

PAPER

View Article Online
View Journal | View IssueCite this: *RSC Adv.*, 2017, 7, 34994Received 14th June 2017
Accepted 5th July 2017DOI: 10.1039/c7ra06662g
rsc.li/rsc-advances

Immobilized boronic acid for Suzuki–Miyaura coupling: application to the generation of pharmacologically relevant molecules†

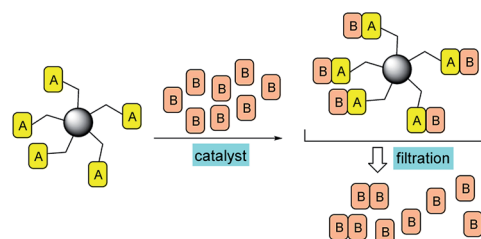
M. Martinez-Amezaga, C. M. L. Delpiccolo and E. G. Mata *

An synthetic strategy for the generation of a variety of biaryl and related derivatives, based on Suzuki–Miyaura coupling using immobilized boronic acid, is described. The importance of the methodology was demonstrated by its further application to biologically interesting compounds such as 4-biaryl- β -lactams, described as cholesterol absorption inhibitors and anti-MRSA active agents, neoflavonoids, imidazoles, isoxazolines, among others.

Introduction

Small organic molecules are of particular interest for medicinal chemistry and drug discovery not only because they constitute most of the medicines marketed today, but also because they are useful as probes to dissect biological systems providing information which eventually leads to the discovery of new drug targets.¹ Through recent decades, solid-phase organic synthesis (SPOS) has become an important tool for the generation of structurally diverse small organic molecules including application to a series of very creative strategies such as diversity-oriented synthesis (DOS).² Apart from the well-known advantages, like the fast isolation of resin-bound intermediates/products by filtering the resin beads, the use of high-boiling solvents and the easy manipulation,³ solid-phase organic synthesis has raised interest in metal-catalyzed cross-coupling reactions since undesirable soluble homodimers can be removed by filtration providing chemoselectivity, while anchoring one of the substrates makes its homodimerization a discouraging process due to the site isolation.⁴ An extra benefit can be considered within the principles of green chemistry: SPOS significantly reduces solvent waste by avoiding many chromatographic purifications (Scheme 1).⁵

The Suzuki–Miyaura coupling is, arguably, one of the most versatile and successful synthetic tool for formation of carbon–carbon bonds. The Suzuki–Miyaura reaction is basically the reaction of arylboronic acids with aryl halides or pseudo halides under palladium catalyst to obtain biaryl fragments, which are present in many biologically relevant molecules. The mild reaction conditions and the broad functional groups tolerance



Scheme 1 Cross-coupling reaction on solid-phase synthesis.

are among the most remarkable features of this transformation, together with the fact that the non-toxic organoboron reagents can be easily synthesized by different procedures and exhibit high stability to air and moisture.⁶ One of the main drawbacks of Suzuki–Miyaura cross-coupling reaction is the formation of undesirable boronic acid homocoupling by-products.⁷ This problem can be avoided by a rigorous exclusion of oxygen giving, however, less support to the claim that Suzuki–Miyaura coupling is an “easy to handle” reaction. Site segregation in the solid-supported version of this reaction, makes self-coupling between immobilized boronic acid moieties a less favorable process. Many examples of this transformation on solid phase have been reported in the literature,⁸ however, very few are based on immobilized boronic acids.⁹

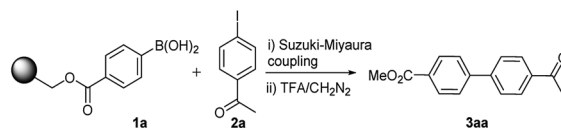
Results and discussion

For some years, our research group has been focused on the mentioned advantage of the combination of solid-phase synthesis and metal-catalyzed chemistry to build libraries of pharmacologically relevant molecules.¹⁰ In the search for alternative source of immobilized biaryl-containing β -lactam derivatives we decided to study the underdeveloped but promising solid-phase Suzuki–Miyaura reaction with a boronic acid

Instituto de Química Rosario (CONICET-UNR), Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Suipacha 531, 2000 Rosario, Argentina. E-mail: mata@iquir-conicet.gov.ar; Fax: +54 341 4370477

† Electronic supplementary information (ESI) available: Experimental details, spectroscopic data: ¹H NMR and ¹³C NMR spectra. See DOI: 10.1039/c7ra06662g

Table 1 Optimization of conditions for the solid-phase version of Suzuki–Miyaura coupling with immobilized boronic acids



Entry	Equiv. of iodide 2a	Pd catalyst (mol%)	Base (equiv.)	Solvent	Conditions ^a	Yield ^b (%)
1	1	Pd(OAc) ₂ (5)	K ₂ CO ₃ (1.2)	MeCN	75 °C, 4 h	30 (60)
2	1	PdCl ₂ dppf (5)	K ₂ CO ₃ (1.2)	DMF	75 °C, 4 h	22 (40)
3	4	Pd(PPh ₃) ₄ (5)	Cs ₂ CO ₃ (1.2)	Diglyme	150 °C, 3 h	37 ^c
4	1	Pd(OAc) ₂ (5)	K ₂ CO ₃ (1.2)	MeCN	75 °C, 7 h	32 (63)
5	4	Pd(OAc) ₂ (10)	K ₂ CO ₃ (2.4)	MeCN	MW, 10', 100 °C	^d
6	4	Pd(OAc) ₂ (10)	K ₂ CO ₃ (2.4)	MeCN	100 °C, 5 h	40 (76)
7	4	Pd(OAc) ₂ (10)	K ₂ CO ₃ 0.5 M (2.4)	MeCN	100 °C, 5 h	96
8	4	Pd(OAc) ₂ (10)	K ₂ CO ₃ 0.5 M (2.4)	Diglyme	150 °C, 3 h	50
9	4	Pd(OAc) ₂ (10)	K ₂ CO ₃ 0.5 M (2.4)	MeCN	Reflux, 5 h ^e	88

^a Except noted otherwise, all reactions were carried in a sealed tube. ^b Yields were determined by ¹H NMR using an internal standard (mesitylene). Conversion by ¹H NMR in brackets. ^c No starting material detected by ¹H NMR. ^d Mixture of products, mostly starting material. ^e Open system, reflux conditions.

phenylboronic acid (**1a**) was treated with the iodide **2a**, Pd(PPh₃)₄ (5 mol%) and Cs₂CO₃ (1,2 equiv.) in diglyme at 150 °C for 3 h,¹² giving the expected biaryl **3aa** in 37% yield but no starting material was detected by ¹H NMR (entry 3). Afterwards, we used the combination of a ligandless catalyst such as Pd₂(dba)₃ and a hindered phosphine ligands [P(*o*-tolyl)]₃¹³ in order to increase Pd catalytic activity, but a small amount of the required biaryl derivative was obtained together with an intractable mixture of products. Taking as reference the conditions of entry 1, we proceeded to increase the reaction time, but conversion and yield were hardly affected (entry 4). Although is clear that heating effects in microwave irradiation are just thermal,¹⁴ it is still an interesting alternative as a rapid way to reach high reaction temperatures¹⁵ in order to improve yields. However, in our case, low conversion together with a mixture of unidentified compounds was obtained under microwave irradiation (entry 5). Going back to conventional heating, we increased the equivalents of the iodide, reagents and temperature, having a slightly better yield (40%, entry 6).

