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Highly Active Oxime-Derived Palladacycle Complexes for Suzuki−Miyaura and Ullmann-Type Coupling Reactions

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Oxime-derived chloro-bridged palladacycles **12** and **13** are efficient complexes for the Suzuki−Miyaura reactions of aryl-, allyl-, and benzyl halides with arylboronic acids. The isolated catalysts are thermally stable, not sensitive to air or moisture, and easily accessible from inexpensive starting materials. The reaction can be performed under aerobic conditions with aryl bromides and chlorides, displaying turnover numbers (TON) of up to 5×10^5 and turnover frequencies (TOF) of up to 198 000 h^{-1} for aryl bromides. Aryl chlorides undergo the Suzuki reaction with arylboronic acids with TON of up to 4700 and TOF up to 4700 h^{-1}. Even inexpensive and readily available benzyl and allyl chlorides undergo the coupling reaction with good turnover numbers. Complexes of **12** catalyze the syntheses of symmetrical biaryls in good yields via reductive coupling of iodoarenes in the presence of Hünig's base.

Introduction

Substituted biaryls are importrant building blocks for the syntheses of many pharmaceutically active compounds, herbicides, polymers, new materials, liquid crystals, and ligands. Among the various methods known to synthesize biaryls,[1] the transition-metal-catalyzed Suzuki−Miyaura cross-coupling of aryl halides with arylboronic acids or esters has emerged as an extremely powerful method in organic synthesis for the formation of $C(sp^2)-C(sp^2)$ bonds under mild conditions.[2] Furthermore, very recently, the Suzuki coupling has been extended to $C(sp^3)-C(sp^2)$ and $C(sp^3)-C(sp^3)$ couplings.[3] A wide variety of palladium catalysts efficiently promote the couplings of aryl halides and other electrophiles with organoboron compounds, usually combinations of palladium salts or complexes with phosphorus ligands, such as phosphines,[4] phosphites,[5] and phosphine-oxides.[6] However, these types of catalysts are sensitive to moisture and air oxidation and therefore require air-free handling to minimize ligand oxidation. Very recently, nitrogen ligands[7] have emerged as efficient partners for the Suzuki reaction in order to circumvent the problems associated with tertiary phosphine derivatives, although very low yields were obtained with electron-rich aryl chlorides even when high catalyst loadings were used (3 mol % Pd). Ligandless palladium systems[8] have also been shown to promote the Suzuki cross-coupling reactions of aryl bromides and activated aryl chlorides, although with very low turnover numbers (TON = mol product/mol Pd) and turnover frequencies (TOF = TON h^{-1}). However, lately, palladacycles have been by far the most developed and studied catalysts, as they are presently the most successful, because of their structural versatility and easy synthetic accessibility, and the most promising catalysts in C−C bond-forming reactions.[9] Among them, phos-

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phapalladacycles **1**,[10] **2**,[11] **3**,[12] and **4**[13] and phosphine-free *N*-heterocyclic carbenes (NHC) **5**,[9c] **6**,[14] **7**,[15] and **8**[16] are able to catalyze the Suzuki couplings of aryl bromides and chlorides with phenylboronic acid in good yields but generally under an inert atmosphere. Benzyl thioethers **9**[17] developed by Dupont have been found to be stable but still active catalysts in Suzuki coupling reactions as well. Milstein[18] has shown that phosphine-free cyclometalated imine dimers **10** are able to mediate Suzuki reactions involving aryl bromides with TON up to 8 × 10^5. Unfortunately, this system was sterile when using inexpensive and readily accessible aryl chlorides. More recently, Bedford[19] has prepared orthometalated monomeric amine complex **11** and has presented it as a very active system in the Suzuki couplings of activated and nonactivated aryl chlorides, although tricyclohexylphosphine had to be used as ligand.

On the other hand, different palladium-catalyzed homocoupling protocols have been developed very recently to prepare symmetrical and unsymmetrical biaryls via Ullmann-type reactions.[20] Palladium acetate was usually the catalyst of choice for this type of coupling[21] which was also especially suitable for the synthesis of binaphthyls and in intramolecular coupling reactions. However, among palladacycles, only phosphine-derived catalyst **1** was shown to promote iodoarenes in reductive homocouplings to produce biaryls in high yields.[22]

We have very recently reported our first results on highly active cyclopalladated oxime-derived catalysts **12** for a wide range of useful and well-known C−C coupling processes such as Heck, Suzuki, Stille, Sonogashira, and Ullmann reactions.[23] These catalyst precursors are very thermally and air stable and promoted the palladium-catalyzed Heck couplings of aryl halides with olefins with impressive turnover numbers of up to 10^{10}.[23,24a] In this paper, we report on the evaluation and optimization of the effect of additives, bases, and solvents on the Suzuki couplings of aryl bromides and chlorides with phenylboronic acids with oxime-derived palladacycles **12** as catalysts as well as on the couplings of benzylic and allylic chlorides with phenylboronic acid. The synthesis of symmetrical biphenyls via reductive homocouplings of iodoarenes is studied as well (Figure 1).

