Basic alumina-supported highly effective Suzuki–Miyaura cross-coupling reaction under microwave irradiation: application to fused tricyclic oxa-aza-quinolones†

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Basic alumina used in lieu of traditional mineral bases efficiently promotes a solvent free, $Pd(PPh_3)_4$ catalyzed Suzuki–Miyaura cross-coupling reaction under microwave irradiation.

Introduction

The Suzuki–Miyaura cross-coupling reaction of aryl halides with aryl boronic acids is one of the most versatile and widely used reactions for the selective construction of carbon–carbon bonds, in particular for the formation of biaryl derivatives.[1] As the biaryl motifs are found in a range of pharmaceuticals, herbicides and natural products,[2] the development of this versatile reaction has received much attention in recent years. A plethora of reports have appeared in the literature regarding improvements that comprise modification of the catalysts[1,3] (with or without palladium), variation of solvents[1,3,4] (organic, aqueous or none), use of bases[1,3,5] (with or without), and reaction tools like classical heating[1,6] or microwave irradiation,[7] with particular emphasis for cleaner and more environmentally benign ways to make target molecules. As biaryl quinolones are known to possess neuroprotective properties,[8] we became interested in constructing the biaryl derivatives from our recently synthesized novel fused tricyclic quinolones[9] using the Suzuki–Miyaura reaction. The emphasis was on the optimization of yield of the biaryl products under green reaction conditions. The microwave irradiation technique was employed in the reactions, as this tool is well known for achieving energy efficiency and enhancing the rate of reaction as well as product yields. We were particularly attracted by the possibility of using a solid-supported reaction, as it is well documented that in such cases organic compounds get adsorbed on the surface of inorganic oxides like alumina or silica which themselves do not absorb or restrict the transmission of microwave irradiation.[10] This is also the case with reagents immobilized on porous solid supports which have an advantage over the conventional solution phase reactions because of the good dispersion of active sites, associated selectivities and easier work up.[10]

A systematic study was performed for optimization of yield of the products on our model systems varying the catalysts, bases, solvents, solid supports, and the time period. Herein, we report an efficient system for the Suzuki–Miyaura reaction of fused tricyclic dihalo quinolones using basic alumina as solid support and $Pd(PPh_3)_4$ as catalyst in a solvent-free medium under microwave irradiation.

Results and discussion

At the outset, we chose 5,7-dibromo-1,4-oxazino quinolone and *p*-methoxy phenyl boronic acid as model reaction partners to evaluate the effects of various conditions under microwave irradiation. The results revealed that the reactions catalyzed by $Pd(OAc)_2/PPh_3$ in toluene-H_2O using bases like KF, Cs_2CO_3 or even K_3PO_4 were ineffective and only low yield was obtained with Na_2CO_3. In alternative solvents, *viz.* dioxane and CH_3CN, the reaction yielded no products, though in DCE and DMF low to moderate yields were obtained. In reactions carried out in DMF using Na_2CO_3 along with $PdCl_2/PPh_3$ or $PdCl_2(PPh_3)_2$ as the catalyst, the yields of the products were found to be 45–50%. Similar reaction protocols with Na_2CO_3 and $Pd(PPh_3)_4$ instead of $PdCl_2(PPh_3)_2$ produced better results. Further studies with $Pd(PPh_3)_4$ using different solvents and bases revealed that moderate yield could be obtained in DMF or H_2O in the presence of Na_2CO_3 within 5 min of the reaction. Taking into account the efficacy of the catalyst $Pd(PPh_3)_4$, the study was further extended using solid supports like silica and alumina because of the fact that organic groups can robustly anchor to their surface.[11] Moreover, these are excellently stable and readily available. Indeed, using 1 mol% of $Pd(PPh_3)_4$, the silica gel-supported reaction in the presence of Na_2CO_3 yielded 75%, neutral alumina in the presence of KF yielded 80% (Table 1, entry 8, 11), whilst basic alumina afforded the most effective conversion (90%) to the biaryl product (Table 1, entry 20). However, lower yields were obtained when the reactions were performed by changing the combination of bases with solid supports with different proportions of the catalyst. It is notable that only 0.1 mol% of Pd $(PPh_3)_4$ with basic alumina could afford 90% yield even in 3 min (Table 1, entry 21), whereas neutral alumina was found to be totally ineffective in absence of a base (Table 1, entry 23–25).

