



In situ generated palladium catalysts bearing 1,3-dialkylperimidin-2-ylidene ligands for Suzuki reactions of aryl chlorides

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Abstract

Four new 1,3-dialkylperimidinium halides have been prepared and characterized. The in situ prepared three component system Pd(OAc)₂/1,3-dialkylperimidinium (**1a–d**) and Cs₂CO₃ catalyses the Suzuki cross-coupling of deactivated aryl chloride substrates in excellent yields under mild conditions.

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1. Introduction

The palladium-catalyzed Suzuki cross-coupling reaction of aryl halides and pseudohalides (e.g. triflates) is a general method employed for the formation of C–C bonds (Scheme 1) [1].

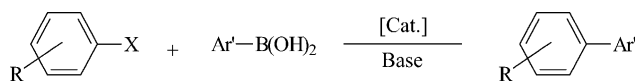
A serious limitation, however, denotes the fact that aryl chlorides, which are the most attractive class of substrates due to their low cost and ready availability, exhibit poor reactivity. Only if the C–Cl bonds are strongly activated by electron withdrawing groups on the arene or by electron deficient heteroaromatic rings they are amenable to cross-coupling under standard conditions [2].

Common methodologies used are the palladium mediated coupling of the organic halides with organoboron reagents where monodentate phosphine are usually employed as ancillary ligands [3]. However, the major drawback of these is that the phosphine ligands are comparatively difficult to make or rather expensive. Furthermore, tertiary phosphines require air-free handling to prevent their oxidation and are susceptible to P–C bond cleavage at elevated temperatures [4].

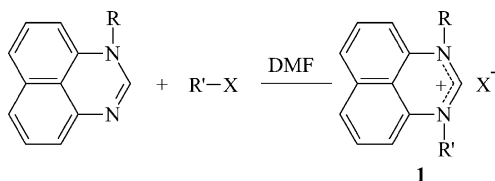
On the other hand, palladium complexes of *N*-heterocyclic carbene ligands (NHCs) [4], in particular, have proved to be excellent catalysts not only for the Suzuki and Heck, but also for Stille and Sonagashira [5,6]. Significant improvements of catalyst performance have recently brought profit to fine chemistry via simple substitution of a phosphine ligand by a nucleophilic heterocyclic diaminocarbene, such as an imidazolylidene ligand. This is largely due to their recently revealed ability to create specific catalytic activity [7] and attempts are currently made to modify the coordination sphere of the metal with the hope to find an even better application profile. Illustrative examples are found in various catalytic reactions with palladium catalysts in cross-coupling or Heck and Suzuki reactions [8,9] and ruthenium catalysts for the formation of furans, cyclopropanation [10,11] alkene metathesis [12,13] and cycloisomerisation [14]. Recently, we have developed improved procedures Heck and Suzuki reactions of aryl chlorides [15].

Although the nature of the NHC ligand on complexes has a tremendous influence on the rate of catalyzed reactions, the use of 1,3-dialkylperimidine-2-ylidene ligands in coupling reactions is a neglected area. In order to find more efficient palladium catalysts we have prepared a series of 1,3-dialkylperimidinium salts (**1a–d**) (Scheme 2). We now report the use of the in situ generated catalytic system composed of commercially available and stable reagents, the Pd(OAc)₂ as palladium source, 1,3-dialkylperimidinium

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Scheme 1. Suzuki reaction.



- | | | |
|----------|--|--------|
| a | R = CH ₂ CH ₂ CH ₂ CH ₃ , R' = CH ₃ | X = I |
| b | R=R' = CH ₂ C ₆ H ₅ | X = Cl |
| c | R=R' = CH ₂ CH ₂ OCH ₃ | X = Cl |
| d | R=R' = C ₁₀ H ₂₁ | X = Br |

Scheme 2. Synthesis of 1,3-dialkylperimidinium salts.

salts (**1a–d**) as a carbene precursor and Cs₂CO₃ as a base for cross-coupling of aryl chlorides with phenyl boronic acid.

