


# Rhodium-Catalyzed Oxidative Homocoupling of Boronic Acids

Thomas Vogler<sup>a</sup> and Armido Studer<sup>a,\*</sup>

<sup>a</sup> Fachbereich Chemie, Organisch-Chemisches Institut, Westfälische Wilhelms-Universität, Corrensstrasse 40, 48149 Münster, Germany  
Fax: (+49)-251-833-6523; e-mail: studer@uni-muenster.de

Received: May 13, 2008; Revised: June 26, 2008; Published online: August 13, 2008

 Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.200800300>.

**Abstract:** Oxidative homocoupling of aryl- and alkenylboronic acids was achieved with Wilkinson's catalyst. Commercially available 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO) was used as a stoichiometric oxidant.

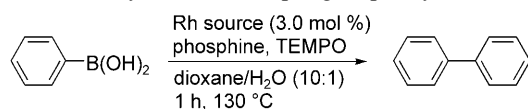
**Keywords:** boronic acids; nitroxides; oxidative coupling; rhodium; TEMPO

Biaryls are an important class of compounds which occur in many natural products.<sup>[1]</sup> Moreover, biaryls have found widespread application as ligands in catalytic asymmetric synthesis.<sup>[2]</sup> They are also found as components in new organic materials.<sup>[3,4]</sup> The oxidative homocoupling of organoboron compounds represents a widely used approach to symmetrical biaryls. This route is particularly useful since many arylboronic acids are commercially available. Various protocols for Pd-catalyzed homocoupling reactions of arylboronic acids have been developed.<sup>[2,5]</sup> Recently it has been reported that other metals such Au,<sup>[6a-c]</sup> Cu,<sup>[6d]</sup> Cr<sup>[6e]</sup> and V<sup>[6f]</sup> can be used to mediate biaryl formation from arylboronic acids. To the best of our knowledge, no reports on Rh-catalyzed oxidative homocouplings of organoboron compounds have appeared to date.<sup>[7]</sup>

It is well known that transmetalation of arylboronic acids to Rh(I) complexes leads to aryl-Rh(I) derivatives,<sup>[8]</sup> and that reductive elimination in R<sup>1</sup>R<sup>2</sup>Rh(III) compounds provides Rh(I) complexes along with R<sup>1</sup>-R<sup>2</sup>.<sup>[9]</sup> The formation of Rh(III) complexes in these catalytic processes generally occurs *via* oxidative addition of an Rh(I) species, for example, by using an aryl halide. However, many Rh-catalyzed reactions do not occur *via* Rh(I)-Rh(III) redox cycles. Rh(I) is preserved throughout the catalytic cycle. We believe that many interesting reactions can be accomplished *via* Rh(I)-Rh(III) redox processes.<sup>[9,10]</sup> There-

fore, new entries to Rh(III) complexes in synthesis are desirable. We envisaged that oxidation of readily generated aryl-Rh(I) complexes by an electron transfer oxidant may offer an alternative approach to the corresponding aryl-Rh(III) species. Indeed, we recently developed an oxidative Rh-catalyzed coupling reaction of arenes and heteroarenes with arylboronic acids *via* direct C-H arylation by using this approach.<sup>[11]</sup> Herein we present our first results on Rh-mediated homocoupling reactions of various arylboronic acids.

We used the commercially available 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO) as a stoichiometric oxidant.<sup>[12]</sup> The homocoupling of phenylboronic acid to give biphenyl was studied first. Reactions were performed in a dioxane/water mixture (10:1)<sup>[13]</sup> by using various Rh(I) complexes (3.0 mol%) and different phosphines with 1.2 equiv. of TEMPO at 130 °C for 1 h (Table 1). With [RhCl(cod)]<sub>2</sub> and PPh<sub>3</sub> (6.0 mol%) as catalyst the desired biphenyl was formed in a low yield (entry 1). The yield could be improved to 79% by using 3.0 equiv. of PPh<sub>3</sub> with respect to the catalyst (entry 2). Reaction works without any additional base. Rh-catalyzed processes with boronic acids as coupling partners often rely on the activation of the boronic acid by a base in order to facilitate transmetalation. In our case TEMPO or the corresponding hydroxylamine might serve this purpose. With the sterically more demanding P(*o*-Tol)<sub>3</sub> as a ligand only traces of biphenyl were formed (entry 3). Moderate results were obtained with electron-rich (entry 4) and with electron-poor arylphosphines (entry 5). Next, the aryl groups of the ligand were gradually replaced by methyl substituents (entries 6 and 7). However, the yield could not be improved. Unsatisfactory results were obtained by using electron-rich alkylphosphines or with phosphites as ligands (entries 8–10). Other Rh(I) precursors such as Rh(acac)(cod)<sub>2</sub>, Rh(cod)<sub>2</sub>OTf and Rh(cod)<sub>2</sub>BF<sub>4</sub> delivered worse results (entries 11–13). The use of Rh(II) and Rh(III) precur-

