

Cross-Coupling

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Efficient Aryl-(Hetero)Aryl Coupling by Activation of C–Cl and C–F Bonds Using Nickel Complexes of Air-Stable Phosphine Oxides**

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Transition-metal-catalyzed cross-coupling reactions of organomagnesium compounds^[1–4] are useful tools for the synthesis of unsymmetrically substituted biaryls, which are valuable building blocks for the synthesis of natural products, liquid crystals, polymers, and ligands.^[5] Predominantly aryl iodides and bromides, and more recently aryl chlorides,^[6] are employed as electrophiles. In contrast, the catalytic activation of unreactive C–F bonds remains extremely challenging because of the inherent strength of the C–F bond.^[7,8] The activation of C–F bonds in general is of utmost importance because this transformation contributes to the fundamental understanding of the reactivity of very stable bonds, and because the selective synthesis of partially fluorinated compounds is still a challenge.

Herrmann showed elegantly that efficient nickel-catalyzed^[9] cross-couplings between electronically nonactivated aryl fluorides and aryl Grignard reagents^[10] can be accomplished at ambient temperature,^[11] if appropriate stabilizing ligands are employed.^[12,13] Recently, we employed modular air-stable dioxo- and diamino-phosphine oxides in palladium-catalyzed Suzuki cross-coupling reactions between aryl chlorides and boronic acids.^[14] Herein, we report the use of air-stable phosphine oxide preligands^[15] for the activation of C–Cl and C–F bonds^[16] in cross-coupling reactions.

The catalytic activity of different preligands was first evaluated in the Kumada cross-coupling reaction of electronically deactivated 4-chloroanisole (**1a**) with phenyl magnesium chloride (**2a**) at ambient temperature (Table 1 and the Supporting Information).^[17] Diaminophosphine oxide **7** gave rise to more efficient catalysis than the corresponding diaminophosphine chloride **6**^[14] (Table 1, entries 1 and 2). However, significant amounts of the undesired homocoupling product **5a** were also generated. Similar results were obtained with dioxophosphine oxides **8** and **9** (Table 1, entries 3 and 4). A more selective reaction was achieved with sterically

Table 1: Ligand optimization studies.^[a]

Entry	Ligand (L)	t [h]	1 a/3 a/4 a/5 a	
1		6	24	16:76:1:6
2		7	1	4:85:1:10
3	8 (EtO) ₂ PHO	8	1	/:89:1:10
4		9	1	/:91:1:7
5		10	1	/:96:/:4
6		11	1	/:97:/:3
7		12	1	41:45:9:5
8		13	1	65:22:10:3
9		14	1	66:29:2:2
10	Ph ₂ PHO	15	1	/:89:1:9
11	<i>t</i> Bu ₂ PHO	16	1	/:97:/:3
12		17	1	/:99:/:1

[a] Reaction conditions: **1a** (1.00 mmol), **2a** (1.50 mmol), [Ni(acac)₂] (3 mol %), L (3 mol %), THF (2 mL); GC yield; Ar = 4-MeOC₆H₄.

hindered phosphine oxide **10** and particularly **11**, which bear aromatic substituents on nitrogen (Table 1, entries 5 and 6). Again, the corresponding phosphine chloride **12** gave rise to less efficient and less selective catalysis (Table 1, entry 7).

Recently, Dankwardt showed that a sterically encumbered phosphite facilitates efficient nickel-catalyzed Kumada cross-coupling reactions at elevated temperature.^[11] However, neither the corresponding phosphite **13** (Table 1,

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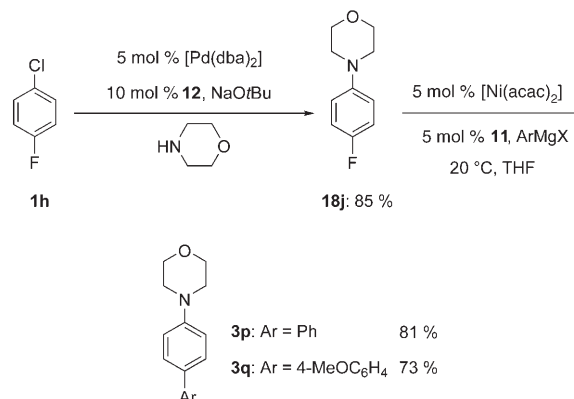
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entry 8) nor arylphosphonate **14**^[18] (Table 1, entry 9) exhibited reactivity comparable to that observed with phosphine oxide **11**. In contrast, alkyl-substituted secondary phosphine oxides yielded quantitative conversion of electrophile **1a** (Table 1, entries 11 and 12). In particular, the sterically hindered 1-adamantyl-substituted derivative **17**^[19] gave rise to selective catalysis (Table 1, entry 12).^[20] The high catalytic activity achieved with secondary phosphine oxides is most likely a result of the generation and subsequent deprotonation of phosphinous acid nickel complexes featuring anionic electron-rich P-bound ligands.^[21]

The catalyst derived from phosphine oxide **11** facilitated efficient conversion of a representative set of electron-rich aryl chlorides at ambient temperature (Table 2). Also the functionalization of pyridyl chlorides (Table 2, entries 8–10) proceeded in high yields.

