Pd-loaded NaY zeolite as a highly active catalyst for ligandless Suzuki–Miyaura reactions of aryl halides at low Pd loadings under aerobic conditions

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Abstract

The Pd(NH$_3$)$_4$$^{2+}$-loaded NaY zeolite was found to be a highly active catalyst precursor for Suzuki–Miyaura (SM) reactions of aryl bromides and aryl chlorides at low Pd concentrations in air. Aryl bromides and arylboronic acids can couple effectively both in pure water and in *N,N*-dimethylacetamide/water mixtures (1/1) within minutes with turnover frequencies (TOF) up to $4 \times 10^5 \, h^{-1}$. The presence of a minute amount of water was crucial for the success of the reaction with chloroarenes. The excess amounts of as-received zeolite provided the necessary water for the reaction. The results suggest that the combined use of the water-zeolite system may have a synergistic effect in the reaction.
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1. Introduction

Substituted biaryls are important intermediates for the production of biologically active substances such as pharmaceuticals and herbicides and engineering materials such as conducting materials and liquid crystals [1–7]. The palladium catalyzed cross-coupling reaction of aryl halides with arylboronic acids (Suzuki–Miyaura (SM) reaction) is currently the most versatile method for the synthesis of these chemicals.

Numerous studies have contributed towards improving the efficiency of this reaction in the last decade. Presently, high turnover numbers (TON) can be achieved even with the electron rich chloroarenes by the catalysis of variety of Pd complexes or Pd-ligand combinations under homogeneous and relatively mild reaction conditions [8–17]. Nevertheless, the pharmaceutical industry in particular is highly reluctant to employ the Pd catalyzed processes since there is always a risk of contamination of the end products by the transition metal and ligand residues. Therefore, effective methods need to be developed for the recovery of the catalyst after the reaction. Numerous reports have proposed techniques which involve the use of heterogeneous Pd catalysts on a variety of supporting materials for the effective recovery of Pd [18].

Ligand-free Pd on widely available active carbon or inorganic supports appears to be the most suitable catalyst for the industrial applications of Pd catalyzed reactions. Zeolites are good candidates for inorganic support materials since they possess large specific surface areas and contain well-defined micropores and mesopores for the encapsulation of the Pd species. Furthermore, the presence of inherent negative sites may lead to better dispersion of the cationic Pd units by ion exchange. Hence, Pd-loaded zeolites were demonstrated to be highly active catalysts for the cross coupling of alkenyl halides with arylboronic acids [19], α-arylation of malonate [20], Heck [21], amination [22], Suzuki–Miyaura [23–25], and Sonogashira [26] reactions.

We reported previously that Pd-loaded NaY zeolites were highly active and re-usable catalysts in Suzuki–Miyaura cross-coupling reactions of aryl bromides at room temperature [23,24]. Nevertheless, the method required high Pd loadings (typically 2.5 mol%) for effective coupling. Also, the activities were not satisfactory for industrially more important aryl chloride reagents under the experimental conditions tested. Therefore, we aimed at extending the study to determine limits of the catalyst for SM coupling of wide range of aryl bromides and chlorides

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with arylboronic acids. We present in this paper that the catalyst functioned very effectively, affording SM reactions with excellent TONs and turnover frequencies (TOF).

2. Experimental

2.1. Catalyst preparation

Pd(NH$_3$)$_4$$^{2+}$ was introduced into the NaY zeolite (Zeolyst International, #CBV100, SiO$_2$/Al$_2$O$_3$ mol ratio: 5.1) by ion exchange using 200 mL, 0.1 M NH$_4$OH solution of Pd(NH$_3$)$_4$Cl$_2$ for 2 of zeolite in as-received form, corresponding, approximately, to 0.2 wt% of Pd on the zeolite. The solution mixture was stirred for 2 h at room temperature, filtered and washed with water until no Cl$^-$ ion was detectable within the filtrate. The solid was left under ambient conditions to eliminate its excess water content since the application of higher temperatures and high vacuum were observed to result in a less active catalyst. In order to analyze the palladium content of the zeolite, Pd(II)-NaY was dissolved in a mixture of concentrated HBF$_4$, HNO$_3$, and HCl (3:3:2) in a Teflon reactor by heating at 180 °C and subjecting it to 600–650 W microwave power.

2.2. Typical reaction procedure

2.2.1. Reactions with aryl bromides

Phenylboronic acid used for the reactions with aryl bromides was a Fluka's reagent. 4-Methoxyphenylboronic acid reagent was supplied from Merck, and 4-acetylphenylboronic acid and 4-(trifluoromethyl)phenylboronic acid reagents were supplied from Alfa Aesar.

Aryl bromide (10 mmol), boronic acid (12 mmol), hexadecane (as an internal standard), Na$_2$CO$_3$ (20 mmol), N,N-dimethylacetamide (DMA)/water (1/1, 20 mL), catalyst and zeolite (1 g overall) were introduced into a two-necked round bottomed flask which was equipped with a condenser and a septum and heated at 100 °C in a preheated oil bath while being stirred vigorously by a magnetic stirrer under ambient atmosphere. Small aliquots were periodically withdrawn by a syringe from these samples during the reaction, diluted in ethyl acetate, dried by MgSO$_4$ and analyzed by gas chromatography (GC). The course of the reaction was followed until no further aryl halide conversion was observed. At the end of the reaction, the mixture was cooled to room temperature, filtered through a 0.2 μm membrane filter and the solid was thoroughly washed successively with ethyl acetate and water.

For the reactions performed in pure water (20 mL), the filtrate was extracted with ethyl acetate and the internal standard was added to the extract.

Microwave heated reactions were performed in a septum sealed 10 mL glass tube using a CEM discoverS system.

Both yield and conversion percentages are reported with respect to the aryl halide. The yields are presented as either isolated products or gas chromatography yields. Conversions were determined by GC. GC data were calculated using response factors determined with authentic samples with respect to the internal standard.

Products were isolated by column chromatography and analyzed by GC, GC/MS and NMR techniques. Most of the products were compounds which were well-known and well-reported in the literature. The physical characteristics and spectroscopic data of these products are consistent with those previously reported.

Others: 2-Amino-5-methylbiphenyl: Hexane/ethyl acetate (12/1); yellow oil; purity: 98%; (400 MHz, CDCl$_3$) δ: 7.49–7.43 (m, 4H), 7.37–7.33 (m, 1H), 7.01–6.98 (m, 2H), 6.73 (d, 1H, J = 7.6 Hz), 3.71 (broad, 2H, NH$_2$), 2.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 140.8, 139.9, 131.2, 129.3, 129.2, 129.0, 128.3, 128.2, 127.3, 116.2, 20.7; MS: 183 (M$^+$), 167. The ^{1}H NMR is almost in agreement with the one reported of this compound [27].

4-Amino-3-methylbiphenyl: Hexane/CH$_2$Cl$_2$ (1/2); yellow oil; purity: 99%; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.59–7.26 (m, 7H), 6.78 (d, 1H, J = 8.0 Hz), 3.67 (broad, 2H, NH$_2$), 2.27 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 144.1, 141.6, 132.1, 129.5, 128.9, 126.7, 126.4, 125.9, 122.9, 115.7, 17.8; MS: 183 (M$^+$), 165.

