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A sustainable heterogenized palladium catalyst for Suzuki-Miyaura cross coupling reaction of azaheteroaryl halides in aqueous media

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ABSTRACT

A unique recyclable Pd catalyst ('SiO_2'-NH_2-Pd) for Suzuki-Miyaura coupling reaction of azaheteroaryl halides is developed. The catalytic system is working under mild aqueous condition with low Pd loading and without the use of phosphine ligand. The plausible mechanism is proposed based on the formation of undesired symmetrical biaryl from the coupling reaction of azaheteroaryl chlorides due to the oxidative homocoupling of nucleophilic arylboronic acid. This catalytic system represents an attractive and promising approach for the synthesis of azaheterobiaryls with high product yields. The catalyst has demonstrated an excellent recyclability.

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1. Introduction

The azaheteroaryl units are integral parts of many active motifs; mostly pharmaceuticals and herbicides are utilizing these units as bioisosteres. These units are functional group alternates, which mimic the nature by 'fooling' it in a very subtle way [1,2]. In the field of charge transport materials, fused azaheterocycles exhibit excellent photophysical properties due to their strong skeletal rigidity and large π-conjugation system [3–6]. Latest research advancements hint the huge commercialization demands for azaheteroaryl analogues. For instance, dual P13K/mTOR inhibitors BEZ235, GDC-0980 [7–9], ATP-competitive mTOR inhibitors Torin 2, AZD8055 [10–14] and semiconducting polymers PDTFTh-BT, PDTFPy-BT [15] are reported with sufficient promise in life style applications (Fig. 1).

Furthermore, functionalization of these molecules can be achieved *via* Suzuki-Miyaura cross coupling reaction to induce structural diversity [16]. However, the potential binding ability of the azaheteroaryl substrates to the metal center imposes certain limitations on cross coupling reactions [17–19]. Therefore, Suzuki-Miyaura cross coupling reaction of azaheteroaryl substrates demands extra precaution to overcome such kind of interventions. In many instances, Pd-catalyzed reactions of these moieties are suffering from undesired Pd-traces in the final active ingredients, phosphine contamination, use of expensive ligands, rigorous inert conditions and excess heating with hydrocarbon solvents [20–22]. Moreover, allowed limit for traces of Pd left in the desired compound is very low (<10 ppm) in many applications. In particular, minimizing the residual palladium in a pharmaceutical substance to its tolerable concentration limit involves costly purification techniques [23]. In contrast, extremely low loading of palladium led to agglomeration of active Pd (0) and consequently, terminate the reaction in the halfway. Thus, aligning the environmental and economic rewards to the large scale manufacturing processes and very importantly to manage sustainable advancements, the inherent approach is to develop an appropriate reusable catalytic system in green solvent. Although many reports are available on solid supported heterogenized catalytic systems for Suzuki-Miyaura reaction [20–22,24–27], only very few dealt with coupling of azaheteroaryl substrates in aqueous medium [28]. In this context, we report here a newly developed efficient heterogenized Pd catalyst ('SiO_2'-NH_2-Pd) prepared by replacing one of the coordinated CH_3CN ligands in $[PdCl_2(CH_3CN)_2]$ with amine present in functionalized silica ('SiO_2'-NH_2). It was deduced that the grafting of the catalyst onto the functionalized silica creates a steric congestion around the active Pd center. This, in turn, retards the displacement of second acetonitrile ligand. Moreover, silica is composed of submicron-sized spheres. These spheres possess

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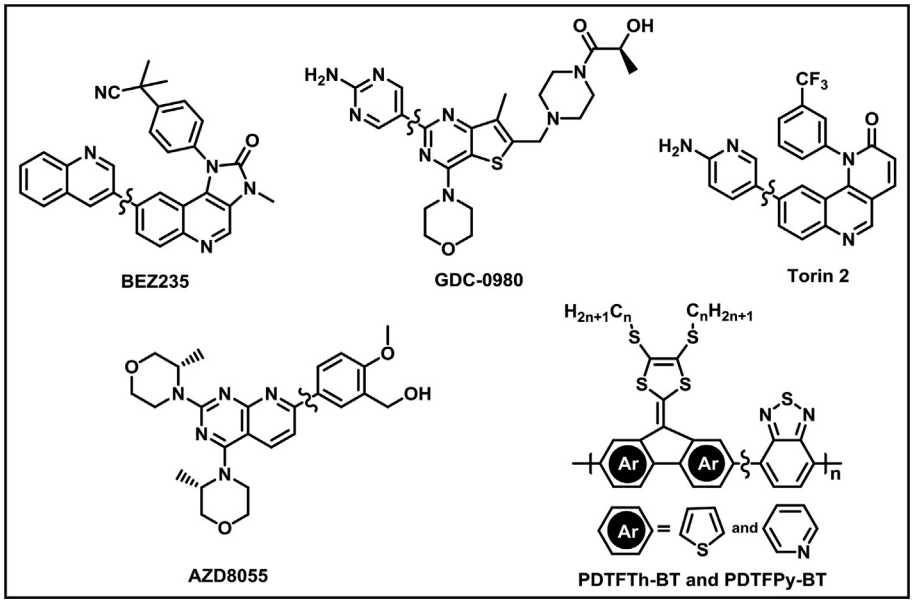


Fig. 1. Commercially important molecules prepared *via* Suzuki-Miyaura cross coupling reaction of azaheteroaryl halides.

uniform pore size, large surface area, large number of silanol groups, and a high chemical and thermal stability. Thus, it is considered as a very promising candidate for catalyst support. This reusable catalyst mediates the Suzuki-Miyaura coupling reaction of azaheteroaryl chlorides as well as bromides in aqueous medium, with Na_2CO_3 as a base, affording excellent conversions. Advantageous feature of this new catalyst is that it does not require typical deaerated and harsh reaction conditions, and expensive ligands for stabilizing the catalyst in aqueous medium. Often these parameters are perceived as critical for Suzuki-Miyaura coupling reactions using Pd catalyst.

2. Experimental section

2.1. Materials

All the reagents used were of chemically pure and analar grade. Commercial grade solvents were distilled according to normal procedures and dried over molecular sieves before use. Silica fumed (0.014 μm, surface area 225 m^2/g) and 3-aminopropyltriethoxysilane were purchased from Sigma Aldrich and used without further purification. [$PdCl_2(CH_3CN)_2$] was prepared according to the literature method [29]. Amine functionalized silica ('SiO_2'−NH_2) was prepared according to the procedure as given below.

Fumed silica (1 g) was dispersed in dry toluene under N_2 atmosphere. To this 3-aminopropyl-1-triethoxysilane (12 mL) was added slowly and refluxed overnight under stirring. The reaction mixture was cooled down to room temperature, 1.5 N HCl was added slowly and stirred for an hour. The mixture was filtered and the resulting solid was washed with acetone several times. The solid was dried at 100 °C under *vacuum* for 6 h to get 'SiO_2'−NH_2.

2.2. Immobilization of [$PdCl_2(CH_3CN)_2$] on to amine functionalized silica ('SiO_2'−NH_2−Pd)

[$PdCl_2(CH_3CN)_2$] (200 mg) and 'SiO_2'−NH_2 (1 g) were stirred at room temperature in dry dichloromethane (20 mL) for 120 h. The mixture was filtered and washed several times with dichloromethane. The obtained solid was subjected to Soxhlet extraction using dichloromethane for two days to ensure leaching out of all unbound Pd complex. The solid was dried at 100 °C under vacuum for 6 h to give a pale yellow powder (1.1 g, 0.061 wt % of Pd).

