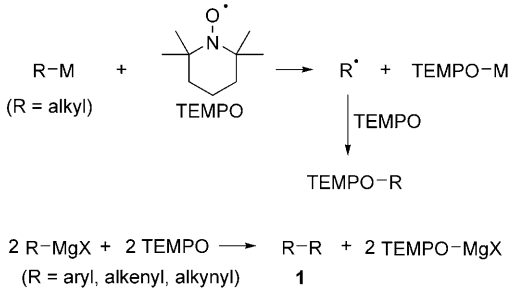
Synthetic Methods

DOI: 10.1002/anie.200804197

Oxidative Homocoupling of Aryl, Alkenyl, and Alkynyl Grignard Reagents with TEMPO and Dioxygen**

*Modhu Sudan Maji, Thorben Pfeifer, and Armido Studer**

The treatment of various alkyl organometallic compounds R–M (M = Li, Mg, Zn, Cu, Sm, Ti) with 2 equivalents of 2,2,6,6-tertramethylpiperidine-*N*-oxyl radical (TEMPO) has been reported to lead to the corresponding alkoxyamines TEMPO–R.[1] In these processes, one equivalent of TEMPO is required for oxidation of the organometallic species to the corresponding C-centered radical, which is subsequently trapped by the second equivalent of TEMPO to provide an alkoxyamine (Scheme 1).[2] Alkyl catecholboranes have been



Scheme 1. Reaction of TEMPO with organometallic compounds.

shown by Renaud and co-workers to react with TEMPO in a similar way.[3] To our knowledge, the reactivity of TEMPO towards aryl, alkenyl, and alkynyl magnesium compounds has not been investigated previously. As aryl, alkenyl, and alkynyl radicals are destabilized, oxidation of the corresponding magnesium compounds by TEMPO should not occur. We therefore expected a different reaction outcome. Herein we report a highly efficient homocoupling of organomagnesium compounds with TEMPO. Such reactions are usually conducted with transition-metal catalysts.[4] In pioneering studies, Knochel, Mayr, and co-workers showed recently that the homocoupling of Grignard reagents proceeds efficiently in the presence of a stoichiometric amount of the organic oxidant 3,3′,5,5′-tetra-*tert*-butyl-4,4′-diphenoquinone.[5]

For initial studies, we chose the conversion of PhMgBr into biphenyl (**1a**) with TEMPO (1.08 equiv) in THF (Table 1). When the reaction was carried out at room temperature for 10 min, **1a** was obtained in 78% yield (Table 1, entry 1). The yield was improved by extending the reaction time to 40 min (92%; Table 1, entries 2 and 3). An even better result was observed when the reaction was carried out at reflux in THF (98%; Table 1, entry 4). Compound **1a** was also obtained in 98% yield from PhMgCl. Thus, the halide ion of the Grignard reagent does not appear to influence the reaction (Table 1, entry 5). All subsequent experiments were conducted in THF at reflux with organomagnesium bromides. To study the scope and limitations of

Table 1: Oxidative homocoupling of RMgBr with TEMPO (1.08 equiv) in THF under different conditions.

Entry	Product	R	*T* [°C]	*t* [min]	Yield [%]
1[a]	**1a**	C_6H_5	20	10	78
2[a]	**1a**	C_6H_5	20	20	91
3[a]	**1a**	C_6H_5	20	40	92
4[a]	**1a**	C_6H_5	66	5	98
5[b]	**1a**	C_6H_5	66	5	98
6	**1b**	4-$CH_3C_6H_4$	66	20	86
7[a]	**1c**	4-CH_3O-C_6H_4	66	10	86
8	**1d**	4-$(CH_3)_2NC_6H_4$	66	15	87
9	**1e**	4-FC_6H_4	66	15	77
10	**1f**	3-$CH_3C_6H_4$	66	30	84
11[a]	**1g**	3-CH_3O-C_6H_4	66	10	87
12	**1h**	2-$CH_3C_6H_4$	66	30	81
13	**1i**	2-$CH_3OC_6H_4$	66	20	79
14	**1j**	β-naphthyl	66	10	96
15[c]	**1k**	$C_6H_5CH{=}CH$	66	25	50[d]
16[c]	**1l**	*n*-$C_6H_{13}CH{=}CH$	66	25	64[d]
17	**1m**	$C_6H_5C{\equiv}C$	20	4320	55
18	**1m**	$C_6H_5C{\equiv}C$	66	240	90
19	**1n**	4-$CH_3OC_6H_4C{\equiv}C$	66	360	86
20	**1o**	4-$CF_3C_6H_4C{\equiv}C$	66	300	94
21	**1p**	*n*-$C_6H_{13}C{\equiv}C$	66	300	94
22	**1q**	$C_6H_{11}C{\equiv}C$	66	300	76
23	**1r**	TMS-C≡C	66	300	65
24	**1s**	1-*c*-hexenyl-C≡C	66	300	72

