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Mild and efficient palladium-catalyzed intramolecular direct arylation reactions

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Abstract

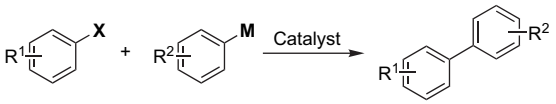
The influence of ligand, stoichiometric base, and additive has been evaluated in the context of intramolecular direct arylation reactions. Under the optimal conditions, arylation of simple arenes can be performed under very mild conditions, with heating to 50 °C. The role of the pivalic acid additive is rationalized by invoking a concerted palladation–deprotonation pathway where the pivalate is behaving as either an intramolecular base from the palladium metal or through an intermolecular deprotonation in a similar manner as that previously described by Echavarren and Maseras.

1. Introduction

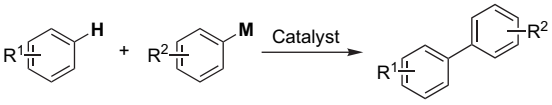
The synthesis of biaryl molecules has been greatly facilitated through the development of palladium-catalyzed cross-coupling reactions, of which the Suzuki reaction is undoubtedly the most renown (Scheme 1, Type 1).[1] Suzuki couplings occur between aryl halide and an arylboronic acid in the presence of a palladium catalyst and base. While widespread, it is important to recognize that both of the arene components must be prepared prior to cross-coupling to install the organometallic and halide moieties. This can involve several steps and ultimately leads to the formation of additional waste subsequent to biaryl formation.

Recognizing both the value of biaryl molecules and the potential for improvement, several research groups have been searching for ways to reduce our reliance on substrate preactivation. One approach involves the replacement of the one of the two pre-activated arenes. In the context of Type 3 biaryl cross-coupling reactions, tremendous success has been achieved with the use of electron-rich heteroaromatic compounds.[3] This can be attributed to the growing appreciation and application of electrophilic aromatic substitution (or metalation) reaction pathways in reaction design. Indeed, from a strategic perspective, replacement of the nucleophilic aryl organometallic component may best be done with electron-rich, π-nucleophilic aromatic compounds whose latent reactivity might mimic that of the organometallic at the transmetalation step of the catalytic cycle. For this reason,

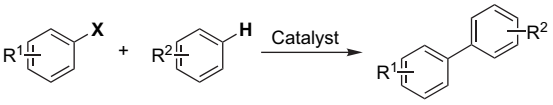
Type 1: Both Arenes are Pre-Activated as a Halide (X) and an Organometallic (M)



Type 2: One Arene Pre-Activated as an Organometallic (M)



Type 3: One Arene Pre-Activated as a Halide (X)



Scheme 1. Strategies for biaryl synthesis.

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much less progress has been realized with simple arenes such as benzene or with electron-deficient arenes/heteroarenes as coupling partners with the simple, unfunctionalized arene itself (Scheme 1, Types 2 and 3).[2] Since more waste and challenge is associated with the preparation and use of the aryl organometallic fragment, it has been most commonly this component which has been removed (Type 3).

