

tert-Butoxide-Mediated Arylation of Benzene with Aryl Halides in the Presence of a Catalytic 1,10-Phenanthroline Derivative

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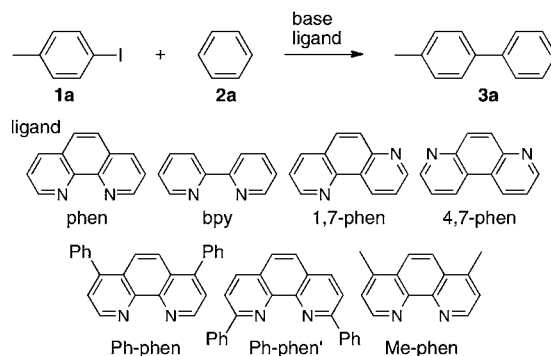
Abstract: Sodium *tert*-butoxide mediates the coupling of aryl halides with benzene derivatives without the aid of transition metal catalysts but with a catalytic 1,10-phenanthroline derivative.

Homolytic aromatic substitution (HAS) with aryl radicals, namely addition of aryl radicals to benzene derivatives followed by elimination of a hydrogen radical, is one of the most straightforward methods to construct biphenyl frameworks.¹ However, its utility has been hampered by laborious procedures for generation of aryl radicals. Aromatic compounds such as arenediazonium salts and diaryl peroxides having an Ar–X bond that readily undergoes homolytic cleavage are efficient precursors but are not always easily accessible.^{1a,2} Use of readily available aryl halides as aryl radical precursors requires a stoichiometric amount of a radical source such as Bu₃SnH and (Me₃Si)₃SiH^{1d,3} or special conditions such as irradiation.⁴ A transition metal catalyst in combination with an aryl halide has recently been introduced as a radical source.⁵ Here we found that the coupling of aryl halides with benzene derivatives is mediated by sodium *tert*-butoxide with the aid of a catalytic 1,10-phenanthroline derivative through an HAS mechanism.⁶

Treatment of 4-iodotoluene (**1a**: 1 equiv) with NaO*t*-Bu (2 equiv) and 1,10-phenanthroline (phen: 20 mol %) in benzene (**2a**: 120 equiv) at 155 °C⁷ for 3 h gave 4-methylbiphenyl (**3a**) in 72% yield (entry 1 of Table 1).⁸ The coupling proceeded at a lower temperature though a longer reaction period is required (entries 2 and 3). Use of a reduced amount of NaO*t*-Bu resulted in a slow rate, and no reaction took place without a base (entries 4–6). A comparable yield of **3a** was obtained with the more basic KO*t*-Bu, whereas weaker bases were much less effective (entries 7–11). No coupling product was obtained in the reaction with no ligands or other types of bidentate *sp*²- or *sp*³-nitrogen ligands (entries 12–14). Phenanthrolines that have nitrogen atoms at 1,7- or 4,7-positions were totally ineffective (entries 15 and 16). Substitution of phen with two phenyl groups at 4- and 7-positions (Ph-phen) increased the yield (entry 17), whereas the substitution at 2,9-positions or introduction of methyl groups resulted in much lower yields with lower activities (entries 18 and 19). Ph-phen was found to be more active than phen, and the reaction was completed in 6 h with a reduced amount (10 mol %) (entries 20–22).⁹

The arylation of arenes is applicable to various aryl and heteroaryl halides (Table 2). Aryl and heteroaryl iodides of various electronic character reacted with benzene to give biaryls in moderate to high yields (entries 1–8). *p*-Tolyl bromide (**1a'**) reacted slower than iodide **1a** but scored a comparable yield (entries 9 and 10). The reaction of **1a'** using KO*t*-Bu instead of NaO*t*-Bu proceeded much faster, but the yield of **3a** was lower (50%) due to coproduction of 3- and 4-(*tert*-butoxy)toluenes derived from the arylene intermediate (entry 11). Introduction of a conjugating or electron-withdrawing group enhanced the

