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Combining enabling techniques in organic synthesis: solid-phase-assisted catalysis under microwave conditions using a stable Pd(II)-precatalyst

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Abstract—The catalytic activity of a 2-pyridinealdoxime-based Pd(II)-complex covalently anchored via the oxime moiety to a glass/polymer composite material was evaluated in Suzuki–Miyaura cross-coupling reactions of aryl and heteroaryl halides, including arylchlorides, with aryl and heteroaryl boronic acids both under thermal as well as microwave irradiating conditions in water. The stability and reusability of this Pd-precatalyst is part of the present study.

1. Introduction

Organic synthesis seems to have become so very advanced that basically every molecular target, how structurally complex it may be, can be addressed. However, these advances are not fully reflected in the industrial context.[1] Many developments from the research laboratories lack practicability as far as scale-up, easy and rapid workup and product isolation as well as recyclability of catalysts are concerned. New synthetic methods need to be combined with new techniques termed 'enabling technologies for organic synthesis' to achieve rapid incorporation into industrial processes.[2] Typical enabling technologies are microwave assistance,[3] new solvent systems,[4] continuous flow reactors[5] and immobilization of chemically active species such as reagents and homogeneous catalysts[6] which have recently seen widespread applications in research laboratories. Truly new synthetic technology platforms, however, will not be based on the individual use of these new techniques but will require the integration of two or more of these enabling techniques (Fig. 1). Various successful examples of combining two or more of these techniques in order to achieve faster synthesis or improved work-up have recently appeared in the literature, particularly in the field of catalysis.

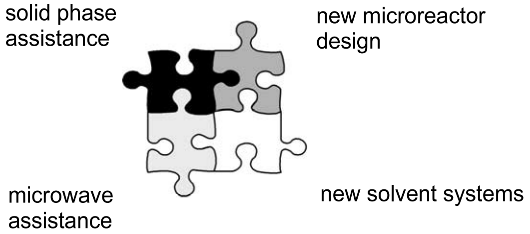

Figure 1.

In this context, we have combined solid-phase assisted synthesis with new continuous flow reactors (PASSflow) leading to an almost workup free procedure for carrying out many different reactions including nucleophilic substitutions, reductive aminations, oxidations, Horner–Wadsworth–Emmons and Pd-catalyzed C–C coupling reactions in the flow through mode.[7]

Other groups have combined microwave-assisted solid-phase technique was applied in the synthesis of several heterocycles,[8] C–C cross couplings[9] and natural products derivatives.[10] However, publications concerning the use of insoluble Pd-catalyst under microwave irradiating conditions are scarce.[11] The combination of immobilized homogeneous catalysts and microwave assistance is particularly appealing in order to overcome the less favourable kinetics of biphasic systems.

Transition metal-mediated cross-coupling reactions, particularly those based on palladium, have become key

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Keywords: Pd(II)-precatalyst; Microwave conditions; Suzuki–Miyaura cross-coupling reaction.

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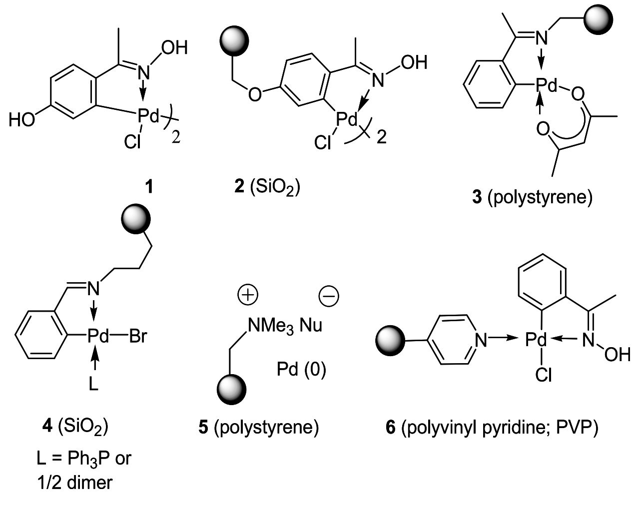
transformations in organic synthesis. However, traditional palladium catalysts often rely on phosphine ligands which show various disadvantages. These are associated with their high price, their air-sensitivity, and difficulties when the ligands and their degradation by-products have to be removed during workup. Recently, new catalytic candidates have appeared in the literature, namely palladacycles which exert high activity and often they are air stable (selected examples are depicted in Fig. 2).[12] In many cases, these compounds are dimeric chloro-bridged *ortho*-palladated complexes such as the acetophenone oxime-based palladacycle **1** utilized by Nájera et al.[13] a versatile complex which is able to catalyze various carbon–carbon coupling reactions such as Suzuki–Miyaura and Heck cross-couplings. Garcia and co-workers[14] covalently anchored these thermally stable palladacycles via an aryl ether linkage to modified silica support yielding catalyst **2**[14] allowing facile recycling of the catalytic species. This species was tested in Suzuki–Miyaura reactions and was found to be a highly active and recyclable complex when heating the reaction mixture conventionally under nitrogen atmosphere. Related examples of immobilized Pd catalysts were disclosed by Nowotny et al.[15] and Bedford et al.[16] who studied palladium(II) complexes **3** and **4** immobilized on polystyrene and silica, respectively. These complexes were found to be highly active in Heck and Suzuki–Miyaura cross coupling reactions, respectively, but were not well suited for recycling protocols. More precisely, the precatalyst **3** lost its activity after the first run of the Heck reaction between iodobenzene and styrene in NMP whereas catalyst **4** was tested in Suzuki–Miyaura cross coupling of only aryl bromides and with recyclability far from being ideal. Recently, evidence has been collected that complexes described here serve as ‘dormant species’[12a] that are not involved in the real catalytic cycle but are a source of a catalytically active species of unknown nature. Thus, solvents like NMP may coordinate and stabilize Pd species that have left the solid phase and therefore, seem not to be well suited as solvents for immobilized Pd species.



1

2 (SiO$_2$)

3 (polystyrene)

4 (SiO$_2$)
L = Ph$_3$P or
1/2 dimer

5 (polystyrene)

6 (polyvinyl pyridine; PVP)

Figure 2.