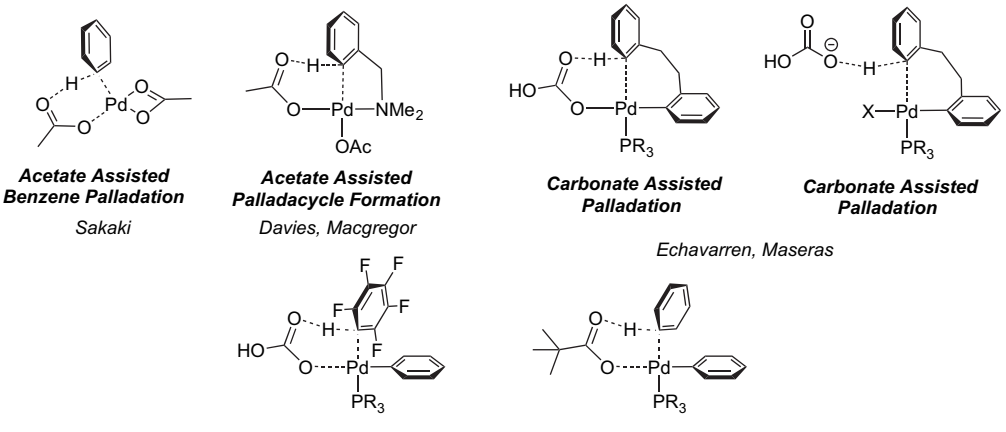
2. Results and discussion

During the course of our methodological work on intramolecular direct arylation reactions, an intriguing effect of fluorine substituents was observed, which appeared incompatible with an S_EAr pathway.[4] To rationalize the reactivity, we invoked concerted palladation–deprotonation pathways where the acidity of the C–H bond might influence both site selectivity and reactivity. Such pathways have been proposed and evaluated by others, including Davies et al.,[5] Echavarran et al.,[6] and Sakaki et al.[7] (Scheme 2). The viability of this alternative pathway as well as computed information regarding the potential transition states played a large role in reaction development efforts, leading to the development of fluorobenzene[8] and benzene[9] arylation reactions. As part of these studies, the beneficial effects associated with the use of a catalytic quantity of pivalic acid in conjunction with a stoichiometric and insoluble inorganic base was noted. These results were rationalized by similar transition states as those proposed for the intramolecular variants.

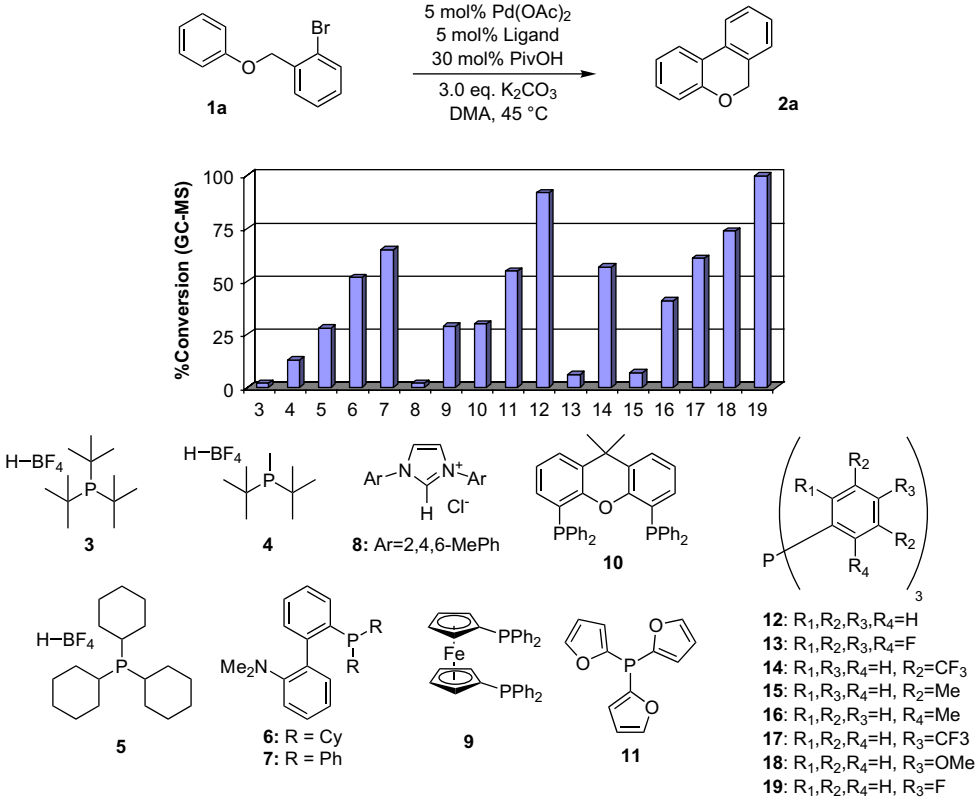
Herein, we describe our work in applying these new conditions to the original source of our inspiration, intramolecular direct arylation reactions of simple arenes. The new conditions permit a dramatic reduction in reaction temperature. While it is not atypical to require forcing conditions with heating in excess of 120 °C for these types of reactions, our new conditions permit intramolecular direct arylation reactions of simple arenes to occur at temperatures as low as 50 °C. The biaryl products are isolated in good to excellent yields and a mechanistic proposal is advanced to explain the enhancement in reactivity.

