Available online at www.sciencedirect.com

SCIENCE DIRECT®

ELSEVIER

Tetrahedron Letters 45 (2004) 3511–3515

Tetrahedron Letters

Suzuki–Miyaura cross-coupling of aryl and alkyl halides using palladium/imidazolium salt protocols

Katherine Arentsen,[a] Stephen Caddick,[b,*] F. Geoffrey N. Cloke,[a,*] Adam P. Herring[c] and Peter B. Hitchcock[a]

[a]*Department of Chemistry, School of Life Sciences, University of Sussex, Falmer, Brighton BN1 9QJ, UK*
[b]*Department of Chemistry, University College London, 20 Gordon Street, London WC1H OAJ, UK*
[c]*AstraZeneca, R&D Charnwood, Loughborough, Leicestershire LE11 5RH, UK*

Received 28 January 2004; revised 17 February 2004; accepted 27 February 2004

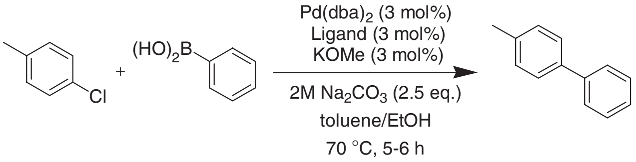
Abstract—A simple new protocol for the high yielding Suzuki–Miyaura cross-couplings of aryl chlorides with aryl boronic acids using a palladium/imidazolium salt catalytic system is presented. The first examples of a palladium/imidazolium salt protocol for sp^3–sp^3 Suzuki–Miyaura couplings of alkyl halides are also disclosed.

Palladium-catalysed formation of carbon–carbon and carbon–heteroatom bonds have become an extremely powerful tool for the organic chemist.[1] Such bond formations, in which an organometallic reagent is coupled to an organic electrophile, are widely used in the preparation of many natural products,[2] as well as in other branches of synthetic chemistry and materials science.[3] Amongst the palladium-catalysed cross-coupling processes, the Suzuki–Miyaura reaction has emerged as one of the most popular,[4] owing, in part, to the tolerance of the reaction to a wide range of functional groups on both substrates. The ease of separation of the nontoxic boron containing reaction by-product from the desired product has ensured that the reaction has found extensive use in the pharmaceutical industry.

As with many other Pd-catalysed coupling processes, the use of aryl chlorides (particularly those that are electron-rich) in the Suzuki–Miyaura reaction was, until recently, uncommon.[5] New catalytic systems, utilising palladacyclic complexes,[6] electron-rich trialkylphosphine ligands[7] and the bulky biphenyl-based phosphines developed by Buchwald and co-workers,[8] amongst others, have allowed couplings of electron-poor, electron-neutral as well as electron-rich aryl chlorides to be achieved.

N-Heterocyclic carbenes (NHCs) are often considered phosphine mimics and have consequently received a great deal of attention as alternatives to phosphine-based ligands in Pd-catalysed chemistry. NHCs are useful alternative ligands to phosphines because the increased thermal stability of the Pd–NHC bond avoids the necessity for excess ligand. This can be a problem in Pd/phosphine-based catalytic systems due to the facile

Table 1. Imidazolium salt ligands in a Suzuki–Miyaura coupling of an aryl chloride



Entry	Ligand	Yield (%)[a]
1	IAd·HCl	0
2	IPr·HCl	17
3	I*t*-Bu·HCl[b]	0
4	IPr·HCl	87[c]

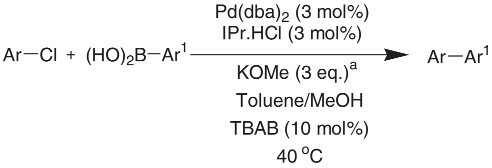
[a] Isolated yield.
[b] I*t*-Bu·HCl = 1,3-bis(*tert*-butyl)imidazolium chloride.
[c] KOMe (3 equiv) used instead of Na_2CO_3.

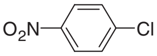
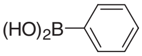
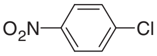
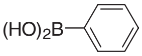
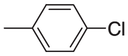
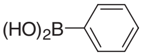
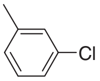
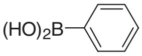
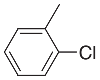
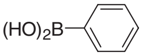
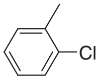
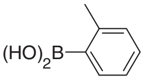
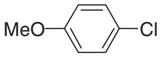
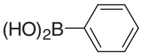
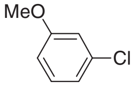
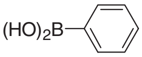
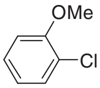
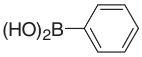
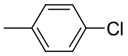
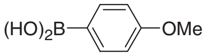
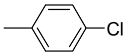
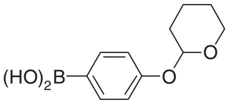
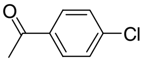
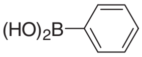
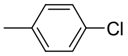
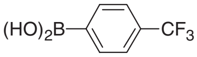
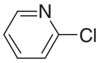
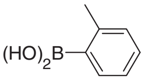
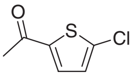
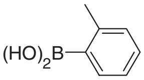
Keywords: Palladium; Suzuki; Aryl chlorides; Alkyl bromides.