Table 1. Arylation of Benzene with *p*-Tolyl Iodide^a



entry	base (equiv)	ligand (mol %)	temp (°C)	time (h)	conv (%) ^b	yield (%) ^b
1	NaO <i>t</i> -Bu (2)	phen (20)	155	3	>99	72
2	NaO <i>t</i> -Bu (2)	phen (20)	130	3	30	21
3	NaO <i>t</i> -Bu (2)	phen (20)	130	48	>99	73
4	NaO <i>t</i> -Bu (1.5)	phen (20)	155	3	43	32
5	NaO <i>t</i> -Bu (1.5)	phen (20)	155	12	>99	74
6	–	phen (20)	155	3	2	<1
7	KO <i>t</i> -Bu (2)	phen (20)	155	3	>99	67
8	LiO <i>t</i> -Bu (2)	phen (20)	155	3	23	7
9	NaOH (2)	phen (20)	155	3	13	2
10	Na ₂ CO ₃ (2)	phen (20)	155	3	8	<1
11	Bu ₃ N (2)	phen (20)	155	3	3	<1
12	NaO <i>t</i> -Bu (2)	–	155	3	<1	<1
13	NaO <i>t</i> -Bu (2)	bpy (20)	155	3	16	1
14	NaO <i>t</i> -Bu (2)	TMEDA (20)	155	3	10	<1
15	NaO <i>t</i> -Bu (2)	1,7-phen (20)	155	3	10	<1
16	NaO <i>t</i> -Bu (2)	4,7-phen (20)	155	3	<5	<1
17	NaO <i>t</i> -Bu (2)	Ph-phen (20)	155	3	>99	82
18	NaO <i>t</i> -Bu (2)	Ph-phen' (20)	155	3	26	12
19	NaO <i>t</i> -Bu (2)	Me-phen (20)	155	3	44	22
20	NaO <i>t</i> -Bu (2)	phen (10)	155	3	40	26
21	NaO <i>t</i> -Bu (2)	Ph-phen (10)	155	3	58	37
22	NaO <i>t</i> -Bu (2)	Ph-phen (10)	155	6	>99	80 ^c

^a The reaction was carried out under a nitrogen atmosphere using 4-iodotoluene (**1a**: 0.225 mmol) and benzene (**2a**: 2.4 mL, 27 mmol) in a sealed tube. ^b Determined by GC. ^c Isolated yield = 76%.

reactivity of aryl halides: *p*-phenylphenyl bromide and *p*-cyanophenyl chloride underwent the coupling in 12 and 6 h, respectively (entries 12 and 13). *p*-Bromo(iodo)benzene was selectively phenylated at the iodo moiety (entry 14). A chloro moiety was intact under standard conditions (entry 15). *p*-Diiodobenzene underwent double phenylation (entry 16).¹⁰

In HAS, which consists of aryl radical generation, its addition to an arene, and hydrogen radical (or H⁺ + e⁻) abstraction, both electron-donating and -withdrawing substituents on a benzene ring accelerate the addition of aryl radicals especially to its ortho-positions.¹ The result that regioisomeric mixtures with a high ortho ratio were obtained in the reaction of **1a** with substituted benzenes (entries 17–19 of Table 2)¹¹ prompted us to consider

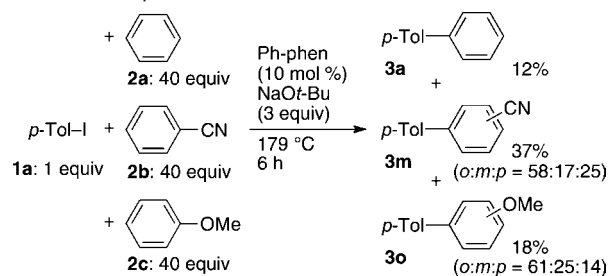
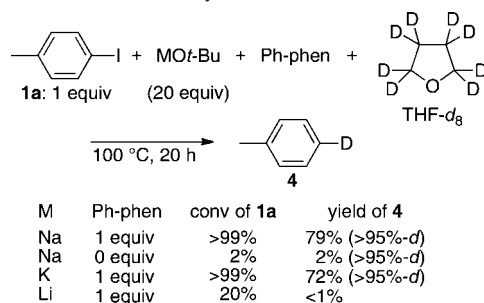
Table 2. Arylation of Arenes with Aryl Halides^a

