One-Pot Preparation of Arylalkynes by a Tandem Catalytic Iodination of Arenes and Palladium-Catalyzed Coupling of Iodoarenes with Terminal Alkynes

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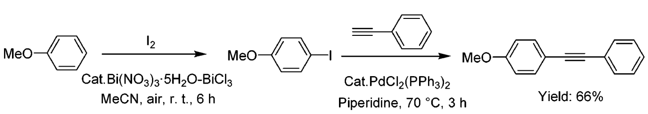

Iodination of activated arenes by air-oxidation is carried out in the presence of catalytic bismuth salts at room temperature. Subsequently, the formed iodoarenes react with terminal alkynes to give arylalkynes under a selected palladium-catalyzed coupling condition in the same pot.

Arylalkynes are very useful intermediates for the preparation of important compounds including natural products, pharmaceuticals,[1] oligomers, and polymers.[2] Their conjugated systems also have received more and more attention in optical[3] and electronic applications.[4]

Palladium-catalyzed coupling of haloarenes, especially iodoarenes with terminal alkynes is a versatile and convenient method to form arylalkynes in organic synthesis.[5] However, iodoarenes as substrates in these coupling reactions have to be generated from simple arenes first,[6] and iodination of arenes is not a catalytic process, which is normally carried out under harsh conditions by using very strong acids, a large amount of oxidant, special reagents, and so on. On the other hand, the palladium-catalyzed coupling of iodoarenes with terminal alkynes proceeds mainly under base and inert conditions. Thus, it is very hard to perform a coupling reaction and an iodination of arenes in one pot.

However, most recently, a few examples of iodination of arenes under mild conditions were reported. Neumann and Branytska discovered an aerobic oxidative iodination of arenes in the presence of polyoxometalate, $H_5PV_2Mo_{10}O_{40}$, as catalyst with 2 atm of O_2 at 80 °C,[7] and Samant and co-workers disclosed an iodination of activated arenes with molecular iodine using silica-supported stoichiometric bismuth(III) nitrate pentahydrate [BNP], $Bi(NO_3)_3{\cdot}5H_2O$ as oxidant at room temperature.[8]

In addition, we have developed an efficient iodination of activated arenes by air-oxidation with catalytic BNP−$BiCl_3$ at room temperature (Scheme 1). In this reaction, no acids or special reagents are required and oxygen from air is the oxidant, so it provides very mild conditions for iodination of arenes and makes the one-pot preparation of arylalkynes by tandem iodination of arenes and palladium-catalyzed coupling of iodoarenes with terminal alkynes possible.

In the initial investigation of this iodination of arenes, based on the work of Samant and co-workers,[8] we found that *p*-iodoanisole (**2a**) was produced in 92% yield from anisole and iodine in the presence of 5.0 mol % of BNP in MeCN at room temperature within 26 h. Meanwhile, just using 1.0 atm of pure O_2 instead of air under the same conditions, a quantitative amount of **2a** was detected by GC. On the other hand, without any catalysts or with only 5 mol % of $NaNO_3$ in the iodination of anisole, a trace or 6% yield of **2a** were observed by GC after 24 h, respectively. These results show that Bi(III) salts as catalyst and oxygen as oxidant are necessary in this catalytic iodination reaction. After the test of many other oxidants in catalytic amount, including $BiCl_3$, Bi_2O_3, $Cu(OAc)_2$, $CuCl_2$, $Cu(NO_3)_2$, $Fe(NO_3)_3$, $K_2S_2O_8$, $KMnO_4$ and various combinations of them,[9] the best result for the iodination of anisole was the use of 2.5 mol % of BNP−$BiCl_3$ as catalyst, giving **2a** in 90% yield in 6 h. Interestingly, $BiCl_3$ as cocatalyst can notably accelerate the rate of this iodination of arenes, although it is not an effective catalyst alone.

Moreover, the effects of solvents on this reaction were also studied. It was found that the reaction proceeded very well in CH_2Cl_2, CH_2ClCH_2Cl, and HOAc, respectively,[9] but a longer reaction time was needed. Without any added solvent, the iodination of anisole (6.0 mmol) with I_2 (3.0 mmol), catalyzed by only 0.4 mol % of BNP−$BiCl_3$, gave **2a** in 87% isolated yield in 12 h.

