ORGANOMETALLICS

Communication

pubs.acs.org/Organometallics

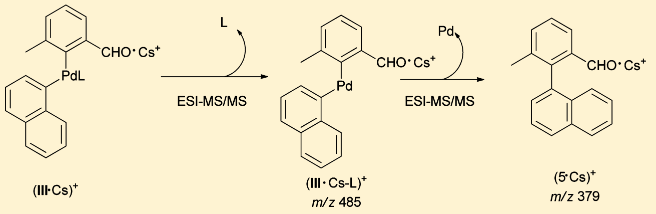
Mechanistic Investigations of a Palladium-Diene Catalyzed Suzuki–Miyaura Cross-Coupling Reaction

Xiaoshuang He, Shusheng Zhang, Yinlong Guo,* Haoyang Wang, and Guoqiang Lin*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, People's Republic of China

Supporting Information

ABSTRACT: The mechanism of the first example of a palladium diene catalyzed asymmetric Suzuki–Miyaura cross-coupling reaction has been validated, with the key palladium intermediates captured and characterized. The identified species corresponding to each catalytic step were firmly associated with the diene ligand in our observations. In the ESI-MS/MS experiments by CID (collision-induced dissociation), the fragmentation of the gas-phase transmetalation species was consistent with the product-yielding process in the reductive elimination step and thus revealed the catalytically active species of the reaction system.



The Pd-catalyzed cross-coupling process between organoboron compounds and organic halides, known as the Suzuki–Miyaura reaction, has been used widely in C–C bond formation, particularly for constructing asymmetric biaryls. Since its discovery in 1979,[1] chemists have made continuing efforts to improve the productivity and enantioselectivity of this reaction by applying elaborately designed chiral ligands,[2] and by far, phosphorus ligands have remained the favorite choice.[3] However, most phosphines show extreme sensitivity to air and moisture. In addition, the degradation of the P–C bond at increased temperature could lead to the aggregation of Pd species and consequently retard the overall reaction process.

In recent years, a diverse set of C_1- and C_2-symmetric chiral diene ligands with rigid bicyclic or polycyclic skeletons have been successfully introduced to asymmetric reaction systems.[4] Despite their great catalytic efficiency, the metals used were limited to Rh and Ir. Moreover, a Pd-diene catalyzed reaction has remained a difficult issue because of possible Pd black formation due to the weaker interaction between the double bond and the Pd metal center. In order to diminish the Pd black and enhance the overall reaction, finding well-designed ligands that possess the proper binding affinity to Pd is of significant importance.

In 2010, our group reported the first example of a Pd-diene catalyzed asymmetric Suzuki–Miyaura cross-coupling reaction.[5] Following the previous mechanistic study, we investigated the reaction in detail by using ESI-MS techniques. Electrospray ionization mass spectrometry (ESI-MS) is a soft ionization tool, which smoothly transfers the ions present in solution into a gas-phase environment for characterization,[6] and therefore, it has rapidly become a major tool in identifying reactive intermediates and has achieved great success in mechanistic investigations.[7]

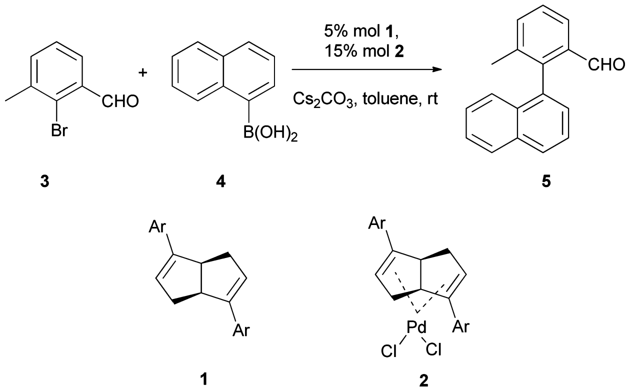
Initially, we chose five analogous ligands in order to evaluate their catalytic activities. The results are shown in Table 1. Before conducting our investigations into the reaction in Table 1, we first proposed its catalytic cycle,[8] which involves four consecutive steps of precatalyst activation, oxidative addition, transmetalation, and reductive elimination, shown in Scheme 1. On the basis of our experience, the ionic Pd species in this scheme would be detectable with the isotopic clusters of Pd in ESI-MS spectra, and the neutral Pd intermediates bearing an aldehyde moiety could also be observed in the form of Cs^+ adducts[9] when Cs_2CO_3 was used as a base in the reaction. In order to monitor the reaction process, we decided to use each catalyst separately and detect the reaction solution in two steps: (1) detection of the precatalyst activation step in the absence of aryl bromide **3** and (2) monitoring of the reaction after the addition of aryl bromide **3**. In our assumptions, the Pd(0) complex **I** could be detected at the precatalyst activation step, while the intermediates formed in the following oxidative addition step and the transmetalation step could be detected after the addition of compound **3**.

