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Arylation of Allyl Alcohols in Organic and Aqueous Media Catalyzed by Oxime-Derived Palladacycles: Synthesis of β-Arylated Carbonyl Compounds

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Dedicated to Prof. Jan Bäckvall on the occasion of his 60th birthday.

Abstract: A 4-hydroxyacetophenone oxime-derived palladacycle catalyzes the Mizoroki–Heck reaction of allyl alcohols with aryl iodides, bromides, and chlorides in aqueous and organic solvents. The reaction takes place in the presence of dicyclohexylmethylamine or cesium carbonate as bases, the addition of tetrabutylammonium bromide (TBAB) as additive for aryl bromides and chlorides being necessary. Under these reaction conditions, β-arylated aldehydes and ketones are mainly obtained using a rather low loading of palladium (0.1–1 mol%). Similar catalytic activity is shown by a Kaiser oxime resin-derived palladacycle, which allows one to perform recycling and reusing experiments with low Pd leaching. The high regio- and chemoselectivity observed supported that these palladacycles, working as a source of Pd(0) species, operates mainly through a neutral mechanism. This methodology has been applied to the synthesis of important β-arylated carbonyl compounds, such as 4-phenylbutan-2-one, 4-(4-hydroxyphenyl)butan-2-one, dihydrochalcones, the anti-inflamatory nabumetone, and the fragance β-lilial®. γ-Arylation is observed in the reactions of allyl alcohol and but-3-en-2-ol with 2-iodoaniline giving mainly the corresponding quinolines. The same tendency is observed in the case of 1,1-dimethylallyl alcohol affording either γ-arylated alcohols or (*E*)-1-arylisoprenes.

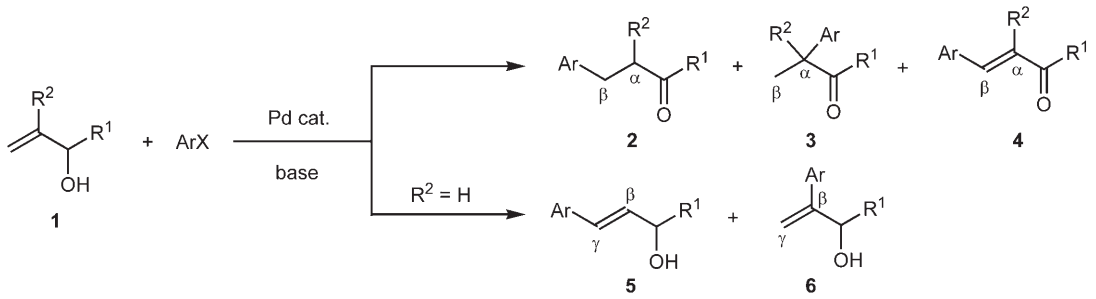
Keywords: allyl alcohols; carbonyl compounds; Heck reaction; palladacycles; polymeric reagents

Introduction

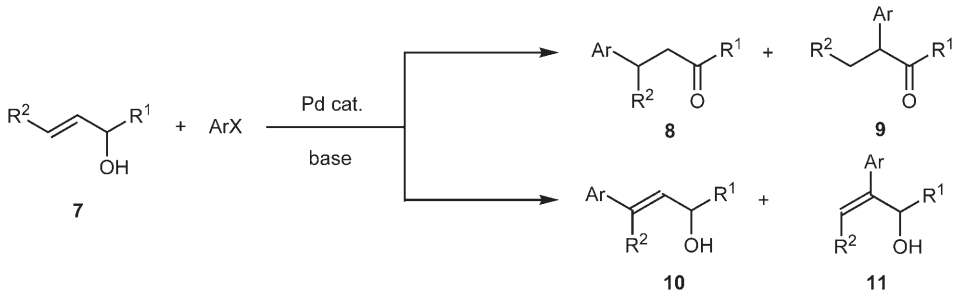
β-Arylated saturated aldehydes and ketones are important products as well as useful intermediates for the synthesis of valuable pharmaceuticals, natural products, and fragrances. Some of these interesting ketones are 4-phenylbutan-2-one, an enzyme inhibitor,[1] 4-(4-hydroxyphenyl)butan-2-one, the precursor of an anticancer agent,[2] and dihydrochalcones,[3] which have shown antifungal, antibacterial,[4] anticancer,[5] antioxidant,[6] and food sweetener[7] properties. Dihydrochalcones have been used as appropriate intermediates for the synthesis of flavenes[8] and anthocyanin-derived dyes.[9] Nabumetone, 4-(6′-methoxy-2′-naphthyl)butan-2-one, has shown good nonsteroidal anti-inflammatory activity like the α-arylpropionic acids, ibuprofen and naproxen.[10] Representative examples of β-arylated saturated aldehydes with similar enzymatic inhibition activity as 4-phenylbutan-2-one are dihydrocinnamaldehyde and 3-phenylbutanal.[1] In addition, β-lilial,® 3-(4-*tert*-butylphenyl)-2-methylpropanal, is a common fragrance and an intermediate in the production of the biodegradable fungicide fenpropimorph (Corbel®).[11]

One of the most direct and general strategies for the preparation of these β-arylated saturated carbonyl compounds is the Pd-catalyzed arylation of allyl alcohols.[12] Allyl alcohols are inexpensive and very convenient starting materials to perform the Mizoroki–Heck reaction. However, there are problems associated with the regioselectivity of this process giving α- and β-arylated carbonyl compounds and also, β- and γ-arylated allyl alcohols with *E* or *Z* configuration (Scheme 1 and Scheme 2).

In the case of γ-unsubstituted primary and secondary allyl alcohols of the type **1**, β- and α-arylated saturated aldehydes or ketones **2** and **3** are predominantly formed (Scheme 1), whereas another secondary product can be the unsaturated ketones **4** when working under air[13] or in the presence of $Cu(OTf)_2$[14]



Scheme 1.



Scheme 2.

(Scheme 1). The formation of γ-arylated allyl alcohols **5** as major products has been observed by Jeffery in the reaction of secondary allyl alcohols **1** with aryl iodides when stoichiometric amount of a silver salt was used as additive,[15] or in the case of using Cs_2CO_3 as base.[16] Similar results have been described when using aryl triflates[17] or iodonium salts.[18] In the case of the reaction of primary and secondary allyl alcohols **1** with aryl bromides, mainly β-arylated allyl alcohols **5** and α-arylated by-products **6** were formed even in the absence of silver salts[19] (Scheme 1). More recently, Caló and colleagues have reported that the arylation of primary and secondary allyl alcohols **1** with aryl bromides in ionic liquids, such as tetra-*n*-butylammonium bromide (TBAB), and $NaHCO_3$ as base gave mainly carbonyl compounds **2** as well as α-arylated compounds **3** as by-products.[20] However, using tetra-*n*-butylammonium acetate (TBAA) as ionic liquid and base, γ- and β-arylated allyl alcohols **5** and **6** were chemoselectively obtained.[21] Moreover, working in 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4 as ionic liquid and 1,3-bis(diphenylphosphino)propane (dppp) as ligand, mainly γ-arylation of allyl alcohol with aryl bromides has been observed.[22] Furthermore, the regioselective formation of β-arylated carbonyl compounds with aryl bromides can be achieved by using the tetraphosphine Tedicyp as ligand in DMF and with K_2CO_3 as base with high turnover numbers (TON).[23] Deactivated aryl bromides have been used for the γ-arylation and applied to the synthesis of a variety of dihydrochalcones using ligand free $Pd(OAc)_2$ or the Herrmann's catalyst in moderate yields.[3]