**Table 1.** Rh-catalyzed homocoupling of phenylboronic acid.

Entry	Rh source	Phosphine	TEMPO (equiv.)	Yield [%] <sup>[a]</sup>
1	[RhCl(cod)] <sub>2</sub>	PPh <sub>3</sub>	1.2	23 <sup>[b]</sup>
2	[RhCl(cod)] <sub>2</sub>	PPh <sub>3</sub>	1.2	79
3	[RhCl(cod)] <sub>2</sub>	P( <i>o</i> -Tol) <sub>3</sub>	1.2	traces
4	[RhCl(cod)] <sub>2</sub>	P( <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>	1.2	48
5	[RhCl(cod)] <sub>2</sub>	P( <i>p</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>	1.2	56
6	[RhCl(cod)] <sub>2</sub>	PMePh <sub>2</sub>	1.2	38
7	[RhCl(cod)] <sub>2</sub>	PMe <sub>2</sub> Ph	1.2	58
8	[RhCl(cod)] <sub>2</sub>	P( <i>n</i> Bu) <sub>3</sub>	1.2	47
9	[RhCl(cod)] <sub>2</sub>	PCy <sub>3</sub>	1.2	<5
10	[RhCl(cod)] <sub>2</sub>	P(OEt) <sub>3</sub>	1.2	<5 <sup>[c]</sup>
11	Rh(acac)(cod) <sub>2</sub>	PPh <sub>3</sub>	1.2	39
12	Rh(cod) <sub>2</sub> OTf	PPh <sub>3</sub>	1.2	51
13	Rh(cod) <sub>2</sub> BF <sub>4</sub>	PPh <sub>3</sub>	1.2	32
14	Rh <sub>2</sub> (OAc) <sub>4</sub>	PPh <sub>3</sub>	1.2	8
15	RhCl <sub>3</sub>	PPh <sub>3</sub>	1.2	17
16	RhCl(PPh <sub>3</sub> ) <sub>3</sub>	–	1.2	81
17	RhCl(PPh <sub>3</sub> ) <sub>3</sub>	–	2.0	86

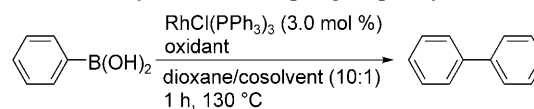
<sup>[a]</sup> Isolated yield.

<sup>[b]</sup> 6.0 mol% of PPh<sub>3</sub> were used.

<sup>[c]</sup> Reaction time 2.5 h at 100 °C.

sors gave inferior yields (entries 14 and 15). Readily available Wilkinson's catalyst gave the best result (entry 16). The yield could be further improved by using 2.0 equiv. of TEMPO (86%, entry 17). All attempts to improve the yield by adding an external base failed.

After having identified an efficient catalyst, we studied the influence of various protic cosolvents on the test reaction. Decreasing the amount of water in dioxane resulted in lower yields (Table 2, entries 1 and 2). A 75% yield of biphenyl was obtained with ethanol as cosolvent (entry 3). By using the more acidic trifluoroethanol as an additive a significantly lower yield was achieved (entry 4). A similar result was obtained with *tert*-butanol as cosolvent (entry 5). As a result of the solvent screening, the following studies were performed in dioxane/water (10:1). As compared to the TEMPO-mediated process, with the sterically more demanding nitroxide **1** as an oxidant (Figure 1), biphenyl was formed in a lower yield (even upon increasing the reaction time to 4 h, entry 6). Presumably, this nitroxide is a worse ligand for Rh as compared to TEMPO (see suggested mechanism below). The TEMPO-derived *N*-oxoammonium salt **2** should act as a two-electron oxidant. However, only a 34% yield was obtained in the test reaction by using 0.6 equiv. of **2** (entry 7). We repeated this ex-