2.3. Catalyst characterization

The morphology and Pd content of the catalyst were analyzed by JEOL, JSM-6701F field emission scanning electron microscope (FE-SEM). FT-IR spectra were obtained on a Perkin Elmer Spectrum 100 FT-IR spectrophotometer as KBr pellet in the frequency range of 400−4000 cm^{-1}. The BET surface area was measured using ASAP 2020 surface area analyzer. The Pd content in the catalyst was measured by Perkin Elmer Optima 5300 DV inductively coupled plasma optical emission spectrometer (ICP-OES). ^{13}C CP-MAS solid state NMR was recorded using Bruker AVANCE III-500 WB solid state NMR spectrometer equipped with 3.2 mm triple resonance (HXY) solid state probe. Shimadzu GC-2010 gas chromatograph was used to monitor Pd-catalyzed Suzuki-Miyaura cross coupling reaction.

2.4. Procedure for Suzuki-Miyaura cross-coupling reaction

Azaheteroaryl halide (1 mmol), catalyst (0.005−0.05 mol %) and 1 M aq. Na_2CO_3 (1.1 mL) were stirred in a mixture of H_2O-EtOH (1:2, 5 mL). The arylboronic acid (1.1 mmol) was added to the above mixture and stirring was continued for required time at 60 °C. After the requisite time, reaction mixture was diluted with ethyl acetate and the catalyst was separated by centrifugation. The centrifugate was dried over anhydrous sodium sulphate and evaporated. Then the product was analyzed by GC-MS or LC-MS. The solution was concentrated and chromatographed on a silica gel column with *n*-hexane-ethyl acetate (4:1) as the eluting solvent to give the coupled product. The product was confirmed by ^1H and ^{13}C NMR spectral analysis. The used catalyst was washed with water, ethanol and dichloromethane, and dried under vacuum before reuse.

3. Results and discussion

3.1. Catalyst characterization

The newly prepared heterogenized catalyst (Fig. 2) was characterized by using different analytical techniques. SEM images and SEM-EDX data are shown in Figs. S1 and S2 respectively. The morphological changes during the grafting process were evident from SEM images. ICP-OES confirms that the Pd loading is approximately 0.06% per weight of the total silica (5.8×10^{-5} mol/g of Pd on silica). A BET surface area of unfunctionalised silica was 225 m^2/g; while Pd anchored silica catalyst showed a surface area of 179 m^2/g. The expected decrease in the surface area is due to the attachment of Pd complex on to silica *via* silyloxy linkage. The ^{13}C CP-MAS NMR spectrum showed five peaks that reveal the presence of four different aliphatic carbons (Fig. S3). The peak at 13.16 ppm is characteristic of methyl carbon in acetonitrile. The intense signals at 24.64, 27.16, 45.10 and 49.83 ppm were assigned to three carbons of the silyloxy amino propyl moiety. The observed split in the resonances indicated that the carbons were attached to two different forms of silicon *i.e.* Q type [Si(O−)$_4$] and T-type [R_1-*Si*-(O−)$_3$]. During the grafting process, there might be unreacted ethoxy groups in 3-aminopropyl-1-triethoxysilane [30]. The peaks at 45.10 and 49.83 ppm were assigned to the middle and terminal (attached to amino group) carbons respectively. This confirms that the amino propyl group was bound to the support. The FT-IR spectrum indicated the heterogenization of Pd complex on to the silica support (Fig. S4). XPS analysis was carried out for the immobilized heterogenized catalyst to understand the chemical states of surface elements (Fig. S5). The overall XPS survey spectrum showed peaks at 101, 152, 283, 336 and 530 eV which correspond to Si2p, Si2s, C1s, Pd3d and O1s states [Fig. S5 (a)]. Gaussian−Lorentzian peak shape curve fitting was used to find the shift in the peak. Prior to this, a Shirley baseline correction was made [31]. The binding energy values of O1s and Pd3p are very close to each other and thereby a merged peak was observed at *ca.* 531 eV. Gaussian−Lorentzian curve fitting of this spectrum gave two peaks at 530.4 and 532.8 eV which were due to O1s and Pd3p respectively [32]. The broad Si2p spectrum was deconvoluted into two peaks with the binding energies of 101.1 and 103.8 eV which respectively confirmed the presence of Si−O and Si−C bonds [33,34]. Similarly, deconvolution of Pd3d spectrum furnished four peaks. The deconvoluted peaks with binding energy values at 336.4 and 341.6 eV clearly authenticated the presence of Pd^{2+} [35]. In addition, a less intense Pd^0 peaks were also identified at 334.2 and 339.1 eV [36]. TEM analysis was carried out to have clear vision on the particle size of Pd catalyst. The magnified image showed that the Pd complexes were well dispersed and uniformly decorated all over the surface of SiO_2 solid support. The ultrafine Pd particles with narrow size range were recognized by the 20 and 10 nm bar scale images and particle size distribution graph (Fig. 3). The particle size distribution was ranging from 1.2 to 2.0 nm and the mean diameter of Pd particle was found to be *ca.* 1.6 nm. Interestingly, no free Pd was identified in the background. It evidenced the strong and complete attachment of nano Pd complex onto the SiO_2 surface. The powder XRD pattern of the catalyst showed a broad peak at $2\theta = 22^\circ$, which indicated low crystalline or amorphous nature of the catalyst (Fig. S5).

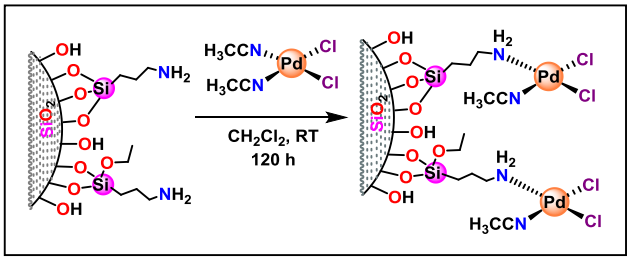


Fig. 2. Preparation of 'SiO_2'−NH_2−Pd.

3.2. Optimization of Suzuki-Miyaura cross coupling reaction of azaheteroaryl halides

To attain the flawless experimental conditions, the impact of various bases, quantity of catalyst and suitable solvent has been studied utilizing 5-bromopyrimidine and naphthalenen-2-boronic acid. Water has been opted as solvent from the economic and green chemistry point of view. Since most of the azaheteroaryl halides possess poor solubility in water, we decided to introduce water-organic solvent mixture to improve the solubility of these substrates. Initially, we screened different combination of solvent mixtures to identify the suitable solvent for optimal catalyst reactivity. Of different solvent mixtures screened, aqueous mixtures of ethanol, DMF and DMSO showed good conversion. The role of water is thought to be of two fold. Firstly, water in the reaction medium is suppose to accelerate the coupling reaction *via* solvolytic transformation of 'SiO_2'-NH_2-Pd^{II} into a more active catalyst 'SiO_2'-NH_2-Pd-OH_2 [37]. Secondly, it facilitates the solubility of base and boronic acid. Thus, water helps the reaction to proceed smoothly even under mild conditions. Initially the common bases like Na_2CO_3, K_2CO_3, NaOH, NaOMe, Et_3N, Cs_2CO_3, K_3PO_4 and CsF were screened using 0.01 mol% of heterogenized catalyst at 60 °C. The NaOH and NaOMe have shown lower conversion under the same reaction conditions as they are prone to compete for aromatic nucleophilic substitution reaction. Noticeably 1.5 equiv. of Na_2CO_3 or K_2CO_3 was found to be more persuasive as it showed good conversion within short span of time. However counter ions were of not much influential, while the amount of base is important. The economic concerns justified the use of Na_2CO_3 as base for all the further studies. We observed homocoupling of boronic acid (~10%) when we used 0.01 mol% of catalyst and 1.5 equiv. of base. The highest level of conversion was realized, when 1.1:1.1:0.00005 equiv. of boronic acid, base and catalyst were used at slightly elevated temperature (60 °C) (Table 1, entry 14). The 1:2 ratio of water and ethanol mixture has given promising conversion rates. It has been noted that the presence of water in the reaction medium is most important.

