Pergamon

Tetrahedron Letters 43 (2002) 9347–9350

TETRAHEDRON
LETTERS

Observations on the intramolecular Heck reactions of aromatic chlorides using palladium/imidazolium salts

Stephen Caddick* and William Kofie

Centre for Biomolecular Design and Drug Development, The Chemistry Laboratory, CPES, University of Sussex, Falmer, Brighton BN1 9QJ, UK

Received 22 August 2002; revised 8 October 2002; accepted 18 October 2002

Abstract—The intramolecular Heck reaction of aromatic amines and ethers using palladium/imidazolium salts is described. The use of tetra-*n*-butylammonium halide salts facilitates the reactivity of aromatic chlorides. An unexpected and novel palladium-mediated cyclisation is also described leading to the formation of a tricyclic adduct. © 2002 Published by Elsevier Science Ltd.

The intramolecular Heck reaction has become widely used for the synthesis of carbocyclic and heterocyclic ring systems.[1] Most conventionally these reactions utilise palladium phosphine complexes and employ aromatic bromides and iodides as substrates. Such is the reliability and practicability of these transformations that they are considered one of the most powerful methods for the construction of polycyclic ring systems. A generally accepted mechanism involves (i) oxidative addition of aryl halide to Pd(0); (ii) intramolecular carbometallation; (iii) β-hydride elimination; (iv) reductive elimination to regenerate the Pd(0) catalyst.[2]

One of the current limitations of many palladium-catalysed transformations is that they require the more usual use of bromide or iodide substrates. There are many important commercial and environmental reasons for trying to develop protocols employing aromatic chlorides. In recent times there has been extraordinary research activity in the generation of new ligands for palladium and the study of their mechanisms of action.[3] The development of novel sterically hindered phosphine ligands for palladium-catalysed transformations has improved the applicability of many palladium-mediated transformations.[4] A key development has been the ability to apply these new protocols to chloride substrates.[5] Further important advances are likely to be made as the mechanistic details of these phosphine systems become clearer.[3]

There is some value in attempting to find practical alternatives to phosphines as ligands.[6] The *N*-heterocyclic carbene (NHC) system is often now regarded as a potential replacement ligand for phosphine.[7] It is known that NHC ligands are excellent donors and tend to form strong bonds with metals.[8] In the case of ruthenium the replacement of PCy_3 with NHC has led to new complexes with good catalytic activity.[9]

The NHC motif has also found use in palladium chemistry. There are many reports of palladium(II) complexes in which the metal is ligated with the NHC ligand and the catalytic activity of these complexes has also been examined.[10] Zero-valent palladium systems are less common but have also been studied and their catalytic activity described. It has been found that such palladium–carbene complexes exhibit excellent catalytic behaviour in amination, Heck, and Suzuki reactions.[7,11]

NHC–palladium complexes have also been invoked as intermediates in systems utilising imidazolium salts[12] and Hartwig,[13] Nolan[14] and others have described systems in which imidazolium salts can be useful additives in palladium-catalysed transformations.[15] Although the detailed mechanistic understanding has yet to be elucidated[16] it seems likely that these systems generate either neutral or cationic[17] palladium–NHC complexes and what is clear is these protocols have enormous potential value in synthetic organic chemistry.

There are fewer reports of the use of NHC–Pd or other reagent systems for intramolecular transformations of aromatic chlorides.[18] As part of our programme directed towards the study of metal–NHC-catalysed

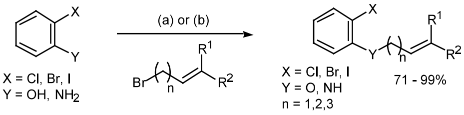
---

* Corresponding author. Tel./fax: +44(1273) 678734; e-mail: s.caddick@sussex.ac.uk

0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)02340-7

protocols for organic synthesis, we have investigated the potential for carrying out intramolecular Heck reactions using aromatic chlorides.[19] We describe our studies on the palladium/imidazolium catalysed intramolecular Heck reactions of aromatic iodides, bromides and chlorides. Our findings indicate that intramolecular Heck reactions of aromatic chlorides is possible using Pd/imidazolium salt protocols.

In order to carry out these preliminary studies we have focused on nitrogen and oxygen containing systems. The substrates described in this study were prepared in good to excellent yields by alkylation of 2-halo-anilines ((a) LDA, THF, −78°C, 72–95%) or 2-halo-phenols ((b) K_2CO_3, NaI, acetone, reflux, 71–99%) (Scheme 1).



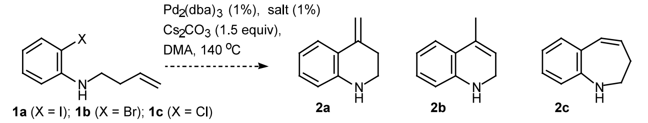
Scheme 1.

