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Arylation of Benzo-Fused 1,4-Quinones by the Addition of Boronic Acids under Dicationic Pd(II)-Catalysis

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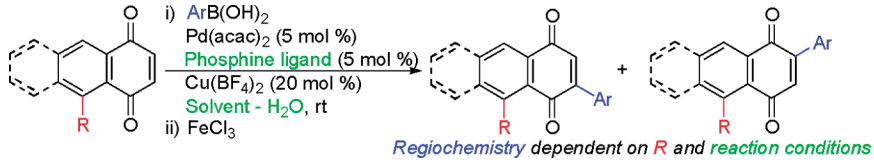
ABSTRACT



The first examples of the direct arylation of benzo-fused 1,4-quinones by the dicationic Pd(II)-catalyzed addition of arylboronic acids are reported. The addition reaction is carried out under very mild conditions (dioxane−H_2O, rt, open air atmosphere) and is tolerant of free OH groups. In addition, the reaction shows high regioselectivity when using nonsymmetrical quinones as starting materials.

Benzo-fused 1,4-quinones are important natural products that undergo a number of biochemical transformations.[1,2] Many of them have been found to exhibit a wide range of pharmacological properties[3] and have also been recognized as part of the core of many useful molecules in organic chemistry.[4] Among them, compounds functionalized at the quinone moiety with aryl groups constitute a common structural motif. Depending on the substitution pattern, these compounds have been obtained only by a few general methods such as oxidation of the corresponding aromatics or cycloadditions yielding the fused quinone core.[1,5] In limited cases, the Meerwein reaction[6] and direct arylation protocols have also been used for the installment of electron-rich aryls or heteroaromatics.[7] Transition-metal mediated cross-couplings are wider in scope than older procedures.[8] However, their application requires the previous selective functionalization at positions 2 or 3 of the starting quinone with a halogen or triflate group. This is not always trivial, especially in those benzo-fused 1,4-quinones which are rendered nonsymmetric due to the presence of other sub-

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(1) (a) *The Chemistry of the Quinonoid Compounds, Vol. 2, Parts 1 and 2*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1988. (b) Thomson, R. H. In *Naturally Occurring Quinones IV*; Blackie Academic: London, 1997.

(2) See for example: (a) Lenaz, G.; Genova, M. L. *Encycl. of Biol. Chem.* **2004**, *3*, 621. (b) Babula, P.; Mikelova, R.; Kizek, R.; Havel, L.; Sladky, Z. *Ceska Slovens. Farm.* **2006**, *55*, 151.

(3) For recent reviews, see: (a) Koyama, J. *Recent Patents Anti-Infect. Drug. Discov.* **2006**, *1*, 113. (b) Babula, P.; Adam, V.; Havel, L.; Kizek, R. *Ceska Slovens. Farm.* **2007**, *56*, 114. (c) Verma, R. P. *Anti-Cancer Agents Med. Chem.* **2006**, *6*, 489.

(4) Bishop, K. J. M.; Klajn, R.; Grzybowski, B. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5348.

(5) (a) Kutyrev, A. *Tetrahedron* **1991**, *47*, 8043. (b) Owton, W. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, *17*, 2409. (c) Gallagher, P. T. *Contemp. Org. Synth.* **1996**, *3*, 433. (d) Couladouros, E. A.; Strongilos, A. T. *Sci. Synth.* **2006**, *28*, 217. (e) Krohn, K.; Boker, N. *Sci. Synth.* **2006**, *28*, 367. (f) Mal, D.; Pahari, P. *Chem. Rev.* **2007**, *107*, 1892, and references cited therein.

(6) (a) Lin, A. J.; Sartorelli, A. T. *J. Med. Chem.* **1976**, *19*, 1336. (b) Wurm, G.; Gurka, H. J. *Pharmazie* **1997**, *52*, 739.

(7) (a) Itahara, T. *J. Org. Chem.* **1985**, *50*, 5546. (b) Wurm, G. *Arch. Pharm.* **1991**, *324*, 491. (c) Batenko, N. G.; Karlivans, G.; Valters, R. *Chem. Heterocycl. Compd.* **2005**, *41*, 691. (d) Mital, A.; Negi, V. S.; Ramachandran, U. *Arkivoc* **2008**, *xv*, 176.