3.3. Suzuki-Miyaura cross coupling reaction of azaheteroaryl bromides

The scope and limitations of this catalytic system for various azaheteroaryl bromides were investigated (Table 2). The previous reports indicated that the position of bromide on the azaheteroaromatic ring influences the efficiency of the coupling reaction [38–40]. It is worth to mention that coupling of 5-bromo-2-nitro pyridine with naphthalene-2-boronic acid led to desired product in good yield (80%) after 8 h at 60 °C (Table 2, entry 1). 5-Bromonicotinic acid afforded coupled product in excellent yield (84%) with the use of 3 equiv. of base (Table 2, entry 2). The C−C coupling reaction of 2-bromonicotinic acid with phenylboronic acid formed the desired heterobiaryl product in good conversion (Table 2, entry 3) which is superior to that of two step cobalt-catalyzed arylation of nicotinic acid [40a,41]. 2-Bromo pyridine reacted with phenylboronic acid or 4-methylphenylboronic acid to afford corresponding coupled product with significant conversion (Table 2, entries 4 and 5). The conversion is better than that obtained from Pd-catalyzed Suzuki reaction of heteroaryl

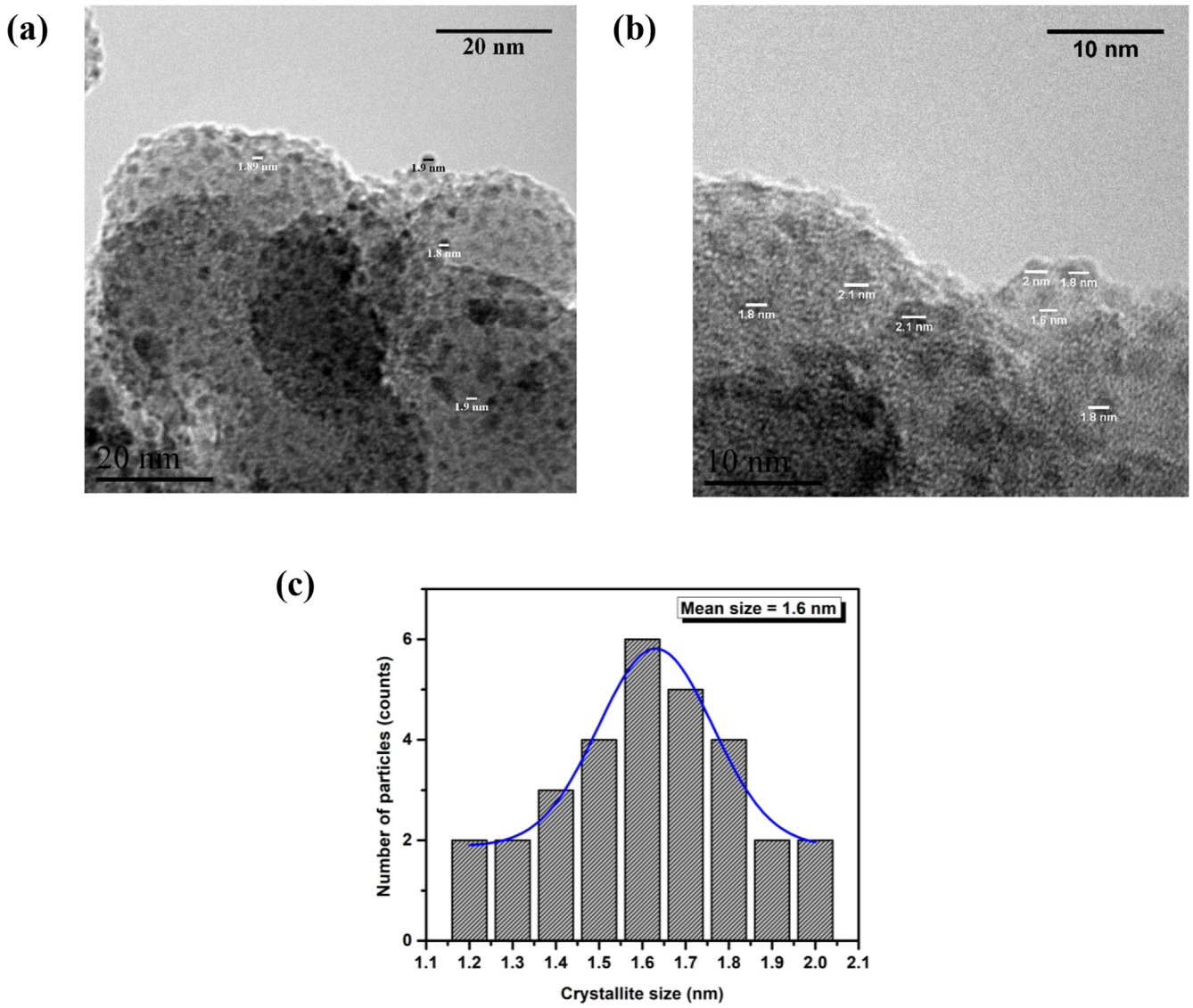
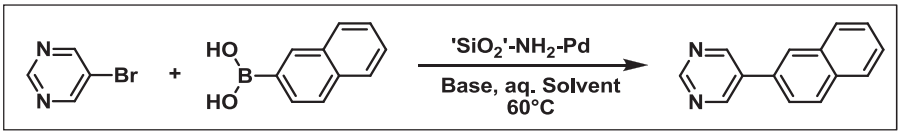


Fig. 3. TEM images of 'SiO_2'–NH_2–Pd with (a) 20 nm, (b) 10 nm magnifications and (c) the corresponding crystallite size distribution of Pd nano complex.

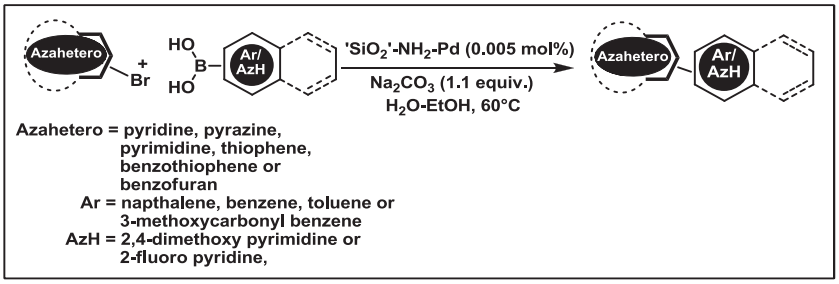
Table 1
Optimization of reaction conditions.[a]



Entry	Solvent	NBA (equiv.)	Base	Base (equiv.)	Catalyst (mol%)	Time (h)	Conv.[b] (%)
1	H_2O-CH_3CN	1.5	Na_2CO_3	1.5	0.01	2	60
2	H_2O-THF	1.5	Na_2CO_3	1.5	0.01	2	60
3	H_2O-Dioxane	1.5	Na_2CO_3	1.5	0.01	2	65
4	H_2O-DMF	1.5	Na_2CO_3	1.5	0.01	2	75
5	H_2O-DMSO	1.5	Na_2CO_3	1.5	0.01	2	79
6	H_2O-C_2H_5OH	1.5	Na_2CO_3	1.5	0.01	2	89
7	H_2O-C_2H_5OH	1.5	K_2CO_3	1.5	0.01	2	85
8	H_2O-C_2H_5OH	1.5	NaOH	1.5	0.01	4	80
9	H_2O-C_2H_5OH	1.5	Cs_2CO_3	1.5	0.01	5	84
10	H_2O-C_2H_5OH	1.5	K_3PO_4	1.5	0.01	4	81
11	H_2O-C_2H_5OH	1.5	NaOMe	1.5	0.01	3	75
13	H_2O-C_2H_5OH	1.5	CsF	1.5	0.01	5	80
14	H_2O-C_2H_5OH	1.1	Na_2CO_3	1.1	0.005	2	90

[a] 5-Bromopyrimidine (1 mmol), 'SiO_2'-NH_2-Pd, aq. solvent (5 mL), 60 °C, NBA = Naphthalenen-2-boronic acid.
[b] Determined by LC-MS.

