CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201000032

Kumada–Corriu Cross-Couplings with 2-Pyridyl Grignard Reagents

Lutz Ackermann,*[a] Harish K. Potukuchi,[a] Anant R. Kapdi,[a] and Carola Schulzke[b]

Substituted heterobiaryls constitute privileged scaffolds of compounds with activities of relevance to various research areas, ranging from medicinal chemistry and catalysis to material sciences.[1–4] Their regioselective syntheses rely strongly on transition-metal-catalyzed cross-coupling reactions, which have matured to being indispensable tools in modern organic syntheses.[3,4] Since organomagnesium reagents are more readily available than are alternative organometallic nucleophiles,[5,6] catalytic cross-couplings of Grignard reagents have proven particularly useful for streamlining heterobiaryl synthesis.[7] Therefore, catalysts derived from various transition metals, such as nickel,[8,9] palladium,[10] iron,[11,12] cobalt,[13–15] or manganese,[16] were developed for Kumada–Corriu-type[17,18] coupling reactions.[3,4,19] While this research significantly expanded the pool of viable electrophiles, cross-coupling reactions of electron-deficient *N*-heterocyclic nucleophiles continue to be challenging because of their reduced nucleophilicities. Hence, a generally applicable protocol for metal-catalyzed arylations of less nucleophilic 2-azine Grignard[20] reagents has, to the best of our knowledge, proven elusive.[2,21,22] As part of our program directed towards the use of air-stable secondary phosphine oxides (SPO) as preligands in transition-metal catalysis,[23,24] we noted that efficient cross-couplings with 2-pyridyl organomagnesium compounds could be accomplished, provided that palladium catalysts derived from air- and moisture-stable SPOs[23] were employed as preligands. Herein, we report on these findings, which highlight the unique reactivity profile of SPO preligands.

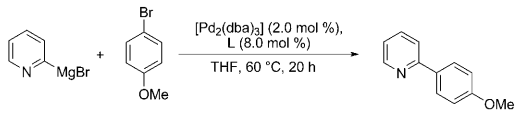
[a] Prof. Dr. L. Ackermann, H. K. Potukuchi, Dr. A. R. Kapdi
Institut für Organische und Biomolekulare Chemie
Georg-August-Universität
Tammannstrasse 2, 37077 Göttingen (Germany)
Fax: (+49) 551-39-6777
E-mail: Lutz.Ackermann@chemie.uni-goettingen.de

[b] Prof. Dr. C. Schulzke
Institut für Anorganische Chemie
Georg-August-Universität
Tammannstrasse 4, 37077 Göttingen (Germany)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200100032.

At the outset of our studies, we probed various transition-metal complexes and ligands in the cross-coupling of challenging 2-pyridyl Grignard **1a** with aryl bromide **2a** (Table 1). Unfortunately, monodentate phosphines **4a**–**4d** provided unsatisfactory results (Table 1, entries 2–5), as did bidentate ligands **4e**–**4g** or phosphite **5** (Table 1, entries 6–9). Further, in situ generated (Table 1, entries 10 and 11) or preformed, well-defined palladium *N*-heterocyclic carbene complexes (Table 1, entries 12 and 13) did not deliver the desired product **3a**.

Table 1. Optimization of palladium-catalyzed coupling with 2-pyridyl Grignard **1a**.[a]