Table 1 presents the results of our studies on intramolecular Heck reactions using Pd_2dba_3 and imidazolium salt **A**.

As anticipated iodide precursors were found to undergo high yielding and rapid intramolecular Heck reactions (entries 1, 5, 9, 13 and 18). Aryl bromides also reacted satisfactorily proceeding in slightly slower reaction times and with slightly lower yields than the iodides (entries 2, 6, 10, 14 and 19). Aromatic chloride substrates were particularly sluggish in their reactivity and the yields of these transformations were poor (entries 3, 7, 11, 15 and 20). However, we found that the yields of these reactions could be dramatically improved to 50–70% (entries 4, 8, 12, 16, and 21) by the addition of one equivalent of tetra-*n*-butylammonium bromide (TBAB)[20] showing that aromatic chlorides can participate effectively in intramolecular Heck reactions. We were interested to note that a similar effect could be observed using an equivalent of tetra-*n*-butylammonium nitrate (TBAN, entry 17).

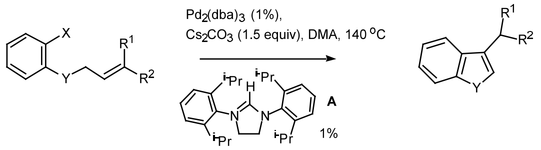
Further studies on substrate **1a–c** were frustrated by problems of isomer separation; however, we have tentatively assigned the product as a mixture of regioisomers **2a–c** (yields, between 20 and 70%) (Scheme 2).

However, more satisfactorily we were able to isolate a single product **4** from reaction of substrates **3a–c**. We found that the iodide **3a** and bromide **3b** proceeded to give the product **4** in good to excellent yields (I, 82%, 1 h; Br, 60%, 5 h) but the chloride **3c** gave only 4% of



Scheme 2.

Table 1.



Entry	R^1	R^2	X	Y	Time (h)	Add[a]	Isolated yield (%)
1	H	H	I	NH	0.5		81
2	H	H	Br	NH	1		77
3	H	H	Cl	NH	24		18
4	H	H	Cl	NH	24	TBAB	65
5	H	Me	I	NH	1		82
6	H	Me	Br	NH	2		71
7	H	Me	Cl	NH	24		21
8	H	Me	Cl	NH	24	TBAB	64
9	H	Ph	I	NH	2		78
10	H	Ph	Br	NH	5		70
11	H	Ph	Cl	NH	24		27
12	H	Ph	Cl	NH	24	TBAB	70
13	Me	Me	I	NH	2		76
14	Me	Me	Br	NH	24		56
15	Me	Me	Cl	NH	48		21
16	Me	Me	Cl	NH	48	TBAB	58
17	Me	Me	Cl	NH	48	TBAN	52
18	H	Ph	I	O	24		84
19	H	Ph	Br	O	48		61
20	H	Ph	Cl	O	48		17
21	H	Ph	Cl	O	48	TBAB	63

Typically these reactions were carried out using 1 mol% catalyst, 1 mol% ligand, Cs_2CO_3 (1.5. equiv.) in DMA at 140°C.

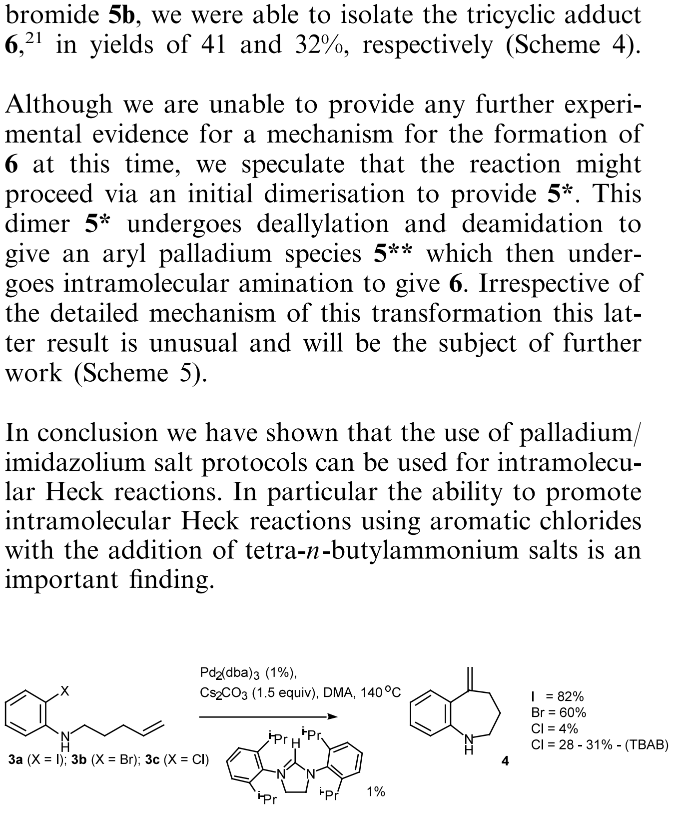
[a] 1 equiv.

product **4**. However, repetition of the reaction but using tetra-*n*-butylammonium bromide[20] or iodide, had a dramatic effect, improving the yield of **4** from 4% to 28–32% (Scheme 3).