The good performance of basic alumina could be ascribed to the presence of 'interfacial' boronic esters, originating from electrostatic interaction between the electron deficient boron

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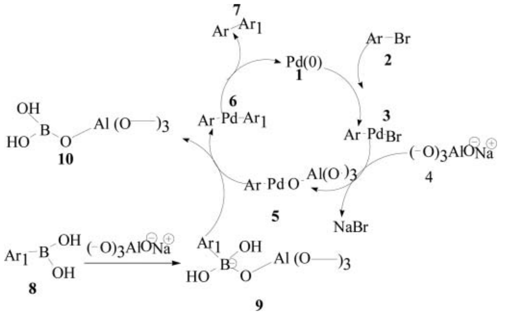
Table 1 Optimization of catalyst [$Pd(PPh_3)_4$] loading on different solid supports in the reaction between **1a** and *p*-methoxyphenyl boronic acid under microwave irradiation[a]

Entry	Solid support–base	$Pd(PPh_3)_4$ (mol%)	Temperature/°C	Time (min)	Yield[b] (%)
1	Silica gel–KF	0.5	90	5	40
2	Silica gel–KF	0.5	110	5	50
3	Silica gel–KF	0.5	120	5	50
4	Silica gel–KF	1.0	120	3	55
5	Silica gel–KF	2.0	120	5	55
6	Silica gel–Na_2CO_3	0.5	110	5	60
7	Silica gel–Na_2CO_3	0.5	120	3	65
8	Silica gel–Na_2CO_3	1.0	120	3	75
9	Silica gel–Na_2CO_3	2.0	120	6	80
10	Neutral alumina–KF	0.5	120	5	75
11	Neutral alumina-KF	1.0	120	4	80
12	Neutral alumina–KF	2.0	120	5	80
13	Neutral alumina–Na_2CO_3	0.5	120	5	55
14	Neutral alumina–Na_2CO_3	1.0	130	5	60
15	Neutral alumina–Na_2CO_3	2.0	130	5	60
16	Basic alumina	0.5	90	3	80
17	Basic alumina	0.5	110	3	85
18	Basic alumina	0.5	120	3	90
19	Basic alumina	0.5	130	3	90
20	Basic alumina	1.0	120	3	90
21	Basic alumina	0.1	120	3	90
22	Basic alumina	0.05	120	5	70
23	Neutral alumina	0.5	120	15	NR[c]
24	Neutral alumina	1.0	120	20	NR
25	Neutral alumina	2.0	120	20	NR

[a] All the studies were performed by using **1a** and *p*-methoxyphenyl boronic acid under microwave irradiation at 180 W. [b] Isolated yield. [c] No reaction.

atom of boronic acid and the oxygen atom of the solid framework, as depicted in Scheme 1, which facilitates the reaction. However, the remarkable difference of efficacy between the two forms of alumina might be due to the structural and compositional differences among various forms of alumina that are associated with differing surface reactivity and catalytic activity.



Scheme 1 Plausible pathway for basic alumina-supported Suzuki–Miyaura cross coupling reaction.

In order to compare the advantages of the use of microwave irradiation, we performed the reaction for **2a** using an oil bath at 120 °C. It is noteworthy that only 21% of **2a** could be isolated after 23 hours of reaction. On the contrary 90% of the same was obtained in 3 min under microwave irradiation.

We then examined the optimal set of reaction conditions with a variety of oxazino (**1a**), oxazepino (**1b**), and oxazocino (**1c**) quinolones with different aryl/heteroaryl boronic acids, (Table 2). It can be seen from the table that the newly developed reaction condition is an effective biarylation protocol with 80–90% yield.

Finally, generalization of this methodology was also established satisfactorily by performing reactions on simpler aryl bromides (*viz.* substituted bromobenzene) with different aryl and heteroaryl boronic acids. The products were characterized by MS, ^1H and ^{13}C NMR spectroscopy. Single crystal X-ray crystallographic analysis of a biaryl derivative (**2c**) was carried out for unambiguous determination of its structure (Fig. 1).†

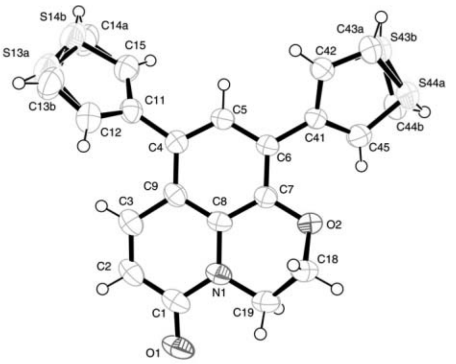
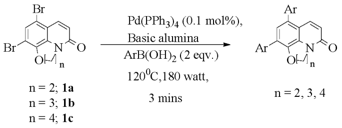
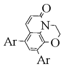
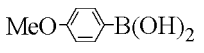
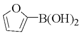
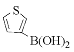
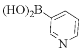
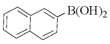
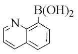
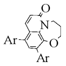
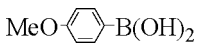
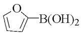
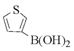
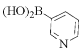
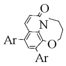
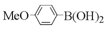
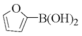
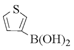
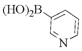


Fig. 1 ORTEP Diagram of 7,9-di-thiophen-3-yl-2,3-dihydro-1-oxa-3a-aza-phenalen-4-one (**2c**); ellipsoids are drawn at 50% probability level.

