JOC The Journal of Organic Chemistry

Article

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Proline Catalyzes Direct C−H Arylations of Unactivated Arenes

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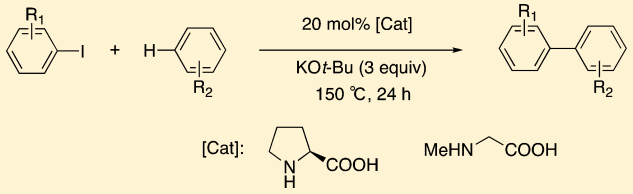
Supporting Information

ABSTRACT: Several amino acids were tested to catalyze the transition-metal-free direct C−H arylation of unactivated benzene derivatives. Among them, proline was found to be an excellent catalyst for the cross-coupling between aryl halides and unactivated arenes. The reaction presumably involves an aryl radical anion as the intermediate based on several experiments. The reaction using this catalyst system offers an option toward establishing an environmentally benign and cost-effective route to biaryls.



INTRODUCTION

Biaryl compounds are frequently found in nature as biologically active molecules, such as antibiotics[1] and enzyme inhibitors, for the treatment of hypertension as well as bipolar disorders. Biaryl units are also an important structural motif for the development of pharmaceuticals[2] and functionalized materials.[3] Consequently, the formation of aryl−aryl bonds has attracted much interest over the past decades.[4]

The traditional synthesis of biaryl compounds involves the transition-metal-catalyzed arylation reactions of organometallic reagents with haloarenes.[5] However, organometallic reagents are usually unstable and need to be initially synthesized from benzene. Recently, the transition-metal-catalyzed arylation between unactivated arenes and aryl halides through substitution at the C−H bonds has been developed.[6] These methods still require a transition metal catalyst, which sometimes consists of forming impurities in the product. A remarkable breakthrough has been conducted by Itami and coworkers, who found that potassium *tert*-butoxide alone can promote the biaryl coupling of electron-deficient nitrogen heterocycles and haloarenes during microwave irradiation.[7] The combinations of an organic catalyst including DMEDA,[8] 1,10-phenanthroline[9] and derivatives,[10] and quinoline-1-amino-2-carboxylic acid[11] and KO*t*-Bu and/or NaO*t*-Bu were subsequently identified as effective catalyst systems for promoting the transition-metal-free cross-coupling reactions of aryl halides with unactivated arenes. Organocatalysis emerged as a very rapidly growing area for recent chemical syntheses because of its environmental friendliness.[12] We now describe an amino-acid-promoted method for accessing biaryl compounds via the direct C−H arylation of unactivated arenes.

RESULTS AND DISCUSSION

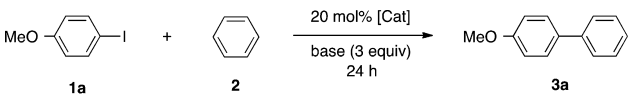
4-Iodoanisole **1a** was selected as a model substrate for the reaction of benzene **2** in the presence of a series of amino acids. Utilizing proline as a catalyst (20 mol %), the reaction afforded the desired 4-methoxybiphenyl **3a** in only 4% yield along with the recovered 4-iodoanisole **1a** (86%) at 80 °C for 24 h in the presence of KO*t*-Bu in a pressure-resistant tube (Table 1, entry 1). Gratifyingly, the yields increased to 47% and 87% for the same reactions when the temperature was increased 120 and 150 °C, respectively (entries 2 and 3). Other amino acids and derivatives were also tested as listed in entries 4−12. Most of the examined amino acids displayed low to moderate efficiencies except for sarcosine, which had an effect comparable to that of proline and was found to be the catalyst of choice for the arylation reaction (entry 9). Binol and 1,2-diaminocyclohexanediylbis(2-pyridinecarboxamide) **L1** also acted as promoters albeit in moderate yields (entries 13 and 14). It was found that the choice and the presence of a base are crucial for this transformation. Notably, the reactions with K_2CO_3, K_3PO_4, and NaO-*t*-Bu and no base did not entirely take place (entries 15−17 and 21). The amount of base (3 equiv) would also be important for the complete consumption of the starting materials (entry 3 vs entry 19). A control experiment without the use of catalyst resulted in a decreased yield (entry 20).