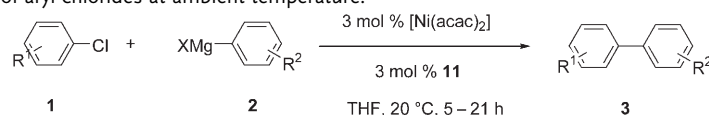
With optimized catalytic systems in hand, we tested the air-stable phosphine oxides **11**, **16**, and **17** as preligands in the cross-coupling of aryl fluoride **18a** (Table 3, entries 1–3). Interestingly, diamminophosphine oxide **11** exhibited superior catalytic activity in the activation of C–F bonds (Table 3, entry 1). Highly efficient catalysis was achieved with this preligand even at ambient temperature with different Grignard reagents (Table 3, entries 1, 4, and 5). These results

suggest an improved reactivity compared to that in known protocols for nickel-catalyzed cross-coupling of aryl fluorides at ambient temperature.^[12] Heteroarenes (Table 3, entries 7–10) gave rise to the corresponding products in high yields.^[13a] Also the synthesis of terphenyl derivatives (Table 3, entries 11 and 12) and an amino-substituted biaryl (Table 3, entry 13), as well as the conversion of sterically more hindered naphtha-



Scheme 1. Selective functionalization of arene **1h**; dba = *trans,trans*-dibenzylideneacetone.

Table 2: Kumada cross-coupling of aryl chlorides at ambient temperature.^[a]



Entry	Aryl chloride	Grignard reagent	Product	Yield [%]
1		ClMgPh 2a		97
2 ^[b]		ClMgPh 2a		99
3		ClMgPh 2a		92
4		4-BrMgC ₆ H ₄ OMe 2b		97
5		4-BrMgC ₆ H ₄ OMe 2b		97
6		4-BrMgC ₆ H ₄ OMe 2b		99
7		4-BrMgC ₆ H ₄ OMe 2b		89
8		4-BrMgC ₆ H ₄ OMe 2b		87
9		ClMgPh 2a		85
10		4-BrMgC ₆ H ₄ OMe 2b		85

[a] Reaction conditions: **1** (1.00 mmol), **2** (1.50 mmol), [Ni(acac)₂] (3 mol%), **11** (3 mol%), THF (2 mL), 20 °C; yield of isolated product. [b] **17** (3 mol%) instead of **11**.

Table 3: Kumada cross-coupling with aryl fluorides.^[a]

Entry	Aryl fluoride	Grignard reagent	Product	Yield [%]
1		ClMgPh		80
2 ^[b]		ClMgPh		55
3 ^[c]		ClMgPh		64
4		4-BrMgC ₆ H ₄ OMe		88
5 ^[d]		4-BrMgC ₆ H ₄ OMe		88
6 ^[e]		4-BrMgMes		88
7		4-BrMgC ₆ H ₄ OMe		90
8		ClMgPh		63
9		ClMgPh		72
10		4-BrMgC ₆ H ₄ OMe		95
11		4-BrMgC ₆ H ₄ OMe		88
12		ClMgPh		89
13 ^[e]		ClMgPh		61
14		ClMgPh		84
15		4-BrMgC ₆ H ₄ OMe		94
16		4-BrMgC ₆ H ₄ OMe	–	–

[a] Reaction conditions: **18** (1.00 mmol), **2** (1.50 mmol), [Ni(acac)₂] (3 mol%), **11** (3 mol%), THF (2 mL), 20 °C; yield of isolated product; Mes = 2,4,6-Me₃C₆H₂. [b] **16** (3 mol%) instead of **11**. [c] **17** (3 mol%) instead of **11**. [d] [Ni(acac)₂] (5 mol%), **11** (5 mol%). [e] [Ni(acac)₂] (8 mol%), **11** (8 mol%).

lene fluoride **18h** (entries 14 and 15), was feasible with phosphine oxide **11**. However, electron-poor polyfluorinated **18i** was not converted.

Finally, a combination of a palladium-catalyzed amination^[14] and a nickel-catalyzed Kumada cross-coupling of the resulting electron-rich aryl fluoride **18j** was used for the

regioselective functionalization of fluoro-benzene **1h** (Scheme 1).

In summary, we reported the first use of air-stable secondary phosphine oxides for the activation of C–F bonds in aryl fluorides. In particular, a complex derived from the sterically congested preligand **11** showed activity superior to that of known protocols for the nickel-catalyzed cross-coupling reactions of aryl Grignard reagents at ambient temperature.

