Palladium-Catalyzed Suzuki–Miyaura Reaction of Aryl Chlorides in Aqueous Media Using Tetrahydrodiazepinium Salts as Carbene Ligands

Ismail Özdemir,*[a] Nevin Gürbüz,[a] Yetkin Gök,[a] Engin Çetinkaya,[b] Bekir Çetinkaya[b]

[a] Inönü University, Faculty of Science and Arts, Chemistry Department, 44280 Malatya, Turkey
Fax +90(422)3410212; E-mail: iozdemir@inonu.edu.tr

[b] Department of Chemistry, Ege University, 35100 Bornova-Izmir, Turkey

Received 13 June 2005

Abstract: A highly effective, easy to handle, and environmentally benign process for palladium-mediated Suzuki cross-coupling was developed. The in situ prepared three-component system of $Pd(OAc)_2$, 1,3-dialkyltetrahydrodiazepinium chlorides (**2a**–**e**), and K_2CO_3 catalyzes quantitatively the Suzuki–Miyaura cross-coupling of deactivated aryl chloride.

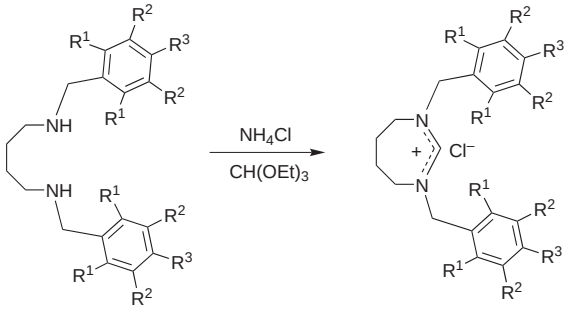
Key words: tetrahydrodiazepinium, Suzuki–Miyaura reaction, palladium, C–C coupling, *N*-heterocyclic carbene

The palladium-catalyzed cross-coupling of aryl halides with arylboronic acids to form biaryls has emerged as an extremely powerful tool in organic synthesis.[1,2] Sterically hindered, electron-rich alkyl phosphines[3] and carbene[4,5] ligands have received increasing interest in recent years. However, the phosphine ligands and the phosphine–palladium complexes are liable to being air- and moisture-sensitive at elevated temperatures, placing significant limits on their synthetic application. Therefore, in terms of practical application, the development of more reactive and stable ligands is of importance for the palladium-catalyzed Suzuki reaction. Recently, nucleophilic *N*-heterocyclic carbenes (NHC's),[6] with a stronger σ-donor electronic property than bulky tertiary phosphines,[7] have emerged as a new family of ligands. In contrast to metal complexes of phosphines, the metal–NHC complexes appeared to be extraordinarily stable towards heat, air, and moisture due to their high metal–carbon bond energies.[8] The development of new ligands or the application of existing ligands in this reaction, particularly those involving aryl chlorides as substrates, is still of considerable importance. A major advance achieved by increasing the catalytic activity is the extension of the Suzuki reaction to unactivated aryl chlorides, as noted by the research groups of Buchwald,[3a,b] Fu,[9] and Herrmann[10] as well as several other groups.[11] The use of water as a solvent for chemical reactions clearly has both economical and environmental advantages because it is inexpensive, abundant, nontoxic, nonflammable, and readily separable from organic compounds.[12] There have been a number of reports of the palladium-mediated Suzuki reaction, being performed using water as solvents,[13] for the coupling of aryl boronic acids with aryl iodides or activated bromide and aryl chlorides, but an oxime-carbapalladacycle is employed as the catalyst.[14] In the course of our search for NHC based ligands, we already reported the use of in situ formed imidazolidin-2-ylidenepalladium(II) system which shows high activities in various coupling reactions of aryl bromides and aryl chlorides.[15] In order to obtain an even more stable and active system we have also investigated benzo-annelated derivatives.[16]

In order to find more efficient palladium catalysts we have prepared a series of new 1,3-dialkyl-4,5,6,7-tetrahydro-1,3-diazepinium chloride (**2**, Scheme 1), containing a saturated diazepine ring and we report here an in situ prepared Pd-carbene-based catalytic system for the Suzuki–Miyaura coupling reaction in aqueous media.[17]

The 1,4-dialkyl-1,4-diaminobutanes were prepared according to a known method.[18] 1,3-Dialkyltetrahydrodiazepinium chlorides **2** are conventional NHC precursors. According to Scheme 1, the salts **2a**–**e** were prepared by treatment of 1,4-dialkyl-1,4-diaminobutane and ammonium chloride with triethyl orthoformate (Scheme 1).[15a] It has been found that in situ formation of the ligand by deprotonation of the bis(imidazolinium)bromides, leads to significantly better results than employing the preformed carbene.[19]

We started our investigation with the coupling of *p*-chloroacetophenone and phenylboronic acid, in the presence of only 1 mol% $Pd(OAc)_2$ and 2 mol% **2**. Table 1 summarizes the results obtained in the presence of **2a**–**e** (Table 1, entries 1–5).