2-Amino-3,5-dimethylbiphenyl: Hexane/CH$_2$Cl$_2$ (17/1); yellow oil; purity: 96%; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.46–7.26 (m, 5H), 6.93 (d, 1H, J = 1.5 Hz), 6.86 (d, 1H, J = 1.5 Hz), 3.64 (broad, 2H, NH$_2$), 2.28 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 140.2, 139.0, 130.7, 129.5, 129.0, 129.0, 128.1, 127.7, 127.3, 123.1, 20.6, 18.1; MS: 197 (M$^+$), 182. The ^{1}H NMR is almost in agreement with the one reported of this compound [28].

2.2.2. Reactions with aryl chlorides

Merck's arylboronic acid reagents were used for the reactions with aryl chlorides. The catalyst exhibited less activity for the reactions with Fluka's and Aldrich's phenylboronic acid reagents.

Aryl bromide (1 mmol), boronic acid (2 mmol), Bu$_4$NBr (1 mmol), hexadecane (as an internal standard), NaOEt (2 mmol), DMA (10 mL), catalyst (0.1 mol% Pd) and zeolite (3 g overall) were introduced into a two-necked round bottomed flask which was equipped with a condenser and a septum and heated at a prescribed temperature in a preheated oil bath while being stirred vigorously by a magnetic stirrer under air.

3. Results and discussion

3.1. Suzuki–Miyaura reactions of aryl bromides in water-polar aprotic solvent mixture

The catalyst was prepared through introduction of Pd(NH$_3$)$_4$$^{2+}$ into NaY zeolite by the ion-exchange method. In our previous report, we showed that this catalyst was inactive for the SM coupling reaction of bromoarenes at room temperature in the presence of an alkali carbonate base, in an N,N-dimethylformamide (DMF)/water mixture (1/1), while its air calcined or reduced forms were highly active under the identical reaction conditions [23,24]. Nevertheless, we noticed in this study that the Pd(NH$_3$)$_4$$^{2+}$-loaded NaY shows very high SM coupling activity at the reaction temperature of 100 °C. Inactiv-

Table 1

Optimization of $[Pd(NH_3)_4]^{2+}$-NaY catalyzed Suzuki reaction of 4-bromoanisole
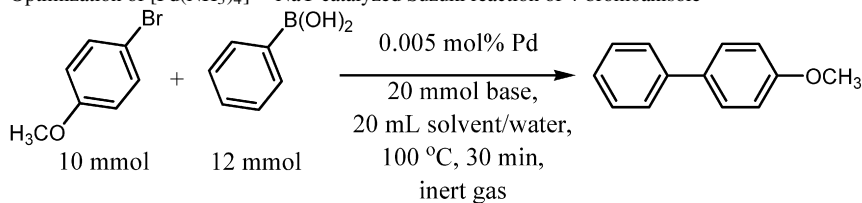
Entry	Catalyst	Base	Solvent/water ratio	Conversion (%)[a]	Yield (mol%)[a]
1	$[Pd(NH_3)_4]^{2+}$-NaY	Cs_2CO_3	DMF (1/1)	52	52
2	$[Pd(NH_3)_4]^{2+}$-NaY	K_2CO_3	DMF (1/1)	62	62
3	$[Pd(NH_3)_4]^{2+}$-NaY	Na_2CO_3	DMF (1/1)	87	86
4	$[Pd(NH_3)_4]^{2+}$-NaY	Na_2CO_3	DMA (1/1)	96	89
5	$[Pd(NH_3)_4]^{2+}$-NaY	Na_2CO_3	NMP (1/1)	81	81
6	$[Pd(NH_3)_4]^{2+}$-NaY	Na_2CO_3	DMA (2/1)	64	64
7	$[Pd(NH_3)_4]^{2+}$-NaY	Na_2CO_3	DMA (1/2)	82	82
8	$[Pd(NH_3)_4]^{2+}$-NaY	Na_2CO_3	DMA (1/3)	74	74
9[b]	$[Pd(NH_3)_4]^{2+}$-NaY	Na_2CO_3	DMA (1/1)	94	94
10[b,c]	$[Pd(NH_3)_4]^{2+}$-NaY	Na_2CO_3	DMA (1/1)	95	94 (92)
11[c]	$PdCl_2$	Na_2CO_3	DMA (1/1)	85	60
12[c]	$Pd(OOCCH_3)_2$	Na_2CO_3	DMA (1/1)	77	55
13[c]	$Pd(OOCCH_3)_2/PPh_3$ (1/2)	Na_2CO_3	DMA (1/1)	87	86

[a] Determined by GC. Isolated yields in parentheses.

[b] The reaction medium contained 1 g of NaY zeolite.

[c] Open to the atmosphere.

ity of the $Pd(NH_3)_4{}^{2+}$-NaY catalyst at room temperature could be associated with the inability of the palladium to reduce its active zero-valent form at the lower temperature.

Initial studies were performed in order to optimize the reaction conditions for the coupling of 4-bromoanisole with $PhB(OH)_2$ using a Pd concentration of 0.005 mol% (0.017 ± 0.02 mmol Pd/g zeolite) at $100\,^{\circ}C$ for 0.5 h under an inert atmosphere. Alkali carbonates were the only bases screened in this study since they had been marked, previously, as being the most suitable base types for the SM coupling activity of palladium-loaded NaY zeolites [23,24]. In this study, sodium carbonate was observed to be the most efficient base when the reactions were performed in a DMF/water mixture (1/1). Other carbonates K_2CO_3 and Cs_2CO_3 were significantly less effective (Table 1, Entries 1–3). Slightly higher product formation was achieved when using DMA as the co-solvent (Table 1, Entry 4), N-methylpyrrolidone (NMP) was somewhat less effective co-solvent for the method (Table 1, Entry 5). The optimum ratio of the DMA/water solvent mixture appeared to be 1/1 (Table 1, Entries 4, 6–8).

The reaction medium contained ≈ 32 mg of palladium-loaded zeolite for the experiments described above. However, the yield increased slightly when overall zeolite content of the reaction medium was increased to 1 g upon addition of NaY zeolite which contained no palladium originally (Table 1, Entry 9). Nevertheless, no further benefit was gained by additional increase in the amount of zeolite. We were also happy to observe that the replacement of the reaction atmosphere from an inert gas to ambient atmosphere had no negative effect on the method (Table 1, Entry 10). For comparison, the SM reaction of 4-bromoanisole and phenylboronic acid was also performed with ligandless $Pd(OAc)_2$, $PdCl_2$ compounds and a regularly used

$Pd(OAc)_2/PPh_3$ (1/2) catalytic system under the established conditions. It was exciting to discover that the supported catalyst exhibited higher activity than that observed with these homogeneous catalysts (Table 1, Entries 11–13).

Using the optimized reaction conditions (in the presence of Na_2CO_3 as the base, in DMA/water (1/1) mixture, with 1 g overall NaY zeolite content, at $100\,^{\circ}C$, in air), we next examined the scope and limitations of the catalyst for the coupling of a variety of aryl bromides with several arylboronic acid reagents. The results are summarized in Table 2. Even though, the reactions were performed in different Pd concentrations for each aryl bromide substrate employed, Table 2 illustrates the yields which are generally >70 mol%. All the activated and deactivated substituted bromobenzenes could successfully couple with $PhB(OH)_2$, albeit the catalyst activity showed dependence on the substitution type and pattern. Typically, electron rich bromoarenes required comparatively longer reaction times and higher Pd loadings for efficient product recovery. As a general trend, the substitution pattern dependence on the reactivity of mono-substituted aryl bromides is as follows: 1,2- < 1,3- < 1,4-.