With the optimized conditions in hand (entries 3 and/or 9, Table 1), we next examined the substrate scope for this transformation, and the results are shown in Table 2. The *p*-substituted iodoarenes despite the electron-donating and electron-withdrawing nature of the substituents were found to be excellent substrates for the arylation to provide the corresponding biaryls in 71−87% yields (entries 1, 4, 7, and 10). For entry 4, *p*-terphenyl was also formed in 14% yield. On the other hand, iodoarenes bearing *o*- and *m*-substituents produced moderate yields (38−63%) of biaryls under the same reaction conditions (entries 2, 3, 5, 6, 8, 9 and 11). Regarding entry 6, 1,2-diphenylbenzene was also isolated in 13% yield. Better conversions were observed when the reactions were carried out with sarcosine instead of proline (in the case of entry 2), at elevated temperature (180 °C, entry 3) and for a prolonged reaction time (48 h, entry 12). The low reactivities

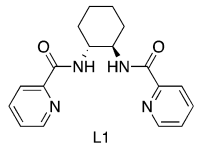
Received: May 9, 2012
Published: August 24, 2012

   dx.doi.org/10.1021/jo3008594 | J. Org. Chem. 2012, 77, 7844−7849

Table 1. Optimization of Reaction Conditions for the Reaction with 4-Iodoanisole 1a and Benzene 2[a]



1a 2 3a



L1

entry	catalyst	base	t (°C)	yield (%)[b]
1	proline	KO*t*-Bu	40	4
2	proline	KO*t*-Bu	120	47
3	**proline**	**KO*t*-Bu**	**150**	**87**
4	2-phenylglycine	KO*t*-Bu	150	62
5	phenylalanine	KO*t*-Bu	150	38
6	leucine	KO*t*-Bu	150	63
7	valine	KO*t*-Bu	150	6
8	pipecolic acid	KO*t*-Bu	150	61
9	**sarcosine**	**KO*t*-Bu**	**150**	**80**
10	*N*,*N*′-dimethylglycine	KO*t*-Bu	150	48
11	*trans*-4-OH-proline	KO*t*-Bu	150	53
12	prolinamide	KO*t*-Bu	150	49
13	BINOL	KO*t*-Bu	150	46
14	**L1**	KO*t*-Bu	150	43
15	proline	K_2CO_3	150	0
16	proline	K_3PO_4	150	0
17	proline	NaO*t*-Bu	150	0
19	proline	KO*t*-Bu (2 equiv)	150	55
20	none	KO*t*-Bu	150	35
21	proline	None	150	0

[a]Unless otherwise stated, reactions were carried out with **1a** (0.50 mmol), **2** (4 mL), catalyst (0.10 mmol), and base (1.50 mmol) under argon atmosphere in a 35 mL pressure-resistant tube. [b]Isolated yield.

of the *o*-substituted iodoarenes would be attributed to the steric effects. The instability of the aryl radicals at the *m*-position of the substituents by the inductive effects would be responsible for the low reactivities of the *m*-substituted iodoarenes (vide infra). Aryl bromide was less reactive for this transformation (entry 12).

Heterocyclic holoarenes were also tested (Table 2, entries 13-16). 2-Iodopyridine was smoothly converted into 2-phenylpyridine by the reaction of benzene in an excellent yield (83%, entry 13). However, the 3-iodo- and 4-iodopyridines were found to be less reactive (entries 14 and 15). The intermediate aryl radical formed from 2-iodopyridine would be stabilized by a neighboring nitrogen atom in the former case to achieve the good conversion. Such an effect is impossible in the latter cases. No transformation was observed when 2-iodothiophene was applied to the reaction of benzene (not shown) despite the 3-iodothiophene being transformed into 3-phenylthiophene in 69% yield (entry 16).

Next, a series of arene variations were also examined in this reaction (Table 3). Monosubstituted arenes, such as benzonitrile and toluene, afforded a mixture of regioisomers favoring the *ortho* isomers (entries 1 and 2). When both coupling partners are electron-rich (entry 2), presumably due to the instability of the intermediate biaryl radical (vide infra), the reaction was ineffective. Reactions with 1,4-difluorobenzene and pyradine afforded the desired biaryls in 48% and 70% yields, respectively (entries 3 and 4).

The coupling reaction presumably involves an aryl radical anion as the intermediate.[7−11] To verify this proposal, a radical-trapping experiment was carried out using TEMPO (1 equiv, Table 4, entry 1), a typical radical scavenger, for the reaction of 4-iodoanisole and benzene. The reaction rate was significantly suppressed to afford only a 10% yield of the biaryl **3a**. On the other hand, the presence of AIBN (0.4 equiv), known as a thermal-free radical initiator, promoted the conversion in the absence of proline (entry 2). When the reaction was performed without both AIBN and proline as a control experiment, the biaryl **3a** was formed in 35% yield (Table 1, entry 20). To examine the effect of trace metal impurities, the transformation with a copper salt was examined, which resulted in a lower yield than in the case without copper (entry 3 vs Table 2, entry 1). These observations strongly suggest the operation of a radical pathway for these conversions.

We next tested the competition experiment using an equimolar amount of benzene along with benzene-d_6 to estimate the rate-determining step in this arylation reaction (Table 5). The observed K_H/K_D (1.27) ratio was low, which indicated that the rate-determining step is not the deprotonation step but is the single electron-transfer process.

