2	$KF \cdot 2H_2O$	toluene	<5
3	HCOONa	toluene	30
4	$LiOH \cdot H_2O$	toluene	59
5	DABCO	toluene	17
6	DBU	toluene	<5
7	NaOAc	toluene	85
8	NaOAc	$CH_3CH_2NO_2$	15
9	NaOAc	DMF	<5
10	NaOAc	DMSO	<5
11	NaOAc	dioxane	<5
12	NaOAc	DCE	<5
13	NaOAc	THF	<5
14	NaOAc	*t*-BuOMe	<5
15	NaOAc (3 equiv)	toluene	91
16	NaOAc (4 equiv)	toluene	93
17[c]	NaOAc (3 equiv)	toluene	95
18[d]	NaOAc (3 equiv)	toluene	96

[a] AII reactions were run with 4-nitrobenzaldehyde (30 mg, 0.2 mmol), phenylboronic acid (48.8 mg, 0.4 mmol), $Cu(OAc)_2 \cdot H_2O$ (4.0 mg, 10 mol %), dppf ligand (10 mol %), and base (0.4 mmol) in 3 mL of solvent at reflux for 24 h under air atmosphere. [b] Isolated yields reported. [c] L/Cu = 1.5:1. [d] L/Cu = 2:1.

L17−**L20**), which had poor activity except for ligand **L18**. Finally, we chose commercial available **L5** as the best ligand in our system.

Further studies on the optimization of the reaction conditions such as bases, solvents and the ratio of **L5**/Cu for phenylation of 4-nitrobenzaldehyde are listed in Table 1. Among the bases, NaOAc was superior to some others such as K_2CO_3, $KF \cdot 2H_2O$, $LiOH \cdot H_2O$, DABCO, DBU, and HCOONa. In addition, we also studied influence of the amount of NaOAc on the reaction yields. It was found that the yield was not significantly affected by adding different amount of NaOAc (Table 1, entries 7, 15, and 16). The choice of solvent was also vital to the success of the

TABLE 2. Copper(ll) Acetate-Catalyzed Addition of Arylboronic Acids to Aromatic Aldehydes[a]

entry	Ar^1	Ar^2	product	yield (%)
1	4-NO_2-C_6H_4 **1a**	4-CF_3-C_6H_4 **2a**	**3aa**	84
2	**1a**	4-F-C_6H_4 **2b**	**3ab**	83
3	**1a**	4-Cl-C_6H_4 **2c**	**3ac**	90
4	**1a**	4-Br-C_6H_4 **2d**	**3ad**	92
5	**1a**	C_6H_5 **2e**	**3ae**	95
6	**1a**	4-Me-C_6H_4 **2f**	**3af**	96
7	**1a**	4-MeO-C_6H_4 **2g**	**3ag**	95
8	**1a**	3-MeO-C_6H_4 **2h**	**3ah**	90
9	**1a**	2-MeO-C_6H_4 **2i**	**3ai**	73
10	**1a**	2-Me-C_6H_4 **2j**	**3aj**	89
11	**1a**	1-nathphyl **2k**	**3ak**	95
12	3-NO_2-C_6H_4 **1b**	**2e**	**3be**	90
13	2-NO_2-C_6H_4 **1c**	**2e**	**3ce**	74
14	4-CN-C_6H_4 **1d**	**2e**	**3de**	91
15	4-OHC-C_6H_4 **1e**	**2e**	**3ee**	92
16	4-MeO_2C-C_6H_4 **1f**	**2e**	**3fe**	57
17	2,4-$(NO_2)_2$-C_6H_3 **1g**	**2e**	**3ge**	89
18	4-MeO_2S-C_6H_4 **1h**	**2e**	**3he**	90
19	C_6H_5 **1i**	**2e**	**3ie**	<5
20	2-furyl **1j**	**2e**	**3je**	<5

[a] All reactions were run with aldehyde (0.2 mmol), arylboronic acid (0.4 mmol), $Cu(OAc)_2 \cdot H_20$ (4.0 mg, 10 mol %), dppf ligand (15 mol %), and NaOAc (49.2 mg, 0.6 mmol) in 3 mL of toluene at reflux for 24 h under air atmosphere. [b] Isolated yields reported.

catalytic reaction. Toluene appeared to be the best choice among the common solvents such as $CH_3CH_2NO_2$, DMF, DMSO, dioxane, DCE, THF, and *t*-BuOMe. $Cu(OAc)_2 \cdot H_2O$ exhibited the highest catalytic activity compared with $CuCl_2$ and CuCl. Increasing the amount of **L5** in the procedure afforded nearly quantitive yield (Table 1, entries 17 and 18). In the light of these results, we adopted conditions with 0.1 equiv of $Cu(OAc)_2 \cdot H_2O$, 0.15 equiv of **L5**, 4-nitrobenzaldehyde, and 3 equiv of NaOAc in the present protocol.

With optimal conditions in hand, the reaction of various arylboronic acids with different aromatic aldehydes was examined to explore the scope of the reaction (Table 2).

The reaction proceeded smoothly with a variety of functional groups and afforded diarylmethanols in excellent yields.

