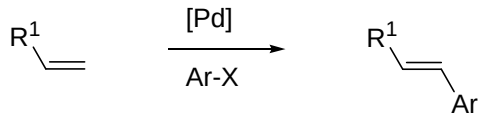
SCOPE AND MECHANISM OF DIRECT CATALYTIC ARYLATION
IS THE C-H BOND ACTIVATED?

Reported by S. Todd Meyer 17 February 2005

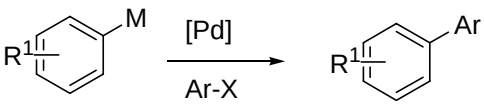
INTRODUCTION

The ability to form C-C bonds is an indispensable tool in synthetic organic chemistry, and the development of powerful catalytic methods has opened new avenues to complex molecule synthesis. Since the discovery of the Heck reaction, the late transition metals have risen to the forefront of this field, with palladium having become a favored metal.[1] Despite the great utility of metal-mediated cross-coupling reactions, they are not without their limitations. The Heck reaction is generally restricted to the coupling of an aryl or alkenyl halide with an electron-deficient olefin, and typically cannot be employed for biaryl synthesis.[2] While the Stille and Suzuki coupling reactions provide efficient routes to biaryl compounds, both methods require a sacrificial metalating agent. The Stille coupling demands the preparation and isolation of toxic organostannanes as one of the coupling partners. The Suzuki coupling method substitutes the more stable, less hazardous organoboranes as the metalating agent. In both cases, the coupling reaction occurs between the organometallic compound and an aryl or alkenyl halide, meaning that both stoichiometric reactants must be functionalized. These methods are outlined in **Scheme 1**.

Heck



Cross-Coupling



Scheme 1. General Cross-Coupling Methods. M= MgX, ZnX, SnR_3, $B(OR)_2$, R_2SiOH

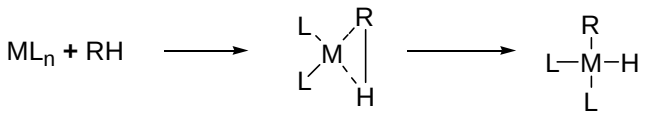
The C-H bond is the most ubiquitous in organic compounds.[3] The ability to perform regioselective couplings at these bonds would present numerous transformable groups in any given starting material. However, these bonds are also inherently unreactive, and the challenge of selectively coupling at one such bond in favor of others is daunting. Herein is reported recent advances in direct couplings at C-H bonds to form biaryl C-C bonds. The available metalating agents will be discussed, and the scope of their stoichiometric and catalytic C-C bond forming reactions will be explored. The evidence supporting the proposed mechanisms of these transformations will also be discussed.

ACTIVATING THE C-H BOND

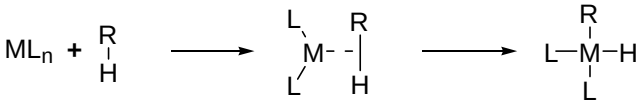
Mechanisms of C-H Bond Activation

While the term "C-H bond activation" is often used loosely in the literature, it carries certain mechanistic weight.[4] The term as used most carefully in the literature implies the insertion of a metal into a C-H bond to form an alkyl-metal hydride complex. This stands in contrast with other available methods of C-H bond metalation, such as electrophilic substitution followed by deprotonation.[5] C-H bond activation may take place stoichiometrically or catalytically, and is most frequently mediated by a late transition metal.