During the course of our investigations on benzene arylation,[9] we found that the combined use of a catalytic amount of pivalic acid (30 mol %) when used in conjunction with an excess of K_2CO_3 provided vastly superior outcomes when compared to the use of K_2CO_3 alone. These observations prompted us to reevaluate the intramolecular direct arylation processes to determine if any benefits would be revealed. Reaction development efforts focused on the appropriate choice of ligand in the reaction of **1a** to give the biaryl **2a**. A variety of ligands were screened in conjunction with $Pd(OAc)_2$ (5 mol %), pivalic acid (30 mol %), K_2CO_3 (3 equiv) in DMA at 45 °C (Scheme 3). From these experiments, two ligands were found to give the highest yields, triphenylphosphine **12** and tri(4-fluorophenyl)phosphine **19**. Since **19** gave slightly superior yield, it was taken on for further optimization work. The observation that electron-deficient phosphines can provide the optimal outcomes in direct arylation has previously been noted by Itami et al.,[10] Baudoin et al.,[11] and by us.[12] It is plausible that the use of such ligands may facilitate arene binding by creating a more electron-deficient palladium metal atom or by providing for a vacant site for arene binding by undergoing more facile displacement from the metal center.

Employing $Pd(OAc)_2$ with ligand **19** a variety of carboxylic acid additives were evaluated in conjunction with K_2CO_3 as the stoichiometric base (Table 1). There is a marked increase in conversion as the steric encumbrance of the acid increases from acetic acid to pivalic acid (entries 2–5). In contrast the use of adamantylcarboxylic acid results in an inferior conversion (entry 6). The use of more acidic additives, such as with trifluoroacetic acid does not influence the reaction outcome compared to a control when no additive is employed (entry 7 vs entry 1). The selection of stoichiometric base also has a profound effect on the transformation. For example, use of sodium carbonate provides slightly lower



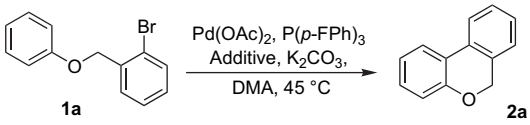
Scheme 2. Mechanistic possibilities for arene palladation in the context of biaryl synthesis.

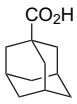
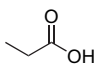
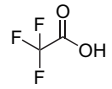
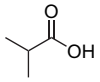


Scheme 3. Ligand evaluation in intramolecular direct arylation reactions.

conversions than the potassium salt while use of cesium carbonate results in very low conversions after the same reaction time (Table 2, entries 1–3). The use of a catalytic quantity of pivalic acid (which generates potassium pivalate in situ when treated with potassium carbonate) is also superior to simply employing potassium pivalate as the terminal stoichiometric base as illustrated by entries 4 and 5. The enhanced reactivity associated with the presence of 30 mol % potassium pivalate in the reaction mixture can be partially gained through the use of a palladium pivalate catalyst precursor. With $Pd(OPiv)_2$ and potassium carbonate as the base, a 71% conversion is observed after 12 h compared to the use of $Pd(OAc)_2$, which provides only 32% (entry 7 vs entry 2).

Table 1
Effect of carboxylic acid additives on direct arylation[a]

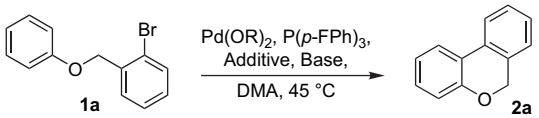


Entry	Additive	Conv.[b] (%)	Entry	Additive	Conv.[b] (%)
1	None	31	5		100
2		32	6		56
3		36	7		28
4		63			

[a] Conditions: substrate **1a**, $Pd(OAc)_2$ (5 mol %), P(*p*-FPh)$_3$ (5 mol %), additive (30 mol %), and K_2CO_3 (3.0 equiv) are dissolved in DMA (0.25 M) and heated to 45 °C for 12 h.

[b] Determined by GC–MS.

