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Simple (Imidazol-2-ylidene)-Pd-Acetate Complexes as Effective Precatalysts for Sterically Hindered Suzuki–Miyaura Couplings

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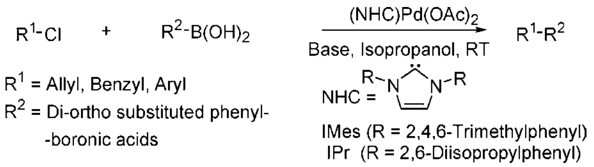
ABSTRACT

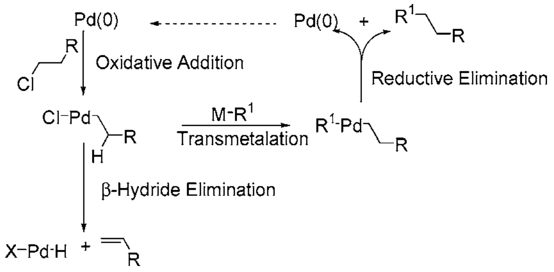


A simplified synthesis of *N*-heterocyclic carbene (NHC)Pd-carboxylate complexes and their activity in Suzuki–Miyaura cross-coupling reactions are described. Coupling of sterically hindered aryl and activated alkyl chlorides bearing *β*-hydrogens has been successfully achieved.

The versatility of the Suzuki−Miyaura reaction has greatly progressed since its early reports.[1] It serves as one of the most useful cross-coupling tools in synthetic chemistry.[2] Remarkable progress in both volume of work and mechanistic investigations has been achieved in recent years. However, barring a few recent advances, the attempts to use alkyl halides (especially chlorides) as electrophile partners have been largely unsuccessful.[3] Moreover, examples of mild reaction conditions are rare when the desirable coupling products are sterically hindered di-ortho or tri-ortho substituted biaryls.[4,5]

The major impediment in Suzuki−Miyaura coupling of alkyl halides is the presence of a facile *β*-hydride elimination pathway (Scheme 1). This undesired side reaction competes with the transmetalation step, hindering a productive coupling process.

Scheme 1. Competing Pathways in Suzuki−Miyaura Coupling



Extensive studies by a number of groups have helped this area take new strides.[6] Elegant work by Fu has helped expand

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(1) (a) Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, 691−694. (b) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314−321. (c) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513−519. (d) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *36*, 3437−3440.

(2) (a) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1470. (b) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633−9695. (c) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11−59. (d) Suzuki, A. J. *J. Organomet. Chem.* **1999**, *576*, 147−168. (e) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(3) (a) Cardenas, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 384−387. (b) Luh, T.-Y.; Leung, M.-K.; Wong, K.-T *Chem. Rev.* **2000**, *100*, 3187−3204. (c) Cardenas, D. J. *Angew Chem., Int. Ed.* **1999**, *38*, 3018−3020.

(4) Room-temperature reactions: (a) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3690−3693. (b) Navarro, O.; Kelly, R. A., III; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 16194−16195.

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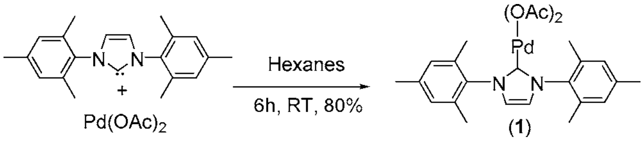
the scope of this reaction by including alkyl chlorides and secondary alkyl bromides as substrates.[7] The Suzuki−Miyaura reactions utilizing C(sp^3)-chlorides reported so far have been either with boranes as coupling partners[8] or catalyzed by phosphine ligands. However, both classes of compounds suffer from drawbacks. Air sensitivity and commercial unavailability of boranes increases the number of steps required to perform the coupling reaction. The boronic acids have been widely accepted as the more convenient transmetalating agents for this reaction. Furthermore, toxic and pyrophoric phosphines can be replaced by user-friendly *N*-heterocyclic carbenes (NHCs).[9]

In previous studies, we have highlighted the use of *N*-heterocyclic carbenes as efficient ligands in various cross-coupling reactions including the Suzuki−Miyaura reaction.[10] In a recent communication, we reported the synthesis of (imidazol-2-ylidene)Pd(OAc)$_2$ complexes.[11,12] The complexes were found to be active catalysts for the hydroarylation of alkynes.

