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Palladium catalysed sequential imine arylation/Suzuki–Miyaura coupling: synthesis of α-(biarylyl)benzylamines

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ABSTRACT

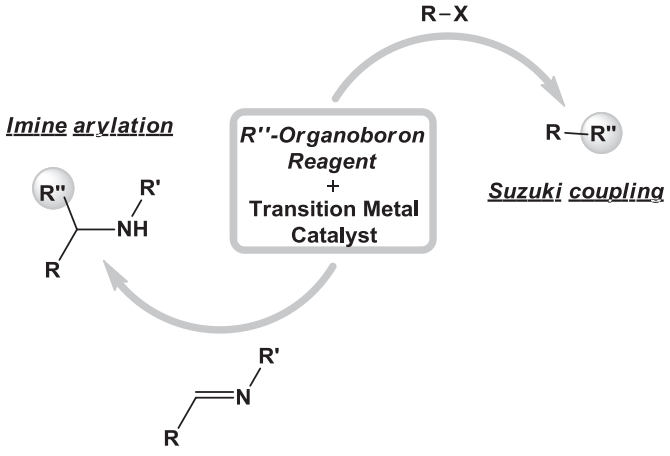
We report an innovative, high yielding one-pot sequential catalytic imine arylation/Suzuki–Miyaura cross-coupling reaction, which converts suitably activated imine substrates to various biarylarylmethyl amine products using several commercial Pd catalysts. Many biarylarylmethyl amine molecules are biologically active. Insightful computational studies detail the mechanism of the imine arylation process. The sequence of reactions is likely to be dependent on the reaction conditions.

1. Introduction

The formation of carbon–carbon single bonds, which lies at the heart of organic chemistry, is today still an enormous challenge for synthetic chemists in many contexts. Over the last number of years great efforts have been made by synthetic chemists to develop concise sequential or cascade catalytic processes for the construction of multiple bonds and the formation of complex structures.[1] Such processes are attractive for reasons of: cost, time, energy consumption and waste reduction. Transition metal catalysts are generally involved.[2] Success with such processes relies on the types of catalysis involved and their compatibility. Two powerful synthetic methodologies that are available to chemists are the Suzuki–Miyaura cross-coupling reaction and the catalytic arylation of imines, both relying on arylboronic acids and derivatives (Scheme 1).[3,4]

Our group is active in this field, having used transition metal catalysts and arylboron reagents for the synthesis of chiral amine units.[4a,5] This methodology has been extended recently, to the formation of α-hydroxyesters[6] and α-amino acid derivatives.[7]

The synthesis of biarylarylmethyl amine (α-(biphenylyl)benzylamine) units is important, considering their presence in some biologically active compounds. Bifonazole (α-(4-biphenylyl)benzyl imidazole, Fig. 1) is a strong antifungal agent, which has been used in the treatment of skin infections.[8a,b] Another example is the potent γ-secretase modulator BIIB042 (Fig. 1), which, contains a 2-phenylbenzylamine.[8c,d] (In fact, we have an active programme running looking at new drugs for treating Alzheimer's disease and this target is of significance to us). Other similar compounds having biological interest, and whose structures are close to the target unit are Valsartan[8e] (Diovan®)—an important angiotensin receptor blocker indicated for treatment of high blood pressure, congestive



Scheme 1. Formation of carbon–carbon single bonds using the Suzuki–Miyaura cross-coupling and the arylation of imines.

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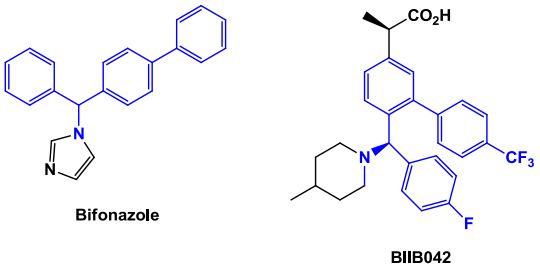
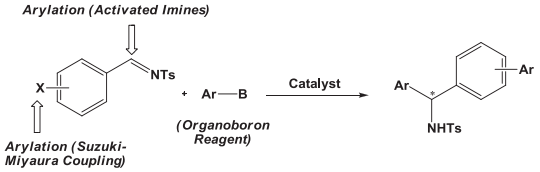


Fig. 1. Some pharmacologically active compounds containing a biarylarylmethylamine unit.

heart failure or post-myocardial infarction, but also the well-known glycopeptide antibiotic, Vancomycin[8f] used for prophylaxis and treatment of infections caused by Gram-positive bacteria. These units—particularly chiral ones—are also of interest for the construction of certain electronic materials, e.g. liquid crystals.[9]

Biaryl scaffolds can currently be accessed by a variety of cross-coupling methods, which includes one-pot processes.[10] Some important developments have come from the laboratories of Lautens who reported an elegant tandem Pd-catalysed Suzuki–Miyaura/direct arylation reaction,[11a] Gembus et al. who reported a Pd-catalysed one-pot sequential Suzuki–Miyaura/direct C–H functionalization of imidazo[1,2-a]pyrazines,[11b] and Bedford's group who reported a novel catalytic one-pot synthesis of carbazoles via consecutive amination and C–H activation.[11c] Although C–H activation methods[10c] are the most effective current approach, as a starting point, we decided to investigate the feasibility of a tandem or sequential catalytic one-pot reaction for the creation of interesting biarylarylmethylamine units (Scheme 2).



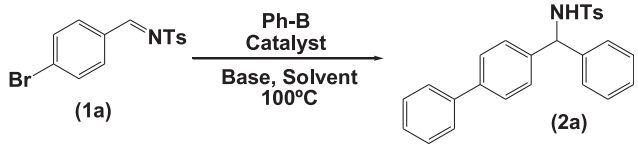
Scheme 2. Sequential one-pot C–C bond-forming catalytic reactions.

2. Results and discussion

Using the aldimine (**1a**) as substrate, we carried out a screening study of a variety of viable palladium catalysts, including, solvents and additives. Our preliminary results, targeting 4-arylbenzylamines, are shown in Table 1. Starting with $Pd(OAc)_2$ and PPh_3 in the presence of phenylboronic acid in toluene, the reaction ran smoothly giving the α-biarylyl benzyl amine (**2a**) in 38% yield (2 steps) (Table 1, entry 1). The use of NaOMe instead of NEt_3 increased the yield to 58% (Table 1, entry 3). When Ph_3B was used as the organoboron source (Table 1, entry 4) a yield of 58% was obtained. The commercial PEPPSI-IPr catalyst (Fig. 2), already used successfully in the Negishi cross-coupling reaction,[12] including interesting applications in the Kumada–Tamao–Corriu reaction,[13] was also investigated.

Upon screening a variety of solvents, it seemed that non-polar solvents like toluene or non-protic polar solvents like, THF (Table 1, entries 5 and 6, respectively) gave the best results. Phenylboronic acid (Table 1, entries 5–7) and sodium tetraphenylborate ($NaPh_4B$) (Table 1, entry 8) gave the expected product. Gratifyingly, $NaPh_4B$ gave the product (**2a**) in almost quantitative yield after only 18 h. (**2a**) was not obtained using other boron reagents, like $PhBF_3K$, $(PhBO)_3$, $C_9H_{11}BO_2$ and Ph_3B with PEPPSI-IPr and NEt_3 in toluene. In fact, in all the test reactions (Table 1) small quantities of the

Table 1
Optimization of the reaction conditions at 100 °C



Entry[a]	Ph-B	Catalyst	Base	Solvent	Tr/h	Yield[b]/%
1	$PhB(OH)_2$	$Pd(OAc)_2/PPh_3$	NEt_3	Toluene	16	38
2	$PhB(OH)_2$	$Pd(OAc)_2/PPh_3$	Cs_2CO_3	Toluene	40	13
3	$PhB(OH)_2$	$Pd(OAc)_2/PPh_3$	NaOMe	Toluene	40	58
4	Ph_3B	$Pd(OAc)_2/PPh_3$	NEt_3	Toluene	21	58
5	$PhB(OH)_2$	PEPPSI-IPr	NEt_3	Toluene	19	36
6	$PhB(OH)_2$	PEPPSI-IPr	NEt_3	THF	18	49
7	$PhB(OH)_2$	PEPPSI-IPr	NEt_3	DME	18	15
8	$NaPh_4B$	PEPPSI-IPr	NEt_3	Toluene	18	95
9	$NaPh_4B$	PEPPSI-IPr	Cs_2CO_3	Toluene	18	9

[a] Reagents and conditions: catalyst (3 mol %), Ph-B (4 equiv), base (4 equiv), solvent (2 mL), 100 °C, rt.
[b] Overall isolated yield from two steps, after liquid chromatography on silica gel.