Table 2
Suzuki-Miyaura cross coupling reaction of azaheteroaryl bromides.[a]



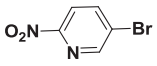
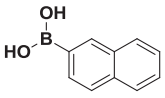
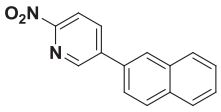
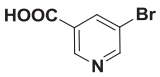
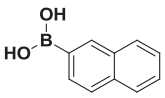
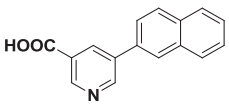
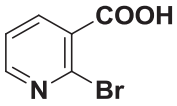
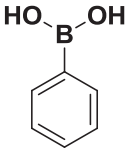
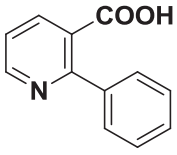
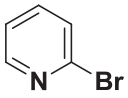
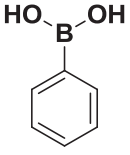
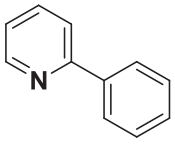
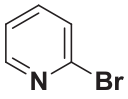
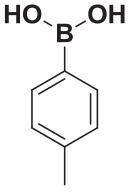
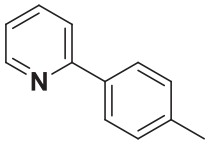
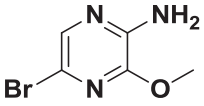
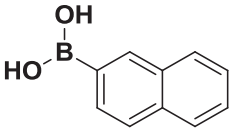
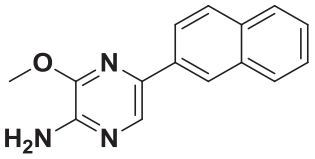
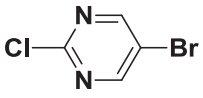
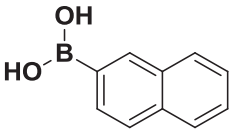
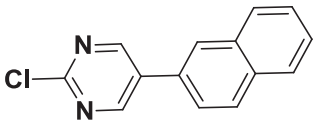
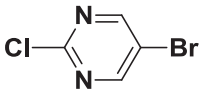
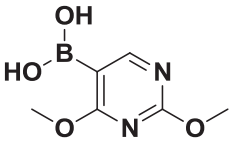
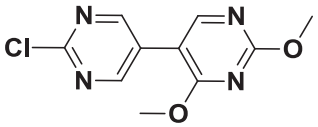
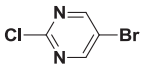
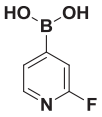
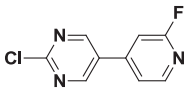
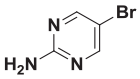
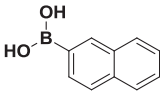
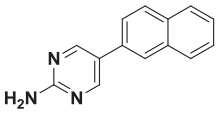
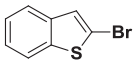
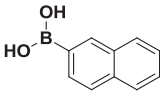
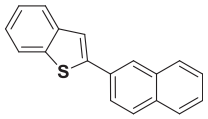
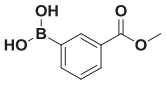
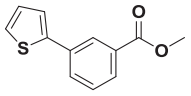
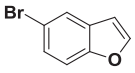
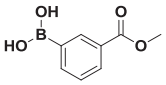
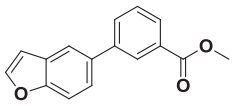
Entry	Ar–Br	Ar'–B(OH)$_2$	Ar–Ar'	Time (h)	Conv. (Yield[b]) (%)	TON	TOF (h^{-1})
1				8	87 (80)	17400	2175
2[c]				5	90 (84)	18000	3600
3 [54,55]				6	87	17400	2900
4 [56,57]				5	86 (77)	17200	3440
5 [58–60]				8	74 (69)	14800	1850
6				6	92 (81)	18400	3067
7				5	96	19200	3840
8				9	92 (87)	18400	2044

Table 2 (*continued*)

Entry	Ar–Br	Ar'–B(OH)$_2$	Ar–Ar'	Time (h)	Conv. (Yield[b]) (%)	TON	TOF (h^{-1})
9				9	90 (78)	18000	2000
10				10	66 (62)	13200	1320
11 [61–68]				7	92	18400	2629
12 [69,70]				12	82 (80)	16400	1367
13				9	93	18600	2067

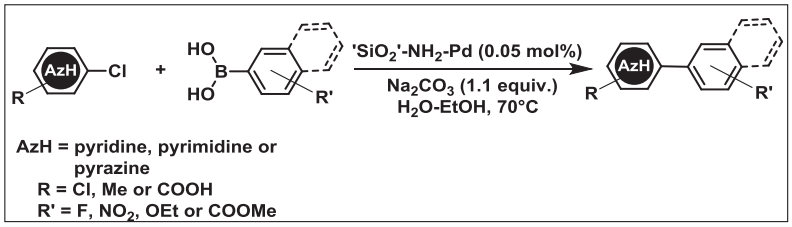
[a] Reaction conditions: Azaheteroaryl bromide (1 equiv.), arylboronic acid (1.1 equiv.), 'SiO_2'-NH_2-Pd (0.005 mol%), Na_2CO_3 (1.1 equiv.), H_2O-C_2H_5OH (1:2) mixture (5 mL).
[b] Isolated yield.
[c] Na_2CO_3, (3 equiv.).

