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High-Yielding Intramolecular Direct Arylation Reactions with Aryl Chlorides

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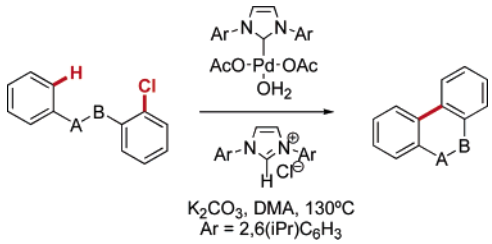
ABSTRACT



An N-heterocyclic carbene palladium catalyst system is used to promote direct arylation of a broad range of aryl chlorides to form six- and five-membered ring biaryls. An influence of the halide on the palladium precatalyst on catalyst activation has been revealed, as has a beneficial effect of NHC salts that allows the turnover numbers to be increased by simple addition of imidazolium salts to the reaction mixture.

N-Heterocyclic carbene (NHC) ligands have become increasingly employed in transition metal catalysis.[1,2] The 1:1 NHC−metal complexes typically exhibit enhanced reactivity compared to analogous 2:1 species,[3] and these observations have prompted the development of several methods to prepare NHC metal complexes with a well defined 1:1 ligand-to-metal ratio.[4] Despite the impressive reactivity of these catalysts, they can be prone to decomposition after insertion of the aryl halide.[5] Cavell, Caddick, and Grushin have shown that in the absence of a good nucleophile, NHC aryl palladium(II) species are unstable and undergo facile aryl-NHC reductive elimination to give the arylimidazolium salts and catalyst death.[6]

Direct arylation processes are an important class of C−H functionalization reaction that uses a simple arene in place of the organometallic component.[7,8] At present, direct arylation processes commonly require the use of aryl iodides or bromides, with near complete exclusion of aryl chlorides.[9,10] The study of NHC catalysts in the context of direct arylation reactions could therefore not only enable the general use of aryl chlorides in these reactions but also provide an opportunity to circumvent NHC catalyst decomposition since these reactions must be able to occur in the absence of a strong nucleophile. Herein, we describe a generally applicable catalyst system for the efficient intramolecular direct aryla-

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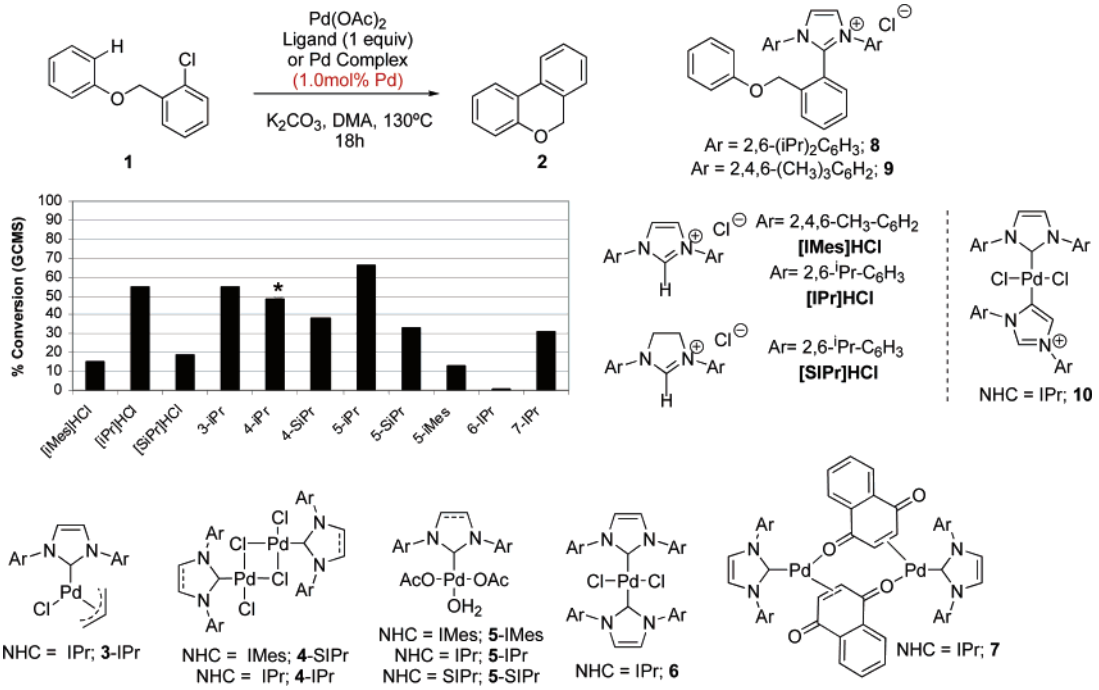
Scheme 1. Catalyst Screens of Various NHC/Pd Systems for Direct Arylation of **1**[a]