Among the five catalysts, **2d** was first chosen to catalyze the Suzuki–Miyaura cross-coupling reaction presented in Table 1. The ESI-MS studies on the reaction were started with the precatalyst activation step.[10] Boronic acid **4** (0.30–0.45 mmol, 1.5 equiv), Cs_2CO_3 (0.5–0.75 mmol, 2.5 equiv), and catalyst **2d** in 1.0 mL of dry toluene were mixed into a Schlenk flask at room temperature under the protection of nitrogen. After 5 min, two Pd(II) species were easily observed by two strong isotopic clusters centered at m/z 547 and 588. The two signals respectively matched the theoretical isotopic distribution patterns of $(\mathbf{IV_d} - \mathrm{Cl})^+$ (m/z 547) and $[(\mathbf{IV_d} - \mathrm{Cl})\cdot(\mathrm{CH_3CN})]^+$ (m/z 588), and their structures were also characterized by the tandem mass spectrometric (ESI-MS/MS)

Received: February 13, 2012
Published: March 27, 2012

dx.doi.org/10.1021/om300115x | *Organometallics* 2012, 31, 2945–2948

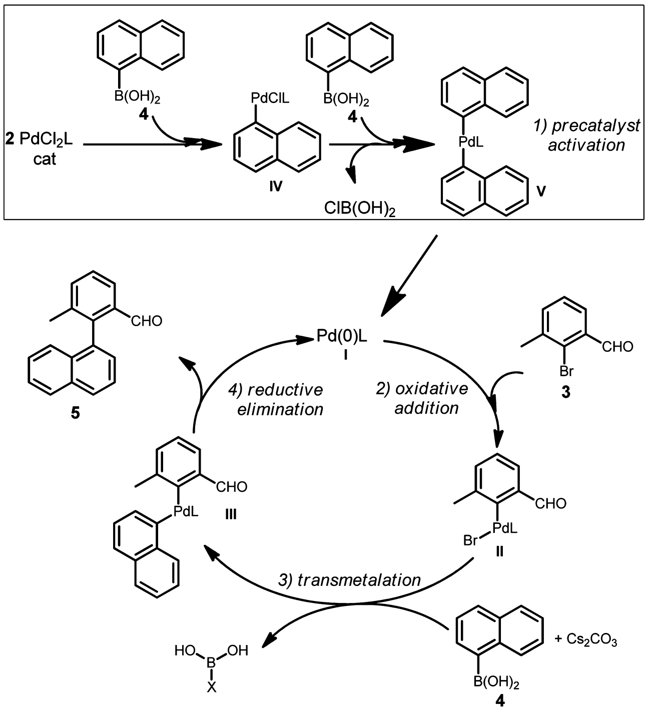
Table 1. Representative Suzuki–Miyaura Cross-Coupling Reactions Catalyzed by Five Pd(II)-Diene Catalysts[a]



entry	diene ligand	time (h)	yield[b] (%)	ee[c](%)
1	**1a** (Ar = Ph)	18	49	73
2	**1b** (Ar = 4-FPh)	24	47	63
3	**1c** (Ar = 4-MeOPh)	24	48	74
4	**1d** (Ar = 3,5-(Me)$_2$Ph)	12	90	87
5	**1e** (Ar = 3,4,5-(MeO)$_3$Ph)	30	24	62

[a]Conditions: aryl bromide (0.2–0.3 mmol, 1.0 equiv), boronic acid (0.3–0.45 mmol, 1.5 equiv), Cs_2CO_3 (0.5–0.75 mmol, 2.5 equiv), and toluene (1.0–1.5 mL). [b]Isolated yield. [c]Determined by HPLC on chiral stationary phases.