In the same catalytic system, iodination of other arenes were screened. The results are summarized in Table 1. Similarly to the case of **1a**, activated arenes, **1b**−**1e** were readily iodinated to produce their corresponding products **2b**−**2e** in good to excellent yields (Table 1, entries 2−5). Arenes having large

(1) (a) *Chemistry and Biology of Naturally-Occurring Acetylenes and Related Compounds*; Lam, J., Breteler, H., Arnason, T., Hansen, L., Eds.; Elsevier: Amsterdam, The Netherlands, 1988. (b) Nova'k, Z.; Kotschy, A. *Org. Lett.* **2003**, *5*, 3495.

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(4) (a) Bumm, L. A.; Arnold, J. J.; Cygan, M. T.; Dunbar, T. D.; Burgin, T. P.; Jones, L., II.; Allara, D. L.; Tour, J. M.; Weiss, P. S. *Science* **1996**, *271*, 1705. (b) Tour, J. M.; Jones, L.; Pearson, D. L.; Lamba, J. J. S.; Burgin, T. P.; Whitesides, G. M.; Allara, D. L.; Parikh, A. N.; Atre, S. *J. Am. Chem. Soc.* **1995**, *117*, 9529. (c) Schumm, J. S.; Pearson, D. L.; Tour, J. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1360.

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(9) For details, see Supporting Information, Table 1, "Effects of Catalysts", and Table 2, "Effects of Solvents".

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SCHEME 1. Iodination of Activated Arenes by Air-Oxidation with Catalytic BNP−$BiCl_3$ at Room Temperature

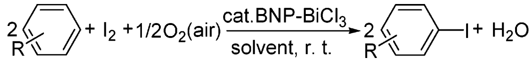
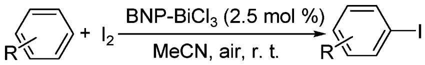
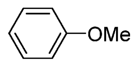
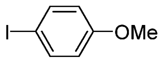
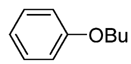
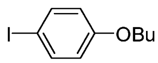
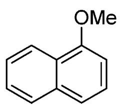
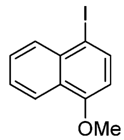
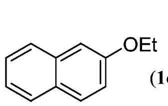
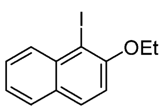
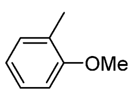
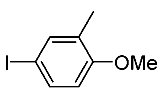
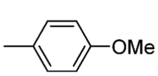
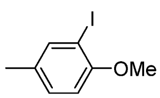
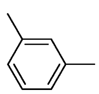
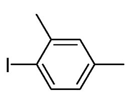
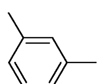
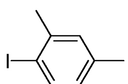
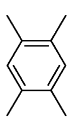
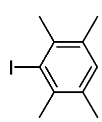


TABLE 1. Oxidative Iodination of Various Activated Arenes Catalyzed by BNP−$BiCl_3$[a]



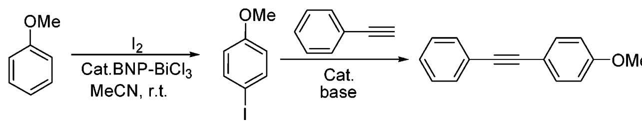
Entry	Arene		Product		Yield (%)[b]
1		(**1a**)		(**2a**)	90
2		(**1b**)		(**2b**)	87
3		(**1c**)		(**2c**)	88
4		(**1d**)		(**2d**)	98
5		(**1e**)		(**2e**)	96
6		(**1f**)		(**2f**)	78[c,e]
7		(**1g**)		(**2g**)	62
8		(**1h**)		(**2h**)	80
9		(**1i**)		(**2i**)	69[d,e]

[a] Conditions: arenes (1.0 mmol), iodine (0.5 mmol), BNP (0.025 mmol, 2.5 mol %), $BiCl_3$ (0.025 mmol, 2.5 mol %), and MeCN (1.0 mL); air; 6 h; rt. [b] Isolated yield (average of two runs). [c] ^{1}H NMR yield. [d] GC yield. [e] After 12 h.

steric hindrance could also be iodinated effectively by this method (Table 1, entries 6−9). All products were monoiodoarenes with high regioselectivity. However, this iodination reaction is not available to deactivated arenes and benzene.