In order to find the optimal conditions, we first synthesized the immobilized 4-carboxyphenylboronic acid **1a** from 4-formylphenylboronic acid by oxidation with sodium permanganate and anchoring to Wang resin by standard procedure. We then analyzed the reaction of **1a** with 4-iodoacetophenone (**2a**) (Table 1 and Fig. 1).

When the immobilized boronic acid (**1a**) was treated with 1 equiv. of 4-iodoacetophenone (**2a**), 1.2 equiv. of K_2CO_3 , under “ligand-free” conditions [$\text{Pd}(\text{OAc})_2$ (5 mol %)], in anhydrous acetonitrile for 4 h at 75 °C,^{9b} an incomplete conversion was observed, and the expected product **3aa** was obtained in 30% yield, after cleavage with TFA and methylation with diazomethane (entry 1). In the case of using $\text{PdCl}_2\text{dppf}^{\text{11}}$ (5 mol %) as catalyst, a similar result was obtained, albeit conversion and yield were lower (entry 2). Other conditions reported in literature were also attempted, thus, Wang resin-bound

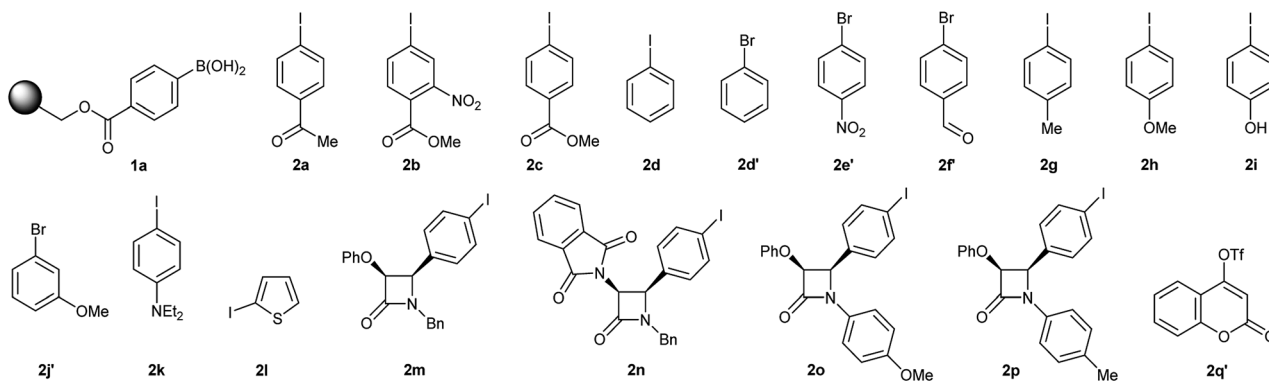


Fig. 1 Structures and numbering of building blocks.

Table 2 Solid-phase Suzuki–Miyaura reaction between organic halides and immobilized boronic acid^a

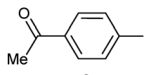
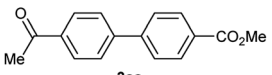
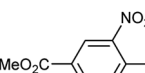
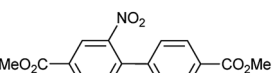
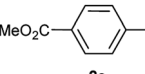
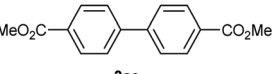

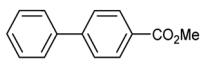

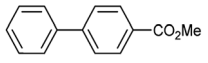
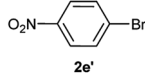
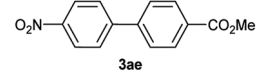
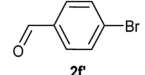
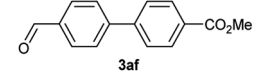
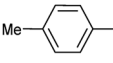
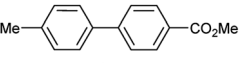
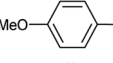
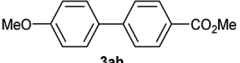
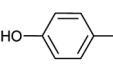
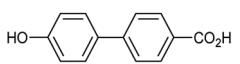
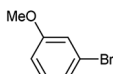
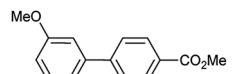
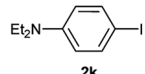
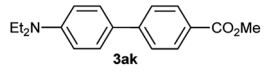

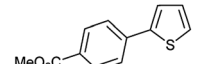
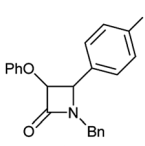
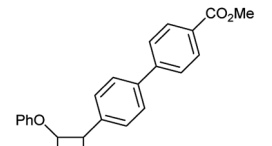
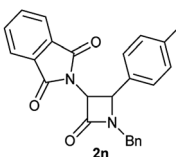
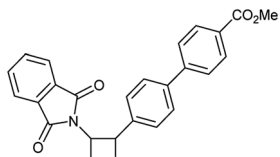
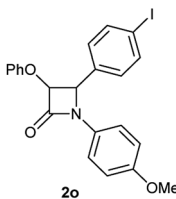
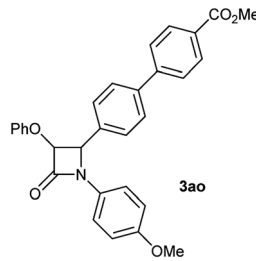
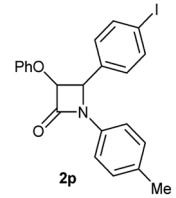
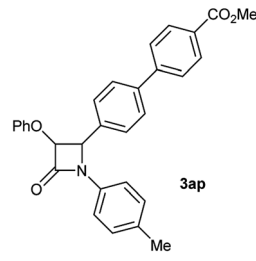
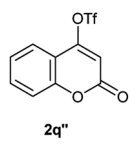
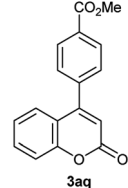
Entry	Halides/pseudohalides	Product	Yield ^b (%)
1	 2a	 3aa	96
2	 2b	 3ab	99
3	 2c	 3ac	96
4	 2d	 3ad	99
5	 2d'	 3ad	99
6	 2e'	 3ae	87
7	 2f'	 3af	81 (78)
8	 2g	 3ag	77
9	 2h	 3ah	52
10	 2i	 3ai	37
11	 2j'	 3aj	20
12	 2k	 3ak	8
13	 2l	 3al	15
14	 2m	 3am	79 (76)
15	 2n	 3an	65 (60)



Table 2 (Contd.)

Entry	Halides/pseudohalides	Product	Yield ^b (%)
16	 2o	 3ao	ND ^c (90)
17	 2p	 3ap	83 (86)
18	 2q [†]	 3aq	ND ^c (48)

^a Conditions: halide or pseudo-halide (4 equiv.), Pd(OAc)₂ (10 mol%), K₂CO₃ (2.4 equiv.) in H₂O (0.2 mL), MeCN, 100 °C, 5 h, in a sealed tube.

^b Determined by ¹H NMR vs. internal standard (mesitylene), isolated yields after column chromatography are reported in brackets. ^c ND = not determined.

Finally, in our initial attempts we have noticed the difficulty of solubilising the carbonate and, since the addition of a base is considered to be crucial for the success of the reaction,¹⁶ we decided to study the addition of an small amount of water to increase dissolution, hoping that would not affect in any significant way the polymer support swelling. Thus, we dissolved the K₂CO₃ (2.4 equiv.) in a small amount of water and added to the suspension of resin **1a**, 4-iodoacetophenone (**2a**) (4 equiv.) and 10 mol% of Pd(OAc)₂ in acetonitrile. To our delight, after 5 h at 100 °C in a sealed tube, followed by cleaving from the resin and methylation with diazomethane, the expected product was achieved in 96% yield (entry 7). At the same time, a variation using more harsh conditions such as heating in diglyme at 150 °C for 5 h, was analyzed giving lower yield, probably due to starting material/product decomposition (entry 8). Good results were obtained using an open system (entry 9), although yield of entry 7 was still the optimum.

