Catal Lett
DOI 10.1007/s10562-015-1490-y

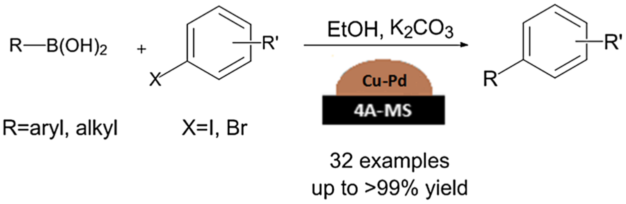
Study of the Structure–Activity Relationship in a Heterogeneous Copper–Palladium Catalysed Suzuki–Miyaura Coupling

Anna Fodor · Ágnes Magyar · Dóra Barczikai · Laurence Pirault-Roy · Zoltán Hell

Received: 14 January 2015 / Accepted: 23 January 2015

Abstract Copper–palladium bimetallic catalyst supported on 4 Å molecular sieve prepared with two-step wet impregnation was successfully applied in the Suzuki–Miyaura reaction. The reaction took place with a variety of substituted boronic acids as well as with a collection of iodo- and bromobenzene derivatives. In some cases steric effects had influence on the reaction, *ortho*-substituted iodo- or bromobenzenes gave lower yield independently from the substituent. But most *m*- and *p*-substituted iodo- and bromobenzenes showed good to excellent activity. Several biphenyls were obtained by two or even three pathways: either the boronic acid or the respective iodo- or bromobenzene was functionalised.

Graphical Abstract



A. Fodor · Á. Magyar · D. Barczikai · Z. Hell (✉)
Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Műegyetem rkp, 3, Budapest 1111, Hungary
e-mail: zhell@mail.bme.hu

A. Fodor · L. Pirault-Roy
Institute of Chemistry of Poitiers: Materials and Natural Resources (IC2MP) UMR-CNRS 7285, University of Poitiers, 4, rue Michel Brunet (Bât B27), 86073 Poitiers Cedex, France

Keywords Cu–Pd bimetallic catalyst · Heterogeneous catalysis · 4 Å molecular sieve · Structure–activity relationship · Suzuki–Miyaura reaction

1 Introduction

Suzuki–Miyaura coupling is known as one of the most important tools for palladium catalysed carbon–carbon bond formation (Fig. 1).

The starting materials (aryl halides and boronic acids) are easily available in stable and widely functionalised form. Short reaction time, easy work up and wide range of products is representative. Since the first publications [1, 2] several methods were elaborated and a great number of publications and reviews were released reporting homogeneous [3–6] and heterogeneous [7–10] pathways to perform this coupling. Suzuki coupling was also the subject of several reviews providing extensive knowledge on certain fields as heterogeneous palladium catalysis [11]; large scale application for pharmaceutical production [12] and efficient, selective and recyclable palladium catalysts [13], etc. Furthermore, studies were also made on the isomer effects in this reaction. Schmidt and Riemer [14] examined the Suzuki reaction of halophenols and phenol boronic acids and revealed that certain combinations of boronophenols and halophenols are disfavoured. Zou et al. [15] found *o*-substitution effect as a reason of low activity caused by steric hindrance and absorption associated with heterogeneous Pd/C.

Ligand-free heterogeneous catalysts are well reported to carry out coupling reactions, for example mesoporous silica-supported Pd catalysed Suzuki–Miyaura and Heck reactions [16], Pd supported on a polyionic resin was also applicable in these reactions as well as in Sonogashira-

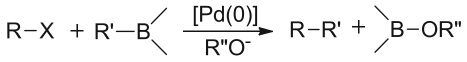


Fig. 1 General scheme of the Suzuki–Miyaura coupling

reaction [17]. Besides these materials monometallic catalytic Pd/Cu bimetallic catalysts attract also great attention. Several publications described nano-Pd/Cu systems as efficient catalysts for the Sonogashira-reaction [18–20] or electrochemical reaction such as electrooxidation of formic acid [21]. It is well reported, that these catalysts possess an increased catalytic activity compared to their monometallic counterparts and a positive synergistic effect of Pd and Cu has also been described [18, 21].