Experimental Section

Representative procedure for nickel-catalyzed cross-coupling reactions of aryl fluorides (Table 3, entry 15): A solution of [Ni(acac)₂] (7 mg, 0.03 mmol, 3 mol%) and **11** (13 mg, 0.03 mmol, 3 mol%) in dry THF (0.5 mL) was stirred for 10 min at ambient temperature under N₂. 1-Fluoronaphthalene (**18h**) (148 mg, 1.01 mmol) was added, and the solution was stirred for 5 min. Thereafter, **2b** (0.5 M in THF, 3.0 mL, 1.50 mmol) was added. The resulting dark solution was stirred at ambient temperature for 15 h. Et₂O (75 mL) and H₂O (75 mL) were added to the reaction mixture. The separated aqueous phase was extracted with Et₂O (2 × 75 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The remaining residue was purified by column chromatography on silica gel (*n*-pentane/Et₂O, 300:1→200:1→150:1→100:1) to yield **3o** as a pale yellow solid (223 mg, 94%).

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[1] K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 4374–4376.

[2] R. J. P. Corriu, J. P. Masse, *J. Chem. Soc. Chem. Commun.* **1972**, 144.

[3] K. Tamao, *J. Organomet. Chem.* **2002**, *653*, 23–26.

[4] P. Knochel, I. Sapountzis, N. Gommermann, in *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**, pp. 671–698.

[5] A. de Meijere, F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., Wiley-VCH, Weinheim, **2004**.

[6] A. F. Littke, G. C. Fu, *Angew. Chem.* **2002**, *114*, 4350–4386; *Angew. Chem. Int. Ed.*

2002, *41*, 4176–4211.

[7] T. G. Richmond, *Angew. Chem.* **2000**, *112*, 3378–3380; *Angew. Chem. Int. Ed.* **2000**, *39*, 3241–3244.

[8] T. Braun, R. N. Perutz, *Chem. Commun.* **2002**, 2749–2757.

[9] T. Takahashi, K. Kanno in *Modern Organonickel Chemistry* (Ed.: Y. Tamaru), Wiley-VCH, Weinheim, **2005**, pp. 41–55.

- [10] For an unselective coupling with an alkyl Grignard reagent, see: Y. Kiso, K. Tamao, M. Kumada, *J. Organomet. Chem.* **1973**, *50*, C12–C14.
- [11] For a recent study on thermal and microwave-mediated reactions, see: J. W. Dankwardt, *J. Organomet. Chem.* **2005**, *690*, 932–938.
- [12] V. P. W. Böhm, C. W. K. Gstöttmayr, T. Weskamp, W. A. Herrmann, *Angew. Chem.* **2001**, *113*, 3500–3503; *Angew. Chem. Int. Ed.* **2001**, *40*, 3387–3389.
- [13] See also: a) F. Mongin, L. Mojovic, B. Guillet, F. Trecourt, G. Quéguiner, *J. Org. Chem.* **2002**, *67*, 8991–8994; b) K. Lamm, M. Stollenz, M. Meier, H. Görls, B. Walther, *J. Organomet. Chem.* **2003**, *681*, 24–36.
- [14] L. Ackermann, R. Born, *Angew. Chem.* **2005**, *117*, 2497–2500; *Angew. Chem. Int. Ed.* **2005**, *44*, 2444–2447.
- [15] N. V. Dubrovina, A. Börner, *Angew. Chem.* **2004**, *116*, 6007–6010; *Angew. Chem. Int. Ed.* **2004**, *43*, 5883–5886.
- [16] For the use of alkyl-substituted phosphine oxides in nickel-catalyzed cross-couplings with aryl chlorides, see: a) G. Y. Li, *Angew. Chem.* **2001**, *113*, 1561–1564; *Angew. Chem. Int. Ed.* **2001**, *40*, 1513–1516; b) G. Y. Li, W. J. Marshall, *Organometallics* **2002**, *21*, 590–591.
- [17] For a thorough evaluation of a variety of preligands, see the Supporting Information in: V. P. W. Böhm, T. Weskamp, C. W. K. Gstöttmayr, W. A. Herrmann, *Angew. Chem.* **2000**, *112*, 1672–1674; *Angew. Chem. Int. Ed.* **2000**, *39*, 1602–1604.
- [18] The corresponding arylphosphonate derived from phosphine oxide **11** could not be obtained by standard synthetic procedures; this underscores the steric demand of preligand **11**. A practical protocol for the synthesis of arylphosphonates: L. J. Gooßen, M. K. Dezfuli, *Synlett* **2005**, 445–448, and references therein.
- [19] J. R. Goerlich, A. Fischer, P. G. Jonas, R. Schmutzler, *Z. Naturforsch. B* **1994**, *49*, 801–811, and references therein.
- [20] For use in C–H bond functionalization reactions with aryl chlorides, see: L. Ackermann, *Org. Lett.* **2005**, *7*, 3123–3125.
- [21] For the synthesis of a phosphinous acid nickel complex, starting from [Ni(acac)₂] and phosphine oxide **15**, see: B. Walther, H. Hartung, M. Maschmeier, U. Baumeister, B. Messbauer, *Z. Anorg. Allg. Chem.* **1988**, *566*, 121–130.