1 **2**

a R^2 = H, R^1, R^3 = CH_3 **d** R^1, R^2 = H, R^3 = OCH_3

b R^2 = H, R^1, R^3 = OCH_3 **e** R^1, R^2 = H, R^3 = $N(CH_3)_2$

c R^1 = H, R^2, R^3 = OCH_3

Scheme 1 The synthesis of 1,3-diazepinium salts.

SYNLETT 2005, No. 15, pp 2394–2396
Advanced online publication: 07.09.2005
DOI: 10.1055/s-2005-872673; Art ID: G16305ST

To survey the reaction parameters for the catalytic Suzuki–Miyaura reaction, we chose to examine Cs_2CO_3, K_2CO_3, and K_3PO_4 as bases with DMF–H_2O (1:1) and dioxane as solvent. We found that the reactions performed in DMF–H_2O (1:1) with Cs_2CO_3 or K_2CO_3 at 60 °C appeared to be the best. In addition, the reactions were performed in air without degassing the water and DMF prior to use.

Under those conditions, *p*-chloroacetophenone, *p*-chlorotoluene, *p*-chlorobenzaldehyde, *p*-chloroanisole, and *p*-chlorobenzene, react very cleanly with phenylboronic acid in goods yields (Table 1, entries 3, 8, 13, and 23). The higher performance of the 1,3-dialkyltetrahydrodiazepinium salts **2** is thought to be due to its better electron-donating ability and greater steric hindrance.

In conclusion, we have demonstrated that in situ generated tetrahydrodiazepin-2-ylidene palladium complexes are very effective in Suzuki–Miyaura coupling reactions, surpassing the corresponding imidazolidin-2-ylidene palladium complexes.[15a] The procedure is simple and efficient for various aryl chlorides and does not require induction periods. The advantage of the catalyst is its low loading capabilities and that it can be used in air. Further work is underway to optimize the reactivity of these *N*-heterocyclic carbene precursors for C–C and C–N coupling with $Pd(OAc)_2$, and transition metal complexes of Ru, Pd, Rh, and Ir to explore their catalytic activity.

Acknowledgment

This work was financially supported by the Technological and Scientific Research Council of Turkey TÜBITAK [TÜBITAK COST D17 and TBAG-2474 (104T085)] and Inönü University Research Fund (B.A.P.: 2005/42)

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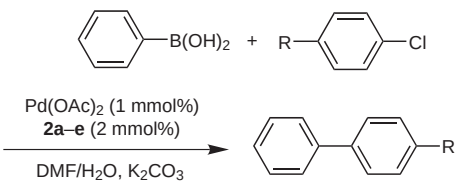
Table 1 The Suzuki–Miyaura Coupling Reaction of Aryl Chlorides with Phenylboronic Acid[a]



Entry	R	LHX	Yield[b] (%)
1	$COCH_3$	**2a**	95
2	$COCH_3$	**2b**	95
3	$COCH_3$	**2c**	98
4	$COCH_3$	**2d**	84
5	$COCH_3$	**2e**	91
6	CH_3	**2a**	82
7	CH_3	**2b**	81
8	CH_3	**2c**	86
9	CH_3	**2d**	74
10	CH_3	**2e**	72
11	CHO	**2a**	89
12	CHO	**2b**	87
13	CHO	**2c**	91
14	CHO	**2d**	86
15	CHO	**2e**	89
16	OCH_3	**2a**	75
17	OCH_3	**2b**	77
18	OCH_3	**2c**	74
19	OCH_3	**2d**	75
20	OCH_3	**2e**	72
21	H	**2a**	78
22	H	**2b**	79
23	H	**2c**	90
24	H	**2d**	73
25	H	**2e**	68

[a] Reaction conditions: *p*-R-C_6H_4Cl (1.0 mmol), phenylboronic acid (1.5 mmol), K_2CO_3 (2 mmol), $Pd(OAc)_2$ (1 mmol%), **2** (2 mmol%), H_2O–DMF (1:1, 6 mL).