Subsequently, the reaction of a variety of aryl halides and pseudohalides under the optimized coupling conditions was examined (Table 2 and Fig. 1). Generally speaking, yields are very high for electron-withdrawing aryl halides and non-substituted aryl halides (entries 1–7), independently of using an iodide or a bromide derivative. In the case of electron-

donating substituents on the aryl halides, Suzuki coupling proved to be less efficient, again with little influence from the halide used (entries 8–12). As expected, 2-iodothiophene gave the corresponding heterobiaryl derivative in low yield probably due to the poisoning of the catalyst (entry 13).¹⁷ In order to apply the methodology to structures of greater complexity and interest, biaryl-containing β-lactam derivatives were synthesized using the optimized conditions. β-Lactam unit is a well-known privileged structure present in numerous bioactive compounds. Aside from their antibacterial properties,¹⁸ β-lactams also show other biological activities, most significantly inhibition of cholesterol absorption, that include the commercial drug ezetimibe,¹⁹ which is one of the most prescribed medicine in US.

Particularly, 4-biaryl-β-lactams have been reported as cholesterol absorption inhibitors²⁰ and antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA).²¹ Thus, biaryl-β-lactams (**3am–ap**) were obtained in very high isolated yield (entries 14 to 17, Table 2). Another synthetic objective of great interest in medicinal chemistry are the coumarin derivatives which are well known for their diverse pharmacological properties.²² Neoflavonoids (4-aryl coumarins) in particular, have shown relevant anticancer activity,²³ while



Avance spectrometer at 300 MHz in CDCl_3 with tetramethylsilane (TMS) as internal standard. ^{13}C NMR spectra were recorded on the same apparatus at 75 MHz with CDCl_3 as solvent and reference (76.9 ppm). The chemical shifts (δ) are reported in ppm downfield from TMS and coupling constants (J) are expressed in hertz. Gas Chromatography-Mass Spectra (GC-MS) were recorded on a Shimadzu QP2010 Plus apparatus at an ionization voltage of 70 eV equipped with a SPBTM-1 capillary column (internal diameter 0.25 mm, length 30 m). The High Resolution Mass Spectra (HRMS) were obtained with a Bruker MicroTOF-Q II instrument (Bruker Daltonics, Billerica, MA). Detection of the ions was performed in electrospray ionization, positive ion mode. Solvents were dried using a MBraun solvent system (SPS-800). Analytical thin-layer chromatography (TLC) was carried out with silica gel 60 F254 pre-coated aluminum sheets. Flash column chromatography was performed using Merck silica gel 60 (230–400 mesh). Elution was carried out with hexane–EtOAc mixtures, under positive pressure and employing gradient of solvent polarity techniques.

Solid-phase reactions were carried out in polypropylene cartridges equipped with a frit (Supelco, Bellefonte, PA), unless reflux conditions were required, in that cases standard glassware was used. All solid-phase reaction mixtures were stirred at the slowest rate.

Except **2m**, **2n**, **2o**, **2p**, **3ak**, **3am**, **3an**, **3ao** and **3ap** which are new compound and thoroughly characterized by ^1H NMR, ^{13}C NMR, HSQC, HMBC, HH-COSY and HRMS, the other compounds obtained have been previously described in literature: **3aa**,³⁵ **3ab**,³⁶ **3ac**,³⁷ **3ad**,³⁶ **3ae**,³⁵ **3af**,³⁸ **3ag**,³⁹ **3ah**,³⁶ **3ai**,⁴⁰ **3aj**,^{10f} **3al**³⁶ and **3aq**.⁴¹

General procedure for the preparation of β -lactams as starting materials (procedure A)⁴²

A mixture of 4-iodobenzaldehyde (290 mg, 1.25 mmol), few grains of molecular sieves (4 Å) and the corresponding amine (1 mmol) in dichloromethane (5 mL) was stirred at 0 °C under nitrogen atmosphere for 1 h. The solution was filtered, the solvent evaporated and the residue analyzed by ^1H NMR to ensure complete consumption of the amine. The crude thus obtained was dissolved in dry dichloromethane (3 mL) and cooled to 0 °C under nitrogen atmosphere. To the resulting solution were successively added triethylamine (0.5 mL, 3.5 mmol) and, dropwise, the corresponding acyl chloride (1.5 mmol). The resulting mixture was stirred overnight at room temperature and then was washed with water (3 × 5 mL), 0.1 N HCl (3 × 5 mL) and a saturated solution of NaHCO_3 (5 mL). The organic layer was dried over MgSO_4 and filtered; the solvent was evaporated under reduced pressure to give the corresponding crude β -lactam, which was further purified by column chromatography (hexane/EtOAc).

Procedure for the preparation of phthalylglycyl chloride (procedure B)⁴³

Oxalyl chloride (386 μL , 4.5 mmol) was added to a solution of anhydrous *N*-phthaloylglycine (615 mg, 3 mmol) in toluene (8 mL) and the reaction mixture was stirred at 60 °C for 3 h. The

excess of solvent and oxalyl chloride were removed by evaporation under reduced pressure and that crude was immediately used for the formation of the corresponding β -lactam.

1-Benzyl-4-(4-iodophenyl)-3-phenoxyazetidin-2-one (**2m**).

Obtained following the general procedure A, starting from 4-iodobenzaldehyde (290 mg, 1.25 mmol) and benzylamine (109 μL , 1 mmol). Then, phenoxyacetyl chloride (207 μL , 1.5 mmol) was added dropwise. Column chromatography (86/14-hexane/EtOAc) provided the desired compound in 80% yield as yellow solid.

Characterization of 2m. ^1H NMR (CDCl_3 , 300 MHz) δ (ppm): 3.87 (d, J = 14.7 Hz, 2H), 4.68 (d, J = 4.5 Hz, 2H), 4.87 (d, J = 14.7 Hz, 2H), 5.39 (d, J = 4.5 Hz, 2H), 6.72 (d, J = 7.8 Hz, 2H), 6.89 (t, J = 7.1 Hz, 1H), 7.01 (d, J = 8.3 Hz, 2H), 7.10–7.16 (m, 4H), 7.29–7.33 (m, 3H), 7.61 (d, J = 8.3 Hz, 2H). ^{13}C NMR (CDCl_3 , 75 MHz) δ (ppm): 44.3, 60.9, 82.0, 94.7, 115.5, 122.2, 128.1, 128.7, 128.9, 129.3, 130.5, 132.7, 134.5, 137.5, 156.8, 165.4. HRMS (ESI) m/z 478.0279 [(M + Na)⁺]; calcd for $\text{C}_{22}\text{H}_{18}\text{INNaO}_2$: 478.0274].

2-(1-Benzyl-2-(4-iodophenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (2n**).** Obtained following the general procedures A, starting from 4-iodobenzaldehyde (298 mg, 1.3 mmol) and benzylamine (115 μL , 1.05 mmol). Then, phthalylglycyl chloride prepared *in situ* (procedure B) (350 mg, 1.56 mmol). Column chromatography (75/25-hexane/EtOAc) provided the desired compound in 41% yield as colorless glass-like solid.