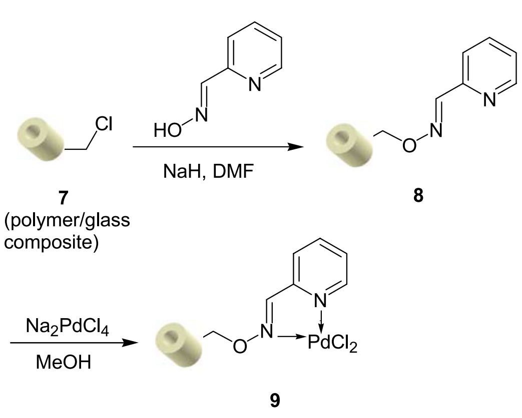
Recently, we initiated a program dedicated to the immobilization of catalytically active Pd species inside a megaporous glass/polymer composite material which we developed for incorporation inside a continuous flow reactor as a monolithic material thereby combining two enabling techniques.[5] For this purpose different strategies of attachment such as physisorption of Pd particles **5**,[17] and immobilization of Najera's catalyst to polyvinyl pyridine by covalent linkage **6**[18] were pursued. The resulting catalysts were tested in a batch set up as well as under continuous flow conditions using the PASSflow system.[7] However, they lack of stability under microwave irradiating conditions and show substantial degree of leaching under continuous flow conditions in PASSflow reactors when polar organic solvents like DMF are required. In order to overcome these drawbacks (a) stability under microwave irradiation and (b) recyclability, search for an alternate Pd(0) catalyst or an appropriate precatalyst were conducted. Here, we report on the development of a new polymer-bound palladium(II) complex **9** which is anchored to the glass/polymer composite material. In order to evaluate its suitability in Suzuki–Miyaura reactions under microwave irradiating conditions we used a composite material shaped as Raschig rings which is a material with relevance in industrial applications (Fig. 3).

Figure 3. Megaporous glass Raschig rings.

2. Results and discussion

2.1. Preparation of Pd-precatalyst

For generating immobilized Pd-precatalyst **9** (Scheme 1), first the monolithic glass/polymer composite phase **7** had to be prepared by precipitation polymerization inside the pores of porous glass which was shaped as Raschig rings according to the protocol that we recently described in detail.[7] 2-Pyridinealdoxime was then coupled to the polymer matrix **7** by heating it at 80 °C in DMF in the presence of sodium hydride. Finally, the heterogeneous precatalyst **9** was obtained by treatment of **8** with a solution



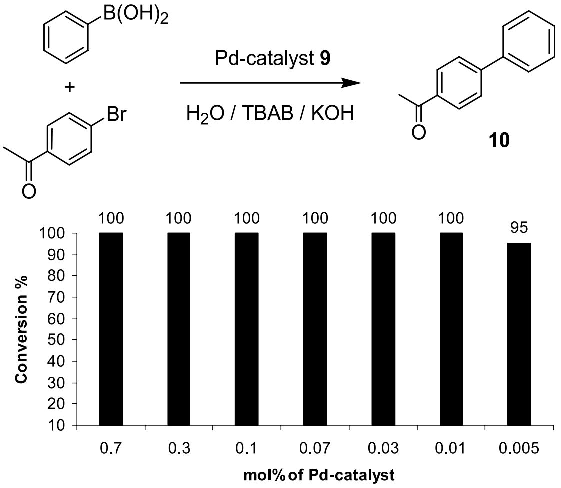
Scheme 1.

of sodium tetrachloropalladate in methanol. The loading of catalyst **9** was estimated to be ca. 0.09 mmol/g Raschig rings according to weight increase.[19]

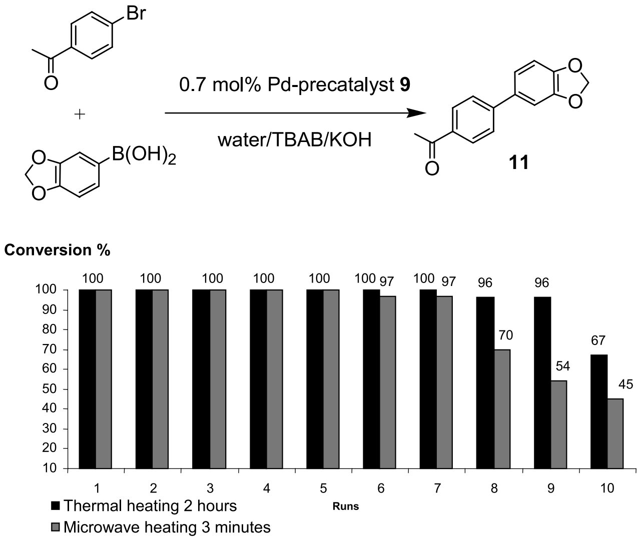
2.2. Optimization of conditions for catalysis

The high price of palladium renders processes based on this metal less attractive unless very active species or catalytic species easy to recycle are available.[20] Therefore, we firstly studied the factors affecting the optimization of the catalytic activity of the Pd-precatalyst **9**. Thus, the effect of concentration of palladium precatalyst **9** on the coupling reaction between phenylboronic acid and *p*-bromoacetophenone under thermal conditions in water at 100 °C was evaluated. At first, the reaction was conducted using 0.7 mol% of precatalyst **9** with a molar ratio of *p*-bromoacetophenone/phenylboronic acid/tetrabutylammonium bromide/potassium hydroxide: 1/1.2/0.6/2, to give 98% isolated yield of 4-acetyl-1,1′-biphenyl (**10**). In the second experiment, we used 0.3 mol% of the catalyst to give full conversion in 97% isolated yield. The reaction was repeated with different catalytic mol% as shown in Scheme 2. Almost full conversion was obtained even in the presence of 0.005 mol% of the catalyst **9** using *p*-bromoacetophenone (40 mmol), phenylboronic acid (48 mmol), tetrabutylammoium bromide (24 mmol), potassium hydroxide (80 mmol) and water (100 mL) to give the 4-acetyl-1,1′-biphenyl (**10**) in 95% (GC-analysis; 92% isolated yield), revealing the good activity of the catalytic system.