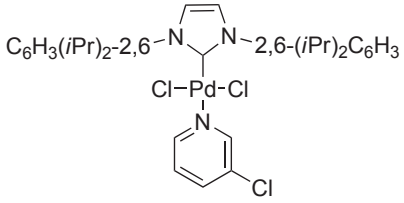


Fig. 2. PEPPSI-IPr catalyst.

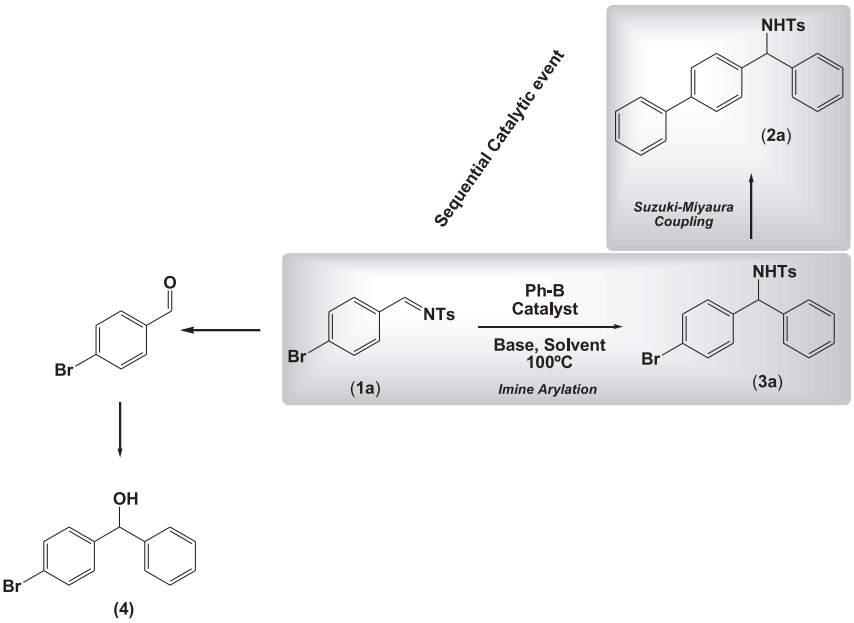
intermediate *p*-bromophenylphenylmethylamine (**3a**) (Scheme 3, (**3a**)) were detected by HPLC, thus suggesting a sequential catalytic event and not a tandem process.[1a] *para*-Bromophenyl alcohol (**4**) (Scheme 3) was also detected by TLC and HPLC analysis. (**4**) arises from hydrolysis of the aldimine to the aldehyde followed by subsequent arylation of the aldehyde.

A final test reaction was made using $NaPh_4B$ (and PEPPSI-IPr catalyst) instead of $PhB(OH)_2$ (Table 1, compare entry 2 with entry 9) but no improvements in the yield were observed. In order to test the scope of this method we applied our best conditions obtained so far (3 mol % PEPPSI-IPr along with $NaPh_4B$ (4 equiv) and NEt_3 (4 equiv) in toluene at 100 °C) to a series of activated aldimine substrates. To widen the scope further, we decided to extend our study to the biphenyl isomers, α-2-biphenylyl-, and α-3-biphenylylbenzyl amine (Table 2).

The best results were obtained with the 2-chloro substituted tosyl imine (**1f**) (59% (for 2 steps) for (**2b**) and 33% for the phenylated amine (**3f**), Table 2, entry 5). Both the 2-iodo (**1b**) and 3-iodo imine (**1c**) also gave the corresponding biphenylphenylmethylamines (**2b**) and (**2c**) in yields of 16 and 21% (2 steps), respectively, with no intermediate products (Table 2, entries 1 and 2, respectively).

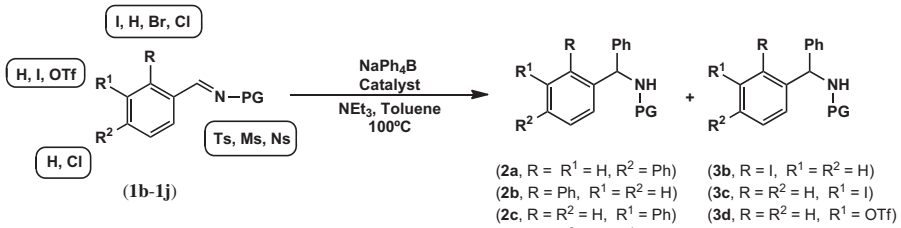
We also employed the conditions developed by Fu and co-workers[14] ($Pd(OAc)_2/PCy_3$) with aldimine substrates. Unfortunately, only the aldimines (**1g**) and (**1h**) gave the corresponding target compounds (**2a**) and (**2h**) in over 15% yields (see Supplementary data).

We then decided to screen other catalytic systems, and gratifyingly we observed that the combination of $Pd(dppf)Cl_2/NEt_3$[15] with $NaPh_4B$ as the phenyl transfer reagent, gave better results for the sequential phenylation of activated imines. (**1e**) was transformed cleanly to (**2b**) (92%) (Table 2, entry 12). Likewise, in the case of (**1b**) and (**1j**) these conditions gave selectively the diphenylated target compounds (**2b**) and (**2j**) in 68% and 30% yields, respectively (Table 2, entry 9 and 17).



Scheme 3. Sequential catalysis on (**1a**) to afford (**2a**) via (**3a**). Formation of (**4**) via phenylation of the aldehyde intermediate.

Table 2
Aldimine substrate and catalyst screening



(**2a**, R = R^1 = H, R^2 = Ph) (**3b**, R = I, R^1 = R^2 = H)
(**2b**, R = Ph, R^1 = R^2 = H) (**3c**, R = R^2 = H, R^1 = I)
(**2c**, R = R^2 = H, R^1 = Ph) (**3d**, R = R^2 = H, R^1 = OTf)
(**2d**, R = R^2 = H, R^1 = Ph) (**3e**, R = Br, R^1 = R^2 = H)
(**2h**, R = R^1 = H, R^2 = Ph) (**3f**, R = Cl, R^1 = R^2 = H)
(**2i**, R = R^1 = H, R^2 = Ph) (**3g**, R = R^1 = H, R^2 = Cl)
(**2j**) R = Ph R^1 = R^2 = H) (**3h**, R = R^1 = H, R^2 = Cl)
(**3i**, R = R^1 = H, R^2 = Cl)
(**3j**, R = Cl R^1 = R^2 = H)

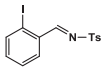
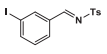
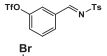
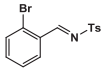
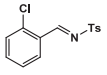
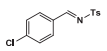
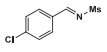
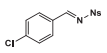
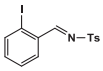
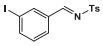
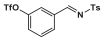
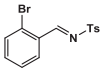
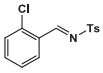
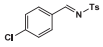
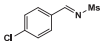
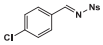
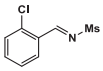
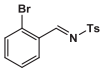
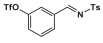
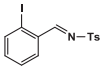
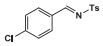
Entry[a]		Imine	Catalyst	Time/h	Yield[b]/%			
					Product (**2**)		Arylation intermediate (**3**)	
1[c]	(**1b**)		PEPPSI-IPr	18	(**2b**)	16	(**3b**)	—
2	(**1c**)		PEPPSI-IPr	18	(**2c**)	21	(**3c**)	—
3[c]	(**1d**)		PEPPSI-IPr	18	(**2d**)	—	(**3d**)	—
4	(**1e**)		PEPPSI-IPr	18	(**2b**)	—	(**3e**)	26
5	(**1f**)		PEPPSI-IPr	18	(**2b**)	59	(**3f**)	33
6	(**1g**)		PEPPSI-IPr	18	(**2a**)	—	(**3g**)	67
7	(**1h**)		PEPPSI-IPr	18	(**2h**)	—	(**3h**)	48
8	(**1i**)		PEPPSI-IPr	18	(**2i**)	—	(**3i**)	30