In conjunction with extensive previous work with Pd(OAc)$_2$ as the palladium source for the Suzuki−Miyaura reaction,[10c,13] we examine here the activity of (NHC)Pd(OAc)$_2$ complexes in this important transformation. We now describe a simplified procedure for the synthesis of (NHC)Pd(OAc)$_2$ complexes and Suzuki−Miyaura reaction involving coupling of activated, β-hydrogens containing C(sp^3)-Cl with boronic acids. The system also allows for synthesis of highly sterically hindered, di-ortho and tri-ortho substituted biphenyls under mild conditions.

We have improved upon our previously reported synthesis of (NHC)Pd(OAc)$_2$ complexes (Scheme 2).[14]

Scheme 2. Synthesis of (IMes)Pd(OAc)$_2$



To analyze the activity of this complex in mediating the Suzuki−Miyaura reaction, coupling of phenylboronic acid and 4-chlorotoluene was examined. The reaction proceeded to furnish a 97% yield of the desired product in 1 h at room temperature. Surprisingly, the IPr analogue, (IPr)Pd(OAc)$_2$ did not show appreciable formation of coupling product at room temperature. However, on raising the temperature 40 °C, it provided quantitative yield in 45 min. To circumvent the inconvenience of previously reported slow addition of halides,[4b] the reactions were tested with a normal rate of addition of the halide substrate (for experimental details see Supporting Information). No formation of dehalogenation byproducts rendered the slow-addition protocol obsolete.

Our previous work emphasizing the important role played by the solvent in the reaction system prompted us to screen various alcohols as solvents. Screening of alcohols indicated that isopropanol (IPA) was the best solvent for these systems.[15] Use of technical grade IPA without prior drying renders this protocol quite practical and amenable to large scale synthesis.

To increase the scope of the reaction, various bases were also screened.[16] In general, alkoxide bases yielded the best results at room temperature. Milder bases such as Cs_2CO_3 and K_3PO_4 performed moderately well (see Supporting Information).

As mentioned earlier, C(sp^3)-chlorides suffer from poor activity in Suzuki−Miyaura coupling. Apart from difficulty in the transmetalation step, the low reactivity of chlorides in this reaction is attributable in part to the strength of the C−Cl bond.[17] However, recently a few systems that allow oxidative addition of alkyl chlorides have been reported.[8,18]

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(5) Harsh conditions for sterically hindered products: (a) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871−1876. (b) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162−1163. (c) Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2001**, *42*, 6667−6670. (d) Griffiths, C.; Leadbeater, N. E. *Tetrahedron Lett.* **2000**, *41*, 2487−2490. (e) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550−9561.

(6) (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, published ASAP March 8, 2005. (b) Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2004** *6*, 2649−2652. (c) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818−11819. (d) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553−5566.

(7) (a) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340−1341. (b) For use of alkyl halides in the Stille reaction, see: Tang, H.; Menzel, K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5079−5082. (c) For Suzuki cross-coupling of β-hydrogen-containing tosylates, see: Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910−3912. (d) Kirchoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945−1947. (e) Coupling of boronic acids with alkyl bromides: Kirchoff, J. H.; Netherton, J. H.; Hills, I. D. Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662−13663. (f) Netherton, M. R.; Dai, C.; Neuschutz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099−10100. (g) Littke, A. F.; Dai, C.; Fu G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028.

(8) During preparation of this manuscript, Capretta et al. reported Suzuki-Miyaura coupling of C(sp^3)-Cl with boronic acids: Brenstrum, T.; Gerristma, D. A.; Adjabeng, G. M.; Frampton, C. S.; Britten, J.; Rabertson, A. J.; Mcnulty, J.; Capretta, A. *J. Org. Chem.* **2004**, *69*, 7635−7639.

(9) (a) Gstottmayr, C. W. K.; Bohm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1363−1365. (b) For the first application of imidazole salts in sp^3-sp^3 Suzuki coupling, see: Arensten, K.; Caddick, S.; Cloke, F. G. N.; Herring, A. P.; Hitchcock, P. B. *Tetrahedron Lett.* **2004**, *45*, 3511−3515.

(10) (a) Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 3173−3180. (b) Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866−2873. (c) Grasa, G. A.; Hillier, A. C.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 1077−1080.

(11) Viciu, M. S.; Stevens, E. D.; Peterson, J. L.; Nolan, S. P. *Organometallics* **2004**, *23*, 3752−3755.