(8) See for example: (a) Tamayo, N.; Echavarren, A. M.; Paredes, M. C. *J. Org. Chem.* **1991**, *56*, 6488. (b) Echavarren, A. M.; Tamayo, N.; De Frutos, O.; García, A. *Tetrahedron* **1997**, *56*, 16835. (c) Echavarren, A. M.; De Frutos, O.; Tamayo, N.; Noheda, P.; Calle, P. *J. Org. Chem.* **1997**, *62*, 4524. (d) Mohri, S.-I.; Stefinovic, M.; Snieckus, V. *J. Org. Chem.* **1997**, *62*, 7072. (e) De Frutos, O.; Atienza, C.; Echavarren, A. M. *Eur. J. Org. Chem.* **2001**, 163, and references cited therein.

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stituents in the benzenoid ring. Therefore, the development of new low-cost general and regioselective arylation methods deserves further consideration.

On the other hand, the conjugate addition reaction of boronic acids to a wide variety of electron-deficient systems under transition-metal catalysis, mainly with Rh(I) species, constitutes a useful synthetic C−C bond-forming method.[9] Organoboron compounds are readily available and have low toxicity. In addition, their transition-metal catalyzed conjugate addition reactions may be conducted in water-containing solvents, so they are especially attractive from an environmental standpoint. Some scattered reports of the Rh(I)-catalyzed addition of boronic acids to quinones have been reported in the literature,[10,11] and very recently, the direct arylation of quinones with the related aryltrifluoroborates has been communicated.[12,13]

However, the high price of Rh has prompted the development of cheaper catalytic systems. In this regard, it has been shown recently that the addition of boronic acids to some electron-deficient alkenes can also be catalyzed by dicationic Pd(II) species.[14] Herein, we have explored the direct arylation of quinones by the dicationic Pd(II)-catalyzed addition of arylboronic acids to benzo-fused quinones (Figure 1).

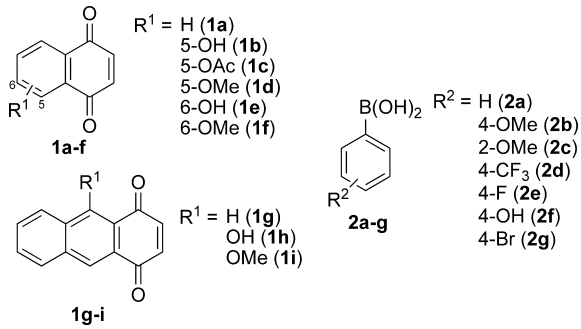
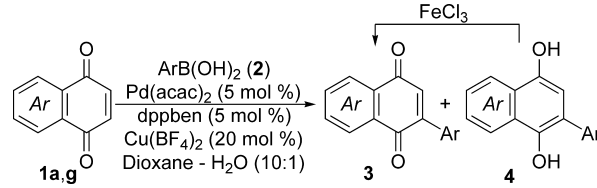


Figure 1. Quinones and boronic acids used in this study.

Particular attention has been paid to situations in which previously reported arylations are weak: (a) the possibility of using electron-poor arylboronic acids; (b) regiochemical issues due to the presence of substituents in the benzenoid ring; (c) the tolerance of unprotected OH groups (phenolic) in either coupling partner. These features are ubiquitous in quinonoid natural products, and previous synthetic strategies require selective protection and deprotection steps, in particular when regiochemistry is concerned. Our study sought to carry out the reactions in an open air atmosphere at room temperature using a water-containing solvent.[13]

Initial screening of reaction conditions (Table 1) with 1,4-naphthoquinone (**1a**) and phenylboronic acid (**2a**, 1.5 equiv)

Table 1. Addition of $ArB(OH)_2$ (**2**) to Quinones **1a**,**g**[a]



entry	1	2	3, yield[b] (%)
1	**1a**	**2a**	**3aa** (85)
2	**1a**	**2b**	**3ab** (85)
3	**1a**	**2d**	**3ad** (75)
4	**1a**	**2e**	**3ae** (80)
5	**1a**	**2f**	**3af** (85)
6	**1g**	**2a**	**3ga** (85)
7	**1g**	**2b**	**3gb** (85)
8	**1g**	**2d**	**3gd** (75)