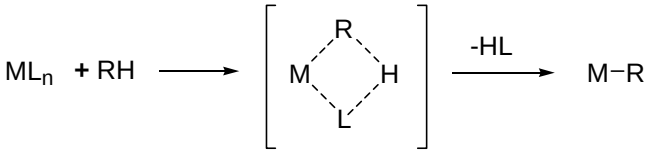
Oxidative Insertion



Electrophilic Addition



σ-Bond Metathesis

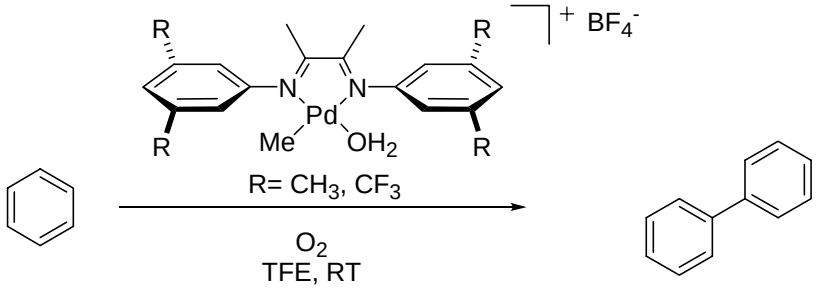


Scheme 2. Mechanisms of C-H Bond Activation

The C-H bond activation step can proceed through any of several mechanisms, depending on factors such as the metal, coordinated ligands, and the nature of the C-H bond (e.g., aromatic compared to aliphatic). The most commonly invoked mechanisms, shown in **Scheme 2**, are electrophilic or oxidative addition into the C-H bond. The σ-bond metathesis process has been postulated but not yet demonstrated for late transition metals.[5]

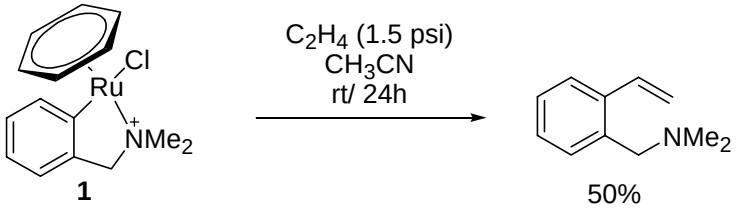
Stoichiometric Metal Complexes

Complexes of the late transition metals Pt, Pd, Rh and Ru readily undergo insertion into the C-H bond of benzene and its simple derivatives.[6] These metal-aryl complexes are often isolable and capable of reacting with other substrates to form C-C bonds. Kubas[7] and Bercaw[8] demonstrated the ability of benzene to react with stoichiometric amounts of Pt and Pd complexes, respectively, to form biphenyl under oxidative conditions (**Scheme 3**). Bercaw extended this method to the



Scheme 3. Stoichiometric biphenyl synthesis.

homocouplings of toluene and trifluoromethyl-benzene, albeit with minimal regioselectivity.[8] Jones showed that rhodium complexes could insert into the C-H bonds of furan and pyrrole derivatives.[9] Gunnoe used ruthenium complexes to accomplish a similar reaction in furan and thiophene regioselectively.[10] These new complexes were shown to react with ethylene to produce the 2-ethyl derivatives of the starting heterocycle. Sirlin and Pfeffer used tertiary amines as internal directors for the activation of an aryl C-H bond via orthometalation by ruthenium complexes.[11] Ruthenacycle **1** was then reactive toward ethylene to form styrene derivative **2** as shown in **Scheme 4**. The stoichiometric use of $Pd(OAc)_2$ to produce biphenyl derivatives has also been employed in the synthesis of pharmacophores and natural products.[12]



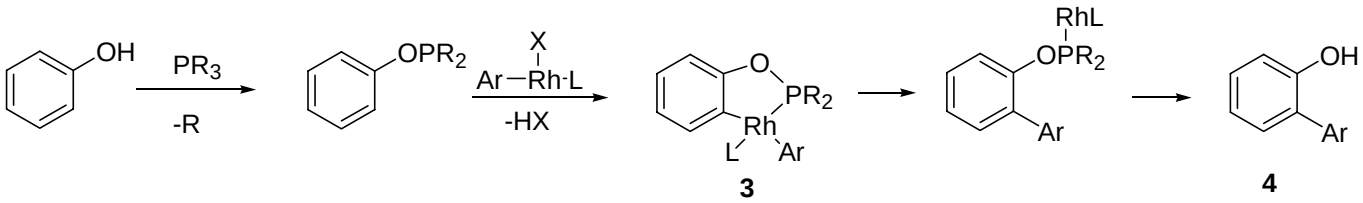
Scheme 4. Directed ortho-metalation.

CATALYTIC DIRECT COUPLING REACTIONS

Biaryl Synthesis

The development of mild, selective, catalytic methods for the preparation of functionalized biaryl structures has been of significant interest from a synthetic perspective. One approach to such scaffolds involves the directed internal metalation of a C-H bond to form a stable but reactive metallacycle. Reaction of this metallacycle with an aryl halide, followed by reductive elimination, affords the desired biaryl product and regenerates the metal catalyst.