* Corresponding authors. Tel./fax: +44-020-76794694 (S.C.); tel.: +44-01273-678735; fax: +44-01273-677196 (F.G.N.C.); e-mail addresses: s.caddick@ucl.ac.uk; f.g.cloke@sussex.ac.uk

doi:10.1016/j.tetlet.2004.02.134

Table 2. Suzuki–Miyaura reactions of aryl chlorides using IPr·HCl



Entry	Ar–Cl	$(HO)_2B$–Ar^1	Time (h)[b]	Yield (%)[c]
1			24	0[d]
2			24	93
3			24	75
4			24	91
5			5	79
6			5	75
7			6	75
8			23	99
9			29	78
10			6	91
11			29	92
12			10	83
13			8	82
14			29	86
15			29	61

[a] KOMe in MeOH added at 0 °C.

[b] Reaction time not optimised.

[c] Isolated yield.

[d] No TBAB used.

degradation of the P–C bond at elevated temperatures.[9] In many catalytic processes where NHCs are employed as the ancillary ligand, the corresponding imidazolium salt is used and is deprotonated in situ, possibly to give the NHC, thus avoiding the problems of handling the air- and moisture-sensitive carbene.

Work by Herrmann and co-workers,[10] Nolan and co-workers[11] and Fürstner and Leitner[12] has shown that Suzuki–Miyaura couplings can be achieved using Pd/imidazolium salt protocols. These reactions have been carried out at elevated temperatures (70–80 °C) and usually with an excess of organoborane. In this Letter, we describe our own findings on the Suzuki–Miyaura reactions of electron-rich and electron-deficient aryl chlorides at *significantly lower temperatures* (40 °C) using a Pd/1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr·HCl) catalytic system (1:1 Pd/ligand ratio).[13] These aryl couplings are very sensitive to the reaction conditions. We also describe the first examples of Suzuki–Miyaura alkyl–alkyl couplings, employing a palladium/NHC protocol.

Initial experiments used the sterically encumbered adamantyl-substituted imidazolium salt, 1,3-bis(adamantyl)imidazolium chloride (IAd·HCl). This ligand has been successfully used by Herrmann and co-workers[14] and we anticipated that an in situ protocol based on this imidazolium salt would be particularly facile. However, when IAd·HCl was used as an ancillary ligand in the coupling of 4-chlorotoluene with phenylboronic acid, none of the desired product, 4-phenyltoluene, was obtained. Different imidazolium salts were evaluated in the reaction and, in accordance with the findings of Fürstner and Leitner,[12] the best results were obtained with the IPr·HCl imidazolium salt (Table 1). We found that the use of KOMe (3 equiv) as the sole base vastly improves the reaction outcome compared to the results obtained using catalytic amounts of KOMe and Na_2CO_3 (Table 1). It is also vital to the success of the cross-coupling procedure that the exotherm generated upon addition of base is controlled by prior cooling of the reaction medium and slow addition.

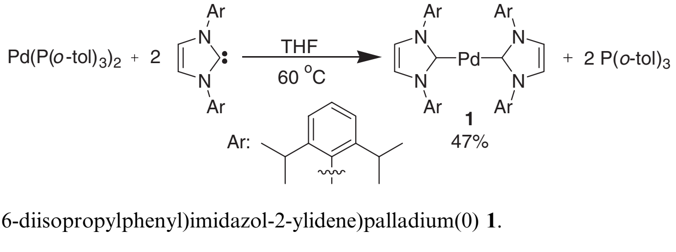
Studies by Nolan and co-workers have demonstrated that Suzuki–Miyaura reactions can be sensitive to changes in Pd(0)/imidazolium salt ratios, with a 1:1 ratio being optimal.[15] However, we found that there was no apparent difference in product yields when different Pd(0)/ligand ratios were used; with both the 1:1 ratio and 1:2 ratio giving yields of 87%.