[a] Reactions carried out at rt with 0.2 mmol of quinones **1**, 1.5 equiv of $ArB(OH)_2$ (**2**), 5 mol % of $Pd(acac)_2$, 5 mol % of dppben and 20 mol % of $Cu(BF_4)_2.6H_2O$ in 0.5 mL of dioxane-H_2O (10:1). [b] Yield of isolated **3** after oxidation ($FeCl_3$, CH_2Cl_2, rt) and column chromatography on silica gel.

led to $Pd(acac)_2$ (5 mol %), 1,2-bis(diphenyl-phosphino)benzene (dppben, 5 mol %) and $Cu(BF_4)_2$ (20 mol %) as the optimum reagent combination for generating the catalytically active dicationic Pd(II)-species at room temperature in dioxane-H_2O (10:1) as solvent.[15] These conditions were used for subsequent studies with **1a** and other boronic acids (**2**), and for 1,4-anthraquinone (**1g**). No regioselectivity concerns were included in these first trials.

Under these reaction conditions (Table 1, entry 1) compound **3aa** was obtained together with the corresponding reduced form **4aa**. Without any attempt of separation, direct oxidation ($FeCl_3$, CH_2Cl_2, rt, 1 h) of the crude reaction mixture afforded **3aa** in high yield. To determine the scope and limitations of the process, several arylboronic acids with electron-rich, electron-poor, or sterically hindering substituents were tested in their reaction with quinone **1a** (Table 1, entries 2−6). All reactions gave the corresponding compounds **3a** in high yield. The reaction with *p*-hydroxyphenylboronic acid (Table 1, entry 5) shows that no protection of OH groups in the arylboronic acid is required. Similar results were obtained in representative reactions with **1g** (Table 1, entries 6−8).

Regiochemical issues come to play when considering nonsymmetrical quinones such as 1,4-naphthoquinones which

(9) For recent reviews, see: (a) Yoshida, K.; Hayashi, T. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; p 55. (b) Yoshida, K.; Hayashi, T. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005; Chapter 4, p 171.

(10) For the rhodium-catalyzed direct addition of arylboronic acids to quinones, see: (a) Shintani, R.; Duan, W.-L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628. (b) Duan, W.-L.; Imazaki, Y.; Shintani, R.; Hayashi, T. *Tetrahedron* **2007**, *63*, 8529.

(11) For the addition of arylboronic acids to quinone monoacetals see: (a) Tokunaga, N.; Hayashi, T. *Adv. Synth. Catal.* **2007**, *349*, 513. (b) Lalic, G.; Corey, E. J. *Tetrahedron Lett.* **2008**, *49*, 4894.

(12) Demchuk, O. M.; Pietrusiewicz, K. M. *Synlett* **2009**, 1149.

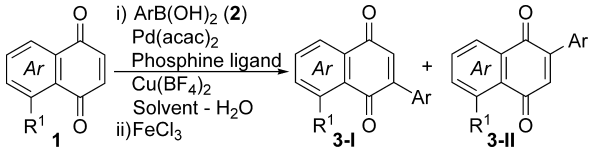
(13) Low yields have been observed by the procedure reported in ref 12 for electron-poor or hindered aryltrifluoroborates. These reactions were carried out in butanone at 83 °C. No regiochemical aspects or the presence of free OH groups were considered in these studies.

(14) Reviews: (a) Yamamoto, Y.; Nishikata, T.; Miyaura, N. *J. Synth. Org. Chem., Jpn.* **2006**, *64*, 1112. (b) Gutnov, A. *Eur. J. Org. Chem.* **2008**, 4547. (c) Yamamoto, Y.; Nishikata, T.; Miyaura, N. *Pure Appl. Chem.* **2008**, *80*, 807. (d) Miyaura, N. *Synlett* **2009**, 2039.

(15) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **2004**, *23*, 4713.

bear substituents at carbons C5 or C6 (compounds **1b**−**f**) or 1,4-anthraquinones with substituents at C9 (compounds **1i**,**j**). These results are gathered in Table 2.