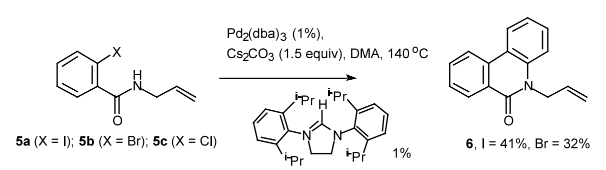
Perhaps the most surprising result was obtained from a study of substrates **5a**–**c**. Although we only isolated traces of products from chloride **5c** we were very surprised to discover that, from either the iodide **5a** or bromide **5b**, we were able to isolate the tricyclic adduct **6**,[21] in yields of 41 and 32%, respectively (Scheme 4).

Although we are unable to provide any further experimental evidence for a mechanism for the formation of **6** at this time, we speculate that the reaction might proceed via an initial dimerisation to provide **5***. This dimer **5*** undergoes deallylation and deamidation to give an aryl palladium species **5**** which then undergoes intramolecular amination to give **6**. Irrespective of the detailed mechanism of this transformation this latter result is unusual and will be the subject of further work (Scheme 5).

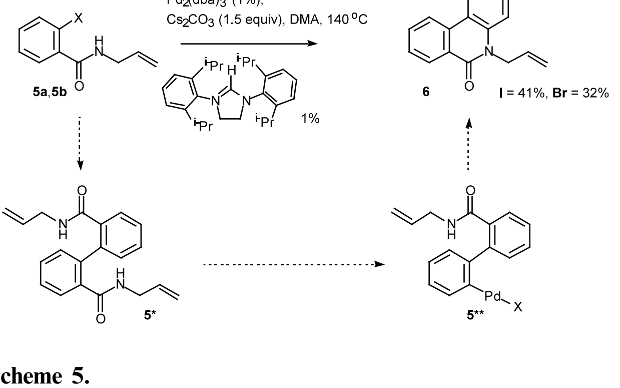
In conclusion we have shown that the use of palladium/imidazolium salt protocols can be used for intramolecular Heck reactions. In particular the ability to promote intramolecular Heck reactions using aromatic chlorides with the addition of tetra-*n*-butylammonium salts is an important finding.



Scheme 3.



Scheme 4.



Scheme 5.

Acknowledgements

We gratefully acknowledge Dr. John Hayler at GSK for his encouragement, support and helpful comments throughout this project. We also gratefully acknowledge support of this project from GSK and EPSRC. We also acknowledge financial support from AstraZeneca, Novartis, Pfizer, BBSRC, and AICR. We are grateful to EPSRC Mass Spectrometry Service at Swansea and Drs. Abdul-Sada, Avent and Hitchcock for their contributions to this work.

References

1. (a) Belestkaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. See also: (b) Grigg, R.; Millington, E. L.; Thornton-Pett, M. *Tetrahedron Lett.* **2002**, *43*, 2605; (c) Oestreich, M.; Dennison, P. R.; Kodanko, J. J.; Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 1439.
2. For an overview see: *Palladium Reagents and Catalysts; Innovations in Organic Synthesis*; Tsuji, J.; J. Wiley & Sons, 1997.
3. For mechanistic studies on palladium catalysed transformations using phosphine ligands see: (a) Alcazar-Roman, L. M.; Hartwig, J. F. *Organometallics* **2002**, *21*, 491. Alcazar-Roman, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 12905; (b) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 1232; (c) Alcazar-Roman, L. M.; Hartwig, J. F.; Rhiengold, A. L.; Liable-Sands, L. M.; Guzei, I. A. *J. Am. Chem. Soc.* **2000**, *122*, 4618 and references cited therein.
4. Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131.
5. For lead references to phosphine based systems, see: (a) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343; (b) Kirchoff, J. H.; Dai, C. Y.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1945; (c) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677; (d) Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 3820; (e) Huang, X.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3417; (f) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158; (g) Kuwano, R.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 6479.
6. Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.
7. For a recent review see: (a) Herrmann, W. A. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1291; Bourissou, D.; Guerret, O.; Gabbai, P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39; (b) Arduengo, A. J. *Acc. Chem. Res.* **1999**, *32*, 913; (c) Regitz, R. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 725 and references therein.
8. Jafarpour, L.; Nolan, S. P. *Adv. Org. Chem.* **2001**, *46*, 181.
9. Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.
10. See for example: (a) Nielsen, D. J.; Cavell, K. J.; Skelton, B. W.; White, A. H. *Inorg. Chim. Acta* **2002**, *327*, 116; (b) Ruther, T.; Done, M. C.; Cavell, K. J.; Peacock, E. J.; Skelton, B. W.; White, A. H. *Organometallics* **2001**, *20*, 5522; (c) McGuinnes, D. S.; Cavell, K. J. *Organometallics* **2000**, *19*, 741; (d) Tulloch, A. A. D.; Danopoulos, A. A.;