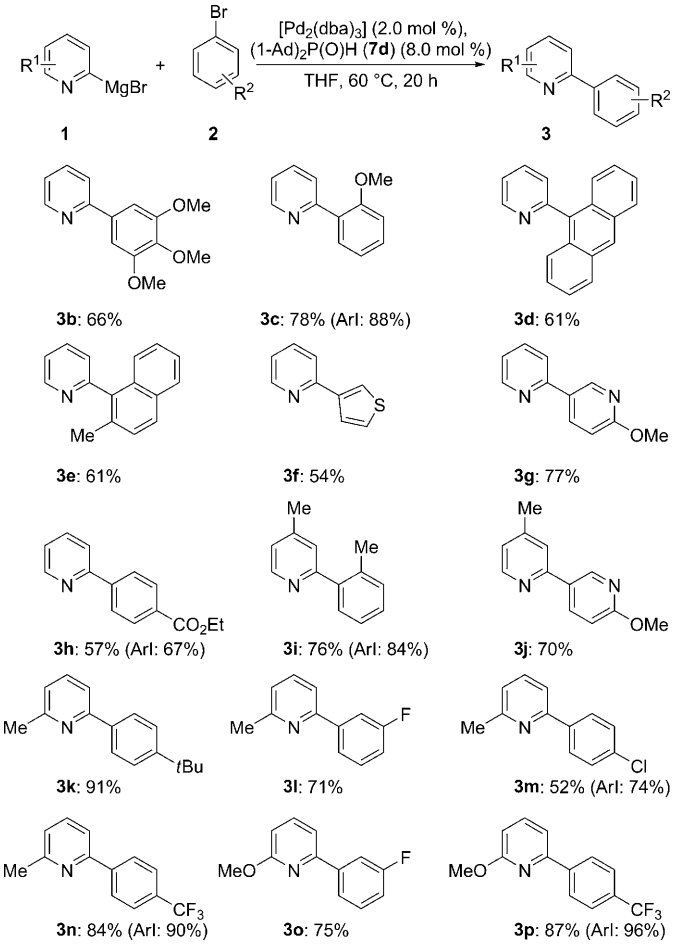
1a **2a** **3a**

Entry	L		Yield [%]
1	–		<2[b]
2	PPh_3	**4a**	<2[b]
3	PCy_3	**4b**	7[b]
4	$[HP(tBu)_3]BF_4$	**4c**	<2[b]
5	X-Phos	**4d**	<2[b]
6	dppp	**4e**	<2[b]
7	dppf	**4f**	14
8	BINAP	**4g**	11
9	$P(OEt)_3$	**5**	<2[b]
10	IPrHCl	**6a**	<2[b]
11	SIPrHCl	**6b**	<2[b]
12	[Pd(SIPr)(allyl)Cl][c]	**6c**	<2[b]
13	Pd-PEPPSI-SIPr[c]	**6d**	<2[b]
14	$Ph_2P(O)H$	**7a**	27
15	$Mes_2P(O)H$	**7b**	8
16	$(tBu)_2P(O)H$	**7c**	47
17			67
18	$(1\text{-Ad})_2P(O)H$	**7d**	64[d]
19			93[e]

[a] Reaction conditions: **1a** (1.5 mmol), **2a** (1.0 mmol), $[Pd_2(dba)_3]$ (2.0 mol%), L (8.0 mol%), THF (1.0 mL), 60 °C, 20 h, yields of isolated products; X-Phos = 2-dicyclohexyl phosphino-2′,4′,6′-triisopropylbiphenyl; (S)IPrH = *N*,*N*′-bis-(2,6-diisopropylphenyl)imidazol(in)ium; Pd-PEPPSI-SIPr = $[Pd(SIPr)(3\text{-Clpy})Cl_2]$. [b] GC-conversion. [c] Instead of $[Pd_2(dba)_3]$. [d] Using 4-MeOC_6H_4OTf. [e] Using 4-MeOC_6H_4I.

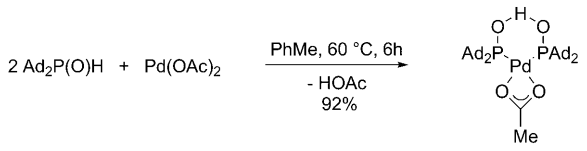
On the contrary, a promising conversion of the starting materials was observed when employing aryl-substituted SPO **7a** (Table 1, entry 14). A catalyst derived from more sterically hindered aryl-substituted preligand **7b**, however, proved to be less efficient (Table 1, entry 15). Interestingly, alkyl-substituted SPO preligands **7c** and **7d** turned out to be superior (Table 1, entries 16 and 17), with sterically demanding, non-hygroscopic $(1\text{-Ad})_2P(O)H$ (**7d**)[25] leading to optimal results (Table 1, entry 17).[26,27] This catalytic system was not restricted to aryl bromides as electrophiles, but was found amenable to aryl triflates or iodides as well (Table 1, entries 18 and 19).