[a] The aryl magnesium bromide was used as received from Acros after titration. [b] The reaction was conducted with C_6H_5MgCl (Acros). [c] The Grignard reagent *trans*-R′CH=CHMgX was prepared by the transmetalation of *trans*-R′CH=CHI with *i*PrMgCl; see Ref. [7]. [d] *E*,*E*/*E*,*Z*/*Z*,*Z* > 99:1:0.

[*] M. S. Maji, Prof. Dr. A. Studer
NRW Graduate School of Chemistry
Organisch-Chemisches Institut, Westfälische Wilhelms-Universität
Corrensstrasse 40, 48149 Münster (Germany)
Fax: (+49) 251-83-36523
E-mail: studer@uni-muenster.de
T. Pfeifer
Institut für Anorganische und Analytische Chemie
Westfälische Wilhelms-Universität
Corrensstrasse 30, 48149 Münster (Germany)

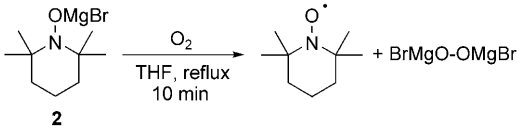
[**] A.S. thanks the Novartis Pharma AG for financial support (Novartis Young Investigator Award). We thank the NRW Graduate School of Chemistry for support of our work (scholarship to M.S.M.).
TEMPO = 2,2,6,6-tertramethylpiperidine-*N*-oxyl.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200804197.

the homocoupling, various organomagnesium compounds were treated under the optimized conditions with TEMPO. Commercially available Grignard reagents were used as received after titration. All other Grignard reagents were freshly prepared from the corresponding bromides with magnesium turnings and a catalytic amount of I_2 and titrated before use.

Aryl Grignard reagents with electron-rich and electron-poor substituents in the *para* position reacted to give the corresponding biphenyls **1b–e** in high yield (77–87%; Table 1, entries 6–9). Similar results were obtained with *meta*-substituted aryl Grignard compounds (Table 1, entries 10 and 11), and *ortho*-substituted congeners were transformed into the corresponding biphenyls **1h** and **1i** in good yield (Table 1, entries 12 and 13). The best result was observed for the oxidative coupling of β-naphthylmagnesium bromide (96%; Table 1, entry 14). Moreover, we found that the oxidative homocoupling of vinyl Grignard reagents to provide dienes is possible with TEMPO: β-Styrylmagnesium chloride and $C_6H_{13}CH{=}CHMgCl$ were transformed into the dienes **1k** and **1l**, respectively (Table 1, entries 15 and 16). Alkynyl magnesium compounds also underwent TEMPO-mediated coupling;[6] however, longer reaction times (4–6 h) were necessary. At room temperature, the homocoupling of $C_6H_5C{\equiv}CMgBr$ was very slow (Table 1, entry 17); at reflux in THF, however, $C_6H_5C{\equiv}CMgBr$ and other aryl alkynyl organomagnesium compounds underwent highly efficient homocoupling to give the corresponding products **1m–o** in 86–94% yield (Table 1, entries 18–20). The diynes **1p** and **1q** were formed in good yield from the corresponding alkyl alkynyl Grignard reagents (Table 1, entries 21 and 22), and trimethylsilylethynyl magnesium bromide was transformed into **1r** in 65% yield (Table 1, entry 23). Enynes also underwent homocoupling under these conditions (Table 1, entry 24).