[b] Purity of compounds was checked by NMR spectroscopy and yields are based on aryl chloride. All reactions were performed three times to show reproducibility and were monitored by GC.

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(17) **General procedure for the synthesis of 1,3-dialkyl-4,5,6,7-tetrahydro-1,3-diazepinium chloride (2):** To a solution of 1,4-bis(alkylamino)butane (1 mmol) in $CH(OEt)_3$ (30 mL), NH_4Cl (1 mmol) was added; the reaction mixture was heated for 18 h at 100 °C. A white solid was precipitated. The precipitate was then crystallized from EtOH–Et_2O (1:2).
1,3-Bis(2,4,6-trimethylbenzyl)-4,5,6,7-tetrahydro-1,3-diazepinium chloride (2a). Yield: 2.20 g (73%); mp 217–218 °C. ^{1}H NMR (300.13 MHz, DMSO): δ = 1.90 (quintet, *J* = 7.2 Hz, 4 H, $NCH_2CH_2CH_2CH_2N$), 2.09 and 2.23 [s, 18 H, 2,4,6-$(CH_3)_3C_6H_2CH_2$], 3.66 (t, *J* = 7.2 Hz, 4 H, $NCH_2CH_2CH_2CH_2N$), 4.58 [s, 4 H, 2,4,6-$(CH_3)_3C_6H_2CH_2$], 6.77 [s, 4 H, 2,4,6-$(CH_3)_3C_6H_2CH_2$], 7.30 (s, 1 H, 2-CH). ^{13}C{^{1}H} NMR (75.47 MHz, DMSO): δ = 19.8, 49.9 ($NCH_2CH_2CH_2CH_2N$), 21.3, 24.9 [2,4,6-$(CH_3)_3C_6H_2CH_2$], 54.3 [2,4,6-$(CH_3)_3C_6H_2CH_2$], 126.7, 129.9, 138.6, 138.9 [2,4,6-$(CH_3)_3C_6H_2CH_2$], 154.5 (2-CH). Anal. Calcd for $C_{25}H_{35}N_2Cl$: C, 75.25; H, 8.84; N, 7.02. Found: C, 75.23; H, 8.85; N, 7.04.
1,3-Bis(2,4,6-trimethoxybenzyl)-4,5,6,7-tetrahydro-1,3-diazepinium chloride (2b). Yield: 1.48 g (90%); mp 233–234 °C. ^{1}H NMR (300.13 MHz, DMSO): δ = 1.66 (quintet, *J* = 7.2 Hz, 4 H, $NCH_2CH_2CH_2CH_2N$), 3.55 and 3.67 [s, 18 H, 2,4,6-$(CH_3O)_3C_6H_2CH_2$], 3.46 (t, *J* = 7.2 Hz, 4 H, $NCH_2CH_2CH_2CH_2N$), 4.50 [s, 4 H, 2,4,6-$(CH_3O)_3C_6H_2CH_2$], 6.02 [s, 4 H, 2,4,6-$(CH_3O)_3C_6H_2CH_2$], 6.92 (s, 1 H, 2-CH). ^{13}C{^{1}H} NMR (75.47 MHz, DMSO): δ = 25.8, 50.2 ($NCH_2CH_2CH_2CH_2N$), 51.3, 56.9 [2,4,6-$(CH_3O)_3C_6H_2CH_2$], 57.3 [2,4,6-$(CH_3O)_3C_6H_2CH_2$], 92.3, 103.4, 156.3, 160.9 [2,4,6-$(CH_3O)_3C_6H_2CH_2$], 163.4 (2-CH). Anal. Calcd for $C_{25}H_{35}N_2O_6Cl$: C, 60.66; H, 7.12; N, 5.65. Found: C, 60.68; H, 7.10; N, 5.67.
1,3-Bis(3,4,5-trimethoxybenzyl)-4,5,6,7-tetrahydro-1,3-diazepinium chloride (2c). Yield: 1.23 g (87%); mp 151–152 °C. ^{1}H NMR (300.13 MHz, DMSO): δ = 1.78 (quintet, *J* = 7.2 Hz, 4 H, $NCH_2CH_2CH_2CH_2N$), 3.34 (t, *J* = 7.2 Hz, 4 H, $NCH_2CH_2CH_2CH_2N$), 3.65 and 3.78 [s, 18 H, 3,4,5-$(CH_3O)_3C_6H_2CH_2$], 4.64 [s, 4 H, 3,4,5-$(CH_3O)_3C_6H_2CH_2$], 6.88 [s, 4 H, 3,4,5-$(CH_3O)_3C_6H_2CH_2$], 9.11 (s, 1 H, 2-CH). ^{13}C{^{1}H} NMR (75.47 MHz, DMSO): δ = 25.0, 48.9 ($NCH_2CH_2CH_2CH_2N$), 56.8, 60.7 [3,4,5-$(CH_3O)_3C_6H_2CH_2$], 60.3 [3,4,5-$(CH_3O)_3C_6H_2CH_2$], 106.9, 131.4, 138.3, 153.8 [3,4,5-$(CH_3O)_3C_6H_2CH_2$], 159.5 (2-CH). Anal. Calcd for $C_{25}H_{35}N_2O_6Cl$: C, 60.66; H, 7.12; N, 5.65. Found: C, 60.67; H, 7.11; N, 5.64.