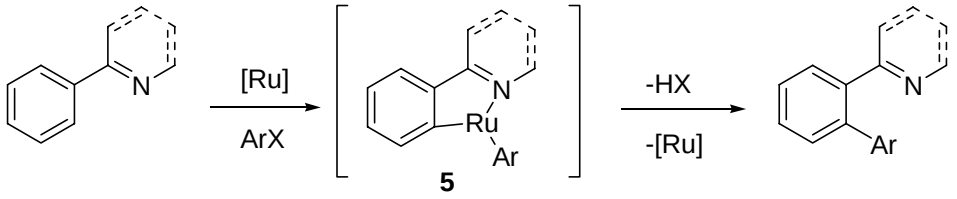
Certain phenols, such as 2-aryl phenols and 1-naphthol, can form stable five- and six-membered metallacycles through coordination of the oxygen to the metal catalyst.[13] Catalytic ortho-metalation of simple phenols was unknown until recently, due to the energy barrier to formation of highly strained four-membered metallacycles. Bedford described the use of phosphinite and amidophosphine ligands which react with phenols and a rhodium catalyst to give metallacycle **3** (**Scheme 5**).[14] Reductive elimination would extrude rhodium to form **4**. The reaction with 2-substituted phenols generally



Scheme 5. Directed ortho-metalation of simple phenols via phosphinites.

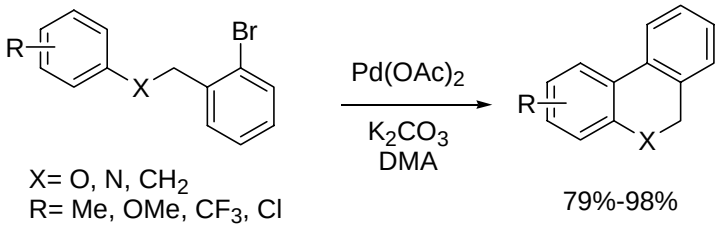
afforded the 6-arylated products in good yields in Bedford's studies.[14] Reaction with simple phenols, however, provided the 2,6-diarylated products in only low-to-moderate yields. Oi and Inoue subsequently applied a similar catalyst system to sterically hindered phenols to provide the mono-arylated products in good yields.[15]

Oi has detailed the use of pyridyl substituents to direct ruthenium-catalyzed ortho arylations (**Scheme 6**).[16] The reaction presumably proceeds through ruthenacycle **5**. Moderate yields of monoarylated products were obtained from unhindered substrates, with some diarylation observed as well. Slightly more sterically demanding substrates afforded the monoarylated product in excellent yields, with nearly complete suppression of the diarylated side product. Of greater synthetic utility may be the use of an imine auxiliary,[17] which putatively forms intermediate **5**. Coupling reactions directed by this auxiliary provided the biaryl products in yields comparable to those observed for the pyridyl directing group, but the imine had the distinct advantage of representing multiple masked functional groups which may be revealed and utilized in subsequent synthetic steps.



Scheme 6. Nitrogen-directed metalation.

Fagnou has shown that biaryl couplings occur intramolecularly between tethered phenyl rings to form tricyclic structures under palladium catalysis, as outlined in **Scheme 7**.[18] The coupling was found to be most efficient for ether linkages, although amide and aliphatic linkers were also tolerated.

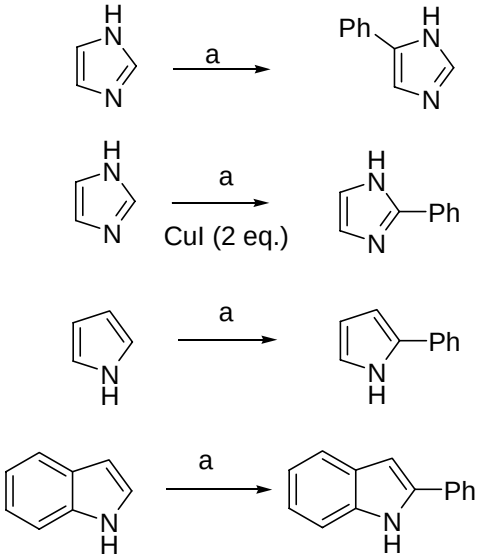


Scheme 7. Intramolecular biaryl synthesis.