In our previous paper [22] the characteristics of the Cu–Pd bimetallic catalyst—supported on 4Å molecular sieve prepared with two-step wet impregnation (Cu–Pd-4A-TSI)—were presented and discussed. This catalyst contains 6.2 wt% Cu and 2.4 wt% Pd, possesses with a BET surface area of 310 m^2/g and its average particle size is 2.5 nm thus it is a nano-structured catalyst. It was used six times in the coupling of iodobenzene with phenylboronic acid without any loss of activity. The used catalyst surface analysis showed the presence of Cu/Pd 1/1 alloy which has been proven to be the catalytically active species in this reaction. According to these results we concluded that the role of Cu in our reactions was stabilizing palladium due to a Pd:Cu interaction, thus Pd could keep its active form. This observation is in accordance with the literature reporting the synergistic effects of these two metals [18, 21]. As in our former article a full study on the catalyst's properties was provided, herein, the wide range of substituted aryl halides and substituted boronic acids, which undergo the Suzuki-coupling in the presence of our copper–palladium bimetallic catalyst, is presented. The steric and electronic effects of the substituents were examined according to the yield of desired product formation.

2 Experimental

GC–MS measurements were performed on an Agilent 6890N-GC-5973N-MSD chromatograph, using a 30 m × 0.25 mm Restek, Rtx-5SILMS column with a film layer of 0.25 μm. The initial temperature of column was 45 °C for 1 min, followed by programming at 10 °C/min up to 310 °C and a final period at 310 °C (isothermal) for 17 min. The temperature of the injector was 250 °C. The carrier gas was He and the operation mode was splitless. ^{1}H NMR spectra were made on BRUKER Avance-300 instrument using TMS as an internal standard in $CDCl_3$.

Typical procedure for the Suzuki–Miyaura-coupling: The catalyst Cu–Pd-4A-TSI was prepared according to the method described in [22]. The catalyst was treated at 120 °C for 1 h before the reaction. Boronic acid (1.5 mmol or 1.2 mmol), aryl halide (1 mmol), potassium carbonate (3 mmol) and the pretreated catalyst Cu–Pd-4A-TSI (0.1 g; 2.26 mol% Pd and 9.86 mol% Cu) were stirred in 5 ml refluxing ethanol for 1 or 1.5 h. Then the solid was filtered out, and washed with ethanol. The filtrate was evaporated. The residue was extracted three times with dichloromethane and with water. The organic phase was dried over anhydrous sodium sulphate, filtered and the solvent was evaporated. The product was subjected to either GC–MS analysis and/or ^{1}H NMR. If required, the product was recrystallized.

All products have satisfactory spectral data (^{1}H NMR, MS). The spectral data of the known compounds were identical with those reported in the literature. Representative physical and spectroscopic data of some products:

3-Methyl-biphenyl (Table 1, entry 2; Table 3, entry 1 and Table 4, entry 7): white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.4 (s, 3H, CH_3), 7.28–7.41 (m, 7H, Ph), 7.55–7.58 (m, 2H, Ph). MS m/z (%): 168 (M^+, 100), 152 (35), 128 (8), 115 (10), 83 (15).

4-Methyl-biphenyl (Table 1, entry 3; Table 3, entry 2 and Table 4, entry 8): white solid, mp: 43–45 °C (literature 44–46 °C [23]). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.38 (s, 3H, CH_3), 7.24 (d, 2H, Ph), 7.31–7.34 (m, 1H, Ph), 7.42 (t, 2H, Ph), 7.48 (d, 2H, Ph), 7.56 (d, 2H, Ph). MS m/z (%): 168 (M^+, 100), 152 (25), 115 (12), 83 (15).

4-Trifluoromethyl-biphenyl (Table 1, entry 4 and Table 4, entry 11): white solid, mp: 64–66 °C (literature 65–67 °C [24]). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.40–7.50 (m, 3H, Ph), 7.59 (d, 2H, Ph), 7.69 (s, 4H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): 125.8 (qua), 127.4, 127.5, 128.3, 129.0, 139.9, 144.8.