In our system, electronic effect on the arylboronic acids had little influence (Table 2, entries 1−7). Electron-withdrawing arylboronic acids, which are less nucleophilic, and hence, transmetalate more slowly than electro-neutral analogues, are prone to homocoupling and protodeboronation side reactions.[9d] However, in our catalytic system, 4-chlorophenylboronic acid **2c** and 4-bromophenylboronic acid **2d** proceeded smoothly with **1a** to afford **3ac** and **3ad** in 90% and 92% yields, respectively. The products of **3ac** and **3ad** had the chloro and bromo group untouched (Table 2, entries 3 and 4). For the aldehydes, electron-withdrawing aromatic aldehydes reacted with **2e** easily and gave diarylmethanols in good yields (Table 2, entries 12−18). Particularly, 4-formylbenzaldehyde **1e** coupled with **2e** and the product of **3ee** left one formyl group untouched (Table 2, entry 15), which may be due to the electronic nature playing important roles, C═O bond activity was decreased in the product **3ee**, and stopped addition of phenylboronic acid **2e** to formal group of **3ee**. Unfortunately, the reaction was unsuccessful using aldehydes with neutral, electron-rich groups or aliphatic aldehydes.

We further examined the steric effect in our system. A monosubstitution group on the ortho or meta position for both

arylboronic acids (Table 2, entries 7−9) and aromatic aldehydes (Table 2, entries 5, 12, and 13) had little effect on the yields in the reaction. For example, **1a** reacted with arylboronic acids **2g**, **2h**, and **2i** efficiently and afforded **3ag**, **3ah**, and **3ai** in 95%, 90%, and 73% yields, respectively (Table 2, entries 7−9).

Of particular note, the reaction rate with aldehydes **1g** or **1h** was faster than others (Table 2, entries 17 and 18), which may be due to the electron-withdrawing groups increasing C═O bond activity and accelerating the reactions. Moreover, the rigorous exclusion of air or moisture is not required in the present protocol.

In summary, describe here the first example of an efficient and practical approach for the synthesis of a variety of carbinol derivatives via the combination of an inexpensive copper(II) acetate catalyst and air-stable dppf ligand. Work to probe the detailed mechanism and apply the reaction in organic synthesis is currently underway.

Experimental Section

General Procedure for the Synthesis of Carbinol Derivatives. Under an air atmosphere, a Schlenk tube was charged with $Cu(OAc)_2 \cdot H_2O$ (4.0 mg, 0.02 mmol), dppf (16.6 mg, 0.03 mmol), arylboronic acid (0.4 mmol), aldehyde (0.2 mmol), NaOAc (49.2 mg, 0.6 mmol), and toluene (3 mL) under ice−salt (−20 °C). The mixture was stirred for 0.5 h at room temperature, refluxed for 24 h, and then cooled in a Schlenk tube to room temperature. The mixture was extracted with ethyl acetate (4 × 5 mL), and the organic layers were washed with water. The organic layers were dried over $MgSO_4$, concentrated, and purified by flash column chromatography on silica gel to give the desired product.

4-Nitrophenyl(4-(trifluoromethyl)phenyl)methanol(3aa)(Table 2, entry 1): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.52 (d, J = 2.6 Hz, 1H), 5.99 (s, 1H), 7.48−7.64 (m, 6H), 8.21 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 74.9, 122.1, 123.9, 125.8, 125.9, 126.9, 127.2, 128.3, 130.3, 146.4, 147.5, 149.9; IR (KBr, cm^{-1}) 3455 (−OH); MS (EI) m/z 297 (M^+). Anal. Calcd for $C_{14}H_{10}F_3NO_3$: C, 56.57; H, 3.39. Found: C, 56.40; H, 3.45.

3-Methoxyphenyl(4-nitrophenyl)methanol (3ah) (Table 2, entry 8): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.74 (s, 1H), 3.79 (s, 3H), 5.86 (s, 1H), 6.82−6.93 (m, 3H), 7.29 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 8.1 Hz, 2H), 8.17 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.2, 75.3, 112.4, 113.5, 118.9, 123.6, 127.0, 129.9, 144.2, 147.1, 150.6, 159.9; IR (KBr, cm^{-1}) 3444 (−OH); MS (EI) m/z 259 (M^+). Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05. Found: C, 64.90; H, 5.11.

2-Methoxyphenyl(4-nitrophenyl)methanol (3ai) (Table 2, entry 9): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.17 (s, 1H), 3.80 (s, 3H), 6.10 (s, 1H), 6.89−6.92 (m, 2H), 7.21−7.32 (m, 2H), 7.55 (d, J = 8.8 Hz, 2H), 8.15 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.4, 71.6, 111.0, 121.1, 123.4, 127.1, 127.8, 128.2, 129.0, 129.5, 130.7, 150.9; IR (KBr, cm^{-1}) 3438 (−OH); MS (EI) m/z 259 (M^+). Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05. Found: C, 64.79; H, 4.98.

Naphthalen-1-yl(4-nitrophenyl)methanol (3ak) (Table 2, entry 11): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.79 (brs, 1H), 6.55 (s, 1H), 7.47−7.51 (m, 4H), 7.58 (d, J = 8.9 Hz, 2H), 7.85−7.91 (m, 2H), 8.01−8.04 (m, 1H), 8.15 (d, J = 8.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 73.4, 123.6, 123.7, 125.3, 125.6, 126.0, 126.6, 127.5, 129.0, 129.4, 130.5, 134.2, 137.8, 147.3, 150.3; IR (KBr, cm^{-1}) 3450 (−OH); MS (EI) m/z 279 (M^+). Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69. Found: C, 73.18; H, 4.75.

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Supporting Information Available: Experimental procedures along with copies of spectroscopic and data. This material is available free of charge via the Internet at http://pubs.acs.org.

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