Similarly, γ-substituted allyl alcohols **7** can suffer γ- and β-arylation with or without double bond isomerization to afford carbonyl compounds **8** and **9** or allyl alcohols **10** and **11**, respectively (Scheme 2). Caló and colleagues have found that when working in TBAB as solvent and using $NaHCO_3$ as base, carbonyl compounds **8** and **9** were formed. However, allylic alcohols **10** and **11** were chemoselectively obtained when using TBAA as solvent and base.[21]

For Heck reactions with electron-rich alkenes it has been proposed that the β-arylation occurred through an ionic pathway and the γ-arylation takes place *via* a neutral mechanism, although steric effects can also be responsible.[21–24] The ionic pathway is mainly observed when the halide anion is not bonded to Pd(II). This is the case when silver or thallium salts are added, when employing triflates as arylating reagents, when using halide-free ionic liquids as solvents, or when adding diphosphines, such as 1,3-bis(diphenylphosphino)propane or 1,1′-bis(diphenylphosphino)ferrocene.[24] On the other hand, the isomerization process can be avoided by working in halide-free ionic liquids to give γ-arylated allyl alcohols, such as **5** and **10**.[21]

In our laboratory we have been working on the use of oxime-derived palladacycles as a source of highly active zero-valent palladium nanoparticles for phosphine-free C–C bond forming reactions, Heck, Suzuki, Stille, Ullmann, Cassar–Heck–Sonogashira,

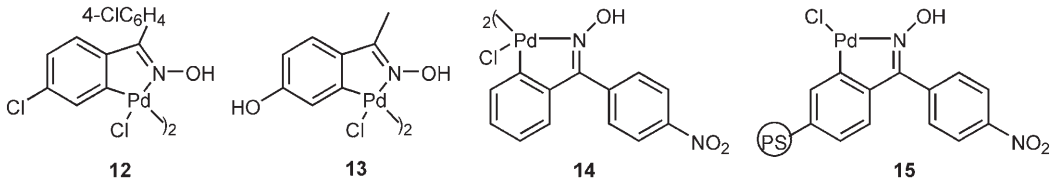
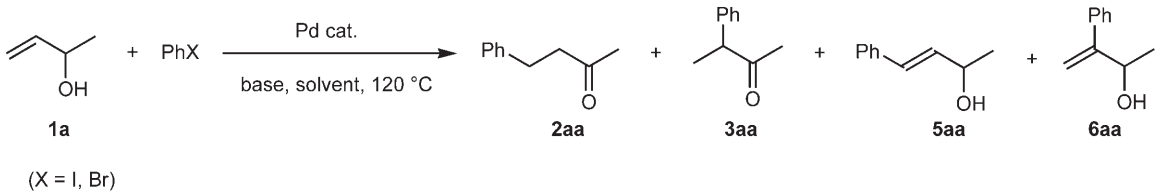


Figure 1.

Glaser, Hiyama and alkoxycarbonylation reactions of alkynes, in organic and aqueous media.[25–28] In this work the application of the dimeric oxime-derived palladacycles **12**–**14** and the Kaiser oxime resin derivative **15** (Figure 1) as precatalysts in the chemo- and regioselective arylation of allyl alcohols in organic and aqueous solvents, focused to the synthesis of β-arylated saturated aldehydes, and ketones, is described.

Results and Discussion

For the preliminary studies, iodobenzene and but-3-en-2-ol (**1a**)[29,30] were allowed to react in H_2O at 120 °C in a pressure tube with different bases and precatalysts (0.1 mol % Pd loading) (Scheme 3 and Table 1). Initially, dicyclohexylmethylamine was chosen as base, because previous results in Heck reactions have shown that this tertiary amine gives better results than triethylamine.[26l,28] Different palladacyles



Scheme 3.

Table 1. Heck reactions of but-3-en-1-ol (**1a**) with iodo- and bromobenzene: reaction conditions study.[a]

Entry	PhX	Cat. [mol % Pd]	Base	Solvent	Additive	*t*	Yield [%][b]	Ratio[c] **2aa/3aa/5aa/6aa**
1	PhI	**12** [0.1]	Cy_2NMe	H_2O	-	6 h	0	-
2		**13** [0.1]	Cy_2NMe	H_2O	-	6 h	98 (89)	44/15/3.5/1
3		**13** [0.1]	Cy_2NMe	H_2O	-	10 min[d]	81	28/1.5/3/1
4		**14** [0.1]	Cy_2NMe	H_2O	-	6 h	93	45/1.5/2.5/1
5		**15** [0.1]	Cy_2NMe	H_2O	-	6 h	99 (92)	44/1.5/3.5/1
6		$Pd(OAc)_2$ [0.1]	Cy_2NMe	H_2O	-	6 h	75	29/1/2.5/1
7		**13** [0.1]	Cs_2CO_3	H_2O	-	6 h	76	33/1/1.5/1.5
8		**15** [0.1]	Cs_2CO_3	H_2O	-	6 h	65	3271/8/1.5
9	PhBr	**13** [1]	Cy_2NMe	H_2O	TBAB[e]	6 h	67	44/1.5/3.5/1
10		**13** [1]	Cs_2CO_3	H_2O	TBAB[e]	6 h	68	35/1/12.5/2
11		**13** [1]	Cy_2NMe	DMA:H_2O[f]	TBAB[e]	6 h	96 (83)	46/1/2.5/1
12		**13** [1]	Cs_2CO_3	DMA:H_2O[f]	TBAB[e]	6 h	94	36/1/12/1.5
13		$Pd(OAc)_2$ [1]	Cy_2NMe	DMA:H_2O[f]	TBAB[e]	6 h	44	30/2/1/0
14		**15** [1]	Cy_2NMe	DMA:H_2O[f]	TBAB[e]	6 h	81	45/2/2/1
15		**15** [1]	Cs_2CO_3	DMA:H_2O[f]	TBAB[e]	6 h	48	34/1/13/2

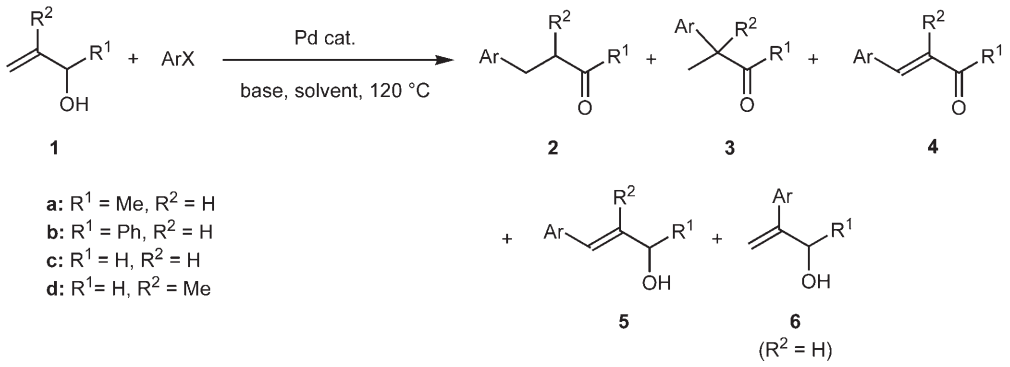
[a] *Reaction conditions:* phenyl halide (1 equiv.), but-3-en-1-ol (1.5 equivs.), Pd catalyst (see column), base (1.5 equivs.), solvent at 120 °C in a pressure tube.
[b] Determined by ^1H NMR by using *N,N*-diphenylformamide as internal standard. In parenthesis yield of compound **2** after flash chromatography.
[c] Determined by GC in the crude products.
[d] Under microwave irradiation at 120 °C (80 W).
[e] 1 equiv.
[f] 4/1.

