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# Air-Stable Secondary Phosphine Oxide or Chloride (Pre)Ligands for Cross-Couplings of Unactivated Alkyl Chlorides

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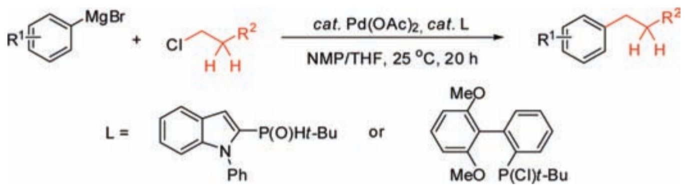
## ABSTRACT



**In situ generated and crystallographically well-defined, isolated palladium complexes derived from seven novel air-stable secondary phosphine oxides or chlorides enabled challenging Kumada−Corriu cross-couplings of unactivated alkyl chlorides bearing *β*-hydrogens and proved applicable to transformations of alkyl-substituted organometallics.**

Transition-metal-catalyzed cross-coupling reactions represent indispensable tools for the regioselective preparation of substituted (hetero)arenes.[1] Generally, organomagnesium reagents are more readily available than alternative organometallic nucleophiles.[2] Therefore, catalytic cross-couplings of Grignard reagents constitute valuable tools for streamlining arene syntheses. Particularly, the development of stabilizing ligands resulted in broadly applicable protocols for metal-catalyzed transformations of aryl or alkenyl halides as electrophiles.[1] However, couplings of unactivated alkyl halides, particularly when bearing $\beta$-hydrogens, continue to be challenging, since facile $\beta$-hydride elimination leads to undesired byproduct formation.[3,4] Alkyl chlorides are arguably the most useful class of alkyl halides due to their lower costs, yet they are more difficult to activate because of the inherently high C−Cl bond strength.[5] As a consequence, efficient palladium-catalyzed[6] Kumada−Corriu cross-couplings with unactivated alkyl chlorides[7] were, to the best of our knowledge, only accomplished with complexes derived from either electron-rich tertiary phosphines[8] or N-heterocyclic carbenes[9] as phosphine mimetics. Contrarily, sec-

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(1) (a) Ackermann, L., Ed. *Modern Arylation Methods*; Wiley-VCH: Weinheim, 2009. (b) de Meijere, A.; Diederich, F., Eds. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, 2004.

(2) (a) Knochel, P., Ed. *Handbook of Functionalized Organometallics*; Wiley-VCH: Weinheim, 2005. (b) Ila, H.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. Commun.* **2006**, 583–593.

(3) Reviews: (a) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656–2670. (b) Nakamura, M.; Ito, S. *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: Weinheim, 2009; pp 155−181. (c) Terao, J.; Kambe, N. *Acc. Chem. Res.* **2008**, *41*, 1545–1554. (d) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674–688. (e) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525–1532. (f) Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 384–387.

(4) For pioneering early examples, see. (a) Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, 691–694. (b) Devasagayaraj, A.; Stuedemann, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1996**, *34*, 2723–2725.

(5) For select examples of pioneering studies on metal-catalyzed cross-couplings with unactivated alkyl chlorides, see: (a) Kirchhoff, J.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945–1947. (b) Netherton, M. R.; Dai, C.; Neuschtz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099–10100.

(6) For representative examples of the use of transition metals other than palladium for couplings with unactivated alkyl chlorides, see: [Ni]. (a) Vechorkin, O.; Proust, V.; Hu, X. *J. Am. Chem. Soc.* **2009**, *131*, 9756–9766. (b) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222–4223. [Fe] (c) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Hird, M. *Chem. Commun.* **2005**, 4161–4163. (d) Martin, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955–3957. (e) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297–1299. (f) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686–3687. [Cu] (g) Cahiez, G.; Gager, O.; Buendia, J. *Synlett* **2010**, 299–303. (h) Terao, J.; Todo, H.; Begum, S. A.; Kuniyasu, H.; Kambe, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2086–2089. [Co] (i) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 1886–1889, and references cited therein. See also, ref 2.