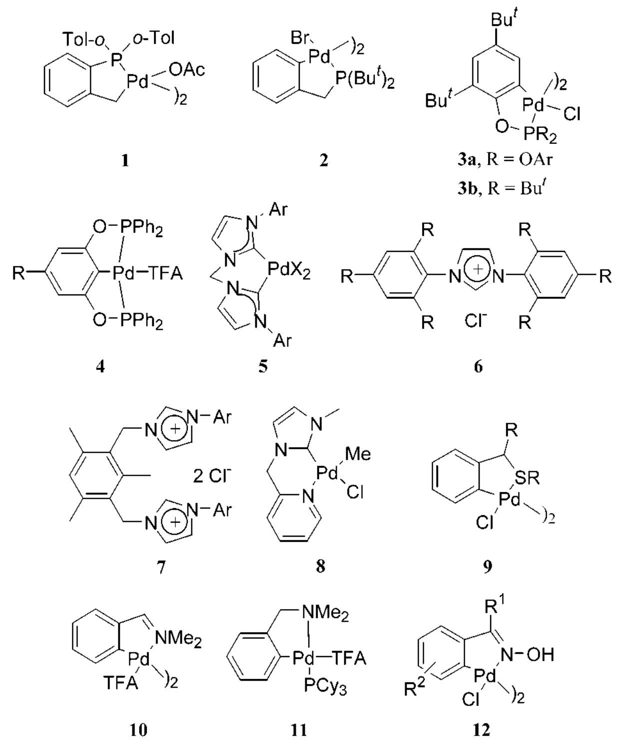

FIGURE 1. Palladacycle catalysts for Suzuki−Miyaura couplings.

Results and Discussion

The catalyst precursors **12** and **13** used for the Suzuki cross-coupling reactions were prepared in high yields from the corresponding oximes through a carbopalladation reaction[25] with lithium tetrachloropalladate (Li_2PdCl_4) in MeOH in the presence of NaOAc as base at room temperature[26] (Figure 2).

The Suzuki−Miyaura arylation of aromatic halides was first evaluated with palladium complexes **12** and **13** in order to study their catalytic activity. We chose as a model reaction the coupling between *p*-bromoacetophenone and phenylboronic acid in toluene at 110 °C in the presence of K_2CO_3 as base and with a catalyst loading of 10^{-3} mol % in Pd (Scheme 1, Table 1). The reaction provided very similar results and quantitative conversions under air for nearly all the dimeric complexes with reaction periods within 0.5 and 1 h. Catalysts derived from benzophenone oxime substrates (**12a**−**c**) presented

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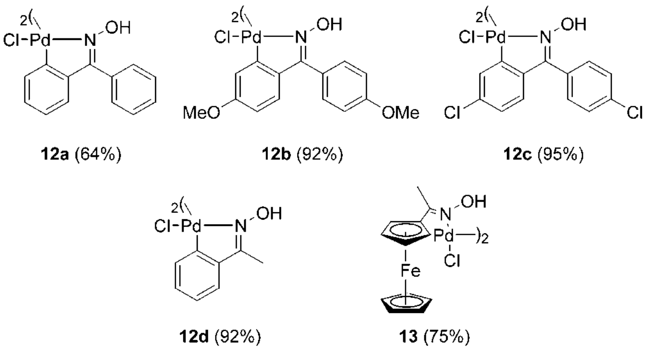


FIGURE 2. Oxime-derived palladacycle catalysts.

SCHEME 1. Suzuki Coupling: Catalyst Study

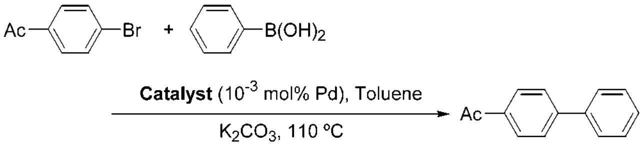


TABLE 1. Suzuki Coupling: Catalyst Study

entry	catalyst ($\times 10^{-3}$ mol % Pd)	time (h)	yield[a] (%)	TON	TOF (h^{-1})
1	**12a**	0.5	92	92 000	184 000
2	**12b**	0.5	82	82 000	164 000
3	**12c**	0.5	99	99 000	198 000
4	**12d**	1	93	93 000	93 000
5	**13**	1	98	98 000	90 800
6	Li_2PdCl_4	5	42	42 000	8400
7	Li_2PdCl_4[b]	5	27	27 000	5400
8	**12c**[c]	2	77	77 000	38 500

[a] Determined by GLC on the basis of *p*-bromoacetophenone using decane as internal standard. [b] **12c** was generated in situ in the reaction medium. [c] 4,4′-Dichlorobenzophenone oxime (10^{-3} mol %) was added to the reaction.