Table 2. Addition of $ArB(OH)_2$ (**2**) to 1,4-Naphthoquinones **1b**−**f** and 1,4-Anthraquinones **1h**,**i**[a]



entry	1	2	ligand	solvent[b]	3, yield[c] (%)	3-I:3-II ratio[d,e]
1	**1b**	**2a**	dppben	A	**3ba** (85)	15:85
2	**1c**	**2a**	dppben	A	**3ca** (80)	40:60
3	**1d**	**2a**	dppben	A	**3da** (90)	95:05
4	**1b**	**2a**	dppben	B	**3ba** (75)	50:50
5	**1b**	**2a**	dppben	C	**3ba** (80)	20:80
6	**1b**	**2a**	dppben	D	**3ba** (75)	40:60
7	**1b**	**2a**	dppben	E	**3ba** (70)	30:70
8	**1b**	**2a**	dppe	A	**3ba** (20)	45:55
9	**1b**	**2a**	dppb	A	**3ba** (*nr*)	*nr*
10	**1b**	**2a**	dppp	A	**3ba** (50)	70:30
11	**1b**	**2a**	dppethy	A	**3ba** (80)	75:25
12	**1b**	**2b**	dppben	A	**3bb** (85)	40:60
13	**1b**	**2c**	dppben	A	**3bc** (85)	20:80
14	**1b**	**2d**	dppben	A	**3bd** (80)	10:90
15	**1b**	**2e**	dppben	A	**3be** (80)	30:70
16	**1d**	**2b**	dppben	A	**3db** (90)	95:05
17	**1d**	**2d**	dppben	A	**3dd** (80)	100:0
18	**1d**	**2g**	dppben	A	**3dg** (85)	70:30
19	**1h**	**2a**	dppben	A	**3ha** (70)	30:70
20	**1h**	**2b**	dppben	A	**3hb** (60)	0:100
21	**1h**	**2g**	dppben	A	**3hg** (50)	0:100
22	**1i**	**2a**	dppben	A	**3ia** (85)	80:20
23	**1i**	**2b**	dppben	A	**3ib** (85)	65:35
24	**1i**	**2d**	dppben	A	**3id** (85)	100:0
25	**1e**	**2a**	dppben	A	**3ea** (65)	65:35
26	**1f**	**2a**	dppben	A	**3fa** (70)	60:40

[a] All reactions were carried out at rt with 0.2 mmol of quinones **1**, 1.5 equiv of $ArB(OH)_2$ (**2**), 5 mol % of $Pd(acac)_2$, 5 mol % of phosphine ligand and 20 mol % of $Cu(BF_4)_2.6H_2O$ in 0.5 mL of solvent-H_2O. [b] A = dioxane−H_2O (10:1), B = dioxane−H_2O (7:3), C = THF−H_2O (10:1), D = MeOH−H_2O (10:1), E = toluene−H_2O (10:1). [c] Combined yield of isolated **3**. [d] Product ratio determined by integration of the ^1H NMR signals of the reaction crudes. [e] Compounds **3-I** and **3-II** were separated by chromatography or crystallization. See Supporting Information

Starting with the C5-substituted 1,4-naphthoquinones (juglone derivatives, compounds **1b**−**d**), we observed that the reaction was tolerant of unprotected phenolic OH groups in the quinone (**1b**, entries 1 and 4 - 15). In this case, variable ratios of the corresponding reduced forms (leuco forms)[16] were noticed in the ^1H NMR spectra of the reaction crude mixtures prior to $FeCl_3$ oxidation. No modification of the regiochemistry was experienced upon oxidation of the crude reaction mixture or upon independent oxidation of the isolated leuco forms.[17] In addition, we have observed a strong dependence of the regiochemisty with the protection of the OH group.[18] Therefore, whereas juglone itself (**1b**) produced a 15:85 mixture of regioisomers (Table 2, entry 1) in the reaction with phenylboronic acid (**2a**), the corresponding acetate (**1c**) behaved rather unselectively (Table 2, entry 2). On the other hand, the methyl ether (**1d**) inverted the regiochemistry to 95:05 (Table 2, entry 3). This result is noteworthy, as the regioselectivity is complementary to that observed for **1b**. Methylation of **3ba-II** afforded **3da-II**, compound which cannot be directly prepared when starting from **3d**.[17]