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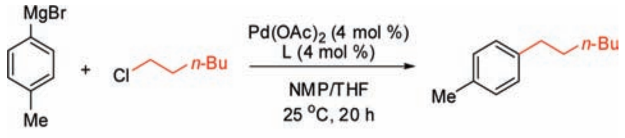
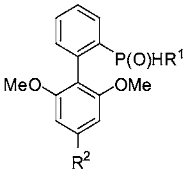
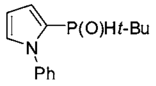
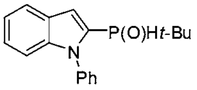
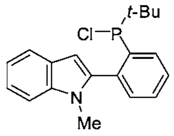
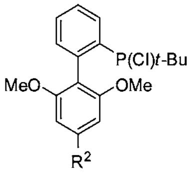
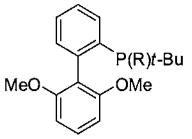
ondary phosphine oxides (SPO) or chlorides were thus far not used for cross-couplings of unactivated alkyl halides.[10] Accordingly, we became interested in developing novel air-stable (pre)ligands for catalytic transformations of inexpensive alkyl chlorides, on which we wish to report herein.

At the outset of our studies, we tested representative known[11] secondary phosphine oxides **4** in the cross-coupling of unactivated alkyl chloride **2a** (Table 1). Unfortunately, previously used preligands **4a**−**4d** provided only unsatisfactory results (entries 1−5), as did biphenyl monophosphine oxides **4e**−**4g** (entries 6−8). Thus, we set out to prepare new sterically hindered SPO preligands (Supporting Information). Interestingly, air- and moisture-stable preligands **4h** (Figure 1) and **4i** bearing either *N*-arylpyrrole or *N*-arylindole substituents,[12] respectively, outperformed the corresponding biphenyl-based preligands **4e**−**4g** (entries 6−10). Likewise, air-stable secondary phosphine chloride **5a**−**5c** (Figure 1) allowed for high-yielding cross-couplings of alkyl chloride

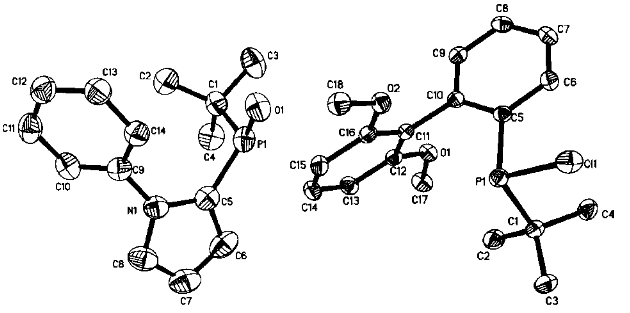
**Table 1.** Ligand Optimization Studies[a]



**1a** **2a** **3a**

| entry | ligand (L) | | yield |
|---|---|---|---|
| 1 | - | -- | < 2% |
| 2 | Ph$_2$P(O)H | **4a** | 23% |
| 3 | Cy$_2$P(O)H | **4b** | 41% |
| 4 | ($t$-Bu)$_2$P(O)H | **4c** | 27% |
| 5 | (1-Ad)$_2$P(O)H | **4d** | 46% |
| 6 |  | $R^1$ = *t*-Bu, $R^2$ = H<br>**4e** | 44% |
| 7 | | $R^1$ = *t*-Bu, $R^2$ = OMe<br>**4f** | 24% |
| 8 | | $R^1$ = Cy, $R^2$ = H<br>**4g** | 37% |
| 9 |  | **4h** | 70% |
| 10 |  | **4i** | 72% |
| 11 |  | **5a** | 80% |
| 12 |  | $R^2$ = H<br>**5b** | 80% |
| 13 | | $R^2$ = OMe<br>**5c** | 85% |
| 14 |  | R = Ar[b]<br>**6a** | 32% |
| 15 | | R = *n*-Hex<br>**6b** | 41% |

[a] Reaction conditions: **1a** (3.0 mmol), **2a** (2.0 mmol), Pd(OAc)$_2$ (4.0 mol %), L (4.0 mol %), NMP (5.0 mL); yields of isolated products. [b] Ar = 4-MeOC$_6$H$_4$.