To gain further insight into the mechanism of the transformation, a competition reaction in the presence of an equimolar amount of the electron-sufficient and electron-deficient haroarenes **1a** and **1b** with benzene was investigated. A mixture of 4-iodoanisole **1a** and 4-fluoroiodobenzene **1b** was reacted with benzene for 1 h to form biaryls **3a** and **3d** favoring **3d** being formed from the electron-deficient substrate **1b** (entry 1). Individual reactions for the haroarenes **1a** and **1b** under the same conditions afforded yields of 31% and 53%, respectively (entries 2 and 3). These phenomena would suggest that the reaction involves a single-electron transfer step because the electron-deficient haroarene would be a better acceptor for the electron.

On the basis of this information, we propose the following possible mechanism (Scheme 1). An electron transfer from the chelate **4** derived from KO*t*-Bu and proline would afford the radical anion **6**, which would be transferred to the aryl radical **7** by release of the halonium ion. The addition of benzene to **7** followed by deprotonation would convert the aryl radical **7** to the biaryl radical anion **8**, which would form the final product **3** by electron transfer to the haroarene to regenerate the radical anion **6**.

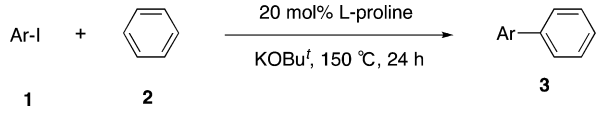
Finally, a gram-scale experiment targeting the synthesis of 1-pentyl-4-phenylbenzene **10**, a key building block for the preparation of liquid crystals, has been achieved (Scheme 2). The reaction of 4-iodopenylbenzene (1.37 g, 5.0 mmol) with benzene (30 mL) in the presence of L-proline (20 mol %) and *t*-BuOK (3 equiv) afforded the desired biaryl **10** (0.85 g, 3.8 mmol) in 76% isolated yield.

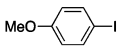
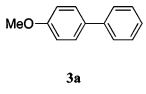
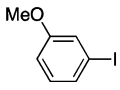
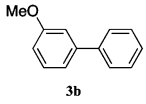
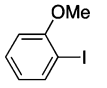
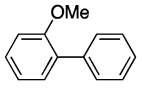
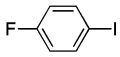
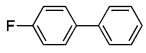
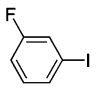
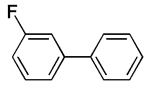
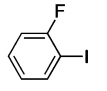
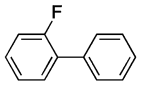
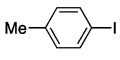
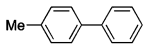
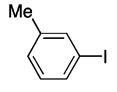
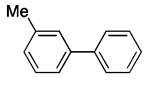
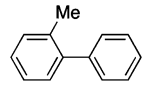
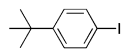
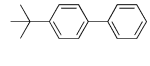
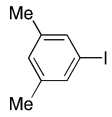
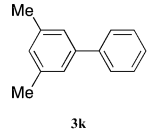
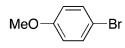
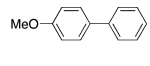
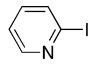
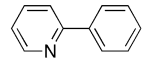
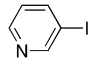
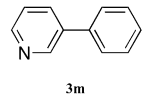
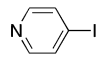
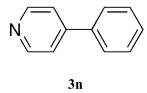
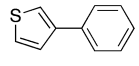
■ CONCLUSION

In conclusion, we have discovered a protocol for the transition-metal-free synthesis of biaryls based upon the utilization of amino acids (L-proline and sarcosine) as organocatalysts with unactivated benzenes as the substrate throughout the direct C−H bond functionalization. This method avoids the use of toxic transition-metal catalyst and organometallic reagents. Therefore, the present results would provide a new insight into the

dx.doi.org/10.1021/jo3008594 | J. Org. Chem. 2012, 77, 7844−7849

Table 2. Proline-Catalyzed Direct Arylation of Benzene with Ar-I[a]



entry	1	3	yield (%)[b]
1		 **3a**	87
2		 **3b**	49 64[c]
3		 **3c**	47 70[d]
4		 **3d**	71[e]
5		 **3e**	38
6		 **3f**	54[f]
7		 **3g**	80
8		 **3h**	48 (57)[g]
9		 **3i**	43 (53)[g]
10		 **3j**	72 (78)[g]
11		 **3k**	63 (72)[g]
12		 **3a**	26[h]
13		 **3l**	83
14		 **3m**	53
15		 **3n**	50
16		 **3o**	69

[a]Reaction conditions: arylhalide (0.50 mmol), L-proline (0.10 mmol), and KO*t*-Bu (1.50 mmol) in benzene (4 mL) at 150 °C under argon atmosphere in a 35 mL pressure-resistant tube. [b]Isolated yield. [c]Sarcosine was employed instead of proline. [d]Reaction at 180 °C. [e]*p*-Terphenyl (14%) was detected. [f]1,2-Diphenylbenzene (13%) was detected. [g]Yields based upon consumed haroarene **1**. [h]Reaction for 48 h.

realization of environmentally benign and cost-effective access to biaryl compounds.