With a highly active catalytic system in hand, we explored its scope in cross-coupling reactions of substituted 2-pyridyl nucleophiles **1** and aryl halides **2** (Scheme 1). Hence, electrophiles **2** bearing valuable functional groups, such as halo or ester substituents, were chemoselectively converted to products **3b**–**3p**. Further, N- or S-heteroarenes were well tolerated by the in situ generated catalytic system (**3f**, **3g**, and **3j**). Additionally, a variety of differently substituted 2-pyridyl nucleophiles **1** was efficiently cross-coupled, thus delivering heterobiaryls **3i**–**3p**. Intermolecular competition experiments revealed i) that more electron-deficient aryl halides **2** reacted preferentially, and that ii) electron-rich 2-pyridyl Grignard reagents **1** were converted with higher efficacy.



Scheme 1. Palladium-catalyzed cross-coupling of 2-pyridyl nucleophiles **1**.

Given the unique reactivity profile of the complex generated in situ from SPO **7d**, we became interested in exploring its coordination chemistry and working mode. Thus, palladium complex **8** bearing a self-assembled bidentate ligand was obtained in an excellent yield, when reacting preligand **7d** with $Pd(OAc)_2$, a transformation that occurred even in the absence of an additional external base (Scheme 2).[28]



Scheme 2. Synthesis of complex **8**.

Importantly, the isolated, well-defined palladium complex **8** (Figure 1) exhibited a remarkably high catalytic activity in the challenging cross-coupling of 2-pyridyl Grignard reagents **1** (Scheme 3). As a result, a significantly lower catalyst loading turned out to be sufficient for achieving effective cross-coupling reactions.[29] Thereby, diversely substituted Grignard reagents **1** were selectively coupled with organic electrophiles **2** bearing useful functionalities.

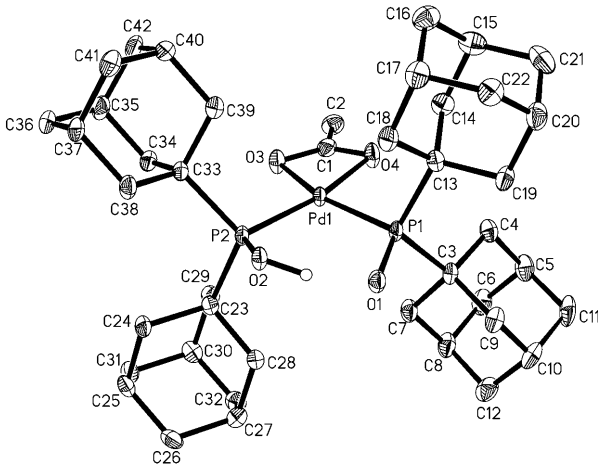
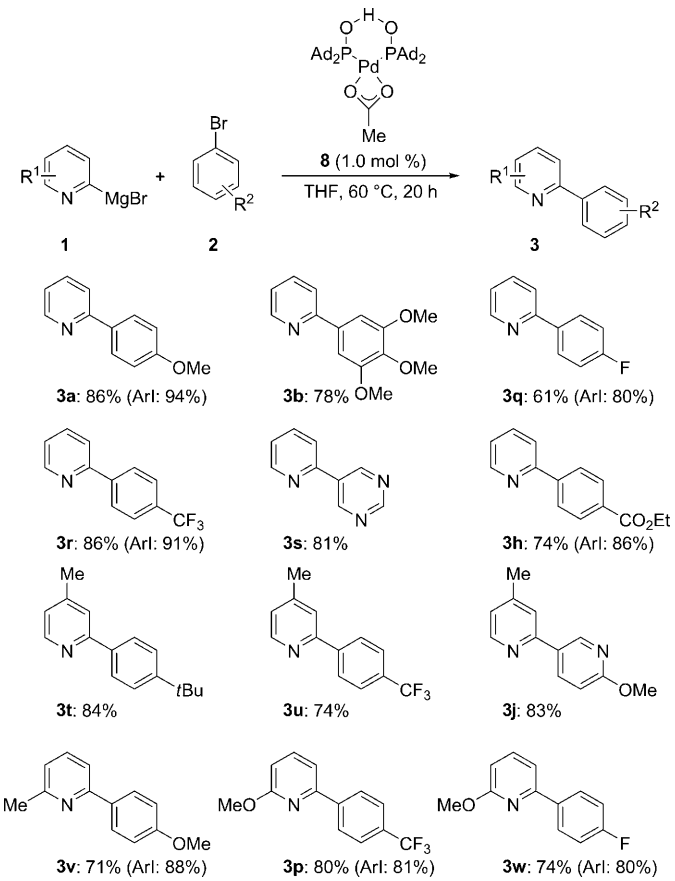
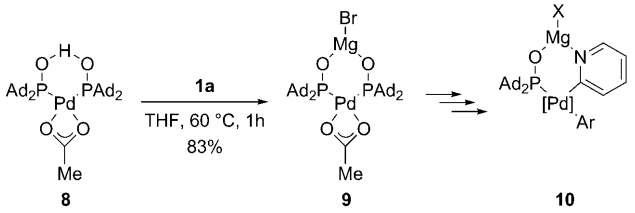