A possible mechanism suggests that molecular iodine is directly oxidized by Bi(III) to I^+-type species that attack arenes to give iodoarenes, which is an electrophilic aromatic substitution, and bismuth salts shuttle between Bi(I) and Bi(III) in the presence of oxygen, as described by Duñach and Antoniotti.[10] Adding 10 mol % of KI and 90 mol % of I_2 as a mixed iodine

TABLE 2. Coupling of Anisole (1a) with Phenyl Acetylene (3a) under Various Palladium-Catalyzed Coupling Conditions[a]



entry	catalyst	base	yield[b] (%)
1[c]	$PdCl_2(PPh_3)_2$	piperidine	72
2	$PdCl_2(PPh_3)_2$	Et_3N	26
3[d]	$PdCl_2$	pyrrolidine	52
4	$Pd(OAc)_2$	DABCO	20
5[d]	$Pd(PPh_3)_4$	K_2CO_3	25
6[d]	$Pd(PPh_3)_4$	KOH	38

[a] Conditions: anisole (1.0 mmol), iodine (0.5 mmol), BNP (0.025 mmol, 2.5 mol %), $BiCl_3$ (0.025 mmol, 2.5 mol %), and MeCN (1.0 mL); air; 6 h; rt. Then, adding base (5.0 mmol), Pd catalyst (0.025 mmol, 2.5 mol %), and phenyl acetylene (1.0 mmol); 24 h; rt. [b] GC yield. [c] 3 h, 70 °C. [d] H_2O (2.0 mL) added after iodination of anisole, 50 °C.

source to the catalytic iodination reaction of anisole just gave a trace amount of product detected by GC in 24 h, which means the I^- anion could block the catalytic cycle and the anion might not be generated during the Bi(III)-catalyzed oxidative iodination of arenes with iodine.

For the palladium-catalyzed coupling of iodoarenes with terminal alkynes, however, the conventional operation is under an Ar or N_2 atmosphere to avoid Glaser-type oxidative dimerization of terminal alkynes. Therefore, those coupling reactions, which can proceed under aerobic conditions, should be considered to connect the oxidative iodination of arenes in one pot. For instance, Liang and co-workers reported a copper-free Sonogashira coupling of iodoarenes with terminal acetylenes in water under aerobic conditions.[11] Li and co-workers described a coupling reaction employing a relatively low palladium catalyst loading under mild, aerobic, copper-free, and ligand-free conditions.[12] Leadbeater and Tominack disclosed a method for easy and rapid copper-free Sonogashira coupling in the presence of bis(triphenylphosphine) palladium dichloride with piperidine at 70 °C.[13]

The first set of experiments was directed toward the establishment of the optimal conditions for the combination of both the iodination of arenes and the subsequent palladium-catalyzed coupling of iodoarenes with terminal alkynes. A variety of coupling conditions including those mentioned above were investigated, and anisole (**1a**) was chosen as a model arene for oxidative iodination and coupling with phenyl acetylene (**3a**).

As shown in Table 2, we were pleased to find that the coupling reaction proceeded very well under the aerobic conditions reported by Leadbeater and Tominack.[13] Compound **4a** was obtained in a yield of 72%, and the oxidative dimerization of phenyl acetylenes was not found by GC detection (Table 2, entry 1).

It was also found that the coupling reaction could run well to give **4a** in 52% yield by using palladium dichloride as catalyst and pyrrolidine as base in water and MeCN at 50 °C under aerobic conditions (Table 2, entry 3). In this case, the merit of using catalytic bismuth salts to avoid byproduct formation was remarkable. By GC detection, no homocoupling products from phenyl acetylenes were found in palladium-catalyzed couplings

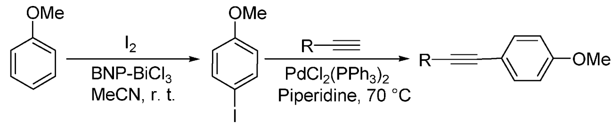
(10) Antoniotti, S.; Duñach, E. *Eur. J. Org. Chem.* **2004**, *69*, 3459.

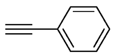
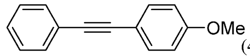
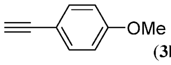
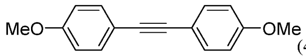
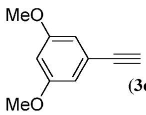
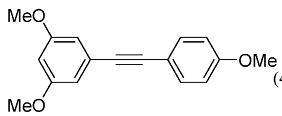
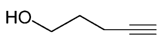
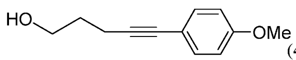
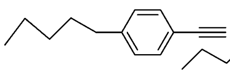
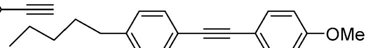
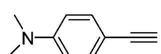
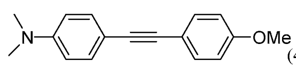
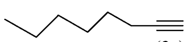
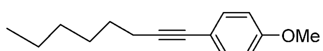
(11) Liang, B.; Dai, M. J.; Chen, J. H.; Yang, Z. *J. Org. Chem.* **2005**, *70*, 391.