In an attempt to increase the regioselectivity further in the case of the OH-free compound (**1b**), several ligand-solvent combinations were examined. Modifications in the regioselectivity were attained either when changing the solvent (Table 2, entries 5−7) or when modifying the phosphine ligand keeping dioxane-H_2O (10:1) as the solvent (Table 2, entries 8−11). Although no further improvement in favor of **3ba-II** was achieved, it is worth mentioning that, opposite to previous reports,[15] the arylation reaction took place with low yield when using dppe (1,2-bis(diphenylphosphino)ethane) as the ligand (Table 2, entry 8), and no reaction was observed in the presence of dppb (1,4-bis(diphenylphosphino)butane, Table 2, entry 9). On the other hand, an inversion of the regiochemistry in favor of isomer **3ba-I** was observed when using dppp (1,3-bis(diphenylphosphino)propane), albeit the yield was low (Table 2, entry 10). However, the use of dppethy (1,2-bis(diphenylphosphino)-ethylene) allowed access to **3ba-I** as the major isomer in good yield (Table 2, entry 11).

The regiocontrol (Figure 2) of the nucleophilic addition reactions to 1,4-naphthoquinones has been attributed to the

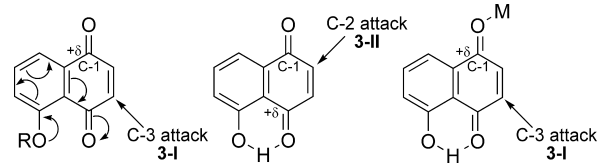


Figure 2. Regiochemistry of the addition reaction.

electronic effects of the substituents on the benzenoid ring.[19] Thus, the presence of an electron-donating substituent at C-5 makes the C-4 carbonyl less electron deficient than the C-1

(16) For substituent effects in the keto-enol tautomerism of 1,4-naphthalenediols, see: Pearson, M. S.; Jensky, B. J.; Greer, F. X.; Hagstrom, J. P.; Wells, N. M. *J. Org. Chem.* **1978**, *43*, 4617.

(17) See Supporting Information for further details.

(18) The regiochemistry of **3ba-II** was assigned by comparison of the NMR data with a sample independently synthesized by the Stille coupling of 2-bromo-5-hydroxy-1,4-naphthoquinone. See: Echavarren, A. M.; Tamayo, N.; Cárdenas, D. J. *J. Org. Chem.* **1994**, *59*, 6075. The regiochemistry of the remaining compounds have been assigned by comparison of their NMR data with those of **3ba-I** and **3ba-II**, and by chemical correlation between OH-free and OMe compounds. See also Supporting Information for further details.

(19) For the regioselectivity in nucleophilic additions to juglone derivatives, see for example: (a) Kelly, T. R.; Gillard, J. W.; Goerner, R. N., Jr.; Lyding, J. M. *J. Am. Chem. Soc.* **1977**, *99*, 5515. (b) Parker, K. A.; Sworin, M. E. *J. Org. Chem.* **1981**, *46*, 3218. (c) Kelly, T. R.; Parekh, N. D.; Trachtenberg, E. N. *J. Org. Chem.* **1982**, *47*, 5009. (d) Couladouros, E. A.; Plyta, Z. F.; Haroutounian, S. A. *J. Org. Chem.* **1997**, *92*, 6, and references cited therein.

carbonyl due to electron delocalization. The electron deficiency at C1 is transferred to C-3, leading to preferential nucleophilic attack at this position (formation of compounds **3-I**). In this context, the electron donation of the OCH_3 group will be bigger than that of the OAc group. However, activation of C-4 by internal chelation of the OH group inverts this situation, rendering C-2 more electron-deficient.[20]

Our results show that the regiochemisty of the addition of arylboronic acids to juglone derivatives catalyzed by dicationic Pd(II) complexes is not only dependent on the electronic structure of the quinone (protection of the OH group), and can be tuned with the nature of the catalyst. This may be understood by coordination of the less hindered carbonyl group (C-1) by the less bulky dicationic Pd(II)-species (dppp and dppethy ligands), which will make C-3 more electron deficient.