[a] Conditions: Substrate **1**, catalyst (1 mol %), and K_2CO_3 (2 equiv) were dissolved in DMA (0.2 M) and heated to 130 °C until catalyst deactivation occurred. *Precatalysts **4** reacted irreproducibly, giving as much as 48 TON for **4**−IPr.

tion of aryl chlorides. As part of these studies we have found that the X ligands of the palladium precatalyst influence the efficiency of catalyst activation. We also reveal that the addition of NHC salts to reactions employing palladium mono-NHC precatalysts can lead to improvements in catalyst turnover number (TON). These observations should be of broader implication in other cross-coupling reactions.

Results from NHC catalyst screens for the intramolecular direct arylation of **1** are outlined in Scheme 1. All reactions were carried out with 1 mol % [Pd] and allowed to react until catalyst deactivation had occurred. Both in situ-generated catalysts and isolated NHC palladium complexes were examined. Mono-NHC complexes **4** and **5** were prepared according to previously reported methods,[4b,d] including previously unreported **5**−IMes and **5**−SIPr.[11] Optimal results were achieved with **5**−IPr, which gives a TON of 66.

The Cl precatalysts **4** were found to react irreproducibly. While a TON of up to 48 can be achieved, we also frequently observed inferior TON or even no reaction under identical conditions. Wondering if catalyst activation is influenced by the catalyst counterion, we tested the use of different silver additives to promote X ligand exchange prior to reaction. When 4 equiv of silver acetate is added to **4**-IPr, activation occurs reproducibly, giving results similar to those obtained with the OAc catalyst **5**. In contrast, however, the bis-NHC precatalyst **6** does not initiate even in the presence of AgOAc.

The IPr catalysts give dramatically better TON than IMes analogues despite showing similar initial rates. This may point to an important steric component in preventing catalyst death. MALDI TOF-MS analysis of the crude reaction mixtures with **5**−IMes and **5**−IPr after catalyst deactivation revealed the presence of mass peaks at 485.687 and 569.728 corresponding to catalyst decomposition products **8** and **9** (Scheme 1), indicating that reductive elimination of the aryl and NHC ligands is a contributing factor to catalyst death.

(7) For recent reviews, see: (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (c) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211. (d) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. For recent intermolecular examples, see: (e) Sezen, B.; Sames D. *J. Am. Chem. Soc.* **2003**, *125*, 5274. (f) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286. (g) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112. (h) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698. For recent intramolecular examples, see: (i) Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506. (j) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460. (k) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 3739. (l) Hennings, D. D.; Iwasa, S.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 2.

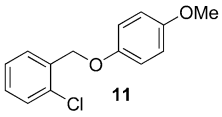
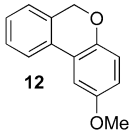
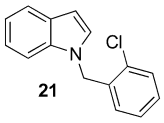
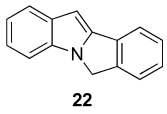
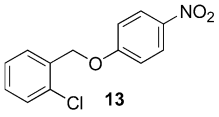
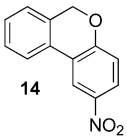
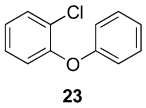
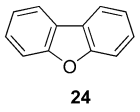
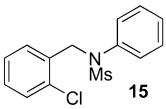
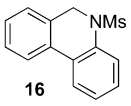
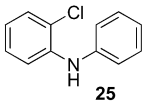
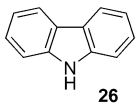
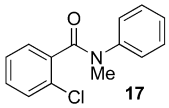
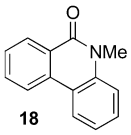
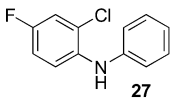
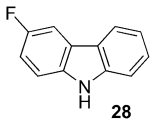
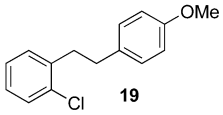
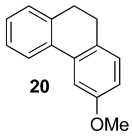
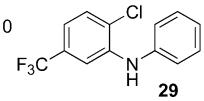
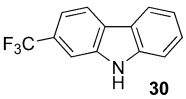
(8) For our own work in this area, see: (a) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186. (b) Lafrance, M.; Blaquiere, N.; Fagnou, K. *Chem. Commun.* **2004**, *24*, 2874.