Table 2 (*continued*)

Entry[a]		Imine	Catalyst	Time/h	Yield[b]/%			
					Product (**2**)		Arylation intermediate (**3**)	
9	(**1b**)		$Pd(dppf)Cl_2$	22	(**2b**)	68	(**3b**)	—
10	(**1c**)		$Pd(dppf)Cl_2$	22	(**2c**)	—	(**3c**)	—
11	(**1d**)		$Pd(dppf)Cl_2$	15	(**2d**)	—	(**3d**)	—
12	(**1e**)		$Pd(dppf)Cl_2$	15	(**2b**)	92	(**3e**)	—
13	(**1f**)		$Pd(dppf)Cl_2$	15	(**2b**)	—	(**3f**)	47
14	(**1g**)		$Pd(dppf)Cl_2$	15	(**2a**)	—	(**3g**)	96
15	(**1h**)		$Pd(dppf)Cl_2$	15	(**2h**)	—	(**3h**)	—
16	(**1i**)		$Pd(dppf)Cl_2$	15	(**2i**)	—	(**3i**)	<10
17	(**1j**)		$Pd(dppf)Cl_2$	15	(**2j**)	30	(**3j**)	—
18	(**1e**)		$PdCl_2(PPh_3)_2$	40	(**2b**)	93	(**3e**)	—
19	(**1d**)		$PdCl_2(PPh_3)_2$	40	(**2d**)	—	(**3d**)	—
20	(**1b**)		$PdCl_2(PPh_3)_2$	40	(**2b**)	50	(**3b**)	—
21	(**1g**)		$PdCl_2(PPh_3)_2$	40	(**2a**)	—	(**3g**)	80

[a] Reagents and conditions: catalyst (3 mol%), Ph-Boron (4 equiv), base (4 equiv), solvent (2 mL), 100 °C.
[b] Isolated yields after liquid chromatography on silica gel.
[c] Reaction run at 80 °C.

Good results were also obtained with $PdCl_2(PPh_3)_2$ and $NaPh_4B$. In the case of (**1e**) the reaction gave selectively the diphenylated product (**2b**) in a yield of 93% (Table 2, entry 18). Compound (**1b**) was selectively phenylated to give (**2b**) in 50% yield (Table 2, entry 20). However, the chloride analogue (**1g**) only afforded the monophenylated amine intermediate (**3g**) (80%) (Table 2, entry 21).

ortho-Substituted substrates gave the best results. This might be attributed to the active intermediate palladium species in the reaction, and the interplay of some specific coordination effects. This was also observed with $PdCl_2(PPh_3)_2$, since only the *ortho*-substituted aldimines (**1e**) and (**1b**) afforded the desired di-arylated product (**2b**) (Table 2, entries 18 and 20).

The triflate substituted imine (**1d**) failed to afford product (Table 2, entries 3, 11 and 19).

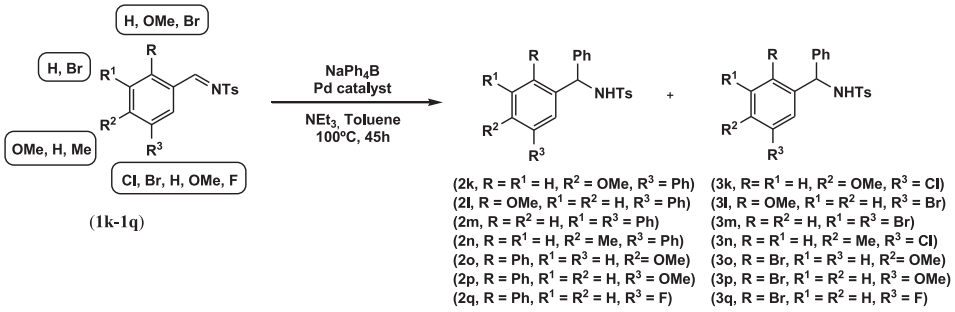
Under the original catalytic conditions, (**1h**) afforded the monophenylated amine intermediate (**3h**) (48%) (Table 2, entry 7). However, the combination of $Pd(dppf)Cl_2/NEt_3$ and $NaPh_4B$ failed to afford any product (Table 2, entry 15).

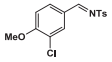
In the case of imine (**1i**)—with a nosyl group—only (**3i**) (imine phenylation) was obtained (Table 2, entries 8, and 16).

We then screened seven novel substituted aldimines (**1k**–**1q**)—synthesized according to literature procedures[4,5]—using our optimized conditions (PEPPSI-IPr and $Pd(dppf)Cl_2$ as catalysts, with $NaPh_4B$ and NEt_3, in toluene at 100 °C). The results are shown in Table 3. But it must be noted that the reaction scope here was limited by the substitution pattern in the aldimine substrate.

The results were quite interesting and intriguing. $Pd(dppf)Cl_2$ proved to be the best catalyst for conducting the desired sequential reaction (Table 3, entries 9, 10, 12–14). The only exception was with (**1n**), which afforded only the amine intermediate (**3n**) in 74% yield (Table 3, entry 11), in fact, the PEPPSI-IPr catalyst also afforded exclusively this product in 70% yield (Table 3, entry 4). This was probably due to the presence of a chlorine atom, which makes Suzuki–Miyaura coupling difficult.[3] The most gratifying result was the imine arylation-double Suzuki–Miyaura coupling of (**1m**), which afforded (**2m**) in 44% yield without any imine arylation intermediate (**3m**) (Table 3, entry 10). In the case of the PEPPSI-IPr catalyst, the same product in a lower yield, but as a mixture with (**3m**) (Table 3, entry 3). Naturally there were some slight steric effects in evidence, as seen by comparing the application of (**1l**) with (**1o**) (Table 3, entries 9 and 12), the diphenylated product (**2l**) was obtained in a higher yield, with a slight bias for the less hindered *m*-bromoarene imine substrate (**1l**). Electronic effects were in evidence too, it seems that electronwithdrawing groups improve the reactivity, as was demonstrated with (**1q**) (Table 3, entry 14) and compared with (**1p**), which gave a lower yield (Table 3, entry 13). In the reactions presented in Table 3 no exclusive Suzuki–Miyaura cross-coupling intermediates (**5**) were obtained for either catalyst,

Table 3
With substituted aldimine substrates



Entry	Substrate		Yield[b]/%			
			Product (**2**)		Arylation intermediate (**3**)	
1[a]	(**1k**)		(**2k**)	—	(**3k**)	58
2[a]	(**1l**)		(**2l**)	48	(**3l**)	24
3[a]	(**1m**)		(**2m**)	35	(**3m**)	17
4[a]	(**1n**)		(**2n**)	—	(**3n**)	70
5[a]	(**1o**)		(**2o**)	—	(**3o**)	—
6[a]	(**1p**)		(**2p**)	31	(**3p**)	31
7[a]	(**1q**)		(**2q**)	25	(**3q**)	28
8[c]	(**1k**)		(**2k**)	—	(**3k**)	33
9[c]	(**1l**)		(**2l**)	78	(**3l**)	—
10[c]	(**1m**)		(**2m**)	44	(**3m**)	—
11[c]	(**1n**)		(**2n**)	—	(**3n**)	74
12[c]	(**1o**)		(**2o**)	64	(**3o**)	—
13[c]	(**1p**)		(**2p**)	75	(**3p**)	—
14[c]	(**1q**)		(**2q**)	95	(**3q**)	—

[a] Reagents and conditions: PEPPSI-IPr (3 mol %), $NaPh_4B$ (4 equiv), NEt_3 (4 equiv), toluene (2 mL), 100 °C, 45 h.
[b] Yields determined by NMR spectroscopy.
[c] $Pd(dppf)Cl_2$ was used as catalyst.