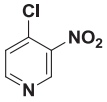
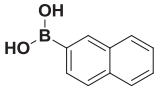
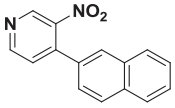
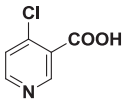
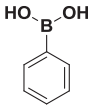
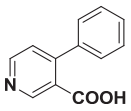
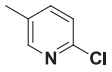
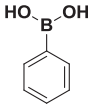
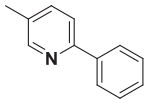
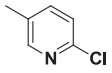
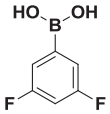
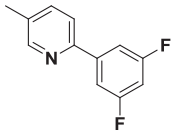
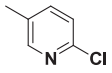
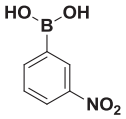
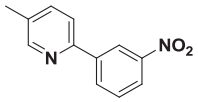
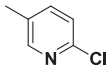
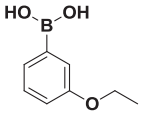
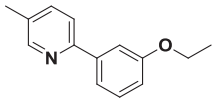
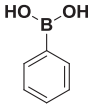
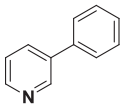
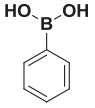
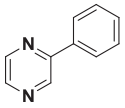
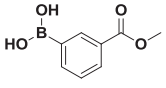
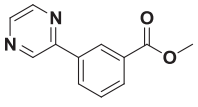
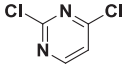
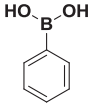
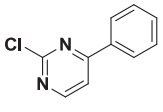
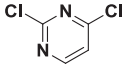
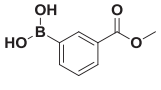
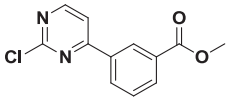
fluorosulfates [42–46]. Generally, *o*-amino group in the azaheteroaryl halides is protected prior to the Pd-catalyzed coupling reaction in order to deactivate the nitrogen atom towards complexation process with Pd [47]. In this regard, 5-bromo-3-methoxypyrazin-2-amine was examined as a substrate, the conversion was essentially quantitative (92%), suggesting that oxidative addition is favored over complexation (Table 2, entry 6). The reaction of 5-bromo-2-chloropyrimidine with aryl or heteroarylboronic acids produced corresponding biaryl products without undergoing coupling at chloro position (Table 2, entries 7, 8 and 9). This clearly indicates the chemoselective nature of 'SiO_2'-NH_2-Pd. Coupling of 5-bromo-2-amino pyrimidine was expected to be problematic, nonetheless underwent complete conversion under optimized reaction conditions (Table 2, entry 10). The catalyst was tested for the coupling of sulphur and oxygen containing heteroaromatic bromides. Notoriously, sulphur atom in the substrates was known to poison the catalyst [48]. But, in the present case, 2-bromobenzothiophene and 2-bromothiophene demonstrated high conversion (Table 2, entries 11 and 12); delightfully, the present catalyst is better than palladacycles derived from phosphinamide [49–58]. Electron rich 5-bromobenzofuran readily reacted with 3-(methoxycarbonyl) pheylboronic acid to produce the corresponding heterocyclic biaryl product in good conversion (Table 2, entry 13). The reaction performed slightly on larger scale (2 g) proved that this reaction can be scaled up without compromising the yield, which revealed the possibility of application of 'SiO_2'-NH_2-Pd in industries.

3.4. Suzuki-Miyaura cross coupling reaction of azaheteroaryl chlorides

The plethora of commercially available azaheteroaryl chlorides deserved to be forerunner starting material for Suzuki-Miyaura coupling partners. The high C–Cl bond strength makes their activation difficult. In the recent past, more efficient coupling reactions involving azaheterocyclic substrates were performed in water or in water-containing solvent mixtures [59–65]. Most of the prominent catalysts display significant reactivity for the coupling of deactivated azaheteroaryl chlorides, while a relatively high catalyst loading and high temperature are often required to attain satisfactory results [66]. Such harsh reaction conditions leading a way to change in stereo chemistry, functional group intolerance, competitive homocoupling of boronic acid, trimerization of boronic acid, undesired aromatic nucleophilic substitution, protodeboronation and protodehalogenation [67]. Considering these facts in mind, reaction conditions were optimized for the coupling of 4-chloro-3-nitro pyridine with naphthalene-2-boronic acid in the presence of 'SiO_2'-NH_2-Pd. When 0.05 mol % of the catalyst was introduced, the reaction was completed in 5 h at 120 °C. The black particles were witnessed, which might be due to the leaching out of reduced Pd. The above observation suggests that new catalyst has limited stability at high temperature. When the reaction temperature was reduced to 70 °C, complete conversion was achieved in 11 h; advantageously no black particles were observed. The scope was extended to study the generality of the new catalyst for cross coupling of azaheteroaryl chlorides under optimized conditions. The chlorides of pyridine, pyrazine and pyrimidine moieties were tested. 4-chloro-3-nitro pyridine was coupled with naphthalene-2-boronic acid to obtain coupled product with 84% conversion in 11 h (Table 3, entry 1). It is evident that electron withdrawing group in the *ortho* position to chloride enhances the C–Cl bond polarization and helps the oxidative addition to proceed smoothly. Nicotinic acids having chloride at different positions were tested using different boronic acids as coupling partners. Coupling reaction of 4-chloro nicotinic acid with phenylboronic acid gave the best conversion of 90% using 3 equiv. of base (Table 3, entry 2) [68]. The electron withdrawing groups on boronic acid led to lower conversion even after prolonged reaction time (Table 3, entries 3–5) [69–71]. This lower conversion can be ascribed to a lower nucleophilicity of the coupling partner due to the presence of the electron withdrawing group that deactivates the polarization of C–B bond and retards transmetalation of the arylboronic acid. Whereas boronic acid containing ethoxy group afforded the coupled product

Table 3
Suzuki-Miyaura cross coupling reaction of azaheteroaryl chlorides.[a]



Entry	Ar–Cl	Ar'–B(OH)$_2$	Ar–Ar'	Time (h)	Conv./(Yield[b]) (%)	TON	TOF (h^{-1})
1				11	84 (78)	1680	153
2 [68]				8	90 (85)	1800	225
3 [37,69]				13	75 (69)	1500	115
4				12	34 (31)	680	57
5 [70,71]				15	14 (12)	280	19
6				10	72 (68)	1440	144
7 [72–78]				13	15 (13)	300	23
8[c] [79,80]				7	90	1800	257
9[c]				10	88	1760	176
10[c] [81,82]				10	92 (87)	1840	184
11[c]				8	87	1740	218

[a] Reaction conditions: Azaheteroaryl chloride (1 equiv.), arylboronic acid (1.1 equiv.), 'SiO$_2$'-NH$_2$-Pd (0.05 mol%), Na_2CO_3 (1.1 equiv.), H_2O-C_2H_5OH (1:2) mixture (5 mL), 70 °C.
[b] Isolated yield.
[c] TBAB (1 equiv.) used.

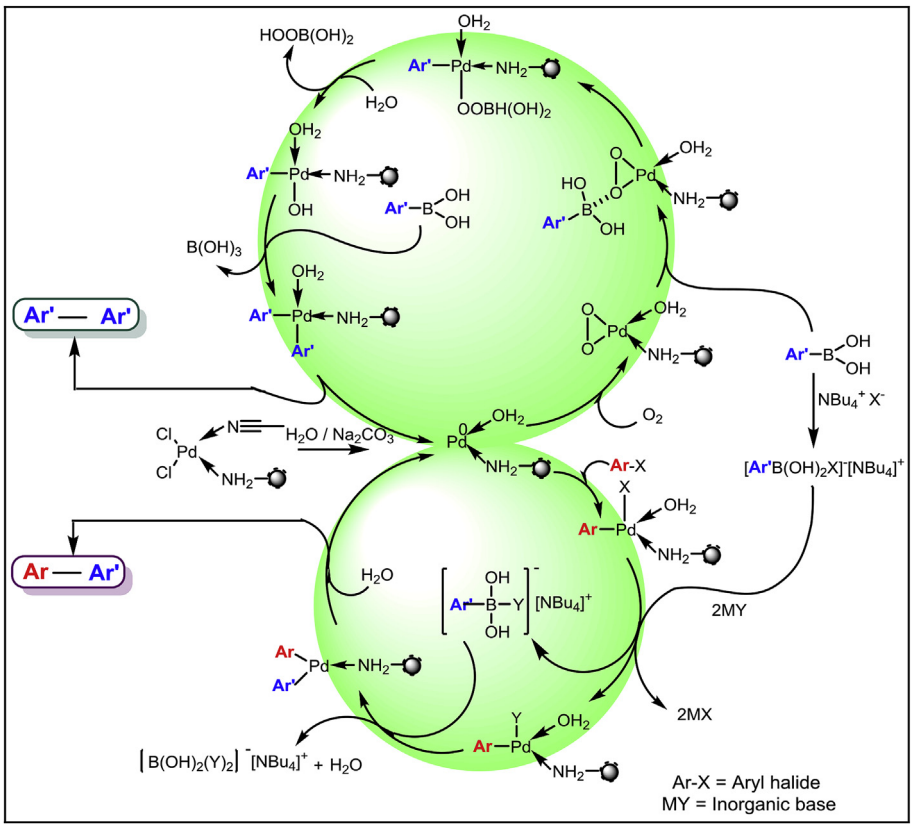


Fig. 4. Proposed mechanism for Suzuki-Miyaura cross coupling reaction of azaheteroaryl chlorides.