**Table 2.** Rh-catalyzed homocoupling of phenylboronic acid.

Entry	Cosolvent	Oxidant	Equiv.	Yield [%] <sup>[a]</sup>
1	H <sub>2</sub> O	TEMPO	1.2	73 <sup>[b]</sup>
2	H <sub>2</sub> O	TEMPO	1.2	51 <sup>[c]</sup>
3	EtOH	TEMPO	1.2	75
4	(CF <sub>3</sub> ) <sub>2</sub> COH	TEMPO	1.2	45
5	<i>t</i> -BuOH	TEMPO	1.2	48
6	H <sub>2</sub> O	<b>1</b>	1.2	25 <sup>[d]</sup>
7	H <sub>2</sub> O	<b>2</b>	0.6	34 <sup>[d]</sup>
8	H <sub>2</sub> O	<b>2</b>	1.2	25 <sup>[e]</sup>
9	H <sub>2</sub> O	(NH <sub>4</sub> ) <sub>2</sub> [Ce(NO <sub>3</sub> ) <sub>6</sub> ]	2.0	traces
10	H <sub>2</sub> O	FeCl <sub>3</sub>	2.0	traces
11	H <sub>2</sub> O	K <sub>3</sub> [Fe(CN) <sub>6</sub> ]	2.0	traces
12	H <sub>2</sub> O	Cu(NO <sub>3</sub> ) <sub>2</sub> ·H <sub>2</sub> O	2.0	17
13	H <sub>2</sub> O	oxygen	–	45 <sup>[f]</sup>

<sup>[a]</sup> Isolated yield.

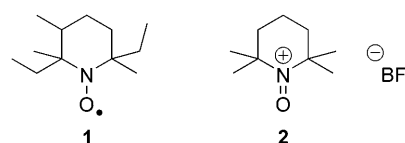
<sup>[b]</sup> Dioxane/H<sub>2</sub>O (50:1).

<sup>[c]</sup> Dioxane/H<sub>2</sub>O (200:1).

<sup>[d]</sup> Reaction time 4 h.

<sup>[e]</sup> Reaction time 6 h at 100 °C.

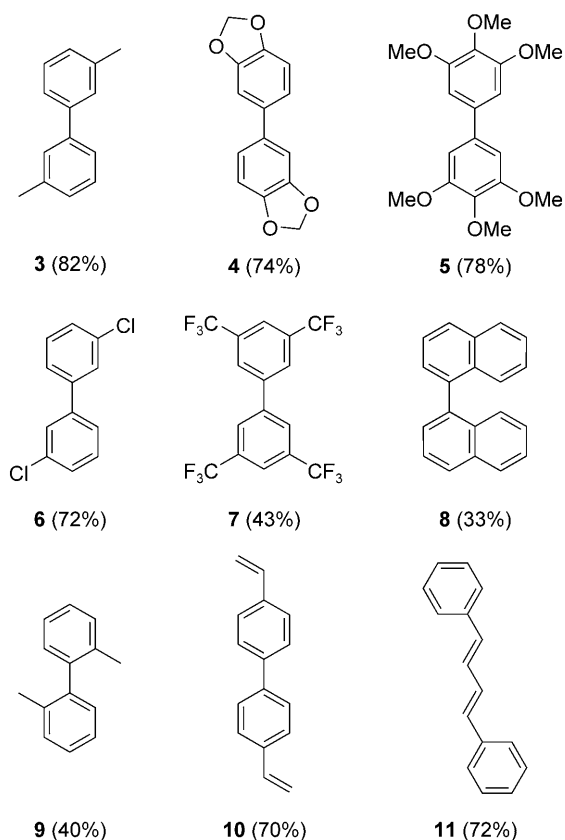
<sup>[f]</sup> Reaction time 14 h at 70 °C, 1 bar of oxygen was used.

**Figure 1.** Tested oxidants for the Rh-catalyzed homocoupling.

periment at 100 °C due to the expected instability of the *N*-oxoammonium salt **2** at higher temperatures. However, an even lower yield (25%) was obtained under these conditions (entry 8).

Finally, metal salts with decreasing redox potentials were investigated as stoichiometric oxidants. However, by using strong oxidants only traces of biphenyl were formed (entries 9–11). Probably catalyst decomposition occurred under these conditions. With Cu(NO<sub>3</sub>)<sub>2</sub>·H<sub>2</sub>O as an external oxidant the product was obtained in 17% yield (entry 12). Pleasingly, the coupling could also be achieved at 70 °C with oxygen as an oxidant. However, a longer reaction time (14 h) was necessary and a lower yield was obtained under these conditions (entry 13). Hence, TEMPO seemed to be the privileged oxidant for this particular homocoupling reaction.

