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Transition-Metal-Free Sonogashira-Type Coupling of *ortho*-Substituted Aryl and Alkynyl Grignard Reagents by Using 2,2,6,6-Tetramethylpiperidine-*N*-oxyl Radical as an Oxidant

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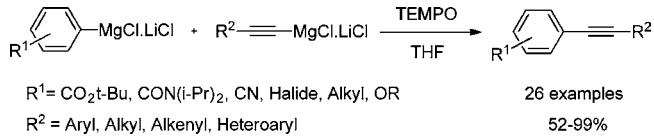
ABSTRACT



Cross coupling of aryl, alkenyl, and alkynyl magnesium compounds by using 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO) as an environmentally benign organic oxidant is described. This coupling reaction can be performed without adding any transition metal on various *ortho*-substituted aryl and alkynyl Grignard reagents. Importantly, functional groups such as esters, amides, and cyanides are shown to be tolerated under the reaction conditions.

Transition-metal-catalyzed Sonogashira cross coupling of terminal alkynes with aryl or alkenyl halides is one of the most widely used methods to build up compounds bearing an internal alkyne moiety.[1] This structural motif can be found in biologically active compounds, in fine chemicals, and also in conjugated polymers.[2] The original Sonogashira coupling protocol uses two transition metal catalysts, a Pd(II)-salt and CuI as the cocatalyst, along with a larger amount of an amine.[3] It is meanwhile well established that Sonogashira couplings can also be accomplished with Pd catalysts in the absence of any copper salt[4] or by using non Pd-based transition metal catalysts.[5] An alternative method to C(sp2)−C(sp) bond formation was developed by Knochel who showed that at low temperature mixed aryl alkynyl organocuprates undergo cross coupling to deliver the corresponding Sonogashira products by using chloranil as an oxidant.[6a] However, a stoichiometric amount of Cu was necessary for these reactions.

More recently, Cahiez reported on Mn-catalyzed Sonogashira-type couplings between aryl and alkynyl Grignard reagents by using molecular oxygen as an oxidant.[6b] There are only very few reports on transition-metal-free Sonogash-

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(2) Nielsen, M. B.; Diederich, F. *Chem. Rev.* **2005**, *105*, 1837.

(3) (a) Dieck, H. A.; Heck, F. R. *J. Organomet. Chem.* **1975**, *93*, 259. (b) Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253. (c) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

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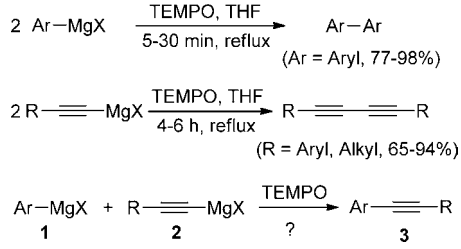
ira-type coupling processes,[7] and to the best of our knowledge, transition-metal-free cross coupling between aryl and alkynyl Grignard reagents are not known. Herein we describe the first results on highly efficient coupling reactions of aryl with alkynyl Grignard reagents by using the 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO)[8] as an environmentally benign commercially available oxidant.

Transition-metal-free oxidative homocoupling of Grignard reagents has recently gained attention.[9] Along this line, we reported on homocoupling reactions of aryl, alkenyl, and alkynyl Grignard reagents by using TEMPO as an oxidant (Scheme 1).[10] More recently, we have also successfully

Scheme 1. Oxidative Homocoupling of Aryl and Alkynyl Grignard Reagents Using TEMPO and Planned Cross Coupling of **1** and **2**

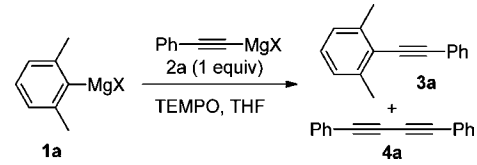


applied these processes for preparation of various conjugated polymers.[11]

During these studies, we made the important observation that TEMPO-mediated homocoupling of aryl Grignard reagents occurs far faster as compared to the analogous reaction with alkynyl Grignard reagents.[10] Moreover, we found that sterically demanding aryl Grignard reagents either react slowly or do not react at all with TEMPO.[10b] On the basis of these two observations, we assumed that transition-metal-free cross coupling reactions between aryl **1** and alkynyl Grignard reagents **2** to form Sonogashira products **3** by using TEMPO as an oxidant should be feasible.