SCHEME 2. Suzuki Coupling of Aryl Bromides

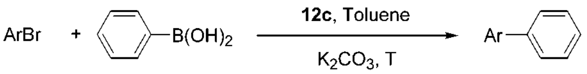
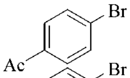
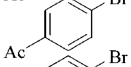
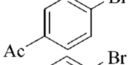
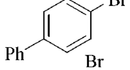
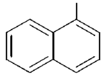
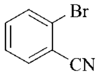
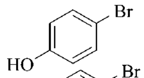
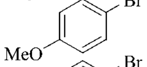
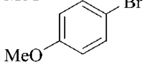
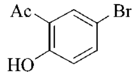
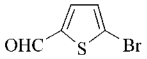
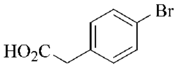
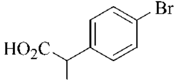
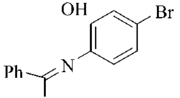
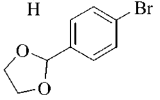


TABLE 2. Suzuki Coupling of Aryl Bromides with $PhB(OH)_2$ Catalyzed by 12c

Entry	ArBr	(mol% Pd)[a]	T (°C)[b]	t(h)	Yield (%)[c]	TON	TOF (h^{-1})
1		10^{-3}	110	0.5	99	99000	198000
2		10^{-4}	160	8.5	50	500000	58823
3		0.2	20	5	>99 (>99)	500	100
4		10^{-2}	110	0.25	91 (92)	9100	36400
5		10^{-2}	110	0.25	97 (99)	9700	38800
6		10^{-2}	110	0.5	98	9800	19600
7		10^{-2}	110	0.5	97	9700	19400
8		10^{-2}	110	2	94	9400	4700
9		10^{-3}	110	3	35	35000	11667
10		10^{-2}	110	0.25	98 (71)	9800	39200
11		10^{-2}	110	0.5	81 (50)	8100	16200
12		10^{-2}	110	2	(79)	7900	3950
13		10^{-2}	110	3.5	(50)	5000	1429
14		10^{-2}	130	0.5	86	8600	17200
15		10^{-2}	130	1	91	9100	9100

[a] Reaction conditions: ArBr (2 mmol), $PhB(OH)_2$ (3 mmol), K_2CO_3 (4 mmol), **12c**, toluene (7 mL). [b] Bath temperature. [c] Determined by GLC on the basis of ArBr using decane as internal standard. In parentheses, isolated yield after flash chromatography or recrystallization.

the highest turnover frequencies (TOF) ranging from 164 000 to 198 000 h^{-1}. Among them, the reaction with the *p*-methoxy-substituted benzophenone complex **12b** was slightly slower under the same reaction conditions (compare entries 1–3, Table 1). Palladacycles **12d** and **13** gave slightly poorer results. Li_2PdCl_4 or a catalyst system prepared in situ from Li_2PdCl_4 (10^{-3} mol % Pd) and 4,4′-dichlorobenzophenone oxime (10^{-3} mol %) in the presence of base (excess of K_2CO_3) were also tested (Table 1, entries 6 and 7). In these cases, the yields were significantly lower after 5 h than those obtained from the straight use of **12c** (full conversion after 0.5 h). Addition of 1 equiv of free ligand to the reaction medium did not improve the catalytic performance (Table 1, entry 8).[27]

The application of oxime-derived palladium precursors **12** as catalysts in the Suzuki reactions of different aryl bromides (Scheme 2) was studied, and the results are summarized in Table 2. Complex **12c** proved to be a very active catalyst for the Suzuki cross-couplings of a broad spectrum of aryl bromides and phenylboronic acid. As illustrated in Table 2, this catalyst furnished the desired biaryls in excellent yields. Under standard conditions, toluene as solvent, K_2CO_3 as base, and **12c** at 110 °C, both electron-poor and -rich aryl bromides were cleanly coupled with turnover numbers of up to 99 000 and 35 000, respectively (Table 2, entries 1 and 9). When the reaction was performed at 160 °C, very high activities were obtained with TON up to 5×10^5 (Table 2, entry 2). Moreover, palladacycle **12c** promotes the Suzuki coupling even at room temperature, although longer reaction times and higher catalyst loadings (0.2 mol % Pd) were necessary (Table 2, entry 3). Aryl bromides with *ortho* substituents, such as 2-bromobenzonitrile, reacted efficiently, affording the corresponding 2-cyanobiphenyl in excellent yield (98%) after only 0.5 h (Table 2, entry 6). Particularly noteworthy were the reactions of very

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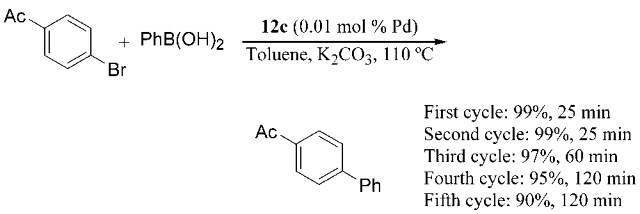
[27] Bedford has demonstrated a positive effect on catalyst productivity upon addition of 1 equiv of free ligand to the catalytic system. See ref 12b.

SCHEME 3. Suzuki Coupling: Catalyst Stability



electron-rich bromides such as *p*-bromophenol and *p*-bromoanisol. These deactivated substrates afforded catalytic activities more in the same range, with TON of $\sim 10^4$ (Table 2, entries 7 and 8), than those of nonactivated bromides (Table 2, entries 4, 5, and 10). The heterocyclic bromide 5-bromo-2-thiophenecarboxaldehyde was likewise converted efficiently to the corresponding biaryl (81%, Table 2, entry 11). Biphenylacetic acid and *p*-phenylmandelic acid, very interesting substrates from the pharmaceutical point of view,[28] could be prepared from the corresponding bromide precursors in short times with very good yields using 10^{-2} mol % Pd at 110 °C (Table 2, entries 12 and 13). As depicted in Table 2, a wide variety of functional groups are tolerated when oxime-derived palladacycles **12** are used as catalysts in the Suzuki–Miyaura reaction.