Under the optimized conditions various biaryls were successfully prepared by using TEMPO as an external oxidant (Figure 2). *meta*- and *para*-substituted electron-rich boronic acids gave the biaryls **3–5**, and **10** in good yields. Lower yields were obtained for



**Figure 2.** Rh-catalyzed homocoupling of various boronic acids [3.0 mol%  $\text{RhCl}(\text{PPh}_3)_3$ , 2.0 equiv TEMPO in dioxane/ $\text{H}_2\text{O}$  (10:1) for 2 h at  $130^\circ\text{C}$ ].

the coupling of electron-deficient arylboronic acids ( $\rightarrow$ **6**, **7**). Alkoxy, chloro and vinyl substituents were tolerated in this reaction. Coupling of sterically more demanding arylboronic acids occurred in lower yields ( $\rightarrow$ **8**, **9**). Naphthalene (54%) was isolated along with the desired binaphthalene **8** (33%) by using 1-naphthaleneboronic acid as substrate. As expected, protodeboration is a competing side reaction in the coupling of sterically hindered aryl-Rh(I) compounds. Furthermore, phenol derivatives could be detected as

side products in less efficient homocoupling reactions. Pleasingly,  $\beta$ -styrylboronic acid could be homocoupled in a good yield with perfect diastereoselectivity. Diene **11** was isolated as a single isomer in 70% yield. Homocoupling of phenyltrifluoroborate gave biphenyl in 38% yield under standard conditions. The reaction did not proceed with phenyltrifluoroborate in the absence of water. Thus, a protic solvent seemed to be essential for this reaction.

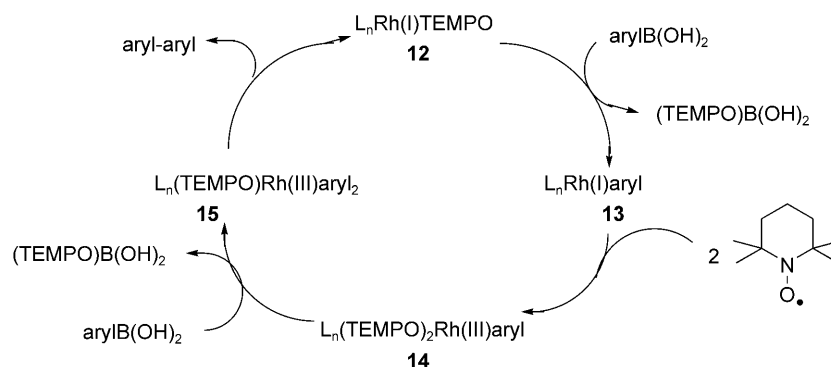
The suggested mechanism is depicted in Scheme 1. Transmetalation of Rh(I) complex **12** with arylboronic acid will generate aryl-Rh(I) complex **13**. We believe that oxidation with 2.0 equiv. of TEMPO leads to Rh(III) complex **14**. Such oxidatively generated mono-aryl-Rh(III) complexes likely act as coupling partners in our recently developed Rh-catalyzed C–H arylation.<sup>[11]</sup> Therefore, we assume that the second transmetalation occurs at the Rh(III) oxidation state, since the conditions for the herein described homocoupling and the C–H arylation are similar. Transmetalation should then lead to **15** and subsequent reductive elimination eventually provides the homocoupling product and regenerates complex **12**. However, since transmetalations of arylboronic acids to Rh(II) have been recently described,<sup>[14]</sup> transmetalation to a  $\text{L}_n(\text{TEMPO})\text{Rh}(\text{II})\text{aryl}$  complex prior to oxidation with the second equivalent TEMPO to **15** can currently not be excluded.

In conclusion, we have presented the first Rh-catalyzed oxidative homocoupling reactions of various aryl- or alkenylboronic acids. All starting materials used (catalyst, oxidant and arylboronic acids) are commercially available and can be used as received.

## Experimental Section

### General

All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in heat-gun-dried glassware under an argon atmosphere and were performed by using



**Scheme 1.** Suggested mechanism.

standard Schlenk techniques. All solvents for filtration and flash chromatography were distilled before use. Ethanol (Acros, 99%) was distilled from Na and was stored under an argon atmosphere. 1,4-Dioxane (Acros, extra dry, water < 50 ppm), *tert*-butanol (Fluka, > 99.7%) was used as received without further purification.