Directed metalation has been exploited by Sames, who demonstrated the ability to arylate the C-2′ position of 2-phenyl-imidazole.[4] Of particular note was the selectivity of the direct arylation reaction, with the C-2′ arylated product isolated exclusively in favor of the competing C-4 or *N*-arylated products (*vide infra*).

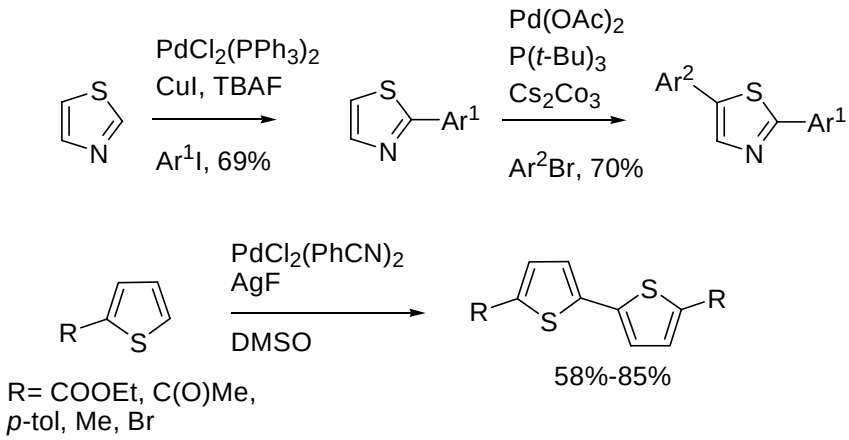
Catalytic Arylation at Heteroaromatic C-H Bonds

Similar catalytic methodology has been applied to the arylation of various heterocycles. Miura first described the catalytic arylation at C-H bonds of imidazoles and thiazoles by $Pd(OAc)_2$ in the presence of a base.[19] The method was limited to *N*-substituted imidazoles, and provided good yields and selectivity only for 2-substituted azoles. Sames subsequently improved on this method by using MgO as the stoichiometric base to afford the C-5 arylated imidazole in good yields as the exclusive product, with complete suppression of *N*-arylation (**Scheme 8**).[20] The same method produced exclusively C-2 arylated pyrrole, pyrazole, and indole.[21] The use of CuI as an additive afforded 2-arylated imidazoles in good yields, in contrast to the C-5 selectivity observed in the absence of CuI (**Scheme 8**).[20]



Scheme 8. Arylation of aromatic heterocylces. [a]Conditions: $Pd(OAc)_2$ (5 mol%), PPh_3 (20 mol%), MgO (1.2 eq.), dioxane.

The different selectivities of the two methods were found to be orthogonal, as Mori demonstrated in synthesizing differently substituted 2,5-diarylthiazoles (**Scheme 9**).[21] Sames exploited this orthogonality in a diversity-oriented synthesis of various arylated imidazoles.[4] Mori also expanded the scope of the method by preparing unsymmetrical 2,5-diarylthiophenes, and discovered a novel method for the homocoupling of thiophenes and thiazoles (**Scheme 9**).[22]



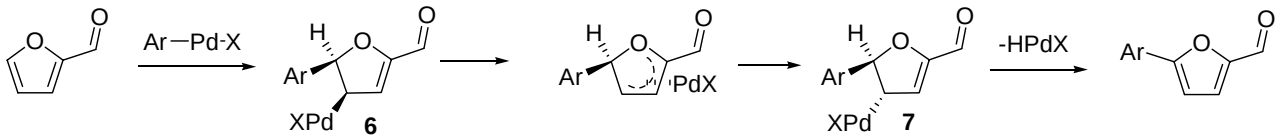
Scheme 9. Arylation of thiazoles and thiophenes.

Although specific conditions for each substrate vary, the general reaction conditions had many common features. Catalyst loadings ranged from 0.05 mol% to 10 mol%, with the ratio of phosphine ligand to metal catalyst generally between 2:1 and 4:1. Polar, aprotic solvents were generally most effective, and functional group tolerance was typically good. Electron-donating and electron-withdrawing groups were

both supported on the heteroaromatic rings, though slightly higher yields were generally observed in the presence of the former. Aromatic bromides and iodides were efficient coupling partners, with iodides reacting more smoothly than their bromide analogues. Aryl chlorides were unreactive or reacted slowly.[23] Electron-deficient aryl halides generally reacted more efficiently. Common side reactions included the unproductive formation of biphenyl,[23] as well as occasional multiple arylation of unsubstituted pyrroles and thiophenes.[22]