The pronounced thermal stabilities of palladacycles **12** were demonstrated when no deactivation of the catalyst was observed in subsequent catalytic runs when coupling *p*-bromoacetophenone and phenylboronic acid under typical conditions (**12c**, 0.01 mol % Pd) and when GC analyses of five cycles yielded a constant rate of conversion of *p*-bromoacetophenone after addition of fresh reagents to the solution (Scheme 3).

Preliminary studies in our group have revealed that cyclopalladated complexes **12** presented very good activities in the Suzuki couplings of aryl chlorides in water.[29] However, under the standard conditions used for the Suzuki couplings of aryl bromides (toluene, K$_2$CO$_3$, 110 °C, **12c**, 0.01 mol % Pd), *p*-chloroacetophenone afforded 4-acetylbiphenyl in very poor yield, accompanied by considerable amounts of biphenyl as a result of phenylboronic acid homocoupling.[30] Then, a preliminary screening of optimal reaction conditions for the Suzuki couplings of aryl chlorides with phenylboronic acid in the presence of catalyst **12c** (0.1 mol % Pd) was carried out with *p*-chloroacetophenone as the test substrate. The optimization of bases and additives, which was studied with toluene as solvent at 110 °C, showed K$_2$CO$_3$, Cs$_2$CO$_3$, and K$_3$PO$_4$ as the inorganic bases to choose, although biphenyl was obtained as a byproduct in all the cases. Other bases such as alkali oxides or hydroxides were substantially less effective, and weak organic bases such as TEA, Pr^{i}NEt, and pyrrolidine failed to promote the reaction, probably because of their ability to bind strongly to palladium. With respect to the additive study, Bu$_4$NBr (TBAB, 20 mol %) was the best additive for the reaction coupling when it was carried out under the above-mentioned reaction conditions, employing K$_2$CO$_3$ as base. Other ammonium salts such as Bu$_4$NCl, Bu$_4$NI, and Bu$_4$NHSO$_4$ gave lower yields. Organic nitrogen ligands such as *N*,*N*-(dimethylamino)pyridine (DMAP), which has been recently shown to be able to stabilize palladium nanoparticles in water,[31] and *N*, *N′*-dimethylglyoxime (DMG)[7] gave no significant amounts of cross-coupling product.

SCHEME 4. Suzuki Coupling of Aryl Chlorides: Reaction Conditions Study

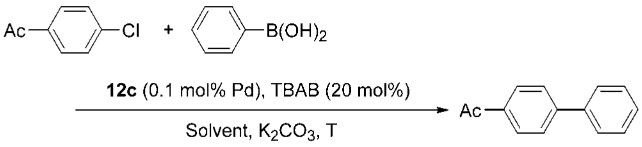


TABLE 3. Suzuki Coupling of Aryl Chlorides: Solvent and Temperature Study[a]

entry	solvent	T^b (°C)	time (h)	yield^c (%)	TON	TOF (h^{-1})
1	toluene	110	5	37 (11)	370	74
2	*p*-xylene	110	5	23 (11)	230	46
3	THF	110	3	1	10	3
4	dioxane	110	5	35 (4)	350	70
5	DMAc	110	5	42 (18)	420	84
6	DMF	110	1	62 (9)	620	620
7	NMP	110	5	66 (11)	660	132
8	DMF/H$_2$O 3:1	110	2	64 (5)	640	320
9	DMF/H$_2$O 95:5	110	6	85 (9)	850	142
10	NMP/H$_2$O 95:5	110	6	78 (9)	780	130
11	DMF	160	0.5	77 (2)	770	1540
12	DMF/H$_2$O 95:5	160	0.5	99 (1)	990	1980

[a] Catalyst loading: 0.1 mol % Pd. [b] Bath temperature. [c] Determined by GLC on the basis of ArCl using decane as internal standard. In parentheses, yield of biphenyl.

The solvent and the temperature were the last reaction parameters studied in the model reaction (Scheme 4, Table 3). We investigated different apolar solvents such as toluene and *p*-xylene (Table 3, entries 1 and 2) with K$_2$CO$_3$ as base and in the presence of 20 mol % TBAB[32] and **12c** (0.1 mol % in Pd). At 110 °C, both solvents gave low conversions of *p*-acetylbiphenyl accompanied by considerable amounts of biphenyl (11%). Next, we investigated other more polar solvents (Table 3, entries 3–7). Reactions conducted at 110 °C were not efficient in THF and gave poor yields when dioxane and DMAc were the solvents of choice (Table 3, entries 4 and 5). The reaction was more efficient in DMF (62%) or NMP (66%) but still with significant amounts of biphenyl as byproduct (Table 3, entries 6 and 7). Using H$_2$O as cosolvent (DMF/H$_2$O 3:1) led to similar conversions, but the quantity of byproduct was reduced significantly (Table 3, entry 8). Interestingly, when the amount of water was reduced to

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(28) (a) *p*-Biphenylacetic acid (felbinac) and 2-ethyl-4-biphenylacetic acid with dimethylaminoethanol (namoxyrate) are anti-inflammatory and analgesic drugs, respectively: *USP Dictionary of USAN and International Drugs Names*. (b) *p*-Biphenylacetamides have been used as mesogenic arms in porphyrin thermotropic liquid crystals: Michaeli, S.; Hugerat, M.; Levanon, H.; Bernitz, M.; Natt, A.; Neumann, R. *J. Am. Chem. Soc.* **1992**, *114*, 3612–3618.