(12) Li, J. H.; Liang, Y.; Xie, Y. X. *J. Org. Chem.* **2005**, *70*, 4393.

(13) Leadbeater, N. E.; Tominack, B. J. *Tetrahedron Lett.* **2003**, *44*, 8653.

TABLE 3. One-Pot Preparation of Arylalkynes from Anisole and Various Terminal Alkynes by Tandem Catalytic Iodination of Anisole and Palladium-Catalyzed Coupling[a]



Entry	Acetylene	Product	Yield (%)[b]
1	 (**3a**)	 (**4a**)	66
2	 (**3b**)	 (**4b**)	85
3	 (**3c**)	 (**4c**)	72
4	 (**3d**)	 (**4d**)	40
5	 (**3e**)	 (**4e**)	68
6	 (**3f**)	 (**4f**)	76
7	 (**3g**)	 (**4g**)	50

[a] Conditions: anisole (1.0 mmol), iodine (0.5 mmol), BNP (0.025 mmol, 2.5 mol %), $BiCl_3$ (0.025 mmol, 2.5 mol %), and MeCN (1.0 mL); air; 6 h; rt. Then, adding piperidine (0.5 mL, 5.0 mmol), $PdCl_2(PPh_3)_2$ (0.025 mmol, 2.5 mol %), and terminal alkyne (1.0 mmol); 3 h; 70 °C. [b] Isolated yield.

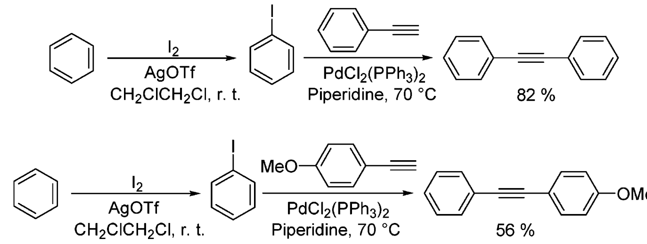
connected with the catalytic oxidative iodination of arenes, but a large amount of them was formed in the coupling reaction after the stoichiometric oxidative iodination of arenes. No positive results were obtained in other cases of coupling reactions due to a large amount of the byproducts generated (Table 2, entries 2 and 4−6). Obviously, not any of palladium-catalyzed couplings of iodoarenes with terminal alkynes can proceed very well after the catalytic iodination of arenes in the same pot.

To examine the scope of this one-pot preparation of arylalkynes, couplings of various terminal alkynes with anisole were studied. The results from these reactions are listed in Table 3. The yields of products from terminal aryl acetylenes (Table 3, entries 1−3, 5, and 6) were better than those from terminal alkyl acetylenes (Table 3, entries 4 and 7). Another arene, 1-methoxy-2-methylbenzene (**1e**) was also tried to couple with phenyl acetylene (**3a**), and it was found that its corresponding product, 1-methoxy-2-methyl-4-(phenylethynyl)benzene (**4h**), was isolated in a good yield, 84%.

For benzene and deactivated arenes, the iodination method described by Zheng and Mulhollandand was used in this one-pot method.[14] Benzene was chosen to be iodinated using I_2−AgOTf reagent first, then iodobenzene reacted with **3a** and **3b** to give 1,2-diphenylethyne **(4i)** in 82% yield and **4a** in 56% yield, respectively, in one pot (Scheme 2).

(14) Mulhollandand, G. K.; Zheng Q. H. *Synth. Commun.* **2001**, *31*, 3059.

SCHEME 2. One-Pot Preparation of Arylalkynes from Benzene and Terminal Alkynes



All of the results above indicate that if both of the reaction conditions for the iodination of arenes and for palladium-catalyzed coupling are compatible, the one-pot preparation of arylalkynes from simple arenes and terminal alkynes is feasible.

In summary, an efficient method has been established for the one-pot synthesis of arylalkynes starting from simple arenes and terminal alkynes by a tandem catalytic iodination of arenes and palladium-catalyzed coupling.