Despite the success we observed with the coupling of 4-chlorotoluene and phenylboronic acid, we were disappointed to find that the coupling of 1-chloro-4-nitrobenzene with phenylboronic acid was completely unsuccessful under the optimised reaction conditions (Table 2, entry 1). Previous work has shown that the use of tetra-*n*-butylammonium bromide (TBAB) in the Heck reaction facilitates the reaction and leads to improved yields.[16] Encouragingly, when a sub-stoichiometric amount (10 mol %) of TBAB was used in the coupling of 1-chloro-4-nitrobenzene with phenylboronic acid, the reaction proceeded to 93% conversion (Table 2, entry 2). Table 2 shows that this methodology is compatible with a variety of functional groups on both substrates. The catalytic system, with the TBAB additive, was tolerant of both electron-donating and electron-withdrawing substituents, resulting in excellent yields. It is particularly noteworthy that these reactions proceed at 40 °C and this present protocol offers a practical method for Suzuki–Miyaura couplings of aryl and hetero-aryl chlorides.

Our working model for the mechanism of this transformation involves the in situ deprotonation of the imidazolium salt to the free carbene, which is then believed to bind to palladium to form a mono-ligated Pd–NHC complex. This complex is considered to be the catalytically active species, which then undergoes oxidative addition. In order to demonstrate that such a palladium(0) species is catalytically active in the reactions, we sought to isolate a bis-carbene Pd(0) species, which could be tested in these cross-coupling processes.

The synthesis of **1** was carried out as shown in Scheme 1[10,14] and crystals suitable for X-ray diffraction were obtained from a toluene solution at −50 °C (Fig. 1). The geometry at Pd is essentially linear with a C1–Pd–C2 angle of 175.98° and the angle of torsion between the planes of the two NHC ligands was found to be 51.7°, which indicates that the Pd centre is less sterically crowded than in other $Pd(NHC)_2$ complexes, for example, 95.6° in bis(1,3-bis(adamantyl)imidazol-2-ylidene)palladium(0)[14] and 90° in bis(1,3-bis(*tert*-butyl)imidazol-2-ylidene)palladium(0).[17]

Complex **1** was able to catalyse the Suzuki–Miyaura coupling of 4-chloroanisole with phenylboronic acid in 68% yield (Scheme 2), complete conversion was achieved after 22 h (a similar yield but longer reaction time than the analogous Pd/IPr·HCl protocol).



Scheme 1. Synthesis of bis(1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene)palladium(0) **1**.

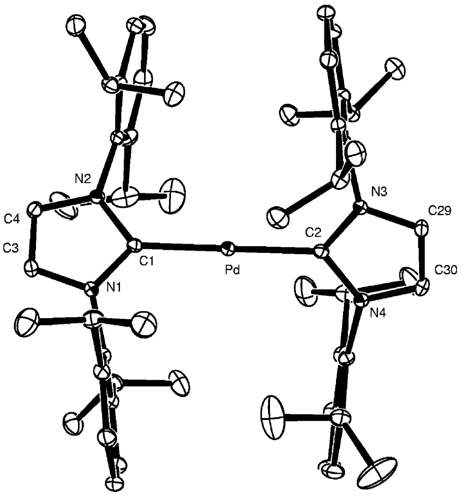
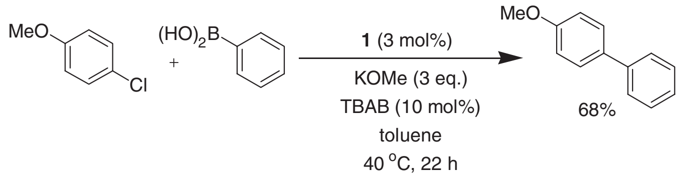


Figure 1. X-ray structure of **1** (thermal ellipsoids at the 50% probability level). Selected bond distances (Å) and angles (°): Pd–C1 = 2.022(4), C1–N2 = 1.377(5), N2–C4 = 1.387(5), C4–C3 = 1.338(5), C3–N1 = 1.377(5), N1–C1 = 1.379(4); C1–Pd–C2 = 175.98, N1–C1–N2 = 101.0(3), C1–N2–C4 = 112.9(3), N2–C4–C3 = 106.2(3), C4–C3–N1 = 106.9(3), C3–N1–C1 = 112.9(3).

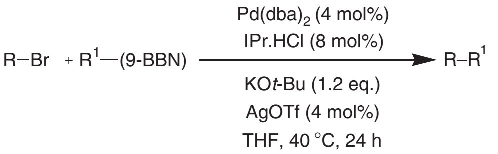
Our attention then turned to alkyl–alkyl couplings using a Suzuki–Miyaura protocol employing an imidazolium salt. The major issue associated with methodologies of this type is that of β-hydrogen elimination.[18] In recent years, Fu and co-workers have exploited the different steric and electronic properties of various phosphine ligands to design successful catalytic systems for the coupling of alkyl halides and tosylates with organoboranes.[19] Recent work by Fu has also demonstrated the first examples of the use of an imidazolium salt protocol to mediate Sonogashira couplings of sp^3-hybridised alkyl halides.[20] Here we show the first application of imidazolium salts for sp^3–sp^3 Suzuki–Miyaura cross-couplings.