Furthermore, we studied the recyclability of Pd-precatalyst **9** in a second model Suzuki–Miyaura cross-coupling reaction using 3,4-methylenedioxyphenylboronic acid (1.2 equiv) and *p*-bromoacetophenone (1 equiv) in the presence of precatalyst **9** (0.7 mol%) in water (3.5 mL) at 100 °C under air, and potassium hydroxide (2 equiv) as base and tetrabutylammonium bromide (TBAB) (0.6 equiv) as phase transfer agent (Scheme 3). Under these conditions, the reaction was completed within 2 h (GC-monitoring). The product of the reaction, 3,4-methylenedioxy-4′-acetyl-1,1′-biphenyl (**11**), was isolated after flash chromatographic purification in 95% yield. At this point, the Pd-precatalyst **9** was removed, washed with ethyl acetate and water and subsequently dried.[21] This used catalyst was reemployed in nine successive runs under identical conditions promoted for the first run. Nearly full conversion was achieved within 2 h up to the 9th run as depicted in Scheme 3. Recyclability of the precatalyst **9** under microwave irradiation conditions was next evaluated using the same model reaction described above at 160 °C and 250 watt for ten successive runs as shown in Scheme 3. Under these conditions, the precatalyst **9** was highly active with almost full transformation up to the 7th run and even at the 10th run it was still active (45% transformation). It is noteworthy to mention that the reaction is highly selective as only the cross-coupled product was formed up to the 7th run and from run 8 to 10 the starting *p*-bromoacetophenone was still present along with the product. Homo-coupled products, which are well known by-products in Suzuki–Miyaura reactions were analyzed to be formed in the range of 1–8%. These results indicate the high stability of precatalyst under microwave irradiating conditions which allows to simply reuse it.



Scheme 2. Effect of concentration of the Pd-precatalyst **9** on the transformation rate. Conditions: Bromide/boronic acid/KOH/TBAB/water (mL): 1/1.2/2/0.6/3.5 mL, reaction time for runs 1–5 was 2 h and for runs 6–7 was 3 h.



Scheme 3. Recyclability of the Pd-precatalyst **9** under thermal and microwave heating. Conditions: bromide/boronic acid/base/TBAB/water (mL): 1/1.2/2/0.6/3.5, 0.7 mol% Pd precatalyst **9**, 100 °C/2 h for thermal heating; 160 °C/250 W/3 min for microwave irradiation.

Additionally, we optimized the reaction temperature under thermal conditions for the coupling between 3,4-methylenedioxyphenylboronic acid (1.2 equiv) and *p*-bromoacetophenone (1 equiv) in the presence of precatalyst **9** (0.7 mol %) in water (3.5 mL), potassium hydroxide (2 equiv) and

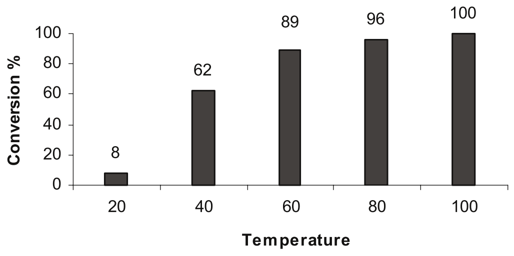
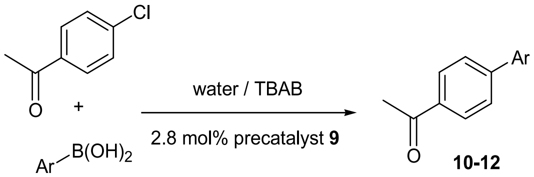
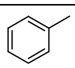
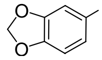
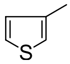


Figure 4. Effect of temperature on the transformation of *p*-bromoacetophenone into **11**. Conditions: Bromide/boronic acid/base/TBAB/water (mL): 1/1.2/2/0.6/3.5, 0.7 mol% Pd-precatalyst **9**, 2 h.

Table 1. Suzuki–Miyaura reactions of aryl chlorides under thermal and microwave heating



	Ar	Base	Product	Thermal heating[a]		µw heating[a]	
				Time (h)	Yield%[b]	Time (min)	Yield%[b]
1		A	**10**	16	65	30	84
2		B	**10**	16	85 (76)	30	98 (92)
3		A	**11**	16	17	15	53
4		B	**11**	16	93 (91)	30	97 (90)
5		A	**12**	16	2	15	11
6		B	**12**	16	22	30	31

[a] Molar ratio of chloride/boronic acid/base/TBAB is 1/1.2/2/0.6, water (3.5 mL), precatalyst **9** (2.8 mol%); thermal heating at 100 °C, microwave heating at 160 °C (250 watt), base A = Cs_2CO_3; B = KOH.

[b] GC-yields; values in parentheses refer to isolated yields of pure products.

TBAB (0.6 equiv). The reaction time was fixed in all cases at two hours. As shown in Figure 4, conversion is best achieved at 100 °C. Interestingly, when the reaction was left shaking at room temperature for an extended time of 20 h, full conversion was also achieved.

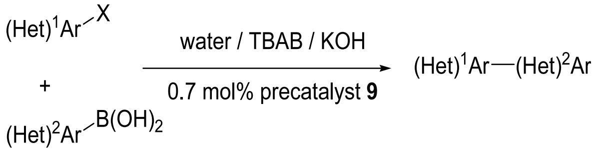
The effect of the absence of tetrabutylammonium bromide (TBAB) and/or palladium catalyst on the above mentioned conversion was also evaluated. Leadbeater and co-workers[22] recently revised there results[23] on a palladium free Suzuki–Miyaura reaction by disclosing that impurities of Pd present in reagents added such as the base K_2CO_3 can result in C–C-coupling of aryl halides and arylboronic acids. In the present case, no product formation was observed without palladium catalyst but in the presence of TBAB and KOH in water both under thermal (2 h) as well as microwave irradiating conditions (3 min). When the reaction was conducted in the presence of palladium precatalyst **9** but without TBAB, the conversion was only 59 and 79% under thermal (2 h) and microwave irradiating conditions (3 min), respectively. These findings show the importance of the palladium source and TBAB in carrying out Suzuki–Miyaura coupling reactions. It is noteworthy to report here, that, when the same reaction was repeated with microwave heating for 3 min in the absence of palladium precatalyst **9** but in glassware that had been used before in Pd-catalysed reactions and that obviously had not been thoroughly cleaned, product **11** was formed in 37% yield.