Experimental Section

Typical Preparation of Iodoarenes. Preparation of 2-Ethoxy-1-iodonaphthalene (2d): 1d (170.9 mg, 1.0 mmol), I_2 (142.1 mg, 0.56 mmol), BNP (12.8 mg, 0.026 mmol, 2.6 mol %), $BiCl_3$ (7.9 mg, 0.025 mmol, 2.5 mol %), MeCN (1.0 mL), and a magnetic stir bar were placed in a dried flask. The mixture was stirred at room temperature for 6 h until complete consumption of the starting material, as detected by TLC and GC analysis. Then the reaction mixture was desorbed by dichloromethane (3 × 10 mL). The organic extracts were successively washed with aq $Na_2S_2O_3$ solution, dried over anhydrous $MgSO_4$, and then evaporated under reduced pressure. The crude product was purified by column chromatography over silica to produce 289.9 mg (98%) of **2d** as a white crystal (mp 76 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (t, $J = 6.8$ Hz, 3H), 4.26 (q, 2H), 7.18 (d, $J = 8.4$ Hz, 1H), 7.407 (td, $J_1 = 8.6$ Hz, $J_2 = 0.9$ Hz, 1H), 7.553 (td, $J_1 = 8$ Hz, $J_2 = 0.9$ Hz, 1H), 7.74 (d, $J = 8.4$ Hz, 1H), 7.80 (d, $J = 8.8$ Hz, 1H), 8.15 (d, $J = 8.8$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.4, 66.3, 89.1, 114.7, 124.6, 128.2, 128.4, 130.2, 130.4, 131.6, 135.9, 156.4. Anal. Calcd for $C_{12}H_{11}$-OI: C, 48.35; H, 3.72. Found: C, 48.71; H, 3.99.

Typical Preparation of Arylalkynes from Activated Arenes and Terminal Alkynes. Preparation of 4-((4-Methoxyphenyl)-ethynyl)-*N*,*N*-dimethylbenzenamine (4f): 1a (110.7 mg, 1.02 mmol), I_2 (123.7 mg, 0.49 mmol), BNP (12.7 mg, 0.026 mmol, 2.6 mol %), $BiCl_3$ (8.8 mg, 0.027 mmol, 2.7 mol %), MeCN (1.0 mL), and a magnetic stir bar were placed in a dried flask. The mixture was stirred at room temperature for 6 h until complete consumption of the starting material, as detected by TLC and GC analysis. Then piperidine (0.5 mL, 5.0 mmol), $PdCl_2(PPh_3)_2$ (17.8 mg, 0.025 mmol, 2.5 mol %), and **3f** (116.2 mg, 0.8 mmol) were added into the reaction flask. The reaction flask was sealed and heated in an oil bath preheated at 70°C until the completion of the coupling reaction (3 h). After cooling to room temperature, water and dichloromethane (3 × 10 mL) were added to the mixture, and the organic material was extracted and then washed with acid (15% v/v HCl) until the washings were neutral. The organic layer was washed with water (40 mL) again before being dried over $MgSO_4$. Finally, the dichloromethane was removed under reduced pressure to obtain the crude product, which was purified by column chromatography to produce 152.7 mg (76%) of **4f** as a white crystal (mp 135−136 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.98 (s, 6H), 3.82 (s, 3H), 6.66 (d, $J = 8.4$ Hz, 2H), 6.85 (d, $J = 8.8$ Hz, 2H), 7.39 (d, $J = 8.0$ Hz, 2H), 7.43 (d, $J = 8.4$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ

40.5, 55.5, 87.32, 89.3, 110.6, 112.1, 114.1, 116.5, 132.8, 132.9, 150.1, 159.3. EI-MS *m*/*z*: 251 (M^+, 100), 236 (58). HRMS calcd for $C_{17}H_{17}NO$, 251.1310; found, 251.1311.

Typical Preparation of Arylalkynes from Benzene and Terminal Alkynes. Preparation of 1,2-Diphenylethyne (4i): Benzene (78.0 mg, 1.0 mmol), silver triflate (256.7 mg, 1.0 mmol), iodine (253.8 mg, 1.0 mmol), CH_2ClCH_2Cl (1.0 mL), and a magnetic stir bar were placed in a darkened flask. The mixture was stirred at room temperature for 5 min until complete consumption of the starting material, as detected by TLC and GC analysis. Then piperidine (0.5 mL, 5.0 mmol), $PdCl_2(PPh_3)_2$ (17.6 mg, 0.025 mmol, 2.5 mol %), and **3a** (102.0 mg, 1.0 mmol) were added into the reaction flask. The reaction flask was sealed and heated in an oil bath preheated at 70 °C until completion of the coupling reaction (3 h). After cooling to room temperature, water and dichloromethane (3 × 10 mL) were added to the mixture, and the organic material was extracted and then washed with acid (15% v/v HCl) until the washings were neutral. The organic layer was washed with water (40 mL) again before being dried over $MgSO_4$. Finally, the dichloromethane was removed under reduced pressure to obtain the crude product, which was purified by column chromatography to produce 146.1 mg (82%) of **4i** as a white crystal (mp 63−64 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.37 (m, 6H), 7.53−7.55 (m, 4H).

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Supporting Information Available: Experimental procedures and characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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