**4h** **5b**

**Figure 1.** Molecular structures of (pre)ligands **4h** and **5b**.[13]

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(7) For select examples of palladium-catalyzed cross-couplings with other alkyl (pseudo)halides, see: (a) Terao, J.; Naitoh, Y.; Kuniyasu, H.; Kambe, N. *Chem. Commun.* **2007**, 825–827. (b) Yang, L.-M.; Huang, L.-F.; Luh, T.-Y. *Org. Lett.* **2004**, *6*, 1461–1463. (c) Terao, J.; Naitoh, Y.; Kuniyasu, H.; Kambe, N. *Chem. Lett.* **2003**, *32*, 890–891, and references cited therein.

(8) Frisch, A. C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4056–4059.

(9) Frisch, A. C.; Rataboul, F.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2003**, *687*, 403–409.

(10) Reviews: (a) Ackermann, L. *Synlett* **2007**, 507–526. (b) Nemoto, T.; Hamada, Y. *Chem. Rec.* **2007**, *7*, 150–158. (c) Ackermann, L. *Synthesis* **2006**, 1557–1571. (d) Ackermann, L.; Born, R.; Spatz, J. H.; Althammer, A.; Gschrei, C. J. *Pure Appl. Chem.* **2006**, *78*, 209–214. (e) Dubrovina, N. V.; Börner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5883–5886.

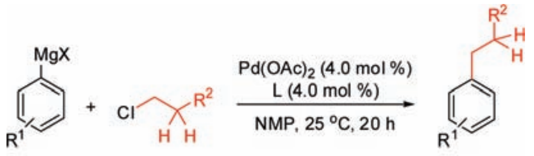
(11) For representative examples of alkyl-substituted secondary phosphine chlorides or oxides in transition-metal-catalyzed arylation reactions, see: (a) Ackermann, L.; Potukuchi, H. K.; Kapdi, A. R.; Schulzke, C. *Chem.—Eur. J.* **2010**, *16*, 3300–3303. (b) Ackermann, L.; Vicente, R.; Hofmann, N. *Org. Lett.* **2009**, *11*, 4274–4276. (c) Yang, D. X.; Colletti, S. L.; Wu, K.; Song, M.; Li, G. Y.; Shen, H. C. *Org. Lett.* **2009**, *11*, 381–384. (d) Xu, H.; Ekoue-Kovi, K.; Wolf, C. *J. Org. Chem.* **2008**, *73*, 7638–7650. (e) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299–2302. (f) Wolf, C.; Xu, H. *J. Org. Chem.* **2008**, *73*, 162–167. (g) Billingsley, K. L.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4695–4698. (h) Zhang, Z.; Hu, Z.; Yu, Z.; Lei, P.; Chi, H.; Wang, Y.; He, R. *Tetrahedron Lett.* **2007**, *48*, 2415–2419. (i) Lerebours, R.; Wolf, C. *Org. Lett.* **2007**, *9*, 2737–2740. (j) Ackermann, L.; Born, R.; Álvarez-Bercedo, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 6364–6367. (k) Lerebours, R.; Wolf, C. *J. Am. Chem. Soc.* **2006**, *128*, 13052–13053. (l) Lerebours, R.; Camacho-Soto, A.; Wolf, C. *J. Org. Chem.* **2005**, *70*, 8601–8604. (m) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123–3125. (n) Wolf, C.; Lerebours, R. *Org. Lett.* **2004**, *6*, 1147–1150. (o) Li, G. Y. *J. Org. Chem.* **2002**, *67*, 3643–3650. (p) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513–1516, and references cited therein.