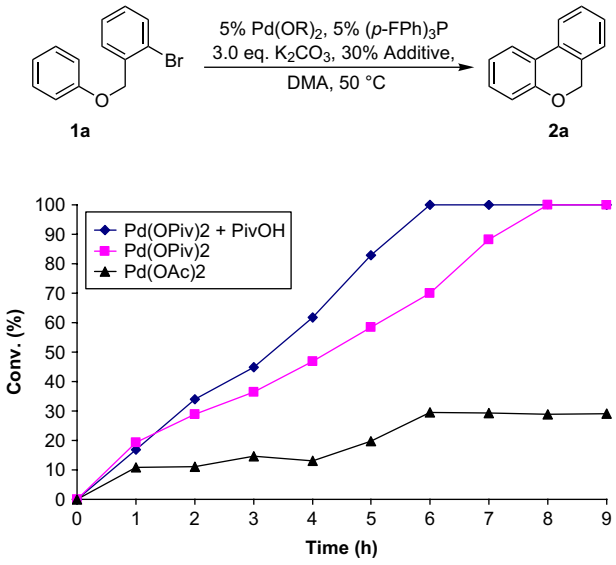
Table 2
Influence of stoichiometric base on direct arylation[a]



Entry	Pd source	Additive	Base	Conv.[b] (%)
1	$Pd(OAc)_2$	None	Na_2CO_3	22
2	$Pd(OAc)_2$	None	K_2CO_3	32
3	$Pd(OAc)_2$	None	Cs_2CO_3	5
4	$Pd(OAc)_2$	None	KOPiv	22
5	$Pd(OAc)_2$	PivOH	K_2CO_3	100
6	$Pd(OPiv)_2$	None	K_2CO_3	71
7	$Pd(OPiv)_2$	PivOH	K_2CO_3	100

[a] Conditions: substrate **1a**, $Pd(OR)_2$ (5 mol %), P(*p*-FPh)$_3$ (5 mol %), additive (30 mol %), and base (3.0 equiv) are dissolved in DMA (0.25 M) and heated to 45 °C for 12 h.

[b] Determined by GC–MS.



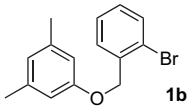
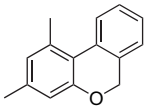
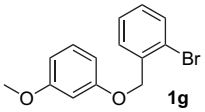
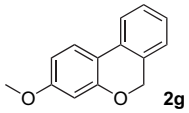
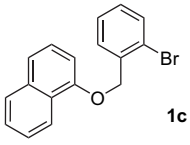
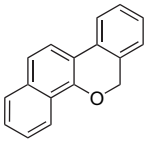
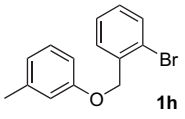
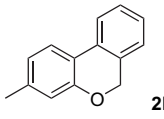
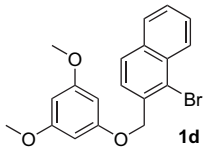
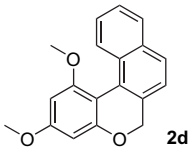
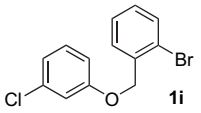
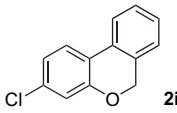
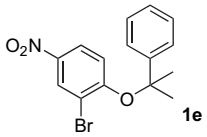
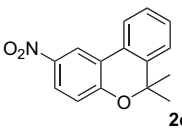
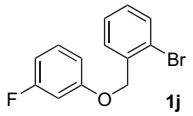
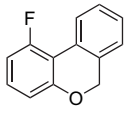
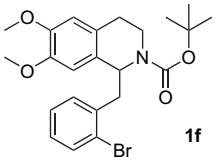
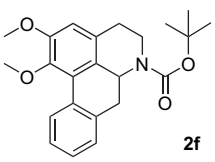
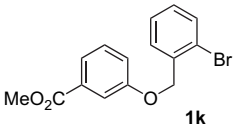
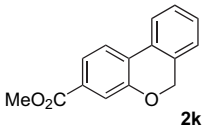
Scheme 4. Ligand evaluation in intramolecular direct arylation reactions.

The acceleration in product formation over time resulting from the addition of pivalic acid is illustrated in Scheme 4. After 6 h, a reaction performed under the standard conditions in the absence of pivalic acid provides approximately 30% conversion while an identical reaction performed with 30 mol % pivalic acid reached 100% conversion. A similar, albeit less pronounced, acceleration is also observed using palladium pivalate as the catalyst precursor in place of palladium acetate.