Characterization of 2n. ^1H NMR: (CDCl_3 , 300 MHz) δ (ppm): 4.15 (d, J = 14.8 Hz, 1H), 4.76 (d, J = 5.3 Hz, 1H), 5.03 (d, J = 14.9 Hz, 1H), 5.23 (d, J = 5.2 Hz, 1H), 6.95 (d, J = 8.2 Hz, 2H), 7.20–7.25 (m, 2H), 7.30–7.34 (m, 3H), 7.51 (d, J = 8.3 Hz, 2H), 7.62–7.70 (m, 4H). ^{13}C NMR: (CDCl_3 , 75 MHz) δ (ppm): 45.6, 59.7, 60.2, 94.3, 123.6, 128.1, 128.6, 129.0, 129.3, 131.1, 132.8, 134.4, 137.6, 163.6, 166.7. HRMS (ESI) m/z 531.0177 [(M + Na)⁺]; calcd for $\text{C}_{24}\text{H}_{17}\text{IN}_2\text{NaO}_3$: 531.0176].

4-(4-iodophenyl)-1-(4-methoxyphenyl)-3-phenoxyazetidin-2-one (2o**).** Obtained following the general procedure A, starting from 4-iodobenzaldehyde (298 mg, 1.3 mmol) and *p*-anisidine (160 mg, 1.05 mmol). Then, phenoxyacetyl chloride (215 μL , 1.56 mmol) was added dropwise. Column chromatography (88/12-hexane/EtOAc) provided the desired compound in 70% yield as yellow solid.

Characterization of 2o. ^1H NMR: (CDCl_3 , 300 MHz) δ (ppm): 3.76 (s, 3H), 5.31 (d, J = 4.9 Hz, 1H), 5.55 (d, J = 4.9 Hz, 1H), 6.78–6.83 (m, 4H), 6.92–7.00 (m, 2H), 7.11 (d, J = 8.3 Hz, 2H), 7.11 (t, J = 7.6 Hz, 1H), 7.27 (d, J = 7.1 Hz, 2H), 7.62 (d, J = 8.3 Hz, 2H). ^{13}C NMR: (CDCl_3 , 75 MHz) δ (ppm): 55.5, 61.7, 81.2, 94.6, 114.5, 115.7, 118.8, 122.4, 129.4, 129.6, 130.1, 132.7, 137.6, 156.7, 156.9, 162.3. HRMS (ESI) m/z 494.0226 [(M + Na)⁺]; calcd for $\text{C}_{22}\text{H}_{18}\text{INNaO}_3$: 494.0224].

4-(4-iodophenyl)-3-phenoxy-1-(*p*-tolyl)azetidin-2-one (2p**).** Obtained following the general procedure A, starting from 4-iodobenzaldehyde (298 mg, 1.3 mmol) and *p*-toluidine (140 mg, 1.05 mmol). Then, phenoxyacetyl chloride (215 μL , 1.56 mmol) was added dropwise. Column chromatography (90/10-hexane/EtOAc) provided the desired compound in 40% yield as yellow solid.



Characterization of 2p. ^1H NMR: (CDCl_3 , 300 MHz) δ (ppm): 2.29 (s, 3H), 5.32 (d, $J = 4.9$ Hz, 1H), 5.55 (d, $J = 4.9$ Hz, 1H), 6.79 (d, $J = 8.3$ Hz, 2H), 6.94 (t, $J = 7.4$ Hz, 1H), 7.07–7.12 (m, 4H), 7.16–7.24 (m, 4H), 7.62 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR: (CDCl_3 , 75 MHz) δ (ppm): 20.9, 61.5, 81.1, 94.6, 115.9, 117.4, 122.4, 129.4, 129.8, 129.9, 132.6, 134.2, 134.6, 137.6, 156.9, 162.6. HRMS (ESI) m/z 478.0268 [(M + Na) $^+$]; calcd for $\text{C}_{22}\text{H}_{18}\text{INaO}_2$: 478.0274].

Procedure for the synthesis of Wang resin-supported aryl boronic acid 1a (procedure C)

0.4 g of Wang resin (0.9 mmol g^{-1} , 0.36 mmol) was swelled by gentle stirring in anhydrous dichloromethane (20 mL). Then, 4-carboxyphenylboronic acid (0.179 g, 1.08 mmol), DCC (*N,N'*-diisopropylcarbodiimide) (0.223 g, 1.08 mmol) and DMAP (catalytic amount) were added at that suspension. The mixture was shaken at 250 rpm overnight at room temperature. After filtration, the resin was sequentially washed with CH_2Cl_2 (3 \times 10 mL), MeOH (3 \times 10 mL), THF (3 \times 10 mL), CH_2Cl_2 (1 \times 10 mL) and finally dried under high vacuum. Mass recovery was used to determine resin loading after cleavage of an aliquot with 10% TFA/ CH_2Cl_2 : 0.45 mmol g^{-1} .

General procedure for the solid-phase Suzuki coupling (procedure D)

0.1 g of the supported arylboronic acid 1a (0.45 mmol g^{-1} , 0.045 mmol) was suspended in MeCN (2 mL) in a dram vessel. Aryl-halide or pseudo-halide 2 (0.18 mmol), $\text{Pd}(\text{OAc})_2$ (1 mg, 0.0045 mmol) and a solution of K_2CO_3 in H_2O (0.54 M, 0.108 mmol) were added. The reaction was stirred 5 h at 100 $^\circ\text{C}$. After cooling to room temperature, the resin was filtered, washed with MeCN (2 \times 5 mL), H_2O (2 \times 5 mL), MeOH (3 \times 5 mL) and DCM (3 \times 5 mL) drying under high vacuum, the compound was cleaved from the resin with 5 mL of a 10% solution of TFA in DCM for 50 minutes at room temperature. Then it was filtered and washed with MeOH (2 \times 3 mL) and CH_2Cl_2 (2 \times 3 mL). The product-containing solution was concentrated under reduced pressure and dried under high vacuum. Esterification with diazomethane afforded the crude product that was analyzed by ^1H NMR and GC/MS and then purified by flash column chromatography (hexane/EtOAc).

Dimethyl 2-nitro-[1,1'-biphenyl]-4,4'-dicarboxylate (3ab). Obtained following the general procedure D, using resin-bound boronic acid 1a (procedure C) (103.5 mg, 0.0465 mmol) as starting material and methyl 4-iodo-3-nitrobenzoate (2b) (57 mg, 0.186 mmol). Column chromatography (96/4-hexane/EtOAc) provided the desired compound in 92% yield as white crystals.

Characterization of 3ab. ^1H NMR (CDCl_3 , 300 MHz) δ (ppm): 3.95 (s, 3H), 4.00 (s, 3H), 7.40 (d, $J = 8.4$ Hz, 2H), 7.54 (d, $J = 8.0$ Hz, 1H), 8.11 (d, $J = 8.5$ Hz, 2H), 8.29 (dd, $J = 8.0$, 1.7 Hz, 1H), 8.55 (d, $J = 1.7$ Hz, 1H). ^{13}C NMR (CDCl_3 , 75 MHz) δ (ppm): 52.3, 52.9, 125.5, 127.9, 130.0, 130.5, 131.0, 132.1, 133.1, 139.5, 141.1, 148.9, 164.7, 166.5.

Dimethyl [1,1'-biphenyl]-4,4'-dicarboxylate (3ac). Obtained following the general procedure D, using resin-bound boronic acid 1a (procedure C) (93.5 mg, 0.042 mmol) as starting material and methyl 4-iodobenzoate (2c) (44 mg, 0.168 mmol). Column

chromatography (98/2-hexane/EtOAc) provided the desired compound in 89% yield as white crystals.

Characterization of 3ac. ^1H NMR (CDCl_3 , 300 MHz) δ (ppm): 3.95 (s, 6H), 7.69 (d, $J = 8.5$ Hz, 4H), 8.12 (d, $J = 8.5$ Hz, 4H). ^{13}C NMR (CDCl_3 , 75 MHz) δ (ppm): 52.2, 127.2, 129.7, 130.2, 144.3, 166.8.