2. Experimental

All reactions were carried out under argon and standard high vacuum-line techniques. Solvents were analytical grade and distilled under nitrogen from sodium benzophenone (Et₂O, dioxane). ¹H NMR and ¹³C NMR spectra were recorded using a Bruker AC300P FT spectrometer operating at 300.13 MHz (¹H), 75.47 MHz (¹³C). Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. FT-IR spectra were recorded on a Mattson 1000 spectrophotometer, wave numbers in cm⁻¹. Elemental analyses were performed by TUBITAK (Ankara, Turkey) Microlab.

2.1. Preparation of 1-methyl-3-butyl-perimidinium iodide (**1a**)

To a solution of 1-methylperimidinium (0.182 g, 1 mmol) in DMF (10 mL) was added slowly *n*-butyl iodide (0.184 g, 1 mmol) at 25 °C and the resulting mixture was stirred at 80 °C for 12 h. Diethyl ether (15 mL) was added to obtain a yellow crystalline solid which was filtered off. The solid was washed with diethyl ether (3 × 15 mL), dried under vacuum. mp = 202–203 °C, and the yield was 0.341 g, 93%, IR ν(CN) = 1659 cm⁻¹. Anal. Calc. for C₁₆H₁₉N₂I: C, 52.47, H: 5.23, N: 7.65; found C: 52.51, H: 5.25, N: 7.62.

¹H NMR (CDCl₃, 25 °C), δ = 0.96 [t, *J* = 7.3, 3H, (CH₂)₃CH₃]; 1.52 [sept., *J* = 7.5 2H, (CH₂CH₂CH₂CH₃); 1.88 [quintet, *J* = 7.3, 2H, CH₂CH₂CH₂CH₃]; 4.21 [t, *J* = 7.5, 2H, CH₂CH₂CH₂CH₃]; 3.76 [s, 3H, CH₃]; 6.76 [d, *J* = 7.6, 2H, 6,7-Ar]; 7.25–7.38 [m, 4H, Ar]; 10.46 [s, 1H, 2-CH].

¹³C{¹H}NMR (CDCl₃, 25 °C), δ = 14.1 [CH₂CH₂CH₂CH₃]; 28.8 [CH₂CH₂CH₂CH₃]; 39.0 [CH₂CH₂CH₂CH₃]; 51.6 [CH₂CH₂CH₂CH₃]; 20.0 [CH₃]; 107.8, 108.1, 115.3,

121.8, 124.9, 125.1, 128.6, 132.0, 133.3, 135.4 [C_{arene}]; 151.9 [2-CH].

2.2. Preparation of 1,3-dibenzylperimidinium chloride (**1b**)

Compound **1b** was prepared in the same way as **1a** from 1-benzylperimidinium (0.257 g, 1 mmol) and benzyl chloride (0.127 g, 1 mmol) to give yellow crystals of **1b** in 0.346 g, 90% yield, mp = 275–276 °C, IR ν(CN) = 1672 cm⁻¹. Anal. Calc. for C₂₅H₂₁N₂Cl: C, 78.02, H: 5.46, N: 7.28; found C: 78.10, H: 5.49, N: 7.31. ¹H NMR (CDCl₃, 25 °C), δ = 5.31 [s, 2H, CH₂C₆H₅]; 7.31–7.69 [m, 14H, Ar-H]; 6.91 [d, *J* = 7.7, 2H, 6,7-Ar-H]; 9.75 [s, 1H, 2-CH]. ¹³C{¹H}NMR (CDCl₃, 25 °C), δ = 55.1 [CH₂Ph]; 109.4, 111.3, 117.3, 121.7, 124.2, 127.8, 128.5, 128.8, 129.3, 131.8, 133.1, 131.6 [C_{arene}]; 148.7 [2-CH].

