Published in final edited form as:
Org Lett. 2013 December 6; 15(23): 6102–6105. doi:10.1021/ol402995e.

Phenyl Hydrazine as Initiator for Direct Arene C-H Arylation via Base Promoted Homolytic Aromatic Substitution

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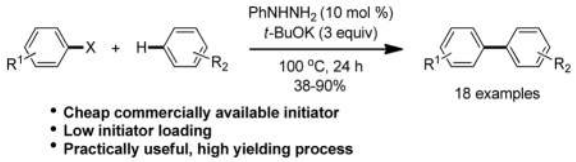
Abstract



A simple and efficient direct radical arylation of unactivated arenes is described which uses cheap and commercially available phenyl hydrazine as an initiator. The reaction occurs through a base promoted homolytic aromatic substitution (BHAS) mechanism involving aryl radicals and aryl radical anions as intermediates and offers a practical approach for preparation of an array of substituted biaryls.

Biaryl compounds belong to a privileged class of structures which are prevalent in a large number of natural products, pharmaceuticals, agrochemicals and functional materials.[1] Transition metal (TM) catalyzed cross coupling reactions between an organohalide (Ar^1–X) and an organometallic reagent (Ar^2–M) to synthesize such compounds suffer from some inevitable drawbacks that are a generation of undesired, toxic and stoichiometric metal waste. Moreover, preactivation of both individual coupling partners is necessary.[2] In this regard, the recent emergence of transition metal catalyzed direct arylation of aromatic C–H bonds provides a valuable and efficient alternative to the conventional cross coupling approach for the synthesis of biaryl compounds.[3]

While mainstream developments are still focusing on transition metal catalyzed/mediated processes, radical chemistry offers a valuable alternative to TM-based arylations.[4] A conceptually different approach for the direct arylation of arenes involving base promoted homolytic aromatic substitution (BHAS) with aryl radicals and radical anions as intermediates utilizing diamine ligands in combination with potassium *tert*-butoxide as base has captivated great attention recently.[5] In these processes, initial aryl radical addition to an arene delivers the corresponding cyclohexadienyl radical which then undergoes deprotonation with a base to provide a biaryl radical anion (Scheme 1). Finally, single

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

electron transfer (SET) from this radical anionic species to the starting arylhalide generates another aryl radical along with the halide anion thereby sustaining the radical chain.[6]

Such BHAS type biarylations can be conducted inter[7] and intramolecularily.[8] Herein, we wish to report that phenyl hydrazine can efficiently initiate the BHAS of unactivated arenes under relatively mild reaction conditions at low initiator loading.

BHAS reactions are generally performed at high temperature using a large amount of a ligand. The amine ligand is supposed to be involved in the initiation step which is currently not well understood. A possibility is that the ligated *t*-BuOK acts as SET reducing reagent in the initiation step. However, it is obvious that such a species is not an ideal SET reducing reagent. A challenge in this field is therefore to find a reagent that allows initiating the BHAS reaction by single electron transfer (SET) to an aryl halide ideally at low temperature and at low initiator loading.

Along these lines, we decided to investigate alcoholates other than *t*-BuOK as initiators for the BHAS reaction between *m*-iodotoluene (**1a**) and benzene (for details see Supporting Information). These studies revealed that the structure of the K-alcoholate does indeed have an effect on the reaction outcome, but the tested alcoholates delivered similar or worse results than the well-established *t*-BuOK (see Supporting Information).[9]

We therefore continued our studies by looking at other potential initiators and assumed that phenyl hydrazine and its derivatives are valuable candidates. Phenyl hydrazines were chosen as initiators for the following two reasons: a) due to the α-effect exerted by the lone pairs of the adjacent nitrogen atoms hydrazines are good electron transfer agents and b) the hydrazinyl radicals resulting from the initial electron transfer are stabilized via a two center three electron bond configuration (compare with the stability of a N-oxyl radical).

The reaction between *m*-iodotoluene (**1a**) and benzene (**2a**) was chosen as model cross coupling for our investigations (Table 1). The initial experiment using 10 mol% of $PhNHNH_2$ (**I**-1) as the initiator and *t*-BuOK (3 equiv) as base afforded the desired product **3a** in encouraging 42% yield along with 31% of unreacted starting material **1a** (entry 1). The yield did not improve upon increasing the amount of hydrazine to 40 mol% (entries 2, 3). Interestingly, GC-MS analysis of the crude reaction mixture revealed formation of toluene and at higher initiator loading formation of this side product became even more prominent.