Methyl [1,1'-biphenyl]-4-carboxylate (3ad). Obtained following the general procedure D, using resin-bound boronic acid 1a (procedure C) (99.6 mg, 0.0448 mmol) as starting material and iodobenzene (2d) (20 μL , 0.18 mmol). Column chromatography (99/1-hexane/EtOAc) provided the desired compound in 98% yield as white crystals.

Characterization of 3ad. ^1H NMR (CDCl_3 , 300 MHz) δ (ppm): 3.95 (s, 3H), 7.36–7.51 (m, 3H), 7.60–7.70 (m, 4H), 8.11 (d, $J = 8.6$ Hz, 2H). ^{13}C NMR (CDCl_3 , 75 MHz) δ (ppm): 52.1, 127.0, 127.3, 128.1, 128.9, 130.1, 140.0, 145.6, 167.0.

Methyl 4'-formyl-[1,1'-biphenyl]-4-carboxylate (3af). Obtained following the general procedure D, using resin-bound boronic acid 1a (procedure C) (97.7 mg, 0.0439 mmol) as starting material and 4-bromobenzaldehyde (2f) (32 mg, 0.175 mmol). Column chromatography (98/2-hexane/EtOAc) provided the desired compound in 78% yield as white crystals.

Characterization of 3af. ^1H NMR (CDCl_3 , 300 MHz) δ (ppm): 3.95 (s, 3H), 7.70 (d, $J = 8.5$ Hz, 2H), 7.78 (d, $J = 8.3$ Hz, 2H), 7.98 (d, $J = 8.3$ Hz, 2H), 8.14 (d, $J = 8.5$ Hz, 2H), 10.08 (s, 1H). ^{13}C NMR (CDCl_3 , 75 MHz) δ (ppm): 52.3, 127.4, 128.0, 130.3, 130.3, 144.0, 145.9, 166.7, 191.8.

Methyl 4'-(diethylamino)-[1,1'-biphenyl]-4-carboxylate (3ak). Obtained following the general procedure D, using resin-bound boronic acid 1a (procedure C) (92.1 mg, 0.041 mmol) as starting material and *N,N*-diethyl-4-iodoaniline (2k) (49 mg, 0.18 mmol). Column chromatography (98/2-hexane/EtOAc) provided the desired compound in 9% yield as yellow fluorescent crystals.

Characterization of 3ak. ^1H NMR (CDCl_3 , 300 MHz) δ (ppm): 1.20 (t, $J = 7.0$ Hz, 6H), 3.40 (q, $J = 7.0$ Hz, 4H), 3.91 (s, 3H), 6.75 (d, $J = 8.9$ Hz, 2H), 7.53 (d, $J = 8.9$ Hz, 2H), 7.61 (d, $J = 8.9$ Hz, 2H), 8.04 (d, $J = 8.9$ Hz, 2H). ^{13}C NMR (CDCl_3 , 75 MHz) δ (ppm): 12.6, 44.4, 51.9, 111.8, 125.5, 126.3, 127.1, 128.1, 130.0, 145.7, 147.8, 167.3. HRMS (ESI) m/z 284.1656 [(M + H) $^+$]; calcd for $\text{C}_{18}\text{H}_{22}\text{NO}_2$: 284.1645].

Methyl 4'-(1-benzyl-4-oxo-3-phenoxyazetidin-2-yl)-[1,1'-biphenyl]-4-carboxylate (3am). Obtained following the general procedure D, using resin-bound boronic acid 1a (procedure C) (93.3 mg, 0.042 mmol) as starting material and 1-benzyl-4-(4-iodophenyl)-3-phenoxyazetidin-2-one (2m) (76 mg, 0.168 mmol). Column chromatography (86/14-hexane/EtOAc) provided the desired compound in 76% yield as yellowish white crystals.

Characterization of 3am. ^1H NMR: (CDCl_3 , 300 MHz) δ (ppm): 3.92 (d, $J = 14.5$ Hz, 1H), 3.94 (s, 3H), 4.81 (d, $J = 4.4$ Hz, 1H), 4.92 (d, $J = 14.7$ Hz, 1H), 5.44 (d, $J = 4.4$ Hz, 1H), 6.75 (d, $J = 7.8$ Hz, 2H), 6.87 (t, $J = 7.3$ Hz, 1H), 7.11 (t, $J = 8.3$ Hz, 2H), 7.18 (m, 2H), 7.33 (m, 2H), 7.37 (d, $J = 8.3$ Hz, 2H), 7.54 (d, $J = 8.2$ Hz, 2H), 7.62 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR: (CDCl_3 , 75 MHz) δ (ppm): 44.3, 52.2, 61.1, 82.3, 115.6, 122.1, 127.0, 127.1, 128.0, 128.7, 128.9, 129.1, 129.2, 130.1, 132.8, 134.7, 140.2, 156.9, 165.5, 166.9. HRMS (ESI) m/z 486.1670 [(M + Na) $^+$]; calcd for $\text{C}_{30}\text{H}_{25}\text{NNaO}_4$: 486.1676].

Methyl 4'-(1-benzyl-3-(1,3-dioxoisindolin-2-yl)-4-oxoazetidin-2-yl)-[1,1'-biphenyl]-4-carboxylate (3an). Obtained following



the general procedure D, using resin-bound boronic acid **1a** (procedure C) (90 mg, 0.0405 mmol) as starting material and 2-(1-benzyl 2-(4-iodophenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (**2n**) (82.3 mg, 0.162 mmol). Column chromatography (78/22-hexane/EtOAc) provided the desired compound in 60% yield as white crystals.

Characterization of 3an. ^1H NMR: (CDCl_3 , 300 MHz) δ (ppm): 3.91 (s, 3H); 4.21 (d, $J = 14.8$ Hz, 1H), 4.90 (d, $J = 5.2$ Hz, 1H), 5.10 (d, $J = 14.8$ Hz, 1H), 5.52 (t, $J = 5.2$ Hz, 1H), 7.28–7.36 (m, 7H), 7.47 (d, $J = 8.4$ Hz, 2H), 7.50 (d, $J = 8.4$ Hz, 2H), 7.59–7.69 (m, 4H), 8.02 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR: (CDCl_3 , 75 MHz) δ (ppm): 45.7, 52.1, 60.0, 60.3, 123.5, 126.8, 127.3, 128.0, 128.1, 128.7, 129.0, 129.1, 130.0, 131.2, 133.0, 134.2, 134.8, 139.9, 144.5, 163.7, 166.8. HRMS (ESI) m/z 539.1587 [(M + Na) $^+$]; calcd for $\text{C}_{32}\text{H}_{24}\text{N}_2\text{NaO}_5$: 539.1577].

Methyl 4'-(1-(4-methoxyphenyl)-4-oxo-3-phenoxyazetidin-2-yl)-[1,1'-biphenyl]-4-carboxylate (3ao). Obtained following the general procedure D, using resin-bound boronic acid **1a** (procedure C) (89.3 mg, 0.04018 mmol) as starting material and 4-(4-iodophenyl)-1-(4-methoxyphenyl)-3-phenoxyazetidin-2-one (**2o**) (76.3 mg, 0.162 mmol). Column chromatography (86/14-hexane/EtOAc) provided the desired compound in 90% yield as yellowish white crystals.