2.3. Preparation of 1,3-di(2-methoxyethyl)perimidinium chloride (**1c**)

Compound **1c** was prepared in the same way as **1a** from 1-(2-methoxyethyl)perimidinium (0.325 g, 1 mmol) and 2-methoxyethyl chloride (0.095 g, 1 mmol) to give pale yellow crystals of **1c** in 0.766 g, 81% yield. Data for **1c**: mp 249–250 °C (dec.), IR ν(CN) = 1663 cm⁻¹. Anal. Calc. for C₁₇H₂₁N₂O₂Cl: C, 63.37; H, 6.60; N, 8.74; found: C, 63.2; H, 6.4; N, 8.7. ¹H NMR (CDCl₃, 25 °C), δ = 3.33 [s, 6H, NCH₂CH₂OCH₃]; 3.75 [t, 4H, *J* = 7.1 Hz, NCH₂CH₂OCH₃]; 4.42 [t, 4H, *J* = 4.75 Hz, NCH₂CH₂OCH₃]; 6.87 [d, *J* = 7.3 Hz, 2H, 6,7-Ar-H]; 7.36–7.13 [m, 4H, Ar-H]; 9.80 [s, 1H, C2-H]. ¹³C{¹H}NMR (CDCl₃, 25 °C), δ = 51.2 [CH₂CH₂OCH₃]; 59.4 [CH₂CH₂OCH₃]; 67.5 [CH₂CH₂OCH₃]; 135.5, 132.0, 128.5, 124.7, 121.9 (C_{arene}); 154.7 [2-CH].

2.4. Preparation of 1,3-decylperimidinium bromide (**1d**)

Compound **1d** was prepared in the same way as **1a** from 1-decylperimidinium (0.309 g, 1 mmol) and decyl bromide (0.221 g, 1 mmol) to give yellow crystals of **1d** in 0.487 g, 92%. Data for **1d**: mp 189–190 °C, IR ν(CN) = 1668 cm⁻¹. Anal. Calc. for C₃₁H₄₉N₂Br: C, 70.30; H, 9.32; N, 5.29; found: C, 70.39; H, 9.31; N, 5.31. ¹H NMR (CDCl₃, 25 °C), δ = 0.82–3.31 [m, 42H, (CH₂)₉CH₃]; 7.12 [d, 2H, *J* = 7.6, 6,7-Ar-H]; 7.47–7.62 [m, 4H, Ar-H]; 9.01 [s, 1H, C2-H]. ¹³C{¹H}NMR (CDCl₃, 25 °C), δ = 13.9, 22.1, 25.6, 25.7, 28.6, 28.7, 28.9, 31.2, 39.4, 51.3 [CH₃(CH₂)₈]; 107.8, 110.4, 112.5, 118.4, 119.6, 123.6, 124.6, 128.4, 129.1, 133.5 [C_{arene}]; 152.4 [2-CH].

2.5. General procedure for the Suzuki type coupling reactions

Pd(OAc)₂ (1.5% mmol), 1,3-dialkylperimidinium salts, **1a–d** (3% mmol), aryl chloride (1.0 mmol), phenylboronic

acid (1.5 mmol), Cs₂CO₃ (1.5 mmol) dioxane (3 mL) were added in a small Schlenk tube under argon and the mixture was heated at 60 °C for 2 h. At the conclusion of the reaction mixture was cooled, diluted with Et₂O, filtered through a pad of silicagel with copious washings, concentrated and purified by flash chromatography on silicagel. Purity of compounds is checked by NMR and yields are based on arylchloride.

3. Results and discussion

1,3-Dialkylperimidinium salts (**1a–d**) are conventional NHC precursors. According to Scheme 2, the salts (**1a–d**) were obtained in almost quantitative yield by quaternization of 1-alkylperimidine [16] in DMF with alkyl halides [17]. The salts are air- and moisture stable both in the solid state and in solution. The structures of **1a–d** were determined by their characteristic spectroscopic data and elemental analyses (Section 2). ¹³C NMR chemical shifts were consistent with the proposed structure, the imino carbon appeared as a typical singlet in the ¹H-decoupled mode in the 151.9, 148.7, 154.7 and 152.4 ppm, respectively, for perimidinium salts **1a–d**. The ¹H NMR spectra of the perimidinium salts further supported the assigned structures; the resonances for C(2)–H were observed as sharp singlets in the 10.46, 9.75, 9.80 and 9.01 ppm, respectively, for **1a–d**. The IR data for perimidinium salts **1a–d** clearly indicate the presence of the –C=N– group with a ν(C=N)