We also investigated the reusability of the solid support, as it is very important for industrial and pharmaceutical application. It was found that basic alumina, on calcination at 150 °C for 5 h (after washing with water and acetone) could be recycled 4–5 times with insignificant change in its activity (Fig. 2).

Table 2 Suzuki cross coupling reaction of 5,7-dibromoquinolone (**1a–c**) with different boronic acids under microwave irradiation



Aryl bromide	Boronic acid	Time/min	Product[a]	Pd(PPh$_3$)$_4$ (mol%)	Yield[b] (%)
					
1a		3	**2a**: Ar = p-OMe Ph	0.1	90
1a		3	**2b**: Ar = furan-2-yl	0.1	86
1a		3	**2c**: Ar = thiophen-3-yl	0.1	88
1a		3	**2d**: Ar = pyridin-3-yl	0.1	88
1a		3	**2e**: Ar = naphthalen-2-yl	0.1	90
1a		3	**2f**: Ar = quinoline-8-yl	0.1	85
					
1b		3	**3a**: Ar = p-OMe Ph	0.1	90
1b		3	**3b**: Ar = furan-2-yl	0.1	84
1b		3	**3c**: Ar = thiophen-3-yl	0.1	88
1b		3	**3d**: Ar = pyridin-3-yl	0.1	88
					
1c		3	**4a**: Ar = p-OMe Ph	0.1	90
1c		3	**4b**: Ar = furan-2-yl	0.1	83
1c		3	**4c**: Ar = thiophen-3-yl	0.1	88
1c		3	**4d**: Ar = pyridin-3-yl	0.1	89

[a] The products were characterized by MS, ^{1}H and ^{13}C NMR spectroscopy. [b] Isolated Yield.

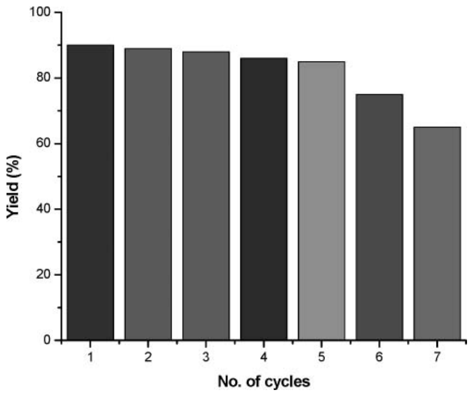


Fig. 2 Reusability of the basic alumina.

To the best of our knowledge this is the first report of basic alumina-supported Suzuki-Miyaura cross-coupling reaction.

Conclusion

In conclusion, we have developed an environmentally benign solid support system for Suzuki–Miyaura cross coupling reaction of heteroaryl bromides and boronic acids under microwave irradiation using basic alumina. The novelty of the system lies in its energy efficiency, low cost, easy availability of the solid support and also elimination of the use of any base or solvent. The operational simplicity and general applicability of the procedure as well as reusability of the basic alumina is expected to contribute to the development of a green technology of biaryl heteroaromatics.

Experimental

General procedure

The substrate, fused tricyclic-oxa-aza-quinolone (1 mol), was dissolved in a minimum amount of chloroform, added to a round-bottomed flask and basic alumina (500 mg) was added to it. The organic solvent was evaporated to dryness under reduced pressure. To the residue, boronic acid (2 mol) and $Pd(PPh_3)_4$ (0.1 mol%) were added. The solid mixture was then stirred at room temperature under inert atmosphere for an additional 10–15 minutes to ensure efficient mixing. The flask was then fitted with a septum, and the mixture was subjected to irradiation in a microwave reactor (CEM, Discover, USA) at 120 °C (180 W) for 3 min (as monitored by TLC). After cooling, ethyl acetate was added and the slurry stirred at room temperature for 10 minutes. The mixture was then vacuum filtered through a sintered glass funnel. The filtrate was evaporated to dryness under reduced pressure and the residue was purified by flash chromatography to isolate the product. In the recycling experiment the residue obtained was washed with acetone and water (3–4 times) and subjected to calcination at 150 °C. The calcinated material could be further utilised in coupling reactions.

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