Scheme 1. Proposed Catalytic Cycle of the Suzuki–Miyaura Cross-Coupling Reaction

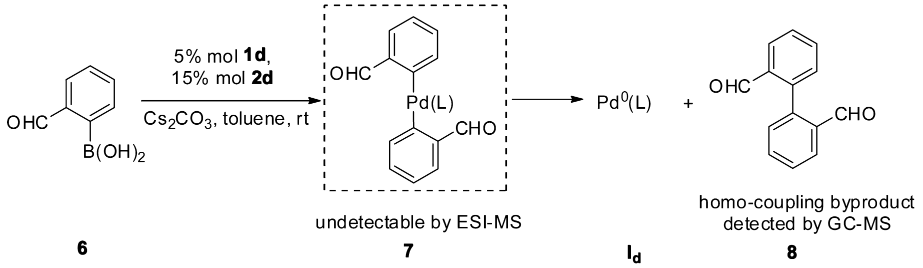


results. On the basis of previous reports,[11] the detected ions of $(\mathbf{IV_d} - \mathrm{Cl})^+$ (m/z 547) and $[(\mathbf{IV_d} - \mathrm{Cl})\cdot(\mathrm{CH_3CN})]^+$ (m/z 588) were probably formed by the heterolysis of the Pd(II)-diene precursor $\mathbf{IV_d}$ in the ionization process. To our disappointment, however, no signals corresponding to Pd(II) intermediate $\mathbf{V_d}$ or Pd(0) intermediate $\mathbf{I_d}$ in the catalytic cycle could be observed.

When the solution turned dark red (indicating the activation of the precatalyst), aryl bromide **3** (0.2–0.3 mmol, 1.0 equiv) was added, and then the reaction solution was sampled and detected by ESI-MS at different time intervals. To our gratification, after 30 min of reaction, three new signals with isotopic envelopes characteristic for mononuclear Pd species appeared in the spectra. In addition, they were also observed after reacting for 43, 66, 75, and 90 min (see the Supporting Information). According to the simulations of the theoretical isotopic distribution patterns, the three cluster signals were assigned to $(\mathbf{II_d} - \mathrm{Br})^+$ (m/z 539), $[(\mathbf{II_d}\cdot\mathrm{CsCl}) - \mathrm{Br}]^+$ (m/z 707), and $(\mathbf{III_d}\cdot\mathrm{Cs})^+$ (m/z 799), respectively. ESI-MS/MS experiments were also conducted to reconfirm their structures. In our speculations, the Cs^+ adduct ions of $(\mathbf{III_d}\cdot\mathrm{Cs})^+$ demonstrated the transmetalation step in the catalytic cycle and such metal adduct species had been reported before.[7g,12] As for the observed ions of $(\mathbf{II_d} - \mathrm{Br})^+$ and $[(\mathbf{II_d}\cdot\mathrm{CsCl}) - \mathrm{Br}]^+$, they probably indicated the existence of the oxidative addition intermediate of $\mathbf{II_d}$, which was undetectable in the form of $(\mathbf{II_d}\cdot\mathrm{Cs})^+$ (m/z 751) during the whole performance. As an explanation, $(\mathbf{II_d} - \mathrm{Br})^+$ was generated via bromide loss from the neutral intermediate of $\mathbf{II_d}$, and $[(\mathbf{II_d}\cdot\mathrm{CsCl}) - \mathrm{Br}]^+$ was formed when Br^- of intermediate $\mathbf{II_d}$ was replaced by Cl^- existing in the solution.[13]

As mentioned above, the Pd(0) intermediate $\mathbf{I_d}$ was not observed in the whole ESI-MS detection. Further efforts were made by replacing the boronic acid **4** with (2-formylphenyl)-boronic acid **6**. With the absence of aryl bromide **3**, the sample solution was analyzed by GC-MS. Excitedly, a homocoupling byproduct of the boronic acid **8** (see the Supporting Information) was detected. As Scheme 2 shows, this byproduct of **8** was possibly formed together with Pd(0) intermediate $\mathbf{I_d}$ by reductive elimination of the presumed precursor **7**, and thus it might indicate the existence of Pd(0) intermediate $\mathbf{I_d}$. At this stage, we have successfully validated the proposed catalytic cycle in Scheme 1 involving catalyst **2d**. In addition, we also monitored the **2d**-catalyzed Suzuki–Miyaura cross-coupling reaction with NMR spectrometers; however, no intermediate species were identified except for the substrate and the product in the ^{13}C and ^{19}F NMR spectra (see the Supporting Information).