We hypothesized that reduction of the initially formed aryl radical by H-abstraction from initiator **I**-1 to be responsible for toluene formation. In order to suppress this side reaction, we added the initiator **I**-1 (20 mol %) within 6 h in four equal portions to keep its concentration low. To our delight, the yield of **3a** improved to 84% (entry 4). A further increase in yield (88%) was achieved upon adding the initiator **I**-1 over 6 h via syringe pump (entry 5). The yield remained unaffected by decreasing the initiator loading to 10 mol % (entry 6). We then screened other phenyl hydrazine derivatives **I**-2, **I**-3 and **I**-4 as initiators. While **I**-4 delivered **3a** in slightly lower yield (78%, entry 9) as compared to the **I**-1-initiated reaction, reaction was not efficiently initiated with **I**-2 and **I**-3 (entries 7, 8). Further decrease in the amount of **I**-1 led to incomplete reaction, although the yield remained almost unaffected (entries 10, 11). Attempts to lowering the reaction temperature and decreasing the amount of *t*-BuOK were not fruitful (entries 12, 13). Moreover, extending the time for phenyl hydrazine addition (slower addition by syringe pump) did also not provide a better result (entries 14, 15). Reaction in the absence of phenylhydrazine provided only 3% of biphenyl **3a** documenting the important role of the hydrazine for this transformation (entry 16). To investigate the importance of the hydrazine structural motif on

we also tested diphenylamine as an initiator and obtained only 6% of **3a** under otherwise identical conditions (not shown in the Table 1).

With optimized conditions in hand (Table 1, entry 6), we explored the scope of the process by reacting several electronically and structurally diverse aryl iodides **1** with benzene (Table 2). Simple iodobenzene **1c**, *m*- and *p*-tolyl iodides (**1a** and **1b**), *p*-phenyl-iodobenzene **1d** and *m*-iodoxylene **1e** underwent efficient coupling with benzene to give the corresponding biaryls **3a–e** in high yields (entries 1–5). Pleasingly, aryl iodides containing both electron donating and electron withdrawing substituents efficiently cross coupled to the corresponding biphenyl derivatives in good yields (entries 6–10). Heteroaryl iodides such as **1l** and **1m** were precursors in the cross coupling reaction delivering the desired products **3l** and **3m** in good yields (entries 12, 13). Notably, sterically encumbered aryl iodides **1h** and **1k** were tolerated and gave the targeted biaryls in isolated yields of 71% and 61%, respectively (entries 8 and 11). Disappointingly, reaction did not work using chloro or bromobenzene as substrates.

Further exploration of substrate scope was performed by reacting aryl iodides **1b** and **1f** with different arenes **2** (toluene, anisole, fluorobenzene) and pyrazine. As expected, reactions of aryl iodides with substituted benzenes afforded regioisomeric mixtures favoring the *ortho* products (Table 2, entries 14–16). In all these cases, products were isolated in moderate to good yields and also pyrazine (**2e**) furnished the coupling product **3q** in high yield (82%, entry 17).

We also studied the phenylhydrazine initiated arylation of **2a** with 1,3- and 1,4-halo-iodobenzenes **1n–q** (Scheme 2). For 4-haloiodobenzenes (**1n**–**p**) *para*-terphenyl **3d** was obtained in 48–58% yields. A similar reactivity was observed with **1q** providing the *meta*-terphenyl **4** in 58% yield. It is remarkable to note that for these haloiodobenzenes bromide and in particular also the chloride showed about the same reactivity as the iodide.

Considering that toluene was observed as a side product in the initial screening using **1a** and noting that a trace amount of biphenyl was formed in all reactions where benzene was used as aryl radical acceptor (as identified by GC-MS), we propose the following mechanism for these BHAS. Phenylhydrazine is first deprotonated by *t*-BuOK. In the initiation step, the deprotonated phenylhydrazine then transfers an electron to iodobenzene **1** generating the intermediate radical anion **B** and hydrazinyl radical **A**. The radical anion **B** undergoes fragmentation to deliver the corresponding aryl radical **C** (if the electron transfer is dissociative, radical anion **B** is not an intermediate). Finally, **C** undergoes BHAS via aryl radical addition to the arene to form the cyclohexadienyl radical **D** followed by deprotonation to give **E**. Electron transfer to the starting aryl halide eventually delivers the final product and completes the radical chain process.

