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# Ni-Catalyzed Stereoselective Arylation of Inert C−O bonds at Low Temperatures

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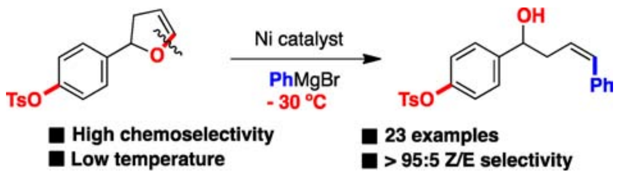
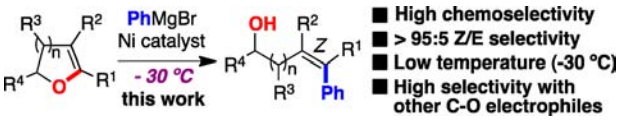
## ABSTRACT



**A Ni-catalyzed arylation of inert C−O bonds that operates at temperatures as low as −40 °C is described. Unlike other methods for C−O bond cleavage utilizing organometallic species, this protocol operates at low temperatures, thus allowing the presence of sensitive functional groups with exquisite site-selectivity and stereoselectivity.**

Metal-catalyzed cross-coupling reactions rank among the most widely employed synthetic methodologies for C−C bond-forming processes.[1] While organic halides are typically employed as coupling partners, the readily availability of phenol and its low toxicity as compared to the aryl halides make C−O electrophiles particularly attractive counterparts for cross-coupling reactions.[2] Although formidable advances have recently been described in the literature employing activated C−OTs, C−OMs, or C−OPiv derivatives, the coupling of rather inert C−O (alkyl) bonds still constitutes a considerable synthetic challenge in modern cross-coupling methodologies.[3] Not surprisingly, a rather limited number of protocols involving the cleavage of C−O(alkyl) bonds have been reported to date, most requiring high temperatures.[3,4] Although the high activation energy for C−O cleavage can be overcome by using Grignard reagents,[3e-i] their low tolerance toward functional groups prompted chemists to use organozinc[5] or organoboron reagents.[6] Still, the use of these organometallic species is not ideal from a step-economical point of view due to their high cost and low availability; indeed,

**Scheme 1.** Low-Temperature C−O(Alkyl) Bond Cleavage



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(1) In *Metal-catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998.

(2) (a) Yamaguchi, J.; Muto, K.; Itami, K. *Eur. J. Org. Chem.* **2013**, 19. (b) Correa, A.; Cornella, J.; Martin, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 1878. (c) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346. (d) Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Acc. Chem. Res.* **2010**, *43*, 1486.

(3) For selected Ni-catalyzed $C(sp^2)$−O(alkyl) activation methodologies, see: (a) Cornella, J.; Gomez-Bengoa, E.; Martin, R. *J. Am. Chem. Soc.* **2013**, *135*, 1997. (b) Alvarez-Bercedo, P.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 17352. (c) Tobisu, M.; Yamakawa, K.; Shimasaki, T.; Chatani, N. *Chem. Commun.* **2011**, *47*, 2946. (d) Sergeev, A. G.; Hartwig, J. F. *Science* **2011**, *332*, 439. (e) Guan, B.-T.; Xiang, S.-K.; Wang, B.-Q.; Sun, Z.-P.; Wang, Y.; Zhao, K.-Q.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 3268. (h) Dankwart, J. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2428. (i) Wenkert, E.; Michelotti, E. L.; Swindell, C. S.; Tingoli, M. *J. Org. Chem.* **1984**, *49*, 4894. (j) Wenkert, E.; Ferreira, T. W. *Organometallics* **1982**, *1*, 1670. (k) Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 2246.

(4) For Ru-catalyzed $C(sp^2)$−O(alkyl) activation methodologies, see: (a) Ueno, S.; Mizushima, E.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2006**, *128*, 16516. (b) Kakiuchi, F.; Usui, M.; Ueno, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2004**, *126*, 2706.