(12) For *tertiary phosphines* bearing 2-substituted *N*-heteroarenes, see: (a) Sergeev, A. G.; Schulz, T.; Torborg, C.; Spannenberg, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7595–7599. (b) Harkal, S.; Rataboul, F.; Zapf, A.; Fuhrmann, C.; Riermeier, T.; Monsees, A.; Beller, M. *Adv. Synth. Catal.* **2004**, *346*, 1742–1748. (c) Rataboul, F.; Zapf, A.; Jackstell, R.; Harkal, S.; Riermeier, T.; Monsees, A.; Dingerdissen, U.; Beller, M. *Chem.—Eur. J.* **2004**, *10*, 2983–2990. (d) Zapf, A.; Jackstell, R.; Rataboul, F.; Riermeier, T.; Monsees, A.; Fuhrmann, C.; Shaikh, N.; Dingerdissen, U.; Beller, M. *Chem. Commun.* **2004**, 38–39. (e) Zapf, A.; Beller, M. *Chem. Commun.* **2005**, 431–440, and references cited therein.

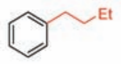
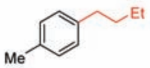
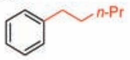
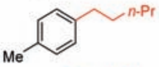
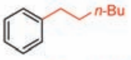
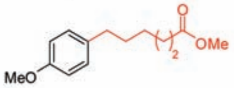
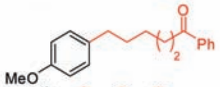
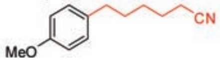
**2a** (entries 11−13). Importantly, this remarkable catalytic efficacy was not due to a potential formation of tertiary phosphines **6a** or **6b**, as was illustrated through their independent synthesis and use in catalysis (entries 14 and 15).

Subsequently, we probed the most active catalytic systems in Kumada−Corriu cross-couplings of further unactivated alkyl chlorides **2** (Table 2). Here, the catalyst derived from ligand **5b** proved superior (entries 1−4), enabling the synthesis of various regioselectively alkylated arenes **3**. Notably, the catalytic system exhibited a useful chemoselectivity, thereby tolerating valuable functional groups, such as an ester (entry 14), a ketone (entries 15 and 16), or a nitrile (entries 17 and 18). Thus, only minor amounts (<10%) of products stemming from nucleophilic addition reactions were observed.