12–15 and $Pd(OAc)_2$[31] were evaluated as precatalysts during 6-h reaction times. Under these aqueous conditions, the 4,4′-dichlorobenzophenone oxime-derived palladacycle **12** failed (Table 1, entry 1). However, 4-hydroxyacetophenone oxime palladacycle **13** gave products in 98% crude yield, the arylation taking place at the γ-position of the allylic alcohol **1a**. A 15:1 ratio of the β-substituted ketone **2aa** and allyl alcohol **5aa** was regioselectively obtained, whereas only a very small proportion of α-products **3aa** and **6aa** were formed (Table 1, entry 2). When this reaction was performed under microwave heating,[32] a lower overall yield of 81% and similar regioisomeric ratio were obtained (Table 1, entry 3). Similar results were observed when using dimeric and polymeric palladacycles **14** and **15**, whereas $Pd(OAc)_2$ gave the lowest yield (Table 1, compare entry 2 with entries 4–6). The dimeric palladacycle **14** was chemically characterized by reduction with sodium cyanoborodeuteride to the corresponding 2-deuteriophenyl 4-nitrophenyl ketone oxime. Polystyrene-supported palladacycle **15** (12.5 mg g^{-1} of polymer) was prepared from commercially available Kaiser oxime resin by treatment with Li_2PdCl_4 in MeOH and NaOAc as base.[28] However, when Kaiser oxime resin was treated with a solution of Li_2PdCl_4 in the absence of NaOAc as base, the resulting polymer gave products **2aa**, **3aa**, **5aa**, and **6aa** in only 16% overall yield working under the same reaction conditions as complex **15** (Table 1, entry 5). The use of inorganic bases, such as KOH, K_2CO_3, K_3PO_4, and NaOAc in the presence of palladacycle **13** provided lower yields and increased the proportion of γ-arylated allyl alcohol **5aa**.[16] The best inorganic base was Cs_2CO_3 which, in the presence of complexes **13** and **15**, gave Heck products in 76 and 65% yield, respectively, with *ca.* 65:30 ratio of **2aa**:**5aa** and 5% of products **3aa** and **6aa** resulting from the β-arylation of **1a** (Table 1, entries 7 and 8).

When the coupling experiments were performed using deactivated bromobenzene in the presence of palladacycle **13** (1 mol% Pd loading) and dicyclohexylmethylamine or Cs_2CO_3 as bases in H_2O as solvent, the addition of 1 equiv. of TBAB[33] was necessary in order to achieve good conversions in a 6-h reaction time (Table 1, entries 9 and 10). Similar studies in a 1:4 mixture of aqueous *N,N*-dimethylacetamide (DMA) and in the presence of TBAB and with palladacycles **13** or **15** (Table 1, entries 11, 12, 14, and 15) afforded higher overall yields than when using $Pd(OAc)_2$ (Table 1, entry 13). Under these reaction conditions dicyclohexylmethylamine gave the highest ratio of 4-phenylbutan-2-one (**2aa**) whereas, as abovementioned for iodobenzene, Cs_2CO_3[16] favored the formation of allyl alcohol **5aa** (Table 1, entries 12 and 15).

On the basis of these experiments it can be concluded that dicyclohexylmethylamine is the base of choice in order to get mainly the β-arylated ketone, 4-phenylbutan-2-one (**2aa**), either with iodo- or bromobenzene. These results indicate that Cs_2CO_3 promotes to some extent the ionic mechanism facilitating the displacement of the halogen atom bonded to the intermediate ArPdX.[21] In the first case, the process can be performed in neat water and in the case of bromobenzene TBAA must be used as additive and aqueous DMA as solvent. Concerning the catalyst, similar results were obtained using dimeric and polymeric palladacycles with relative low loadings of Pd, whereas $Pd(OAc)_2$ gave lower yields.

Optimized reaction conditions were employed for the Heck reaction of secondary (**1a,b**) and primary (**1c,d**) allyl alcohols with different aryl halides using dimeric and polymeric palladacycles **13–15** as precatalysts (Scheme 4 and Table 2). The arylation of but-3-en-1-ol (**1a**) was performed with iodobenzene (Table 1, entries 2 and 5) and 4-iodophenol using dicyclohexylmethylamine as base in H_2O as solvent (Table 2, entries 1 and 2) and with palladacycles **13** and **15** as precatalyst in order to prepare 4-phenylbutan-2-one (**2aa**)[1] and the precursor of an anticancer agent 4-(4-hydroxyphenyl)butan-2-one (**2ab**),[2] respectively, in very good yields. The arylation with the highly deactivated 4-iodophenol needed the addition of TBAB and to increase to 1 mol% the loading of



Scheme 4.

Table 2. Heck arylations of allyl alcohols **1** in the presence of palladacycles **13–15**.[a]

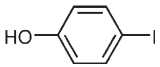
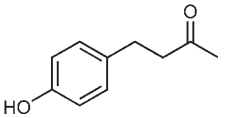
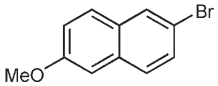
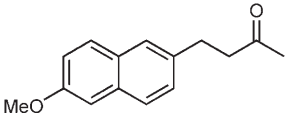
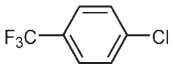
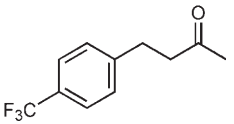
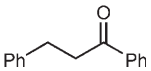
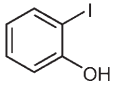
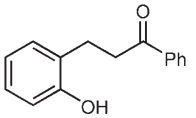
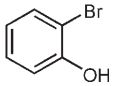
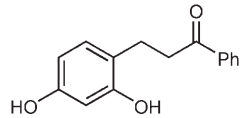
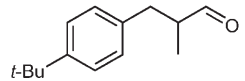
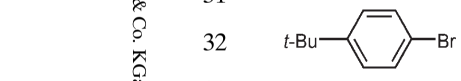
Entry	ArX	Allyl alcohol	Cat. [mol% Pd]	Base	Solvent	Additive	*t*	Ratio[b] **2/3/5/6**	Yield [%][c]	No.	Product
1		**1a**	**13** [1]	Cy_2NMe	H_2O	TBAB	5 h	17/3/1/1	76 (54)	**2ab**	
2		**1a**	**15** [1]	Cy_2NMe	H_2O	TBAB	20 h	11/2/1/1	88 (81)	**2ab**	
3		**1a**	**13** [1]	Cy_2NMe	DMA:H_2O[d]	TBAB	9 h	32/0/1/0	86 (82)	**2ac**	
4		**1a**	**14** [1]	Cy_2NMe	DMA:H_2O[d]	TBAB	10 h	32/0/1/0	93	**2ac**	
5		**1a**	**15** [1]	Cy_2NMe	DMA:H_2O[d]	TBAB	14 h	32/0/1/0	84	**2ac**	
6		**1a**	**13** [0.5]	Cy_2NMe	DMA:H_2O[d]	TBAB	1 d	24/0/1/0	82	**2ac**	
7		**1a**	**13** [0.5]	Cy_2NMe	DMA	TBAB	1 d	49/0/1/0	90	**2ac**	
8		**1a**	**15** [0.5]	Cy_2NMe	DMA	TBAB	1 d	32/0/1/0	56	**2ac**	
9		**1a**	**13** [1]	Cy_2NMe	DMA	TBAB	1 d	11/0/1/0	74[e] (70)	**2ad**	
10		**1a**	**15** [1]	Cy_2NMe	DMA	TBAB	1 d	9/0/1/0	56[e]	**2ad**	
11	PhI	**1b**	**13** [0.1]	Cy_2NMe	H_2O	-	10 h	62/3/1/1	92 (85)	**2ba**	
12		**1b**	**15** [0.1]	Cy_2NMe	H_2O	-	16 h	47/2.5/1/0	83	**2ba**	
13		**1b**	**13** [0.1]	Cy_2NMe	H_2O	TBAB	14 h	10/1/2/1	68[f]	**2be**	
14		**1b**	**13** [0.1]	Cy_2NMe	H_2O	-	14 h	9/0/1/1	55[f] (42)	**2be**	
15		**1b**	**15** [0.1]	Cy_2NMe	H_2O	-	14 h	6/0/1/1	54[f]	**2be**	
16		**1b**	**13** [0.1]	Cy_2NMe	DMA:H_2O[d]	TBAB	4 h	11/0/1/1	87[f]	**2be**	
17		**1b**	**13** [3]	Cy_2NMe	DMA:H_2O[d]	TBAB	14 h	5/0/1/1	61[g]	**2be**	
18		**1b**	**15** [3]	Cy_2NMe	DMA:H_2O[d]	TBAB	1 d	6/0/1/1	56[g]	**2be**	
19		**1b**	**13** [3]	Cy_2NMe	DMA	TBAB	14 h	6/0/1/1	58[g] (49)	**2be**	