Figure 1. Molecular structure of complex **8**.

It is well documented that the stabilizing proton in bidentate complexes derived from secondary phosphine oxides are significantly acidified.[23] Indeed, palladium complex **8** reacted with basic Grignard reagent **1a** to yield heterobimetallic complex **9** (Scheme 4). We propose that this heterobimetallic structural motif enables efficient coupling reactions with challenging 2-pyridyl nucleophiles through the formation of intermediates of type **10**.



Scheme 3. Catalyzed cross-couplings with isolated, well-defined palladium complex **8**.



Scheme 4. Synthesis of heterobimetallic complex **9** and proposed working mode of SPO-derived palladium complexes.

In summary, we have reported on a first protocol for generally applicable cross-coupling reactions of easily available 2-pyridyl organomagnesium reagents. A valuable asset of this methodology is represented by the air- and moisture-stable nature of preligand $(1\text{-Ad})_2P(O)H$ (**7d**), which proved to be superior to commonly used ligands.

Experimental Section

Representative procedure for palladium-catalyzed cross-coupling with 2-pyridyl Grignard reagents: Synthesis of 3a (Table 1, entry 17): A suspension of $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone; 18 mg, 0.02 mmol, 2.0 mol %) and **7d** (25 mg, 0.08 mmol, 8.0 mol %) in THF (1.0 mL) was stirred for 10 min at ambient temperature. Compound **2a** (187 mg, 1.00 mmol) was added and the suspension was stirred for a further 5 min. Then, **1a** (5.0 mL, 1.50 mmol, 0.3 M in THF) was added dropwise over 3 min and the resulting suspension was stirred for 20 h at 60 °C. EtOAc (50 mL) and H_2O (50 mL) were added to the cold reaction mixture. The separated aqueous phase was extracted with EtOAc (2×50 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The remaining residue was purified by column chromatography on silica (*n*-hexane/EtOAc 10/1) to yield **3a** as a colorless solid (124 mg, 67 %).

Acknowledgements

Support by the DFG, the DAAD (fellowship to H.K.P.), and the Alexander-von-Humboldt foundation (fellowship to A.K.) is gratefully acknowledged.