Characterization of 3ao. ^1H NMR: (CDCl_3 , 300 MHz) δ (ppm): 3.75 (s, 3H), 3.93 (s, 3H), 5.41 (d, $J = 4.8$ Hz, 1H), 5.65 (d, $J = 4.8$ Hz, 1H), 6.82 (d, $J = 8.9$ Hz, 2H), 6.92 (t, $J = 7.3$ Hz, 1H), 7.16 (t, $J = 8.0$ Hz, 2H), 7.33 (d, $J = 8.9$ Hz, 2H), 7.46 (d, $J = 8.2$ Hz, 2H), 7.55 (d, $J = 8.2$ Hz, 2H), 7.60 (d, $J = 8.3$ Hz, 2H), 8.07 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR: (CDCl_3 , 75 MHz) δ (ppm): 52.2, 55.5, 61.8, 81.4, 114.5, 115.8, 118.9, 122.3, 127.0, 127.2, 128.7, 129.1, 129.3, 130.1, 130.4, 132.8, 140.3, 144.8, 156.6, 157.0, 162.4, 166.9. HRMS (ESI) m/z 502.1634 [(M + Na) $^+$]; calcd for $\text{C}_{30}\text{H}_{25}\text{NNaO}_5$: 502.1625].

Methyl 4'-(4-oxo-3-phenoxy-1-(*p*-tolyl)azetidin-2-yl)-[1,1'-biphenyl]-4-carboxylate (3ap). Obtained following the general procedure D, using resin-bound boronic acid **1a** (procedure C) (90 mg, 0.0405 mmol) as starting material and 4-(4-iodophenyl)-3-phenoxy-1-(*p*-tolyl)azetidin-2-one (**2p**) (73.7 mg, 0.162 mmol). Column chromatography (88/12-hexane/EtOAc) provided the desired compound in 86% yield as white crystals.

Characterization of 3ap. ^1H NMR: (CDCl_3 , 300 MHz) δ (ppm): 2.28 (s, 3H); 3.93 (s, 3H); 5.43 (d, $J = 4.8$ Hz, 1H), 5.60 (d, $J = 4.8$ Hz, 1H), 6.82 (d, $J = 8.0$ Hz, 2H), 6.92 (t, $J = 7.4$ Hz, 1H), 7.09 (d, $J = 8.2$ Hz, 2H), 7.17 (t, $J = 8.0$ Hz, 2H), 7.29 (d, $J = 8.3$ Hz, 2H), 7.46 (d, $J = 8.3$ Hz, 2H), 7.54 (d, $J = 8.3$ Hz, 2H), 7.61 (d, $J = 8.3$ Hz, 2H), 8.07 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR: (CDCl_3 , 75 MHz) δ (ppm): 21.0, 52.2, 61.7, 81.3, 115.8, 117.5, 122.3, 126.9, 127.2, 128.7, 129.1, 129.3, 129.7, 130.1, 132.8, 134.5, 134.5, 140.2, 144.8, 157.0, 162.8, 166.9. HRMS (ESI) m/z 486.1677 [(M + Na) $^+$]; calcd for $\text{C}_{30}\text{H}_{25}\text{NNaO}_4$: 486.1676].

Methyl 4-(2-oxo-2H-chromen-4-yl)benzoate (3aq). Obtained following the general procedure D, using resin-bound boronic acid **1a** (procedure C) (92.9 mg, 0.0418 mmol) as starting material and 4-iodo-2H-chromen-2-one (**2q''**) (49.1 mg, 0.167 mmol). Column chromatography (90/10-hexane/EtOAc) provided the desired compound in 48% yield as white crystals.

Characterization of 3aq. ^1H NMR (CDCl_3 , 300 MHz) δ (ppm): 3.98 (s, 3H), 6.40 (s, 1H), 7.24 (m, 1H), 7.38–7.45 (m, 2H), 7.52–

7.60 (m, 3H), 8.20 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ (ppm): 52.5, 115.6, 117.5, 118.6, 124.4, 126.7, 128.6, 130.1, 131.4, 132.2, 139.6, 154.2, 154.6, 160.4, 166.3.

Procedure for the solid-phase reductive amination (procedure E)

0.3 g of the supported compound **3af** (0.438 mmol g^{-1} , 0.135 mmol) was suspended in anhydrous THF (2 mL) in a dram vessel. Benzylamine (75 μL , 0.673 mmol) and methyl orthoformate (15 μL , 0.135 mmol) were added and the reaction was stirred 18 h at room temperature. After that time, the imine-resin was filtered, washed with THF (2×5 mL), absolute MeOH (2×5 mL), DCM (2×5 mL) and MeOH (2×5 mL) and dried under high vacuum. This resin was suspended in a mixture of THF-MeOH 3 : 1 v/v and treated with NaBH_4 (51 mg, 1.347 mmol) for 6 to 8 hours. The resin was washed with THF (2×5 mL), EtOH (2×5 mL), H_2O (2×5 mL), EtOH (2×5 mL), THF (2×5 mL) and MeOH (2×5 mL) and dried under high vacuum. The compound was cleaved from the support with 5 mL of a 10% solution of TFA in DCM for 50 minutes at room temperature. Then it was filtered and washed with MeOH (2×3 mL) and CH_2Cl_2 (2×3 mL). The product-containing solution was concentrated under reduced pressure and dried under high vacuum. Esterification with diazomethane afforded the crude product that was analyzed by ^1H NMR and GC/MS and then purified by column chromatography (hexane/EtOAc).

Methyl 4'-((benzylamino)methyl)-[1,1'-biphenyl]-4-carboxylate (5af). Employing procedure E, with supported **3af**. Column chromatography (90/10-hexane/EtOAc) provided the desired product in 63% overall isolated yield (five reactions steps) as white crystals.

Characterization of 5af. ^1H NMR (CDCl_3 , 300 MHz) δ (ppm): 3.85 (s, 2H), 3.87 (s, 2H), 3.94 (s, 3H), 7.27–7.37 (m, 5H), 7.52–7.60 (m, 3H), 7.45 (d, $J = 8.3$ Hz, 2H), 7.59 (d, $J = 8.2$ Hz, 2H), 7.66 (d, $J = 8.3$ Hz, 2H), 8.10 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ (ppm): 52.1, 52.7, 53.2, 126.9, 127.0, 127.3, 128.2, 128.5, 128.8, 130.1, 138.7, 140.1, 140.4, 145.4, 167.0. HRMS (ESI) m/z 332.1659 [(M + H) $^+$]; calcd for $\text{C}_{22}\text{H}_{22}\text{NO}_2$: 332.1645].

Procedure for the solid-phase synthesis of Δ^2 -isoxazoline (procedure F)

0.24 g of the supported **3af** (0.736 mmol g^{-1} , 0.178 mmol) was suspended in a mixture of anhydrous MeOH (1 mL) and DCM (1 mL) in a dram vessel. Anhydrous triethylamine (124 μL , 0.89 mmol) and hydroxylamine hydrochloride (62 mg, 0.89 mmol) were added and the reaction was stirred 36 h at room temperature. After that time, the oxime-resin was filtered, washed with DMF (2×5 mL), DCM (2×5 mL), MeOH (2×5 mL) and DCM (2×5 mL) and dried under high vacuum. This oxime-resin was suspended in THF and treated with bleach (6 mL, 0.0018 mmol) and acrylic acid (62 μL , 0.9 mmol) at room temperature for 4 hours. The resin was washed with MeOH (2×5 mL), H_2O (2×5 mL), MeOH (2×5 mL) and DCM (2×5 mL) and dried under high vacuum. The compound was cleaved from the support with 5 mL of a 20% solution of TFA in DCM for 50 minutes at room temperature. Then it was filtered and washed with MeOH (2×3 mL) and CH_2Cl_2 (2×3 mL). The



product-containing solution was concentrated under reduced pressure and dried under high vacuum. Methylation with diazomethane afforded the crude product that was analyzed by ^1H NMR and GC/MS and then purified by column chromatography (hexane/EtOAc).