Table 2. (Continued)

Entry	ArX	Allyl alcohol	Cat. [mol% Pd]	Base	Solvent	Additive	*t*	Ratio[b] **2/3/5/6**	Yield [%][c]	No.	Product
20		**1b**	**13** [3]	Cy_2NMe	DMA:H_2O[d]	TBAB	20 h	8/1/0/0	46[h] (33)	**2bf**	
21		**1b**	**14** [3]	Cy_2NMe	DMA:H_2O[d]	TBAB	15 h	8/1/0/0	45[h]	**2bf**	
22		**1b**	**15** [3]	Cy_2NMe	DMA:H_2O[d]	TBAB	16 h	7/1/0/0	42[h]	**2bf**	
23	PhI	**1c**	**13** [0.1]	Cs_2CO_3	H_2O	-	8 h	18/0/2.4/1	90	**2ca**	
24		**1c**	**15** [0.1]	Cs_2CO_3	H_2O	-	10 h	20/0/3/1	75	**2ca**	
25		**1c**	**13** [0.1]	Cy_2NMe	H_2O	-	7 h	18/1/1/0	91	**2ca**	
26		**1c**	**15** [0.1]	Cy_2NMe	H_2O	-	10 h	16/1/1/0	93 (81)	**2ca**	
27	PhBr	**1c**	**13** [1]	Cy_2NMe	DMA:H_2O[d]	TBAB	7 h	20/1/1/0	88	**2ca**	
28		**1c**	**15** [1]	Cy_2NMe	DMA:H_2O[d]	TBAB	19 h	18/1/1/0	83 (71)	**2ca**	
29		**1d**	**13** [0.1]	Cy_2NMe	H_2O	-	6 h	100/0/0/0	89 (76)	**2dg**	
30		**1d**	**14** [0.1]	Cy_2NMe	H_2O	-	5 h	100/0/0/0	93	**2dg**	
31		**1d**	**15** [0.1]	Cy_2NMe	H_2O	-	10 h	100/0/0/0	97	**2dg**	
32		**1d**	**13** [1]	Cy_2NMe	DMA:H_2O[d]	TBAB	4 h	100/0/0/0	65	**2dg**	
33		**1d**	**13** [1]	Cy_2NMe	DMA	TBAB	8 h	100/0/0/0	89(74)	**2dg**	
34		**1d**	**15** [1]	Cy_2NMe	DMA	TBAB	14 h	100/0/0/0	84	**2dg**	

[a] *Reaction conditions:* aryl halide (1 equiv.), allyl alcohol **1** (1.5 equivs.), catalyst (see column), base (1.5 equiv.), TBAB (1 equiv.), solvent, 120°C in a pressure tube.
[b] Determined by GC of the crude products.
[c] Yield determined by ^{1}H NMR, by using *N,N*-diphenylformamide as internal standard. In parenthesis yield of compound **2** after flash chromatography.
[d] 4/1.
[e] 8% of 4,4′-bis(trifluoromethyl)biphenyl and 8% of (*E*)-4-(4-trifluoromethylphenyl)but-3-en-2-one (**4ad**) were also obtained.
[f] 12% of 2-hydroxychalcone (**4be**) also was obtained.
[g] 10% of 2-hydroxychalcone (**4be**) also was obtained.
[h] Several unidentified products were obtained.

Pd, taking place without protection of the OH group as occurred in the case of the arylation in ionic liquids.[20] In this case the proportion of allyl alcohol **5ab** was higher than in the former case for **5aa**.

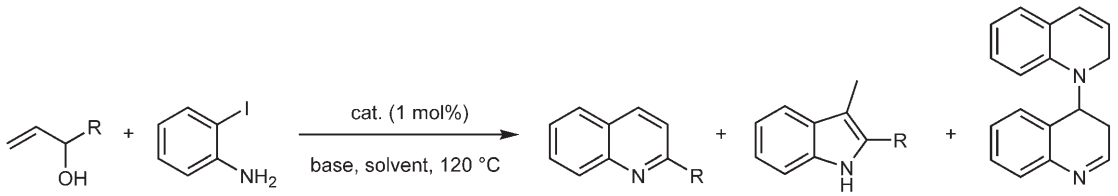
The synthesis of 4-phenylbutan-2-one (**2aa**)[1] and the anti-inflamatory nabumetone (**2ac**)[10] was performed by the Heck reaction of but-3-en-2-ol (**1a**) with bromobenzene (Table 1, entry 11) and 6-methoxy-2-bromonaphthalene (Table 2, entry 3), respectively, under the reaction conditions described in Table 1. These arylations were performed in aqueous DMA using TBAB as additive and 0.5 mol% loading of palladacycle **13**. In the case of nabumetone (**2ac**), less than 3% of allyl alcohol **5ac** was obtained and the ketone could be isolated in 82% yield. Similar results were obtained by using dimeric and polymeric palladacycles **14** and **15**, respectively (Table 2, entries 4 and 5). The Pd loading could be decreased to 0.5 mol% in the case of catalyst **13**, the reaction time being increased from to 9 h to 1 d (Table 2, compare entries 3 and 6). Similar results were observed using DMA as solvent with palladacycles **13** and **15**, giving nabumetone (**2ac**) in very good yields (Table 2, entries 7 and 8). An activated aryl chloride, such as 4-trifluoromethyl-1-chlorobenzene could also be used as arylating reagent of **1a** with palladacycles **13** or **15 (**1 mol% of Pd) working in neat DMA and in the presence of TBAB in 1 d reaction time, giving exclusively compounds **2ad** and **5ad** in 13/1 or 9/1 ratio, respectively, in moderate yields (Table 2, entries 9 and 10). In these last two cases, 8% of the homocoupling product 4,4′-bis(trifluoromethyl)biphenyl and 8% of the α,β-unsaturated ketone (*E*)-4-(4-trifluoromethylphenyl)but-3-en-2-one (**4ad**) were also obtained.

