Tetrahedron Letters 51 (2010) 3883–3885

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Ligand-free Suzuki–Miyaura reactions in PEG 300

Aires da Conceição Silva [a], Jaqueline Dias Senra [b], Lucia C. S. Aguiar [a], Alessandro B. C. Simas [b], Andréa Luzia F. de Souza [c,*], Luiz Fernando Brum Malta [a], O. A. C. Antunes [a]

[a] Instituto de Química, Universidade Federal do Rio de Janeiro, CT Bloco A Lab. 641, Rio de Janeiro, 21949-909 RJ, Brazil
[b] Núcleo de Pesquisas de Produtos Naturais, Universidade Federal do Rio de Janeiro, CCS Bloco H, Rio de Janeiro, 21941-614 RJ, Brazil
[c] CCBS, Universidade Estadual da Zona Oeste, Avenida Manuel Caldeira de Alvarenga n. 1203, Rio de Janeiro, 23070-200 RJ, Brazil

ARTICLE INFO

Article history:
Received 4 January 2010
Revised 21 April 2010
Accepted 21 April 2010
Available online 29 April 2010

This work is dedicated to the memory of this brilliant scientist and eternal friend, Professor Dr. O.A.C. Antunes

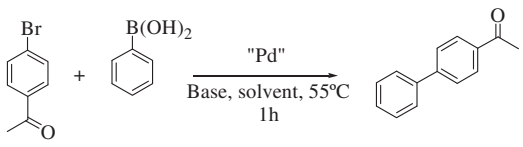
ABSTRACT

In this work, we present ligand-free Suzuki cross-coupling reactions in PEG 300 under thermal conditions at 55 °C with good yields of conversion; better results were obtained with low reaction time. In 1 hour, 1-iodo-4-nitrobenzene and phenylboronic acid reached 98% of the yield and 9700 of TON. Better results were obtained with Pd(0) sources. The reaction system was recycled up to three times with good activity.

Palladium-catalyzed carbon–carbon cross-couplings are capable to generate a wide variety of useful compounds.[1] Suzuki–Miyaura reaction[2] is used in academic research as well as in pharmaceutical and fine chemical industries in the synthesis of organic frameworks.[3] Ligands such as triphenylphosphines and quaternary ammonium salts may reduce and stabilize palladium by the formation of Pd(0) species which can accelerate the coupling reaction.[4] Nevertheless, they are toxic, expensive, and usually unrecoverable. Ligand-free reactions are economically and environmentally viable, so an increasing interest in these reactions has been noticed. Indeed, the replacement of expensive and flammable solvents by water or aqueous systems is highly desirable due to the cost reduction and greener appeal. Polyethylene glycols (PEGs)[5] are linear hydrosoluble polymers which have been emerging as effective green solvents in several cross-coupling reactions.

Our group has been studying Suzuki reactions promoted by ultrasound,[6] microwaves,[7] and thermal conditions[8] using both organic and aqueous reaction media. Hence, continuing the study of a new methodology for these reactions, we have performed experiments using varying solvents, palladium sources, bases, and reaction conditions. Our studies started by establishing the best condition for the Suzuki coupling between phenylboronic acid and 4-bromoacetophenone, the model reaction[9] (Scheme 1). Besides PEG 300, ethanol and water were also investigated as reaction media. To verify the influence of the reaction temperature along with the activation mode, we have carried out experiments under conventional heating and ultrasound power at room temperature or 55 °C, the highest temperature achieved by our ultrasonic bath.[10] As palladium sources, supported and unsupported ones, such as $Pd_2(dba)_3$, $Pd(OAc)_2$, Pd/C, and $Pd/BaSO_4$, were screened. Due to the important role of bases in the Suzuki reaction,[11] we have investigated inorganic and organic ones. The results are summarized in Table 1. Gratifyingly, for this model reaction, one hour was enough to promote the quantitative conversion of 4-bromoacetophenone. However, it was also observed a small amount of biphenyl as a result of the phenylboronic acid homocoupling.

Entries 1–3 show that PEG 300 was the best solvent among those tested. Entry 4 evidences that Pd/C 0.1% was not catalytically active while $Pd_2(dba)_3$, $Pd/BaSO_4$, and $Pd(OAc)_2$ allowed to obtain highly chemoselective products (Table 1, entries 3, 5, and 6). In face of these good results, a palladium amount of 0.05% was tested. With this condition, the aryl halide conversion could not be effective under heterogeneous catalysis (Table 1, entry 7); by contrast, good yields could be achieved under homogeneous one (Table 1, entries 8 and 9). A further decrease of palladium concentration to 0.01% permitted to reach a 93% yield with $Pd_2(dba)_3$ (Table 1, entry 10) and a 77% yield with $Pd(OAc)_2$ (Table 1, entry 11). These results impelled us to apply $Pd_2(dba)_3$ 0.01% in further catalytic tests. Entries 12–14 clearly show that K_2CO_3 is the best base for this system. No reaction was observed using organic bases as also evidenced by the results of Han et al.[5b] Concerning the reaction



Scheme 1. Suzuki reaction between 4-bromoacetophenone and phenyl boronic acid.