Tizzard, G. J.; Coles, S. J.; Hursthouse, M. B.; Hay-Motherwell, R. S.; Motherwell, W. B. *J. Chem. Soc.*, *Chem. Commun.* **2001**, 1270; (e) Tulloch, A. A. D.; Danopoulos, A. A.; Tooze, R. P.; Cafferkey, S. M.; Kleinhenz, S.; Hursthouse, M. B. *Chem. Commun.* **2000**, 124; (f) Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449; (g) Batey, R. A.; Shen, M.; Lough, A. J. *Org. Lett.* **2002**, *4*, 1411; (h) Viciu, M. S.; Kissling, R. M.; Stevens, E. D.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 2229.

11. (a) Arnold, P. L.; Cloke, F. G. N.; Goldbach, T.; Hitchcock, P. B. *Organometallics* **1999**, *18*, 3228; (b) Caddick, S.; Cloke, F. G. N.; Clentsmith, G. K. B.; Hitchcock, P. B.; McKerrecher, D.; Titcomb, L. R.; Williams, M. R. V. *J. Organomet. Chem.* **2001**, *617*, 635; (c) Titcomb, L. R.; Caddick, S.; Cloke, F. G. N.; Wilson, D. J.; McKerrecher, D. *J. Chem. Soc.*, *Chem. Commun.* **2001**, 1388; (d) Green, J. C.; Scurr, F. G.; Arnold, P. L.; Cloke, F. G. N. *J. Chem. Soc.*, *Chem. Commun.* **1997**, 1963; (e) McGuiness, D. S.; Cavell, K. J.; Skelton, B. W.; White, A. H. *Organometallics* **1999**, *18*, 1596; (f) Kackstell, R.; Andreu, M. G.; Frisch, A.; Selvakumar, K.; Zapf, A.; Klein, H.; Apannenberg, A.; Rottger, D.; Briel, O.; Karch, R.; Beler, M. *Angew Chem.*, *Int. Ed. Engl.* **2002**, *41*, 986.
12. Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C. L.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69.
13. Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423.
14. Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307.
15. See for example: (a) Furtsner, A.; Seidel, G. *Org. Lett.* **2002**, 4, 541; (a) Furstner, A.; Leitner, A. *Synlett* **2001**, *2*, 290.
16. For studies, see: (a) Caddick, S.; Cloke, F. G. N.; Hitchcock, P. B.; Leonard, J.; Lewis, A. K. de K.; McKerrecher, D.; Titcomb, L. R. *Organometallics* **2002**, *21*, 4318; (b) McGuiness, D. S.; Cavell, K. J.; Yates, B. F.; Skelton, B. W.; White, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 8317; (c) McGuiness, D. S.; Saendig, N.; Yates, B. F.; Cavell, K. J.; Skelton, B. W. *J. Am. Chem. Soc.* **2001**, *123*, 4029.
17. Grundemann, S.; Albrecht, M.; Kovacevic, A.; Faller, J. W.; Crabtree, R. H. *J. Chem. Soc.*, *Dalton Trans.* **2002**, 2163.
18. For some lead references on intramolecular heteroatom bond formation see: (a) Shaugnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546; (b) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402; (c) Gaertzen, O.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 465; (d) Kuwabe, S.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202; (e) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451.
19. For a specific example of intramolecular Heck using aromatic chlorides, see: Li, J. J. *J. Org. Chem.* **1999**, *64*, 8425.
20. (a) Hassan, J.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron* **1998**, *54*, 13793–13804; (b) Herrmann, W. A.; Elison, M.; Fischer, J.; Kocher, C.; Artus, G. R. J. *Angew. Chem.*, *Int. Ed. Engl.* **1995**, *34*, 2371; (c) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.
21. (a) Murphy, J. A.; Rasheed, F.; Gastaldi, S.; Ravishanker, T.; Lewis, N. *J. Chem. Soc.*, *Perkin Trans. 1* **1997**, 1549; (b) Togo, H.; Kikuchi, O. *Heterocycles* **1989**, *28*, 373.