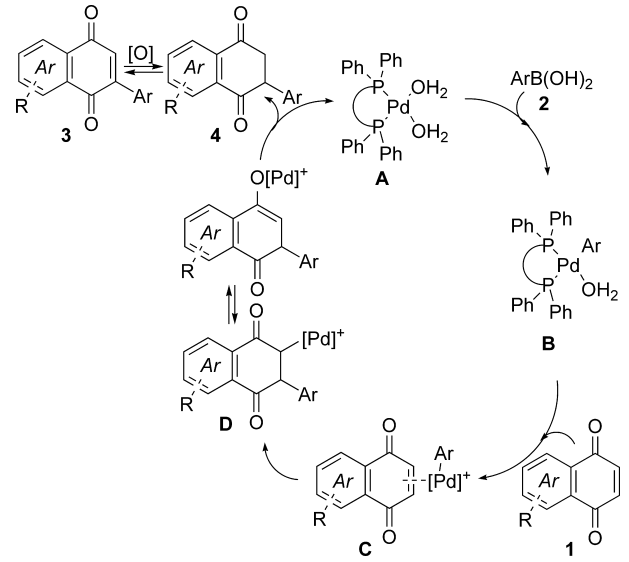
The arylation of **1b** and **1d** with several other representative arylboronic acids has also been investigated (Table 2, entries 12−18), and a similar trend has been observed as for **2a**.

In a similar fashion, reactions of the 1,4-anthraquinone derivatives **1h**,**i** afforded the corresponding aryl derivatives **3**. A predominance of compounds **3h-II** was observed when using the OH-free compound **1h** as the starting material (Table 2, entries 19−21). On the other hand, a predominance of compounds **3i-I** was observed when starting from the OMe derivative **1i** (Table 2, entries 22−24). Also, methylation of **3ha-II** afforded **3ia-II**.[17]

However, in the case of 6-substituted-1,4-naphthoquinones (**1e**,**f**), we observed that the regioselectivity was low (Table 2, entries 25, 26); thus, the presence of a remote substituent has a low impact on the regioselectivity of the arylation.

A plausible mechanism of this reaction is shown in Scheme 1. First, the dicationic palladium species **A** is formed from the *in situ* reaction of $Pd(acac)_2$, the bisphosphine ligand and $Cu(BF_4)_2.6H_2O$. This enables smooth transmetalation with the arylboronic acids **2** to yield a cationic arylpalladium(II) species **B**. Next, π-coordination of the carbon−carbon double bond of quinones **1** to the cationic palladium center occurs to form **C**. Then, regioselective conjugate addition of the arylpalladium species to the α,β-unsaturated system takes place to yield the cationic Pd(II) enolates **D**, which exist in solution as equilibrating C- and O-bound tautomers

Scheme 1. Plausible Reaction Course for the Arylation Reaction



and are highly susceptible to hydrolytic cleavage.[21] Protonation in the aqueous solvent affords the leuco forms **4** with regeneration of a dicationic palladium(II) species able to restart the catalytic cycle. Compounds **4** may be in equilibrium with the quinones **3** by oxidation with air.

In conclusion, we have developed a new type of arylation of quinones by the dicationic Pd(II)-catalyzed addition of boronic acids at room temperature in open air conditions and using water-containing solvents. The reaction is tolerant of free OH groups in either coupling partner, permits regiocontrol, and works efficiently for sterically hindered substrates and for electron-poor boronic acids. The mild reaction conditions anticipate a possible extension of this protocol to the synthesis of densely functionalized molecules.

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Supporting Information Available: Preparative methods, NMR spectra and assignment of the reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) For the influence of the coordination with Lewis acids, see for example: (a) Jiang, C.; Wang, S. *Synlett* **2009**, 1099. (b) Valderrama, J. A.; Ibacache, J. A. *Tetrahedron Lett.* **2009**, *50*, 4361.

(21) (a) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 5816–5817. (b) Albéniz, C. A.; Catalina, M. M.; Espinet, P.; Redón, R. *Organometallics* **1999**, *18*, 5571.