The Grignard reagent **1a** used in our initial studies was generated via I−Mg-exchange reaction of 2,6-dimethyliodobenzene with *i*-PrMgCl·LiCl,[12] and Mg-acetylide **2a** was readily obtained via deprotonation of phenylacetylene with *i*-PrMgCl·LiCl.[10] Both yield and **3a**/**4a** selectivity were improved by using 1.6 equiv of aryl Grignard reagent **1a** (Table 1, entry 2). Upon increasing the amount of **1a** to 2.0

Table 1. Oxidative Coupling between **1a** and **2a** at 66 °C under Different Conditions



entry	**1a** (equiv)	tempo (equiv)	time [h]	**3a**[a] [%]	**4a** [%]
1	1	2.20	1.5	60[b]	18[c]
2	1.6	2.86	3.0	79[b]	7[c]
3	2.0	3.30	0.75	71	<2%[d]
4	2.0	3.30	2.5	84	<2%[d]
5	2.5	3.85	2.5	90	<2%[d]
6	2.5	2.16	2.5	61	<2%[d]
7[e]	2.5	3.85	72	76	<2%[d]
8[f]	2.5	3.85	2.5	40	<2%[d]
9[g]	2.5	3.85	2.5	75	<2%[d]
10[h]	2.5	3.85	2.5	45	<2%[d]

[a] Isolated yield. [b] Isolated as a mixture of **3a** and **4a**. [c] Yield was calculated by ^{1}H NMR analysis from the **3a**/**4a** mixture. [d] In GC, **4a** was identified in traces. [e] Run at 25 °C. [f] Aryl Grignard was generated from 2,6-dimethylbromobenzene by using Mg-turnings, and phenyl alkynyl Grignard was generated by using *i*-PrMgCl. [g] Aryl Grignard was generated from 2,6-dimethylbromobenzene by using Mg-turnings in the presence of 1.0 equiv of LiCl. [h] Aryl Grignard **1a** was prepared from 2,6-dimethylbromobenzene via Br−Li exchange with *t*-BuLi followed by Li−Mg exchange by using $MgBr_2$.

equiv, yield further increased to 71% without diminishing the **3a**/**4a** selectivity (45 min, entry 3). A slightly better yield was noted by extending the reaction time to 2.5 h (entry 4). The best result was obtained when 2.5 equiv of **1a** and 3.85 equiv of TEMPO were used in the coupling reaction (90%, entry 5). Decreasing the amount of TEMPO provided a worse result (61%, entry 6). Selective cross coupling could also be achieved at room temperature (entry 7). However, reaction time had to be extended to 72 h. To check whether aryl bromides can also be used as precursors, we generated Grignard **1a** from 2,6-dimethylbromobenzene by using Mg-turnings. Oxidative cross coupling with **2a** occurred with excellent **3a**/**4a** selectivity; however, yield was moderate (40%, entry 8). Importantly, yield was improved to 75% when Grignard generation was performed in the presence of LiCl, clearly showing that also the cheaper aryl bromides are suitable substrates for our oxidative coupling (entry 9).[13] However, when Grignard **2a** was generated via Br−Li exchange followed by transmetalation with $MgBr_2$·OEt_2,[11]