**Table 2.** Kumada−Corriu Cross-Couplings of Alkyl Chlorides **2**[a]



**1** + **2** → **3**

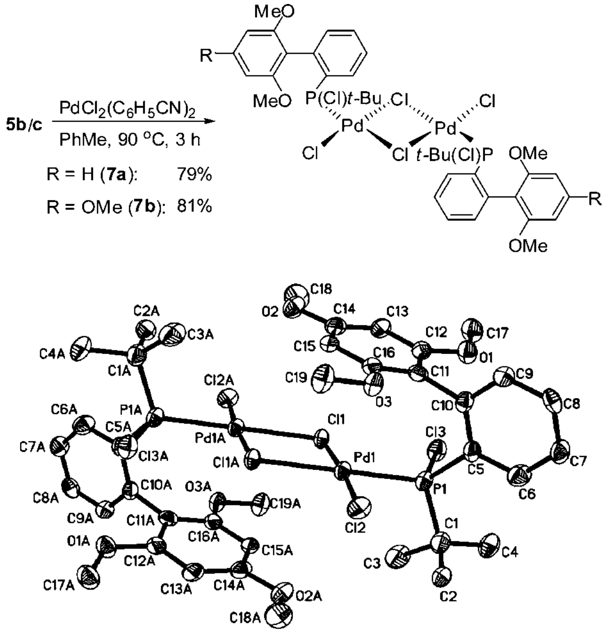
| entry | L | $R^2$ | 3 | | yield |
|---|---|---|---|---|---|
| 1 | **4h** | Et |  | **3b** | 51% |
| 2 | **5a** | | | | 52% |
| 3 | **5b** | | | | 60% |
| 4 | **5c** | | | | 55% |
| 5 | **4d** | | | | 84%[b] |
| 6 | **5b** | Et |  | **3c** | 62% |
| 7 | **5b** | *n*-Pr |  | **3d** | 65% |
| 8 | **4d** | | | | 81%[b] |
| 9 | **5b** | *n*-Pr |  | **3e** | 67% |
| 10 | **5b** | *n*-Bu |  | **3f** | 70% |
| 11 | **4d** | | | | 90%[b] |
| 12 | **5b** | *n*-Hex |  | **3g** | 58% |
| 13 | **4d** | | | | 85%[b] |
| 14 | **5b** | $(CH_2)_3CO_2Me$ |  | **3h** | 51% |
| 15 | **5b** | $(CH_2)_3C(O)Ph$ |  | **3i** | 56% |
| 16 | **5b** | $(CH_2)_3C(O)Ph$ |  | **3j** | 71%[c] |
| 17 | **5b** | $(CH_2)_3CN$ |  | **3k** | 69%[c] |
| 18 | **5b** | $(CH_2)_3CN$ |  | **3l** | 64%[c] |

[a] Reaction conditions: **1** (3.0 mmol), **2** (2.0 mmol), $Pd(OAc)_2$ (4.0 mol %), L (4.0 mol %), NMP (5.0 mL), 25 °C, 20 h. [b] Using *n*-AlkBr (2.0 mmol) instead of **2**. [c] 60 °C.

A side reaction was represented by homocouplings of alkyl chlorides **2**, which was addressed through the use of alkyl bromides as electrophiles, among others, with a catalyst derived from preligand **4d** (entries 5, 8, 11, and 13).

Given the remarkable activity of palladium complexes derived from ligands **5b** and **5c**, we explored their coordination chemistry. As a result, structurally well-defined complexes **7a** and **7b** were prepared in high yields (Scheme 1).[14]

**Scheme 1.** Synthesis and Molecular Structure of Complexes **7**



**7a**

Notably, homobimetallic complex **7a** highlighted a monophosphine-coordinated palladium, a general[15] feature of relevance for achieving high efficacy in challenging cross-coupling reactions.

Importantly, preformed palladium complexes **7a** and **7b** showed an improved catalytic performance toward cross-coupling of unactivated alkyl chloride **2a**, which allowed the use of a lower catalyst loading (Scheme 2).

Finally, isolated palladium catalysts **7a** and **7b** were evaluated for cross-coupling reactions of alkyl-substituted

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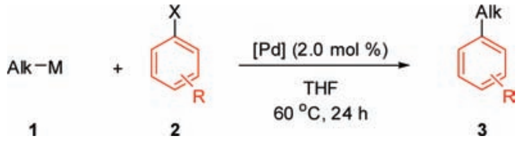
(13) CCDC-713169 and CCDC-715042 contain the supplementary crystallographic data for (pre)ligands **4h** and **5b**, respectively. The data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

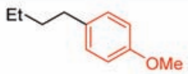
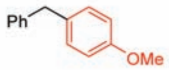
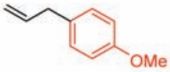
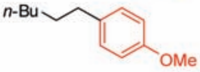
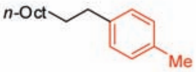
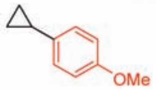
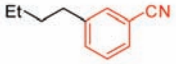
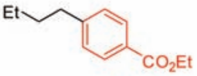
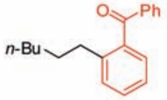
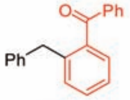
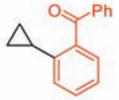
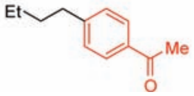
(14) CCDC-731586 contains the supplementary crystallographic data for palladium(II) complex **7a**. The data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