Next, the synthesis of dihydrochalcones by Heck reaction, recently described by Mioskowski and colleagues,[3] was attempted by performing the arylation of the secondary alcohol 1-phenylprop-2-en-1-ol (**1b)** with different aryl iodides and bromides (Table 2, entries 11–22). In the case of iodobenzene, 1,4-diphenylpropan-2-one (**2ba**) was formed with a high chemo- and regioselectivity when using water as solvent in the presence of low loading (0.1 mol% of Pd) of **13** or **15** with (Table 2, entries 11 and 12). We also attempted a difficult coupling partner under Heck conditions, such as 2-iodophenol.[3] In our hands, when the reaction with **1b** was performed in H_2O in the presence of TBAB as additive, a 68% yield of a mixture of **2be/3be/5be/6be** in a 10/1/2/1 ratio was obtained (Table 2, entry 13). In the absence of TBAB lower yields were obtained using both Pd complexes **13** and **15** (Table 2, entries 14 and 17). The best results were obtained working in aqueous DMA as solvent and in the presence of TBAB, giving product **2be** in the highest ratio and with 87% overall yield (Table 2, entry 16). In all these experiments, a 12% yield of the β-arylated α,β-unsaturated ketone **4be** was also formed. The synthesis of **2be** in moderate yields was also performed with 2-bromophenol, increasing the loading of palladacycles **13** and **15** to 3 mol% of Pd (Table 2, entries 17 and 18), similar results being obtained in DMA as solvent (Table 2, entry 19). In these couplings 10% of 2-hydroxychalcone (**4be**) was also formed.

The presence of an additional OH group in the aryl bromide, as in 3-hydroxy-6-bromophenol, transforms it into a complicated coupling partner. It has been coupled previously with 1-phenylprop-2-en-1-ol (**1b**) by using 3 mol% of Herrmann's phosphapalladacycle at 140°C to give ketone **2bf** in 45% yield.[3] In our case, the developed palladacycles **13–15** were assayed for this arylation reaction under the typical reaction conditions for aryl bromides: dicyclohexylmethylamine, TBAB in aqueous DMA at 120°C (Table 2, entries 20–22). The same results were obtained in all cases and the dihydrochalcone **2bf** was isolated in 33% yield (Table 2, entry 20).

Primary alcohols **1c** and **1d** were arylated with aryl iodides in water as solvent (Table 2, entries 23–34). Thus, allyl alcohol (**1c**) reacted with iodobenzene in water in the presence of palladacycles **13** or **15** (0.1 mol% Pd loading) giving mainly 3-phenylpropanal (**2ca**) in good yields (Table 2, entries 23–26). In general, product **2ca** could be obtained in a higher proportion using dicyclohexylmethylamine as base than with Cs_2CO_3 (Table 2, compare entries 23 and 24 with 25 and 26). When this coupling was performed with phenyl bromide, similar results were obtained with precatalysts **13** and **15** (1 mol% Pd), working in aqueous DMA (Table 2, entries 27 and 28). Methallyl alcohol (**1d**) was coupled with 4-*tert*-butylphenyl iodide and bromide in order to synthesize 3-(4-*tert*-butylphenyl)-2-methylpropanal (**2dg**) or β-lilial.® The arylations with the iodide were performed in water as solvent using complexes **13–15** (0.1 mol% Pd loading), affording exclusively the expected product **2dg** in high yields (Table 2, entries 29–31). Alternatively, 4-*tert*-butylphenyl bromide can be used for the preparation of **2dg** increasing the Pd loading to 1 mol% and after addition of TBAB, DMA being the best solvent (Table 2, compare entries 32–34).

A one-pot synthesis of quinolines *via* vinylation or indoles by sequential *N*-allylation-vinylation[34,35] was attempted by coupling of 2-iodoaniline with but-3-en-2-ol (**1a**) and allyl alcohol (**1c**) in water or aqueous DMA using palladacycles **13** and **15** (1 mol% Pd) as precatalysts (Scheme 5 and Table 3). In the case of alcohol **1c**, a *ca.* 4/1 mixture of quinoline (**16c)** and 3-methylindole (**17c**) was obtained either in water or in aqueous DMA using K_2CO_3 or dicyclohexylmethylamine as bases (Table 3, entries 1–6). In addition, the dimeric compound **18** was also formed, probably by 1,4-conjugate addition of intermediate 1,2-dihydroquinoline to quinoline. When but-3-en-2-ol (**1a**) was al-



1 16 17 18

a: R = Me
c: R = H

Scheme 5.

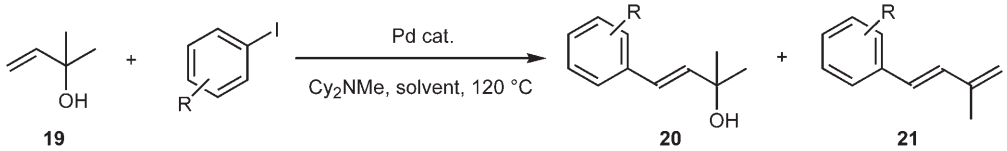
Table 3. Heck reactions of allyl alcohol (**1c**) and but-3-en-1-ol (**1a**) with 2-iodoaniline.[a]

Entry	Allyl Alcohol	Cat.	Base	Solvent	Additive	*t* [h]	Conv. [%][b]	Ratio[c] **16/17**	Yield **16** [%][d]	Yield **18** [%][d]
1	**1c**	**13**	K_2CO_3	H_2O	-	24	76	4/1	36	20
2	**1c**	**13**	Cy_2NMe	H_2O	-	14	82	6/1	41 (34)	24 (18)
3	**1c**	**15**	Cy_2NMe	H_2O	-	24	74	4/1	33	19
4	**1c**	**13**	Cy_2NMe	DMA:H_2O[e]	TBAB	8	80	4/1	39	16
5	**1c**	**15**	Cy_2NMe	DMA:H_2O[e]	TBAB	20	81	5/1	43	15
6[f]	**1c**	**15**	Cy_2NMe	DMA:H_2O[e]	TBAB	20	82	6/1	45	19
7	**1a**	**13**	Cy_2NMe	DMA:H_2O[e]	TBAB	8	79	9/1	52[g] (44)	-
8	**1a**	**15**	Cy_2NMe	DMA:H_2O[e]	TBAB	16	82	8/1	49[h]	-

[a] *Reaction conditions:* 2-iodoaniline (1 mmol), allyl alcohol (1.5 mmol), Pd catalyst (1 mol%), base (1.5 mmol), TBAB (1 mmol), H_2O (2 mL) or DMA:H_2O (5 mL) at 120 °C in a pressure tube.
[b] Determined by GC in the crude products.
[c] Determined by ^{1}H NMR in the crude product.
[d] Determined by ^{1}H NMR. In parenthesis yield after flash chromatography.
[e] Under microwave irradiation at 120 °C (80 W).
[f] 4/1.
[g] The reaction was performed in a flask with a reflux condenser.
[h] A 6% of 2-methyl-1,2,3,4-tetrahydroquinoline was also obtained.
[i] A 11% of 2-methyl-1,2,3,4-tetrahydroquinoline was also obtained.

lowed to react with 2-iodoaniline in aqueous DMA a 9/1 mixture of 2-methylquinoline (**16a**) and 2,3-dimethylindole (**17a**) was mainly obtained together with small amounts (6–11%) of 2-methyl-1,2,3,4-tetrahydroisoquinoline (Table 3, entries 7 and 8). All these compounds could be isolated after flash chromatography.

The former tendency to vinylation has also been observed in the Heck coupling of 1,1-dimethylallyl alcohol (**19**)[34,36] with iodobenzene and 2-iodoaniline (Scheme 6 and Table 4). Thus, the arylation of **19** with iodobenzene in water in the presence of complexes **13** and **15** (0.1 mol% Pd) gave a *ca.* 4:1 mixture of alcohol **20a** and arylated isoprene **21a** (Table 4, entries 1 and 2). Diene **21a** was exclusively obtained after treatment of the reaction mixture with 2 M HCl for 5 min (Table 4, entries 3 and 4). When the same arylation was carried out in aqueous DMA, similar results were obtained (Table 4, entries 5–7). In the absence of TBAB, the ratio **20a/21a** increased up to 11:1 (Table 4, entry 6). However, the coupling of dimethylallyl alcohol (**19**) with 2-iodoaniline in water failed



19 20 21

a: R = H
b: R = 2-NH_2

Scheme 6.