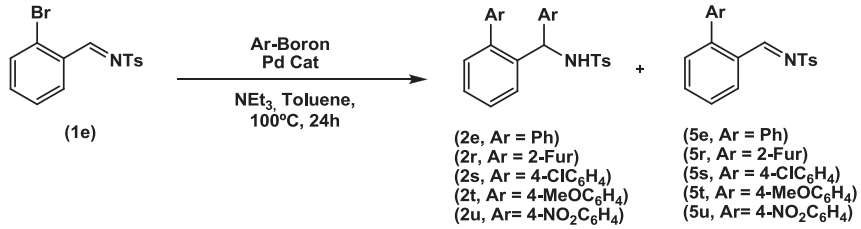
supporting the hypothesis that the imine arylation precedes the Suzuki–Miyaura reaction, since imine arylation intermediates (**3k**, **3l**, **3m**, **3n**, **3p** and **3q**) were obtained (see Table 3, entries 1, 2, 3, 4, 6, 7, 8 and 11). The results were inferior with the PEPPSI-IPr catalyst, the diarylated product was obtained only with (**1l**), (**1m**), (**1p**) and (**1q**) (Table 3, entries 2, 3, 6 and 7), in the other cases only the mono-phenylated amine was obtained or the reaction did not proceed at all, this clearly demonstrated the greater difficulty in achieving the Suzuki–Miyaura reaction with this catalyst. The PEPPSI-IPr catalyst is less sensitive to electronic effects (compare entry 6 with 7 in Table 3). But like the Pd(dppf)Cl_2 catalyst it is sensitive to steric effects (Compare entry 2 with 5 in Table 3). To conclude, Pd(dppf)Cl_2 is the catalyst of choice for these imine arylation/Suzuki–Miyaura coupling reactions in substituted aldimine substrates.

In an attempt to enlarge the product diversity, we decided to screen a series of commercial arylboronic acids—containing both electron-withdrawing and -donating groups—(Table 4), but limited it to a single aldimine substrate (**1e**) (which had previously given a very good result, see Table 2, entry 12). We choose PEPPSI-IPr and Pd(dppf)Cl_2 as the catalysts.

(Table 4, entries 6, 7, 12 to 15). We observed that by using a mixture of NEt_3 and KF (1/1) the desired products (**2r**) and (**2s**) were obtained, but in low yields (Table 4, entries 12, 6 and 13, respectively). The observation that the Suzuki–Miyaura reaction was favoured over the aldimine arylation, thwarted us, to use a mixture of aryl transfer reagents, to enforce the sequential process. Thus we used a mixture of the arylboronic acid and $NaPh_4B$ in a 1:1 ratio (Table 4, entries 16 to 19). Both (**2r**) and (**2s**) were obtained, albeit in low yields (see Table 4, entries 16 and 17). When a mixture of 4-$MeOC_6H_4B(OH)_2$ and $NaPh_4B$ was used (Table 4, entry 18), only the Suzuki–Miyaura product (**5t**) was obtained.

To shed some light on the mechanism some DFT studies were carried out (using the M06 functional,[16] see computational details below). To model the catalyst we chose to calculate Pd(IPr), since it is the active species derived from the Pd(II) PEPPSI catalyst, which is one of the best catalysts for the reactions here reported. We also selected the simple $PhB(OH)_2$ as the boron reagent, and the aldimine substrate (**1a**), bearing a Ms-group instead of a Ts-group in order to reduce the computational load. We first looked at the three possible coordination modes between the aryl imine and the palladium centre. The first possibility is the adduct (**Add_1**) showing

Table 4
Catalytic screening with arylboronic acids



Entry[a]	Ar–boron	Pd Cat	Yield[b]/%			
			Product (**2**)		Suzuki–Miyaura intermediate (**5**)	
1	$PhB(OH)_2$	Pd(dppf)Cl_2	(**2e**)	—	(**5e**)	47
2	2-Fur$B(OH)_2$	Pd(dppf)Cl_2	(**2r**)	—	(**5r**)	34
3	4-$ClC_6H_4B(OH)_2$	Pd(dppf)Cl_2	(**2s**)	—	(**5s**)	66
4	4-$MeOC_6H_4B(OH)_2$	Pd(dppf)Cl_2	(**2t**)	—	(**5t**)	37
5	4-$NO_2C_6H_4B(OH)_2$	Pd(dppf)Cl_2	(**2u**)	—	(**5u**)	—
6[c]	4-$ClC_6H_4B(OH)_2$	Pd(dppf)Cl_2	(**2s**)	<15	(**5s**)	—
7[c]	4-$NO_2C_6H_4B(OH)_2$	Pd(dppf)Cl_2	(**2u**)	—	(**5u**)	—
8	2-Fur$B(OH)_2$	PEPPSI-IPr	(**2r**)	—	(**5r**)	42
9	4-$ClC_6H_4B(OH)_2$	PEPPSI-IPr	(**2s**)	—	(**5s**)	11
10	4-$MeOC_6H_4B(OH)_2$	PEPPSI-IPr	(**2t**)	—	(**5t**)	43
11	4-$NO_2C_6H_4B(OH)_2$	PEPPSI-IPr	(**2u**)	—	(**5u**)	—
12[c]	2-Fur$B(OH)_2$	PEPPSI-IPr	(**2r**)	25	(**5r**)	—
13[c]	4-$ClC_6H_4B(OH)_2$	PEPPSI-IPr	(**2s**)	<5	(**5s**)	—
14[c]	4-$MeOC_6H_4B(OH)_2$	PEPPSI-IPr	(**2t**)	—	(**5t**)	—
15[c]	4-$NO_2C_6H_4B(OH)_2$	PEPPSI-IPr	(**2u**)	—	(**5u**)	—
16	2-Fur$B(OH)_2$ $NaPh_4B$ (1/1)	PEPPSI-IPr	(**2r**)	<10	—	—
17	4-$ClC_6H_4B(OH)_2$ $NaPh_4B$ (1/1)	PEPPSI-IPr	(**2s**)	<15	—	—
18	4-$MeOC_6H_4B(OH)_2$ $NaPh_4B$ (1/1)	PEPPSI-IPr	—	—	(**5t**)	44
19	4-$NO_2C_6H_4B(OH)_2$ $NaPh_4B$ (1/1)	PEPPSI-IPr	—	—	—	—

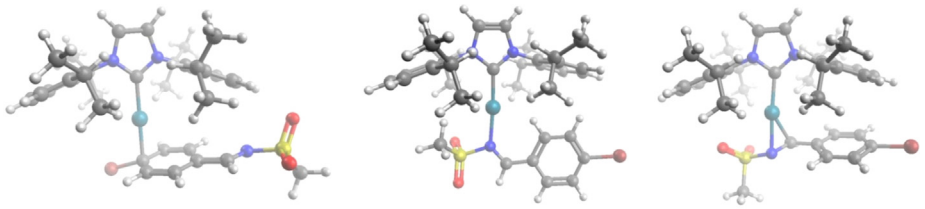
[a] Reagents and conditions: Pd Cat (3 mol%), Ar–Boron (4 equiv), NEt_3 (4 equiv), Toluene (2 mL), 100 °C, 24 h.
[b] Yields determined by NMR spectroscopy.
[c] Base: NEt_3 and KF (1/1).

Almost only exclusive Suzuki–Miyaura cross-coupling products (**5**) were obtained with both PEPPSI-IPr and Pd(dppf)Cl_2 (see Table 4, entries 1 to 4, 8 to 10 and 18), and in the cases where the sequential reaction occurred, the overall yield was low. 4-$NO_2C_6H_4B(OH)_2$ was unreactive with these systems (Table 4, entries 5, 7, 11, 15 and 19). In an attempt to get the desired compounds (**2r**–**2u**) we decided also to use an inorganic base (KF) as additive

an interaction between the C–Br bond of the substrate and the metal centre, similar to the adduct formed before the transition state of the oxidative addition step of the Suzuki–Miyaura coupling. Two other potential adducts have interactions between the palladium and the imine group: **Add_2** with a Pd–N bond of 2.13 Å, and **Add_3**, which shows η^2 like interaction between the palladium centre and the C=N bond (Pd–N=2.12 Å, Pd–C=2.14 Å). The three

structures are shown in Fig. 3, together with their corresponding stabilities. It appears that the three adducts are very similar in energy (**Add_2**, **Add_3** even being isoenergetic), which indicates that none of the two processes, the Suzuki–Miyaura coupling or the imine arylation, are initially favoured over the other.