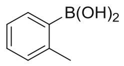
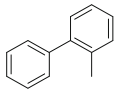
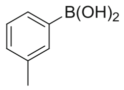
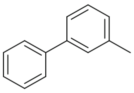
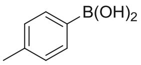
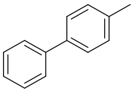
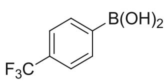
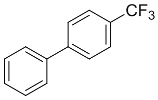
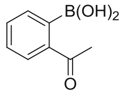
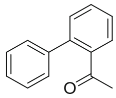
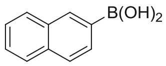
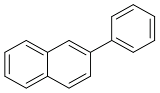
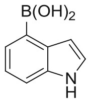
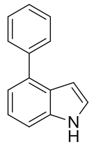
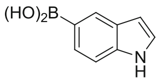
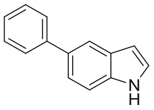
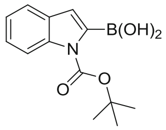
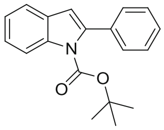
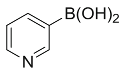
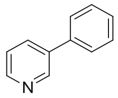
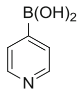
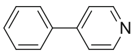
3-Nitro-biphenyl (Table 3, entry 3): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.43–7.52 (m, 3H, Ph), 7.58–7.63 (m, 3H, Ph), 7.91 (d, 1H), 8.2 (d, 1H), 8.45 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 122.2, 122.3, 127.4, 128.8, 129.4, 129.9, 133.3, 138.9, 143.1.

4-Nitro-biphenyl (Table 3, entry 4): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.45–7.53 (m, 3H, Ph), 7.62 (d, 2H, Ph), 7.74 (d, 2H), 8.3 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 124.2, 127.5, 127.9, 129.0, 129.3, 138.9, 147.7.

4-Methoxy-biphenyl (Table 3, entry 5): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.85 (s, 1H CH_3O), 6.97 (d, 2H, Ph), 7.3 (m, 1H, Ph), 7.41 (t, 1H, Ph), 7.54 (m, 4H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): 55.4, 114.3, 126.7, 126.8, 128.2, 128.8, 133.9, 159.2.

Biphenyl-4-carboxylic acid (Table 3, entry 6): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.41–7.51 (m, 3H, Ph), 7.64 (d, 2H, Ph), 7.71 (d, 2H), 8.19 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 127.0, 127.3, 128.1, 128.9, 130.4, 137.6, 140.1, 145.4.

Table 1 Reaction of iodobenzene with boronic acid derivatives

Entry	Boronic acid	Product	Yield (%)[a]
1			92
2			91
3			72
4			98
5			<5
6			80
7			~30
8			~60
9			–[b]
10			–[b]
11			–[b]

Reaction conditions: boronic acid (1.5 mmol), iodobenzene (1 mmol), potassium carbonate (3 mmol), 0.1 g catalyst Cu–Pd-4A-TSI (2.26 mol% Pd and 9.76 mol% Cu) in EtOH, 78 °C, 1 h

[a] Isolated yield, the purity was verified by ^{1}H NMR spectroscopy

[b] No reaction was observed

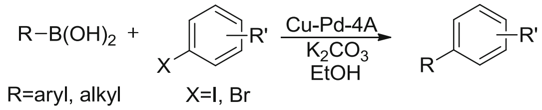


Fig. 2 Suzuki–Miyaura coupling in the presence of Cu–Pd-4A-TSI catalyst

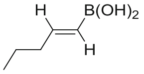
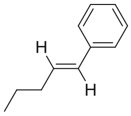
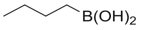
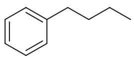
3 Results and Discussion

The reaction of boronic acid with aryl halides was performed in the presence of Cu–Pd-4A-TSI as a catalyst, K_2CO_3 as a base, in boiling ethanol. The reaction of iodo- and bromobenzene with boronic acid derivatives and the reaction of phenylboronic acid with substituted aryl iodides and -bromides (Fig. 2) were examined.