(9) Successful reaction with simple aryl chlorides has been achieved in intermolecular reactions with electron-rich zinc pyrrole anions[9a] and in the formation of five-membered rings in moderate yield.[9b] (a) Rieth, R. D.; Mankad, N. P.; Calimano, E.; Sadighi, J. P. *Org. Lett.* **2004**, *6*, 3981. (b) Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2002**, 2310. To our knowledge, no intramolecular examples with larger ring sizes have appeared.

(10) For a review of palladium-catalyzed cross-coupling reactions of aryl chlorides, see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

(11) For experimental procedures, complete characterization, and X-ray crystal structures of all new palladium complexes, see Supporting Information.

Table 1. Scope of Intramolecular Biaryl Formation[a]

Entry	Substrate	Product	Yield(%)[b]	Entry	Substrate	Product	Yield (%)[b]
1	 **11**	 **12**	91	6	 **21**	 **22**	89
2	 **13**	 **14**	88	7	 **23**	 **24**	86
3	 **15**	 **16**	82	8	 **25**	 **26**	99
4	 **17**	 **18**	97	9	 **27**	 **28**	89
5	 **19**	 **20**	84[c]	10	 **29**	 **30**	92

[a] Conditions: Substrate, **5-IPr** (1−3 mol %), [IPr]HCl (1−3 mol %), K_2CO_3 (2 equiv) were dissolved in DMA (0.2 M) and heated to 130 °C for 10−16 h. [b] Isolated yield. [c] Conducted using an in situ-generated catalyst from $Pd(OAc)_2$ and 2 equiv of [IPr]HCl. Ms = CH_3SO_2−.

The superior reactivity of mono-NHC palladium catalysts[3] would appear to make deliberate addition of NHC hydrochloride salts (pre-NHC ligands) to mono-NHC catalyst **5**−IPr counterproductive since bis-NHC complexes would be produced in situ, which should produce slower reactions. Nonetheless, when we explored the use of [IPr]HCl and [IMes]HCl as additives in reactions with the palladium IPr and IMes complexes **5**, substantial improvements in TON were obtained with no loss in reactivity (Figure 1).[12,13] For example, addition of 0.5 mol % [IMes]HCl to **5**−IMes led to a modest, but reproducible, TON enhancement of approximately 10. More significantly, the TON with **5**−IPr increased from 70 to 116 when 0.5 mol % [IPr]HCl was added. This catalyst combination, **5**−IPr/[IPr]HCl, was consequently employed to investigate the scope of these reactions.

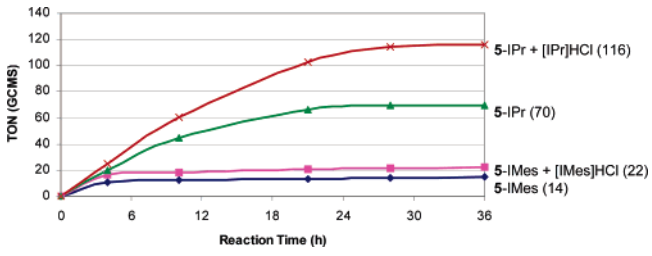


Figure 1. Effect of added imidazolium salts on catalyst TON. Conditions: **1**, K_2CO_3 (2 equiv), Pd catalyst (0.5 mol %), and imidazolium salt additive if used (0.5 mol %) were dissolved in DMA (0.2 M) and heated to 130 °C in a screw-capped vial for 36 h. Aliquots were periodically removed via syringe to determine % conversion by GCMS analysis.