Keywords: cross-coupling · heteroarenes · organomagnesium reagents · palladium · pyridines · secondary phosphine oxides

[1] J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337–2347.
[2] M. Hapke, L. Brandt, A. Luetzen, *Chem. Soc. Rev.* **2008**, *37*, 2782–2797.
[3] L. Ackermann, *Modern Arylation Methods*, Wiley-VCH, Weinheim, **2009**.
[4] M. Beller, C. Bolm, *Transition Metals for Organic Synthesis*, 2nd ed., Wiley-VCH, Weinheim, **2004**.
[5] P. Knochel, *Handbook of Functionalized Organometallics*, Wiley-VCH, Weinheim, **2005**.
[6] H. Ila, O. Baron, A. J. Wagner, P. Knochel, *Chem. Commun.* **2006**, 583–593.
[7] For an alternative approach involving direct arylations of pyridines, which requires high reaction temperatures of usually 130–190 °C, see: a) A. M. Berman, J. C. Lewis, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130*, 14926–14927; b) M. Tobisu, I. Hyodo, N. Chatani, *J. Am. Chem. Soc.* **2009**, *131*, 12070–12071. For a representative recent example of direct arylations with usually overstoichiometric amounts of pyridine *N*-oxides as activated pyridine surrogates, see: c) L.-C. Campeau, D. R. Stuart, J.-P. Leclerc, M. Bertrand-Laperle, E. Villemure, H.-Y. Sun, S. Lasserre, N. Guimond, M. Lecavallier, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 3291–3306; and references therein.
[8] J. Terao, N. Kambe, *Acc. Chem. Res.* **2008**, *41*, 1545–1554.
[9] Representative examples: a) O. Vechorkin, V. Proust, X. Hu, *J. Am. Chem. Soc.* **2009**, *131*, 9756–9766; b) N. Yoshikai, H. Matsuda, E. Nakamura, *J. Am. Chem. Soc.* **2009**, *131*, 9590–9599; c) N. Yoshikai, H. Matsuda, E. Nakamura, *J. Am. Chem. Soc.* **2008**, *130*, 15258–15259; d) L. Ackermann, R. Born, J. H. Spatz, D. Meyer, *Angew. Chem.* **2005**, *117*, 7382–7386; *Angew. Chem. Int. Ed.* **2005**, *44*, 7216–7219; e) 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; f) G. Y. Li, *Angew. Chem.* **2001**, *113*, 1561–1564; *Angew. Chem. Int. Ed.* **2001**, *40*, 1513–1516; and references therein.
[10] Recent examples of palladium-catalyzed cross-couplings with Grignard reagents, see: a) G. Manolikakes, P. Knochel, *Angew. Chem.* **2009**, *121*, 211–215; *Angew. Chem. Int. Ed.* **2009**, *48*, 205–209; b) C. Wolf, H. Xu, *J. Org. Chem.* **2008**, *73*, 162–167; c) R. Martin, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3844–3845; d) L. Ackermann, A. Althammer, *Org. Lett.* **2006**, *8*, 3457–3460; e) M. G. Organ, M. Abdel-Hadi, S. Avola, N. Hadei, J. Nasielski,