Bromobenzene, 4-bromophenol, 3- and 4-bromobenzoic acids, and all other 4-substituted activated bromobenzenes used in this study reacted smoothly with $PhB(OH)_2$ in the presence of 0.001 mol% palladium. The reactions yielded the corresponding coupling products above 90 mol% within 15–105 min with TONs and TOFs (calculated on the basis of coupling product) varying in the range of 90,000–98,000, and 52,000–344,000 h^{-1}, respectively. To our knowledge, these are the highest TONs and TOFs achieved for the SM reactions of aryl bromides catalyzed by any supported or colloidal Pd catalysts (Table 2, Entries 2, 5, 6, 8–11, 19).

Table 2
[Pd(NH$_3$)$_4$]$^{2+}$-NaY catalyzed Suzuki–Miyaura cross-coupling reaction of aryl bromides and arylboronic acids[a]
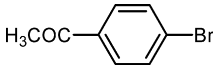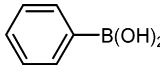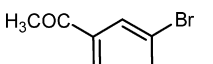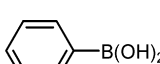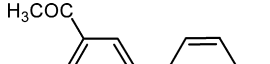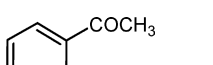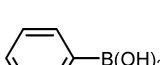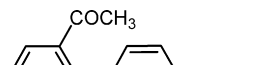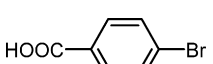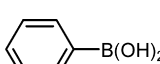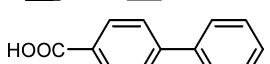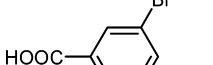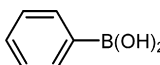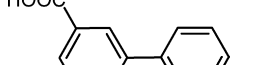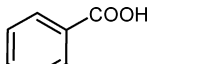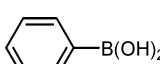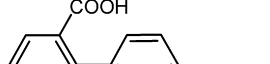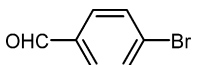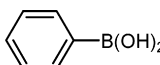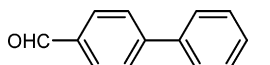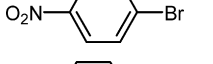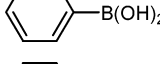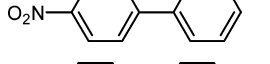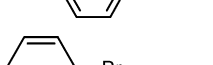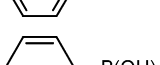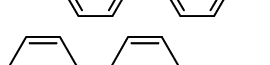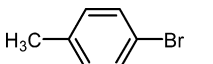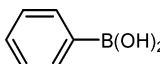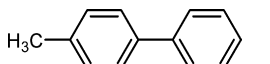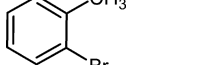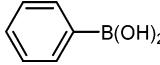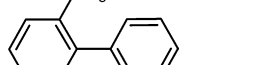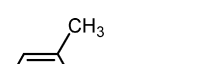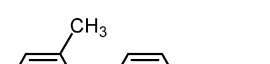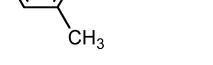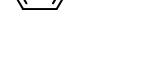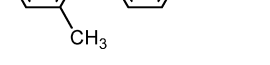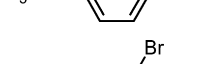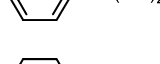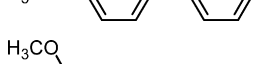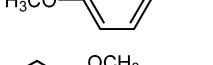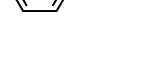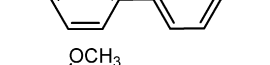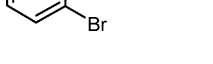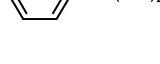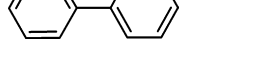
Entry	Aryl bromide	Arylboronic acid	Product	Pd (mol%)	Time (min)	Yield (mol%)[b]	TON	TOF
1				0.005	15	(95)	19000	76000
2				0.001	45	97	97000	129333
3				0.005	15	(95)	19000	76000
4[c]				0.05	90	0	0	0
5				0.001	30	(98)	98000	196000
6				0.001	60	(98)	98000	98000
7[c]				0.05	60	0	0	0
8				0.001	30	(95)	95000	190000
9				0.001	30	(97)	97000	194000
10				0.001	105	(91)	91000	52000
11				0.001	45	90	90000	120000
12				0.005	15	93	18600	74400
13				0.01	15	(93)	9300	37200
14				0.005	15	85	17000	68000
15[c]				0.1	15	(58)	580	2320
16				0.005	15	(93)	18600	74400
17				0.005	15	(95)	19000	76000
18				0.01	30	(92)	9200	18400