Methyl 3-(4'-(methoxycarbonyl)-[1,1'-biphenyl]-4-yl)-4,5-dihydroisoxazole-5-carboxylate (7af). Employing procedure F, with supported **3af**. Column chromatography (92/8 hexane/EtOAc) provided the desired compound in 21% overall isolated yield (five reactions steps), as white crystals.

Characterization of 7af. ^1H NMR (CDCl_3 , 300 MHz) δ (ppm): 3.69 (ABX, $J = 17.1, 11.5, 9.5, 5.2$ Hz, 2H), 3.84 (s, 3H), 3.95 (s, 3H), 5.23 (dd, $J = 10.7, 7.4$ Hz, 1H), 7.67 (d, $J = 8.3$ Hz, 4H), 7.78 (d, $J = 8.6$ Hz, 2H), 8.12 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR (CDCl_3 , 75 MHz) δ (ppm): 38.8, 52.2, 52.9, 78.1, 127.0, 127.5, 127.6, 128.2, 129.5, 130.2, 142.0, 144.4, 155.7, 166.8, 170.7. HRMS (ESI) m/z 362, 0998 [(M + Na $^+$); calcd for $\text{C}_{19}\text{H}_{17}\text{NNaO}_5$: 362, 0999].

Procedure for the solid-phase synthesis of imidazole (procedure G)

0.13 g of the supported **3af** ($0.736 \text{ mmol g}^{-1}$, 0.097 mmol) was suspended in Glacial AcOH in a dram vessel. Benzylamine (212 μL , 1.94 mmol), benzil (408 mg, 1.94 mmol) and ammonium acetate (9 μL , 0.136 mmol) were added and the reaction was stirred 4 h at 100 $^\circ\text{C}$. After that time, the resin was filtered, washed MeOH ($2 \times 5 \text{ mL}$), H_2O ($2 \times 5 \text{ mL}$), MeOH ($2 \times 5 \text{ mL}$) and DCM ($2 \times 5 \text{ mL}$) and dried under high vacuum. The compound was cleaved from the support with 5 mL of a 20% solution of TFA in DCM for 50 minutes at room temperature. Then it was filtered and washed with MeOH ($2 \times 3 \text{ mL}$) and CH_2Cl_2 ($2 \times 3 \text{ mL}$). The product-containing solution was concentrated under reduced pressure and dried under high vacuum. Methylation with diazomethane afforded the crude product that was analyzed by ^1H NMR and then purified by column chromatography (hexane/EtOAc).

Methyl 4'-(1-benzyl-4,5-diphenyl-1H-imidazol-2-yl)-[1,1'-biphenyl]-4-carboxylate (9af). Employing procedure G, with supported **3af**. Column chromatography (96/4 hexane/EtOAc) provided the desired compound in 20% overall isolated yield (four reactions steps), as yellow crystals.

Characterization of 9af. ^1H NMR (CDCl_3 , 300 MHz) δ (ppm): 3.94 (s, 3H), 5.16 (s, 3H), 6.86 (m, 2H), 7.20 (m, 8H), 7.32 (m, 3H), 7.59 (m, 2H), 7.67 (m, 4H), 7.77 (d, $J = 8.4$ Hz, 2H), 8.11 (d, $J = 8.0$ Hz, 2H). ^{13}C NMR (CDCl_3 , 75 MHz) δ (ppm): 48.4, 52.2, 125.9, 126.5, 126.8, 127.0, 127.6, 128.1, 128.7, 128.8, 129.2, 129.5, 130.2, 130.4, 130.6, 130.9, 131.0, 134.3, 137.5, 138.3, 140.3, 144.8, 147.5, 166.9. HRMS (ESI) m/z 521, 2222 [(M + H $^+$); calcd for $\text{C}_{36}\text{H}_{29}\text{N}_2\text{O}_2$: 521, 2223].

Acknowledgements

Support from CONICET, ANPCyT and Universidad Nacional de Rosario from Argentina is gratefully acknowledged. MMA thanks CONICET for fellowship.

Notes and references

- (a) T. E. Nielsen and S. L. Schreiber, *Angew. Chem., Int. Ed.*, 2008, **47**, 48; (b) C. J. O'Connor, L. Laraia and D. R. Spring, *Chem. Soc. Rev.*, 2011, **40**, 4332.
- (a) W. R. J. D. Galloway, A. Isidro-Llobet and D. R. Spring, *Nat. Commun.*, 2010, **1**, 80; (b) H. Beckmann, C. J. O'Connor and D. R. Spring, *Chem. Soc. Rev.*, 2012, **41**, 4444.
- E. Schütznerová, P. Verdía and V. Krchnak, *ACS Comb. Sci.*, 2016, **18**, 655.
- D. D. Young and A. Deiters, *Solid-phase organic synthesis: concepts, strategies, and applications*, ed. P. H. Toy and Y. Lam, John Wiley & Sons, Inc., Hoboken, New Jersey, 2012, pp. 171–201.
- G. S. Yellol and C.-M. Sun, *Solid-Supported Synthesis en Green Techniques for Organic Synthesis and Medicinal Chemistry*, ed. W. Zhang and B. W. Cue Jr, John Wiley & Sons, Ltd, 2012, p. 394.
- N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457.
- For articles related to the suppression of the oxidative homocoupling, see: (a) W. D. Miller, A. H. Fray, J. T. Quatroche and C. D. Sturgill, *Org. Process Res. Dev.*, 2007, **11**, 359; (b) N. Miyaura, *Metal-Catalyzed Cross-Coupling Reaction*, ed. F. Diederich and A. de Meijere, Wiley-VCH, New York, 2004, p. 41; (c) A. J. J. Lennox and G. C. Lloyd-Jones, *Isr. J. Chem.*, 2010, **50**, 664; (d) A. J. J. Lennox and G. C. Lloyd-Jones, *J. Am. Chem. Soc.*, 2012, **134**, 7431; (e) A. J. J. Lennox and G. C. Lloyd-Jones, *Angew. Chem., Int. Ed.*, 2013, **52**, 7362; (f) A. J. J. Lennox and G. C. Lloyd-Jones, *Chem. Soc. Rev.*, 2014, **43**, 412.
- (a) S. Bräse, J. H. Kirchhoff and J. Köbberling, *Tetrahedron*, 2003, **59**, 885; (b) N. Ljungdahl, K. Bromfield and N. Kann, *Top. Curr. Chem.*, 2007, **278**, 89; (c) S. A. Testero and E. G. Mata, *J. Comb. Chem.*, 2008, **10**, 487.
- To the best of our knowledge, two examples have been reported dealing with the use of immobilized boronic acid in organic synthesis, in both cases, the sticky PEG-PS resin was the favorite support used: (a) B. Ruhland, A. Bombrun and M. A. Gallop, *Tetrahedron Lett.*, 2006, **47**, 19; (b) X. Li, A. K. Szardenings, C. P. Holmes, L. Wang, A. Bhandari, L. Shi, M. Navre, L. Jang and J. R. Grove, *Tetrahedron Lett.*, 2006, **47**, 19.
- (a) S. A. Testero and E. G. Mata, *Org. Lett.*, 2006, **8**, 4783; (b) A. A. Poeylout-Palena, S. A. Testero and E. G. Mata, *J. Org. Chem.*, 2008, **73**, 2024; (c) A. A. Poeylout-Palena and E. G. Mata, *J. Comb. Chem.*, 2009, **11**, 791; (d) A. A. Poeylout-Palena, S. A. Testero and E. G. Mata, *Chem. Commun.*, 2011, **47**, 1565; (e) A. La-Venia, S. A. Testero, M. Mischne and E. G. Mata, *Org. Biomol. Chem.*, 2012, **10**, 2514; (f) C. I. Traficante, C. M. L. Delpiccolo and E. G. Mata, *ACS Comb. Sci.*, 2014, **16**, 211; (g) L. Méndez and E. G. Mata, *ACS Comb. Sci.*, 2015, **17**, 81; (h) C. I. Traficante, C. Fagúndez, G. L. Serra, E. G. Mata and C. M. L. Delpiccolo, *ACS Comb. Sci.*, 2016, **18**, 225.