In the terphenyl synthesis internal electron transfer of the biaryl radical anion to generate a biaryl radical is faster than intermolecular SET to the substrate dihaloarene.[10] The initially generated hydrazinyl radical **A** and the initiator **I**-1 can reduce aryl radicals via H-transfer which likely accounts for the observed dehalogenated arene side products. PhN=NH, generated after H-transfer from **A**, can act as good H-transfer reagent which after H-transfer and subsequent nitrogen fragmentation yields the phenyl radical, which in the BHAS with an arene generates the corresponding biaryl identified by GC-MS as side product.

In conclusion, we have disclosed phenyl hydrazine as a cheap and commercially available initiator for the direct arylation of several unactivated arenes using a diverse array of aryl and heteroaryl iodides, which in turn enabled efficient construction of several structurally and electronically diverse biaryls. Reactions occur through base promoted homolytic

aromatic substitution (BHAS) and involves aryl radicals and aryl radical anions as intermediates. Double C-H arylation is successfully demonstrated which allowed construction of extended π-electron systems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

AD thanks the NRW Graduate School of Chemistry for a stipend and DPC thanks the NIH for financial support.

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9. During our studies an interesting report demonstrating that simple alcohols such as *n*-BuOH act as efficient promoters for direct BHAS-type C–H arylations was disclosed (see ref. 7j). However, in our hands *n*-BuOH showed only a small positive effect (see SI).
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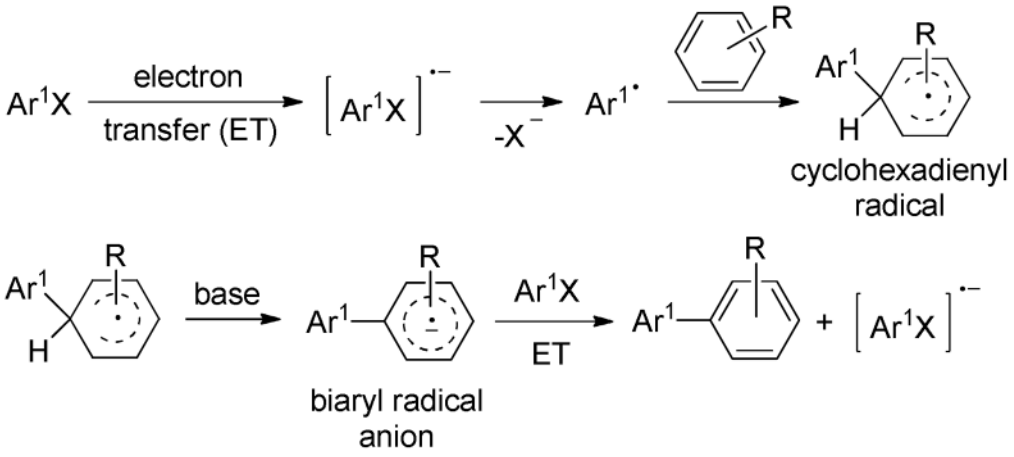
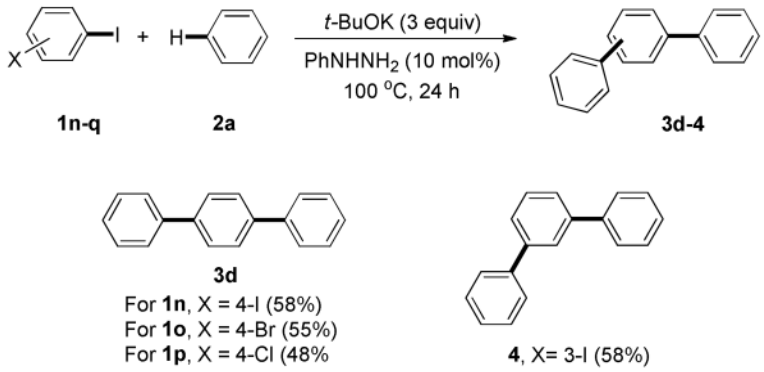
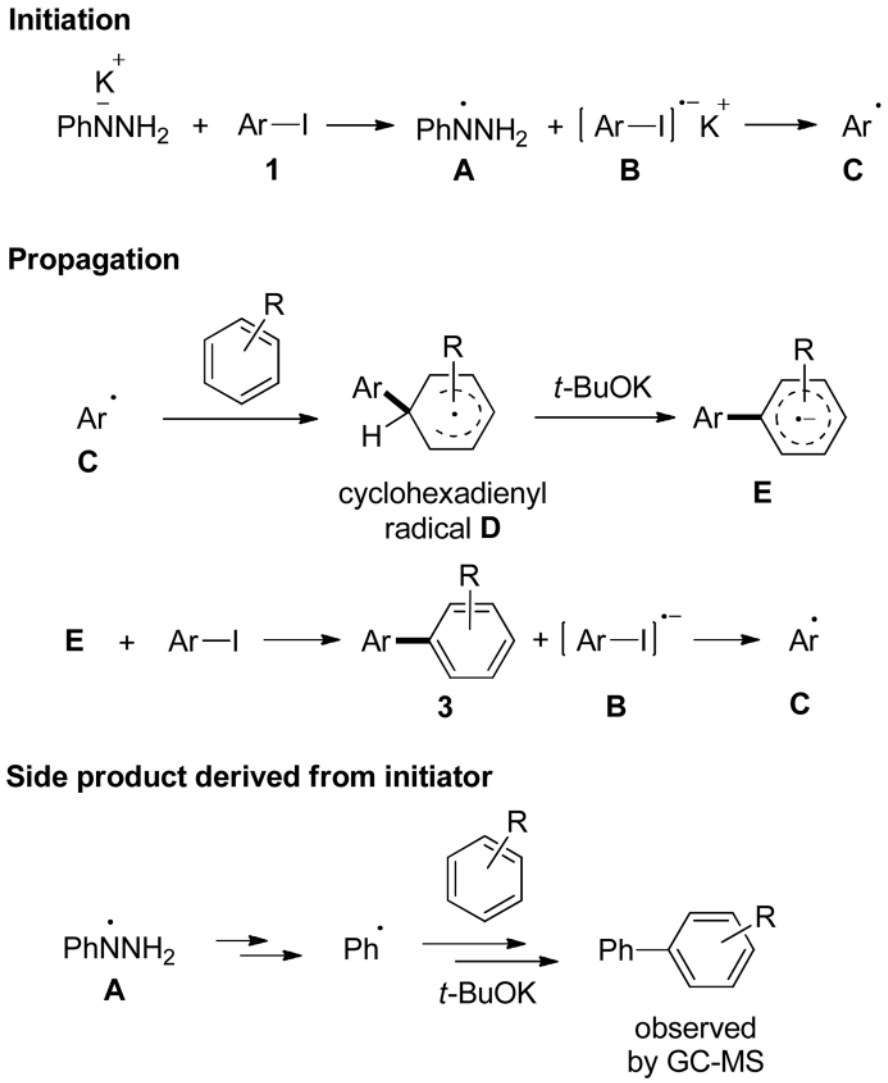


Scheme 1.
Base Promoted Biaryl Synthesis *via* Homolytic Aromatic Substitution



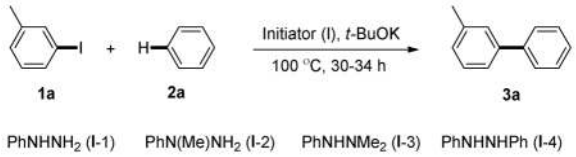
Scheme 2.
Terphenyl Synthesis *via* Direct Bisarylation of Haloiodoarenes



Scheme 3.
Proposed Mechanism

Table 1

Optimization of Arylation Reaction Conditions



entry	initiator (mol %)	duration of addition (h)	yield (%)[b]	unreacted 1a (%)[b]
1	I_1 (10)	-	42	31
2	I_1 (20)	-	48	30
3	I_1 (40)	-	53	5
4	I_1 (20)	6[c]	84	-
5	I_1 (20)	6[d]	88	-
6	**I_1 (10)**	**6**[d]	**88**	**-**
7	I_2 (10)	6[d]	3	83
8	I_3 (10)	6[d]	7	73
9	I_4 (10)	6[d]	78	4
10	I_1 (5)	6[d]	87	5
11	I_1 (7.5)	6[d]	85	2
12[e]	I_1 (10)	6[d]	58	28
13[f]	I_1 (10)	6[d]	86	3
14	I_1 (10)	8[d]	88	-
15	I_1 (10)	10[d]	88	-
16	I_1 (0)	6[d]	3	90

[a] The reaction was carried out with 0.31 mmol of **1a** in 3.1 mL of benzene as solvent.