Table 4. Heck reactions of 2-methylbut-3-en-2-ol (**19**) with aryl iodides.[a]

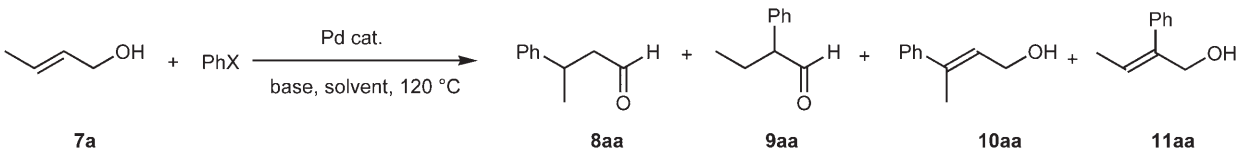
Entry	R	Cat. [mol% Pd]	Solvent	Additive	*t* [h]	Ratio[b] **20/21**	Yield [%][c]
1	H	**13** [0.1]	H_2O	-	6	4/1	76
2	H	**15** [0.1]	H_2O	-	6	3/1	71 (62)
3	H	**13** [0.1]	H_2O	-	6	0/100[d]	72 (65)[e]
4	H	**15** [0.1]	H_2O	-	6	0/100[d]	61[e]
5	H	**13** [0.1]	DMA:H_2O[f]	TBAB	3	7/3	61
6	H	**13** [0.1]	DMA:H_2O[f]	-	4	12/1	71
7	H	**15** [0.1]	DMA:H_2O[f]	-	4	8/1	74
8	2-NH_2	**13** [1]	DMA:H_2O[f]	TBAB	8	-	88 (70)[g]
9	2-NH_2	**14** [1]	DMA:H_2O[f]	TBAB	20	-	72[h]
10	2-NH_2	**15** [1]	DMA:H_2O[f]	TBAB	10	-	81[h]
11	2-NH_2	**13** [1]	DMA:H_2O[f]	-	14	1/13	51 (38)[i]
12	2-NH_2	**13** [1]	DMA:H_2O[f]	-	24	1/12	62[j]

[a] *Reaction conditions:* aryl iodide (1 mmol), allyl alcohol **19** (1.5 mmol), Pd catalyst (see column), Cy_2NMe (1.5 mmol), TBAB (1 mmol), H_2O (2 mL) or DMA:H_2O (5 mL) at 120 °C in a pressure tube.
[b] Determined by GC in the crude products.
[c] Determined by ^1H NMR. In parenthesis yield of compound **20** after flash chromatography.
[d] Acid work up (2 M HCl).
[e] Only compound **21b** was obtained.
[f] 4:1.
[g] For compound **21b**. A 35% of homocoupled 2,2′-biphenyldiamine and 5% of compound **20b** were also obtained.
[h] For compound **21b**.
[i] For compound **21b**.
[j] A 21% of homocoupled 2,2′-biphenyldiamine and 5% of compound **20b** were also obtained.

and in aqueous DMA gave mainly the diene **21b** (Table 4, entries 8–12). This methodology is a good strategy for the stereoselective synthesis of (*E*)-1-aryl-isoprenes.[37,38]

When crotyl alcohol (**7a**), a γ-substituted allylic alcohol, was cross-coupled with iodobenzene under water reflux in the presence of dicyclohexylmethylamine or Cs_2CO_3 as bases, products **8aa, 9aa, 10aa**, and **11aa** were formed (Scheme 7 and Table 5). The best yields and isomer ratios for the β-arylated aldehyde **8aa** were observed when dicyclohexylmethylamine was used as base (Table 5, compare entries 1 with 2 and 4 with 5), palladacycle **14** giving the highest yield (Table 5, entry 3). When the arylation was performed with phenyl bromide, a higher loading of Pd (1 mol%), aqueous DMA as solvent, and TBAB as additive were used (Table 5, entries 6 and 7). Allyl alcohols **10aa** and **11aa** were obtained in very low ratio and with *E*-configuration.

For the recycling studies of the polymeric complex **15**, the coupling of iodobenzene with but-3-en-1-ol (**1a**) in water to provide 4-phenylbutan-2-one (**2aa**) was chosen as the first model reaction (Table 6, entries 1–10). After 4 runs at 120 °C and 0.1 mol% loading of Pd the yield decreased until 44% and the reaction time increased from 7 to 36 h. Lowering the temperature down to 80 °C under 1 mol% Pd loading, allowed us to keep the yield in the range 81–88% during 5 runs, the reaction time being increased from 4 to 24 h (Table 6, entries 5–10). In the sixth run the yield decreased to 61% after 24 h reaction time, and the Pd contents in the polymer was determined to be 51% with respect to the starting complex (ICP-OES), which means that the average leaching of Pd per cycle was around 8%. For the coupling of 2-bromo-6-methoxynaphthalene with **1a** to give nabumetone (**2ac**), DMA was used as solvent with 1 mol% of Pd at 120 °C (Table 5, entries 11–14). The polymeric precatalyst was active during 3 runs and started to diminish the activity in the fourth cycle, the Pd loading of the polymer being 80%. The temperature and the long reaction times seem to deteriorate the polymeric complex, especially in organic solvents as it was described before with electron-poor alkenes.[28]



Scheme 7.

Table 5. Heck reactions of (*E*)-but-2-en-1-ol (**7a**) with iodo- and bromobenzene.[a]

Entry	PhX	Cat. [mol% Pd]	Base	Additive	Solvent	*t* [h]	Ratio [%][b] **8aa/9aa/10aa/11aa**	Yield [%][c]
1	PhI	**13** [0.1]	Cs_2CO_3	-	H_2O	14	20/1/3/1	65
2	PhI	**13** [0.1]	Cy_2NMe	-	H_2O	9	14/1/1/0	79
3	PhI	**14** [0.1]	Cy_2NMe	-	H_2O	10	16/1/1/0	88
4	PhI	**15** [0.1]	Cs_2CO_3	-	H_2O	14	45/1.5/2.5/1	63
5	PhI	**15** [0.1]	Cy_2NMe	-	H_2O	10	15/1.5/1/0	83 (74)
6	PhBr	**13** [1]	Cy_2NMe	TBAB	DMA:H_2O[d]	10	16/1/1/0	74 (60)
7	PhBr	**15** [1]	Cy_2NMe	TBAB	DMA:H_2O[d]	19	11/1/1/0	61

[a] *Reaction conditions:* halobenzene (1 mmol), (*E*)-but-2-en-1-ol (**7a**) (1.5 mmol), Pd catalyst (see column), base (1.5 mmol), TBAB (1 mmol), H_2O (2 mL) or DMA/H_2O (5 mL) at 120 °C in a pressure tube.
[b] Determined by GC in the crude products.
[c] Determined by ^{1}H NMR by using *N,N*-diphenylformamide as internal standard. In parenthesis yield of compound **8aa** after flash chromatography.
[d] 4:1.