Table 1 summarizes the results obtained in the coupling of iodobenzene with different substituted boronic acids. The reaction of iodobenzene with 4-trifluoromethyl-phenylboronic acid (Table 1, entry 4) and tolylboronic acids (Table 1, entries 1–3) gave excellent yield, in the case of 2-naphthylboronic acid (Table 1, entry 6) good yield was observed. In the reaction of tolylboronic acids small amount of the corresponding dimethyl-biphenyls, yielding from the homocoupling of the boronic acids, were also obtained. In the reaction of 2-acetylphenylboronic acid with iodobenzene (Table 1, entry 5) the expected product was formed only in negligible amount, in the GC–MS spectra a compound with 220 Da molar mass was found as main product. Earlier we have observed that in the Pd-catalysed reaction of acetophenone derivatives in basic alcohol a transfer hydrogenation reaction could also occur, where ethanol would oxidise to acetaldehyde. [25] In this case a similar reaction might be assumed, and the acetaldehyde formed can react with the acetyl group in an aldol type reaction.

Heteroaryl boronic acids showed less activity (Table 1, entries 7–11). Indoleboronic acids gave the corresponding products with moderate to poor yield (Table 1, entries 7–8), moreover, 1-(*tert*-butoxycarbonyl)-indole-2-boronic acid (Table 1, entry 9) failed to react. According to the GC–MS analysis of the reaction mixture, in this case 1-*tert*-butoxycarbonyl indole was formed as a result of boronic acid function loss. This weak reactivity can be explained by two facts. These indoleboronic acids proved to be quite unstable. In addition, copper and palladium on the catalyst might form a complex with the amine function of the starting material, and this complex is inactive in the reaction. This hypothesis was verified by XRF examination of the product. Considerable amount of copper as well as some palladium was detectable, while in the products obtained from the reaction of homoaromatic boronic acids no metal contamination of the product was found. The lack

Table 2 Reaction of iodobenzene with aliphatic boronic acids

Entry	Boronic acid	Reaction time (h)	Product	Yield (%)[a]
1		1		<15
		3		<10
2		1		–[b]
		6		–[b]

Reaction conditions: boronic acid (1.5 mmol), iodobenzene (1 mmol), potassium carbonate (3 mmol), 0.1 g catalyst Cu–Pd-4A-TSI (2.26 mol% Pd and 9.76 mol% Cu) in EtOH, 78 °C

[a] Yield estimated from the ^1H NMR spectra of the product

[b] No reaction was observed

of reactivity of pyridineboronic acids can also be explained by this complex formation, as none of the expected products were isolated in these cases either (Table 1, entries 10–11).

The reaction of iodobenzene with aliphatic boronic acids was also performed. The results obtained are summarized in Table 2. As in these cases after 1 h reaction time significant amount of starting material was detected by TLC, longer reaction times were used. Nevertheless, no better results were obtained. In case of *trans*-1-penten-1-ylboronic acid (Table 2, entry 1) after 3 h reaction time the yield was lower. Butyl-1-boronic acid (Table 2, entry 2) failed to react in the presence of Cu–Pd-4A-TSI irrespectively of the reaction time. The aliphatic boronic acids are known as less active in the coupling reactions, thus the use of a ligand and/or stronger base might have been needed to perform the coupling [26, 27].

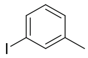
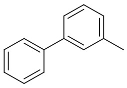
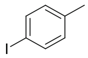
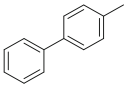
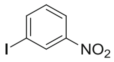
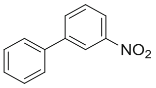
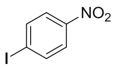
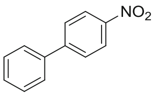
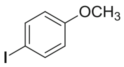
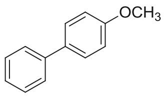
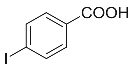
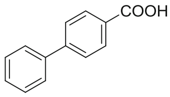
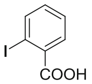
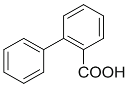
Substituted iodobenzenes showed excellent activity (Table 3 entries 1–6) except 2-iodobenzoic acid (Table 3, entry 7) which can be explained by steric effects.