* Corresponding author. Tel.: +55 21 2562 7248; fax: +55 21 2562 7559.
E-mail address: andrealuziasouza@yahoo.com.br (Andréa Luzia F. de Souza).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.04.092

Table 1
Study of the best condition for Suzuki reaction between 4-bromoacetophenone and phenyl boronic acid

Entry	Catalyst	Base	Solvent	Conversion (%)	4-Phenylacetophenone yield[a] (%)	Biphenyl yield[a] (%)	TON[b]
1	$Pd_2(dba)_3$ 0.1%	K_2CO_3	Water	56	55	1	560
2	$Pd_2(dba)_3$ 0.1%	K_2CO_3	Ethanol	55	54	1	550
3	$Pd_2(dba)_3$ 0.1%	K_2CO_3	PEG 300	100	90	10	1000
4	Pd/C 0.1%	K_2CO_3	PEG 300	0	—	—	0
5	$Pd/BaSO_4$ 0.1%	K_2CO_3	PEG 300	100	93	7	1000
6	$Pd(OAc)_2$ 0.1%	K_2CO_3	PEG 300	100	92	8	1000
7	$Pd/BaSO_4$ 0.05%	K_2CO_3	PEG 300	2	2	-	40
8	$Pd_2(dba)_3$ 0.05%	K_2CO_3	PEG 300	100	94	6	2000
9	$Pd(OAc)_2$ 0.05%	K_2CO_3	PEG 300	100	95	5	2000
10	$Pd_2(dba)_3$ 0.01%	K_2CO_3	PEG 300	93	89	4	9300
11	$Pd(OAc)_2$ 0.01%	K_2CO_3	PEG 300	77	75	2	7700
12	$Pd_2(dba)_3$ 0.01%	K_3PO_4	PEG 300	63	63	—	6300
13	$Pd_2(dba)_3$ 0.01%	$N(et)_3$	PEG 300	0	—	—	0
14	$Pd_2(dba)_3$ 0.01%	DBU	PEG 300	0	—	—	0
15[c]	$Pd_2(dba)_3$ 0.01%	K_2CO_3	PEG 300	63	61	2	6300
16[d]	$Pd_2(dba)_3$ 0.01%	K_2CO_3	PEG 300	75	74	1	7500

[a] Measured by GC–MS.
[b] n mols products/n mols catalyst.
[c] Under room temperature.
[d] Under ultrasound.

temperature, entries 10 and 15 show that heating was needed to give better results. Finally, comparing entries 10 and 16 it is clear that ultrasound was not as effective as the thermal method. Hence, the best set of conditions for the model reaction is presented in entry 10, which has a great TON (9300). The corresponding reaction was then reproduced three times with minimal differences among them.

The capacity of recycling the catalyst was also investigated. Good yields were obtained up to three runs. The results are summarized in Table 2.[12]

Table 2
Catalyst recycle of the Suzuki reaction between 4-bromoacetophenone and phenyl boronic acid using PEG 300, K_2CO_3, $Pd_2(dba)_3$ 0.01% at thermal condition at 55 °C for 90 min[a]

Entry	Run	Conversion (%)	4-Phenylacetophenone yield[b] (%)	Biphenyl yield[b] (%)
1	1st	99	95	4
2c	2nd	91	88	3
3c	3rd	84	82	2
4c	4th	55	55	—

[a] The time was increased by 30 min here to give a higher yield in the first run in order to do the recycle.
[b] Measured by GC–MS.
[c] Run without adding base, solvent, and catalyst.

Table 3
Suzuki reaction between different aryl halides and boronic acids using PEG 300, K_2CO_3, and thermal condition at 55 °C