2.3. Scope and limitations of the precatalyst 9

To test the scope and limitations of precatalyst **9** in Suzuki–Miyaura reactions we first chose aryl chlorides[24] as substrates and applied aqueous conditions which would be beneficial when accelerating the C–C-coupling under microwave irradiating condtions.[25,26]

Thus, we therefore focused on the reaction of *p*-chloroacetophenone with various aryl and heteroarylboronic acids. The results for thermal as well as microwave heating are summarized in Table 1. Treatment of *p*-chloroacetophenone (1 equiv) with phenylboronic acid (1.2 equiv), tetrabutylammonium bromide (0.6 equiv) and potassium hydroxide (2 equiv) in the presence of the precatalyst **9** (2.8 mol%) in water (3.5 mL) at 100 °C under air for 16 h resulted in the formation of 4-acetyl-1,1′-biphenyl (**10**) in 76% isolated yield. When this transformation was repeated under identical conditions except that heating was conducted for 30 min with microwave irradiation (160 °C, 250 watt), the coupling product **10** was isolated in 92% yield. The microwave conditions were optimized with respect to energy and reaction time. Therefore, the degree of conversion under microwave heating (160 °C, 250 watt) for the coupling of phenylboronic acid with *p*-chloroacetophenone was analyzed after 2 min (16%), 4 min (45%), 8 min (63%), 15 min (78%) and 30 min (84%; entry 1, Table 1). When reducing the amount (0.7 mol%) of Pd-precatalyst **9** the product **10** was obtained in 55% after 30 min of microwave irradiation. Suzuki–Miyaura reactions of *p*-chloroacetophenone were also conducted with 3,4-methylenedioxyphenylboronic acid (entry 4, Table 1) and with 3-thienylboronic acid (entry 6, Table 1) both under thermal as well as microwave irradiating conditions using potassium hydroxide as base. For comparison reason also, cesium carbonate was employed which has been found by Glorius et al.[27] and Mino et al.[28] to be an effective base for transformations of aryl chlorides into biaryls in Suzuki cross couplings. However, the former base turned out to be superior to cesium carbonate. Homo-coupled products, which are by-products commonly observed in Suzuki–Miyaura reactions were found to be well below 5% as determined by GC-analysis.

In the following we investigated the general utility of precatalyst **9** in Suzuki–Miyaura cross-coupling reactions (Scheme 4 and Table 2). Aryl and heteroaryl bromides were



Scheme 4. For details refer to Table 2.

Table 2

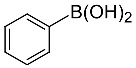
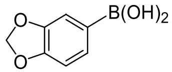
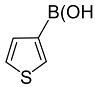
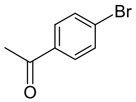
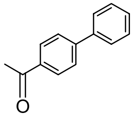
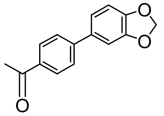
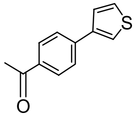
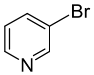
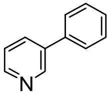
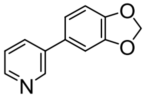
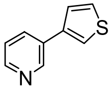
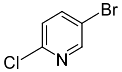
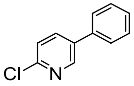
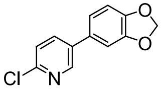
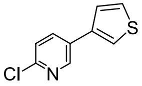
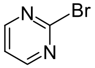
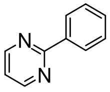
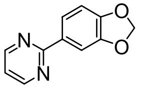
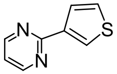
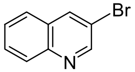
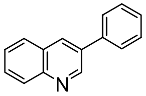
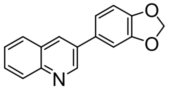
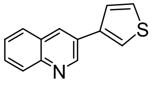
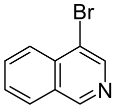
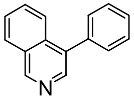
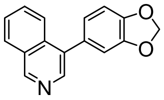
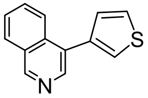
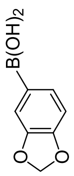
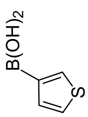
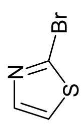
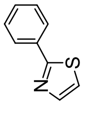
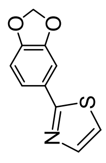
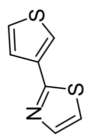
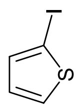
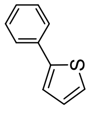
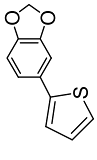
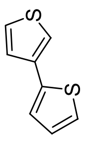
(Het)^{1}Ar-X												
	Thermal ^{a}		Microwave^a		Thermal ^{a}		Microwave^a		Thermal ^{a}		Microwave^a	
	Yield%^{b}	Time (h)	Yield%^{b}	Time (min)	Yield%^{b}	Time (h)	Yield%^{b}	Time (min)	Yield%^{b}	Time (h)	Yield%^{b}	Time (min)
			 **10**				 **11**				 **12**	
	100 (97)	2	100 (98)	2	100 (90)	2	100 (95)	3	94	7	100 (75)	3
			 **13**				 **14**				 **15**	
	100	6	100 (92)	7	64	7	77 (61)	10	85	6	100 (91)	10
			 **16**				 **17**				 **18**	
	100 (81)	4	100	5	100 (85)	4	100 (88)	8	100	2	100 (93)	4
			 **19**				 **20**				 **21**	
	11	7	100 (91)	15	12	7	17	15	35	4	96 (79)	15
			 **22**				 **23**				 **24**	
	100 (97)	4	100 (94)	8	100 (78)	6	100 (93)	10	100 (88)	4	94	11
			 **25**				 **26**				 **27**	
	64	4	100 (89)	10	100 (96)	7	92	10	92 (84)	8	50	10

Table 2 (*continued*)

(Het)^{1}Ar-X												
	Thermal [a]		Microwave[a]		Thermal [a]		Microwave[a]		Thermal [a]		Microwave[a]	
	Yield%[b]	Time (h)	Yield%[b]	Time (min)	Yield%[b]	Time (h)	Yield%[b]	Time (min)	Yield%[b]	Time (h)	Yield%[b]	Time (min)
	 **28** 0	6	17	15	 **29** 0	20	6	15	 **30** 0	18	18	15
	 **31** 100 (89)	6	100 (94)	5	 **32** 100 (88)	2	100 (98)	3	 **33** 100 (85)	7	100 (96)	5

[a] Conditions: halide (1 mmol), boronic acid (1.2 mmol), KOH (2 mmol), TBAB (0.6 mmol), water (3.5 mL), Pd-precatalyst **9** (0.7 mol%), 100 °C thermal heating; 160 °C (250 watt) microwave heating.