The proposed mechanism for the imine arylation is depicted in Fig. 5. Both substrates form adducts with the metal centre. The phenyl group of the boronate is first transferred to palladium, whilst the aryl imine binds to the metal centre through η^2-like interaction. This occurs with a very low energy barrier (**IA_TS1** of



Add_1 **Add_2** **Add_3**

-22.7 *-23.8* *-23.8*

Fig. 3. Three adducts between the aryl imine and the active Pd catalyst. Free energy values in kcal/mol compared to the separated reactants (Pd(0) catalyst and the substrates).

The precise mechanism of the Suzuki–Miyaura coupling[3b] is still a matter of debate, the transmetalation step and the role of the base have been scrutinized in a number of studies.[17] Some studies show the importance of a Pd(OH) intermediate (where hydroxide substitutes the halide bound to the palladium after the oxidative addition step).[18,19] On the other hand, recent kinetic studies and extensive computational data suggest that the boronic acid should be activated by the base (forming a boronate) in order for the transmetalation to occur.[20,21] In our case, we experimentally used a variety of conditions, which included boronic acid reagents (together with a base), or $NaPh_4B$ (see Tables 1, 3 and 4). We decided to model the Suzuki–Miyaura coupling assuming that the boronate is the active species in the transmetalation step, and did the same for the imine arylation. The energy profile starts with **Add_1** (Fig. 4), and all the proceeding steps appear to be facile having energy barriers lower than 8 kcal/mol. Such values are rather low for the Suzuki–Miyaura coupling, and suggests that other steps (such as the formation of the NHC(Pd) species from the PEPPSI catalyst) might have higher energy barriers.

ca. 4 kcal/mol higher than **IA_1**), which is likely to be due to activation of the boron by the fluoride. A very stable intermediate **IA_2** is calculated to be formed, having $B(OH)_2F$ bound to palladium through hydrogen interactions. This step is followed by the imine arylation itself, i.e. the C–C bond formation, which has a significantly higher energy barrier (25.9 kcal/mol in fact between **IA_2** and **IA_TS2**). This leads to the imine arylation product, with the release of the Pd catalyst and $B(OH)_2F$ and then proceeded by the Suzuki–Miyaura coupling step.

If we compare the energy barriers for the reaction steps shown in Figs. 4 and 5, we observe than the imine arylation requires more energy than the Suzuki–Miyaura coupling, suggesting than the Suzuki–Miyaura coupling should occur prior to the imine arylation. However, this assumption needs to be considered with some caution. Indeed, the experimental observation of (see Tables 2 and 3) only the imine arylation product would indicate otherwise. This might be explained on the basis that we used $NaPh_4B$ instead of an arylboronic acid and a base, which are the usual conditions for the Suzuki–Miyaura reaction. It should also be taken into account that

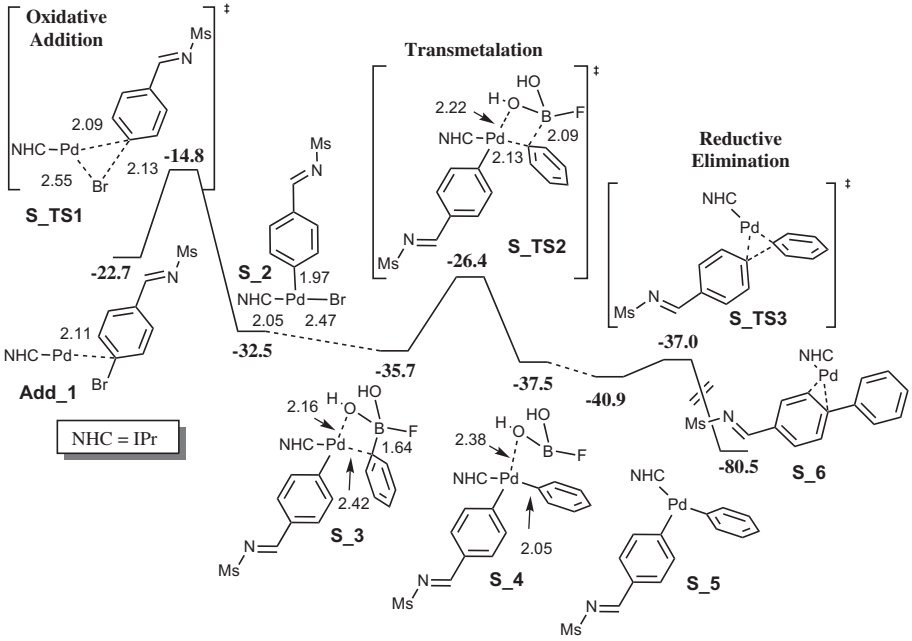


Fig. 4. Mechanism of the three main steps in our Suzuki–Miyaura coupling reaction. (Values in bold pertain to the free energy in the gas phase in kcal/mol, relative to the starting species (aryl imine, boronate, and the (NHC) Pd catalyst). Selected bond distances (in Å) are shown with an arrow in some cases.).

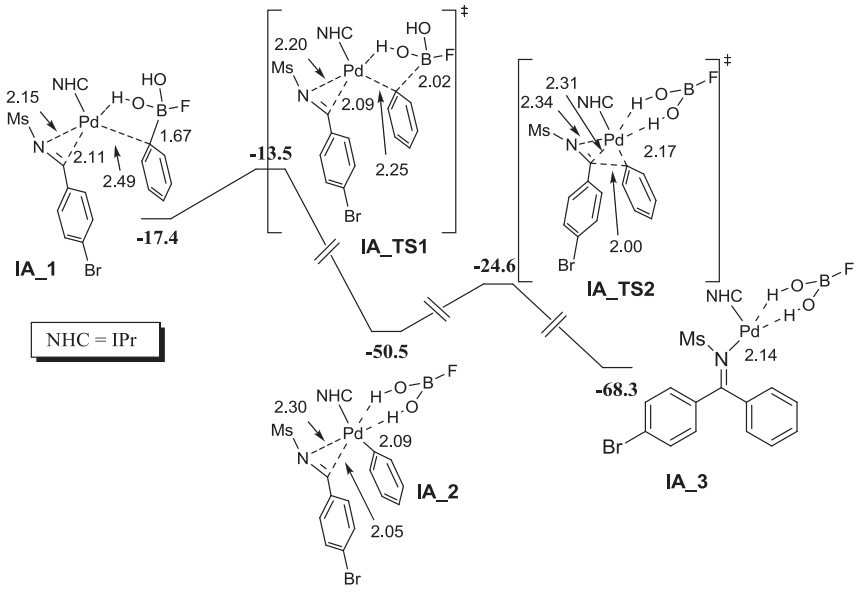


Fig. 5. Proposed mechanism for the imine arylation. (Values in bold pertain to the free energy in the gas phase in kcal/mol, relative to the starting species (aryl imine, boronate, and the (NHC) Pd catalyst). Selected bond distances (in Å) are shown with an arrow in some cases.).

for the purpose of expediency, we did not calculate the energy barrier for the initial Pd(II)/Pd(0) step. It is thus difficult to generalize, which of the two processes occurs first, since it is likely to be strongly dependent on the experimental conditions, and the reagents used.

3. Conclusions

In conclusion, we have developed a conceptually interesting method to synthesize biarylarylmethylamine units through a one-pot sequential catalytic procedure, which involves the arylation of activated imines followed (or preceded) by a Suzuki–Miyaura cross-coupling reaction. We found that the reaction was highly dependent on the palladium catalyst used and on the position of the halogen substituent in the aryl ring of the imine substrate. After testing several aldimine substrates and commercially available palladium catalysts, we found that Pd(dppf)Cl_2 was overall the best catalyst(in conjunction with $NaPh_4B$) for achieving this objective. To the best of our knowledge this is the first report on this sequential catalytic reaction to date. Based on DFT calculations, a mechanism for the imine arylation has been proposed.