C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2006**, *12*, 150–157; and references therein.
[11] B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500–1511.
[12] B. Plietker, *Iron Catalysis in Organic Chemistry*, Wiley-VCH, Weinheim, **2008**.
[13] W. Hess, J. Treutwein, G. Hilt, *Synthesis* **2008**, 3537–3562.
[14] C. Gosmini, J.-M. Begouin, A. Moncomble, *Chem. Commun.* **2008**, 3221–3233.
[15] H. Yorimitsu, K. Oshima, *Pure Appl. Chem.* **2006**, *78*, 441–449.
[16] G. Cahiez, C. Duplais, J. Buendia, *Chem. Rev.* **2009**, *109*, 1434–1476.
[17] R. J. P. Corriu, J. P. Masse, *J. Chem. Soc. Chem. Commun.* **1972**, 144a.
[18] K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 4374–4376.
[19] L. Ackermann, A. Althammer, *Chem. Unserer Zeit* **2009**, *43*, 74–83.
[20] For select recent examples of Suzuki–Miyaura cross-couplings with 2-pyridyl nucleophiles, see: a) D. M. Knapp, E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2009**, *131*, 6961–6963; b) K. L. Billingsley, S. L. Buchwald, *Angew. Chem.* **2005**, *117*, 4773–4776; *Angew. Chem. Int. Ed.* **2008**, *47*, 4695–4698; c) L. Ackermann, H. K. Potukuchi, *Synlett* **2009**, 2852–2856; d) for examples of Stille couplings with 2-pyridyltin reagents, see: Y. Yamamoto, A. Y. Azuma, M. Mitoh, *Synthesis* **1986**, 564–565; e) R. Wittenberg, J. Srogl, M. Egi, L. S. Liebeskind, *Org. Lett.* **2003**, *5*, 3033–3035; and references therein.
[21] A low-yielding example of a palladium-catalyzed Kumada–Corriu cross-coupling reaction with 2-pyridyl organomagnesium reagents was reported, which highlights the difficulties associated with the use of these nucleophiles: a) C. M. Amb, S. C. Rasmussen, *Eur. J. Org. Chem.* **2008**, 801–804; b) for further unsuccessful attempts, see, for example: K. Tamao, S. Kodama, I. Nakajima, M. Kumada, A. Minato, K. Suzuki, *Tetrahedron* **1982**, *38*, 3347–3354; see, however, also: A. Fürstner, A. Leitner, G. Seidel, *Org. Synth.* **2005**, *81*, 33–41.
[22] L.-C. Campeau, K. Fagnou, *Chem. Soc. Rev.* **2007**, *36*, 1058–1068.
[23] Reviews: a) L. Ackermann, *Synlett* **2007**, 507–526; b) L. Ackermann, *Synthesis* **2006**, 1557–1571; c) L. Ackermann, R. Born, J. H. Spatz, A. Althammer, C. J. Gschrei, *Pure Appl. Chem.* **2006**, *78*, 209–214.
[24] Select examples: a) L. Ackermann, S. Barfüßer, *Synlett* **2009**, 808–812; b) L. Ackermann, C. J. Gschrei, A. Althammer, M. Riederer, *Chem. Commun.* **2006**, 1419–1421; c) L. Ackermann, A. Althammer, R. Born, *Angew. Chem.* **2006**, *118*, 2681–2685; *Angew. Chem. Int. Ed.* **2006**, *45*, 2619–2622; d) L. Ackermann, R. Born, *Angew. Chem.* **2005**, *117*, 2497–2500; *Angew. Chem. Int. Ed.* **2005**, *44*, 2444–2447.
[25] For examples of preligand $(1\text{-Ad})_2\text{P(O)H}$ (**7d**) in catalytic functionalizations of C–H bonds, see: a) L. Ackermann, R. Vicente, N. Hofmann, *Org. Lett.* **2009**, *11*, 4274–4276; b) L. Ackermann, R. Vicente, A. Althammer, *Org. Lett.* **2008**, *10*, 2299–2302; c) L. Ackermann, *Org. Lett.* **2005**, *7*, 3123–3125.
[26] The remaining mass balance was unreacted electrophilic starting material.
[27] Under otherwise identical reaction conditions the use of $[\text{Ni(cod)}_2]$ (cod = 1,5-cyclooctadiene), $[\text{Ni(acac)}_2]$ (acac = acetylacetonate), or $[\text{Fe(acac)}_3]$ did not lead to formation of the desired product.
[28] CCDC-713168 contains the supplementary crystallographic data for complex **8**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[29] Lower yields of product **3a** were obtained at this catalyst loading with in situ generated complexes: Pd(OAc)_2 (1.0 mol%)/**7d** (2.0 mol%): 46%; $[\text{Pd}_2\text{(dba)}_3]$ (0.5 mol%)/**7d** (2.0 mol%)/NaOAc (1.0 mol%): 55%.

Received: January 6, 2010
Published online: February 18, 2010