(5) Wang, C.; Ozaki, T.; Takita, R.; Uchiyama, M. *Chem.—Eur. J.* **2012**, *18*, 3482.

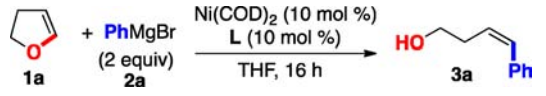
(6) (a) Shimasaki, T.; Konno, Y.; Tobisu, M.; Chatani, N. *Org. Lett.* **2009**, *11*, 4890. (b) Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4866.

10.1021/ol4031815

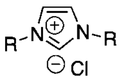
organozinc and organoboron derivatives are typically prepared from Grignard reagents via a transmetalation event.[7]

We hypothesized that a low-temperature Ni-catalyzed C($sp^2$)−O(alkyl) cleavage would allow the use of Grignard reagents in a chemoselective fashion, thus achieving an elusive goal in the C−O bond-cleavage arena.[8] Herein, we describe a method that not only meets this challenge, but also provides a new route to homoallylic alcohols with high *Z*-selectivity (Scheme 1). Importantly, the targeted C($sp^2$)−O(alkyl) bond cleavage can be performed, for the first time, in the presence of commonly more reactive C−O electrophiles such as aryl tosylates or aryl pivalates,[2] thus becoming a powerful strategy for our ever-growing synthetic repertoire.

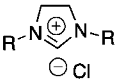
**Table 1.** Stereoselective Arylation of **1a**[a]



| entry | *t* (°C) | L | additive (%) | 3a (%)[b] |
|---|---|---|---|---|
| 1 | 0 | L1 | - | 18 |
| 2 | 0 | L2 | - | 85 |
| 3 | 0 | L3 | - | 37 |
| 4 | 0 | L4 | - | 38 |
| 5 | 0 | L5 | - | 90 |
| 6 | 0 | L6 | - | 19 |
| 7 | 0 | L5 | LiCl (100) | 99 |
| ***8*** | ***-30*** | ***L5*** | ***LiCl (100)*** | ***99[c], 82[d]*** |
| 9 | -30 | L5 | LiCl (100) | 44[e] |
| 10 | -30 | L5 | LiCl (50) | 91 |
| 11 | -30 | L5 | LiOtBu (100) | 76 |
| 12 | -30 | L5 | $MgBr_2$ (100) | 59 |
| 13 | -30 | L5 | $MgCl_2$ (100) | 0 |



R = 2,4,6-(Me)$_3$C$_6$H$_2$ (**L1**)
R = 2,6-(*i*Pr)C$_6$H$_3$ (**L2**)
R = *t*-Bu (**L3**)



R = 2,4,6-(Me)$_3$C$_6$H$_2$ (**L4**)
R = 2,6-(*i*Pr)C$_6$H$_3$ (**L5**)
R = *t*-Bu (**L6**)

[a] **1a** (0.50 mmol), **2a** (1.00 mmol), Ni(COD)$_2$ (10 mol %), **L** (10 mol %), additive (*x* %), THF (2 mL). [b] GC yield using dodecane as internal standard; in all cases, **3a** was obtained with >95:5 (*Z*:*E*) selectivity. [c] Isolated yield. [d] Ni(COD)$_2$ (5 mol %). [e] NiCl$_2$(glyme) was utilized.