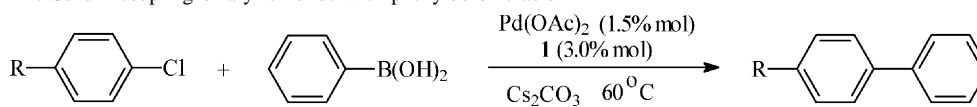
vibration at 1659, 1672, 1663 and 1668 cm⁻¹, respectively, for **1a–d**. The NMR and FT-IR values are similar to those found for other 1,3-dialkylazolanium salts [17].

The palladium-catalyzed cross-coupling of arylboronic acids with aryl halides has been shown to proceed under a variety of conditions: A wide range of bases and solvents, as well as catalysts, have been employed with varying degrees of success according to the substrates [2]. To find optimum conditions a series of experiments has been performed with *p*-chlorotoluene and phenylboronic acid as model compounds. As a base Cs₂CO₃ was the best choice and as a solvent dioxane was found to be better than other solvents. After having established the optimised coupling reaction conditions, the scope of the reaction and efficiencies of the perimidinium salts were evaluated by investigating the coupling of C₆H₅B(OH)₂ with various *p*-substituted aryl chlorides. The results were summarized in Table 1.

Under those conditions, *p*-chloroanisole, *p*-chlorobenzaldehyde, *p*-chlorotoluene, *p*-chloroacetophenone and chlorobenzene react very cleanly with phenylboronic acid in goods yields (Table 1, entries 3, 7, 8, 11, 15, 16 and 19). From the results in Table 1, it is evident that the NHC precursors that contain electron donating methoxyethyl substituent (**1c**) is the most effective of the salt examined. The coordinating ability of the alkoxy group may be an important contributor to the increase in reactivity, as has been demonstrated by previous examples [11,15].

Previous researchers have reported induction periods for Suzuki reactions promoted by Pd(OAc)₂/imidazolium

Table 1
The Suzuki coupling of aryl chloride with phenylboronic acid



Entry	R	LHX	Yield (%) ^a
1	OCH ₃	1a	81
2	OCH ₃	1b	84
3	OCH ₃	1c	87
4	OCH ₃	1d	80
5	CHO	1a	91
6	CHO	1b	93
7	CHO	1c	97
8	CHO	1d	94
9	CH ₃	1a	78
10	CH ₃	1b	85
11	CH ₃	1c	89
12	CH ₃	1d	87
13	COCH ₃	1a	82
14	COCH ₃	1b	92
15	COCH ₃	1c	98
16	COCH ₃	1d	93
17	H	1a	85
18	H	1b	87
19	H	1c	94
20	H	1d	81

^a Reaction conditions: 1.0 mmol of R-C₆H₄Cl-*p*, 1.5 mmol of phenylboronic acid, 1.5 mmol Cs₂CO₃, 1.50 mmol% Pd(OAc)₂, 3.0 mmol% **1**, dioxane (3 mL). Purity of compounds is checked by NMR and yields are based on arylchloride. All reactions were monitored by TLC. 60 °C and 2 h.

salts. It was proposed that during these induction periods Pd(II)/NHC complexes were formed and were then slowly reduced to catalytically active Pd(0)/NHC complexes [8]. It is important to note that these induction periods could be avoided with the present catalyst system.

4. Conclusion

From readily available starting, four 1,3-dialkylperimidinium salts (**1a–d**) have been prepared and characterized. A convenient and highly user friendly method for Suzuki cross-coupling reaction is presented which employs a catalyst formed in situ from Pd(OAc)₂, the readily accessibly and fully air stable 1,3-dialkylperimidinium salts. We report an efficient synthesis of a new carbene ligands architecture and these ligand family allows highly efficient coupling reactions of electron rich as well as electron poor aryl chlorides with phenylboronic acid under mild conditions. Detailed investigations, focusing on perimidine-2-ylidene substituent effects, functional group tolerance and catalytic activity in this and other coupling reactions are ongoing.