(12) For other examples of (NHC)-palladium acetate systems, see: (a) Schultz, M. J.; Hamilton, S. S.; Jensen, D. R.; Sigman, M. S. *J. Org. Chem.* **2004**, published ASAP December 30, 2004. (b) Mueller, J. A.; Goller, C. P.; Sigman, M. S. *J. Am. Chem. Soc*. **2004**, *126*, 9724−9734. (c) Konnick, M. M.; Guzei, I. A.; Stahl S. S. *J. Am. Chem. Soc.* **2004**, *126*, 10212−10213.

(13) For a few recent examples, see: (a) Itoh, T.; Hirai, K.; Tomioka, H. *J. Am. Chem. Soc.* **2004**, *126*, 1130−1140. (b) Wei, H.; Sudini, R.; Yin, H. *Org. Process Res. Dev.* **2004**, *8*, 955−957. (c) Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2003**, *6*, 2649−2652. (d) Andrus, M. B.; Song, C. *Org. Lett.* **2001**, *3*, 3761−3764.

(14) Synthesis of (IMes)Pd(OAc)$_2$: equimolar solutions of recrystallized Pd(OAc)$_2$ and IMes in hexanes are prepared. The solutions are mixed and allowed to stir for 6 h at room temperature. The insoluble product is filtered and washed with hexanes. See Supporting Information for details.

(15) For screening of solvents (Table 4) see Supporting Information.

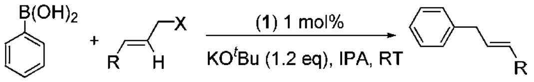
(16) For detailed table of base screening (Table 5) and discussion see Supporting Information.

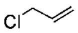
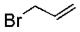
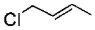
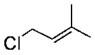
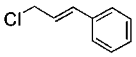
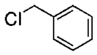
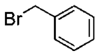
Our desire to contribute to solving the problem of coupling chloride substrates with β-hydrogens led us to explore this aspect in Suzuki−Miyaura coupling.

In this regard, our efforts with unactivated C(sp^3) chlorides such as lauryl and hexyl chloride did not result in the desired coupling products. In these attempts, formation of dehalogenation products was observed, indicating a problem at the transmetalation step rather than an unachievable oxidative addition of the alkyl chloride to the palladium center.

However, reactions of activated C(sp^3)-chlorides (allylic and benzylic) proceeded to give excellent yields of coupling products despite the presence of β-hydrogens in the allylic substrates (Table 1).

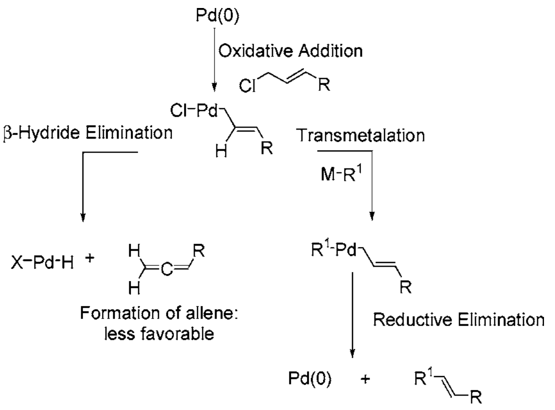
Table 1. Screening of Activated C(sp^3)-Chlorides[a]



entry	halide substrate	time (h)	yield (%)[b]
1		0.5	80(72)
2		2	100(93)
3		0.5	78(74)
4		-	NR[c]
5		0.5	78(72)
6		3	98(86)
7		1	85(58)

[a] Reaction conditions: 1 mol % of (IMes)Pd(OAc)$_2$, 1 mmol of halide, 1.1 mmol of phenylboronic acid, 1.2 mmol of KO^{t}Bu, 2 mL of IPA. [b] GC yield (isolated yield), average of two runs. [c] Unidentified mixture of products.