Selected examples demonstrating the scope are outlined in Table 1. Hydrodehalogenation can be a severely limiting side process in intramolecular processes that results in nonproductive consumption of starting material. While this can be effectively overcome in intermolecular processes through the use of an excess of the aryl halide, intramolecular reactions must rely on catalyst selectivity. We were therefore gratified to find that, in all cases, only trace amounts of hydrodechlorination (<1%) were detected by GCMS analysis of the crude reaction mixtures. The catalyst system of **5**−IPr/[IPr]HCl was found to be highly reactive and selective for the formation of five- and six-membered rings. A variety of tethers can be employed, as illustrated in the formation of six-membered rings with an ether (entries 1, 2), amine (entry 3), amide (entry 4), or alkyl (entry 5) tether. Cyclization of **21** with a methylene tether occurs rapidly to close the five-membered ring, underlining the superior reactivity associated with heteroaromatic coupling partners. Biaryl ethers such as **23** can also be efficiently arylated in high yield (entry 7).

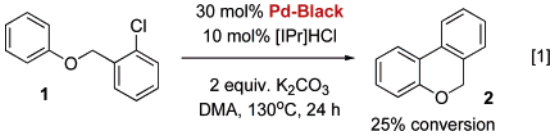
(12) Addition of [IPr]HCl to **3**−IPr only leads to modest increases in TON.

(13) This kind of TON increase upon NHC−HCl addition was also observed in telomerization of dienes with alcohols, but increased reaction rates were observed with higher imidazolium salt additive concentrations: Jackstell, R.; Harkal, S.; Jiao, H.; Spannenberg, A.; Borgmann, C.; Röttger, D.; Nierlich, F.; Elliot, M.; Niven, S.; Cavell, K.; Navarro, O.; Viciu, M. S.; Nolan, S. P.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 3891

This methodology enables carbazole synthesis (entries 8−10) without the protection of the nitrogen functionality and is a very efficient route to this class of molecule, which has demonstrated medicinal importance.[14]

We have conducted initial experiments to probe how the imidazolium additives may be influencing the TON. Under some conditions, unusual palladium NHC complexes[15] can be formed in situ that possess different activity. Consequently, we prepared the previously uncharacterized complex **10**[11] (Scheme 1). Complex **10** is a poor catalyst, giving only 10 turnovers after 18 h. Furthermore, we have ruled out that the [IPr]HCl is simply behaving as a chloride additive, since added Bu_4NCl does not induce the same beneficial effects.

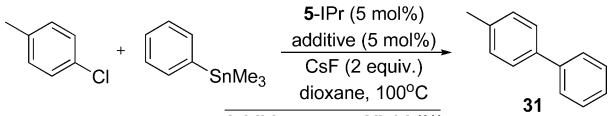
Another possibility is that the reactivity of the **5**−IPr catalyst, once reduced to palladium(0), is not negatively influenced by the presence of a slight excess of IPr. Once catalyst decomposition has occurred and the bound IPr ligand has been consumed by the formation of **8**, the excess IPr may intercept the unligated palladium(0) prior to the formation of palladium black, thereby regenerating an active NHC catalyst. We have obtained support for this notion by reaction with palladium black as the palladium source, which is otherwise completely inactive. Treatment of **1** with 30 mol % palladium black and 10 mol % [IPr]HCl in the presence of K_2CO_3 in DMA at 130 °C results in 25% conversion, proving that even after palladium black formation has occurred, catalyst recovery is viable (reaction 1). MALDI-TOF analysis of the crude reaction mixture shows peaks corresponding to IPr−Pd complexes and aryl-imidazolium salt **8** proving that discrete palladium NHC catalysts can be produced under the reaction conditions.



[1]

To investigate the pertinence of these discoveries to other reaction classes, we selected the Stille coupling.[16] Preliminary results indicate that the use of imidazolium salt additives can increase the TON in Stille couplings (Scheme 2). In the absence of additive, biaryl **31** is obtained in 19% isolated yield. When 5 mol % [IPr]HCl is added, 55% yield is obtained.

Scheme 2. Effect of Imidazolium Salt Additives on Stille Reactions



Additive	Yield (%)
none	19
[IPr]HCl	55

In conclusion, we have developed a general and high-yielding intramolecular direct arylation reaction with aryl chloride substrates. We have revealed that the TON of palladium−NHC catalysts can be substantially improved through the use of imidazolium salt additives in conjunction with mono-NHC palladium precatalysts. Preliminary results with Stille couplings indicate that this discovery should also be more generally applicable in other reaction classes.

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Supporting Information Available: Complete characterization data for all new metal complexes and biaryl products, as well as experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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