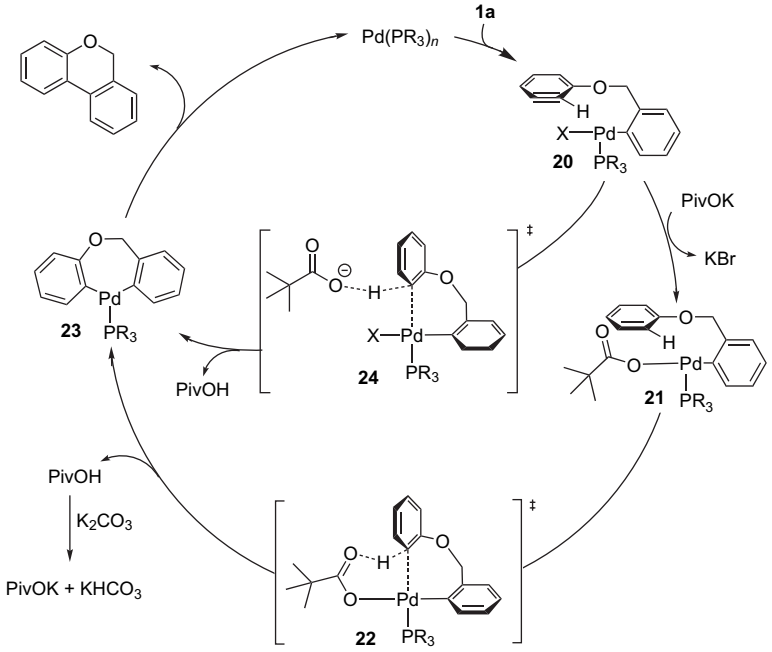
Application of these optimized reaction conditions to a range of substrates is included in Table 3. A variety of activated and deactivated aryl bromides are compatible including reactions for the formation of sterically encumbered biaryls. These are rare examples where the arylation of a broad range of simple arenes can be achieved under such mild conditions. A range of substitution patterns are compatible including electron-donating (entries 3, 5, and 6) and withdrawing groups (entries 4, 9, and 10). Reaction at more sterically encumbered positions can also occur in high yield (entries 1, 3, and 5). More highly functionalized substrates can also be employed as illustrated by the use of a precursor for aporphine synthesis in entry 5.

The presence of primary kinetic isotope effects is strong evidence for a mechanism where the C–H bond cleavage is a kinetically significant step in the catalytic cycle—a feature, which is inconsistent with electrophilic aromatic substitution pathways. Under the current reaction conditions, reaction of **1l** reveals the presence of a pronounced primary intramolecular

Table 3
Substrate scope in intramolecular direct arylation[a]

Entry	Substrate	Product	Yield[b] (%)	Entry	Substrate	Product	Ratio[c]	Yield[b] (%)
1	 **1b**	 **2b**	96[d]	6	 **1g**	 **2g**	>30:1	99
2	 **1c**	 **2c**	97	7	 **1h**	 **2h**	>30:1	98
3	 **1d**	 **2d**	95	8	 **1i**	 **2i**	15:1	96
4	 **1e**	 **2e**	94	9	 **1j**	 **2j**	1.2:1	93
5	 **1f**	 **2f**	70[e]	10	 **1k**	 **2k**	>30:1	92

[a] Conditions: substrate, $Pd(OPiv)_2$ (5 mol %), P(*p*-FPh)$_3$ (5 mol %), PivOH (30 mol %), and K_2CO_3 (3.0 equiv) are dissolved in DMA (0.25 M) and heated to 50 °C for 12 h.
[b] Isolated yield.
[c] Ratio of regioisomers formed at the *ortho* positions.
[d] Reaction performed at 60 °C.
[e] Reaction performed at 70 °C.