Scheme 3. Competing Pathways in Suzuki−Miyaura Coupling of Allylic Substrates

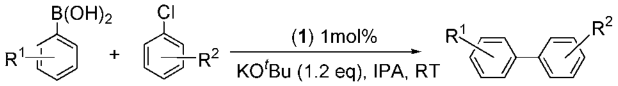


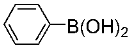
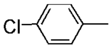
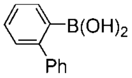
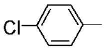
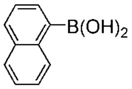
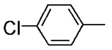
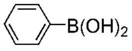
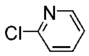
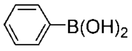
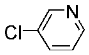
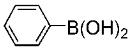
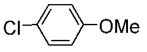
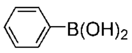
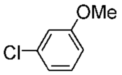
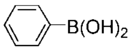
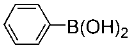
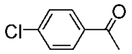
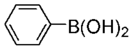
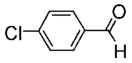
Conceivably, for allylic substrates, the transmetalation step is more favored relative to the β-hydride elimination, which if favored would lead to formation of allenes (Scheme 3). Hence the final outcome is the coupling of the substrates rather than dehalogenation of the chlorides.

As mentioned earlier, boronic acids serve as excellent transmetalating agents. To test the limits of compatibility of various functionalities using our protocol, various boronic acids were tested for activity. Excellent yields were obtained in most cases, including reactions leading to formation of ortho-substituted products (entries 2, 3, and 8, Table 2). Functional group variance on the halides was also studied (entries 4−10, Table 2). We were able to achieve coupling of electron-donating (entries 6−8, Table 2) as well as electron-withdrawing (entries 9 and 10, Table 2) groups containing chlorides. Formation of 2-phenylpyridine and 3-phenylpyridine (entries 4 and 5, Table 2) demonstrated compatibility of heteroaromatic aryl chlorides in the coupling process.

Synthesis of sterically hindered products was also achieved using this system. Whereas preparation of di-ortho biphenyls proceeded at room temperature, the tri-ortho biphenyls

Table 2. Substrate Screening[a]



entry	boronic acid	halide	time (h)	yield (%)[b]
1			1	97(94)
2			2	100(94)
3			2	100(91)
4			20	63(61)
5[c]			7	77(74)
6			3	90(81)
7			2	72(68)
8			2	90(85)
9			24	93(88)
10			2	65(63)

[a] Reaction conditions:1 mol % of (IMes)Pd(OAc)$_2$, 1 mmol of halide, 1.1 mmol of boronic acid, 1.2 mmol of KO^{t}Bu, 2 mL of IPA. [b] GC yield (isolated yield), average of two runs. [c] $T = 40$ °C

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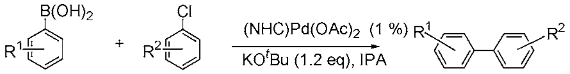
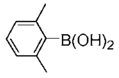
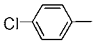
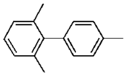
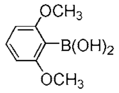
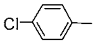
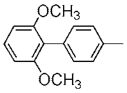
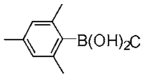
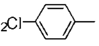
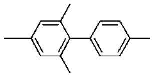
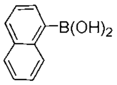
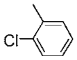
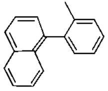
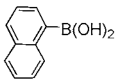
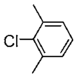
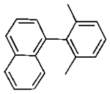
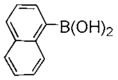
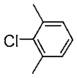
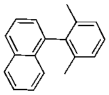
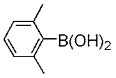
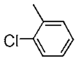
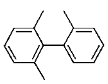
(17) The stronger C−Cl bond as compared to C−Br and C−I in alkyl halides makes the alkyl chlorides more resistant to oxidative addition. Initially, only the use of vinyl or aromatic substrates allowed for the use of chlorides in this reaction. (Bond-dissociation energy values: $CH_3{-}Cl$ = 227 kcal/mol, $CH_3{-}Br$ = 219 kcal/mol, $CH_3{-}I$ = 212 kcal/mol, $CH_2{=}CH{-}Cl$ = 207 kcal/mol, Ph−Cl = 219 kcal/mol). Morrison, R. T.; Boyd, R. N. *Organic Chemistry*, 6th ed.; Prentice Hall: New York, 1996; p 22.

(18) Fu has reported Suzuki−Miyaura coupling of alkyl chlorides and alkyl boranes in a palladium-phosphine system (See ref 7d).

required temperature of 40 °C and proceeded in excellent yields using (IPr)Pd(OAc)$_2$ as the catalyst (compare entries 5 and 6, Table 3).