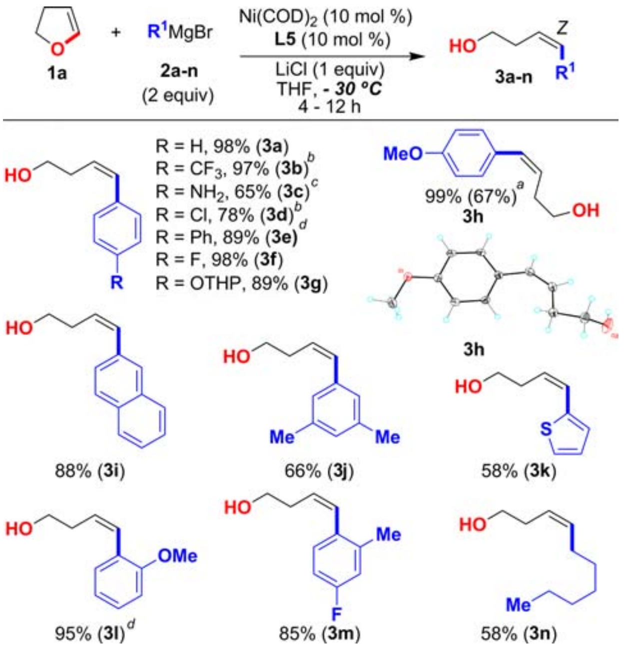


**Figure 1.** Scope of the Grignard reagent. Reaction conditions as for Table 1, entry 8 (no *E*-isomer was detected in the crude reaction mixtures); Yields are of isolated pure material (average of at least two runs). (a) reaction conducted at −40 °C; (b) Grignard reagent prepared according to Knochel's procedure; see ref 12; (c) using 4-[bis(trimethylsilyl)amino]phenylmagnesium bromide; (d) *Z*:*E* ratio 20:1.

We started our investigation with **1a** as the model substrate and using phenylmagnesium bromide (**2a**) as the coupling partner (Table 1). We anticipated that a particularly electron-rich ligand would be critical for activating the rather inert C−O(alkyl) bond. Toward this end, we turned our attention to easily tuned *N*-heterocyclic carbenes (NHC) since these ligands are strong $\sigma$-donors with a remarkable solubility and stability (entries 1−6).[9] Among all ligands examined, **L5** provided the best results at 0 °C (entry 5). While the use of other Ni sources or additives had a deleterious effect on reactivity (entries 7−13), the addition of LiCl allowed for the reaction to operate at −30 °C, affording **3a** in quantitative yields (entry 8).[10] To the best of our knowledge, this is the lowest temperature achieved for an unactivated C−O(alkyl) bond-cleavage event reported to date. It is noteworthy that, under the limits of detection, only the *Z*-isomer was detected by $^1$H NMR spectroscopy of the crude material. These results are in sharp contrast with the ability of other organometallic species to deliver *E*-configured isomers using related coupling approaches.[11]

With these conditions in hand, we set out to explore the generality of our protocol by using differently substituted Grignard reagents (Figure 1). As depicted, high yields were obtained when using either electron-rich or electron-deficient Grignard reagents. The use of LiCl as additive suggested that Knochel-type Grignards could be employed under our protocol;[12] as shown for **3d** and **3e**, this was

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(7) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340.

(8) For a low temperature Kumada−Corriu reaction employing aryl iodides or bromides as substrates, see: (a) Joshi-Pangu, A.; Wang, C.-Y.; Biscoe, M. R. *J. Am. Chem. Soc.* **2011**, *133*, 8478. (b) Martin, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3844.

(9) For recent reviews, see: (a) Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 6940. (b) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2768.

(10) LiCl might break the polymeric aggregates of the Grignard reagent, producing more reactive monomeric ArMgBr·LiCl species. See: (a) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333. (b) Buttrees, N. H.; Eaborn, C.; E−Khely, M. N. A.; Hitchcock, P. B.; Smith, J. D.; Tavakkoli, K. *J. Chem. Soc., Dalton Trans.* **1988**, 381.

(11) See, for example: (a) Le Menez, P.; Brion, J.-D.; Lensen, N.; Evelyne, C.; Pancrazi, A.; Ardisson, J. *Synthesis* **2003**, 2530. (b) Le Menez, P.; Fargeas, V.; Poisson, J.; Ardisson, J.; Lallemand, J.−J.; Pancrazi, A. *Tetrahedron Lett.* **1994**, *35*, 7767. (c) Fujisawa, T.; Kurita, Y.; Kawashima, M.; Sato, T. *Chem. Lett.* **1982**, 1641.