(29) Botella, L.; Nájera, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 179–181.

(30) For the palladium-catalyzed homocoupling of arylboronic acids, see: (a) Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346–2351. (b) Smith, K. A.; Campi, E. M.; Jackson, W. R.; Marcuccio, S.; Naeslund, C. G. M.; Deacon, G. B. *Synlett* **1997**, 131–132. (c) Wong, M. S.; Zhang, X. L. *Tetrahedron Lett.* **2001**, *42*, 4087–4089.

(31) Gittins, D. I.; Caruso, F. *Angew. Chem., Int. Ed.* **2001**, *40*, 3001–3004.

(32) No improvement on catalyst efficiency was observed when the reaction was carried out in the presence of different amounts of TBAB (40, 60, and 80 mol %).

SCHEME 5. Suzuki Coupling of Aryl Chlorides

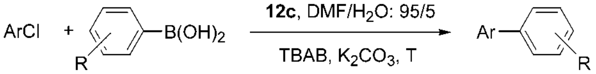
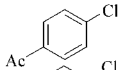
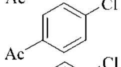
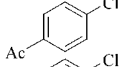
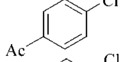
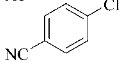
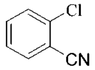
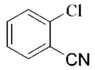
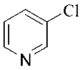
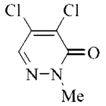
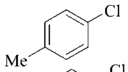
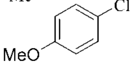
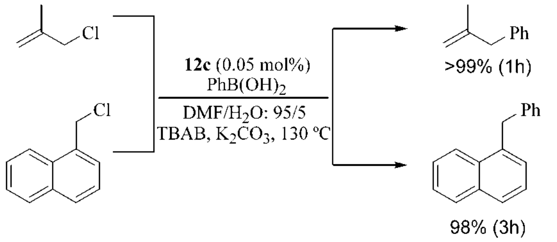


TABLE 4. Suzuki Coupling of Aryl Chlorides with $ArB(OH)_2$ Catalyzed by 12c

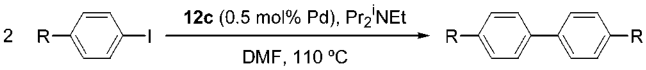
Entry	Aryl Chloride	(mol% Pd)[a]	R	T (°C)[b]	t(h)	Yield (%)[c]	TON	TOF (h^{-1})
1		0.1	H	130	2	86 (91)	860	430
2		0.1[d]	H	130	2	66	660	330
3		0.1	H	160	0.5	99	990	1980
4		10^{-2}	H	160	1	47	4700	4700
5		0.1	H	130	2	98	980	490
6		0.1	H	130	1	77	770	770
7		0.2	*p*-Me	130	1	93 (90)	465	465
8		0.1	H	130	6	75	750	125
9		0.1[e]	H	130	6	79	790	132
10		0.1	H	160	2	28	160	80
11		0.5	H	160	6	40	80	13

[a] Reaction conditions: ArCl (2 mmol), $PhB(OH)_2$ (3 mmol), K_2CO_3 (4 mmol), **12c**, TBAB (20 mol %), DMF/H_2O 95:5 (7 mL). [b] Bath temperature. [c] Determined by GLC on the basis of ArCl using decane as internal standard. In parentheses, isolated yield after flash chromatography. [d] $Pd(AcO)_2$ was used as catalyst. [e] Reaction conditions: ArCl (2 mmol), $PhB(OH)_2$ (3 mmol), K_2CO_3 (4 mmol), **12c**, TBAB (20 mol %).

SCHEME 6. Suzuki Coupling: Allylic and Benzylic Chlorides



SCHEME 7. Ullmann Coupling of Aryl Iodides



just 5% in volume, both DMF and NMP gave the best yields of *p*-acetylbiphenyl (entries 9 and 10).[33] Finally, the temperature resulted as a decisive factor when combined with the correct solvent mixture. As seen in entry 12, when the reaction was carried out at 160 °C in DMF/H_2O 95:5, the yield of product was improved to 99%, and what is more important, only traces of biphenyl were detected by GLC analysis of the crude reaction mixture.