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References

- [1] A. Suzuki, *J. Organomet. Chem.* 576 (1999) 147; A. Suzuki, in: F. Diederich, P.J. Stang (Eds.), *Metal-catalyzed Cross-coupling Reactions*, Wiley-VCH, Weinheim, 1998.
- [2] N. Miyaruna, A. Suzuki, *Chem. Rev.* 36 (1995) 2457; A. Suzuki, *J. Organomet. Chem.* 576 (1999) 147; P.S. Stanforth, *Tetrahedron* 54 (1998) 263; A.F. Littke, G.C. Fu, *J. Org. Chem.* 64 (1999) 10; B.C. Hamann, J.F. Hartwig, *J. Am. Chem. Soc.* 120 (1998) 7369.
- [3] C.A. Busacca, M.C. Eriksson, R. Fiaschi, *Tetrahedron Lett.* 40 (1999) 3101; J.A. Miller, R.P. Farrell, *Tetrahedron Lett.* 39 (1998) 7274; A. Suzuki, *J. Organomet. Chem.* 653 (2002) 83; L. Xu, W. Chen, J. Xiao, *J. Mol. Catal. A* 187 (2002) 189; J.P. Wolfe, R.A. Singer, B.H. Yang, S.L. Buchwald, *J. Am. Chem. Soc.* 121 (1999) 9550; J. Yin, M.P. Rainka, X.X. Zhang, S.L. Buchwald, *J. Am. Chem. Soc.* 124 (2002) 1162; A.F. Littke, G.C. Fu, *Angew. Chem. Int. Ed. Engl.* 37 (1998) 3387; A.F. Littke, C. Dai, G.C. Fu, *J. Am. Chem. Soc.* 122 (2000) 4020.
- [4] W.A. Herrmann, in: B. Cornils, B.W.A. Herrmann (Eds.), *Applied Homogeneous Catalysis with Organometallic Compounds*, VCH, Weinheim, 1996, p. 712.
- [5] M.F. Lappert, *J. Organomet. Chem.* 358 (1988) 185; D. Bourissou, O. Guerret, F.P. Gabbaï, G. Bertrand, *Chem. Rev.* 100 (2000) 39; W.A. Herrmann, T. Wescamp, V.P.M. Böhm, *Adv. Organomet. Chem.* 48 (2001) 1; A.C. Hillier, G.A. Grasa, M.S. Viciu, H.M. Lee, C. Yang, S.P. Nolan, *J. Organomet. Chem.* 653 (2002) 69; A. Fürstner, A. Leitner, *Synlett* 2 (2001) 290.
- [6] W.A. Herrmann, C. Köcher, *Angew. Chem. Int. Ed. Engl.* 36 (1997) 2162; W.A. Herrmann, *Angew. Chem. Int. Ed. Engl.* 41 (2002) 1290; T. Wescamp, V.P.W. Böhm, W.A. Herrmann, *J. Organomet. Chem.* 585 (1999) 348.
- [7] W.A. Herrmann, N. Elison, J. Fischer, C. Köcher, G.R.J. Artus, *Angew. Chem. Int. Ed. Engl.* 34 (1995) 2371; D.S. McGuinness, N. Saendig, B.F. Yates, K.J. Cavell, *J. Am. Chem. Soc.* 123 (2001) 4029; D.S. McGuinness, K.J. Cavell, K.F. Yates, B.W. Skelton, B.H. White, *J. Am. Chem. Soc.* 123 (2001) 8317.
- [8] V.P.W. Böhm, C.W.K. Gstöttmayr, T. Wescamp, W.A. Herrmann, *J. Organomet. Chem.* 595 (2000) 186; C. Zhang, J. Huang, M.L. Trudell, S.P. Nolan, *J. Org. Chem.* 64 (1999) 3804; D.S. McGuinness, K.J. Cavell, *Organometallics* 19 (2000) 741.
