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Radical coupling of aryl halides to arenes facilitated by Ni(COD)(DQ) and other nickel sources†‡

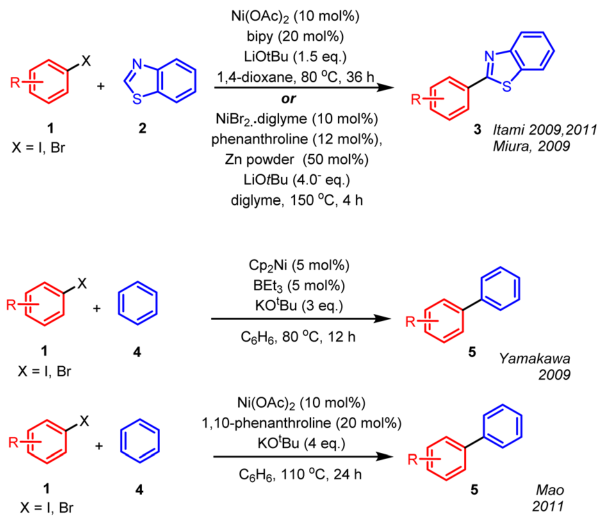
Seb Tyerman,[a] Craig M. Robertson[b] and John A. Murphy *[a]

The air-stable complex Ni(COD)(DQ) (COD = 1,5-cyclooctadiene, DQ = duroquinone) promotes the coupling of aryl halides to arenes in the presence of KO*t*Bu. This complex has recently been shown to perform coupling reactions based on organonickel intermediates, but in this case the coupling reactions proceed *via* aryl radicals as shown by our newly developed assay for aryl radicals. Coupling with this nickel source is more efficient than with Ni(COD)$_2$, Ni(PPh$_3$)$_4$ and Ni(acac)$_2$, all of which we also show to operate through aryl radical pathways.

Introduction

Nickel complexes have been used to couple aryl halides with arenes through C–H functionalisation of the arene. (For reviews, see references.[1–3]) Itami coupled azoles to haloarenes with Ni(OAc)$_2$ and 2,2′-bipyridine or dppf in the presence of LiO*t*Bu[4,5] proposing a standard mechanism involving a Ni(0)/Ni(II) cycle and organonickel intermediates. Simultaneously, Miura coupled azoles to haloarenes with NiBr$_2$ in the presence of phenanthroline, LiO*t*Bu and zinc powder and also proposed a classic Ni(0)/Ni(II) pathway (Scheme 1).[6]

Meanwhile, in 2009 Yamakawa *et al.* used Cp$_2$Ni (Cp = cyclopentadienyl), BEt$_3$ and KO*t*Bu to couple iodo- and bromoarenes with unactivated arenes such as benzene.[7] With naphthalene or pyridine as the arene, the product regioisomer ratios suggested a complicated reaction mechanism, as acknowledged by the authors. In 2011 Mao *et al.* utilised Ni(OAc)$_2$, 1,10-phenanthroline and KO*t*Bu to carry out similar transformations and cited evidence for a radical mechanism.[8] However, prior and subsequent reports showed that 1,10-phenanthrolines form strong electron donors *in situ* with KO*t*Bu[9–16] in the absence of nickel salts, and these electron donors are known to initiate coupling of haloarenes with arenes *via* base-assisted homolytic aromatic substitution (BHAS).[17–19] In support of this, Mao reported a reaction (4-iodoanisole coupling with toluene in the presence of KO*t*Bu (2 eq.) at 110 °C for 24 h) in the absence of Ni(OAc)$_2$ that gave only slightly decreased yield of 37% [*vs.* 54% when Ni(OAc)$_2$ was added]. Since this coupling proceeds in the absence of a nickel source, the importance and role of nickel needs clarification. Thus, the nickel-promoted mechanism of coupling of haloarenes to arenes like benzene has been unclear for some time. As the accompanying paper shows, we have recently developed a stringent assay for aryl radicals, and the mechanism of coupling of haloarenes to arenes was a clear case where the assay could be applied. This paper now details our investigation into the cross-coupling of aryl halides with unactivated arenes using nickel sources.



Scheme 1 Cross-coupling between aryl halides and unactivated arenes, facilitated by nickel salts and complexes.