[b] GC-yields; values in parentheses refer to isolated yields of pure products.

coupled with boronic acids both under thermal as well as microwave irradiating conditions. The reaction conditions and molar ratios of the reaction components are cited in the legend of Table 2.

Again heating under microwave conditions led to an acceleration of the C–C-coupling reaction. In some cases, yields dramatically improved when switching from conventional heating to microwave heating as is particularly well demonstrated for the formation of biaryls **19**, **21**, and **25**. Chemoselectivity was encountered in the formation of biaryls **16** to **18**. However, the catalyst derived from precatalyst **9** is even not reactive enough to efficiently couple 2-bromothiazole under Suzuki–Miyaura cross-coupling reactions when microwave irradiating conditions are employed.

Although there had been speculations that palladacycles may operate through a Pd(II)/(IV) cycle,[29] studies by Hartwig et al.[30] strongly suggest that, as expected, Pd(0) species have to be made responsible as active catalysts. Therefore, complexes that are listed in Figure 2 as well as **9** may serve as reservoirs that are not involved in the real catalytic cycle[12a] but are a source of coordinative unsaturated 'PdL_n' species of unknown nature or release a considerable amount of colloidal Pd(0) which also can show catalytic activity at low concentrations. Indeed, De Vries and co-workers noted for Heck reactions that low concentrations of Pd(0) in solution will aggregate and deactivate much more slowly than high concentrations.[31] For related SCS–Pd complexes strong evidence has been collected in Heck reactions that they are actually reservoirs of a catalytically active but ill-defined form of Pd(0).[32] However, the picture is more complex as the choice of solvent is crucial in this context, specifically its complexing properties. Other solvents than water (which we applied in our studies) such as DMF or NMP can give supernatants which unlike in cases of aqueous solvents still show catalytic activity in Heck reactions.[15] However, the pyridine ligand present on our polymeric phase still has the potential to scavenge any catalytic species that may have leached into solution during the catalytic process which would explain the low amount of Pd (1.6×10^{-3}–1.28×10^{-3}%) that we determined by ICP-MS after having cooled the reaction mixture to room temperature. In addition, this process may retard the formation and growth of colloids.

3. Conclusions

In conclusion, we demonstrated that Pd-complex **9** is an efficient and highly active, reusable solid-phase anchored precatalyst with extraordinary potential for Suzuki–Miyaura cross-coupling reactions in aqueous media. Importantly, it not only shows activity under thermal but also under microwave irradiating conditions in water thereby showing sufficient reactivity even for arylchlorides. Having tested this precatalyst on the megaporous monolith glass/polymer composite allows us to utilize this material under continuous flow conditions in PASSflow reactors. These are ongoing studies in our laboratories.

4. Experimental

4.1. Materials and methods

NMR spectra were recorded with a Bruker DPX-400 spectrometer at 400 MHz (^{1}H NMR) and at 100 MHz (^{13}C NMR) using $CDCl_3$ as solvent and internal standard (δ = 7.26 and 77.36 ppm, for ^{1}H NMR and ^{13}C NMR, respectively). Mass spectra (EI) were obtained at 70 eV with a type VG autospec apparatus (Micromass). GC analyses were conducted using an HPGC series 6890 Series Hewlett Packard equipped with an SE-54 capillar column (25 m, Macherey–Nagel) and an FID detector 19231 D/E. Melting points were determined in open glass capillaries with a Gallenkamp apparatus and are uncorrected. Analytical thin-layer chromatography was performed using precoated silica gel 60 F254 plates (Merck, Darmstadt), and the spots were visualised with UV light at 254 nm. Merck silica gel 60 (230–400 mesh) was used for flash column chromatography. Microwave experiments were carried out using a CEM Discover Labmate^{TM} microwave apparatus (300 W with ChemDriver^{TM} Software). Commercially available reagents and dry solvents were used as received.

4.2. Preparation of Pd-precatalyst 9

To a mixture of glass/polymer composite shaped Raschig rings (10 g, 5 mmol) containing 10% chloromethylpolystyrene-divinyl benzene polymer (0.53 mmol polymer/g Raschig rings) **7** and *cis*−2-pyridinealdoxime (3.66 g, 30 mmol) in dimethylformamide (DMF) (50 mL), sodium hydride (0.72 g, 60% in oil, 30 mmol) was added portionwise over a period of 20 min. The mixture was shaken at 80 °C for three days then cooled to room temperature and quenched with water (100 mL). The Raschig rings were filtered and washed successively with DMF, water, ethanol, dichloromethane and again with ethanol (20 mL, each time) and finally well-dried under vacuum. These well-dried Raschig rings to which *cis*-2-pyridinealdoxime was bound **8** (6.92 g) were added to a solution of sodium tetrachloropalladate (1.2 g, 4 mmol) in methanol (80 mL) and the mixture was left to be shaken at room temperature for additional three days. The resulting Raschig rings were dried in vacuo and the loading of catalyst **9** was estimated to be ca. 0.09 mmol/g Raschig rings according to weight increase (the weight increase of each single raschig ring was determined; each ring was loaded with about 2.8 mol% palladium with reference of 1 mmol scaled reactions).

4.3. Effect of concentration of the palladium catalyst 9 on the Suzuki–Miyaura coupling in water with thermal heating

A mixture of *p*-bromoacetophenone (1 mmol), phenylboronic acid (1.2 mmol), TBAB (0.6 mmol), palladium catalyst **9** (0.7 mol%), KOH (2 mmol) and water (3.5 mL) was shaken at 100 °C under air for 2 h (monitored by GC). The same experiment was repeated using 0.3 mol% of palladium precatalyst. The amount (mol%) of the palladium precatalyst **9** was changed with respect to *p*-bromoacetophenone (0.1, 0.07, 0.03 and 0.01 mol% Pd-catalyst with scales of 2, 5, 10 and 20 mmol of *p*-bromoacetophenone, respectively). Finally, the same reaction was repeated using 40 mmol of *p*-bromoacetophenone and only 0.005 mol% palladium-complex **9** and the reaction mixture was heated in this case for 3 h at 100 °C under air. The molar ratio of the reaction components were in all cases as follows; *p*-bromoacetophenone, phenylboronic acid, tetrabutylammonium bromide (TBAB), KOH: 1/1.2/0.6/2 (in 3.5 mL water). The conversion (in %) versus concentration of palladium catalyst is shown in Scheme 2.