in moderate yield (68%) (Table 3, entry 6). The coupling reaction of 3-chloropyridine with phenylboronic acid resulted 15% of desired product and remaining 80% was identified as undesired symmetrical biaryl resulted from homocoupling of boronic acid (Table 3, entry 7) [72–78]. To address this issue, one equiv. of tetrabutylammonium bromide (TBAB) was introduced to form a stable complex $[ArB(OH)_2X]^-[Bu_4N]^+$ between boronic acid and the quaternary ammonium salt [79], which led to the desired coupled product formation after extended reaction hours. However, cross coupling reaction of 3-chloropyridine with phenylboronic acid was not satisfactory even in the presence of TBAB. In presence of TBAB and the heterogenized catalyst, highly electron-deficient 2-chloropyrazine gave cheering conversion (Table 3, entry 8) which is higher than that observed in the palladium-catalyzed ligand-free cross coupling reaction of heteroaryl chlorides with N-methyliminodiacetic acid (MIDA) boronates [80,81]. Usually, biologically important pyrimidines are detrimental to the catalytic activity of Pd. In contrary, 2,4-dichloro pyrimidine selectively underwent coupling reaction smoothly to give 4-coupled product (Table 3, entries 10 and 11) [82,83]. The present catalytic system is compatible to functional groups such as ester, ether and nitro.

3.5. Proposed mechanism

The plausible mechanism is proposed based on the formation of undesired symmetrical biaryl from the Suzuki-Miyaura reaction of azaheteroaryl chlorides due to the oxidative homocoupling of nucleophilic arylboronic acid (Fig. 4).

To illustrate the theoretical possibilities, a rational mechanism was proposed. Initially the catalyst is converted into an aqua complex under basic aqueous medium. While the high degree of C–Cl bond strength restricts the rapid oxidative addition of azaheteroaryl chloride, Pd aqua species is transformed into peroxo complex *in situ* by availing oxygen from the air [84]. Then one of the oxygen atoms in the Pd peroxo complex interacts with the oxophilic boron atom of the arylboronic acid, which provides a way to impetuous reaction under stoichiometric concentration of $ArB(OH)_2$. A subsequent transmetalation by a second molecule of $ArB(OH)_2$, followed by reductive elimination generates undesired symmetrical biaryl product. To bypass this anomaly, at first the arylboronic acid was treated with TBAB to form an adduct. This would make the boron atom less oxophilic and allowed to react with less reactive azaheteroaryl chlorides. Secondly, prior to the catalyst addition, the argon gas was bubbled into the reaction mixture to drive out dissolved oxygen from the medium. This action favors the Pd insertion (oxidative addition) into azaheteroaryl chloride over peroxo complex formation. A shift in the peak in the ^{11}B NMR spectrum proved the formation of boronic acid adduct with TBAB (Fig. S7).

3.6. Heterogeneous nature of the catalyst

The split test was performed during the coupling of 2-chloro-5-bromo pyrimidine with phenylboronic acid to prove the durability of the heterogenized catalyst (Fig. 5). The portion of reaction mixture at approximately 50% conversion was filtered and the filtrate was allowed to react further without the catalyst. After extended period, both the reactions were monitored. The filtrate showed no further conversion whereas original reaction mixture proceeded to completion, which showed that no traces of Pd metal leach out from the support into the reaction medium. Further to confirm these results, half of the filtrate was again treated with recovered Pd catalyst and the reaction was monitored. The reaction started to proceed as soon as the recovered catalyst was added, which clearly indicates that the recovered Pd catalyst is

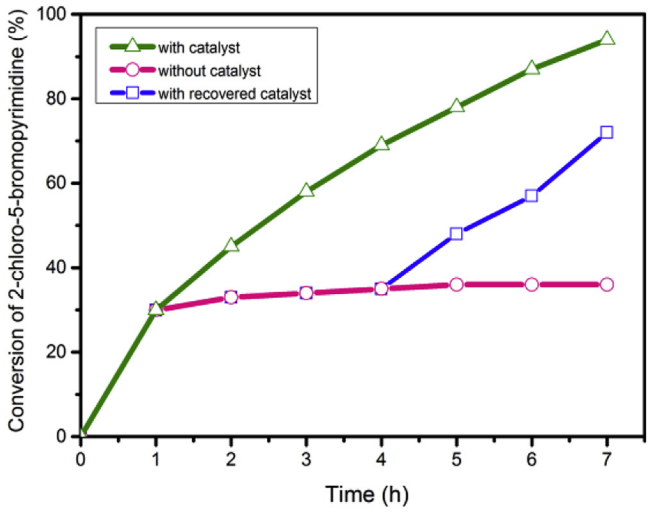


Fig. 5. Split test for coupling reaction of 2-chloro-5-bromo pyrimidine with phenylboronic acid.

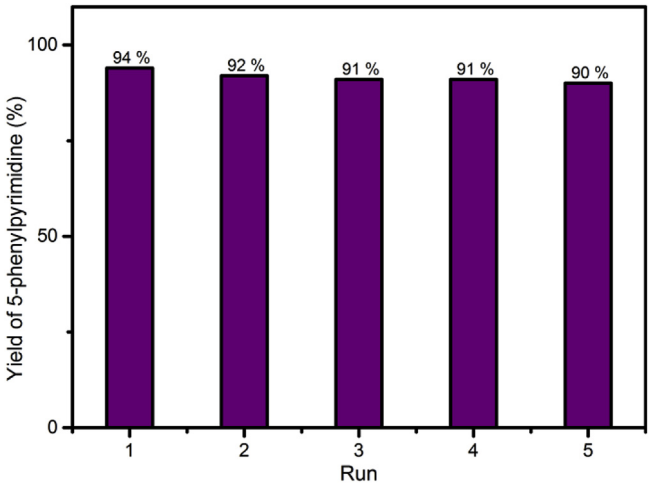


Fig. 6. Reusability of 'SiO_2'-NH_2-Pd for the coupling reaction of 5-bromopyrimidine with phenylboronic acid.

active.

3.7. Reusability

The catalyst was reused five times for the coupling reaction of 5-bromo pyrimidine with 2-naphthalene boronic acid without significant loss of catalytic activity (Fig. 6). At 5th run the conversion remained at 90%, indicating that the 'SiO_2'-NH_2-Pd has an ability to consider as a reusable catalyst. Even though reusability test showed a decrease in activity after the first run, the activity remains good. The ICP-OES of recovered catalyst confirmed that there was no much variation in the Pd content. The IR spectrum of recovered catalyst was recorded and compared with the fresh catalyst. It demonstrated that the IR spectrum of the recovered catalyst matched well with the fresh catalyst except C≡N stretching frequency (Fig. S8).

4. Conclusion

In conclusion, we have demonstrated that a new recyclable 'SiO_2'-NH_2-Pd catalyst for Suzuki-Miyaura coupling reaction of heteroaryl halides can be synthesized from [$PdCl_2(CH_3CN)_2$]. This is an efficient and mild protocol for the Suzuki-Miyaura cross coupling reaction of azaheteroaryl bromides and azaheteroaryl chlorides with a diverse range of arylboronic acids. It also offers an efficient system for mediating the reaction in aqueous medium under mild conditions with low Pd loading; a reaction of appreciable interest in the present scenario. The catalyst was reused up to five runs without any substantial lack in the reactivity. High product yields (89–99% isolated yields) were observed. Undoubtedly, these results will advance the scope of the Suzuki-Miyaura cross coupling reactions in the industrial arena and add tremendous value to the process research.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jorganchem.2018.02.030.