After finding the most efficient reaction conditions, the reactivities of various aryl chlorides in the Suzuki reactions were studied (Scheme 5, Table 4). At this point we thought it interesting to compare, first of all, the catalytic efficiencies of oxime-derived palladacycle **12c** and more simple palladium catalysts such as $Pd(OAc)_2$ in the Suzuki couplings of chloroarenes with phenylboronic acid. As depicted in Table 4, entries 1 and 2, $Pd(OAc)_2$ (0.1 mol %) is less efficient than catalyst **12c** (0.1 mol % Pd) in the coupling of *p*-chloroacetophenone with phenylboronic acid in DMF at 130 °C under aerobic conditions.[34] When using **12c** as catalyst precursor, electron-poor *p*-chloroacetophenone and *p*- and *o*-chlorobenzonitrile were coupled with phenylboronic acid in very good yields (Table 4, entries 1, 3−7). With *p*-chloroacetophenone, it was possible to decrease the catalyst loading to 10^{-2} mol % Pd by just increasing the reaction temperature from 130 °C (0.1 mol % Pd, 86% yield, 2 h) to 160 °C (10^{-2} mol % Pd, 47% yield, 1 h). *ortho*-Substituted chlorides such as 2-chlorobenzonitrile reacted very efficiently with both phenylboronic acid and *p*-tolylboronic acid, producing, with the latter, 2-cyano-4′-methylbiphenyl, a key intermediate in the syntheses of angiotensin II receptor antagonists that are used for the treatment of hypertension.[35] Chloro-substituted heteroarylic derivatives such as 3-chloropyridine and 2-methyl-4,5-dichloro-3(2*H*)-pyridazinone (Table 4, entries 8 and 9), which potentially could bind to palladium through the nitrogen atom, are also suitable substrates for the Suzuki coupling reactions. Deactivated *p*-chlorotoluene and *p*-chloroanisole gave the desired biarylic products in 28% and 40% yields, respectively (Table 4, entries 10 and 11).

The Suzuki palladium-catalyzed methodology was also extended to the coupling of allylic and benzylic chlorides with phenylboronic acid, as depicted in Scheme 6. Both 1-chloro-2-methylpropene and 1-chloromethylnaphthalene afforded the corresponding coupled products in excellent yields and short reaction times under low catalyst loadings.

Finally, diverse symmetrical biphenyls were synthesized in high yields via reductive homocouplings of different iodobenzenes using complex **12c** (0.5−2 mol % Pd), as depicted in Scheme 7. Using hydroquinone as additive[21b] (50 mol %), K_2CO_3 as base, and DMF at 110 °C and in the presence of **12c**, iodobenzene was not efficiently coupled, giving, after 22 h, a modest 48% yield of biphenyl even when employing high catalyst loadings (2 mol % Pd). However, in the absence of hydroquinone and by employing *N*,*N*-diisopropylethylamine as base,[22] we could reduce the catalyst loading to 0.5 mol % Pd. Activated and nonactivated iodobenzenes gave the corresponding products in short times (5−7 h) and with very good yields under aerobic conditions (Table 5). The rate was slower in the case of deactivated substrates such as

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[33] The solvent/water ratio has been previously used to control the selectivity of the reaction. See ref 8b.

[34] Dupont has shown that simple palladium catalysts, such as $PdCl_2(SEt)_2$ and $Pd(OAc)_2$, are able to catalyze the Suzuki coupling of *p*-ciano and *p*-nitro aryl chlorides under inert atmosphere with low turnover numbers. See ref 8c.

[35] Goubet, D.; Meric, P.; Dormoy, J.-R.; Moreau, P. *J. Org. Chem.* **1999**, *64*, 4516−4518.

TABLE 5. Ullmann-Type Symmetrical Coupling of Aryl Iodides Catalyzed by 12c[a]

entry	R	time (h)	yield[b] (%)	TON	TOF (h^{-1})
1	CH_3CO	5	>99 (99)	100	20
2	NO_2	5	>99	100	20
3	Cl	5	90	90	18
4	F	7	95	95	14
5	H	5	93	93	19
6	MeO	7	83 (95)	83	12

[a] Catalyst loading: 0.5 mol % Pd. [b] Determined by GLC using decane as internal standard. In parentheses, isolated yield after workup (the purity of the crude products after workup was always >95%, determined by ^1H NMR).

p-iodoanisole (Table 5, entry 6), but still, a good yield was obtained without traces of protiodeiodination product.[36] A proposed mechanism for this type of homocoupling reaction involves the oxidation of the tertiary amine by the palladacycle with formation of a Pd(IV) complex, which after reductive elimination yields the corresponding biaryl, an iminium salt, and hydrogen iodide.[22]

Conclusions

In summary, oxime-derived palladacycles **12** represent a very efficient family of catalyst precursors for the Suzuki–Miyaura couplings of aryl, allyl, and benzyl bromides and chlorides with arylboronic acids. Very good turnover numbers and rates have been obtained *under aerobic conditions* for aryl bromides and chlorides. Moreover, we have shown these systems as competent catalysts for the palladium-catalyzed reductive homocouplings of different iodoarenes to afford symmetrical biaryls in excellent yields. The stability of oxime-derived palladacycles **12** against air, moisture, and temperature and the fact that they can be synthesized from inexpensive and readily available starting materials using a straightforward procedure make these complexes very promising catalysts, and further studies of their applicability in other organic transformations are currently under investigation.