Performing the reaction with bromobenzene after 1 h biphenyl was formed with 80 % yield [22]. As aryl bromides are generally less active in the Suzuki–Miyura reaction, the reaction time was increased to 1.5 h which resulted in the product formation with good to excellent yield (Table 4). In case of certain *o*-, and *m*-substituents the yield dropped (Table 4, entries 1, 4, 7).

The results obtained show that functional groups in the *o*-position of the aryl halide can hinder the desired product formation. No electronic effect can be found, as the yields are similar with both electron withdrawing groups (EWG) and electron donating groups (EDG) in *ortho*-position.

Comparing the experiments yielding *o*-, *m*-, and *p*-tolylbiphenyls from substituted boronic acids (Table 1. entries 1–3), iodobenzenes (Table 3, entries 1–2) and bromobenzenes (Table 4, entries 6–8) it can be concluded

Table 3 Reaction of phenylboronic acid with substituted iodobenzenes

Entry	Aryl iodide	Product	Yield (%)[a]
1			77
2			89
3			91
4			96
5			87
6			94[b]
7			–[b, c]

Reaction conditions: boronic acid (1.2 mmol), iodobenzene (1 mmol), potassium carbonate (3 mmol), 0.1 g catalyst Cu–Pd-4A-TSI (2.26 mol% Pd and 9.76 mol% Cu) in EtOH, 78 °C, 1 h

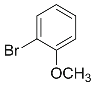
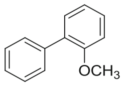
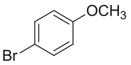
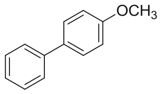
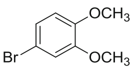
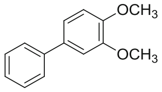
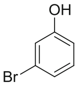
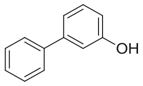
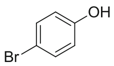
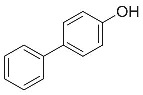
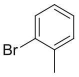
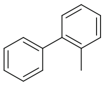
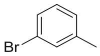
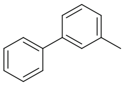
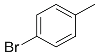
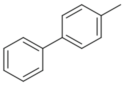
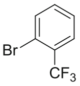
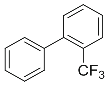
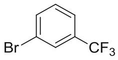
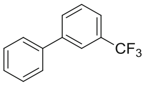
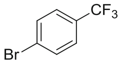
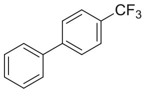
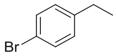
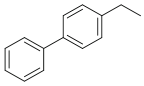
[a] Isolated yield, the purity was verified by ^1H NMR spectroscopy

[b] 4 mmol potassium carbonate was used

[c] Unidentified by-product was formed

that the position of the functional group has an importance. The *ortho*- and *meta*-substituents should be favourably on the boronic acid moiety, as in this case excellent yields were obtained. But better results were obtained with *para*-substituted aryl halides. However, from economic considerations, in large scales the iodo- or bromobenzene derivative might be favoured as their application results still in good yield. The place of the functional group had no importance in case of *p*-trifluoromethyl-biphenyl as excellent yields were achieved in both cases (Table 1, entry 4; Table 4, entry 11). *p*-Methoxybiphenyl can be formed from *p*-bromoanisole with excellent yield (Table 3, entry 5), with good yield from *p*-iodoanisole (Table 4, entry 2). Comparing iodo- (Table 3, entries 1–2) and bromobenzenes (Table 4, entries 6–8) one can conclude that higher yields were achieved with the application of bromobenzenes during a slightly elevated reaction time.