Table 2 (*Continued*)
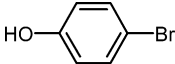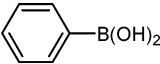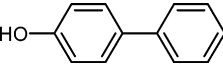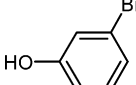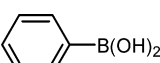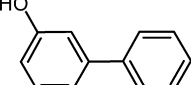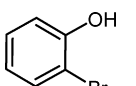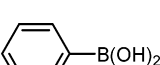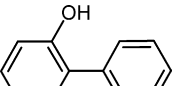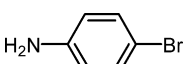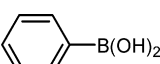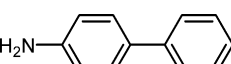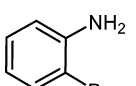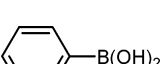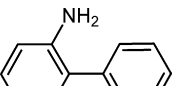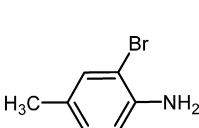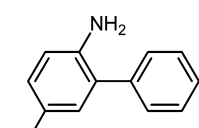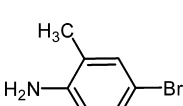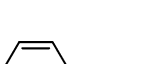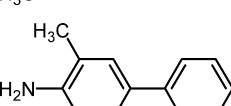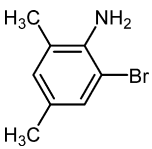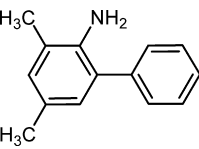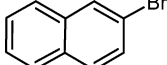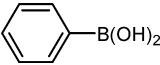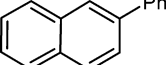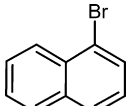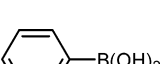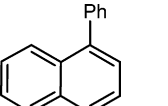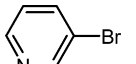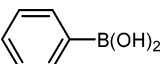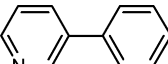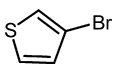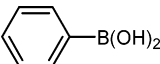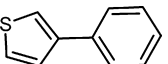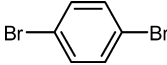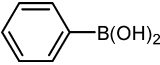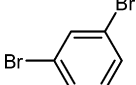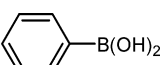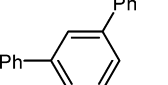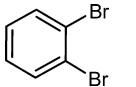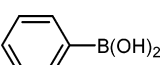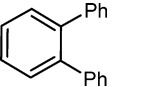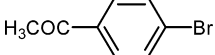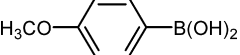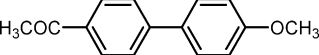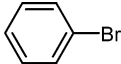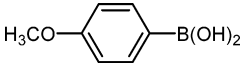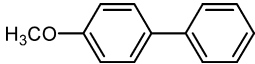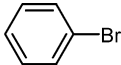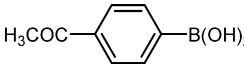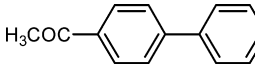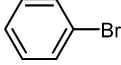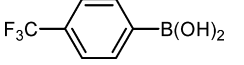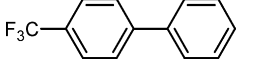
Entry	Aryl bromide	Arylboronic acid	Product	Pd (mol%)	Time (min)	Yield (mol%)[b]	TON	TOF
19				0.001	15	(86)	86000	344000
20				0.01	15	(98)	9800	39200
21				0.005	15	(76)	15200	60800
22				0.005	45	(94)	18800	25067
23[c]				0.05	15	(99)	1980	7920
24[c]				0.05	15	(78)	1560	6240
25[c]				0.05	15	(93)	1860	7440
26[c]				0.05	15	(85)	1700	6800
27				0.001	120	(93)	93000	46500
28				0.005	60	(99)	19800	19800
29				0.01	240	(78)	7800	325
30				0.01	120	0	0	0
31[d]				0.005	15	(97)	19400	77600
32[d]				0.005	15	(96)	19200	76800
33[d]				0.005	15	(98)	19600	78400
34				0.001	45	(99)	99000	132000

Table 2 (*Continued*)

Entry	Aryl bromide	Arylboronic acid	Product	Pd (mol%)	Time (min)	Yield (mol%)[b]	TON	TOF
35	Ph–Br	H_3CO–C$_6$H$_4$–B(OH)$_2$	H_3CO–C$_6$H$_4$–C$_6$H$_5$	0.005	15	97	19400	77600
36				0.001	15	72[e]	72000	288000
37	Ph–Br	H_3COC–C$_6$H$_4$–B(OH)$_2$	H_3COC–C$_6$H$_4$–C$_6$H$_5$	0.01	15	85	8500	34000
38[c]	Ph–Br	F_3C–C$_6$H$_4$–B(OH)$_2$	F_3C–C$_6$H$_4$–C$_6$H$_5$	0.05	15	(77)	1540	6160
39				0.001	15	67[e]	67000	268000

[a] Aryl bromide: 10 mmol; arylboronic acid: 12 mmol; Na$_2$CO$_3$: 20 mmol; DMA/water (1/1): 20 mL; NaY: 1 g; 100 °C.

[b] GC product. The isolated products are given in parantheses.

[c] Aryl bromide: 1 mmol; arylboronic acid: 1.2 mmol; Na$_2$CO$_3$: 2 mmol; DMA/water (1/1): 10 mL.

[d] Arylboronic acid: 24 mmol; Na$_2$CO$_3$: 40 mmol; DMA/water (1/1): 40 mL.

[e] Conversion is not complete.

4-Bromoacetophenone afforded the coupling product at the isolated yield of 95 mol% within just 15 min when reacted with PhB(OH)$_2$ at 0.005 mol% Pd level, whereas the reaction took 45 min to produce 97 mol% of the isolated product at a Pd loading of 0.001 mol% (Table 2, Entries 1,2). 3-Bromoacetophenone coupled to phenylboronic acid gave 95 mol% of the isolated product with a Pd concentration of 0.005 mol% in 15 min (Table 2, Entry 3).

The quantitative conversion of 3-bromobenzoic acid required a longer time with 0.001 mol% Pd loading as compared to its 4-substituted isomer (60 min versus 30 min) (Table 2, Entries 5, 6). Interestingly, 2-bromoacetophenone and 2-bromobenzoic acid reagents could not couple with PhB(OH)$_2$ even with a relatively high Pd loading (0.05 mol%) under the established conditions (Table 2, Entries 4, 7). This could not be attributed solely to the sterically demanding structures of these substrates since the catalyst could allow the coupling of a variety of other 2-substituted haloarenes. For example, the reaction of 2-bromotoluene with PhB(OH)$_2$ at 0.005 mol% Pd loading for 15 min yielded 85 mol% of the coupling product (Table 2, Entry 14). Even 2,6-dimethylbromobenzene was observed to give rise to 58 mol% of the corresponding biaryl product at 0.1 mol% Pd within 15 min (Table 2, Entry 15). The lack of reactivity of 2-bromobenzoic acid and 2-bromoacetophenone could be due to chelation of the palladium in arylpalladium intermediates by the neighboring carbonyl or carboxyl group, which reduces the overall reactivity and increases the steric hindrance of these intermediates towards the transmetallation step.

SM coupling was also successful with all bromoanisoles, bromophenols, and bromoanilines to yield the corresponding biaryl structures under low Pd concentrations in short times (Table 2, Entries 16–23). Even highly inactivated multi-substituted anilines, like 2-bromo-4-methylaniline, 4-bromo-2-methylaniline, and 2-bromo-4,6-dimethylaniline substrates led to high yields of the desired coupling products with a Pd concentration of 0.05 mol% within 15 min without the need for the protection of the amino groups (Table 2, Entries 24–26). 1-Bromonaphthalene required a relatively higher Pd amount for the formation of more than 90 mol% product than with 2-bromonaphthalene (0.001 mol% versus 0.005 mol%; Table 2, Entries 27–28). The activities of 3-bromopyridine and 3-bromothiophene were also evaluated for the SM reaction to probe heteroaryl halide molecules. While 3-bromopyridine led to a good coupling product formation, the latter molecule failed to couple with phenylboronic acid (Table 2, Entries 29, 30). It seems that the sulfur containing substrate poisoned the catalyst.

All dibromobenzene reagents were equally reactive in the SM reaction, converting almost quantitatively to terphenyl products at 0.005 mol% Pd level within 15 min (Table 2, Entries 31–33).

The activity of the catalyst was also evaluated for several arylboronic acids. Electron rich arylboronic acids showed better activity with the catalyst than did electron poor ones (Table 2, Entries 34–39).

Important criteria in the commercial application of Pd catalysts are to obtain Pd free end products, since metal contamination is of great concern for food and pharmaceutical industries, and to consume little amounts of the expensive Pd catalyst.

The amount of Pd leached to the solution at the end of the reactions was very minute in our case. The ICP-MS analyses revealed the presence of less than 15 ppb Pd within the filtrates of the reactions with aryl bromides, corresponding less than 0.6 mol% of the Pd initially charged.