Scheme 2. Investigations of the Precatalyst Activation Step by GC-MS



We next conducted analogous experiments by using the other four catalysts separately. As shown in Table 2, each spectrum obtained at the precatalyst activation step also showed two strong respective signals, which corresponded to the activated Pd(II) catalyst **IV** and their CH_3CN adducts. In addition, in the cases of catalysts **2c**,**e**, signals given by $(\mathbf{III_c}\cdot Cs)^+$ (*m*/*z* 803) were observed at 40 min and $(\mathbf{III_e}\cdot Cs)^+$ (*m*/*z* 923) at 35 min after aryl bromide **3** was added, both of which corresponded to the transmetalation step. However, such species were undetectable when catalysts **2a**,**b** were used. In comparison to catalyst **2d**, oxidative addition species were missed in the spectra by using any one of these four catalysts.

Table 2. Detected Species of Reactions Catalyzed by Different Pd-Diene Catalysts by ESI-MS

cat.	activated precat. ion of $(\mathbf{IV} - Cl)^+$ and $[(\mathbf{IV} - Cl)\cdot(CH_3CN)]^+$ (*m*/*z*)	oxidative addition ion of $(\mathbf{II} - Br)^+$ and $[(\mathbf{II} - Br)\cdot CsCl)]^+$ (*m*/*z*)	transmetalation ion of $(\mathbf{III}\cdot Cs)^+$ (*m*/*z*)
2a	491 and 532		
2b	527 and 568		
2c	551 and 592		803
2d	547 and 588	539 and 707	799
2e	671 and 712		923

Thus far, we have identified and characterized the key intermediates concerning the five $PdCl_2$(diene) catalysts. According to Table 2, the intermediates corresponding to the oxidative addition step were more difficult to detect (only observed in the case of **2d**) than those corresponding to the transmetalation step (observed in the cases of **2c**–**e**), strongly indicating that the oxidative addition species of **II** were transient, while the transmetalation species of **III** were formed immediately and accumulated before being slowly consumed and transformed in the reductive elimination step. Recalling previous studies on this reaction by in situ IR, an unknown peak occurred upon the addition of bromide **3** and disappeared when the reaction finished, in addition to the detectable **3** and **5**. This new peak also explained the existence of intermediate **III** at the transmetalation step. As a result, different from the widely accepted note that transmetalation step is the rate-determining step of the Suzuki–Miyaura reaction,[14] the rate of this Pd-diene catalyzed Suzuki reaction should depend on the reductive elimination step, because the precursor ions of this step accumulated before being transformed into biaryl **5** and Pd(0)-diene **I**. Similar conclusions had been reported in the self-coupling reaction of arylboronic acids.[12]

As mentioned above, ESI-MS/MS experiments have been conducted for characterizing all the detected intermediates. Interestingly, on reviewing the three intermediates formed in the transmetalation step (Figure 1), the parent ions of $(\mathbf{III_c}\cdot Cs)^+$ (*m*/*z* 803), $(\mathbf{III_d}\cdot Cs)^+$ (*m*/*z* 799), and $(\mathbf{III_e}\cdot Cs)^+$ (*m*/*z* 923) all produced $(\mathbf{5}\cdot Cs)^+$ (*m*/*z* 379) by the consecutive loss of the diene ligand and palladium upon being subjected to a collision energy of 20 eV (Scheme 3). These results matched the product-yielding process in the reductive elimination step perfectly. Furthermore, for these three species, the ratios of peak intensities of the parent ions of $(\mathbf{III}\cdot Cs)^+$ and the product ions of $(\mathbf{III}\cdot Cs - \text{diene})^+$ were respectively 42:100 (**1c**), 30:100 (**1d**), and 100:20 (**1e**), implying that the binding energy of the diene ligand to palladium was **1d** < **1c** < **1e**, and this was quite consistent with the product yields shown in Table 1: **1d** (90%) > **1c** (48%) > **1e** (24%). Therefore, the fragment patterns of these gas-phase species in the ESI-MS/MS experiments represented their relative intrinsic catalytic activities.[9,10]