4.4. Recycling of the palladium precatalyst 9 with thermal heating in water

A mixture of *p*-bromoacetophenone (1 mmol), 3,4-methylenedioxyphenyl boronic acid (1.2 mmol), TBAB (0.6 mmol), palladium catalyst **9** (0.7 mol%), KOH (2 mmol) and water (3.5 mL) was shaken at 100 °C under air for 2 h (monitored by GC). The solid catalyst was removed by filtration, washed with water followed by EtOAc, dried and then reused in a new reaction mixture with the same molar ratio of components mentioned above. Then the mixture was shaken again at 100 °C under air for 2 h. This experiment was repeated in another nine runs (2 h for each run), as shown in Scheme 3. The product was purified by flash column chromatography on silica gel using EtOAc/petroleum ether (1:10) as eluent.

4.5. Recycling of the palladium precatalyst 9 under microwave irradiating conditions in water

The same reaction mixture used under thermal conditions was mixed in a properly capped process vial and thereafter the mixture was subjected to microwave irradiating conditions at 160 °C and 250 watt for 3 min (monitored by GC). The solid catalyst was removed, washed with water followed by EtOAc, dried and then re-used for the next run with the same molar ratio of components. As shown in Scheme 3, the experiment was repeated in another nine runs, each time irradiating for 3 min.

4.6. General procedure for the Suzuki–Miyaura coupling of *p*-chloroacetophenone in water with thermal heating

A mixture of *p*-chloroacetophenone (1 mmol), aryl(heteroaryl) boronic acid (1.2 mmol), tetrabutylammonium bromide (TBAB) (0.6 mmol), palladium precatalyst **9** (2.8 mol%), KOH or Cs_2CO_3 (2 mmol) and distilled water (3.5 mL) was shaken at 100 °C under air for 16 h. The solid catalyst was removed by filtration, washed with water followed by EtOAc. The combined washings were extracted with EtOAc (3×20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ then filtered and the solvent was evaporated under reduced pressure. The product was purified as described above.

4.7. General procedure for the Suzuki–Miyaura coupling of *p*-chloroacetophenone in water under microwave heating

A mixture of *p*-chloroacetophenone (1 mmol), aryl(heteroaryl) boronic acid (1.2 mmol), TBAB (0.6 mmol), palladium catalyst **9** (2.8 mol%), KOH or Cs_2CO_3 as a base (2 mmol) and water (3.5 mL) were mixed in a process vial. The vial was capped properly, and thereafter the mixture was heated under microwave irradiating conditions at 160 °C and 250 watt for the appropriate reaction time as listed in Table 1. After the reaction was completed (monitored by GC), the solid catalyst was removed by filtration and washed. The reaction mixture was extracted with EtOAc (3×10 mL) and combined with the washings. After drying over $MgSO_4$, and concentration in vacuo, the product was isolated by flash column chromatography.

4.8. General procedure for the Suzuki–Miyaura coupling of aryl(heteroaryl) bromides in water with thermal heating

A mixture of aryl(heteroaryl) bromide (1 mmol), aryl(heteroaryl) boronic acid (1.2 mmol), TBAB (0.6 mmol), palladium catalyst **9** (0.7 mol%), KOH (2 mmol) and distilled water (3.5 mL) was shaken at 100 °C under air for the appropriate reaction time listed in Table 2. After the reaction was completed (monitored by GC), the solid catalyst was removed by filtration, washed with water then EtOAc, and the washings were added to the reaction mixture which was then extracted with EtOAc (3×20 mL). The products were purified as described above for the procedure with *p*-bromoacetophenone.

4.9. General procedure for the Suzuki–Miyaura coupling of aryl(heteroaryl) bromides in water under microwave irradiating conditions

A mixture of the appropriate aryl(heteroaryl) bromide (1 mmol), aryl(heteroaryl) boronic acid (1.2 mmol), TBAB (0.6 mmol), palladium catalyst **9** (0.7 mol%), KOH (2 mmol) and water (3.5 mL) were mixed in a process vial. The vial was capped properly, and thereafter the mixture was heated under microwave irradiating conditions at 160 °C and 250 watt for the appropriate reaction time as listed in Table 2. The products were purified according to the procedure described above for *p*-bromoacetophenone.

4.9.1. 4-Acetyl-1,1′-biphenyl (10). Colorless crystals, mp 119–120 °C (Ref.[33] mp 118–120 °C); ^1H NMR ($CDCl_3$) δ 2.64 (s, 3H, CH_3CO), 7.36–7.42 (m, 1H), 7.46–7.49 (m, 2H), 7.62–7.65 (m, 2H), 7.69 (d, 2H, $J=8.52$ Hz), 8.03 (d, 2H, $J=8.52$ Hz); ^{13}C NMR δ 27.0, 127.5, 127.6, 128.6, 129.2, 129.3, 136.2, 140.2, 146.1, 198.1; MS (*m/e*) 196 (M^+), 181, 152, 127, 102, 91, 76.

4.9.2. 3,4-Methylenedioxy-4′-acetylbiphenyl (11). Colorless crystal, mp 140–141 °C; ^1H NMR ($CDCl_3$) δ 2.62 (s, 3H, CH_3CO), 6.01 (s, 2H, $-OCH_2O-$), 6.89 (d, 1H, $J=8.3$ Hz), 7.09–7.13 (m, 2H), 7.59 (d, 2H, $J=8.4$ Hz), 7.99 (d, 2H, $J=8.4$ Hz); ^{13}C NMR δ 26.9, 101.7, 107.9, 109.1, 121.4, 127.1, 129.2, 134.4, 135.8, 145.7, 148.2, 148.7, 197.9; MS (*m/e*) 240 (M^+), 225, 197, 167, 139, 112, 98, 69. Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.96; H, 4.83.