The catalyst cost is a significant concern for industrial applications, which could be minimized by using readily available catalysts, by working at minimum catalyst amounts, and/or by the recovery and re-use of the catalyst many times. Pd-loaded NaY catalysts evidently worked at very high TONs, and we already showed that the catalyst can be re-used in the SM reactions of aryl bromides at room temperature with Pd concentration of 2.5 mol% after regeneration [23,24]. Nevertheless, we have determined in this study that the catalyst is not quite re-usable at low Pd loadings. For example, the catalyst which was recovered from the reaction of Entry 1 in Table 2 following filtering and washing with ethyl acetate and water gave only 21 mol% of the target product following its second use under otherwise similar conditions. Yet, we should note at this point

that, to our knowledge, there has been no example of the use of any immobilized Pd systems in recycling tests at such low Pd levels. Gladysz pointed out that TON is more important for a catalyst than its recyclability for practical applications [29].

Many immobilized palladium catalysts claimed to be recyclable [30–55]. Nevertheless, this conclusion is quite dubious because the lessened yields, elongated reaction periods and high reaction temperatures required during subsequent uses of the catalysts indicate a progressive deactivation of the catalysts used. Given the rather high catalyst levels studied (typically 0.1–10 mol%), 100–10,000 recycles would be needed to match the effectiveness of our catalyst in terms of TON values [56]. This seems to be highly unlikely considering the progressive deactivation of the catalysts mentioned above.

There are several studies with no indication of catalyst deactivation after several re-uses in SM reactions [57–69]. However, as was addressed by Das and Sayari [70], and by our recent study [71], excessive conditions such as high reaction temperatures, high level of Pd loading, and using highly reactive substrates could provide highly favorable conditions to obtain complete conversions for several uses.

Likewise, Das and Sayari showed that a pore-expanded MCM-41 supported Pd could be recycled at least three times in the SM reaction of iodobenzene and phenylboronic acid at $100\,°C$ without any decrease in the yield at each re-use [70]. In contrast, the catalyst failed to exhibit any recyclability at the reaction temperature of $22\,°C$. The yield was lower at each re-use of the catalyst at the lower temperature. In another example, it was found that a silica immobilized di(2-pyridyl)methylamine-$PdCl_2$ complex was recyclable for the coupling of 4-bromoacetophenone and phenylboronic acid,

whereas the practical recycling of the catalyst was not possible when a more challenging aryl halide, *m*-nitrochlorobenzene was employed [30]. An oxime-carbopalladacycle anchored on a soluble PEG was determined to be a re-usable catalyst for the SM reaction of 4-bromoacetophenone, but it was not re-usable for the reactions involving 4-chloroacetophenone [31]. A $Pd(OAc)_2$/DABCO/PEG system could be recycled 10 times for the coupling of bromobenzene without any significant drop in conversion level using 3 mol% of Pd, but the product formation significantly diminished at each subsequent re-use of the catalyst when the Pd level was held at 0.1 mol% [32]. Barnabé et al. claimed that a dendritic perfluoro-tagged Pd catalyst is re-usable on the basis of recycling tests done in the SM reactions of 4-bromoacetophenone with phenylboronic acid. The catalyst afforded the target product almost quantitatively for three consecutive runs at 0.5 mol% Pd level, but the catalyst activity deteriorated just after the first use when using 0.1 mol% Pd [33].

3.2. Suzuki–Miyaura reactions of aryl bromides in water

Our next efforts focused on the SM reactions of bromoarenes in pure water, since the catalyst was observed to preserve its activity in water. Basic-water-soluble *meta*- or *para*-substituted aryl bromides, such as bromobenzoic acids and bromophenols, reacted promptly with phenylboronic acid, yielding nearly quantitative coupling products at a Pd loading of 0.001 mol% with TOF values of about $4 \times 10^5\,h^{-1}$ (Table 3, Entries 1–4). 2-Bromophenol and other water immiscible substrates required relatively higher Pd concentrations, typically 0.01 mol%, for effective coupling.

The presence of 0.5 equiv. of tetrabutylammonium bromide (Bu_4NBr) or cetyltrimethylammonium bromide (with

Table 3
$[Pd(NH_3)_4]^{2+}$-NaY catalyzed Suzuki–Miyaura cross-coupling reaction of aryl bromides in water
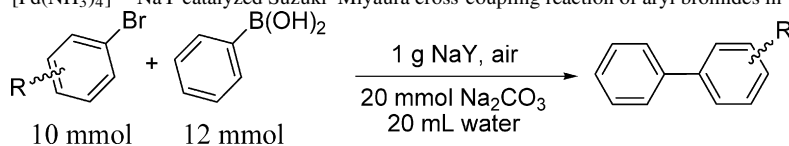
Entry	R	Pd (mol%)	Time (min)	Conversion (%)[a]	Yield (mol%)[a]	TON	TOF (h^{-1})
1	4-COOH	0.001	15	100	(100)	100,000	400,000
2	3-COOH	0.001	15	100	(100)	100,000	400,000
3	4-OH	0.001	15	100	(100)	100,000	400,000
4	3-OH	0.001	15	100	(99)	99,000	396,000
5	2-OH	0.01	15	100	(75)	7,500	30,000
6	4-COCH$_3$	0.01	15	100	74	7,400	29,600
7	4-COCH$_3$[b]	0.01	15	100	77	7,700	30,000
8	4-COCH$_3$[c]	0.01	15	100	79	7,900	31,600
9	H	0.01	60	47	7	–	–
10	H[b]	0.01	30	95	82	8,200	16,400
11	4-CH$_3$[b]	0.01	15	63	56	5,600	22,400
12	4-OCH$_3$	0.01	60	3	1	–	–
13	4-OCH$_3$[b]	0.01	30	93	86	8,600	17,200
14	4-COCH$_3$[d]	0.01	15	88	43	4,300	17,200

[a] Determined by GC, isolated products in parantheses.
[b] 5 Mmol of Bu_4NBr was added.
[c] 5 Mmol of cetyltrimethylammonium bromide was added.
[d] Microwave heated at $100\,°C$; 1 mmol of 4-bromoacetophenone; 1.2 mmol of $PhB(OH)_2$; 2 mmol of base; 2 ml of water; 0.5 mmol of Bu_4NBr.

respect to the aryl bromide substrate) additives in the reaction medium had little effect on the SM coupling of 4-bromoacetophenone (Table 3, Entries 6–8). Nevertheless, the presence of a quaternary ammonium salt appeared to be crucial for the reactions of bromobenzene and deactivated aryl bromides (Table 3, Entries 9–13). An SM reaction with 4-bromoacetophenone was also conducted under microwave heating in water. The comparison of the results revealed that thermal conditions were superior to microwave heating (Table 3, Entry 14).

3.3. Suzuki–Miyaura reactions of aryl chlorides

There are only a few reports that have shown supported Pd catalysts having sufficient activity for the SM reactions of more readily available aryl chlorides.