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[a] *Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow G1 1XL, UK. E-mail: John.murphy@strath.ac.uk*

[b] *GSK Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts SG1 2NY, UK*

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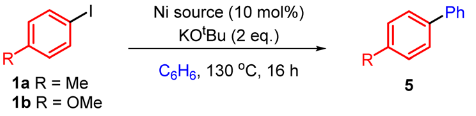
Results and discussion

Recently, the Engle lab reported that bench-stable 18-electron complex Ni(COD)(DQ) (COD = 1,5-cycloctadiene; DQ = duroquinone) serves as an active pre-catalyst in Ni-mediated reactions, including Suzuki–Miyaura reactions and Buchwald–Hartwig aminations.[20,21] However, coupling of haloarenes to arenes was not reported. Inspired by the simple synthesis and remarkable stability of this Ni(0) complex, it was employed in our system. Ni(COD)(DQ) promoted the coupling of iodoarenes **1a,b** in excellent yields (Table 1, entries 1 and 2), with near quantitative coupling of **1a** (95%). Other nickel sources, Ni(acac)$_2$ (acac = 2,4-pentanedionate), Ni(PPh$_3$)$_4$ and Ni(COD)$_2$ (COD = 1,5-cyclooctadiene) were less effective (63%–69%, entries 3–8). A blank reaction featuring no nickel source gave a low yield of products. (entries 9 and 10) which, under these conditions, is proposed to arise *via* a benzyne-initiated BHAS mechanism.[12] Ni(OAc)$_2$ provided only marginally improved yields over the blank (entries 11 and 12).

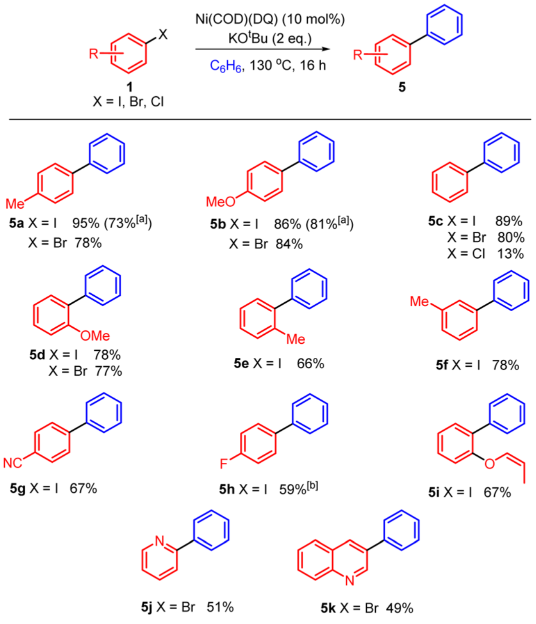
To demonstrate the synthetic utility of Ni(COD)(DQ), examples of substrates were now employed in the coupling reaction with benzene under our standard conditions (Scheme 2). Unactivated aryl iodides and those bearing electron-donating *para*-substituents coupled in excellent yields (**5a–c**, 95–86%), with the corresponding aryl bromides giving slightly lower yields (84–78%). The reactions yielding **5a** and **5b** were repeated at a shorter reaction time of 4 h and, while good yields were obtained, the reactions were not complete; thus, it was decided to retain a 16 h reaction time to allow all substrates to react fully. Aryl chlorides were not amenable to coupling, yielding only 13% of the biphenyl product **5c**. Substrates with *ortho*- or *meta*-substituents (**5d–f**) coupled satisfactorily (78–66%). Products **5g–5h**, where substrates had electron-withdrawing substituents, afforded moderate to good yields. When 1-(allyloxy)-2-iodobenzene was employed, product **5i** was obtained. Here the allyl group is rapidly isomerised to the *Z*-vinyl ether by KO^{t}Bu,[22] which cannot undergo unfavourable 5-*endo-trig* or 4-*exo-trig* cyclisations and thus the intermolecular coupling product is obtained (67%). Pyridine-based heteroaryl-derived products **5j–k** were obtained from the corresponding bromides in moderate yields (51–49%), expanding the potential applications of this system to heteroaryl halides.