Importantly, we found that TEMPO–MgBr (**2**), which was formed as a by-product, was reoxidized readily to TEMPO with dioxygen in refluxing THF within 10 min, as indicated by TLC [Eq. (1)]. Following this observation, we investigated the TEMPO-catalyzed aerobic oxidation of aryl Grignard reagents.[8]



2 (1)

When O_2 was bubbled through a solution of PhMgBr at room temperature in the absence of TEMPO, biphenyl (**1a**) was obtained in 5% yield. The same experiment at reflux in THF gave **1a** in 12% yield. We repeated this experiment in the presence of TEMPO (20 mol%): Biphenyl (**1a**) was isolated in 61% yield along with phenol (24%). Thus, the reoxidation of TEMPO–MgBr with O_2 is too slow to completely suppress the reaction of PhMgBr with O_2. We therefore developed a procedure for the in situ recycling of TEMPO. To this end, PhMgBr (14 mol%) was treated with TEMPO (14 mol%) for 10 min in THF at reflux. The reaction mixture was then purged with dioxygen for another 10 min. The renewed addition of PhMgBr (14 mol%, 10 min reaction time) was followed by purging with O_2 (10 min).[9] The reaction sequence (addition of PhMgBr and treatment with O_2), which takes about 20 min, was then repeated a further six times.[10] With in situ recycling by this procedure, **1a** was obtained in 81% yield along with phenol in 8% yield (Table 2, entry 1). At room temperature under similar conditions (with 15 mol% TEMPO), biphenyl was formed in 74% yield (Table 2, entry 2). A decrease in the amount of TEMPO used to 10 mol% led to the formation of **1a** in slightly lower yield (Table 2, entry 3).

Table 2: Homocoupling of RMgBr with catalytic amounts of TEMPO.

Entry	Product	R	TEMPO [mol%]	*t* [min]	Yield [%]
1	**1a**	C_6H_5	14	10	81
2[a]	**1a**	C_6H_5	15	25	74
3	**1a**	C_6H_5	10	10	76
4	**1b**	$4\text{-}CH_3C_6H_4$	14	15	80
5	**1c**	$4\text{-}CH_3OC_6H_4$	14	10	81
6	**1d**	$4\text{-}(CH_3)_2NC_6H_4$	15	15	84
7	**1e**	$4\text{-}FC_6H_4$	15	10	61
8	**1f**	$3\text{-}CH_3C_6H_4$	15	15	63
9	**1g**	$3\text{-}CH_3OC_6H_4$	15	10	57
10	**1h**	$2\text{-}CH_3C_6H_4$	15	25	44
11	**1i**	$2\text{-}CH_3OC_6H_4$	14	25	70
12	**1j**	β-Naphthyl	15	10	81
13[b]	**1k**	$C_6H_5CH{=}CH$	18	25	64[c]

[a] The reaction was conducted at room temperature. [b] The Grignard reagent was prepared from *trans*-$C_6H_5CH{=}CHBr$ with Mg turnings. [c] The product was obtained as a mixture of isomers: *E*,*E*/*E*,*Z*/*Z*,*Z* 18:4:1.

We tested the aerobic TEMPO-mediated homocoupling under the optimized conditions with other substrates. For less reactive Grignard reagents, we increased the reaction time (up to 25 min; see Table 2). The *para*-substituted biphenyl derivatives **1b–e** were isolated in moderate to good yield (61–84%) when a catalytic amount of TEMPO was used (14 or 15 mol%). Thus, the yields were slightly lower than for the equivalent reactions in the presence of a stoichiometric amount of TEMPO (see Table 1), but still good. Aryl Grignard compounds with *meta* and *ortho* substituents underwent homocoupling in the presence of substoichiometric amounts of TEMPO in 44–70% yield (Table 2, entries 8–11). A very good result was observed with β-naphthylmagnesium bromide (Table 2, entry 12), and dienes were also accessible by this method (Table 2, entry 13).