It was demonstrated that a Pd/C catalyzed Suzuki cross-coupling reactions of activated chloroarenes with various arylboronic acids were possible upon fine adjustment of the DMA/water ratio [72]. However, these reactions were performed at high Pd concentrations (5 mol%) and over long reaction times (24 h). The results of Köhler and co-workers also exhibited the activity of Pd/C for the SM reaction of 4-chloroacetophenone at relatively low Pd concentrations (0.05–0.25 mol%) in an NMP/water mixture (10:3) at 120 °C [73]. Pd/C was also demonstrated to be an active catalyst for the SM reactions of aryl chlorides in water [74]. Choudary et al. determined that Mg–Al layered double hydroxide supported Pd nanoparticles were highly active in SM and Mizoroki-Heck cross-coupling reactions when the reactions were carried out in ionic liquids [67]. Kantam et al. recently illustrated the activity of a nanocrystalline magnesium oxide-stabilized Pd(0) (3 mol% Pd) for aryl chlorides [68]. Others used various Pd-complexes anchored onto a solid matrix [32,39,50,61,63,75–78].

We also present herein that a Pd-loaded NaY zeolite can catalyze the SM reactions of activated aryl chlorides with very high TOFs under aerobic conditions.

A systematic study was carried out to establish the optimum conditions for the activity of the Pd-NaY catalyst towards the SM reaction using 4-chloroacetophenone and PhB(OH)$_2$ reagents in DMA solvent and 0.1 mol% Pd at 160 °C under ambient atmosphere and in the presence of overall 1 g NaY zeolite (zeolite content of the reaction medium was completed to 1 g by the addition of NaY zeolite in as-received form). The presence of Bu$_4$NBr (1 molar equivalent with respect to aryl halide) was necessary for the effectiveness of the coupling and NaOEt was found to be the most suitable base compared to the various bases tested, e.g. alkali carbonates, Ca(OH)$_2$, K$_3$PO$_4$, NaOH, and KOH. In contrast to the aryl bromides, the presence of water as a co-solvent was detrimental for the reaction of aryl chlorides. The reaction was extremely fast under these conditions, generating 90 mol% coupling product within only 5 min (Table 4, Entry 1).

In order to clarify if there was any benefit from as-received zeolite addition, we also carried out a control reaction without any extra zeolite (the reaction medium contained about ∼60 mg of Pd-loaded zeolite only). It was surprising to observe that product formation was negligible in the control experiment (Table 4, Entry 2). It was even more interesting to observe that, the catalyst displayed no activity when the as-received zeolite additive was vacuum dried at 140 °C for 2 h prior to the addition (Table 4, Entry 3), indicating that the intrinsic water content of the zeolite (which was measured to be around 23% based on the weight loss during vacuum drying at 140 °C for 2 h) was somehow responsible for the activity increase in the system. In a Suzuki reaction performed in the presence of 230 mg of water (equivalent to the amount of water that would be introduced by the addition of 1 g of NaY as-received zeolite, a moderate product formation (61 mol%) was observed. This indicates that the reaction can

Table 4
Effect of zeolite and water additives on the SM reaction of 4-chloroacetophenone
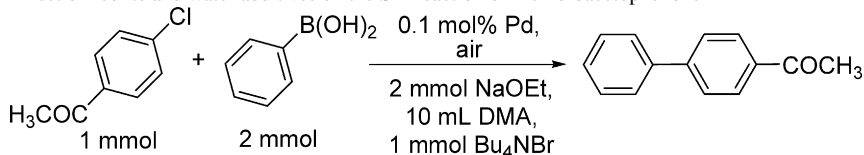
Entry	Zeolite[a] (g)	Water (g)	T (°C)	Time (min)	Conversion (%)[b]	Yield (mol%)[b]
1	1	–	160	5	100	90
2	0.06	–	160	60	17	<1
3[c]	1	–	160	60	18	<1
4	0.06	0.23	160	5	70	61
5	1	–	140	5	63	48
6	2	–	140	10	87	75
7	3	–	140	5	100	90
8	4	–	140	5	94	91
9[d]	1	1	140	5	60	49
10[e]	1	3	140	45	95	2

[a] As-received.
[b] Determined by GC.
[c] The zeolite was dried under vacuum at 140 °C for 2 h prior the reaction.
[d] With 9 mL of DMA.
[e] With 7 mL of DMA.

operate only in moist medium (Table 4, Entry 4) but also points out to the existence of a synergism arising from the water-zeolite combination.

The effect of changing the amount of the as-received zeolite addition was also examined at 140 °C (Table 4, Entries 5–8). The product formation was modest (48 mol%) when the reaction was carried out with an overall zeolite amount of 1 g for 5 min (Table 4, Entry 5). About 3–4 g of the zeolite seemed to be required for the optimum product recovery (Table 4, Entries 7, 8). Four grams of NaY zeolite would introduce nearly 1 g of water into the reaction medium. Therefore, a reaction was conducted in the presence of 1 g of as-received zeolite along with 1 g of added water in order to clarify if the yield improvement was solely due to the increased water amount in the system. The yield was identical to that obtained in the experiment performed with 1 g original zeolite alone (compare Entries 5 and 9 in Table 4). Moreover, the presence of a larger amount of water (with DMA/water ratio of 7/3) completely destroyed the activity of the catalyst (Table 4, Entry 10). These results clearly show that improvement gained by introducing higher amounts of original zeolite is not solely due to the increased amount of free water within the reaction medium, but rather due to the presence of water encapsulated within the zeolite matrix, pointing out to a synergistic effect.

Even though the underlying reasons for the observed synergism seem rather complicated, the fact remains that the presence of a little amount of water is crucial for the activation of the reaction system. The presence of zeolite probably controls the behavior of the water in the reaction system. On the other hand, it can be considered that an acid–base reaction of NaOEt and the water mixture should lead to OH^- and EtOH components. NaOH has been much less promotive for the coupling reaction, and this could account for the deleterious effect of excess amounts of water to the reaction efficiency.

The coupling reactions seemed to be catalyzed by the dissolved Pd species leached from the Pd-NaY catalyst, because the presence of 30,000 molar equivalent of an insoluble cross-linked poly(vinylpyridine) polymer (PVPy) greatly reduced the activity of the catalyst under the established reaction conditions (only 20% coupling product after 4 h of reaction). It was shown previously that PVPy weakens the activity of Pd by strongly coordinating the soluble Pd(II) species while remaining inert towards the solid Pd [79,80]. Therefore, if the reactions were catalyzed heterogeneously, no change in the reaction progress should be expected. This result is consistent with the previous findings that Pd-loaded zeolites and other supported Pd catalysts act as soluble Pd reservoirs for C–C coupling reactions [21,81–90].

The ICP-MS analyses revealed less than 0.2 ppm Pd concentrations within the filtrates after the reactions with aryl chlorides, these corresponding to less than 2 mol% of the Pd initially charged.