We are currently working on an application of this methodology for the synthesis of analogues of the γ-secretase modulator BIIB042 and other targets, which could be important in the treatment of Alzheimer's disease, and on the development of the asymmetric catalytic version.

4. Experimental

4.1. General remarks

All the reagents were obtained from Aldrich, Fluka, Acros and Alfa Aeser. The solvents used were dried using current laboratory techniques.[22] All the reagents applied in this work were used as received. All substrates (**1a**)-(**1q**) were synthesized according to literature procedures.[4,5] All reactions with transition metals (Pd) were conducted under a nitrogen atmosphere. Column chromatography was carried out on silica gel (SDS, 70–200 μm). Thin layer chromatography (TLC) was carried out on aluminium backed Kiselgel 60 F254 plates (Merck). Plates were visualized either by UV light or with phosphomolybdic acid in ethanol. Melting points were determined on a Barnstead Electothermal 9100 apparatus and were uncorrected. The NMR analyses were recorded on a Bruker Avance III instrument (400 MHz) using $CDCl_3$ as solvent and the signal from the residual $CHCl_3$ as an internal standard. The mass spectra were recorded on a Waters-Micromass instrument (MaldiTOF, MicroTOF, ESI).

4.2. General procedure for the synthesis of aldimine substrates[4,5]

By using a Dean–Stark apparatus to facilitate water removal, $BF_3 \cdot Et_2O$ (0.6 mmol) was added (through a syringe) to a refluxing solution of the aldehyde (0.036 mol) and the protected amine (0.036 mol) in benzene (135 mL). The mixture was heated at reflux until the theoretical quantity of water (0.036 mol) was collected. The solution was then cooled and washed with NaOH (2 M solution) and water. The organic phase was separated and dried with anhydrous $MgSO_4$, and the solvent was evaporated under vacuum to yield a solid, which was crystallized from dichloromethane/petroleum ether (bp 60–80 °C) to give the desired product. The following aldimines have already been reported in the literature: *N*-(4-bromobenzylidene)*p*-toluenesulfonamide (**1a**), *N*-(2-chlorobenzylidene)*p*-toluenesulfonamide (**1f**), *N*-(4-chlorobenzylidene)*p*-toluenesulfonamide (**1g**), *N*-(4-chlorobenzylidene)methanesulfonamide (**1h**) and *N*-(2-chloroben zylidene)methanesulfonamide (**1j**).

*4.2.1. N-(2-Iodobenzylidene)-4-methylbenzenesulfonamide (**1b**).*[23] White solid (35% yield). Mp 96.2–98.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (s, CH_3, 3H), 7.23–7.31 (m, Ar, 1H), 7.35–7.38 (m, Ar, 2H), 7.80–7.82 (d, J=8 Hz, Ar, 1H), 7.89–7.91 (d, J=8 Hz, Ar, 2H), 7.93–7.95 (m, Ar, 1H), 8.08–8.11 (m, Ar, 1H), 9.21 (s, HC=N, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.75, 104.58, 126.58, 128.48, 128.85, 129.83, 130.03, 130.91, 133.77, 134.63, 135.82, 140.66, 145.00, 173.48.

*4.2.2. N-(3-Iodobenzylidene)-4-methylbenzenesulfonamide (**1c**).* White solid (29% yield). Mp 105.6–106.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.45 (s, CH_3, 3H), 7.21–7.25 (m, Ar, 2H), 7.35–7.37 (d, J=8 Hz, Ar, 2H), 7.84–7.95 (m, Ar, 4H), 8.93 (s, HC=N, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.78, 128.38, 129.42, 130.05, 130.83, 130.89,

134.38, 134.86, 139.19, 139.36, 142.66, 143.60, 145.06, 168.24. MS (ESI-TOF) (*m*/*z*): 385.98 (M^+).

*4.2.3. N-(2-Bromobenzylidene)-4-methylbenzenesulfonamide (**1e**).*[23] White solid (68% yield). Mp 115.3–117.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.45 (s, CH_3, 3H), 7.35–7.37 (d, *J*=8 Hz, Ar, 2H), 7.39–7.45 (m, Ar, 2H), 7.64–7.67 (m, Ar, 1H), 7.89–7.91 (d, *J*=8 Hz, Ar, 2H), 8.13 (m, Ar, 1H), 9.43 (s, HC=N, 1H).

*4.2.4. N-(4-Chlorobenzylidene)-4-nitrobenzenesulphonamide (**1i**).*[24] Pale yellow solid (44% yield). Mp 191.5–193.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49–7.52 (d, Ar, 2H), 7.88–7.90 (d, *J*=8 Hz, Ar, 2H), 8.19–8.22 (d, Ar 2H), 8.39–8.41 (d, *J*=8 Hz, Ar, 2H), 9.09 (s, HC=N, 1H).

*4.2.5. N-(2-Chlorobenzylidene)methanesulfonamide (**1j**).*[25] White solid (48% yield). Mp 62.5–63.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.18 (s, CH_3, 3H), 7.36–7.38 (m, Ar, 1H), 7.45–7.51 (m, 3H, Ar), 8.02–8.04 (d, *J*=8 Hz, HC=N, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 38.18, 126.85, 128.55, 131.66, 132.64, 133.74, 134.93, 170.84.

*4.2.6. N-(3-Chloro-4-methoxybenzylidene)-4-methylbenzenesulfonamide (**1k**).* Yellow solid (43% yield). Mp 137.5–138.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (s, CH_3, 3H), 3.98 (s, OCH_3, 3H), 6.99–7.01 (d, *J*=8 Hz, Ar, 1H), 7.33–7.35 (d, *J*=8 Hz, Ar, 2H), 7.77–7.79 (m, Ar, 1H), 7.86–7.88 (d, Ar, 2H), 8.00 (m, Ar, 1H), 8.90 (s, HC=N, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.79, 56.72, 111.98, 124.15, 126.01, 128.17, 129.95, 131.33, 132.34, 132.76, 135.50, 144.68, 160.45, 168.15. MS (ESI-TOF) (*m*/*z*): 324.05 (M^+).

*4.2.7. N-(5-Bromo-2-methoxybenzylidene)-4-methylbenzenesulfonamide (**1l**).*[26] White solid (27% yield). Mp 121.0–123.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (s, CH_3, 3H), 3.91 (s, OCH_3, 3H), 6.84–6.87 (d, Ar, 1H), 7.33–7.35 (d, *J*=8 Hz, Ar, 2H), 7.61–7.64 (m, Ar, 1H), 7.87–7.89 (d, *J*=8 Hz, Ar, 2H), 8.15 (m, Ar, 1H), 9.45 (s, HC=N, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.80, 56.22, 113.53, 113.65, 122.66, 128.24, 129.94, 131.76, 135.41, 139.22, 144.71, 160.69, 165.03.

*4.2.8. N-(3,5-Dibromobenzylidene)-4-methylbenzenesulfonamide (**1m**).* Light brown solid (87% yield). Mp 145.3–146.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.45 (s, CH_3, 3H), 7.36–7.38 (d, *J*=8 Hz, Ar, 2H), 7.87–7.89 (m, Ar, 3H), 7.98 (s, Ar, 2H), 8.89 (s, HC=N, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.83, 123.91, 128.47, 130.12, 131.33, 132.45, 134.47, 135.64, 139.80, 145.33, 167.07.

*4.2.9. N-(3-Chloro-4-methylbenzylidene)-4-methylbenzenesulfonamide (**1n**).* White solid (21% yield). Mp 97.6–99.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (s, CH_3, 3H), 2.46 (s, CH_3, 3H), 7.34–7.36 (d, *J*=8 Hz, Ar, 3H), 7.66–7.69 (m, Ar, 1H), 7.84–7.92 (m, Ar, 3H), 8.94 (s, HC=N, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.82, 21.81, 126.62, 128.28, 129.83, 129.99, 131.10, 131.75, 131.83, 135.11, 135.69, 144.08, 144.88, 168.69. MS (ESI-TOF) (*m*/*z*): 308.05 (M^+).