Since the oxidation of alkynyl magnesium bromide derivatives with TEMPO was slow, we did not believe that the procedure for the in situ regeneration of TEMPO would be efficient with these systems. To our surprise, we found that alkynyl magnesium bromide derivatives could transformed into the corresponding diynes with dioxygen without the addition of TEMPO. Thus, when O_2 was bubbled through a solution of $C_6H_5C{\equiv}CMgBr$ in THF at reflux for 2 h, the diyne **1m** was obtained in 60% yield (Table 3, entry 2). The same

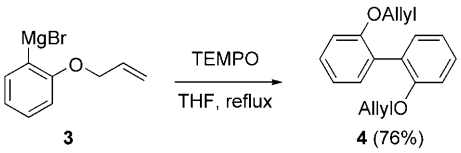
Table 3: Oxidative homocoupling of RC≡CMgBr with dioxygen.

Entry	Product	R	*T* [°C]	*t* [h]	Yield [%]
1	**1m**	$C_6H_5C{\equiv}C$	20	2	10
2	**1m**	$C_6H_5C{\equiv}C$	66	2	60
3[a]	**1m**	$C_6H_5C{\equiv}C$	66	2	–
4	**1n**	4-$CH_3OC_6H_4C{\equiv}C$	66	2	62
5	**1o**	4-$CF_3C_6H_4C{\equiv}C$	66	2	52
6	**1p**	*n*-$C_6H_{13}C{\equiv}C$	66	4	46
7	**1q**	$C_6H_{11}C{\equiv}C$	66	4	41

[a] The reaction was conducted in the absence of O_2.

experiment at room temperature provided **1m** in only 10% yield (Table 3, entry 1). In the absence of O_2 under otherwise identical conditions, **1m** was not identified in the reaction mixture (Table 3, entry 3). To our knowledge, the high-yielding homocoupling of Grignard compounds with dioxygen in the absence of a transition-metal catalyst is unprecedented.[11] Aryl alkynyl magnesium compounds with *para* substituents also underwent homocoupling under aerobic conditions in satisfactory yield (Table 3, entries 4 and 5). Lower yields were observed for the oxidative homocoupling of alkyl alkynyl organomagnesium derivatives (Table 3, entries 6 and 7).

The mechanism of the TEMPO-mediated oxidation of organomagnesium compounds is not yet known. Since the treatment of the Grignard reagent **3** with TEMPO afforded exclusively the homocoupling product **4** (76%), without any trace of products derived from a 5-*exo* radical cyclization, we exclude free aryl radicals as intermediates at present [Eq. (2)].



3 **4** (76%) (2)

As the mechanism was not clear, and aryl Grignard reagents are known to undergo homocoupling in the presence of Mn and Fe catalysts under oxidative conditions,[8] we decided to measure the concentrations of transition metals in our reaction mixtures (Table 4; see also the Supporting Information). We analyzed for the presence of Fe and Mn, but also for traces of Pd and Cu, as these transition metals are also known to mediate the homocoupling of Grignard reagents. The measurements were performed on reaction mixtures for an aryl coupling and an alkynyl coupling.

Palladium was detected in the reaction mixtures, but could not be quantified (< 0.01 ppm). In the reaction mixture for the aryl homocoupling, we found Mn and Fe, each at a concentration of around 8 ppm, and Cu (1 ppm). Slightly larger amounts of these transition metals were detected in the crude reaction mixture for the alkynyl homocoupling (Mn: 22 ppm, Fe: 11 ppm, Cu: 2 ppm). The alkynyl Grignard reagent was prepared by using commercially available *i*PrMgCl, in which we identified a significant amount of Mn

Table 4: Trace analysis (all data in ppm = $\mu g\,g^{-1}$).

Metal	Table 1 entry 10	Table 3 entry 2	TEMPO	*i*PrMgCl
^{55}Mn	7.78 ± 0.28	21.5 ± 0.1	0.28 ± 0.03	12.6 ± 0.03
^{56}Fe	8.35 ± 0.39	11.2 ± 1.6	26.6 ± 2.7	1.81 ± 1.22
^{63}Cu	1.19 ± 0.49	2.12 ± 1.03	< LOQ[a]	1.14 ± 0.61
^{105}Pd	< LOQ[a]	< LOQ[a]	< LOQ[a]	< LOQ[a]

[a] LOQ = limit of quantification.