entry	Ar-X (1)	R in 2	temp (°C)	time (h)	yield (%) ^b	ratio of o/m/p ^c	prod
1	Ph-I	H	155	6	65	—	3b
2	<i>p</i> -MeOC ₆ H ₄ -I	H	155	6	82	—	3c
3	<i>m</i> -MeOC ₆ H ₄ -I	H	155	6	76	—	3d
4	<i>p</i> -CF ₃ C ₆ H ₄ -I	H	155	6	80	—	3e
5	<i>p</i> -NCC ₆ H ₄ -I	H	155	6	71	—	3f
6	3-pyridyl-I	H	155	6	75	—	3g
7	2-pyridyl-I	H	155	6	72	—	3h
8	3-thienyl-I	H	155	6	69	—	3i
9	<i>p</i> -MeC ₆ H ₄ -Br	H	155	6	13 ^d	—	3a
10	<i>p</i> -MeC ₆ H ₄ -Br	H	155	48	80	—	3a
11 ^e	<i>p</i> -MeC ₆ H ₄ -Br	H	155	6	50 ^f	—	3a
12	<i>p</i> -PhC ₆ H ₄ -Br	H	155	12	79	—	3j
13	<i>p</i> -NCC ₆ H ₄ -Cl	H	155	6	75	—	3f
14 ^g	<i>p</i> -BrC ₆ H ₄ -I	H	155	6	73 ^h	—	3k
15	<i>p</i> -ClC ₆ H ₄ -I	H	155	6	80	—	3l
16 ⁱ	<i>p</i> -IC ₆ H ₄ -I	H	155	12	77 ^j	—	3j
17 ⁱ	<i>p</i> -MeC ₆ H ₄ -I	CN	182	6	73	58/17/25	3m
18 ⁱ	<i>p</i> -MeOC ₆ H ₄ -I	CN	182	6	68	56/16/28	3n
19	<i>p</i> -MeC ₆ H ₄ -I	OMe	178	6	51	59/26/15	3o

^a The reaction was carried out under a nitrogen atmosphere using an aryl halide (**1**: 0.225 mmol), an arene (**2**: 27 mmol), NaOr-Bu (0.450 mmol), and 4,7-diphenyl-1,10-phenanthroline (Ph-phen: 0.023 mmol) in a sealed tube. ^b Isolated yield based on **1**. ^c Determined by ¹H NMR and GC. ^d Conv = 18%. ^e KOt-Bu was used instead of NaOt-Bu. ^f A 1:1 mixture of 3- and 4-(*tert*-butoxy)toluene was produced in 18% yield. ^g NaOt-Bu (0.338 mmol) was used. ^h *p*-Terphenyl also was produced in 2% yield. ⁱ NaOt-Bu (0.675 mmol) was used. ^j The yield of *p*-terphenyl. The yield of 4-iodobiphenyl was estimated by GC to be less than 1%.

that the coupling proceeds through HAS. The result that both benzonitrile and anisole coupled with *p*-tolyl iodide (**1a**) preferentially over benzene in a competition reaction between these arenes (Scheme 1) is consistent with the HAS mechanism.¹²

Aryl halides are known to be transformed to aryl radicals via radical anions [Ar-X]^{•-} upon reaction with a single electron donor,¹³ whereas metal *tert*-butoxides are reported to act as single electron donors toward alkyl iodides, ketones, and polynuclear aromatic hydrocarbons.¹⁴ Treatment of **1a** with NaOt-Bu (20 equiv) and Ph-phen (1 equiv) at 100 °C for 20 h in THF-*d*₈ gave a 79% yield of 4-deuteriotoluene (**4**) (Scheme 2), implying that a tolyl radical is generated by reaction of **1a** with NaOt-Bu to abstract a deuterium radical from THF-*d*₈. The low conversion (2%) in the absence of Ph-phen indicates that Ph-phen is essential for the radical generation. Phenanthroline derivatives, which are highly conjugated and thus have a low-lying LUMO, are known to accept single electron transfer (SET).¹⁵ Assuming that they act as SET mediators that receive an electron to form radical anions and then pass the electron to aryl halides, we can understand the marked difference in efficiency in the coupling reaction between 1,10-phenanthroline (phen) and 2,2'-bipyridyl (bpy) in spite of their structural similarity (*cf.* entries 1 and 13 of Table 1) in addition to the improvement of the ability of phen with the introduction of two phenyl groups (*cf.* Table 1: entries 1 and 17; entries 20 and 21). The large decrease in efficiency by the introduction of phenyl groups to 2- and 9-positions of phen is possibly ascribed to insufficient complexation with NaOt-Bu for steric reasons.¹⁶ The result that 1,7- and 4,7-phenanthrolines, which have similar reduction potentials to phen,¹⁵ were totally ineffective (entries