Table 6. Recycling experiments for the heck reaction of but-3-en-1-ol (**1a**) with iodobenzene or 2-bromo-6-methoxynaphthalene catalyzed by palladacycle **15**.[a]

Entry	Run	mol% Pd	Solvent	*T* [°C]	Additive	*t* [h]	Ratio[c] **2/3/5/6**	Yield [%][b]	Product **2**
1	1	0.1	H_2O	120	-	7	58/3/4/1	98	**2aa**
2	2	0.1	H_2O	120	-	14	89/5/5/1	84	**2aa**
3	3	0.1	H_2O	120	-	24	43/3.5/2.5/1	85	**2aa**
4	4	0.1	H_2O	120	-	36	19/3/1/1	44	**2aa**
5	1	1	H_2O	80		4	91/0/8/1	83	**2aa**
6	2	1	H_2O	80		6	90/3/6/1	88	**2aa**
7	3	1	H_2O	80		10	45/1/3/1	86	**2aa**
8	4	1	H_2O	80		15	23/2/1/1	84	**2aa**
9	5	1	H_2O	80		24	37/1/2/0	81	**2aa**
10	6	1	H_2O	80		24	17/1/1/1	62	**2aa**
11	1	1	DMA	120	TBAB[d]	8	24/1/0/0	86	**2ac**
12	2	1	DMA	120	TBAB[d]	14	97/2/1/0	81	**2ac**
13	3	1	DMA	120	TBAB[d]	24	49/1/0/0	76	**2ac**
14	4	1	DMA	120	TBAB[d]	24	28/1/0/1	38	**2ac**

[a] *Reaction conditions:* aryl halide (1 equiv.), but-3-en-1-ol (1.5 equivs.), **15** (see column), dicyclohexylmethylamine (1.5 equiv.), TBAB (see column), solvent, in a pressure tube.
[b] Determined by ^{1}H NMR by using *N,N*-diphenylformamide as internal standard.
[c] Determined by GC in the crude products.
[d] 1 equiv.

Conclusions

In conclusion, we have found that dimeric and polymeric oxime-derived palladacycles are appropriate precatalysts for the synthesis of β-arylated ketones or aldehydes using a Heck reaction with allyl alcohols, employing dicyclohexylmethylamine better than Cs_2CO_3 as base at 120 °C. However, $Pd(OAc)_2$ gave lower yields under the same reaction conditions. Aryl iodides can be coupled with 0.1 mol% of Pd in water as solvent, and aryl bromides in aqueous DMA in the presence of TBAB as additive with higher Pd loading (1 mol%). These reaction conditions are very convenient for the synthesis of 4-phenylbutan-2-one, 4-(4-hydroxyphenyl)butan-2-one, dihydrochalcones, nabumetone and β-lilial.® In the case of 2-iodoaniline, vinylation followed by dehydrogenation took place preferentially instead of *N*-allylation-vinylation to afford mainly quinolines. The same tendency to vinylation was observed in the reaction of 1,1-dimethylallyl alcohol to give γ-arylated alcohols, which suffer easy diastereoselective dehydration to the corresponding (*E*)-1-arylisoprenes. The results in the Heck reaction, with electron-rich alkenes employing these Pd nanoparticle-generating palladacycles,[28] support a neutral mechanism for this process. The Kaiser oxime resin derivative **15** has been reused when working in water and in DMA as solvents, giving the best performance in water at 80 °C with relative low leaching of Pd.

Experimental Section

General Remarks

The reagents and solvents were obtained from commercial sources and were generally used without further purification. Flash chromatography was performed on silica gel 60 (0.040–0.063 mm, Merck). Thin layer chromatography was perfomed on Polygram® SIL G/UV_{254} plates. Melting points were determined on a Reichert Thermovar apparatus. Gas chromatographic analyses were performed on a HP-6890 instrument equipped with a WCOT HP-1 fused silica capillary column. IR data were collected on a Nicolet Impact-400D-FT spectrophotometer in cm^{-1}. ^1H NMR spectra were recorded on Bruker AC-300 (300 MHz) and Bruker AC-400 (400 MHz). Chemical shifts are reported in ppm using tetramethylsilane (TMS, 0.00 ppm) as internal standard. ^{13}C NMR spectra were recorded at 75 or 100 MHz. EI-MS were measured on a Mass Selective Detector G2579 A from Agilent Technologies 5973N in *m/z* (rel. intensity in % of base peak). The catalysts were weighed up in an electronic microscale (Sartorius, XM1000P) with precision of 1 μg. ICP-OES analyses were performed in a Perkin–Elmer Optima 4300 spectrometer. Microwave reactions were performed with a CEM Discover Synthesis Unit in glass vessels (10 mL) sealed with a septum under magnetic stirring. Palladacycles **12** and **13** and Kaiser oxime resin are commercially available.

Synthesis of Palladacycle 14

A methanolic solution (2 mL) of the corresponding oxime (0.484 g, 2 mmol) and NaOAc (0.165 g, 2 mmol) was added over a solution of Li_2PdCl_4 (0.524 g, 2 mmol) in MeOH (4 mL). Then, the solution was stirred for 3 days at room temperature. After adding water (10 mL), the resulting precipitate was filtered off (G-3) and dried under reduced pressure over P_2O_5 to give the title compound **14**; yield: 0.723 g (94%); yellow solid; mp 245 °C; IR (KBr): $\nu = 3307$ (OH), 1612 (C=N), 1518, and 1352 (N=O) cm^{-1}; ^1H NMR (300 MHz, DMF-d_7): $\delta = 6.75$ (d, 1H, $J = 4.35$ Hz), 7.04 (m, 2H), 7.78 (m, 1H), 7.95 (d, 2H, $J = 8.6$ Hz), 8.50 (d, 2H, $J = 8.3$ Hz), 11.15 (br s, 1H); ^{13}C NMR (75 MHz, DMF-d_7): $\delta =$ 124.2, 124.9, 127.7, 128.6, 131.2, 136.6, 142.8 (ArC), 149.0 (C=N); anal. calcd.: C 40.76, H 2.37, N 7.31; found: C 41.98, H 2.39, N 7.16%.

Reduction of Palladacycle 14; Synthesis of 2-Deuteriophenyl 4-Nitrophenyl Ketone Oxime

To a solution of complex **14** (77 mg, 0.1 mmol) in THF (5 mL) and MeOH (1 mL) was added sodium cyanoborodeuteride (26 mg, 0.4 mmol) at 0 °C and the mixture was stirred for 1 h while being allowed to warm to room temperature. The black precipitate was filtered off and the filtrate was evaporated (15 mm Hg). To the residue was added H_2O and the solution was extracted with EtOAc. The organic layer was dried and evaporated to give a solid, which was purified by recrystallization to give the title compound; yield: 44 mg (91%); green solid; mp 133–135 °C; IR (KBr): $\nu = 3300$ (OH), 1612 (C=N), 1532, 1338 (N=O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 7.39$ (m, 4H), 7.59 (d, $J = 7.5$ Hz, 2H), 8.31 (d, $J = 8.7$ Hz, 2H), 11.70 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 123.4$, 126.8, 128.5, 128.6, 130.5 (ArCH), 128.9 (t, $J = 31.0$ Hz, ArC-D), 129.3, 135.5, 140.4, 147.3 (ArC), 153.8 (C=N); MS: *m/z* (%) = 243 (M^+, 100), 226 (40), 196 (10), 180 (52), 166 (20), 78 (26); anal. calcd.: C 64.19, H 4.56, N 11.52; found: C 63.85, H 4.52, N 11.26%.

Synthesis of Kaiser Oxime-Derived Complex 15

To a suspension of Kaiser oxime resin (1.4 g, 1.5 mmol) and NaOAc (0.124 g, 1.5 mmol) in MeOH (4 mL) was added a 0.5 M methanolic solution of Li_2PdCl_4 (3 mL, 1.5 mmol). The mixture was stirred during 7 d at 25 °C. After adding water (10 mL), the corresponding polymer was filtered off and dried over P_2O_5 to give 1.4 g of a brown solid. The palladium content was determined by ICP-OES: 12.5 mg Pd/g of polymer. For the ICP-OES analyses, the resin was decomposed with HNO_3. When the palladation was performed in the absence of NaOAc the resulting polymer had 73 mg Pd/g of polymer.