References

[1] N.A. Meanwell, Synopsis of some recent tactical application of bioisosteres in drug design, J. Med. Chem. 54 (2011) 2529–2591.
[2] J.A. Joule, K. Mills, G.F. Smith, Heterocyclic Chemistry, third ed., Chapman & Hall, London, UK, 1995.
[3] V. Balzani, A. Credi, M. Venturi, Molecular Devices and Machines: a Journey into the Nano World, Wiley-VCH, Weinheim, 2003.
[4] A.C. Grimsdale, K. Müllen, Angew. Chem. Int. Ed. 44 (2005) 5592–5629.
[5] F.J.M. Hoeben, P. Jonkheijm, E.W. Meijer, A.P.H.J. Schenning, Chem. Rev. 105 (2005) 1491–1546.
[6] J. Wu, W. Pisula, K. Müllen, Chem. Rev. 107 (2007) 718–747.
[7] S. Park, N. Chapuis, V. Bardet, J. Tamburini, N. Gallay, L. Willems, Z.A. Knight, K.M. Shokat, N. Azar, F. Viguie, N. Ifrah, F. Dreyfus, P. Mayeux, C. Lacombe, D. Bouscary, Leukemia 22 (2008) 1698–1706.
[8] V. Serra, B. Markman, M. Scaltriti, P.J.A. Eichhorn, V. Valero, M. Guzman, M.L. Botero, E. Llonch, F. Atzori, S. Di Cosimo, M. Maira, C. Garcia-Echeverria, J.L. Parra, J. Arribas, J. Baselga, Canc. Res. 68 (2008) 8022–8030.
[9] D.P. Sutherlin, L. Bao, M. Berry, G. Castanedo, I. Chuckowree, J. Dotson, A. Folks, L. Friedman, R. Goldsmith, J. Gunzner, T. Heffron, J. Lesnick, C. Lewis, S. Mathieu, J. Murray, J. Nonomiya, J. Pang, N. Pegg, W.W. Prior, L. Rouge, L. Salphati, D. Sampath, Q. Tian, V. Tsui, N.C. Wan, S. Wang, B. Wei, C. Wiesmann, P. Wu, B.-Y. Zhu, A. Olivero, J. Med. Chem. 54 (2011) 7579–7587.
[10] Q. Liu, J. Wang, S.A. Kang, C.C. Thoreen, W. Hur, T. Ahmed, D.M. Sabatini, N.S. Gray, J. Med. Chem. 54 (2011) 1473–1480.
[11] D.S. Mortensen, S.M. Perrin-Ninkovic, R. Harris, B.G.S. Lee, G. Shevlin, M. Hickman, G. Khambatta, R.R. Bisonette, K.E. Fultz, S. Sankar, Bioorg. Med. Chem. Lett 21 (2011) 6793–6799.
[12] F. Cohen, P. Bergeron, E. Blackwood, K.K. Bowman, H. Chen, A.G. DiPasquale, J.A. Epler, M.F.T. Koehler, K. Lau, C. Lewis, L. Liu, C.Q. Ly, S. Malek, J. Nonomiya, D.F. Ortwine, Z. Pei, K.D. Robarge, S. Sideris, L. Trinh, T. Truong, J. Wu, X. Zhao, J.P. Lyssikatos, J. Med. Chem. 54 (2011) 3426–3435.
[13] S. Amriou, C. Wang, A.S. Batsanov, M.R. Bryce, D.F. Perepichka, E. Ortí, R. Viruela, J. Vidal-Gancedo, C. Rovira, Chem. Eur J. 12 (2006) 3389–3400.
[14] Y. Hou, G. Long, D. Sui, Y. Cai, X. Wan, A. Yu, Y. Chen, Chem. Commun. 47 (2011) 10401–10403.
[15] D.D. Mysyk, I.F. Perepichka, D.F. Perepichka, M.R. Bryce, A.F. Popov, L.M. Goldenberg, A.J. Moore, J. Org. Chem. 64 (1999) 6937–6950.
[16] R. Jana, T.P. Pathak, M.S. Sigman, Chem. Rev. 111 (2011) 1417–1492.
[17] T. Maegawa, Y. Kitamura, S. Sako, T. Udzu, A. Sakurai, A. Tanaka, Y. Kobayashi, K. Endo, U. Bora, T. Kurita, A. Kozaki, Y. Monguchi, H. Sajiki, Chem. Eur J. 13 (2007) 5937–5943.
[18] S. Li, Y. Lin, J. Cao, S. Zhang, J. Org. Chem. 72 (2007) 4067–4072.
[19] H. Qiu, S.M. Sarkar, D.-H. Lee, M.-J. Jin, Green Chem. 10 (2008) 37–40.
[20] S. Paul, J.H. Clark, Green Chem. 5 (2003) 635–638.
[21] B. Karimi, F. Mansouri, H. Vali, Green Chem. 16 (2014) 2587–2596.
[22] A. Deriblé, C. Diebold, J. Dentzer, R. Gadiou, J.-M. Becht, C. Le Drian, Eur. J. Org Chem. 2014 (2014) 7699–7706.
[23] C.E. Garrett, K. Prasad, Adv. Synth. Catal. 346 (2004) 889–900.