(12) (a) Piller, F, M.; Metzger, A.; Schade, M. A.; Haag, B. A.; Gavryushin, A.; Knochel, P. *Chem.−Eur. J.* **2009**, *15*, 7192. (b) Piller, F.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 6802.

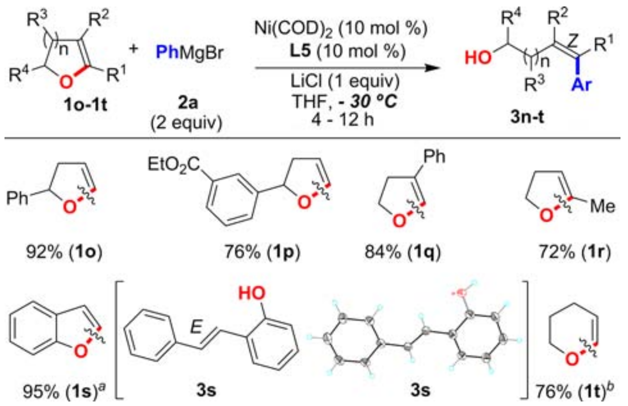
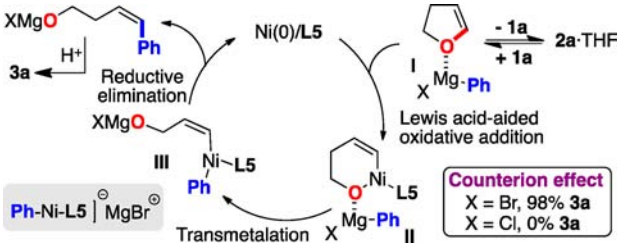


**Figure 2.** Scope of the dihydrofuran backbone. Reaction conditions as for Table 1, entry 8 (no *E*-isomer was detected in the crude reaction mixtures); Yields are of isolated pure material (average of at least two runs). (a) 80 °C; no *Z* isomer was detected; (b) 0 °C.

indeed the case, and we obtained high yields and stereoselectivities of the corresponding coupling products. Interestingly, the presence of aryl methyl ethers (**3h** and **3l**) as well as aryl halides (**3d**, **3f**, and **3m**) was perfectly tolerated. These results illustrate the selectivity of our protocol in the presence of groups that have shown to be reactive under other related Ni-catalyzed arylation events at higher temperatures.[3,13] In line with the same notion, while thiophene motifs have shown to rapidly undergo C−S bond-cleavage with Ni catalysts,[14] we found that **3k** was exclusively obtained at −30 °C, albeit in lower yields.[15] It is noteworthy that the reaction can even be conducted at temperatures as low as −40 °C (**3h**). Substrates containing labile OTHP ethers (**3g**) and amino groups (**3c**) were also perfectly accommodated. As shown for **3l** and **3m**, the presence of *ortho* substituents on the Grignard reagent did not have a negative impact on reactivity. Importantly, we could extend the scope of our reaction to alkyl Grignard reagents as well (**3n**). As judged by $^1$H NMR spectroscopy of the crude reaction mixtures for all compounds in Figure 1, a complete control of the diastereoselectivity was observed in favor of the less stable *Z*-isomer. X-ray diffraction analysis of **3h** confirmed our initial assignment of the double bond geometry.