1,3-Bis(*p*-methoxybenzyl)-4,5,6,7-tetrahydro-1,3-diazepinium chloride (2d). Yield: 1.82 g (79%); mp 298–299 °C. ^{1}H NMR (300.13 MHz, DMSO): δ = 1.71 (quintet, *J* = 6.8 Hz, 4 H, $NCH_2CH_2CH_2CH_2N$), 3.01 (t, *J* = 6.8 Hz, 4 H, $NCH_2CH_2CH_2CH_2N$), 3.81 (s, 6 H, *p*-$CH_3OC_6H_4CH_2$), 4.64 (s, 4 H, *p*-$CH_3OC_6H_4CH_2$), 7.01 and 7.39 (d, *J* = 8.4 Hz, 8 H, *p*-$CH_3OC_6H_4CH_2$), 8.89 (s, 1 H, 2-CH). ^{13}C{^{1}H} NMR (75.47 MHz, DMSO): δ = 23.1, 46.3 ($NCH_2CH_2CH_2CH_2N$), 50.7 (*p*-$CH_3OC_6H_4CH_2$), 55.8 (*p*-$CH_3OC_6H_4CH_2$), 115.0, 123.5, 131.9 (*p*-$CH_3OC_6H_4CH_2$), 160.2 (2-CH). Anal. Calcd for $C_{21}H_{27}N_2O_2Cl$: C, 67.27; H, 7.25; N, 7.47. Found: C, 67.30; H, 7.23; N, 7.46.
1,3-Bis(*p*-dimethylaminobenzyl)-4,5,6,7-tetrahydro-1,3-diazepinium chloride (2e). Yield: 3.11 g (92%), mp 247–248 °C. ^{1}H NMR (300.13 MHz, DMSO): δ = 1.68 (quintet, *J* = 6.8 Hz, 4 H, $NCH_2CH_2CH_2CH_2N$), 2.89 [s, 12 H, *p*-$(CH_3)_2NC_6H_4CH_2$], 3.52 (t, *J* = 6.8 Hz, 4 H, $NCH_2CH_2CH_2CH_2N$), 4.54 [s, 4 H, *p*-$(CH_3)_2NC_6H_4CH_2$], 6.73 and 7.27 (d, *J* = 8.4 Hz, 8 H, *p*-$(CH_3)_2NC_6H_4CH_2$), 8.87 (s, 1 H, 2-CH). ^{13}C{^{1}H} NMR (75.47 MHz, DMSO): δ = 24.7, 48.5 ($NCH_2CH_2CH_2CH_2N$), 40.7 [*p*-$(CH_3)_2NC_6H_4CH_2$], 60.1 [*p*-$(CH_3)_2NC_6H_4CH_2$], 112.9, 122.2, 130.1, 151.1 [*p*-$(CH_3)_2NC_6H_4CH_2$], 158.3 (2-CH). Anal. Calcd for $C_{23}H_{33}N_4Cl$: C, 68.89; H, 8.29; N, 13.97. Found: C, 68.88; H, 8.30; N, 13.97.
General procedure for the Suzuki–Miyaura coupling reaction
$Pd(OAc)_2$ (1.0 mmol%), 1,3-dialkyltetrahydrodiazepinium chlorides, **2** (2.0 mmol%), aryl chloride (1.0 mmol), phenylboronic acid (1.2 mmol), K_2CO_3 (2 mmol), H_2O–DMF (6 mL, 1:1) were added to a small Schlenk tube in air and the mixture was heated at 60 °C for 0.5 h. At the conclusion of the reaction, the mixture was cooled, extracted with Et_2O, filtered through a pad of silica gel, washed thoroughly, concentrated, and purified by flash chromatography on silica gel. The purity of the compounds was checked by GC and yields are based on aryl chloride.
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