EXPERIMENTAL SECTION

General Remarks. NMR spectra were recorded on a spectrometer, operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$ are reported on the δ scale relative to $CHCl_3$ (7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR) as an internal reference. The following abbreviations are used to multiplicities: s (singlet), d (doublet), t (triplet), m (multiplet), br (broad). Column chromatography was carried out with silica gel (230−400 mesh). Reactions were carried out in dry solvents under an argon atmosphere.

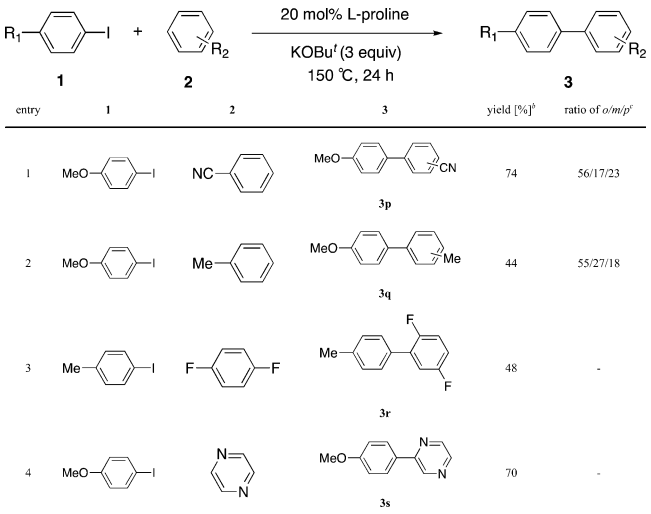
General Procedure: Cross-Coupling of Aryl Iodides with Arenes. Aryl iodides (0.5 mmol) and L-proline (0.1 mmol, 20 mol %) were added to a 35 mL oven-dried pressure-resistant tube with a tap. KO*t*-Bu (1.5 mmol, 3.0 equiv) was then added. Benzene (4 mL) was added to the tubes using a syringe. The mixture was then stirred in a sealed tube under argon atmosphere. Then the mixture was stirred at 150 °C until complete consumption of starting material as monitored by TLC. After completion of the reaction, the mixture was diluted with ethyl acetate and passed through a fritted glass filter to remove the inorganic salts, and solvent was removed with the aid of rotary evaporator. The residue was purified by column chromatography on silica gel using hexane/ethyl acetate as eluent to provide the desired product.

*4-Methoxy-biphenyl (**3a**; Table 1, entry 3).*[11a] Eluent hexane/ethyl acetate (22:1). A white solid. Yield, 80.6 mg, 87%. Mp 86−88 °C (lit.[11a] 85.6−86.8 °C); R_f 0.13 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.49 (m, 4H), 7.42 (t, 2H, J = 7.7 Hz), 7.31 (d, 1H, J = 7.2 Hz), 6.98 (d, 2H, J = 8.5 Hz), 3.86 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 140.8, 133.7, 128.7 (2C), 128.1 (2C), 126.7 (2C), 126.6, 114.2 (2C), 55.3.

*3-Methoxy-biphenyl (**3b**; Table 2, entry 2).*[11a] Eluent hexane/ethyl acetate (22:1). A colorless oil. Yield, 45.6 mg, 64%. R_f 0.13 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, 2H, J = 7.3 Hz), 7.43 (t, 2H, J = 7.4 Hz), 7.39−7.31 (m, 2H), 7.18 (d, 1H, J = 7.8 Hz), 7.15−7.10 (m, 1H), 6.90 (dd, 1H, J = 2.1, 8.1 Hz), 3.86 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 142.7, 141.1, 129.7, 128.7 (2C), 127.4, 127.2 (2C), 119.7, 112.9, 112.6, 55.3.

dx.doi.org/10.1021/jo3008594 | J. Org. Chem. 2012, 77, 7844−7849

Table 3. Proline-Catalyzed Direct Arylation of Various Arenes with Ar-I[a]



[a]Reaction conditions: 4-iodoanisole (0.50 mmol), L-proline (0.10 mmol), and KO*t*-Bu (1.50 mmol) in benzene (4 mL) at 150 °C under argon atmosphere in a 35 mL pressure-resistant tube. [b]Isolated yield. [c]The ratio was determined by NMR analysis.