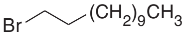
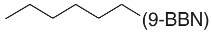
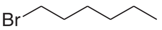
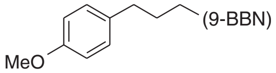
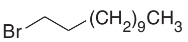
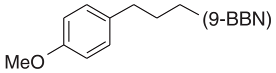
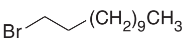
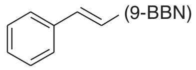
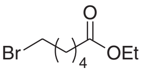
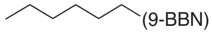
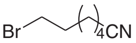
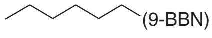
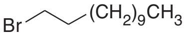
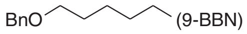
Initial experiments demonstrated that, in the coupling of 1-bromohexane to *B*-(4-propylanisole)-9-BBN, KO*t*-Bu was the most effective base and $Pd(dba)_2$ the most successful palladium source. Elevation of the reaction temperature to 40 °C was found to be beneficial to the reaction outcome. A number of different imidazolium salts were examined in the reaction, however, after considerable experimentation, we found that IPr·HCl



Scheme 2. Suzuki–Miyaura reaction of an aryl chloride using **1**.

Table 3. Suzuki–Miyaura reactions of alkyl bromides using IPr·HCl



Entry	R–Br	R^1–(9-BBN)[a]	Yield (%)[b]
1			56
2			46
3			39
4			37
5			53
6			52
7			28

[a] Organoboranes prepared from 9-BBN dimer (0.6 equiv) and terminal alkene/alkyne (1.2 equiv), not isolated or purified prior to use.

[b] Isolated yield.

was optimal. Table 3 shows preliminary results for a selection of sp^3–sp^3 Suzuki–Miyaura couplings. Although the yields are modest for these transformations, their success is noteworthy. As with the aryl Suzuki–Miyaura couplings, we were able to confirm that the isolated complex **1** could be used, although at this stage the yields are poor (around 20%) and do not yet represent a practical procedure.

In summary, we have developed a new imidazolium salt protocol for efficient and high yielding aryl Suzuki–Miyaura cross-couplings, employing aryl chlorides and boronic acids. We have also confirmed that two-coordinate palladium carbene complexes can promote these transformations. Key to success has been the use of TBAB.[21] We have also presented the first evidence that sp^3–sp^3 Suzuki–Miyaura reactions are possible using certain imidazolium salt protocols.

Acknowledgements

We thank AstraZeneca and EPSRC for financial support of this work. We also thank Glaxo-SmithKline and BBSRC for the support of our program. We also thank the University of Sussex for providing funds to establish the Centre for Biomolecular Design and Drug Development. We also gratefully acknowledge the contributions of Dr. A. G. Advent, Dr. A. Abdul-Sada and the EPSRC Mass Spectroscopy Service at Swansea.

References and notes

1. (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; (b) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, 1995.
2. Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263–303.
3. Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.
4. Reviews: (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168; (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; (c) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998.
5. For a review on aryl chlorides in cross-coupling reactions, see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211.
6. Bedford, R. B.; Cazin, C. S. J. *Organometallics* **2003**, *22*, 987–999.
7. Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.
8. (a) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413–2416; (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561.
9. Jafarpour, L.; Nolan, S. P. *Adv. Organomet. Chem.* **2001**, *46*, 181–222.
10. Böhm, V. P. W.; Gstöttmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, *595*, 186–190.
11. Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804–3805.
12. Fürstner, A.; Leitner, A. *Synlett* **2001**, 290–292.
13. IPr·HCl available from Strem Chemicals, catalog number: 07-0590.
14. Gstöttmayr, C. W. K.; Böhm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1363–1365.
15. Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866–2873.
16. Caddick, S.; Kofie, W. *Tetrahedron Lett.* **2002**, *43*, 9347–9350.
17. Arnold, P. L.; Cloke, F. G. N.; Geldbach, T.; Hitchcock, P. B. *Organometallics* **1999**, *18*, 3228–3233.
18. Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 384–387.
19. (a) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099–10100; (b) Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945–1947; (c) Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910–3912; (d) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662–13663.
20. Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642–13643.
21. For the use of TBAB in Pd free Suzuki reactions, see: Leadbeater, N. E.; Marco, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1407–1409.