4.9.3. *p*-(3-Thienyl)acetophenone (12).[34] Colorless crystals, mp 149–150 °C (no mp given in Ref.[34]); ^1H NMR ($CDCl_3$) δ 2.62 (s, 3H, CH_3CO), 7.42–7.44 (m, 2H), 7.57–7.58 (m, 1H), 7.68 (d, 2H, $J=8.52$ Hz), 7.98 (d, 2H, $J=8.52$ Hz); ^{13}C NMR δ 26.9, 122.4, 126.5, 126.7, 127.1, 129.4, 135.9, 140.5, 141.4, 197.9; MS (*m/e*) 202 (M^+), 187, 159, 115, 93, 79.

4.9.4. 3-Phenylpyridine (13).[35] Colorless oil; ^1H NMR ($CDCl_3$) δ 7.33–7.61 (m, 6H), 7.84–7.90 (m, 1H), 8.59 (dd, 1H, $J=4.86$, 1.62 Hz), 8.85 (d, 1H, $J=1.76$ Hz); MS (*m/e*) 155 (M^+), 127, 102, 87, 77, 64.

4.9.5. 3-(3,4-Methylenedioxyphenyl)pyridine (14). Pale brown crystals, mp 99–100 °C; ^1H NMR ($CDCl_3$) δ 5.99 (s, 2H, $-OCH_2O-$), 6.89 (d, 1H, $J=8.5$ Hz), 7.01–7.04 (m, 2H), 7.29–7.32 (dd, 1H, $J=7.9$, 7.9 Hz), 7.76–7.78 (m, 1H), 8.54 (dd, 1H, $J=4.8$, 1.5 Hz), 8.77 (d, 1H, $J=1.9$ Hz); ^{13}C NMR δ 101.6, 107.7, 109.1, 121, 123.7, 132.2, 134.2, 136.6, 148, 148.3, 148.3, 148.6; MS (*m/e*) 198 (M^+), 140, 114, 99, 86, 62. Anal. Calcd for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.20; H, 4.32; N, 6.96.

4.9.6. 3-(3-Thienyl)pyridine (15).[36] Colorless crystals, mp 76–77 °C (Ref.[36] mp 73–74 °C); ^1H NMR ($CDCl_3$) δ 7.26–7.32 (m, 1H), 7.37–7.44 (m, 2H), 7.50–7.52 (m, 1H), 7.84 (m, 1H), 8.52 (dd, 1H, $J=4.8$, 1.72 Hz), 8.86 (d, 1H, $J=1.72$ Hz); ^{13}C NMR δ 121.7, 123.9, 126.2, 127.3, 131.8, 133.8, 139.1, 147.9, 148.5; MS (*m/e*) 161 (M^+), 134, 117, 108, 81, 63, 45.

4.9.7. 2-Chloro-5-phenylpyridine (16).[37] Colorless crystals, mp 54–55 °C (Ref.[37] mp 55–56 °C); ^1H NMR ($CDCl_3$) δ 7.37–7.58 (m, 6H), 7.81–7.87 (dd, 1H, $J=8.26$, 2.52 Hz), 8.61 (d, 1H, $J=2$ Hz); MS (*m/e*) 189 (M^+), 154, 127, 102, 95, 63, 51.

4.9.8. 2-Chloro-5-(3,4-methylenedioxyphenyl)pyridine (17). Pale yellow powder, mp 150–151 °C; ^1H NMR ($CDCl_3$) δ 6.02 (s, 2H, $-OCH_2O-$), 6.90 (d, 1H, $J=8.6$ Hz), 6.99–7.02 (m, 2H), 7.35 (d, 1H, $J=8.3$ Hz), 7.75 (dd, 1H, $J=8.3$, 2.5 Hz), 8.52 (d, 1H, $J=2.4$ Hz); ^{13}C NMR δ 101.8, 107.7, 109.3, 121.1, 124.4, 130.9, 135.7, 137.2, 148, 148.4, 148.9, 150.2; MS (*m/e*) 233 (M^+), 140, 113, 99, 85. Anal. Calcd for $C_{12}H_8ClNO_2$: C, 61.69; H, 3.45; N, 5.99. Found: C, 61.62; H, 3.32; N, 5.97.

4.9.9. 2-Chloro-5-(3-thienyl)pyridine (18). Colorless crystals, mp 95–96 °C; ^1H NMR ($CDCl_3$) δ 7.33–7.35 (m, 2H), 7.44–7.46 (m, 1H), 7.50–7.51 (m, 1H), 7.81 (dd, 1H, $J=8.3$, 2.6 Hz), 8.61 (d, 1H, $J=2$ Hz); ^{13}C NMR δ 122.1, 124.6, 126, 127.6, 130.8, 136.6, 137.7, 147.6, 150.1; MS (*m/e*) 195 (M^+), 160, 133, 116, 89, 63. HRMS, calcd for C_9H_6ClNS: 195.9988. Found: 195.9981. Anal. Calcd for C_9H_6ClNS: C, 55.24; H, 3.09; N, 7.16. Found: C, 55.81; H, 3.19; N, 6.99.

4.9.10. 2-Phenylpyrimidine (19).[38] Pale yellow oil (Ref.[38] mp 36–38 °C); ^1H NMR ($CDCl_3$) δ 7.18 (dd, 1H, $J=4.88$, 4.76 Hz), 7.44–7.51 (m, 3H), 8.42–8.48 (m, 2H), 8.81 (d, 2H, $J=4.78$ Hz); MS (*m/e*) 156 (M^+), 128, 103, 76, 51.

4.9.11. 2-(3-Thienyl)pyrimidine (21).[39] Pale yellow powder, mp 95–97 °C (Ref.[39] mp 95 °C); ^1H NMR ($CDCl_3$) δ 7.12 (dd, 1H, $J=4.90$, 4.76 Hz), 7.36–7.41 (dd, 1H, $J=5.02$, 1.12 Hz), 7.28–7.30 (dd, 1H, $J=3.02$, 1.12 Hz), 8.74 (d, 1H, $J=4.90$ Hz); MS (*m/e*) 162 (M^+), 135, 109, 81, 45.