*4.2.10. N-(2-Bromo-4-methoxybenzylidene)-4-methylbenzenesulfonamide (**1o**).*[27] Light brown solid (75% yield). Mp 76.5–79.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.42 (s, CH_3, 3H), 3.86 (s, OCH_3, 3H), 6.92–6.94 (d, *J*=8 Hz, Ar, 2H), 7.26–7.35 (m, Ar, 2H), 7.79–7.81 (d, *J*=8 Hz, Ar, 2H), 8.09–8.12 (d, Ar, 1H), 9.31 (s, HC=N, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.64, 55.97, 114.29, 118.66, 126.56, 128.22, 129.82, 129.91, 131.49, 143.67, 144.62, 164.68, 168.62.

*4.2.11. N-(2-Bromo-5-methoxybenzylidene)-4-methylbenzenesulfonamide (**1p**).* Light yellow solid (72% yield). Mp 98.9–101.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (s, CH_3, 3H), 3.80 (s, OCH_3, 3H), 6.99–7.04 (m, Ar, 2H), 7.35–7.40 (d, Ar, 2H), 7.49–7.51 (d, *J*=8 Hz, Ar, 1H), 7.88–7.90 (d, *J*=8 Hz, Ar, 2H), 9.34 (s, HC=N, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.79, 55.78, 112.83, 113.44, 119.96, 123.19, 123.84, 126.53, 128.46, 130.01, 134.52, 134.66, 145.01, 159.19, 169.37.

*4.2.12. N-(2-Bromo-5-fluorobenzylidene)-4-methylbenzenesulfonamide (**1q**).* Light brown solid (81% yield). Mp 78.4–80.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.45 (s, CH_3, 3H), 7.17–7.20 (m, Ar, 1H), 7.30–7.38 (m, Ar, 2H), 7.59–7.65 (m, Ar, 2H), 7.80–7.85 (m, Ar, 1H), 7.89–7.91 (d, *J*=8 Hz, Ar, 1H), 9.36 (s, HC=N, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.84, 116.34, 116.57, 117.00, 117.24, 126.60, 128.52, 129.85, 130.10, 134.43, 135.48, 135.55, 145.27, 163.16, 163.47, 168.20.

4.3. General sequential Pd catalytic procedure

In a round bottom flask, under an inert atmosphere, was added the catalyst (3 mol % Pd plus 3.3 mol % ligand, when necessary), the aldimine substrate (**1**) (0.15 mmol), the boronic acid derivative (0.6 mmol), the base (0.6 mmol) and the solvent (2 mL). The mixture was stirred at 100 °C and monitored by TLC. The solvent was evaporated under reduced pressure and the crude product was purified by liquid chromatography (SiO_2 gel, Hex/AcOEt (5:1)) providing the final bi-phenyl product.

4.3.1. N-([1,1′-Biphenyl]-4-yl(phenyl)methyl)-4-methylbenzene sulfonamide[28] *(**2a**).* White solid, mp 135.9–136.4 °C (mp[24] 149.9–151.0 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.35 (s, 3H, CH_3), 5.28–5.30 (d, *J*=8 MHz, 1H, CH), 5.62–5.63 (d, *J*=4 MHz, 1H, NH), 7.12–7.19 (m, 6H, Ar), 7.22–7.24 (m, 3H, Ar), 7.32–7.36 (t, *J*=8 MHz, 1H, Ar), 7.42–7.44 (m, 4H, Ar), 7.51–7.53 (d, *J*=8 MHz, 2H, Ar), 7.57–7.59 (d, *J*=8 MHz, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.44, 61.14, 127.14, 127.36, 127.50, 127.55, 127.80, 127.97, 128.75, 128.91, 129.49, 137.49, 139.60, 140.57, 140.63, 143.33.

*4.3.2. N-([1,1′-Biphenyl]-2-yl(phenyl)methyl)-4-methylbenzenesulfonamide (**2b**).* White solid. Mp 145.9–147.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.37 (s, 3H, CH_3), 5.31–5.33 (d, *J*=8 Hz, 1H, CH), 5.67–5.68 (d, *J*=4 Hz, 1H, NH), 6.87–6.89 (m, 2H, Ar), 7.00–7.01 (d, *J*=4 Hz, 2H, Ar), 7.08–7.15 (m, 6H, Ar), 7.23–7.32 (m, 5H, Ar), 7.42–7.46 (m, 3H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.41, 57.85, 127.24, 127.32, 127.34, 127.47, 127.52, 127.56, 127.61, 127.71, 127.85, 128.20, 128.51, 128.61, 128.63, 129.27, 129.40, 129.52, 129.65, 130.27, 137.25, 137.86, 140.39, 141.15, 141.31, 143.15. HRMS (ESI): *m*/*z* calcd for $C_{26}H_{23}NO_2S$ $[M]^+$: 413.14495, found for $C_{26}H_{23}NNaO_2S$: 436.13443.

*4.3.3. N-([1,1′-Biphenyl]-3-yl(phenyl)methyl)-4-methylbenzenesulfonamide (**2c**).* White solid. Mp 68.7–70.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.34 (s, 3H, CH_3), 5.19–5.21 (d, *J*=8 Hz, 1H, CH), 5.63–5.65 (d, *J*=8 Hz, 1H, NH), 7.08–7.13 (m, 2H, Ar), 7.22–7.25 (m, 4H, Ar), 7.30–7.37 (m, 2H, Ar), 7.40–7.48 (m, 4H, Ar), 7.55–7.63 (m, 4H, Ar), 7.69–7.71 (d, *J*=8 Hz, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.67, 61.14, 127.14, 127.35, 127.49, 127.82, 128.13, 128.46, 128.67, 128.72, 128.94, 128.97, 129.51, 129.61, 129.78, 130.17, 131.51, 132.75, 133.68, 135.79, 137.31, 137.34, 137.83, 140.25, 140.97, 143.63. HRMS (ESI): *m*/*z* calcd for $C_{26}H_{23}NO_2S$ $[M]^+$: 413.14495, found for $C_{26}H_{23}NO_2S$: 413.15394.

*4.3.4. N-([1,1′-Biphenyl]-4-yl(phenyl)methyl)methanesulfonamide (**2h**).* White solid. Mp 111.9–113.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.72 (s, 3H, CH_3), 5.13–5.14 (d, *J*=4 Hz, 1H, CH), 5.81–5.83 (d, *J*=8 Hz, 1H, NH), 7.32–7.45 (m, 10H, Ar), 7.53–7.60 (m, 4H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 42.20, 61.17, 127.19, 127.47, 127.59, 127.70, 127.73, 128.00, 128.26, 128.98, 129.14, 129.23, 139.74, 140.43, 140.72,

141.09. HRMS (ESI): *m/z* calcd for $C_{20}H_{19}NO_2S$ $[M]^+$: 337.11365, found for $C_{20}H_{19}NNaO_2S$: 360.10143.

*4.3.5. N-([1,1′-Biphenyl]-2-yl(phenyl)methyl)methanesulfonamide (**2j**).* White oily/solid. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.41 (s, 3H, CH_3), 5.11–5.12 (d, *J*=4 Hz, 1H, CH), 5.19 (d, 1H, NH), 6.85–6.86 (d, *J*=4 Hz, 1H, Ar), 6.93–6.96 (m, 2H, Ar), 7.24–7.28 (m, 4H, Ar), 7.35–7.40 (m, 1H, Ar), 7.45–7.48 (m, 2H, Ar), 7.61–7.63 (m, 1H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.50, 59.05, 115.43, 120.79, 127.30, 127.38, 128.24, 128.89, 129.78, 141.38, 155.77. HRMS (ESI): *m/z* calcd for $C_{20}H_{19}NO_2S$ $[M]^+$: 337.11365, found for $C_{20}H_{19}NNaO_2S$: 360.10143.