*2-Methoxy-biphenyl (**3c**; Table 2, entry 3).*[11a] Eluent hexane/ethyl acetate (22:1). A colorless oil. Yield, 65.2 mg, 70%. R_f 0.13 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.53 (m, 1H), 7.53−7.49 (m, 1H), 7.41 (t, 2H, J = 7.4 Hz),7.35−7.29 (m, 3H), 7.06−6.95 (m, 2H), 3.81 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 138.5, 130.8, 130.7, 129.5 (2C), 128.6, 128.0 (2C), 126.9, 120.8, 111.2, 55.5.

*4-Fluoro-biphenyl (**3d**; Table 2, entry 4).*[11a] Eluent hexane/ethyl acetate (22:1). A white solid. Yield, 61.0 mg, 71%. Mp 74−76 °C (lit.[11a] 71.1−72.5 °C); R_f 0.39 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59−7.50 (m, 4H), 7.49−7.40 (m, 2H), 7.34 (t, 1H, J = 7.6 Hz), 7.18−7.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 161.2, 140.2, 137.3, 137.3, 128.8, 128.7, 128.6, 127.2, 127.0, 115.7, 115.5.

*3-Fluoro-biphenyl (**3e**; Table 2, entry 5).*[14] Eluent hexane/ethyl acetate (22:1). A white solid. Yield, 32.9 mg, 38%. R_f 0.39 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59−7.55 (m, 2H), 7.48−7.42 (m, 2H), 7.41−7.34 (m, 3H), 7.31−7.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (d, $^1J_{CF}$ = 245.0 Hz), 143.4, 139.9 (d, $^4J_{CF}$ = 2.5 Hz), 130.2 (d, $^3J_{CF}$ = 8.3 Hz), 128.9, 127.8, 127.1, 122.7 (d, $^4J_{CF}$ = 2.5 Hz), 114.1(d, $^2J_{CF}$ = 20.7 Hz), 113.9.

*2-Fluoro-biphenyl (**3f**; Table 2, entry 6).*[15] Eluent hexane/ethyl acetate (22:1). A white solid. Yield, 46.7 mg, 54%. Mp 71−72 °C (lit.[15] 70−72 °C); R_f 0.39 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.50 (m, 2H), 7.48−7.40 (m, 3H), 7.40−7.26 (m, 2H), 7.25−7.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8 (d, $^2J_{CF}$ = 247.5 Hz), 135.8, 130.8 (d, $^3J_{CF}$ = 3.3 Hz), 129.1 (d, $^2J_{CF}$ = 8.3 Hz), 129.0, 129.0, 128.9, 128.4, 127.6, 124.3 (d, $^3J_{CF}$ = 4.1 Hz), 116.1 (d, $^2J_{CF}$ = 22.3 Hz).

*4-Methyl-biphenyl (**3g**; Table 2, entry 7).*[11a] Eluent hexane/ethyl acetate (22:1). A white solid. Yield, 67.1 mg, 80%. Mp 46−47 °C (lit.[11a] 42.7−44.2 °C); R_f 0.35 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 2H, J = 7.6 Hz), 7.49 (d, 2H, J = 8.0 Hz), 7.43 (t, 2H, J = 7.6 Hz), 7.32 (t, 1H, J = 7.3 Hz), 7.25 (d, 2H, J = 7.8 Hz), 2.40 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 138.3, 137.0, 129.5 (2C), 128.7 (2C), 127.0 (2C), 127.0 (3C), 21.1.

*3-Methyl-biphenyl (**3h**; Table 2, entry 8).*[11a] Eluent hexane/ethyl acetate (22:1). A colorless oil. Yield, 40.5 mg, 48%. R_f 0.49 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.56 (m, 2H), 7.47−7.38 (m, 4H), 7.38−7.30 (m, 2H), 7.16 (d, 1H, J = 7.1 Hz), 2.42 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 141.2, 138.3, 128.7, 128.6, 128.0 (3C), 127.2 (2C), 127.1, 124.3, 21.6.

*2-Methyl-biphenyl (**3i**; Table 2, entry 9).*[11a] Eluent hexane/ethyl acetate (22:1). A colorless oil. Yield, 40.7 mg, 43%. R_f 0.25 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.38 (m, 2H), 7.38−7.30 (m, 3H), 7.29−7.20 (m, 4H), 2.28 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 135.3, 130.3, 129.8, 129.2 (2C), 128.0 (2C), 127.2, 127.1, 126.7, 125.8, 20.5.

*4-Phenyl-1-tert-butylbenzene (**3j**; Table 2, entry 10).*[16] Eluent hexane/ethyl acetate (22:1). A white solid. Yield, 76.0 mg, 72%. Mp 48−51 °C (lit.[16] 51 °C); R_f 0.26 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.56 (m, 2H), 7.56−7.50 (m, 2H), 7.50−7.40 (m, 4H), 7.36−7.30 (m, 1H), 1.37 (s, 9H, $C(C\underline{H}_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 141.0, 138.3, 128.7 (2C), 127.0 (2C), 127.0, 126.8 (2C), 125.7 (2C), 34.5, 31.4 (3C).