4.9.12. 3-Phenylquinoline (22).[40] Pale yellow powder, mp 49–50 °C (Ref.[40] mp 52 °C); ^{1}H NMR ($CDCl_3$) δ 7.36–7.56 (m, 4H), 7.64–7.73 (m, 3H), 7.80 (d, 1H, $J=8.4$ Hz), 8.15 (d, 1H, $J=8.4$ Hz), 8.22 (d, 1H, $J=1.88$ Hz), 9.18 (d, 1H, $J=2.28$ Hz); MS (*m/e*) 205 (M^+), 176, 151, 126, 102, 88, 76, 63.

4.9.13. 3-(3,4-Methylenedioxyphenyl)quinoline (23). Pale yellow powder, mp 110–111 °C; ^{1}H NMR ($CDCl_3$) δ 6.02 (s, 2H, –OCH_2O–), 6.94 (d, 1H, $J=8.5$ Hz), 7.13–7.19 (m, 2H), 7.51–7.59 (m, 1H), 7.65–7.73 (m, 1H), 7.81 (d, 1H, $J=7.7$ Hz), 8.12 (d, 1H, $J=8.3$ Hz), 8.18 (d, 1H, $J=2$ Hz), 9.11 (d, 1H, $J=2.2$ Hz); ^{13}C NMR δ 101.7, 108, 109.3, 121.4, 127.3, 128.2, 128.3, 129.4, 129.5, 132.2, 133, 133.8, 147.3, 148.1, 148.8, 150; MS (*m/e*) 249 (M^+), 190, 163, 124, 110, 96, 81, 62. Anal. Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found: C, 77.00; H, 4.23; N, 5.54.

4.9.14. 3-(3-Thienyl)quinoline (24).[41] Pale yellow powder; mp 88–89 °C (Ref.[41] mp 86–88 °C); ^{1}H NMR ($CDCl_3$) δ 7.45–7.58 (m, 3H), 7.63–7.74 (m, 2H), 7.81–7.86 (dd, 1H, $J=8.14$, 1.12 Hz), 8.12 (d, 1H, $J=8.24$ Hz), 8.27 (d, 1H, $J=2$ Hz), 9.20 (d, 1H, $J=2$ Hz); ^{13}C NMR δ 121.9, 126.4, 127.4, 128.2, 128.4, 129.1, 129.5, 129.6, 132.4, 139.1, 147.4, 149.7; MS (*m/e*) 211 (M^+), 179, 167, 139, 105, 92, 79.

4.9.15. 4-Phenylisoquinoline (25).[42] Light yellow oil; (Ref[42] mp 76–78 °C); ^{1}H NMR ($CDCl_3$) δ 7.37–7.62 (m, 7H), 7.86–7.99 (m, 2H), 8.48 (s, 1H), 9.23 (s, 1H); MS (*m/e*) 205 (M^+), 176, 151, 102, 88, 76.

4.9.16. 4-(3,4-Methylenedioxyphenyl)isoquinoline (26). Yellow-brownish powder, mp 157–158 °C; ^{1}H NMR ($CDCl_3$) δ 6.04 (s, 2H, –OCH_2O–), 6.95–6.98 (m, 3H), 7.58–7.68 (m, 2H), 7.94 (d, 1H, $J=8.5$ Hz), 8.01 (d, 1H, $J=8.5$ Hz), 8.46 (s, 1H), 9.23 (s, 1H); ^{13}C NMR δ 101.5, 108.8, 110.7, 123.9, 125, 127.4, 128.1, 128.7, 130.8, 130.9, 133.2, 134.6, 143, 147.8, 148.1, 152; MS (*m/e*) 249 (M^+), 190, 163, 110, 96, 82, 63. HRMS, calcd for $C_{16}H_{11}NO_2$: 250.0868. Found: 250.0857. Anal. Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found: C, 76.61; H, 4.16; N, 5.51.

4.9.17. 4-(3-Thienyl)isoquinoline (27).[43] Yellow oil (Ref.[43] mp 198–200 °C); ^{1}H NMR ($CDCl_3$) δ 7.31 (dd, 1H, $J=4.88$, 1.36 Hz), 7.44–7.50 (m, 2H), 7.58–7.69 (m, 2H), 8.01 (dd, 1H, $J=7.76$, 7.64 Hz), 8.54 (s, 1H), 9.22 (s, 1H); ^{13}C NMR δ 124.6, 124.9, 126.3, 127.5, 128.2, 128.5, 128.7, 129.4, 130.9, 134.5, 137.6, 143.0, 152.2; MS (*m/e*) 211 (M^+), 184, 166, 152, 139, 105, 91, 83.

4.9.18. 2-Phenylthiophene (31).[44] Colorless powder, mp 33–34 °C (Ref.[44] mp 35 °C); ^{1}H NMR ($CDCl_3$) δ 7.08 (dd, 1H, $J=5.14$, 5.02 Hz), 7.26–7.42 (m, 5H), 7.58–7.64 (m, 2H); MS (*m/e*) 160 (M^+), 134, 115, 102, 89, 63, 45.

4.9.19. 2-(3,4-Methylenedioxyphenyl)thiophene (32). Pale green powder, mp 58–59 °C; ^{1}H NMR ($CDCl_3$) δ 5.94 (s, 2H, –OCH_2O–), 6.79 (d, 1H, $J=8.5$ Hz), 7.01 (m, 1H), 7.07 (m, 2H), 7.14 (d, 1H, $J=3.9$ Hz), 7.18 (d, 1H, $J=5$ Hz); ^{13}C NMR δ 101.5, 106.9, 108.9, 120, 122.8, 124.3, 128.2, 129.1, 144.6, 147.4, 148.4; MS (*m/e*) 204 (M^+), 145, 102, 87, 63. Anal. Calcd for $C_{11}H_8O_2S$: C, 64.69; H, 3.95. Found: C, 64.67; H, 3.84.

4.9.20. 2,3′-Bithienyl (33).[45] Brown crystals, mp 64–66 °C (Ref.[45] mp 62–64 °C); ^{1}H NMR ($CDCl_3$) δ 7.02 (dd, 1H, $J=4.38$, 4.26 Hz), 7.17 (s, 1H), 7.18–7.20 (m, 1H), 7.29–7.31 (m, 2H), 7.34–7.37 (m, 1H); MS (*m/e*) 166 (M^+), 134, 121, 108, 90, 69, 45.

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