[24] B. Yuan, Y. Pan, Y. Li, B. Yin, H. Jiang, Angew. Chem. Int. Ed. 49 (2010) 4054–4058.
[25] Y. Xu, Z. Zhang, J. Zheng, Q. Du, Y. Li, Appl. Organomet. Chem. 27 (2013) 13–18.
[26] G. Borja, A. Monge-Marcet, R. Pleixats, T. Parella, X. Cattoën, M. Wong Chi Man, Eur. J. Org Chem. 2012 (2012) 3625–3635.
[27] P. Li, L. Wang, L. Zhang, G.-W. Wang, Adv. Synth. Catal. 354 (2012) 1307–1318.
[28] S. Shi, Y. Zhang, Green Chem. 10 (2008) 868–872.
[29] G.K. Anderson, M. Lin, A. Sen, E. Gretz, Bis(Benzonitrile)Dichloro Complexes of Palladium and Platinum, Inorg. Synth., John Wiley & Sons, Inc, 2007, pp. 60–63.
[30] A.R. McDonald, H.P. Dijkstra, B.M.J.M. Suijkerbuijk, G.P.M. van Klink, G. van Koten, Organometallics 28 (2009) 4689–4699.
[31] M. Gopiraman, S. Ganesh Babu, Z. Khatri, W. Kai, Y.A. Kim, M. Endo, R. Karvembu, I.S. Kim, J. Phys. Chem. C 117 (2013) 23582–23596.
[32] D. Zemlyanov, B. Aszalos-Kiss, E. Kleimenov, D. Teschner, S. Zafeiratos, M. Hävecker, A. Knop-Gericke, R. Schlögl, H. Gabasch, W. Unterberger, K. Hayek, B. Klötzer, Surf. Sci. 600 (2006) 983–994.
[33] Y. Zhang, X. He, J. Ouyang, H. Yang, Sci. Rep. 3 (2013) 2948.
[34] T. Grünzel, Y.J. Lee, K. Kuepper, J. Bachmann, Beilstein J. Nanotechnol. 4 (2013) 655–664.
[35] G. Ketteler, D.F. Ogletree, H. Bluhm, H. Liu, E.L.D. Hebenstreit, M. Salmeron, J. Am. Chem. Soc. 127 (2005) 18269–18273.
[36] P. Zhang, Y. Gong, H. Li, Z. Chen, Y. Wang, Nat. Commun. 4 (2013) 1593.
[37] S. Ganesamoorthy, K. Shanmugasundaram, R. Karvembu, J. Mol. Catal. A: Chem. 371 (2013) 118–124.
[38] K.L. Billingsley, K.W. Anderson, S.L. Buchwald, Angew. Chem. Int. Ed. 45 (2006) 3484–3488.
[39] I. Kondolff, H. Doucet, M. Santelli, Synlett 2005 (2005) 2057–2061.
[40] N. Kudo, M. Perseghini, G.C. Fu, Angew. Chem. Int. Ed. 45 (2006) 1282–1284; (a) M.T. DuPriest, C.L. Schmidt, D. Kuzmich, S.B. Williams, J. Org. Chem. 51 (1986) 2021–2023.
[41] K.M. Liu, R. Zhang, X.F. Duan, Org. Biomol. Chem. 14 (2016) 1593–1598.
[42] G.A. Molander, B. Biolatto, Org. Lett. 4 (2002) 1867–1870.
[43] J. Dutta, M.G. Richmond, S. Bhattacharya, Dalton Trans. 44 (2015) 13615–13632.
[44] Z. Xi, B. Liu, W. Chen, J. Org. Chem. 73 (2008) 3954–3957.
[45] X. Rao, C. Liu, Y. Xing, Y. Fu, J. Qiu, Z. Jin, Asian J. Org. Chem. 2 (2013) 514–518.
[46] E. Zhang, J. Tang, S. Li, P. Wu, J.E. Moses, K.B. Sharpless, Chem. Eur J. 22 (2016) 5692–5697.
[47] A.S. Guram, X. Wang, E.E. Bunel, M.M. Faul, R.D. Larsen, M.J. Martinelli, J. Org. Chem. 72 (2007) 5104–5112.
[48] A.S. Guram, A.O. King, J.G. Allen, X. Wang, L.B. Schenkel, J. Chan, E.E. Bunel, M.M. Faul, R.D. Larsen, M.J. Martinelli, P.J. Reider, Org. Lett. 8 (2006) 1787–1789.
[49] X. Zhang, W. Zeng, Y. Yang, H. Huang, Y. Liang, Synlett 24 (2013) 1687–1692.
[50] Y. Uozumi, Y. Nakai, Org. Lett. 4 (2002) 2997–3000.
[51] B. Liégault, D. Lapointe, L. Caron, A. Vlassova, K. Fagnou, J. Org. Chem. 74 (2009) 1826–1834.
[52] S. Tamba, Y. Okubo, S. Tanaka, D. Monguchi, A. Mori, J. Org. Chem. 75 (2010) 6998–7001.
[53] A.B. Bíró, A. Kotschy, Eur. J. Org Chem. 8 (2007) 1364–1368.
[54] S. Tanaka, D. Tanaka, A. Sugie, A. Mori, Tetrahedron Lett. 53 (2012) 1173–1176.
[55] H. Yu, M. Zhang, Y. Li, J. Org. Chem. 78 (2013) 8898–8903.
[56] G.J. Wu, F.S. Han, Y.L. Zhaob, RSC Adv. 5 (2015) 69776–69781.
[57] R. Gerber, O. Blacque, C.M. Frech, Dalton Trans. 40 (2011) 8996–9003.
[58] W. Miao, T.H. Chan, Org. Lett. 5 (2003) 5003–5005.
[59] E.C. Western, J.R. Daft, E.M. Johnson, P.M. Gannett, K.H. Shaughnessy, J. Org. Chem. 68 (2003) 6767–6774.
[60] R.B. DeVasher, L.R. Moore, K.H. Shaughnessy, J. Org. Chem. 69 (2004) 7919–7927.
[61] C.-J. Li, Chem. Rev. 105 (2005) 3095–3166.
[62] P. Capek, R. Pohl, M. Hocek, Org. Biomol. Chem. 4 (2006) 2278–2284.
[63] H.V. Huynh, Y. Han, J.H.H. Ho, G.K. Tan, Organometallics 25 (2006) 3267–3274.
[64] K.H. Shaughnessy, Eur. J. Org Chem. 2006 (2006) 1827–1835.
[65] C. Fleckenstein, S. Roy, Leuthau, H. Plenio, Chem. Commun. (2007) 2870–2872.
[66] C.A. Fleckenstein, H. Plenio, Chem. Eur J. 14 (2008) 4267–4279.
[67] G.A. Molander, N. Ellis, Acc. Chem. Res. 40 (2007) 275–286.
[68] P. Jain, J.T. Slama, L.A. Perez-Haddock, T.F. Walseth, J. Med. Chem. 53 (2010) 7599–7612.
[69] E. Zhang, J. Tang, S. Li, P. Wu, J.E. Moses, K.B. Sharpless, Chem. Eur J. 22 (2016) 5692–5697.
[70] I. Sasaki, L. Vendier, A. Sournia-Saquet, P.G. Lacroix, Eur. J. Inorg. Chem. 2006 (2006) 3294–3302.
[71] R. Garrido, P.S. Hernández-Montes, Á. Gordillo, P. Gómez-Sal, C. López-Mardomingo, E. de Jesús, Organometallics 34 (2015) 1855–1863.
[72] S. Naik, M. Kumaravel, J.T. Mague, M.S. Balakrishna, Dalton Trans. 43 (2014) 1082–1095.
[73] S.D. Ramgren, L. Hie, Y. Ye, N.K. Garg, Org. Lett. 15 (2013) 3950–3953.
[74] S. Yanagisawa, K. Ueda, T. Taniguchi, K. Itami, Org. Lett. 10 (2008) 4673–4676.
[75] T. Wanga, L. Liu, K. Xu, H. Xie, H. Shena, W.X. Zhao, RSC Adv. 6 (2016) 100690–100695.
[76] S. Ando, H. Matsunaga, T. Ishizuka, J. Org. Chem. 82 (2017) 1266–1272.
[77] A. Shen, Y.C. Hu, T.T. Liu, C. Ni, Y. Luo, Y.C. Cao, Tetrahedron Lett. 57 (2016) 2055–2058.
[78] T. Wang, H. Xie, L. Liu, W.X. Zhao, J. Organomet. Chem. 804 (2016) 73–79.
[79] D. Badone, M. Baroni, R. Cardamone, A. Ielmini, U. Guzzi, J. Org. Chem. 62 (1997) 7170–7173.
[80] H. Peng, Y.Q. Chen, S.L. Mao, Y.X. Pi, Y. Chen, Z.Y. Lian, T. Meng, S.H. Liu, G.A. Yu, Org. Biomol. Chem. 12 (2014) 6944–6952.
[81] C. Liu, X. Li, C. Liu, X. Wang, J. Qiu, RSC Adv. 5 (2015) 54312–54315.
[82] T. Taldone, Y. Kang, H.J. Patel, M.R. Patel, P.D. Patel, A. Rodina, Y. Patel, A. Gozman, R. Maharaj, C.C. Clement, A. Lu, J.C. Young, G. Chiosis, J. Med. Chem. 57 (2014) 1208–1224.
[83] M.L. Brown, W. Aaron, R.J. Austin, A. Chong, T. Huang, B. Jiang, J.A. Kaizerman, G. Lee, B.S. Lucas, D.L. McMinn, J. Orf, M. Rong, M.M. Toteva, G. Xu, Q. Ye, W. Zhong, M.R. DeGraffenreid, D. Wickramasinghe, J.P. Powers, R. Hungate, M.G. Johnson, Bioorg. Med. Chem. Lett 21 (2011) 5206–5209.
[84] C. Adamo, C. Amatore, I. Ciofini, A. Jutand, H. Lakmini, J. Am. Chem. Soc. 128 (2006) 6829–6836.