*3,5-Dimethylbiphenyl (**3k**; Table 2, entry 11).*[11a] Eluent hexane/ethyl acetate (22:1). A colorless oil. Yield, 76.0 mg, 72%. R_f 0.23 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, 2H, J = 7.3 Hz), 7.42 (t, 2H, J = 7.7 Hz), 7.32 (t, 1H, J = 7.3 Hz), 7.21 (s, 2H), 7.00 (s, 1H), 2.38 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 141.2, 138.2 (2C), 128.9, 128.6 (2C), 127.2 (2C), 127.1, 125.1 (2C), 21.4 (2C).

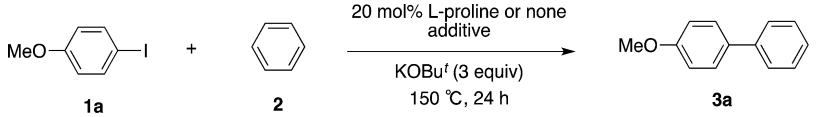
*2-Phenyl-pyridine (**3l**; Table 2, entry 13).*[17] Eluent hexane/ethyl acetate (3:1). A colorless oil. Yield, 62.8 mg, 83%. R_f 0.49 (hexane/AcOEt = 3:1) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73−8.68 (m, 1H), 8.02−7.97 (m, 2H), 7.77−7.70 (m, 2H), 7.52−7.45 (m, 2H), 7.45−7.39 (m, 1H), 7.25−7.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 149.6, 139.4, 136.7, 128.9, 128.7 (2C), 126.9 (2C), 122.0, 120.5.

*3-Phenyl-pyridine (**3m**; Table 2, entry 14).*[17] Eluent hexane/ethyl acetate (3:1). A yellow oil. Yield, 41.0 mg, 53%. R_f 0.30 (hexane/AcOEt = 3:1) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.60 (d, 1H, J = 4.4 Hz), 7.78 (d, 1H, J = 8.0 Hz), 7.59 (d, 2H, J = 7.1 Hz), 7.49 (t, 2H, J = 7.4 Hz), 7.42 (d, 1H, J = 7.1 Hz), 7.37 (dd, 1H, J = 4.9, 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 148.3, 137.8, 136.6, 134.3, 129.1 (2C), 128.1, 127.1 (2C), 123.5.

*4-Phenyl-pyridine (**3n**; Table 2, entry 15).*[17] Eluent hexane/ethyl acetate (3:1). A brown solid. Yield, 38.5 mg, 50%. Mp 72−74 °C (lit.[17] 73−74 °C); R_f 0.12 (hexane/AcOEt = 3:1) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, 2H, J = 4.9 Hz), 7.65 (d, 2H, J = 7.1 Hz), 7.56−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3 (2C), 148.3, 138.1, 129.1 (2C), 129.0, 127.0 (2C), 121.6 (2C).

*3-Phenyl-thiophene (**3o**; Table 2, entry 16).*[17] Eluent hexane/ethyl acetate (22:1). A white solid. Yield, 55.5 mg, 69%. Mp 81−84 °C (lit.[17]

Table 4. Arylation Reaction with a Radical-Trapping Agent, a Radical Initiator, and a Transition Metal[a]

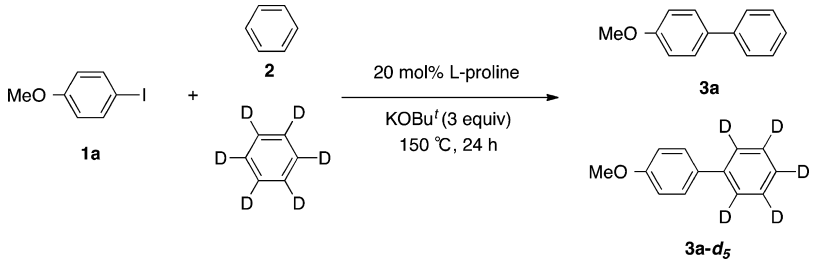


entry	catalyst	additive (equiv)	yield (%)[b]
1	proline	TEMPO (1.0)	10
2	none	AIBN (0.4)	60
3	proline	CuI (0.1)	75

[a]Reaction conditions: 4-iodoanisole (0.50 mmol), L-proline (0.10 mmol) or none, and KO*t*-Bu (1.50 mmol) in benzene (4 mL) at 150 °C under argon atmosphere in a 35 mL pressure-resistant tube. [b]Isolated yield.