Typical Experimental Procedure for the Heck Reaction of Aryl Iodides and Allyl Alcohols in Water

A mixture of allyl alcohol (1.5 mmol) and the base (1.5 mmol) in water (2 mL) was stirred during 15 min at room temperature. Then, the catalyst (see Tables 1–6) and the aryl iodide (1 mmol) were added, the bath temperature was raised to 120 °C in a pressure tube and the reaction was monitored by GC. After the reaction was completed, it was cooled at room temperature and an aqueous solution of 2 M HCl (5 mL) was added to the reaction mixture and stirred for 10 min. Then, the reaction crude was poured into ethyl acetate (40 mL) and the organic layer washed with brine (3×20 mL) and dried over $MgSO_4$. The solution was evaporated (15 mm Hg) and the residue was purified by flash chromatography in hexane/ethyl acetate.

Typical Experimental Procedure for Heck Reaction of Iodobenzene and But-3-en-2-ol (1a) under Microwave Irradiation

A pressure glass vessel (10 mL) was charged with allyl alcohol **1a** (0.090 mL, 0.75 mmol) and Cy_2NMe (0.160 mL, 0.75 mmol) in water (1 mL) and the reaction mixture was stirred during 10 min at 25 °C. Then, the complex **13** (0.1 mol% Pd, 0.145 mg) and iodobenzene (0.055 mL, 0.5 mmol) were added and the pressure tube was sealed with a septum, starting the microwave heating (40 W, 3.5 bar, 120 °C, 10 min with air-stream cooling). The product was extracted with diethyl ether (5×10 mL), the combined organic layers were washed with aqueous solutions of 2 M HCl (2×25 mL), and water (2×20 mL). Finally, the organic layer was dried over $MgSO_4$ and the solvents were removed under vacuum (15 mm Hg) to give an oil.

Typical Experimental Procedure for the Heck Reaction of Aryl Bromides or Chlorides and Allyl Alcohols in Organic Solvents

A mixture of allyl alcohol (1.5 mmol), Cy_2NMe (0.320 mL, 1.5 mmol) or Cs_2CO_3 (0.488 g, 1.5 mmol) and TBAB (0.322 g, 1 mmol) was stirred for 15 min in DMA (3 mL) or

4/1 DMA/H_2O (5 mL) in a pressure tube at room temperature. Then, the catalyst (see Tables 1–6) and aryl halide (1 mmol) were added, the temperature was increased to 120 °C and the progress of reaction was analyzed by GC. After the reaction was completed, it was cooled at room temperature and an aqueous solution of 2 M HCl (5 mL) was added to the reaction mixture, stirring for 10 min. Then, the reaction crude was poured into ethyl acetate (40 mL) and washed with brine (3×20 mL). The organic layer dried over $MgSO_4$, evaporated (15 mm Hg) and the residue was purified by flash chromatography in hexane/ethyl acetate.

Typical Experimental Procedure for the Heck Reaction with Allyl Alcohols and Aromatic Halides; Recycling Experiments

The reaction was performed under the previously described conditions: aromatic halide (1 mmol), allylic alcohol (1.5 mmol), Cy_2NMe (0.320 mL, 1.5 mmol), catalyst **15** (0.1–1 mol%, 8.2–82 mg), solvent H_2O (2 mL) or DMA (4 mL) and TBAB (0.322 g, 1 mmol, see Tables), heating at the corresponding temperature (see, Table 5). When the reaction was finished, the catalyst was filtered off (G-4, 1 cm diameter and 8 cm height), washed with ethyl acetate and dried under vacuum for 20 min. Work-up of the crude was performed as has been described before.

The compounds **2aa**, **2ab**, **2ac**, **2ca**, **2dg**, **8aa**, **16a**, **16c**, **17a**, **17c** and **20a** are commercially available and compounds **2ad**,[39] **2be**,[40] **2bf**[3] and **21a**[37,38] have been previously reported.

3′,4′-Dihydro-2*H*-1,4′-biquinoline (18): Yellow solid; mp 95–97 °C; R_f 0.17 (hexane/AcOEt, 5/1); IR (film): ν=3058 (=C–H), 1615 (C=C), 1308 (C–N) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=02.09–2.30 (m, 2H), 2.70–2.80 (m, 1H), 2.90–3.05 (m, 1H), 4.67 (dd, J=11.9 and 4.4 Hz, 1H), 6.62 (d, J=10.4 Hz, 1H), 6.70 (t, J=7.2 Hz, 1H), 6.95–7.10 (m, 2H), 7.54 (t, J=7.5 Hz, 1H), 7.67 (t, J=8.1 Hz, 1H), 7.80 (d, J=8.2 Hz, 1H), 8.05–8.15 (m, 2H), 8.93 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=26.2 (NCH_2), 31.0 (NCH*C*H_2), 54.2 (N*C*HCH_2), 114.4, 120.9 (CH=CH), 117.9, 127.0, 127.2, 127.9, 128.1, 129.2, 129.4, 129.5 (ArCH), 133.4, 137.5, 144.3, 147.8 (ArC), 150.2 (CH=N); MS: m/z (%)= 262 (M^++2, 1), 261 (M^++1, 16), 260 (M^+, 100), 259 (M^+–1, 33), 256 (61), 132 (39), 130 (31); HR-MS: m/z=260.1305, calcd. for $C_{18}H_{16}N_2$: 260.1313.

(*E*)-3-(2-Aminophenyl)-1-methylbut-3-en-2-ol (20b): White solid; mp 92–93 °C; R_f 0.30 (hexane/AcOEt, 1/1); IR (film): ν=3389, 3307 (NH_2), 3223 (OH), 2969 (CH_3), 1649, 1602 (C=C), 1492 (C–C), 1158–1141 (C–O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=1.39 (s, 6H), 3.21 (br s, 3H), 6.19, 6.63 (2d, J=15.9 Hz, 2H), 6.66 (m, 1H), 6.74 (t, J=7.5 Hz, 1H), 7.06 (dt, J=7.6, 1.5 Hz, 1H), 7.23 (d, J=7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=30.1 (2CH_3), 71.3 (CO), 116.2, 119.1, 128.4, 139.5 (ArCH), 121.7, 127.3 (*C*H=*C*HCO), 123.4, 143.7 (ArC); MS: m/z (%)=177 (2) 159 (M^+–H_2O, 60), 158 (41), 144 (100), 143 (62), 128 (14); HR-MS: m/z=177.1151, calcd. for $C_{11}H_{15}NO$: 177.1154.

(*E*)-2-(3-Methylbuta-1,3-dienyl)aniline (21b): Brown oil; R_f 0.28 (hexane/AcOEt, 5/1); IR (film): ν=3461, 3349 (NH_2), 3076 (=C–H), 1626, 1616 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.97 (s, 3H), 3.75 (br s, 2H), 5.06, 5.09 (2 s, 2H), 6.58 (d, J=15.9 Hz, 1H), 6.68 (d, J=7.9 Hz, 1H), 6.75 (m, 1H) 6.78 (d, J=16.4 Hz, 1H), 7.05 (m, 1H), 7.32 (d, J=7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$). δ=18.7 (CH_3), 116.3 (CH_2), 117,2, 119.2, 123.9, 124.0 (ArCH), 127.7, 128.5 (CH=CH), 133.4 (ArC), 142.3 (*C*=CH_2), 143.9 (C-N); MS: m/z (%)=160 (M^++1, 7), 159 (M^+, 60), 158 (M^+-1, 62), 144 (100), 143 (63), 128 (15), 127 (15), 115 (14); HR-MS: m/z= 159.1052, calcd. for $C_{11}H_{13}N$: 159.1048.

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