We next turned our attention to study the scope on the 2,3-dihydrofuran backbone.[16] As depicted in Figure 2, a wide variety of substitution patterns could all be accommodated, invariably affording high yields of the corresponding *Z*-configured homoallylic alcohol. As for Figure 1, the high reaction rates translated into an excellent chemoselectivity profile including functional groups that are susceptible to nucleophilic attack by Grignard reagents (**1p**). As shown for **1r**, the reaction was not limited to aromatic-substituted 2,3-dihydrofurans. Interestingly, our methodology could also be extended to 3,4-dihydro-2*H*-pyran derivatives (**1t**); although in this case the reaction required a slightly higher temperature, the *Z*-isomer was exclusively formed as well. Strikingly, the *E*-isomer was only obtained when benzo[*d*]furan was utilized at 80 °C (**3s**). Such structure was unambiguously characterized by X-ray crystallography. In line with these observations, we anticipated that the *E*-selectivity might be a thermal- and catalyst-dependent event. We confirmed this hypothesis upon raising the temperature of a crude reaction of **1a** with **2a** at −30 °C to +40 °C, exclusively obtaining **3a-*E***.[17,18] We believe this result illustrates the simplicity, robustness, and synthetic potential of our protocol for controlling the diastereoselectivity of the double-bond geometry.

**Scheme 2.** Mechanistic Hypothesis



Next, we decided to conduct preliminary mechanistic experiments to shed light on the striking high reactivity at low temperatures. Thus, we monitored by $^1$H NMR spectroscopy a reaction of **1a** with stoichiometric Ni(COD)$_2$, SIPr, and LiCl in THF-$d_8$ at −30 °C.[17] Interestingly, no oxidative addition of the initially formed Ni(0)/**L5** species into the C−O bond was observed, even after prolonged reaction times. In sharp contrast, the addition of **2a** to this mixture allowed for the rapid formation of **3a**. This result leaves a reasonable doubt that the reaction is initiated by "classical" oxidative addition and advocates the notion that a different mechanism comes into play.[19] In light of these observations, we propose a mechanism based upon a Lewis acid aided oxidative addition (Scheme 2).[20] Additional support for such

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(13) For reviews on C−F activation, see: (a) Torrens, H. *Coord. Chem. Rev.* **2005**, *249*, 1957. (b) Jones, W. D. *Dalton Trans.* **2003**, 3991. (c) Mazurek, U.; Schwarz, H. *Chem. Commun.* **2003**, 1321. (d) Murphy, E. F.; Murugavel, R.; Roesky, H. W. *Chem. Rev.* **1997**, *97*, 3425.

(14) For selected examples, see: (a) Hintermann, L.; Schmitz, M.; Chen, Y. *Adv. Synth. Catal.* **2010**, *352*, 2411. (b) Kanemura, S.; Kondoh, A.; Yorimitsu, H.; Oshima, K. *Synthesis* **2008**, 2659. (c) Torres-Nieto, J.; Arevalo, A.; García, J. J. *Organometallics* **2007**, *26*, 2228. (d) Shimada, T.; Cho, Y.-H.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 13396.

(15) No arylation via C−S bond-cleavage was observed by NMR spectroscopy of the crude reaction mixture

(16) Substituted 2,3-dihydrofurans are either commercially available or easily obtained in one step from dihydrofuran. See ref 17.

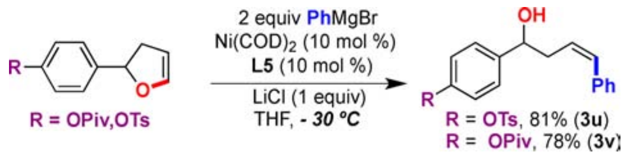
(17) See the Supporting Information for details

(18) Upon exposure of analytically pure *Z*-configured **3a** to catalytic amounts of Ni(COD)$_2$/**L5** at 50 °C in the absence of **2a**, we found that **3a-*E*** was obtained in >98:2 selectivity after 8 h reaction time. Interestingly, no apparent *Z*/*E* isomerization was observed when **3a** was simply treated with **2a** at 40 °C. Such experiments likely suggest the intermediacy of nickel $\pi$-allyl complexes that are responsible for the stereoselectivity switch at 40 °C.

(19) For a mechanistic study that rules out a "classical" oxidative addition of Ni(0) into C−O(alkyl) bonds, see ref 3a.