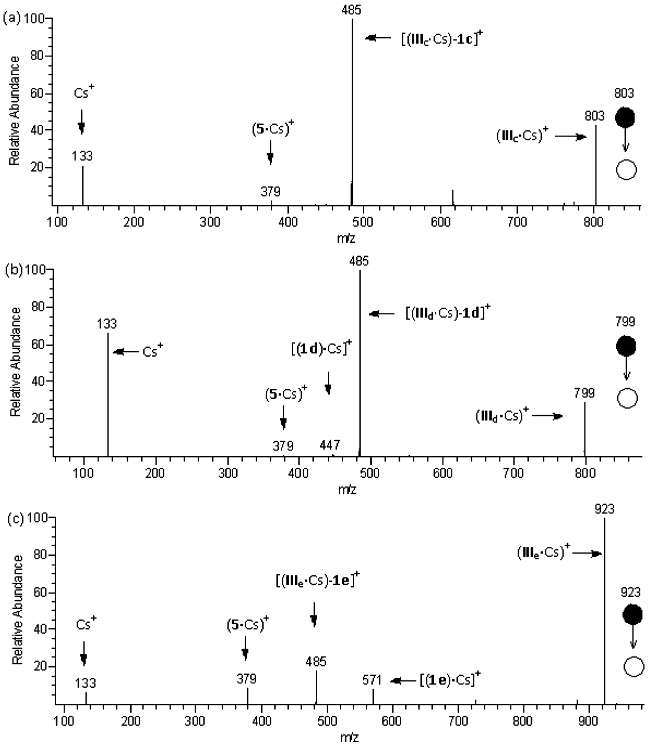
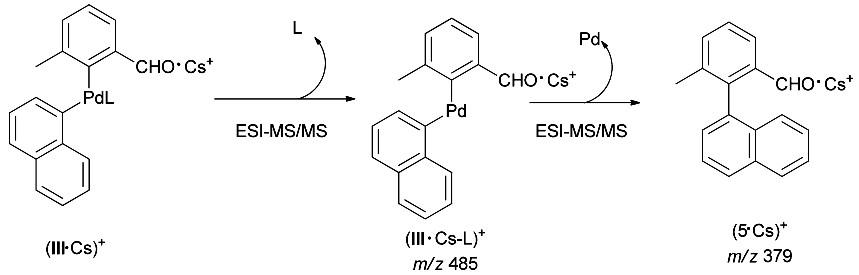


Figure 1. ESI-MS/MS spectra for the transmetalation species: (a) MS/MS of $(\mathbf{III_c}\cdot Cs)^+$ at *m*/*z* 803; (b) MS/MS of $(\mathbf{III_d}\cdot Cs)^+$ at *m*/*z* 799; (c) MS/MS of $(\mathbf{III_e}\cdot Cs)^+$ at *m*/*z* 923.

In summary, we have successfully validated the catalytic cycle for the Pd-diene catalyzed Suzuki–Miyaura cross-coupling reaction, with the key palladium intermediates captured and characterized. Our observations demonstrate the catalytically active species of the reaction by the fragmentation patterns of the transmetalation species. In particular, the reductive elimination step determines the rate of the whole process. We believe that this protocol provides a valuable tool for fast

Scheme 3. Fragmentation of (III·Cs)$^+$ in the ESI-MS/MS Experiments



screening of the well-defined ligands and thus contributes to the transition-metal-catalyzed asymmetric system.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, figures, and tables giving experimental procedures, structures, mass spectra, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ylguo@sioc.ac.cn (Y.G.); lingq@sioc.ac.cn (G.L.). Tel: +86-021-54925300. Fax: +86-021-64166128.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by research grants from the NSFC (20902104, 21072215, 21172250), CAS (YZ200938 and YG2010056), the Major State Basic Research Development Program (2010CB833202), and the State Key Laboratory of Bioorganic and Natural Product Chemistry.

■ REFERENCES

(1) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, *19*, 866. (c) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419.

(2) (a) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 3565. (b) Fleckenstein, C. A.; Plenio, H. *Chem. Eur. J.* **2007**, *13*, 2701. (c) Zawartka, W.; Gniewek, A.; Trzeciak, A. M.; Ziółkowski, J. J.; Pernak, J. *J. Mol. Catal. A: Chem.* **2009**, *304*, 8. (d) Kozlov, V. A.; Aleksanyan, D. V.; Nelyubina, Y. V.; Lyssenko, K. A.; Petrovskii, P. V.; Vasil'ev, A. A.; Odinets, I. L. *Organometallics* **2011**, *30*, 2920. (e) Díez-González, S; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612. (f) Marion, N.; Navarro, O.; Mei, J. G.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101.