- 11 The large P-Pd-P angle of the dppf ligand is believed to make the reductive elimination of the coupling product much faster than the β -elimination. See: T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi and K. Hirotsu, *J. Am. Chem. Soc.*, 1984, **106**, 158.
- 12 M. Ruda, N. Kann, S. Gordon, J. Bergman, W. Nelson, P. Agback, L. Hagberg and K. F. Koehler, *J. Comb. Chem.*, 2005, **7**, 567.
- 13 V. Cerezo, M. Amblard, J. Martinez, P. Verdié, M. Planas and L. Feliu, *Tetrahedron*, 2008, **64**, 10538.
- 14 A. A. Poeylout-Palena and E. G. Mata, *Org. Biomol. Chem.*, 2010, **8**, 3947.
- 15 C. O. Kappe and D. Dallinger, *Mol. Diversity*, 2009, **13**, 71.
- 16 C. Amatore, G. Le Duc and A. Jutand, *Chem.-Eur. J.*, 2013, **19**, 10082.
- 17 Y. Liu, C. Khemtong and J. Hu, *Chem. Commun.*, 2004, 398.
- 18 S. A. Testero, J. F. Fisher and S. Mobashery, β -Lactam Antibiotics in Burger's Medicinal Chemistry, *Drug Discovery and Development, Vol. 7 (Antinfectives)*, ed. D. J. Abraham and D. P. Rotella, Wiley and Sons, 2010, pp. 259–404.
- 19 D. A. Burnett, *Curr. Med. Chem.*, 2004, **11**, 1873.
- 20 E. Martinez, J. J. Talley, S. Antonelli, T. Barden, R. Lundrigan-Soucy, W. Schairer, J. J. Yang and D. Zimmer, 4-Biaryl-1-phenylazetidin-2-ones, *US Pat.*, 2005/0209165 A1, 22 September 2005.
- 21 E. Turos, C. Coates, J.-Y. Shim, Y. Wang, J. M. Leslie, T. E. Long, G. S. K. Reddy, A. Ortiz, M. Culbreath, S. Dickey, D. V. Lim, E. Alonso and J. Gonzalez, *Bioorg. Med. Chem.*, 2005, **13**, 6289.
- 22 D. Ashok, B. V. Lakshmi, S. Ravi, A. Ganesh and S. Adam, *Chem. Heterocycl. Compd.*, 2015, **51**, 462.
- 23 (a) W. Kemnitzer, S. Kashibhatla, S. Jiang, H. Zhang, J. Zhao, S. Jia, L. Xu, C. Crogan-Gundy, R. Denis, N. Rarriault, L. Vaillancourt, S. Charron, J. Dodd, G. Attardo, D. Labreque, S. Lamothe, H. Gourdeau, B. Tseng, J. Drewe and S. X. Cai, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4745; (b) S. Combes, P. Barbier, S. Douillard, A. McLeer-Florin, V. Bourgarel-Rey, J.-T. Pierson, A. Y. Fedorov, J.-P. Finet, J. Boutonnat and V. Peyrot, *J. Med. Chem.*, 2011, **54**, 3153.
- 24 M. L. Yao and M. Z. A. Deng, *Chem. Heterocycl. Compd.*, 2000, **11**, 380.
- 25 S. Wattanasin, *Synth. Commun.*, 1988, **18**, 1919.
- 26 N. Zou and B. Jiang, *J. Comb. Chem.*, 2000, **2**, 6.
- 27 J. F. Cheng and A. M. Mjalli, *Tetrahedron Lett.*, 1998, **39**, 939.
- 28 A. Alam, C. Pal, M. Goyal, M. K. Kundu, R. Kumar, M. S. Iqbal, S. Dey, S. Bindu, S. Sarkar, U. Pal, N. C. Maiti, S. Adhikari and U. Bandyopadhyay, *Bioorg. Med. Chem.*, 2011, **19**, 7365.
- 29 B. S. Priya and K. S. Rangappa, *Heterocycl. Commun.*, 2006, **12**, 35.
- 30 S. L. Gaonkar, K. L. Rai and B. Prabhuswamy, *Med. Chem. Res.*, 2007, **15**, 407.
- 31 R. E. Sammelson, T. Ma, L. J. Galletta, A. S. Verkman and M. J. Kurth, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2509.
- 32 (a) Y. Al-Abed and S. VanPatten, *Future Med. Chem.*, 2011, **3**, 45; (b) Y. Al-Abed, D. Dabideen, B. Aljabari, A. Valster, D. Messmer, M. Ochani, M. Tanovic, K. Ochani, M. Bacher, F. Nicoletti, C. Metz, V. A. Pavlov, E. J. Miller and K. J. Tracey, *J. Biol. Chem.*, 2005, **280**, 36541.
- 33 For recent reviews on the biological activity of imidazoles, see: (a) M. M. Heravi, M. Daraie and V. Zadsirjan, *Mol. Diversity*, 2015, **19**, 577; (b) N. Rani, A. Sharma and R. Singh, *Mini-Rev. Med. Chem.*, 2013, **13**, 1812; (c) A. Mumtaz, A. Saeed, N. Fatima, M. Dawood, H. Rafique and J. Iqbal, *Bangladesh J Pharmacol*, 2016, **11**, 756.
- 34 (a) G. V. M. Sharma, Y. Jyothi and P. S. Lakshmi, *Synth. Commun.*, 2006, **36**, 2991; (b) S. Sarshar, D. Siev and A. M. Mjalli, *Tetrahedron Lett.*, 1996, **37**, 835.
- 35 F. Izquierdo, M. Corpet and S. P. Nolan, *Eur. J. Org. Chem.*, 2015, 1920.
- 36 C. Liu, T. Li and N. L. Rosi, *J. Am. Chem. Soc.*, 2012, **134**, 18886.
- 37 Y. A. Chen and C. Y. Liu, *RSC Adv.*, 2015, **5**, 74180.
- 38 T. Cornilleau, P. Hermange and E. Fouquet, *Chem. Commun.*, 2016, **52**, 10040.
- 39 C. I. Traficante, E. G. Mata and C. M. L. Delpiccolo, *RSC Adv.*, 2015, **5**, 26796.
- 40 K. Kawabata, M. Takeguchi and H. Goto, *Macromolecules*, 2013, **46**, 2078.
- 41 N. P. Cheval, A. Dikova, A. Blanc, J. M. Weibel and P. Pale, *Chem.-Eur. J.*, 2013, **19**, 8765.
- 42 C. Palomo, M. Oiarbide, A. Esnal, A. Landa, J. I. Miranda and A. Linden, *J. Org. Chem.*, 1998, **63**, 5838.
- 43 D. L. Boger and J. B. Myers Jr, *J. Org. Chem.*, 1991, **56**, 5385.