- [9] C. Yang, H.M. Lee, S.P. Nolan, *Org. Lett.* 3 (2001) 1511.
- [10] B. Çetinkaya, İ. Özdemir, C. Bruneau, P.H. Dixneuf, *J. Mol. Catal. A* 118 (1997) L1; İ. Özdemir, B. Yiğit, B. Çetinkaya, D. Ülkü, M.N. Tahir, C. Arıcı, *J. Organomet. Chem.* 633 (2001) 27; B. Çetinkaya, T. Seçkin, N. Gürbüz, İ. Özdemir, *J. Mol. Catal. A* 184 (2002) 31.
- [11] B. Çetinkaya, İ. Özdemir, P.H. Dixneuf, *J. Organomet. Chem.* 534 (1997) 153.
- [12] D. Semeril, C. Bruneau, P.H. Dixneuf, *Adv. Synth. Catal.* 344 (2002) 585; C.W. Bielowski, R.H. Grubbs, *Angew. Chem. Int. Ed. Engl.* 39 (2000) 2903; A.K. Chatterjee, J.P. Morgan, M. Scholl, R.H. Grubbs, *J. Am. Chem. Soc.* 122 (2000) 3783; S.B. Garber, J.S. Kingsbury, B.L. Gray, A.H. Hoveyda, *J. Am. Chem. Soc.* 122 (2000) 8168.
- [13] S. Randt, S. Gessler, H. Wakamutsu, S. Blechert, *Synlett* 3 (2001) 430; T.M. Trnka, R.H. Grubbs, *Acc. Chem. Res.* 34 (2001) 18; M. Scholl, T.M. Trnka, J.P. Morgan, R.H. Grubbs, *Tetrahedron Lett.* 40 (1999) 2247.
- [14] B. Çetinkaya, S. Demir, İ. Özdemir, L. Toupet, D. Sémeril, C. Bruneau, P.H. Dixneuf, *New J. Chem.* 25 (2001) 519; B. Çetinkaya, S. Demir, İ. Özdemir, L. Toupet, D. Sémeril, C. Bruneau, P.H. Dixneuf, *Chem. Eur. J.* 9 (2003) 2323.
- [15] N. Gürbüz, İ. Özdemir, S. Demir, B. Çetinkaya, *J. Mol. Catal.* 209 (2004) 23; İ. Özdemir, S. Demir, B. Çetinkaya, *J. Mol. Catal. A* 208 (2004) 109; T. Seçkin, S. Köytepe, S. Demir, İ. Özdemir, B. Çetinkaya, *J. Inorg. Organomet. Polym.* 13 (2003) 223; N. Gurbuz, İ. Özdemir, B. Çetinkaya, T. Seçkin, *Appl. Organomet. Chem.* 17 (2003) 776.
- [16] A.F. Pozharskii, V.V. Dal'nikovskaya, *Russ. Chem. Rev.* 50 (1981) 816; B. Alıcı, T. Hökelek, E. Çetinkaya, B. Çetinkaya, *Heteroatom Chem.* 14 (2003) 82.
- [17] O.A. Tarasova, E.Yu. Shmidt, L.V. Baikolova, A.I. Mikhaleva, B.A. Trofimov, *Izv. Ross. Akad. Nauk. Ser. Khim.* (1997) 2005; M.R. Haque, M. Rasmussen, *Tetrahedron* 50 (1994) 5535; E. Çetinkaya, P.B. Hitchcock, H.A. Jasim, M.F. Lappert, K. Spyropoulos, *J. Chem. Soc., Perkin Trans. 1* (1992) 561; O.V. Starikova, G.V. Dolgushin, L.I. Larina, P.E. Ushakov, T.N. Komarova, V.A. Lopyrev, *Russ. J. Org. Chem.* 39 (2003) 1536.