(3) (a) Olsson, D.; Wendt, O. F. *Organomet. Chem.* **2009**, *694*, 3112. (b) Zim, D.; Nobre, S. M.; Monteiro, A. L. *J. Mol. Catal. A: Chem.* **2008**, *287*, 16. (d) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461.

(4) (a) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508. (b) Paquin, J. F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850. (c) Wang, Z. Q.; Feng, C. G.; Xu, M. H.; Lin, G. Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336.

(5) Zhang, S. S.; Wang, Z. Q.; Xu, M. H.; Lin, G. Q. *Org. Lett.* **2010**, *12*, 5546.

(6) (a) Agrawal, D.; Schröder, D. *Organometallics* **2011**, *30*, 32. (b) Qian, R.; Guo, H.; Guo, Y. L.; Liao, Y. X.; Ma, S. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4771. (c) Schröder, D.; Schwarz, H.; Schenk, S.; Anders, E. *Angew. Chem., Int. Ed.* **2003**, *42*, 5087.

(7) (a) Trage, C.; Schröder, D.; Schwarz, H. *Chem. Eur. J.* **2005**, *11*, 619. (b) Tomazela, D. M.; Moraes, L. A. B.; Pilli, R. A.; Eberlin, M. N. *J. Org. Chem.* **2002**, *67*, 4652. (c) Chen, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 2832. (d) Meurer, E. C.; Santos, L. S.; Pilli, R. A.; Eberlin, M. N. *Org. Lett.* **2003**, *5*, 1391. (e) Sabino, S. A.; Machado, A. H. L.; Correia, C. R. D.; Eberlin, M. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 2514. (f) Chevrin, C.; Bras, J. L.; Hénin, F.; Muzart, J.; Pla-Quintana, A.; Roglans, A.; Pleixats, R. *Organometallics* **2004**, *23*, 4796. (g) Masllorens, J.; González, I.; Roglans, A. *Eur. J. Org. Chem.* **2007**, *2007*, 158. (h) Eberlin, M. N. *Eur. J. Mass. Spectrom.* **2007**, *13*, 19. (i) Svennebring, A.; Sjöberg, P. J. R.; Larhed, M.; Nilsson, P. *Tetrahedron* **2008**, *64*, 1808. (j) Santos, L. S. *Reactive Intermediates: MS Investigations in Solution*; Wiley-VCH: Weinheim, Germany, 2010.

(8) (a) Nasielski, J.; Hadei, N.; Achonduh, G.; Kantchev, E. A. B.; O'Brien, C. J.; Lough, A.; Organ, M. G. *Chem.—Eur. J.* **2010**, *16*, 10844. (b) Miyaura, N. In *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, Germany, 2008; p 41.

(9) (a) Wang, H. Y.; Yim, W. L.; Klüner, T.; Metzger, J. O. *Chem. Eur. J.* **2009**, *15*, 10948. (b) Decker, C.; Henderson, W.; Nicholson, B. K. *J. Chem. Soc., Dalton Trans.* **1999**, *19*, 3507. (c) Wang, H. Y.; Metzger, J. O. *Organometallics* **2008**, *27*, 2761. (d) Wang, H. Y.; Yim, W. L.; Guo, Y. L.; Metzger, J. O. *Organometallics* **2012**, *31*, 1627.

(10) Taccardi, N.; Paolillo, R.; Gallo, V.; Mastrorilli, P.; Nobile, C. F.; Räisänen, M.; Repo, T. *Eur. J. Inorg. Chem.* **2007**, *2007*, 4645.

(11) (a) Henderson, W.; Evans, C. *Inorg. Chim. Acta* **1999**, *294*, 183. (b) Chisholm, D. M.; Oliver, D. G.; McIndoe, J. S. *Dalton Trans.* **2010**, *39*, 364.

(12) Aramendía, M. A.; Lafont, F.; Moreno-Mañas, M.; Pleixats, R.; Roglans, A. *J. Org. Chem.* **1999**, *64*, 3592.

(13) Agrawal, D.; Schröder, D.; Frech, C. M. *Organometallics* **2011**, *30*, 3579.

(14) (a) Amatore, C.; Jutand, A.; Le Duc, G. *Chem. Eur. J.* **2011**, *17*, 2492. (b) Smith, G. B.; Dezeny, G. C.; Hughes, D. L.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1994**, *59*, 8151. (c) Yamamoto, Y.; Takada, S.; Miyaura, N.; Iyama, T.; Tachikawa, H. *Organometallics* **2009**, *28*, 152.