Entry	Aryl halide	Boronic acid	Yield (%)	TON[a]
1[c]	4-Iodonitrobenzene	Phenyl boronic acid	98[b]	9700
2[d]	4-Iodotoluene	Phenyl boronic acid	95[b]	9500
3[d]	4-Iodoanisol	Phenyl boronic acid	84[b]	8400
4[e]	Iodobenzene	Phenyl boronic acid	78[h]	7800
5[f]	Iodobenzene	Phenyl boronic acid	98[b]	980
6[g]	Bromobenzene	Phenyl boronic acid	74[h]	7400
7[g]	Chlorobenzene	Phenyl boronic acid	17[h]	3100
8[i]	Chlorobenzene	Phenyl boronic acid	31[h]	31
9[i]	2-Bromopyridine	Phenyl boronic acid	30[h]	30
10[j]	4-Bromoacetophenone	4-Fluorophenylboronic acid	96[b]	9600
11[i]	4-Iodonitrobenzene	2-Furanboronic acid	13[h]	13
12[i]	4-Iodoanisol	2-Furanboronic acid	10[h]	10
13[i]	4-Bromoanisol	2-Furanboronic acid	—	—
14[i]	4-Bromoanisol	2-Thiopheneboronic acid	—	—
15[i]	5-Bromopyrimidine	Phenyl boronic acid	98[b]	98

[a] n mols products/n mols catalyst.
[b] Isolated yield (procedure in Ref. 9).
[c] 1 h of reaction, $Pd_2(dba)_3$ 0.01%.
[d] 2 h of reaction, $Pd_2(dba)_3$ 0.01%.
[e] 5 h of reaction, $Pd_2(dba)_3$ 0.01%.
[f] 3 h of reaction, $Pd_2(dba)_3$ 0.1%.
[g] 24 h of reaction, $Pd_2(dba)_3$ 0.01%.
[h] Yield measured by GC–MS.
[i] 24 h of reaction, $Pd_2(dba)_3$ 1%.
[j] 3 h of reaction.

To generalize our methodology, other substrates were used. The results are shown in Table 3.

Entry 1 (Table 3) presents the highest TON (9700) since it corresponds to the most activated aryl halide among those tested; for less activated aryl iodides, reaction time (Table 3, entries 2 and 3) or Pd load (Table 3, entries 4 and 5) enhancements were needed to improve yields of the corresponding reactions. Aryl bromide (Table 3, entry 6) and chloride (Table 3, entry 7) needed 24 h to react and gave yields of 74% and 17%, respectively, corresponding to the order of reactivity of aryl halides. Even when a greater Pd amount was supplied using chlorobenzene as substrate (Table 3, entry 8), a yield of only 31% was obtained, which led to a dramatic decrease of TON value. Entry 9 (Table 3) evidences low conversion, so the GC–MS yield was used, and the corresponding product was not isolated. On the other hand, as in entries 1 and 2 (Table 3), entry 10 shows an excellent result. Heteroarylboronic acids were also tested, showing low reactivity toward aryl halides, whichever be the substituent, electron-withdrawing and electron-donating (entries 11 and 12). These results are not appealing as those observed when couplings with phenyl boronic acid were accomplished (Table 3, entries 1 and 3). Such results allowed us to infer that the transmetallation is a slow step of the Suzuki–Miyaura catalytic cycle. For entries 13 and 14, the occurrence of reaction is not observed. By contrast, entry 15 shows that 5-bromopyrimidine is as reactive as 4-iodonitrobezene (Table 3, entry 1), resulting in 98% of isolated yield. All the compounds were characterized and analyzed by GC–MS, ^{1}H NMR and ^{13}C NMR.[13]

We can conclude that the set with $Pd_2(dba)_3$ 0.01%, PEG 300, K_2CO_3 at thermal conditions with a temperature of 55 °C works better for aryl–aryl than heteroaryl–aryl couplings in Suzuki reactions. The use of small Pd amounts resulting in good yields of isolated products after a simple workup must be underlined as the main advantage of the proposed system.

Acknowledgments

Financial support from CNPq, CAPES, FAPERJ, and FUJB is acknowledged.