[b] Yield was calculated from NMR using CH_2Br_2 as an internal standard.

[c] **I**-1 was added batchwise (4 x 5 mol %).

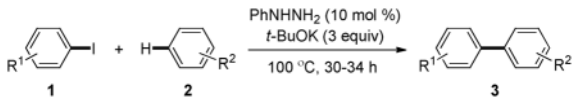
[d] Initiator was added as a solution in benzene (0.15 M) using a syringe pump.

[e] Reaction was performed at 80 °C.

[f] 2.5 equiv of *t*-BuOK was used.

Table 2

Direct Arylation of Arenes with Aryl Halides[a]



entry	Ar-X, 1	arene, 2	3	yield (%)[b]
1	*m*-MeC_6H_4–I, **1a**	Benzene, **2a**	**3a**	77
2	*p*-MeC_6H_4–I, **1b**	**2a**	**3b**	81
3	C_6H_5–I, **1c**	**2a**	**3c**	78
4	*p*-PhC_6H_4–I, **1d**	**2a**	**3d**	90
5	3,5-$(Me)_2C_6H_3$–I, **1e**	**2a**	**3e**	76
6	*p*-$MeOC_6H_4$–I, **1f**	**2a**	**3f**	85
7	*m*-$MeOC_6H_4$–I, **1g**	**2a**	**3g**	76
8	*o*-$MeOC_6H_4$–I, **1h**	**2a**	**3h**	71
9	*p*-$CF_3OC_6H_4$–I, **1i**	**2a**	**3i**	68[c]
10	*p*-FC_6H_4–I, **1j**	**2a**	**3j**	60[d]
11	1-naphthyl-I, **1k**	**2a**	**3k**	61
12	3-thienyl-I, **1l**	**2a**	**3l**	68
13	3-pyridyl-I, **1m**	**2a**	**3m**	64
14	*p*-$MeOC_6H_4$–I, **1f**	Toluene, **2b**	**3n**	38[e]
15	*p*-MeC_6H_4–I, **1b**	Anisole, **2c**	**3o**	59[f]
16	*p*-$MeOC_6H_4$–I, **1f**	Fluorobenzene, **2d**	**3p**	47[g]
17	*p*-$MeOC_6H_4$–I, **1f**	Pyrazine, **2e**	**3q**	82[h]

[a] The reaction was carried out at 100 °C using 0.3 mmol aryl iodide, 0.9 mmol *t*-BuOK, 0.03 mmol $PhNHNH_2$ and 3 mL of arene. 0.15 M solution of $PhNHNH_2$ in arene was added by a syringe pump over 6 h.

[b] Yield of isolated product.

[c] *p*-Terphenyl was produced in 21% yield.

[d] *p*-Terphenyl was produced in 18% yield.

[e] Reaction was carried out at 135 °C. 40 mol % of 0.15 M $PhNHNH_2$ solution in arene was added by a syringe pump over 10 h. Regioisomeric mixture with *o:m:p* ratio 1.0:0.48:0.26 was isolated.

[f] Reaction was carried out at 130 °C. 20 mol % of 0.15 M $PhNHNH_2$ solution in arene was added by a syringe pump over 10 h. Regioisomeric mixture with *o:m:p* ratio 1.0:0.24:0.22 was isolated.

[g] Reaction was carried out at 110 °C. 40 mol % of 0.15 M $PhNHNH_2$ solution in arene was added by a syringe pump over 10 h. Regioisomeric mixture with *o:m:p* ratio 1.0:0.58:0.17 was isolated.

[h] $PhNHNH_2$ was added in two batches (5 mol % x 2) with 3 h interval.