$^1\text{H}$  NMR (300 MHz) and  $^{13}\text{C}$  NMR (75 MHz) spectra were recorded on a Bruker DPX 300 spectrometer. Chemical shifts  $\delta$  in ppm are referenced to the solvent residual peak as an internal standard. TLC was carried out on Merck silica gel 60 F<sub>254</sub> plates; detection by UV or dipping into a solution of Ce(SO<sub>4</sub>)<sub>2</sub>·H<sub>2</sub>O (10 g), phosphormolybdic acid hydrate (25 g), concentrated H<sub>2</sub>SO<sub>4</sub> (60 mL) and H<sub>2</sub>O (0.94 L) or NaHCO<sub>3</sub> (5.0 g), KMnO<sub>4</sub> (1.5 g) and H<sub>2</sub>O (0.40 L) followed by heating. Flash chromatography (FC) was carried out on Merck or Fluka silica gel 60 (40–63  $\mu\text{m}$ ) with an argon pressure of about 0.1–0.5 bar. GC spectra were acquired on a Hewlett–Packard HP 6890 Series GC system equipped with a HP 5 column (30 m × 0.32 mm, film thickness 0.25  $\mu\text{m}$ ) by using hydrogen as carrier gas. IR spectra were recorded on a Digilab FTS 4000 equipped with a MKII Golden Gate Single Reflection ATR System. Melting points were determined with a Stuart SMP10 and are uncorrected. GC-MS (EI) and HR-MS were performed on a Waters-Micromass GC TOF.

### General Procedure for the Rhodium-Catalyzed Homocoupling

A solution of the corresponding boronic acid (1.00 mmol), TEMPO (313 mg, 2.00 mmol) and tris(triphenylphosphine)rhodium(I) chloride (28 mg, 30  $\mu\text{mol}$ ) in dioxane (1.0 mL) and H<sub>2</sub>O (0.1 mL) was heated in a sealed tube at 130 °C for 2 h. The reaction mixture was filtered through a plug of silica gel (MTBE as eluent). The filtrate was concentrated under vacuum, and the residue was purified by FC.

### Rhodium-Catalyzed Homocoupling by using Oxygen

A flask containing a solution of phenylboronic acid (122 mg, 1.00 mmol) and tris(triphenylphosphine)rhodium(I) chloride (28 mg, 30  $\mu\text{mol}$ ) in dioxane (1.0 mL) and H<sub>2</sub>O (0.1 mL) was equipped with a balloon filled with O<sub>2</sub>. The reaction mixture was stirred at 70 °C for 14 h and filtered through a plug of silica gel (MTBE as eluent). The filtrate was concentrated under vacuum, purification of the residue by FC (pentane/MTBE = 100:1) afforded biphenyl as a white solid; yield: 35 mg (0.23 mmol, 45%).

### Supporting Information

Further experimental procedures and compound characterization data are available as Supporting Information.

### Acknowledgements

We thank Novartis Pharma AG (Young Investigator Award to A.S.) and the Fonds der Chemischen Industrie for a stipend (T.V.). Ciba Specialty Chemicals is acknowledged for donation of chemicals (TEMPO, nitroxide **1**).