Table 3. Synthesis of Di- and Tri-Ortho Substituted Biaryls[a]

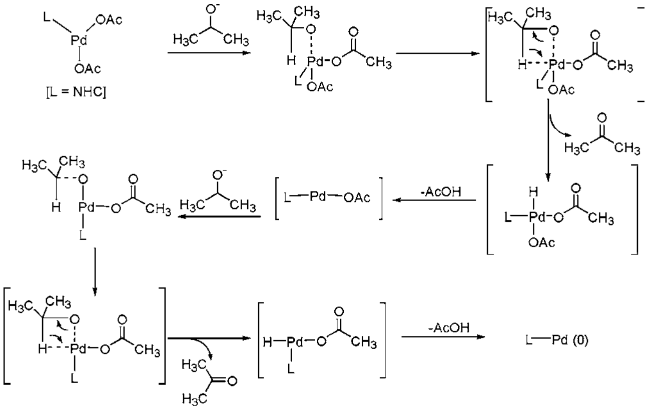


entry	boronic acid	Ar-Cl	product	method[b]	time (h)	yield (%)[c]
1				A	2	80(75)
2				A	2	92(81)
3				A	2	78(72)
4				A	1	91(89)
5				A	-	NR[d]
6				B	3	100(91)
7				B	6	90(88)

[a] Reaction conditions: 1 mmol of halide, 1.1 mmol of boronic acid, 1.2 mmol of KO^{t}Bu, 2 mL of IPA. [b] Method A: 1 mol % of (IMes)Pd(OAc)$_2$, rt. Method B: 1 mol % of (IPr)Pd(OAc)$_2$, 40 °C. [c] GC yield (isolated yields), average of two runs. [d] Unidentified mixture of products.

A pathway for the activation of the catalyst is proposed (Scheme 4). Initial deprotonation of IPA by the base (KO^{t}Bu) can generate an isopropoxide anion that can attack the (NHC)Pd(OAc)$_2$ complex. Analogous to previously reported β-hydride elimination from a palladium coordinated isopropoxide, formation of a Pd-hydride species with elimination of a molecule of acetone can be envisaged.[4b] Next, elimination of acetic acid from H-Pd(OAc)$_2$ can generate a (NHC)-Pd(OAc) species. Sigman has previously proposed this type of pathway in the oxidation of alcohols.[19] The monoacetate species, (NHC)Pd(OAc), can then undergo a second isopropoxide anion attack, with subsequent elimination of a molecule of acetone and acetic acid. This could finally generate the required NHC-Pd(0) species available for oxidative addition of the halide substrate.

Scheme 4. Proposed Activation of Catalyst



In summary, we have described a convenient synthetic protocol for preparation of imidazol-2-ylidene-based palladium acetate complexes. We have established these complexes as efficient mediators of Suzuki–Miyaura coupling. A broad spectrum of parameters has been surveyed, optimizing reaction conditions to a protocol that is user-friendly and environmentally benign.[20]. The protocol has been used to couple β-hydrogen-containing activated C(sp^3)-chlorides with boronic acids, providing an alternative to the Friedel–Crafts reaction for synthesis of allylic aromatics.[21] Sterically hindered substrates have also been coupled using mild conditions. Ongoing studies are directed toward further expanding the scope of these reactions.[22]

Acknowledgment. The National Science Foundation is gratefully acknowledged for financial support of this work and Umicore AG is gratefully acknowledged for the gift of Pd(OAc)$_2$.

Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Jensen, D. R.; Schultz, M. J.; Mueller, J. A.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3810–3813.

(20) Palladium loadings have been reduced to 0.01 mmol, technical grade solvents are used, base loading has been reduced to 1.2 equiv, presence of additives (such as TBAB) is not required, slow addition of halide substrate is not required and excellent yields can be obtained at room temperature.

(21) (a) Moreno-Manas, M.; Pajuelo, F.; Pleixats, R. *J. Org. Chem.* **1995**, *60*, 2396–2397. (b) Chowdhury, S.; Georghiou, P. E. *Tetrahedron Lett.* **1999**, *40*, 7599–7603. (c) Botella, L.; Najera, C. *J. Organomet. Chem.* **2002**, *663*, 46–57.

(22) Couplings of unactivated C(sp^3)-chlorides (lauryl chloride, hexyl chloride) and secondary bromides (cyclohexyl bromide) with boronic acids did not furnish the desired product.