Scheme 5. Proposed catalytic cycle.

hydrogen/deuterium kinetic isotope effect of 5.4. This magnitude of KIE is in line with our previously observed KIE of 3.5[12] for similar reactions performed in the absence of pivalic acid and of 3.0[8] and 5.5[9] for intermolecular direct arylation reactions with perfluorobenzenes and benzene, respectively. It is also consistent with KIEs reported by Echavarren and Maseras with similar substrates for intramolecular reactions.[6] Pronounced KIEs are compatible with, and characteristic of, mechanisms where C–H bond cleavage is occurring simultaneously with carbon–palladium bond formation.[13]

In line with Echavarren's and Maseras's proposed mechanism for intramolecular direct arylation[6] and our own work in intermolecular processes[4] we favor the involvement of a catalytic cycle similar to that illustrated in Scheme 5. Subsequent to oxidative insertion into the carbon–halide bond, two pathways may be followed. The first involves an anion exchange of a pivalate for the bromide ligand to give **21**. This species can then undergo a concerted deprotonation–palladation to give the biarylpalladium(II) intermediate **23**, which will reductively eliminate to give the observed product and regenerate the catalyst. Alternatively, the pivalate may be acting as an external base at the C–H bond cleaving transition state via **24** to intercept intermediate **23** of the other pathway. The reason for the superior reactivity of pivalic acid as an additive in these reactions compared to other carboxylic acids may be related to both its steric bulk and the increased basicity of its conjugate base. The ability to control the amount of pivalate present is crucial to achieve maximal reactivity. It is also noteworthy that some bidentate ligands such as **9** and **10** exhibited moderate reactivity under these conditions. This may indicate the involvement of a pentacoordinate pathway[16] or a cationic manifold may be operating with an intermolecular deprotonation such as that illustrated by **24**.

While evidence points to the involvement of concerted palladation–deprotonation pathways in the present reactions, insufficient data exists to state whether one, the other, or both of these pathways are responsible for the observed reactivity. Indeed, as previously pointed out,[6] the intimate reaction mechanism may change from reaction to reaction as the substrate, solvent, base, and additives are changed. If accurate, such a flat thermodynamic landscape can make a detailed understanding of the exact mechanism for any precise reaction elusive. Nonetheless, we have, and are continuing, to use these transition states and reaction pathways as an enabling technology in the development of other, novel carbon–carbon bond forming processes.

3. Conclusion

These reactions, and more importantly, the reaction conditions that enable them should be of use in the synthetic community for the preparation of biaryl molecules. The particular mildness of these conditions with respect to the base and temperature should enable an application to more complex molecules that may be prone to decomposition under more forcing reaction conditions and the commonly employed elevated reaction temperatures that are commonly associated with direct arylation protocols.

4. Experimental section

4.1. General methods

N,*N*-Dimethylacetamide was purchased from commercial sources and degassed with argon prior to every use. $Pd(OPiv)_2$ was synthesized according to the known literature procedure.[14]

All other solvents or chemical were purchased from commercial sources and used as received. Experiments were carried out under an atmosphere of argon. ^{1}H, ^{19}F, and ^{13}C NMR were recorded in $CDCl_3$ solutions using a Bruker AVANCE 400 or 500 MHz spectrometer. ^{1}H and ^{13}C chemical shifts were determined relative to internal tetramethylsilyl at δ=0. NMR high-resolution mass spectra were obtained on a Kratos Concept IIH. Infra red analysis was performed with a Bruker EQUINOX 55.

Bromoether **1a**,[4] **1b**,[4] **1c**,[12] **1d**,[4] **1f**,[15] **1g**,[4] **1h**,[4] **1i**,[4] **1j**,[4] **1k**[4] were prepared accordingly and exhibited spectral data identical to literature. Tricyclic compound **2a**,[4] **2b**,[4] **2c**,[12] **2d**,[4] **2f**,[15] **2g**,[4] **2h**,[4] **2i**,[4] **2j**,[4] **2k**[4] were prepared using the general cyclization procedure and exhibited spectral data identical to literature.

4.2. 1-(2-(2-Bromo-5-nitrophenoxy)propan-2-yl)benzene *1e*

To a flask containing a suspension of potassium hydride (0.27 g, 2.0 mmol, 1.1 equiv) in THF (3 mL) at 0 °C was added slowly the 2-phenylpropan-2-ol (0.4 g, 2.0 mmol, 1.1 equiv) and the solution was stirred for 10 min. This solution was then added slowly to a solution of 2-bromo-1-fluoro-4-nitrobenzene (0.4 g, 1.8 mmol, 1.0 equiv) in THF (9 mL) at 0 °C. The solution was then allowed to warm to room temperature and was stirred for an additional 2 h. Saturated aqueous ammonium chloride was then added and the solution was extracted with DCM and dried over magnesium sulfate. Compound **1e** was then purified by column chromatography on silica gel using 3% ether/hexanes as the eluant. Yield 83%: R_f=0.30 (SiO_2, 5% ether/hexane); IR (ν_{max}/cm^{-1}): 2984, 1516, 1473, 1341, 1275, 1138; ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 1.85 (6H, s), 6.36 (1H, d, J=9.2 Hz), 7.28–7.41 (5H, m), 7.80 (1H, dd, J=9.2, 2.8 Hz), 8.42 (1H, d, J=2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 29.3, 83.9, 114.5, 116.8, 123.4, 124.9, 127.8, 128.9, 128.9, 141.0, 144.1, 158.4; HRMS calcd for $C_{15}H_{14}O_3NBr$ (M^+) 335.0157, found: 335.0105.