dx.doi.org/10.1021/jo3008594 | J. Org. Chem. 2012, 77, 7844−7849

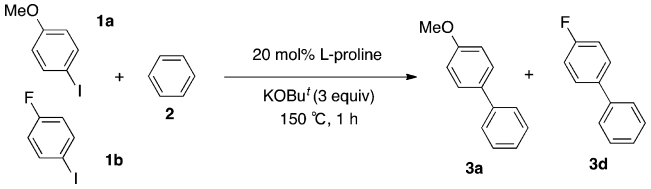
Table 5. Competition Reaction between Benzene and Benzene-d_6[a]



entry	benzene (equiv)	benzene-d_6 (equiv)	yield of **3a** (%)[b]	yield of **3**-d_5 (%)[b]	K_H/K_D
1	45	45	84	65	1.27
2	0	90		71	
3	90	0	87	0	

[a]Reaction conditions: 4-iodoanisole (0.50 mmol), L-proline (0.10 mmol), and KO*t*-Bu (1.50 mmol) in benzene (2 mL) and benzene-d_6 at 150 °C under argon atmosphere in a 35 mL pressure-resistant tube. [b]Isolated yield.

Table 6. Competition Reaction between Electron-Rich and Electron-Poor Haroarene with Benzene[a]



entry	**1a** (equiv)	**1b** (equiv)	yield of **3a** (%)[b]	yield of **3d** (%)[b]
1	0.5	0.5	53	59
2	1.0	0	49	
3	0	1.0		53

[a]Reaction conditions: 4-iodoanisole (0.25 mmol) and 1-fluoro-4-iodobenzene (0.25 mmol), L-proline (0.10 mmol), and KO*t*-Bu (1.50 mmol) in benzene (4 mL) at 150 °C under argon atmosphere in a 35 mL pressure-resistant tube. [b]Isolated yield.

89–91 °C); R_f 0.26 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, 2H, J = 7.8 Hz), 7.48–7.24 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 135.8, 128.8 (2C), 127.1, 126.4 (2C), 126.3, 126.2, 120.3.

*(p-Methoxyphenyl)benzonitrile (a mixture of o:m:p = 56:17:23) (**3p**; Table 3, entry 1).*[10] Eluent hexane/ethyl acetate (22:1). A pale yellow oil. Yield, 77.7 mg, 74%. R_f 0.15 (hexane/AcOEt = 22:1) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.81 (m, 0.17H), 7.80–7.72 (m, 0.75H), 7.72–7.7.68 (m, 0.46H), 7.68–7.7.46 (m, 4.06H), 7.40 (dt, 0.56H, J = 1.2, 7.5 Hz), 7.05–6.98 (m, 1.93H), 3.87 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 145.2, 133.7, 132.8, 132.6, 131.5, 131.0, 130.5, 130.2, 130.0, 130.0, 129.8, 129.5, 128.3, 128.1, 127.1, 127.0, 119.0, 114.5, 114.1, 111.0, 55.4, 55.3.

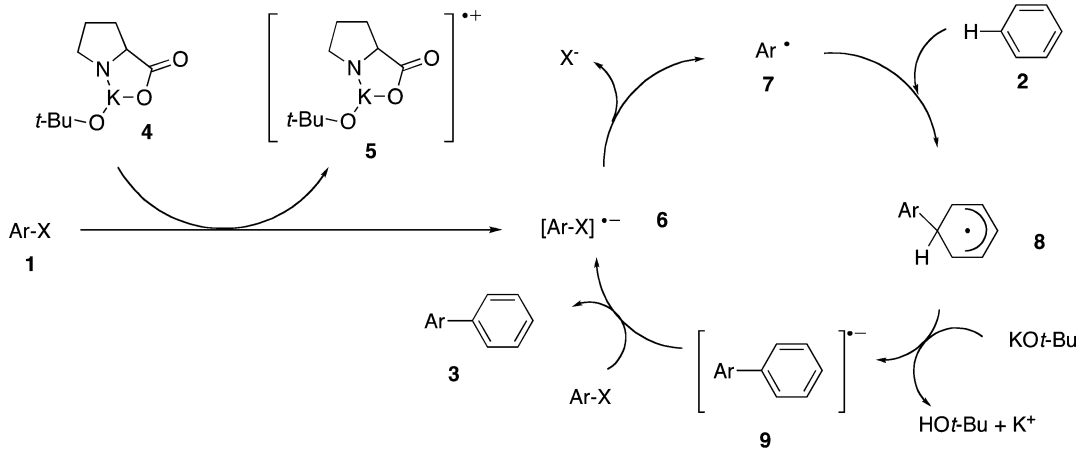
*(p-Methoxyphenyl)toluene (a mixture of o:m:p = 55:27:18) (**3q**; Table 3, entry 2).*[11d] Eluent hexane/ethyl acetate (22:1). A pale yellow oil. Yield, 43.6 mg, 44%. R_f 0.13 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.10 (m, 6H), 7.00–6.90 (m, 2H), 3.84 (s, 3H, OCH_3), 2.41 (s, 0.82H, *o*-$\underline{CH_3}C_6H_4$), 2.38 (s, 0.55H, *p*-$\underline{CH_3}C_6H_4$), 2.28 (s, 1.65H, *o*-$\underline{CH_3}C_6H_4$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 158.5, 141.5, 140.8, 138.3, 136.3, 135.5, 134.3, 133.8, 133.7, 130.3, 130.2, 129.9, 129.4, 128.6, 128.1, 127.9, 127.5, 127.4, 126.9, 126.6, 125.7, 123.8, 114.1, 113.4, 55.3, 55.2, 21.5, 21.0, 20.5.