Using the optimal conditions determined (2 equiv. of $PhB(OH)_2$, 2 equiv. sodium ethoxide, 1 equiv. Bu_4NBr, 3 g NaY zeolite and, under aerobic conditions), we explored the scope of the reaction for a range of aryl chlorides with $PhB(OH)_2$ at various temperatures. The results obtained with activated aryl chlorides were quite good (Table 5). 4-Substituted electron poor chloroarenes led to desired coupling products within 5 min at 140 °C (Table 5, Entries 1, 4, 6, 8) with high TOF values, which, to the best of our knowledge, are the highest TOFs that have been achieved for chloroarenes using a supported Pd catalyst. 4-Chloroacetophenone and 4-chloronitrobenzene both could couple with $PhB(OH)_2$ at 120 °C as well, though they required longer reaction periods (45 and 60 min, respectively), whereas others donated only moderate yields at this lower temperature. Sterically congested 2-chloroacetophenone, also yielded 80 mol% isolated product after 60 min of reaction time at 140 °C (Table 5, Entry 10). It must be noted that 2-bromoacetophenone and 2-bromobenzoic acid were unreactive under the optimized conditions for bromoarenes. Nevertheless, 2-bromoacetophenone could couple successfully to donate 86 mol% product when reacted under the conditions established for chloroarenes (the conditions of Entry 1 in Table 5). The pro-

Table 5
$[Pd(NH_3)_4]^{2+}$-NaY catalyzed Suzuki cross-coupling reaction of aryl chlorides
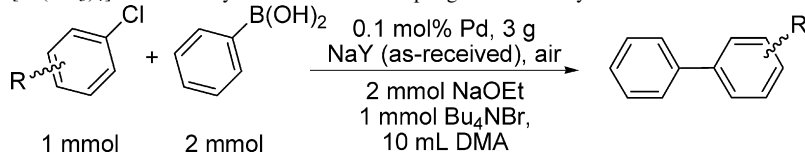
Entry	R	T (°C)	Time (min)	Conversion (%)[a]	Yield (mol%)[a]	TOF (h^{-1})
1	4-COCH₃	140	5	100	90 (86)	10320
2		120	45	100	90	1200
3		100	60	40	40	400
4	4-NO₂	140	5	100	(92)	11040
5		120	60	100	95	950
6	4-CHO	140	5	100	(78)	9360
7		120	60	45	40	400
8	4-CN	140	5	100	(90)	10800
9		120	60	77	63	560
10	2-COCH₃	140	60	100	(80)	800
11		120	60	28	22	220

[a] Determined by GC. The isolated yields are given within parantheses.

cess was not so satisfactory for chlorobenzene and inactivated chloroarenes.

4. Conclusion

In summary, it has been shown in this study that a Pd-loaded NaY zeolite is a highly active catalyst for Suzuki–Miyaura cross-coupling reactions of aryl bromides and activated chloroarenes with arylboronic acids under aerobic conditions. Cross-coupling of bromoarenes can be performed both in a DMA/water mixture and in pure water with excellent TONs and TOFs. The coupling of chloroarenes can be achieved in the presence of a minute amount of water. Our results show that the water to the reaction system is supplied, in a controlled manner, by the addition of as-received zeolite. It seems that there is an apparent synergism arising from the use of zeolite and water together in the reactions.

Acknowledgements

References

[1] N. Miyaura, A. Suzuki, Chem. Rev. 95 (1995) 2457.
[2] A. Suzuki, J. Organomet. Chem. 576 (1999) 147.
[3] S. Kotha, K. Lahiri, D. Kashinath, Tetrahedron 58 (2002) 9633.
[4] J. Hassan, M. Sevignon, C. Gozzi, E. Schultz, M. Lemaire, Chem. Rev. 102 (2002) 1359.
[5] A.F. Littke, G.C. Fu, Angew. Chem. Int. Ed. 41 (2002) 4176.
[6] F. Bellina, A. Carpita, R. Ross, Synthesis (2004) 2419.
[7] M. Miura, Angew. Chem. Int. Ed. 43 (2004) 2201.
[8] D.W. Old, J.P. Wolfe, S.L. Buchwald, J. Am. Chem. Soc. 120 (1998) 9722.
[9] R.B. Bedford, S.L. Hazelwood, M.E. Limmert, D.A. Albisson, S.M. Draper, P.N. Scully, S.J. Coles, M.B. Hursthouse, Chem. Eur. J. 9 (2003) 3216.
[10] N. Kataoka, Q. Shelby, J.P. Stambuli, J.F. Hartwig, J. Org. Chem. 67 (2002) 5553.
[11] S.D. Walker, T.E. Barder, J.R. Martinelli, S.L. Buchwald, Angew. Chem. Int. Ed. 43 (2004) 1871.
[12] A. Zapf, A. Ehrentraut, M. Beller, Angew. Chem. Int. Ed. 39 (2000) 4153.
[13] J.P. Wolfe, R.A. Singer, B.H. Yang, S.L. Buchwald, J. Am. Chem. Soc. 121 (1999) 9550.
[14] J.P. Wolfe, S.L. Buchwald, Angew. Chem. Int. Ed. 38 (1999) 2413.
[15] A.F. Littke, G.C. Fu, Angew. Chem. Int. Ed. 37 (1998) 3387.
[16] C.W.K. Gstottmayr, V.P.W. Bohm, E. Herdtweck, M. Grosche, W.A. Herrmann, Angew. Chem. Int. Ed. 41 (2002) 1363.
[17] I. Özdemir, B. Alici, N. Gürbüz, E. Çetinkaya, B. Çetinkaya, J. Mol. Catal. A. 217 (2004) 37.
[18] See the recent review: L. Yin, J. Liebscher, Chem. Rev. 107 (2007) 133 (and references therein).
[19] Y. Sun, Y. LeBlond, J.R. Sowa Jr., US Patent 6,603,013 (August 2003).
[20] L. Djakovitch, K. Köhler, J. Organomet. Chem. 606 (2000) 101.
[21] S.S. Pröckl, W. Kleist, M.A. Gruber, K. Köhler, Angew. Chem. Int. Ed. 43 (2004) 1881.
[22] L. Djakovitch, M. Wagner, K. Köhler, J. Organomet. Chem. 592 (1999) 225.
[23] H. Bulut, L. Artok, S. Yilmaz, Tetrahedron Lett. 44 (2003) 289.
[24] L. Artok, H. Bulut, Tetrahedron Lett. 45 (2004) 3881.
[25] A. Corma, H. García, A. Leyva, Appl. Catal. A: Gen. 236 (2002) 179.
[26] P. Rollet, W. Kleist, V. Dufaud, L. Djakovitch, J. Mol. Catal. A: Chem. 241 (2005) 39.
[27] H. Takeuchi, K. Takano, J. Chem. Soc. Perkin Trans. I (1986) 611.
[28] C. Wu, E.R. Decker, N. Blok, H. Bui, T.J. You, J. Wang, A.R. Bourgoyne, V. Knowles, K.L. Berens, G.W. Holland, T.A. Brock, R.A.F. Dixon, J. Med. Chem. 47 (2004) 1969.
[29] J.A. Gladysz, Pure Appl. Chem. 73 (2001) 1318.
[30] M. Trilla, R. Pleixats, M.W.C. Man, C. Bied, J.J.E. Moreau, Tetrahedron Lett. 47 (2006) 2399.
[31] A. Corma, H. García, A. Leyva, J. Catal. 240 (2006) 87.
[32] J.-H. Li, W.-J. Liu, Y.-X. Xie, J. Org. Chem. 70 (2005) 5409.
[33] A.G. Barnabé, C.C. Tzschuchke, W. Bannwarth, R. Haag, Adv. Synth. Catal. 347 (2005) 1389.
[34] H. Hagio, M. Sugiura, S. Kobayashi, Org. Lett. 8 (2006) 375.
[35] F.-X. Felpin, J. Org. Chem. 70 (2005) 70.
[36] G. Lu, R. Franzén, Q. Zhang, Y. Xu, Tetrahedron Lett. 46 (2005) 4255.
[37] N. Jiang, A.J. Ragauskas, Tetrahedron Lett. 47 (2006) 197.
[38] C.C. Tzschucke, C. Markert, H. Glatz, W. Bannwarth, Angew. Chem. Int. Ed. 41 (2002) 4500.
[39] L. Wu, B.-L. Li, Y.-Y. Huang, H.-F. Zhou, Y.-M. He, Q.-H. Fan, Org. Lett. 8 (2006) 3605.
[40] J.-W. Byun, Y.-S. Lee, Tetrahedron Lett. 45 (2004) 1837.
[41] S. Paul, J.H. Clark, Green Chem. 5 (2003) 635.
[42] J.R. Ruiz, C.J. Sanchidrián, M. Mora, Tetrahedron 62 (2006) 1.
[43] R. Narayanan, M.A.E. Sayed, J. Catal. 234 (2005) 348.
[44] J. Lemo, K. Heuzé, D. Astruc, Org. Lett. 7 (2005) 2253.
[45] F. Lu, J. Ruiz, D. Astruc, Tetrahedron Lett. 45 (2004) 9443.
[46] G. Lu, R. Franzén, Q. Zhang, Y. Xu, Tetrehedron Lett. 46 (2005) 4255.
[47] A. Datta, K. Ebert, H. Plenio, Organometallics 22 (2003) 4685.
[48] H. Sakurai, T. Tsukuda, T. Hirao, J. Org. Chem. 67 (2002) 2721.
[49] K. Glegola, E. Framery, K.M. Pietrusiewicz, D. Sinou, Adv. Synth. Catal. 348 (2006) 1728.
[50] C.A. Parrish, S.L. Buchwald, J. Org. Chem. 66 (2001) 3820.
[51] A. Corma, D. Das, H. García, A. Leyva, J. Catal. 229 (2005) 322.
[52] Y. Liu, C. Khemtong, J. Hu, J. Chem. Commun. (2004) 398.
[53] J.-H. Li, X.-C. Hu, Y.-X. Xie, Tetrahedron Lett. 47 (2006) 9239.
[54] Z. Zhang, Z. Wang, J. Org. Chem. 71 (2006) 7485.
[55] L. Wu, B.-L. Li, Y.-Y. Huang, J.-F. Zhou, Y.-M. He, Q.-H. Fan, Org. Lett. 8 (2006) 4259.
[56] V. Farina, Adv. Synth. Catal. 346 (2004) 1553.
[57] Y.M.A. Yamada, K. Takeda, H. Takahashi, S. Ikegami, J. Org. Chem. 68 (2003) 7733.
[58] N. Gurbuz, İ. Özdemir, B. Çetinkaya, T. Seçkin, Appl. Organomet. Chem. 17 (2003) 776.
[59] K. Okamoto, R. Akiyama, S. Kobayashi, Org. Lett. 6 (2004) 1987.
[60] M. an der Heiden, H. Plenio, Chem. Eur. J. 10 (2004) 1789.
[61] C.M. Crudden, M. Sateesh, R. Lewis, J. Am. Chem. Soc. 127 (2005) 10045.
[62] K.-I. Shimizu, S. Koizumi, T. Hatamachi, H. Yoshida, S. Komai, T. Kodama, Y. Kitayama, J. Catal. 228 (2004) 141.
[63] C. Baleizão, A. Corma, H. García, A. Leyva, J. Org. Chem. 69 (2004) 439.
[64] F.-T. Luo, C. Xue, S.-L. Ko, Y.-D. Shao, C.-J. Wu, Y.-M. Kuo, Tetrahedron 61 (2005) 6040.
[65] P.G. Steel, C.W.T. Teasdale, Tetrahedron Lett. 45 (2004) 8977.
[66] K.-I. Shimizu, R. Maruyama, S.-I. Komai, T. Kodama, Y. Kitayama, J. Catal. 227 (2004) 202.
[67] B.M. Choudary, S. Madhi, N.S. Chowdari, M.L. Kantam, B. Sreedhar, J. Am. Chem. Soc. 124 (2002) 14127.
[68] M.L. Kantam, S. Roy, M. Roy, B. Sreedhar, B.M. Choudary, Adv. Synth. Catal. 347 (2005) 2002.
[69] H. Kosslick, I. Mönnich, E. Paetzold, H. Fuhrmann, R. Fricke, D. Müller, G. Oehme, Microporous Mesoporous Mater. 44–45 (2001) 537.
[70] D.D. Das, A. Sayari, J. Catal. 246 (2007) 260.