(20) Selected examples: (a) Hirata, Y.; Yada, A.; Morita, E.; Nakao, Y.; Hiyama, T.; Ohashi, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2010**, *132*, 10070. (b) Nakao, Y.; Yada, A.; Hiyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 10024. (c) Matsubara, R.; Jamison, T. F. *J. Am. Chem. Soc.* **2010**, *132*, 6880. (d) Ghosh, I.; Jacobi, P. A. *J. Org. Chem.* **2002**, *67*, 9304.

**Scheme 3.** Selectivity Issues with Other C−O Electrophiles



scenario comes from the observation that PhMgCl failed to provide **3a**, indicating that the nature of the counterion on the Grignard reagent plays a critical role. At present, we believe the reaction is initiated by coordination of the Lewis basic oxygen donor to the Mg center,[21] thus forming **I** and significantly weakening the C−O bond. Subsequently, the electron-rich Ni(0) center would be capable of promoting an oxidative addition (**II**) followed by a fast transmetalation and reductive elimination with concomitant regeneration of the active Ni(0) catalyst. At present, we can not rule out an alternate pathway consisting of the intermediacy Ni(0)-*ate* complexes formed by reacting Ni(COD)$_2$/**L5** with **2a**.[22,23] Although premature, we anticipate that other related C−O bond-cleavage reactions might follow a similar mechanistic scenario.[24]

Our mechanistic data indicated that a Lewis basic oxygen donor was required for the C−O bond cleavage, suggesting that an orthogonal reactivity with commonly more reactive electrophilic counterparts could be possible. Gratifyingly, we found that the coupling of substrates containing pivaloyl or tosylate motifs resulted in the clean formation of *Z*-configured **3u** and **3v** in high yields (Scheme 3). To the best of our knowledge, this is the first time that a Ni-catalyzed methodology favors the coupling of inert C−O(alkyl) bonds in the presence of a priori more reactive C−OPiv and C−OTs bonds.

In summary, we have developed a Ni-catalyzed direct C−O arylation of 2,3-dihydrofurans and Grignard reagents at temperatures as low as −40 °C. The high reaction rates are translated into an excellent chemoselectivity profile, allowing for the preparation of *Z*-configured homoallylic alcohols. Preliminary mechanistic studies suggest a Lewis acid-aided oxidative addition, an issue that can be turned into a strategic advantage in the presence of more reactive electrophilic counterparts. Further mechanistic studies and the extension to other substrates are currently underway in our laboratories.

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**Supporting Information Available.** Experimental procedures, spectral data, and crystallographic data (CIF) for compounds **3h** and **3s**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Hill, C. M.; Walker, R. A.; Hill, M. E. *J. Am. Chem. Soc.* **1951**, *73*, 1663.

(22) For Ni−ate complexes in cross-coupling events, see: (a) Yu, D.-G.; Li, B.-J.; Zheng, S.-F.; Guan, B.-T.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4566. (b) Hatakeyama, T.; Hashimoto, S.; Ishizuka, K.; Nakamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 11949. (c) Cámpora, J.; Reyes, M. L.; Hackl, T.; Monge, A.; Ruiz, C. *Organometallics* **2000**, *19*, 2950. (d) Poerschke, K. R.; Klaus, J.; Wilke, G.; Benn, R.; Mynott, R.; Goddard, R.; Krueger, C. *Chem. Ber.* **1985**, *118*, 275.

(23) For other cross-coupling reactions involving ate complexes, see: (a) Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773. (b) Fürstner, A.; Majima, K.; Martin, R.; Krause, H.; Kattnig, E.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 1992. (c) Fürstner, A.; Martin, R.; Majima, K. *J. Am. Chem. Soc.* **2005**, *127*, 12236. (d) Martin, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955. (e) Amatore, C.; Jutand, A. *Acc. Chem. Rev.* **2000**, *33*, 314.

(24) We found no reaction using 2-methoxynaphthalene, 2-(methoxymethyl)naphthalene, or butyl vinyl ether as substrate.

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The authors declare no competing financial interest.