Experimental Section

General. The reagents and solvents were obtained from commercial sources and were generally used without further purification. Gas chromatographic analyses were performed on a GLC instrument equipped with a fused silica capillary column. ^1H NMR spectra were recorded on a 300 MHz apparatus. Chemical shifts are in ppm using tetramethylsilane (TMS, 0.00 ppm) as internal standard. ^{13}C NMR spectra were recorded at 75 MHz with $CDCl_3$ or CD_3COCD_3 as the internal reference. The catalysts were weighed in an electronic microscale with a precision of 1 μg. IR data were collected on an FTIR apparatus. The reactions were set up in parallel with the aid of carousel reaction equipment equipped with gastight threaded caps with a valve, cooling reflux head system, and digital temperature controller. Entries 1,[4a] 4,[17] 5,[17] 6,[37] 7,[4a] 8,[4a] 10,[38] 11,[21] 12,[39] and 13[38] from Table 2 have been previously reported and were characterized by comparisons of their GC/MS and ^1H NMR spectra; their purities were confirmed by GC analyses. For entries 14 and 15 (new compounds), see Experimental Section. Entries 5,[4a] 8,[29] 9,[40] and 10[4a] from Table 4 have been previously reported and were characterized by comparisons of their GC/MS and ^1H NMR spectra; their purities were confirmed by GC analyses. Entries 1, 2, 5, and 6 from Table 5 have been previously reported[21b] and were characterized by comparisons of their GC/MS and ^1H NMR spectra; their purities were confirmed by GC analyses. Entries 3 and 4 from Table 5 are commercially available and were characterized by comparisons of their GC/MS and ^1H NMR spectra.

Typical Experimental Procedure for Suzuki Coupling of Aryl Bromides with Phenylboronic Acid. A 25-mL round-bottom flask was charged with 4-bromobiphenyl (2 mmol, 468 mg), phenylboronic acid (3 mmol, 377 mg), potassium carbonate (4 mmol, 553 mg), catalyst **12c** (0.0001 mmol, 82 μg, 0.01 mol % Pd), and 7 mL of toluene. The mixture was stirred at 110 °C in air, and the reaction progress was analyzed by GC. After completion, the reaction mixture was poured into an excess of water and extracted with ethyl acetate (3 × 15 mL). The organic phases were dried, evaporated (15 mmHg), and washed with hot hexane (3 × 10 mL) to eliminate triphenylboroxine, yielding 424 mg of pure 1,4-diphenylbenzene (92% yield).

Entry 14, Table 2. Mp (EtOAc) 143 °C; ^1H NMR ($CDCl_3$) δ 7.29–7.65 (m, 12H), 7.91–7.94 (m, 2H), 8.52 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 121.4, 126.9, 127.2, 127.8, 128.76, 128.81, 131.4, 136.2, 138.9, 140.6, 151.1, 160.2; IR (KBr, cm^{-1}) 3054, 3030, 1622; GC–EIMS *m/z* (rel intensity) 258 ($M^+ + 1$, 21), 257 (M^+, 100), 256 ($M^+ - 1$, 52), 153 (16), 152 (46), 1514 (10), 129 (10), 128 (19). HRMS calcd for $C_{19}H_{15}N$: 257.1204. Found: 257.1204.

Entry 15, Table 2. Mp (hexane/EtOAc) 57 °C; ^1H NMR ($CDCl_3$) δ 4.06–4.19 (m, 4H), 5.87 (s, 1H), 7.35–7.63 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 65.3, 103.6, 126.9, 127.2, 127.4, 128.8, 136.8, 140.8, 142.2; IR (CH_2Cl_2) 3074, 3026, 2891, 2847, 1388, 1221, 1077, 981, 951; GC–EIMS *m/z* (rel intensity) 226 (M^+, 47), 225 ($M^+ - 1$, 67), 181 (36), 167 (15), 165 (26), 155 (13), 154 (100), 153 (28), 152 (43), 151 (11). HRMS calcd for $C_{15}H_{14}O_2$: 226.0994. Found: 226.0958.

Typical Experimental Procedure for Suzuki Coupling Using Less Than 10^{-3} mol % Pd. A reaction tube of the carousel reaction equipment was charged with 4-bromoacetophenone (2 mmol, 406 mg), phenylboronic acid (3 mmol, 377 mg), decane (2 mmol, 390 μL), potassium carbonate (4 mmol, 553 mg), catalyst **12c** (333 μL of a solution, 2.45×10^{-3} mg of **12c**/mL of toluene), and 4 mL of DMF. The mixture was stirred at 160 °C in air, and the reaction progress was analyzed by GC.

Typical Procedure for Suzuki Coupling of Aryl Bromides at Room Temperature. A 25-mL round-bottom flask was charged with 4-bromoacetophenone (2 mmol, 406 mg), phenylboronic acid (3 mmol, 377 mg), decane (2 mmol, 390 μL), potassium hydroxide (4 mmol, 264 mg), catalyst **12c** (0.002 mmol, 1.632 mg, 0.2 mol % Pd), and 7 mL of toluene. The mixture was stirred at room temperature in air, and the reaction progress was analyzed by GC. After completion, the product was isolated by pouring the reaction mixture into an excess of water and extracting the aqueous phase with ethyl acetate (3 × 15 mL). The organic phases were dried and evaporated (15 mmHg) to afford 390 mg (>99% yield) of pure product (^1H NMR).