[71] Ö. Aksın, H. Türkmen, L. Artok, B. Çetinkaya, C. Ni, O. Büyükgüngör, E. Özkal, J. Organomet. Chem. 691 (2006) 3027.

[72] C.R. LeBlond, A.T. Andrews, Y. Sun, R.S. Sowa Jr., Org. Lett. 3 (2001) 1555.

[73] R.G. Heidenreich, K. Köhler, J.G.E. Krauter, J. Pietsch, Synlett (2002) 1118.

[74] M. Lysén, K. Köhler, Synlett (2005) 1671.

[75] J. Lemo, K. Heuze, D. Austruc, Org. Lett. 7 (2005) 2253.

[76] M. van der Heiden, H. Plenio, Chem. Eur. J. 10 (2004) 1789.

[77] J.-H. Li, Y.-X. Xie, Tetrahedron Lett. 47 (2006) 9239.

[78] W.J. Sommer, M. Weck, Adv. Synth. Catal. 348 (2006) 2101.

[79] K. Yu, W. Sommer, M. Weck, C.W. Jones, J. Catal. 226 (2004) 101.

[80] K. Yu, W. Sommer, J.M. Richardson, M. Werck, C.W. Jones, Adv. Synth. Catal. 347 (2005) 161.

[81] F. Zhao, M. Shirai, Y. Ikushima, M. Arai, J. Mol. Catal. A: Chem. 180 (2002) 211.

[82] R.G. Heidenreich, J.G.E. Krauter, J. Pietsch, K. Köhler, J. Mol. Catal. A: Chem. 182–183 (2002) 499.

[83] D.A. Conlon, B. Pipik, S. Ferdinand, C.R. LeBlond, J.R. Sowa Jr., B. Izzo, P. Collins, G.-J. Ho, J.M. Williams, Y.-J. Shi, Y. Sun, Adv. Synth. Catal. (2003) 931.

[84] Y. Ji, S. Jain, R.J. Davis, J. Phys. Chem. B 109 (2005) 17232.

[85] J.-S. Chen, A.N. Vasiliev, A.P. Panarello, J.G. Khinast, Appl. Cat. A: Gen. 325 (2007) 76.

[86] N.T.S. Phan, M.V.D. Sluys, C.W. Jones, Adv. Synth. Catal. 348 (2006) 609.

[87] M. Weck, C.W. Jones, Inorg. Chem. 46 (2007) 1865.

[88] K. Köhler, W. Kleist, S.S. Pröckl, Inorg. Chem. 46 (2007) 1876.

[89] D. Astruc, Inorg. Chem. 46 (2007) 1884.

[90] A.M. Trzeciak, J.J. Ziółkowski, Coord. Chem. Rev. 251 (2007) 1281.