(13 ppm). Another source of transition metals, particularly of Fe (27 ppm), is TEMPO. We also analyzed the solvent used (THF). However, all metals tested for were below the limit of quantification. In the reported oxidative iron- and manganese-catalyzed homocoupling reactions, 5 mol% of the metal had to be used.[8] Copper-mediated homocoupling reactions of aryl Grignard reagents are generally conducted with a stoichiometric amount of a copper salt,[12] and copper-catalyzed acetylide homocoupling reactions require around 5 mol% of the copper catalyst.[13] Therefore, we believe that it is unlikely that the trace amounts of transition metals present are able to catalyze these coupling reactions efficiently. As also suggested by Knochel, Mayr, and co-workers, we currently assume that these coupling reactions proceed without the aid of a transition metal.

In conclusion, we have described "transition-metal-free" homocoupling reactions of various organomagnesium compounds in the presence of commercially available TEMPO as an organic oxidant. The reactions could be conducted with 15 mol% of TEMPO by using dioxygen as the terminal oxidant. Moreover, we found that alkynyl magnesium compounds underwent homocoupling to provide the corresponding diynes upon treatment with dioxygen at higher temperatures in the absence of a catalyst.

Received: August 25, 2008
Published online: November 3, 2008

Keywords: biaryls · C–C coupling · dienes · diynes · nitroxides

[1] G. M. Whitesides, T. L. Newirth, *J. Org. Chem.* **1975**, *40*, 3448; T. Nagashima, D. P. Curran, *Synlett* **1996**, 330; P. I. Dalko, *Tetrahedron Lett.* **1999**, *40*, 4035.
[2] For reviews on the use of TEMPO in synthesis, see: a) T. Vogler, A. Studer, *Synthesis* **2008**, 2163; b) A. Studer, T. Schulte, *Chem. Rec.* **2005**, *5*, 27; c) A. Studer, *Chem. Soc. Rev.* **2004**, *33*, 267; d) A. Studer, *Chem. Eur. J.* **2001**, *7*, 1159; for the use of TEMPO as an oxidant in rhodium-catalyzed C–H arylation reactions, see: e) T. Vogler, A. Studer, *Org. Lett.* **2008**, *10*, 129.
[3] A.-P. Schaffner, P. Renaud, *Eur. J. Org. Chem.* **2004**, 2291; for a review, see: C. Ollivier, P. Renaud, *Chem. Rev.* **2001**, *101*, 3415.
[4] J. Hassan, M. Sévignon, C. Cozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359.
[5] A. Krasovskiy, A. Tishkov, V. del Amo, H. Mayr, P. Knochel, *Angew. Chem.* **2006**, *118*, 5132; *Angew. Chem. Int. Ed.* **2006**, *45*, 5010.
[6] For the coupling of alkynyl metal compounds with dinitrogen tetroxide, see: C. J. Woltermann, H. Shechter, *Helv. Chim. Acta* **2005**, *88*, 354.
[7] a) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem.* **2003**, *115*,

4438; *Angew. Chem. Int. Ed.* **2003**, *42*, 4302; b) H. Ren, A. Krasovskiy, P. Knochel, *Org. Lett.* **2004**, *6*, 4215.
[8] G. Cahiez, A. Moyeux, J. Buendia, C. Duplais, *J. Am. Chem. Soc.* **2007**, *129*, 13788.
[9] It was not necessary to stir the solution to remove the remaining O_2 (after purging with O_2) prior to the renewed addition of PhMgBr. (The product was obtained in the same yield with or without this extra step.)
[10] The following amounts of PhMgBr were added: 13 mol% in the third and fourth cycles, 12 mol% in the fifth and sixth cycles, and 11 mol% in the seventh and eighth cycles.
[11] For transition-metal-catalyzed aerobic oxidations, see: J. Piera, J.-E. Bäckvall, *Angew. Chem.* **2008**, *120*, 3558; *Angew. Chem. Int. Ed.* **2008**, *47*, 3506.
[12] a) B. H. Lipshutz, K. Siegmann, E. Garcia, *Tetrahedron* **1992**, *48*, 2579; b) R. S. Coleman, E. B. Grant, *Tetrahedron Lett.* **1993**, *34*, 2225; c) C. M. P. Kronenburg, C. H. M. Amijs, P. Wijkens, J. T. B. Jastrzebski, G. van Koten, *Tetrahedron Lett.* **2002**, *43*, 1113.
[13] A. S. Hay, *J. Org. Chem.* **1962**, *27*, 3320.