*2,5-Difluoro-4′-methylbiphenyl (**3r**; Table 3, entry 3).*[18] Eluent hexane/ethyl acetate (22:1). A colorless oil. Yield, 41.6 mg, 41%. R_f 0.26 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, 2H, J = 6.3 Hz), 7.26 (d, 2H, J = 8.3 Hz), 7.15–7.05 (m, 2H), 7.00–6.93 (m, 1H), 2.40 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7 (dd, J_F = 2.5, 241.7 Hz), 155.7 (dd, J_F = 2.5, 243.3 Hz), 138.1, 132.1, 130.3–130.5 (m), 129.3, 128.7 (d, J_F = 3.3 Hz), 126.8, 114.6–117.2(m), 21.2.

*4-Methoxyphenylpyrazine (**3s**; Table 3, entry 4).*[7] Eluent hexane/ethyl acetate (1:1). A white solid. Yield, 65.4 mg, 70%. Mp 87–89 °C (lit.[7] 95 °C); R_f 0.58 (hexane/AcOEt = 1:1) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (d, 1H, J = 1.5 Hz), 8.59 (t, 1H, J = 2.0 Hz), 8.45 (d, 1H, J = 2.4 Hz,), 8.02–7.95 (m, 2H), 7.06–7.00 (m, 2H), 3.89 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 152.5, 144.0, 142.1, 141.6, 128.8, 128.3 (2C), 114.5 (2C), 55.4.

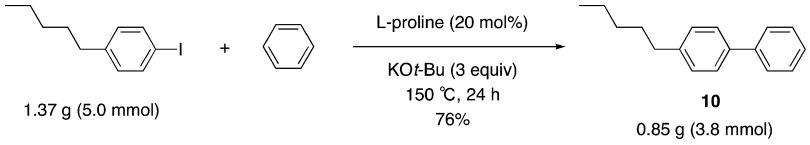
*2,3,4,5,6-Pentadeuterio-4′-methoxy-biphenyl (**3a**-d_5; Table 5, entry 2).*[8] Eluent hexane/ethyl acetate (22:1). A white solid. Yield, 67.1 mg, 71%. Mp 87–88 °C (lit.[19] 133–134 °C); ^{1}H NMR (400

Scheme 1. Proposed Catalyst Cycle



dx.doi.org/10.1021/jo3008594 | J. Org. Chem. 2012, 77, 7844–7849

Scheme 2. Gram-Scale Synthesis of 1-Pentyl-4-phenylbenzene



MHz, $CDCl_3$) δ 7.53 (d, 2H, J = 8.5 Hz, Ar), 6.98 (d, 2H, J = 8.5 Hz, Ar), 3.86 (s, 3H, OCH_3).

*1-Pentyl-4-phenylbenzene (**10**; Scheme 2).*[20] 4-Iodopentylbenzene (1.37 g, 5.0 mmol) and L-proline (115.0 mg, 1.0 mmol, 20 mol %) were added to a 100 mL oven-dried pressure-resistant tube with a tap. KO*t*-Bu (1.68 g, 15.0 mmol, 3.0 equiv) was then added. Benzene (30 mL) was added to the tubes using a syringe. The mixture was then stirred in a sealed tube for 24 h under argon atmosphere. The mixture was diluted with ethyl acetate and passed through a fritted glass filter, and solvent was removed with the aid of rotary evaporator. The residue was purified by column chromatography on silica gel using hexane/ethyl acetate (22:1) as eluent to provide the desired biaryl **10** (853.6 mg, 76%) as a pale yellow oil. R_f 0.28 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.05 Hz, 2H), 7.51 (d, J = 7.81 Hz, 2H), 7.43 (t, J = 7.68 Hz, 2H), 7.36−7.28 (m, 1H), 7.26 (d, 2H), 2.64 (t, J = 7.81 Hz, 2H), 1.70−1.60 (m, 2H), 1.40−1.30 (m, 4H), 0.91 (t, J = 6.71 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 141.2, 138.5, 128.8 (2C), 128.7 (2C), 127.0 (2C), 127.0 (2C), 126.9, 35.6, 31.5, 31.2, 22.6, 14.0.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge Ms. Sachiko Asami, Mrs. Ikuhiro Inada, Atsushi Isayama, and Hiroaki Ohmukai for generous support in some of the experiments.

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