Scheme 1. Competition Reaction between Arenes**Scheme 2.** Involvement of Aryl Radical Intermediates

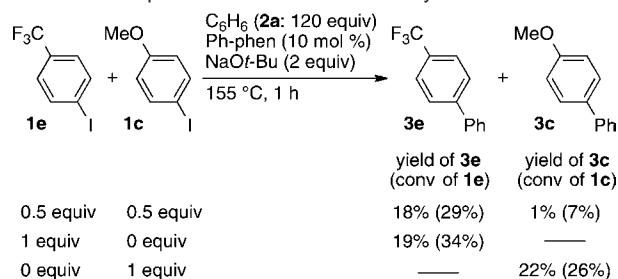
15 and 16 of Table 1) also implies the importance of chelate coordination.

Use of KOt-Bu having a higher basicity than NaOt-Bu in the reduction of **1a** (Scheme 2) scored a comparable yield, whereas **4** was not obtained at all using the less electron-rich LiOt-Bu, showing a correlation with the base effect in the coupling reaction. The coupling of *p*-tolyl bromide (**1a'**) proceeded much faster with KOt-Bu than NaOt-Bu though with a lower yield (*cf.* entries 9 and 11 of Table 1). These results are consistent with the SET mechanism, where a *tert*-butoxide as a single electron donor shows higher ability with higher electron density.

According to the mechanism involving aryl radical generation through SET, more electron-deficient aryl halides must have higher reactivities.^{13a} A competition reaction of aryl iodides described in Scheme 3 shows that a more electron-deficient aryl iodide selectively reacts with benzene. Conjugating and electron-withdrawing substituents make aryl bromides and even chlorides sufficiently reactive in the coupling reaction (entries 12 and 13 of Table 2).

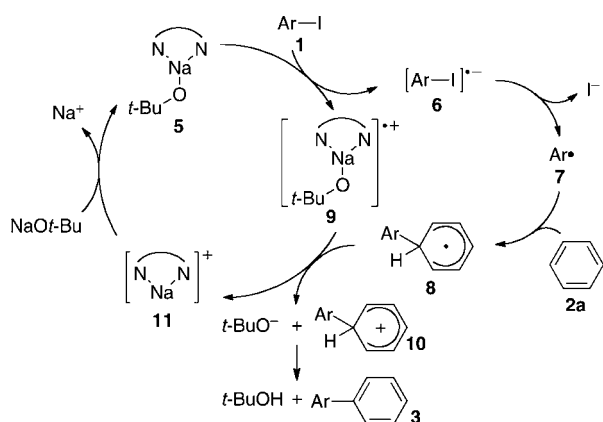
A plausible mechanism is shown in Scheme 4.¹⁷ SET from NaOt-Bu-Ph-phen complex **5** to Ar-I (**1**) gives radical anion **6**, which is transformed to aryl radical **7** to add to benzene, giving cyclohexadienyl radical **8**. Single electron oxidation of **8** by radical cation **9** gives cation **10**, which is deprotonated by *t*-BuO⁻ to give coupling product **3** and *t*-BuOH.¹⁸ Complex **11** (or free phen) reacts with NaOt-Bu to regenerate complex **5**.

In HAS with aryl radicals, the addition step giving relatively stable **8** is considered to be fast and irreversible.^{1b} Scheme 1

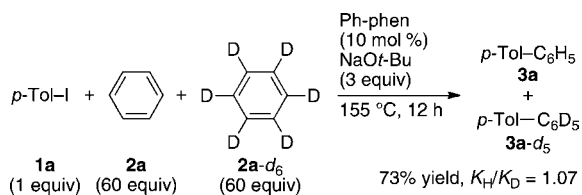
Scheme 3. Competition Reaction between Aryl Iodides

shows that substituted benzenes more readily accept the addition of aryl radicals than benzene but their overall reaction rates are lower,¹⁹ showing that the addition step is not the rate-determining step. The aryl radical generation step also is unlikely to be the rate-determining step except in the reaction of aryl halides of low reactivity such as *p*-tolyl bromide (**1a'**) because the overall reaction rates are not reflected by the reactivities of aryl iodides as shown in Scheme 3. To clarify which is the rate-determining step among the last two steps, we conducted the competition reaction between C₆H₆ (60 equiv) and C₆D₆ (60 equiv) in Scheme 5. The observed low *K_H/K_D* value (1.07) implies that the rate-determining step does not contain C–H bond cleavage. Thus, the rate-determining step is the single electron oxidation from **8** to **10** but not deprotonation from **10** to give **3**. This result excludes an alternative pathway, which involves C–H bond cleaving hydrogen radical abstraction as a single step transformation from **8** to **3**.