Table 1 Screen of nickel sources in the coupling of simple aryl halides to benzene



Entry	Aryl halide	Ni source	**5** (yield %)^a
1	**1a**	Ni(COD)(DQ)	95
2	**1b**	Ni(COD)(DQ)	86
3	**1a**	Ni(acac)$_2$	69
4	**1b**	Ni(acac)$_2$	66
5	**1a**	Ni(PPh$_3$)$_4$	63
6	**1b**	Ni(PPh$_3$)$_4$	65
7	**1a**	Ni(COD)$_2$	69
8	**1b**	Ni(COD)$_2$	64
9	**1b**	—	15
10	**1a**	—	13
11	**1a**	Ni(OAc)$_2$	15
12	**1b**	Ni(OAc)$_2$	20

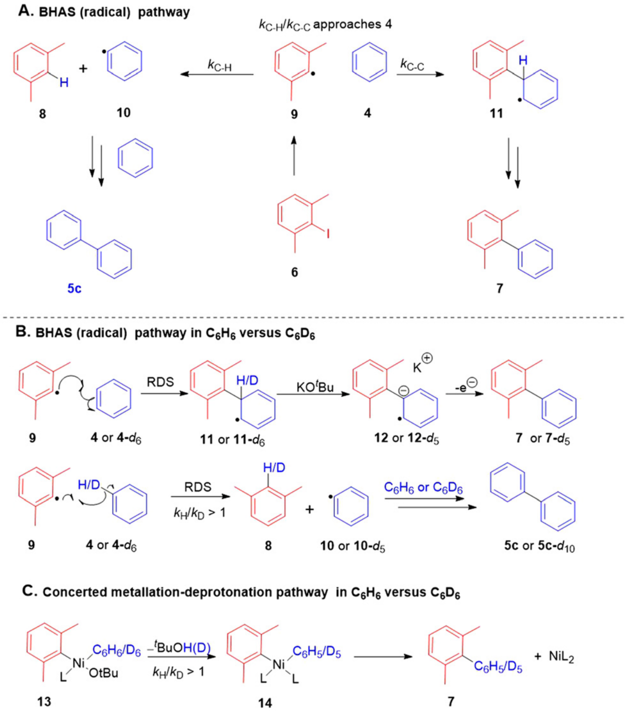
^{a} Isolated yields.



Scheme 2 Substrate scope. ^{a}reaction run for 4 h. ^{b}*p*-Terphenyl also obtained in 16% yield.

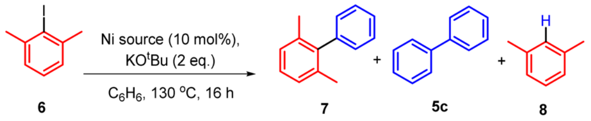
To determine the mechanism, our assay was then applied to the coupling reactions. The hindered 2,6-dimethyliodobenzene (**6**) was employed as the mechanistic test substrate.[12,23] The first part of our assay is based on ratio of products when aryl radicals are formed from **6**; two products are formed, namely **5c** and **7** (Scheme 3) in a ratio approaching 4 : 1 (this ratio results from the relative rate constants for the two reactions that occur between aryl radical **9** and benzene **4**, namely hydrogen atom abstraction ($k_{C–H}$) and addition to benzene ($k_{C–C}$) (for details of the rationale, see the accompanying paper)). Table 2 shows that nickel sources that proved active in the reaction (entries 1–4) all gave ratios **5c** : **7** that were in line with BHAS chemistry involving aryl radicals (for full screen including control reactions, see ESI‡).

The second part of the assay examines the effect of employing deuterated benzene, C_6D_6. In the formation of **7** in a standard BHAS reaction in C_6H_6 *vs.* C_6D_6, no primary kinetic isotope effect (KIE) would be observed, as the deprotonation step (**11** → **12**) in all BHAS reactions examined to date is known not to be the rate-determining step (RDS).[10,24,25] However, formation of *m*-xylene (**8**) involves a challenging hydrogen atom abstraction by radical **9** from benzene **4** as the RDS, which would therefore incur a primary KIE (Scheme 3A). Thus, the rate of formation of biphenyl (**5c-*d*$_{10}$**) would also decrease *versus* **5c**, as fewer phenyl radicals **10-*d*$_5$** *versus* **10**



Scheme 3 Expected KIE effects *via* organometallic or radical reaction routes.