(15) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366–374.

organometallic nucleophiles (Table 3). Here, complex **7a** provided optimal results in Kumada−Corriu reactions of aromatic[11] electrophiles **2** (entries 1−4). Notably, catalyst **7a** was not restricted to the use of basic Grignard reagents as nucleophilic substrates but also proved applicable to the synthesis of functionalized arenes **3t**−**3y** through Negishi[16] cross-coupling technology (entries 9−14).[17]

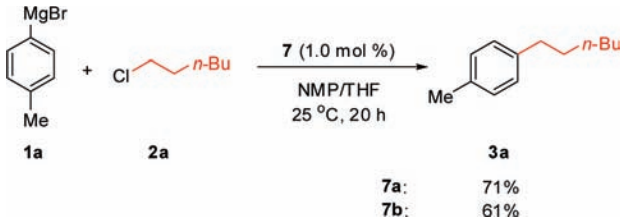
**Table 3.** Kumada−Corriu and Negishi Cross-Couplings with Alkyl-Substituted Nucelophiles **1**[a]



| entry | 1 | [Pd] | 3 | | yield |
|---|---|---|---|---|---|
| 1 | *n*-BuMgCl | **7a** |  | **3m** | 92% |
| 2 | | **7b** | | | 79% |
| 3 | BnMgCl | **7a** |  | **3n** | 87% |
| 4 | | **7b** | | | 75% |
| 5 | AllylMgBr | **7a** |  | **3o** | 82% |
| 6 | *n*-HexMgBr | **7a** |  | **3p** | 85% |
| 7 | *n*-DecMgBr | **7a** |  | **3q** | 79% |
| 8 | *c*-PrMgBr | **7a** |  | **3r** | 84% |
| 9 | *n*-BuZnCl | **7a** |  | **3s** | 70% |
| 10 | *n*-BuZnCl | **7a** |  | **3t** | 84% |
| 11 | *n*-HexZnCl | **7a** |  | **3u** | 87% |
| 12 | BnZnCl | **7a** |  | **3v** | 93% |
| 13 | *c*-PrZnCl | **7a** |  | **3w** | 72% |
| 14 | *n*-BuZnCl | **7a** |  | **3x** | 88% |

[a] Reaction conditions. Kumada−Corriu: ArBr (1.0 mmol), ArMgX (1.5 mmol), **7** (2.0 mol %), THF (2.0 mL), 60 °C, 24 h. Negishi: ArI (1.0 mmol), ArZnCl (1.5 mmol), **7a** (2.0 mol %), THF (2.0 mL), 60 °C, 24 h.

**Scheme 2.** Cross-Couplings with Isolated Complexes **7**



In summary, we have reported on the synthesis of seven novel air-stable secondary phosphine oxide or chloride (pre)ligands and their unprecedented use in challenging cross-couplings of unactivated alkyl halides. Specifically, in situ generated as well as isolated well-defined complexes of secondary phosphine chlorides enabled Kumada−Corriu cross-coupling of alkyl chlorides bearing $\beta$-hydrogens and could be employed for $C(sp^2)-C(sp^3)$ bond formations through cross-couplings with alkyl magnesium or alkyl zinc reagents.

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**Supporting Information Available:** Experimental procedures, characterization data, and $^1$H and $^{13}$C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For representative examples of Negishi cross-coupling reactions, see: (a) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298–3299. (b) Thaler, T.; Haag, B.; Gavryushin, A.; Schober, K.; Hartmann, E.; Gschwind, R. M.; Zipse, H.; Mayer, P.; Knochel, P. *Nat. Chem.* **2010**, *2*, 125–130, and references cited therein.

(17) As of yet, couplings of aryl chlorides as well as $C(sp^3)-C(sp^3)$ bond-forming reactions proceeded with lower efficacies.