Scheme 4. A Plausible Mechanism



Scheme 5. KIE Experiment



In conclusion, we have disclosed that the coupling of aryl halides with benzene derivatives is mediated by NaOt-Bu with the aid of a catalytic phenanthroline derivative through a homolytic aromatic substitution mechanism involving aryl radical intermediates.²⁰

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Supporting Information Available: Experimental procedures and characterization data for all the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (6) The coupling of aryl halides with π -deficient N-heteroarenes but not with benzene derivatives has been reported to be promoted by KOR-Bu under microwave irradiation. Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 4673–4676.
- (7) The reaction was conducted in a 35 mL oven-dried pressure-resistant tube (Ace Pressure Tube, Ace Glass 864807, available via Aldrich). Heating the reaction mixture at a temperature (bath temperature = 185 °C) above the boiling point of the solvent (benzene: 80 °C) causes some pressure and, consequently, reduces the temperature in the tube to 155 °C.
- (8) As byproducts, toluene (7%) and five isomers of dimethylterphenyls (5%) resulting from the tolylation of **3a** were formed. The formation of 4,4'-dimethylbiphenyl was not observed. The reaction using a reduced amount (10 equiv) of benzene gave **3a** (25%), toluene (18%), the dimethylterphenyls (five isomers: 10%), and 4,4'-dimethylbiphenyl (3%) with full conversion of **1a**. All the yields were determined by GC, GC-MS, and ¹H NMR.
- (9) Recently, Charette reported the same type of reaction catalyzed by Fe(II) at a lower temperature (80 °C). Vallée, F.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 1514–1516. Our reaction system (entry 22 of Table 1) did not promote the coupling of **1a** with **2a** at 80 °C. ICP-AES and/or -MS analysis showed that the contents of transition metals (Fe, Co, Ni, Cu, Ru, Rh, Pd, Ag, Ir, Pt, Au) in NaOt-Bu and Ph-phen are less than 0.05 ppm except for Fe (1.0 ppm) and Cu (0.18 ppm) in NaOt-Bu.
- (10) The reaction of **1a** with pyrazine (30 equiv) and NaOt-Bu (2 equiv) in the presence (10 mol%) or absence of Ph-phen at 100 °C for 12 h gave 2-(*p*-tolyl)pyrazine in a yield (conv) of 63% (>99%) or 7% (16%), respectively.
- (11) For the coupling of benzonitrile, an increased amount of NaOt-Bu was used to compensate loss from its reaction with the nitrile moiety.
- (12) Similar selectivities were observed also in competition reactions between **2a** and **2b** as well as **2a** and **2c**. For details, see Supporting Information.
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- (16) Upon mixing of Ph-phen and NaOt-Bu (1:4) in C₆D₆, changes (ppm) of their chemical shifts in ¹H NMR were observed: for Ph-phen, H2/9.13 to 9.06, H3/7.07 to 7.14, and H5/7.63 to 7.61; for NaOt-CMe₃/1.28 to 1.45.
- (17) After the reaction giving **3a** under similar conditions of entry 22 of Table 1, 74% of Ph-phen was recovered, implying that it acts as a catalyst rather than an initiator. See Supporting Information for details.
- (18) *t*-BuO• is considered to oxidize cyclohexadienyl radicals to arenes. (a) Bowman, W. R.; Bridge, C. F.; Brookes, P.; Cloonan, M. O.; Leach, D. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 58–68. (b) Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 95–98.
- (19) The reaction of **1a** (1.0 equiv) with **2b** or **2c** (120 equiv) under the same conditions as entry 20 of Table 1 (155 °C, 6 h) gave **3m** or **3o** in 40% or 5% yield (85% or 19% conversion of **1a**), respectively.
- (20) Very recently, a report on KOR-Bu-mediated arylation of benzene with aryl iodides in the presence of a catalytic *N,N'*-dimethylethylenediamine appeared. Liu, W.; Cao, H.; Zhang, H.; Zhang, H.; Chung, K. H.; He, C.; Wang, H.; Kwong, F. Y.; Lei, A. *J. Am. Chem. Soc.* doi: 10.1021/ja103050x.

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