4.3. General cyclization procedure

K_2CO_3 (1.7 mmol, 3.0 equiv), $Pd(OPiv)_2$ (0.03, 0.05 equiv), P(*p*-FPh)$_3$ (0.03 mmol, 0.05 equiv), and pivalic acid (0.17 mmol, 0.3 equiv) were weighed to air and placed in a screw capped vial (4 mL) with a magnetic stir bar. The reaction vessel was evacuated and backfilled with argon three times. The cyclization precursor (0.57 mmol, 1.0 equiv) was then added to the reaction vessel as a solution in *N*,*N*-dimethylacetamide (3 mL). The reaction was heated to 50–60 °C for 12 h. Upon completion, the reaction was cooled to room temperature. The products were loaded directly onto a silica gel packed column and eluted using ether/hexane mixtures.

4.4. 6,6-Dimethyl-2-nitro-6H-benzo[c]chromene *2e*

The compound was prepared following the general cyclization procedure at 50 °C. Yield 94%; mp=92–95 °C(ether); R_f=0.23 (SiO_2, 3% ether/hexane); IR (ν_{max}/cm^{-1}): 2982, 1518, 1339, 1266, 1106; ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS): 1.67 (6H, s), 7.00 (1H, d, J=8.9 Hz), 7.25–7.27 (1H, m), 7.36–7.43 (2H, m), 7.76–7.79 (1H, s), 8.10 (1H, dd, J=8.9, 2.7 Hz), 8.64 (1H, d, J=2.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, TMS): 27.9, 79.5, 118.4, 118.9, 122.4, 122.5, 123.4, 124.9, 126.3, 128.2, 129.4, 138.7, 142.2, 158.2; HRMS calcd for $C_{15}H_{13}O_3N$ (M^+) 255.0895, found: 255.0873.

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References and notes

1. For reviews on this topic, see: (a) *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, NY, 1998; (b) Hassan, J.; Se'vignon, M.; Gozzi, C.; Shulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
2. For recent reviews, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174; (b) Seregin, I. V.; Gevorgyan, V. *J. Chem. Soc., Chem. Rev.* **2007**, *36*, 1173; (c) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35.
3. (a) Wang, X.; Gribkov, D. V.; Sames, D. *J. Org. Chem.* **2007**, *72*, 1476; (b) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972; (c) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996; (d) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897; (e) Lewis, J. C.; Wiedemann, S. H.; Bergmann, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 35; (f) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159; (g) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, *5*, 4835; (h) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286; (i) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698; (j) McClure, M. S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M. H.; Roschangar, F. *Org. Lett.* **2001**, *3*, 1677.
4. Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, F. *J. Am. Chem. Soc.* **2006**, *128*, 581.
5. Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754.
6. (a) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 8755; (b) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880.
7. Biswas, B.; Sugimoto, M.; Sakaki, S. *Organometallics* **2000**, *19*, 3895.
8. Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754.
9. Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496.
10. Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748.
11. Hitce, J.; Retailleau, P.; Baudoin, O. *Chem.—Eur. J.* **2007**, *13*, 792.
12. Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186.
13. Zollinger, H. *Adv. Phys. Org. Chem.* **1964**, *2*, 162.
14. Kiss, G. *J. Mol. Catal.* **1983**, *18*, 223.
15. Lafrance, M.; Blaquiere, N.; Fagnou, F. *Chem. Commun.* **2004**, 2874.
16. For a pertinent discussion of analogous intermediates in C–X insertion, see: Lam, K. C.; Marder, T. B.; Lin, Z. *Organometallics* **2007**, *26*, 758.