Table 4 Reaction of phenylboronic acid with substituted bromobenzene

Entry	Bromobenzene derivative	Product	Yield (%)[a]
1			59
2			97
3			92
4			<45[b,c]
5			88[b]
6			80
7			65
8			>99
9			72
10			90
11			95
12			60

Reaction conditions: boronic acid (1.2 mmol), iodobenzene (1 mmol), potassium carbonate (3 mmol), 0.1 g catalyst Cu–Pd-4A-TSI (2.26 mol% Pd and 9.76 mol% Cu) in EtOH, 78 °C, 1.5 h

[a] Isolated yield, the purity was verified by ^{1}H NMR spectroscopy

[b] 4 mmol potassium carbonate was used

[c] Unidentified by-product was formed

4 Conclusions

In summary, a series of substituted biphenyls were synthesized starting from substituted boronic acids and iodobenzene or bromobenzene derivatives in the presence of the bimetallic Cu–Pd-4A-TSI catalyst. The *m*- and *p*-substituted derivatives gave excellent yield, while *o*-substituted aryl halide derivatives sometimes gave weaker results because of steric effects. No significant electronic effect was observed. Substituted biphenyls from two or three pathways were achieved at least with good yields. Excellent yields were resulted in *ortho*-, *meta*-position with substituted boronic acid, while in *para*-position with aryl halides. Aliphatic boronic acids didn't undergo the coupling.

Acknowledgments The authors would like to thank the French Government for the scholarship that made the cooperation between the two research groups possible.

References

1. Miyaura N, Yamada K, Suzuki A (1979) Tetrahedron Lett 20:3437–3440
2. Miyaura N, Suzuki A (1979) J Chem Soc Chem Commun 19:866–867
3. Sabounchei SJ, Ahmadi M, Panahimehr M, Bagherjeri FA, Nasri Z (2014) J Mol Catal A 383–384:249–259
4. Zhang A, Liu M, Liu M, Xiao Y, Li Z, Chen J, Sun Y, Zhao J, Fang S, Jia D, Li F (2014) J Mater Chem A 2:1369–1374
5. Verma PR, Mandal S, Gupta P, Mukhopadhyay B (2013) Tetrahedron Lett 54:4914–4917
6. Liu L, Wang W, Xiao C (2014) J Organomet Chem 749:83–87
7. Prakash SP, Gopidas KR (2014) ChemCatChem 6:1641–1651
8. Chen L, Gao Z, Li Y (2014) Catal Today. doi:10.1016/j.cattod.2014.03.074

9. Mondal M, Bora U (2014) Appl Organomet Chem 28:354–358
10. Bester K, Bukowska A, Bukowski W (2013) J Mol Catal A 378:124–134
11. Yin L, Liebscher J (2007) Chem Rev 107:133–173
12. Magano J, Dunetz JR (2011) Chem Rev 111:2177–2250
13. Molnár Á (2011) Chem Rev 111:2251–2320
14. Schmidt B, Riemer M (2014) J Org Chem 79:4104–4118
15. Ke H, Chen X, Zou G (2014) Appl Organometal Chem 28:54–60
16. Basu B, Paul S (2013) Appl Organometal Chem 27:588–594
17. Basu B, Das S, Das P, Mandal B, Banerjee D, Almqvist F (2009) Synthesis 7:1137–1146
18. Xu W, Sun H, Yu B, Zhang G, Zhang W, Gao Z (2014) ACS Appl Mater Interfaces 6:6970–6973
19. Korzec M, Bartczak P, Niemczyk A, Szade J, Kapkowski M, Zenderowska P, Balin K, Lelatko J, Polanski J (2014) J Catal 313:1–8
20. Sengupta D, Saha J, De G, Basu B (2014) J Mater Chem A 2:3986–3992
21. Ho SF, Mendoza-Garcia A, Guo S, He K, Su D, Liu S, Metin O, Sun S (2014) Nanoscale 6:6970–6973
22. Fodor A, Hell Z, Pirault-Roy L (2014) Appl Catal A 484:39–50
23. Endo Y, Shudo K, Okamoto T (1982) J Am Chem Soc 104:6393–6397
24. Molander GA, Iannazzo L (2011) J Org Chem 76:9182–9187
25. Németh J, Kiss Á, Hell Z (2013) Tetrahedron Lett 54:6094–6096
26. Kirchhoff JH, Netherton MR, Hills ID, Fu GC (2002) J Am Chem Soc 124:13662–13663
27. Saito B, Fu GC (2007) J Am Chem Soc 129:9602–9603