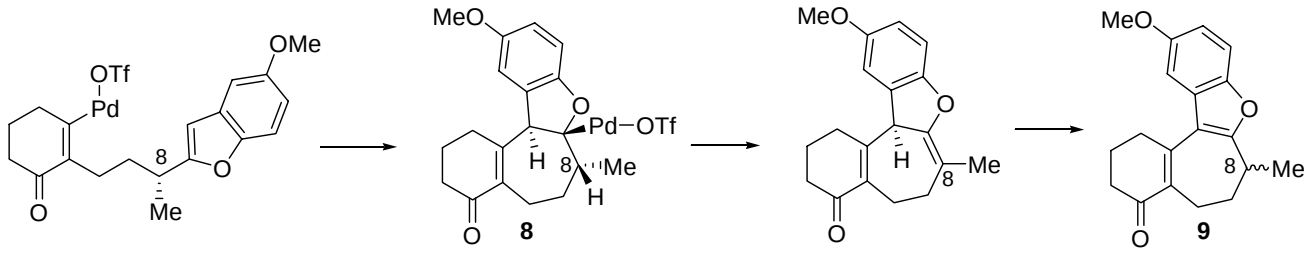
MECHANISM OF DIRECT ARYLATION

Although the mechanism of direct arylation is unknown, much speculation and experimentation has been focused on this issue. By analogy to other metal-catalyzed cross coupling reactions, oxidative insertion of the metal catalyst into the aryl-halide bond is presumed to occur, with concomitant loss of the associated ligands. Beyond this step, the mechanism becomes less clear. Sharp has proposed a mechanism similar to that of the Heck reaction for the arylation of furans and thiophenes.[24] Such a mechanism would require either elimination of the trans β-hydride or stereomutation of **6** to **7** prior to elimination (**Scheme 10**).[25] Gevorgyan provided evidence against a Heck mechanism in investigating the mechanism of indolizine arylation.[26] In these experiments, the product of a cascade Heck reaction was unavailable. Attempts to perform a reductive Heck reaction were also unsuccessful.



Scheme 10. Stereomutation to allow β-hydride elimination.

Trauner elegantly provided further evidence against a Heck mechanism in the synthesis of (-)-frondosin B, which employed a novel intramolecular direct vinylation.[27] As shown in **Scheme 11**, syn-β-hydride elimination from **8** would destroy the stereochemistry at C-8. Subsequent tautomerization to the aromatized product would provide the racemic **9**. However, the integrity of the stereocenter was



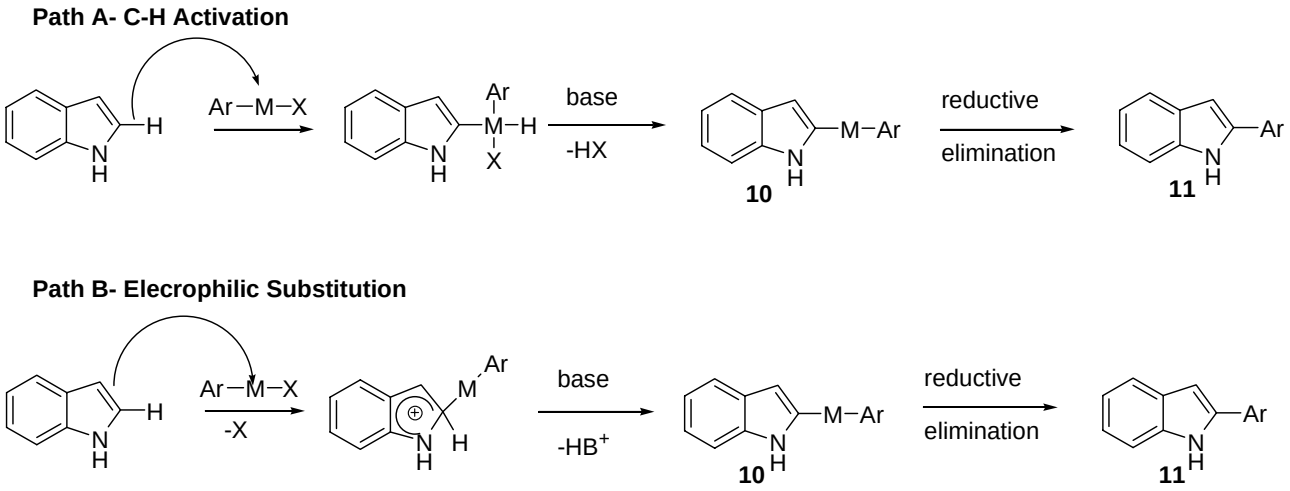
Scheme 11. *Syn*-elimination would afford racemic **9**.

completely retained, showing that the direct coupling does not occur via carbopalladation, as in a Heck reaction.