*4.3.6. N-((4-Methoxy-[1,1′-biphenyl]-3-yl)(phenyl)methyl)-4-methylbenzenesulfonamide (**2l**).* White solid. Mp 161.9–163.2 °C. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.21 (s, 3H, CH_3), 3.65 (s, 3H, OCH_3), 5.67–5.70 (d, *J*=12 Hz, 1H, CH), 5.85–5.87 (d, *J*=8 Hz, 1H, NH), 6.74–6.76 (d, *J*=8 Hz, 1H, Ar), 6.99–7.01 (d, *J*=8 Hz, 2H, Ar), 7.13 (m, 1H, Ar), 7.19–7.25 (m, 5H, Ar), 7.30–7.41 (m, 6H, Ar), 7.51–7.53 (d, *J*=8 Hz, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.47, 55.64, 59.48, 111.70, 126.71, 126.92, 127.07, 127.20, 127.31, 127.40, 127.89, 128.33, 128.55, 128.89, 129.17, 133.78, 137.56, 140.25, 140.53, 143.05, 156.07. HRMS (ESI): *m/z* calcd for $C_{27}H_{25}NO_3S$ $[M]^+$: 443.15551, found for $C_{27}H_{25}NNaO_3S$: 466.14474.

*4.3.7. N-([1,1′:3′,1″-Terphenyl]-5′-yl(phenyl)methyl)-4-methylbenzenesulfonamide (**2m**).* White solid. Mp 119.9–122.5 °C. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.18 (s, 3H, CH_3), 5.28–5.30 (d, *J*=8 Hz, 1H, CH), 5.65–5.67 (d, *J*=8 Hz, 1H, NH), 6.98–7.00 (d, *J*=8 Hz, 2H, Ar), 7.17–7.18 (m, 4H, Ar), 7.28–7.42 (m, 12H, Ar), 7.51–7.55 (m, 3H, Ar), 7.73–7.75 (d, *J*=8 Hz, 1H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.52, 61.06, 125.32, 125.39, 127.16, 127.27, 127.34, 127.54, 127.71, 127.88, 128.04, 128.82, 128.89, 129.17, 129.47, 129.74, 131.17, 134.85, 137.51, 140.57, 140.67, 141.46, 142.14, 143.44. HRMS (ESI): *m/z* calcd for $C_{32}H_{27}NO_2S$ $[M]^+$: 489.17625, found for $C_{32}H_{27}NNaO_2S$: 512.16547.

*4.3.8. N-((5-Methoxybiphenyl-2-yl)(phenyl)methyl)-4-methylbenzenesulfonamide (**2o**).* Orange oily/solid. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.39 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 5.39–5.41 (d, *J*=8 Hz, 1H, CH), 5.61–5.62 (d, *J*=4 Hz, 1H, NH), 6.70 (d, 1H, Ar), 6.80–6.83 (m, 1H, Ar), 6.92–6.94 (m, 2H, Ar), 7.04–7.06 (m, 2H, Ar), 7.10–7.16 (m, 5H, Ar), 7.30–7.34 (m, 4H, Ar), 7.46–7.47 (m, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.54, 53.35, 57.56, 113.65, 115.27, 127.72, 127.38, 127.46, 128.21, 128.44, 128.99, 129.12, 129.37, 129.61, 137.70, 140.32, 141.48, 142.53, 143.06, 158.45. HRMS (ESI): *m/z* calcd for $C_{27}H_{25}NO_3S$ $[M]^+$: 443.15551, found for $C_{27}H_{25}NNaO_3S$: 466.14474.

*4.3.9. N-((4-Methoxy-[1,1′-biphenyl]-2-yl)(phenyl)methyl)-4-methylbenzenesulfonamide (**2p**).* White solid. Mp 112.9–113.4 °C. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.40 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 5.05–5.07 (d, *J*=8 Hz, 1H, CH), 5.66–5.67 (d, *J*=4 Hz, 1H, NH), 6.80–6.82 (m, 1H, Ar), 6.90–6.92 (m, 3H, Ar), 6.99–7.00 (d, *J*=4 Hz, 2H, Ar), 7.07–7.17 (m, 6H, Ar), 7.27–7.31 (m, 3H, Ar), 7.46–7.48 (d, *J*=8 Hz, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.62, 55.37, 58.23, 112.97, 127.15, 127.30, 127.57, 127.68, 128.24, 128.61, 129.44, 129.61, 131.52, 134.07, 137.32, 138.93, 140.21, 141.00, 143.23, 159.16. HRMS (ESI): *m/z* calcd for $C_{27}H_{25}NO_3S$ $[M]^+$: 443.15551, found for $C_{27}H_{25}NNaO_3S$: 466.14474.

*4.3.10. N-((4-Fluoro-[1,1′-biphenyl]-2-yl)(phenyl)methyl)-4-methylbenzenesulfonamide (**2q**).* White solid. Mp 154.4–155.3 °C. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.37 (s, 3H, CH_3), 4.83–4.84 (d, *J*=4 Hz, 1H, CH), 5.58–5.59 (d, *J*=4 Hz, 1H, NH), 6.76–6.78 (d, *J*=8 Hz, 2H, Ar), 6.93–6.97 (m, 3H, Ar), 7.08–7.14 (m, 5H, Ar), 7.24–7.31 (m, 5H, Ar), 7.45–7.47 (d, *J*=8 Hz, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.84, 58.13, 114.43, 127.29, 127.56, 127.94, 127.97, 128.32, 128.77, 129.44, 129.03, 129.56, 139.51, 140.32, 143.54, 161.09, 163.55. HRMS (ESI): *m/z* calcd for $C_{26}H_{22}FNO_2S$ $[M]^+$: 431.13553, found for $C_{26}H_{22}FNNaO_2S$: 454.12475.

*4.3.11. N-(Furan-2-yl(2-(furan-2-yl)phenyl)methyl)-4-methylbenzenesulfonamide (**2r**).* White solid. Mp 82.0–83.5 °C. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.30 (s, 3H, CH_3), 5.35–5.37 (d, *J*=8 Hz, 1H, CH), 5.88–5.93 (m, 2H,=CH–CH=), 6.14 (s, 1H,=CH), 7.02 (m, 1H,=CH), 7.08–7.12 (m, 5H, Ar), 7.28–7.29 (m, 1H, NH), 7.37–7.47 (m, 2H, Ar), 7.56–7.58 (m, 3H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.63, 55.21, 108.82, 110.58, 123.14, 127.39, 127.75, 128.94, 129.42, 129.54, 131.02, 133.16, 137.04, 137.33, 142.94, 143.51, 151.27. MS (ESI-TOF) (*m/z*): 391.28 (M^+).

*4.3.12. N-((4′-Chlorobiphenyl-2-yl)(4-chlorophenyl)methyl)-4-methylbenzenesulfonamide (**2s**).* Light brown oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.41 (s, 3H, CH_3), 5.04–5.06 (d, *J*=8 Hz, 1H, CH), 5.55–5.57 (d, *J*=8 Hz, 1H, NH), 6.75–6.77 (d, *J*=8 Hz, 1H, Ar), 6.81–6.83 (d, *J*=8 Hz, 1H, Ar), 6.91–6.93 (d, *J*=8 Hz, 1H, Ar), 7.12–7.19 (m, 4H, Ar), 7.24–7.36 (m, 5H, Ar), 7.43–7.45 (d, *J*=8 Hz, 2H, Ar), 7.55–7.57 (d, *J*=8 Hz, 1H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.67, 57.42, 127.20, 127.26, 127.52, 127.85, 128.44, 128.56, 128.67, 128.82, 128.95, 129.58, 129.61, 129.79, 129.90, 130.23, 130.43, 130.54, 133.66, 136.96, 137.56, 138.75, 139.35, 140.12, 140.81, 143.60.

4.4. Computational details

Calculations were performed by DFT methods with the M06 functional,[16] as implemented in the Gaussian09 suite of programs.[29] Palladium was described using the SDD effective core potential for the inner electrons and its associated basis set for the outer ones.[30] The standard 6-31G(d) basis set was used for all other atoms.[31] Stationary points were fully optimized without any symmetry restriction. Vibrational frequency calculations were performed to verify the nature of the stationary points (i.e., minima or transition states). Connectivity of the transition states was confirmed by relaxing the transition state structures towards both reactant and product sides. Reported energy values are free energy in the gas phase.

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Supplementary data

Supplementary data (additional data, NMR and mass spectra, and computational data) related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.03.105.

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