Table 2 Screen of nickel sources in the coupling of 2,6-dimethyl-iodobenzene to benzene[a]

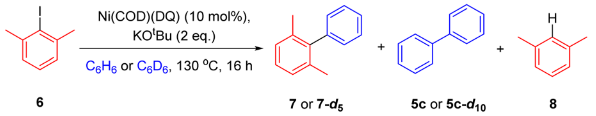


Entry[a]	Ni source	**6** (yield %)	**7**	**5c**	**8**	Ratio **5c** : **7**
1	Ni(COD)(DQ)	Trace	6.1	22.1	75.9	3.6
2	$Ni(COD)_2$	49.0	1.2	3.6	31.0	3.1
3	$Ni(acac)_2$	66.6	1.5	4.8	13.9	3.2
4	$Ni(PPh_3)_4$	43.0	1.3	4.7	15.9	3.6
3	$Ni(OAc)_2$	86.9	Trace	Trace	0.8	—
6	$NiCl_2$	87.7	Trace	Trace	Trace	—
7	—	88.3	Trace	Trace	Trace	—

[a] Measured using GC-FID with *n*-dodecane as internal standard.

would be formed in the respective experiments. Alternatively, if the coupling were proceeding through an organometallic pathway, for example through concerted metalation–deprotonation (CMD) of **13** to give **14**, a primary KIE would be expected (Scheme 3C).[26]

Table 3 The effect of solvent deuteration on the reaction



Entry	Solvent	**6**	**7**/**7-*d*$_5$**	**5c**/**5c-*d*$_{10}$**	**8**
1	C_6H_6	Trace	6.1	22.1	75.9
2	C_6D_6	30.4	4.2	1.5	48.4

The outcomes of reactions in C_6H_6 *vs.* C_6D_6 (Table 3) show a significant decrease in the yields of the **5c-*d*$_{10}$** relative to **5c** in the C_6H_6 experiment, as expected from a hydrogen atom abstraction pathway. The yield of **8**, which interestingly was not significantly deuterated (we estimate 3% from mass spectra), also declined. The non-deuteration points towards an alternative hydrogen atom source in the reaction mixture for abstraction by radical **9** that outcompetes abstraction from *d*$_6$-benzene to form phenyl radical **10-*d*$_5$** (see ESI‡ for this investigation; this outcome was mirrored in the accompanying paper under nickel-free conditions[23]). This could also explain why there was a small drop in the yield of **7-*d*$_5$** relative to **7**, as abstraction of hydrogen atoms by radical **9** from sources other than benzene would not easily lead to the radical anion required to propagate the chain. Substrate **6** was not fully consumed in this reaction (entry 2), supporting this explanation.

This result rationalises the formation of large quantities of *m*-xylene (**8**) in reactions employing substrate **6**. Radical scavengers were employed to probe for radical intermediates, and 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) was added to the reaction of **6** in both 0.5 and 3.0 equivalents (see ESI‡). When 0.5 equivalents of TEMPO were added the yields of **7**, **5c** and **8** decreased significantly (2.9%, 6.8% and 30.0% respectively), and when 3.0 equivalents were added the reaction was completely inhibited. This supports radical intermediates, although the result should be interpreted with caution, as it should be noted that TEMPO can affect reactions due to alternative effects, *e.g.* TEMPO has been shown to coordinate to Ni^0 centres as a ligand.[27]

Conclusions

In summary, it is shown that, under ground-state conditions, air-stable Ni(COD)(DQ) and KO^{t}Bu promote the coupling of a range of simple aryl halides to benzene in high yields. Mechanistic studies support aryl radicals and radical anions as intermediates, and it is proposed that this nickel system acts as an initiator to produce aryl radicals, which then go onto react *via* a base-assisted homolytic aromatic substitution (BHAS) radical chain reaction. While Ni(COD)(DQ) was found to be by far the most effective complex employed, other nickel sources also facilitate this reaction, with evidence that they may also proceed *via* radical intermediates in a BHAS pathway.

Author contributions

ST performed the experiments, analysed the results and drafted the paper. CMR and JAM supervised the research, analysed the data and edited the draft paper and JAM conceived of the research.

Conflicts of interest

There are no conflicts to declare.

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