References and notes

1. (a) Dehlinger, V.; Cordier, F.; Dell, C. P.; Dreyfus, N.; Jenkins, N.; Sanderson, A. J.; Smith, C. W. *Tetrahedron Lett.* **2006**, *47*, 8973–8976; (b) Li, S.; Lin, Y.; Xie, H.; Zhang, S.; Xu, J. *Org. Lett.* **2006**, *8*, 391–394; (c) Mariampillai, B.; Herse, C.; Lautens, M. *Org. Lett.* **2005**, *7*, 4745–4747; (d) Senra, J. D.; Malta, L. F. B.; Souza, A. L. F.; Medeiros, M. E.; Aguiar, L. C. S.; Antunes, O. A. C. *Tetrahedron Lett.* **2007**, *48*, 8153–8156; (e) Barros, J. C.; Souza, A. L. F.; Lima, P. G.; Silva, J. F. M.; Antunes, O. A. C. *Appl. Organomet. Chem.* **2008**, *22*, 249–252.
2. (a) Li, C. *Chem. Rev.* **2005**, *105*, 3095–3166; (b) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178–184.
3. (a) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15*, 2419–2440; (b) Smith, G. B.; Dezeny, G. C.; Hughes, D. L.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1994**, *59*, 8151–8156; (c) Ennis, D. S.; McManus, J.; Wood-Kaczmar, W.; Richardson, J.; Smith, G. E.; Carstairs, A. *Org. Proc. Res. Dev.* **1999**, *3*, 248–252; (d) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
4. Castanet, A. S.; Colobert, F.; Desmurs, J. R.; Schlama, T. *J. Mol. Catal. A: Chem.* **2002**, *182*, 481–487.
5. (a) Razler, T. M.; Hsiao, Y.; Qian, F.; Fu, R.; Khan, R. K.; Doubleday, W. *J. Org. Chem.* **2009**, *74*, 1381–1384; (b) Han, W.; Liu, C.; Jin, Z. *Adv. Synth. Catal.* **2008**, *350*, 501–508; (c) Han, W.; Liu, C.; Jin, Z.-L. *Org. Lett.* **2007**, *9*, 4005–4007; (d) Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 888–892.
6. Silva, A. C.; Souza, A. L. F.; Antunes, O. A. C. *J. Organomet. Chem.* **2007**, *692*, 3104–3107.
7. Souza, A. L. F.; Silva, L. C.; Oliveira, B. L.; Antunes, O. A. C. *Tetrahedron Lett.* **2008**, *49*, 3895–3898.
8. Souza, A. L. F.; Silva, A. C.; Antunes, O. A. C. *Appl. Organomet. Chem.* **2009**, *23*, 5–8.
9. *General procedure for Suzuki reaction*: In a 25 mL flask containing aryl halide (1 mmol), boronic acid (1.1 mmol), K_2CO_3 (3 mmol), and $Pd_2(dba)_3$ (0.01 mol %) in PEG 300 (4 g). The reaction was then kept under stirring at 55 °C for 1 hour. After the reaction was complete, the reaction mixture was extracted with diethyl ether, then the organic phase was filtered under Celite, washed with water and dried over anhydrous sodium sulfate, and the solvent was eliminated by vacuum. The crude product was analyzed by GC–MS, ^{1}H NMR, and ^{13}C NMR.
10. Sonication was performed in a thermostatic Branson 1210 ultrasonic cleaner with a frequency of 47 kHz and a power of 250 W.
11. (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168; (b) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263–303; (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, 9633–9695.
12. After each run, the product was extracted with diethyl ether as in Ref. 9. Then, the catalyst solution was reused after a solvent elimination by vacuum.
13. *Biphenyl*: White solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.81–7.65 (4H, d), 7.55–7.42 (4H, dd), 7.37–7.27 (2H, d); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 141.47, 128.95, 127.45, 127.37; GC–MS: m/z = 77, 154. *4-Methoxybiphenyl*: White solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.48–7.42 (4H, m), 7.36 (2H, t), 7.32 (1H, d), 6.91 (2H, d), 3.75 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.36, 141.03, 133.98, 128.91, 128.34, 126.85, 114.41, 55.52; GC–MS: m/z = 115, 141, 169, 184. *4-Nitrobiphenyl*: Yellow solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.30 (2H, d), 7.74 (2H, d), 7.64 (2H, d), 7.52–7.44 (3H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 146.6, 146.09, 137.74, 128.13, 127.89, 126.76, 126.35, 123.06; GC–MS: m/z = 141, 152, 199. *4-Phenylacetophenone*: Pale yellow solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.06–8.02 (2H, d), 7.72–7.62 (4H, m), 7.52–7.27 (3H, m), 2.65 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.86, 145.96, 140.06, 136.09, 129.13, 129.08, 128.40, 127.44, 127.39, 26.78; GC–MS: m/z = 76, 152, 181, 196. *1-(4′-Fluoro-biphenyl-4-yl)-ethanone*: White solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.95–7.91 (2H, d), 7.56–7.46 (4H, m), 7.11–7,02 (2H, t), 2.54 (3H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 197.68, 165.56, 160.63, 144.79, 136.12, 135.98, 129.08, 128.92, 127.14, 116.20, 115.77, 26.68. GC–MS: m/z = 171, 199, 214. *4-Methylbiphenyl*: White solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.59 (2H, d), 7.49 (2H, d), 7.40 (2H, dd), 7.34 (1H, d), 7.28 (2H, d), 2.46 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.31, 138.51, 137.14, 129.78, 129.61, 128.84, 127.30, 127.10, 21.22; GC–MS: m/z = 152, 168. 5-Phenylpyrimidine: White solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.16 (1H, s), 8.90 (1H, s), 7.52–7,47 (5H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 157.31, 154.72, 134.15, 129.32, 128.93, 126.80. GC–MS: m/z = 102, 129, 156.