C-H bond activation has been postulated as a step in the mechanism, although it is unclear whether this step would occur prior to, or after, oxidative insertion of the metal into the aryl-halide bond. It is also not obvious which mechanism of C-H bond activation would be available, as this depends on several factors. A proposed C-H bond activation pathway is described in Path A, **Scheme 12**.[26]

An alternative mechanism invokes an electrophilic attack by the arylpalladium (II) species. Elimination of HX would produce intermediate **10** which, upon reductive elimination, would afford the biaryl product **11** (Path B, **Scheme 12**).[26]

Scheme 12. Possible Mechanisms of C-H Arylation.



Most of the experimental results are thought to favor Path B, although no definitive evidence has been provided in the literature. The general selectivity for arylation at the most nucleophilic site of the various heteroaromatic substrates implicates an electrophilic metalation step. Gevorgyan and co-workers observed no kinetic isotope effect (k_H/k_D=1) for the arylation of indolizine, where Path A would be expected to show a marked KIE, assuming C-H bond activation to be the rate determining step.[26]

CONCLUSION

The direct, catalytic arylation of various aromatic C-H bonds has been developed, obviating the need for a sacrificial electrophile such as a stannane or boronate. These methods afford the arylated products in good to excellent yields, often with exclusive regioselectivity. Reaction conditions are general and mild, and the method has been exploited in several syntheses. The mechanism continues to be under investigation.

REFERENCES

(1) Negishi, E-I. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E-I., Ed. Wiley & Sons: New York, 2002; pp. 215-227.
(2) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211.
(3) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507.
(4) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 10580.
(5) Goldman, A. S.; Goldberg, K. I. In *Activation and Functionalization of C-H Bonds*; Goldman, A. S.; Goldberg, K. I., Eds.; ACS Symposium Series 885; American Chemical Society: Washington, DC, 2004; pp. 1-43.
(6) Gossage, R. A.; van Koten, G. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; *Top. Organomet. Chem.* **1999**, *3*, 9.
(7) Konze, W. V.; Scott, B. L.; Kubas, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 12550.
(8) Ackerman, L. J.; Sadighi, J. P.; Kurtz, D. M.; Labinger, J. A.; Bercaw, J. E. *Organometallics* **2003**, *22*, 3884.
(9) Jones, W. D.; Dong, L.; Myers, A. D. *Organometallics* **1995**, *14*, 855.
(10) Lail, M.; Arrowood, B. N.; Gunnoe, T. B. *J. Am. Chem. Soc.* **2003**, *126*, 7506.
(11) Ritleng, V.; Pfeffer, M.; Sirlin, C. *Organometallics* **2003**, *22*, 347.
(12) (a)Harayama, T.; Akiyama, T.; Nakano, Y. *Chem. Pharm. Bull.* **1997**, *45*, 1723. (b) Futagami, S.; Ohashi, Y.; Imura, K.; Hosoya, T.; Ohmori, K.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 1063.
(13) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1740.
(14) Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*, 8669.
(15) Oi, S.; Watanabe, S.-i.; Fukita, S.; Inoue, Y. *Tetrahedron Lett.* **2003**, *44*, 8665.
(16) Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, 2579.
(17) Oi, S.; Ogino, Y.; Fukita, S.; Inoue, Y. *Org. Lett.* **2002**, *4*, 1783.
(18) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **204**, *126*, 9186.
(19) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467.
(20) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 5274.
(21) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700.
(22) Masui, K.; Mori, A.; Okano, K.; Takamura, K.; Kinoshita, M.; Ikeda, T. *Org. Lett.* **2004**, *6*, 2011.
(23) Lane, B.S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897.
(24) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, *5*, 301.
(25) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, *46*, 4003.
(26) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159.
(27) Hughes, C. C.; Trauner, D. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 1569.