Typical Procedure for Suzuki Coupling of Aryl Chlorides with Arylboronic Acids. A 25-mL round-bottom flask was charged with 4-chloroacetophenone (2 mmol, 267 μL), phenylboronic acid (3 mmol, 377 mg), decane (2 mmol, 390 μL),

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(36) Palladium-catalyzed Ullmann-type couplings are usually run under inert atmosphere in order to avoid side reactions such as protiodehalogenation of the starting material. See refs 21 and 22.

(37) Lipshutz, B. H.; Sclafani, J. A.; Blomgren, P. A. *Tetrahedron* **2000**, *56*, 2139–2144.

(38) Matsura, H.; Tsuchiya, T.; Imafuku, K. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3519–3520.

(39) Dyer, U. C.; Shapland, P. D.; Tiffin, P. D. *Tetrahedron Lett.* **2001**, *42*, 1765–1767.

(40) Maes, B. U. W.; R'kyek, O.; Košmrlj, J.; Lemière, G. L. F.; Esmans, E.; Rozenski, J.; Dommisse, R. A.; Haemers, A. *Tetrahedron* **2001**, *57*, 1323–1330.

potassium carbonate (4 mmol, 553 mg), tetrabutylammonium bromide (0.4 mmol, 129 mg), catalyst **12c** (0.001 mmol, 816 μg, 0.1 mol % Pd), and 4 mL of the mixture DMF/H_2O 95:5. The reaction was stirred at 130 °C in air, and the reaction progress was analyzed by GC. The reaction mixture was poured into an excess of water and extracted with ethyl acetate (3 × 15 mL). The organic extracts were dried and evaporated (15 mmHg) to afford the crude product in a 91% yield (pure by ^{1}H NMR).

Typical Experimental Procedure for Suzuki Coupling of Benzyl Chlorides with Phenylboronic Acid. A 25-mL round-bottom flask was charged with 1-chloromethylnaphthalene (2 mmol, 333 μL), phenylboronic acid (3 mmol, 377 mg), decane (2 mmol, 390 μL), potassium carbonate (4 mmol, 553 mg), tetrabutylammonium bromide (0.4 mmol, 129 mg), catalyst **12c** (0.001 mmol, 816 μg, 0.1 mol % Pd), and 4 mL of the mixture DMF/H_2O 95:5. The reaction was stirred at 130 °C in air, and the reaction progress was analyzed by GC. When completed, the reaction mixture was poured into an excess of water and extracted with ethyl acetate (3 × 15 mL). The organic extract was dried and evaporated (15 mmHg) to afford the crude product in a 98% yield (pure by ^{1}H NMR).

Typical Experimental Procedure for Suzuki Coupling of Allyl Chlorides with Phenylboronic Acid. A 25-mL round-bottom flask was charged with 3-chloro-2-methylpropene (2 mmol, 205 μL), phenylboronic acid (3 mmol, 377 mg), decane (2 mmol, 390 μL), potassium carbonate (4 mmol, 553 mg), tetrabutylammonium bromide (0.4 mmol, 129 mg), catalyst **12c** (0.001 mmol, 816 μg, 0.1 mol % Pd), and 4 mL of the mixture DMF/H_2O 95:5. The mixture was stirred at 130 °C in air, and the reaction progress was analyzed by GC. After completion, the reaction mixture was poured into an excess of water and extracted with ethyl acetate (3 × 15 mL). The organic extracts were dried and evaporated (15 mmHg) to afford the crude product in a >99% yield (pure by ^{1}H NMR).

Typical Experimental Procedure for Ullmann Homocoupling of Aryl Iodides Using Hydroquinone as Additive. A 25-mL round-bottom flask was charged with iodobenzene (2 mmol, 228 μL), hydroquinone (1 mmol, 110 mg), decane (2 mmol, 390 μL), potassium carbonate (2 mmol, 277 mg), catalyst **12c** (0.02 mmol, 16.3 mg), and 5 mL of DMF. The mixture was stirred at 110 °C in air, and the reaction progress was analyzed by GC. After 22 h, the reaction mixture was poured into an excess of water and extracted with ethyl acetate (3 × 15 mL). GC analyses of the organic extracts showed 50% conversion of the iodobenzene versus the internal standard.

Typical Experimental Procedure for Ullmann Homocoupling of Aryl Iodides Using a Tertiary Amine as Base. A 25-mL round-bottom flask was charged with 4-iodoacetophenone (2 mmol, 492 mg), diisopropylethylamine (4.8 mmol, 822 μL), decane (2 mmol, 390 μL), catalyst **12c** (0.005 mmol, 4.079 mg), and 4 mL of DMF. The mixture was stirred at 110 °C for 5 h. Then the reaction mixture was poured into an excess of water, extracted with ethyl acetate (3 × 15 mL), and washed with H_2O (4 × 10 mL). The organic extracts were dried and evaporated (15 mmHg) to afford the crude product in a >99% yield (pure by ^{1}H NMR).

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Supporting Information Available: Characterization data for new compounds (Table 2, entries 14 and 15). This material is available free of charge via the Internet at http://pubs.acs.org.

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