### References

- [1] G. Bringmann, M. Breuning, S. Tasler, *Synthesis* **1999**, 525–558, and references cited therein.
- [2] a) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1469; b) L. Pu, *Chem. Rev.* **1998**, *98*, 2405–2494.
- [3] A. Kraft, A. C. Grimsdale, A. B. Holmes, *Angew. Chem. Int. Ed.* **1998**, *37*, 402–428.
- [4] J. Roncali, *Chem. Rev.* **1992**, *92*, 711–738.
- [5] For leading references see: a) M. J. Burns, I. J. S. Fairlamb, A. R. Kapdi, P. Sehnal, R. J. K. Taylor, *Org. Lett.* **2007**, *9*, 5397–5400; b) Y. Yamamoto, *Synlett* **2007**, 1913–1916; c) C. Adamo, C. Amatore, I. Ciofini, A. Jutand, H. Lakmini, *J. Am. Chem. Soc.* **2006**, *128*, 6829–6836; d) C. Zhou, R. C. Larock, *J. Org. Chem.* **2006**, *71*, 3184–3191; e) H. Yoshida, Y. Yamaryo, J. Ohshita, A. Kunai, *Tetrahedron Lett.* **2003**, *44*, 1541–1544; f) D. J. Koza, E. Carita, *Synthesis* **2002**, 2183–2186; g) A. Lei, X. Zhang, *Tetrahedron Lett.* **2002**, *43*, 2525–2528; h) M. Moreno-Mañas, M. Pérez, R. Pleixats, *J. Org. Chem.* **1996**, *61*, 2346–2351; i) Z. Z. Song, H. N. C. Wong, *J. Org. Chem.* **1994**, *59*, 33–41.
- [6] a) H. Sakurai, H. Tsunoyama, T. Tsukuda, *J. Organomet. Chem.* **2007**, *692*, 368–374; b) S. Carrettin, J. Guzman, A. Corma, *Angew. Chem. Int. Ed.* **2005**, *44*, 2242–2245; c) C. González-Arellano, A. Corma, M. Iglesias, F. Sánchez, *Chem. Commun.* **2005**, 1990–1992; d) A. S. Demir, Ö. Reis, M. Emrullahoglu, *J. Org. Chem.* **2003**, *68*, 10130–10134; e) J. R. Falck, S. Mohapatra, M. Bondlela, S. K. Venkataraman, *Tetrahedron Lett.* **2002**, *43*, 8149–8151; f) H. Mizuno, H. Sakurai, T. Amaya, T. Hirao, *Chem. Commun.* **2006**, 5042–5044.
- [7] For Rh-catalyzed oxidative homocoupling of aryl- and alkenylmercury compounds see: R. C. Larock, J. C. Bernhardt, *J. Org. Chem.* **1977**, *42*, 1680–1684; for Rh-catalyzed oxidative homocoupling of phenols see: A. G. M. Barrett, T. Itoh, E. M. Wallace, *Tetrahedron Lett.* **1993**, *34*, 2233–2234.
- [8] *Modern Rhodium-Catalyzed Organic Reactions*, (Ed.: P. A. Evans), Wiley-VCH, Weinheim, **2005**.
- [9] For example: a) M.-Y. Ngai, J.-R. Kong, M. J. Krische, *J. Org. Chem.* **2007**, *72*, 1063–1072; b) S. Gatard, R. Çelenligil-Çetin, C. Guo, B. M. Foxman, O. V. Ozerov, *J. Am. Chem. Soc.* **2006**, *128*, 2808–2809; c) R. Shintani, T. Yamagami, T. Hayashi, *Org. Lett.* **2006**, *8*, 4799–4801; d) X. Wang, B. S. Lane, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 4996–4997.
- [10] For examples in C–H activation and arylation: a) M. Montag, L. Schwartzburd, R. Cohen, G. Leitus, Y. Ben-David, J. M. L. Martin, D. Milstein, *Angew. Chem. Int. Ed.* **2007**, *46*, 1901–1904; b) S. Proch, R. Kempe, *Angew. Chem. Int. Ed.* **2007**, *46*, 3135–3138; c) J. C. Lewis, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2007**, *129*, 5332–5333; d) S. Yanagisawa, T. Sudo, R. Noyori, K. Itami, *J. Am. Chem. Soc.* **2006**, *128*, 11748–11749; e) X. Wang, B. S. Lane, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 4996–4997; f) K. Ueura, T. Satoh, M. Miura, *Org. Lett.* **2005**, *7*, 2229–2231; g) R. B. Bedford, S. J. Coles, M. B. Hursthouse, M. E. Limmert, *Angew. Chem. Int. Ed.* **2003**, *42*, 112–114; h) S. Oi, S.-i. Wata-

- nabe, S. Fukita, Y. Inoue, *Tetrahedron Lett.* **2003**, *44*, 8665–8668.
- [11] T. Vogler, A. Studer, *Org. Lett.* **2008**, *10*, 129–131.
- [12] T. Vogler, A. Studer, *Synthesis* **2008**, 1979–1993.
- [13] Other solvents such as toluene, DME, acetonitrile, THF, DMF were tested and were found to lead to lower yields.
- [14] P. M. P. Gois, A. F. Trindade, L. F. Veiros, V. André, M. T. Duarte, C. A. M. Afonso, S. Caddick, F. G. N. Cloke, *Angew. Chem. Int. Ed.* **2007**, *46*, 5750–5753.
-