(7) (a) Luque, R.; Macquarrie, D. J. *Org. Biomol. Chem.* **2009**, *7*, 1627. (b) Prüger, B.; Hofmeister, G. E.; Jacobsen, C. B.; Alberg, D. G.; Nielsen, M.; Jørgensen, K. A. *Chem.—Eur. J.* **2010**, *16*, 3783. (c) Protti, S.; Fagnoni, M.; Albini, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5675. (d) DeRoy, P. L.; Surprenant, S.; Laperle, M. B.; Yoakim, C. *Org. Lett.* **2007**, *9*, 2741. (e) Borah, H. N.; Prajapati, D.; Boruah, R. C. *Synlett* **2005**, 2823. (f) Appukkuttan, P.; Dehaen, W.; Eycken, E. V. *Eur. J. Org. Chem.* **2003**, 4713. (g) Leadbeater, N. E.; Marco, M.; Tominack, B. J. *Org. Lett.* **2003**, *5*, 3919.

(8) Review: (a) Vogler, T.; Studer, A. *Synthesis* **2008**, 1979. See also: (b) Vogler, T.; Studer, A. *Org. Lett.* **2008**, *10*, 129. (c) Guin, J.; De Sarkar, S.; Grimme, S.; Studer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8727. (d) Kirchberg, S.; Vogler, T.; Studer, A. *Synlett* **2008**, *18*, 2841. (e) Vogler, T.; Studer, A. *Adv. Synth. Catal.* **2008**, *350*, 1963. (f) Kirchberg, S.; Fröhlich, R.; Studer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4235.

(9) (a) Krasovskiy, A.; Tishkov, A.; del Amo, V.; Mayr, H.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 5010. (b) Woltermann, C. J.; Shechter, H. *Helv. Chim. Acta* **2005**, *88*, 354.

(10) (a) Maji, M. S.; Pfeifer, T.; Studer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9547. (b) Maji, M. S.; Studer, A. *Synthesis* **2009**, 2467.

(11) Maji, M. S.; Pfeifer, T.; Studer, A. *Chem.—Eur. J.* **2010**, *16*, 5872.

(12) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.

(13) Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2219.

the cross coupling product was formed with moderate yield (45%, entry 10).

It is important to note that the side product of our cross coupling reaction derived from the organic oxidant is the TEMPOMgX salt which could readily be reoxidized to TEMPO by purging the reaction mixture with dioxygen.[10a] The mechanism of our TEMPO-mediated oxidative cross coupling reaction between aryl and alkynyl Grignard derivatives is currently not known.

We next studied substrate scope by reacting various alkynyl Grignard reagents **2** with 2.5 equiv of aryl Grignard reagent **1a** under optimized conditions (Table 2). Mg-acetylides **2** were generated from the corresponding terminal alkynes via deprotonation with *i*-PrMgCl·LiCl.[10] Arylalkynyl

Table 2. Oxidative Coupling of **1a** (2.5 equiv) with Various Alkynyl Grignard Reagents by Using TEMPO (3.85 equiv) in Refluxing THF

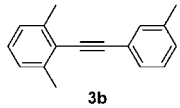
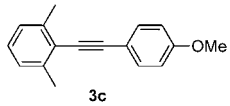
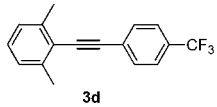
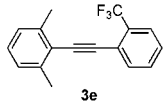
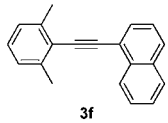
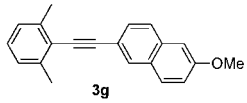
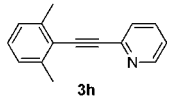
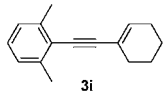
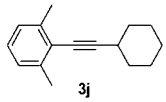
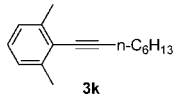
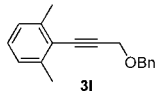
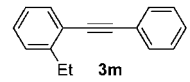
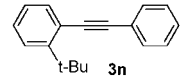
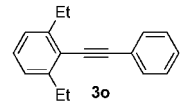
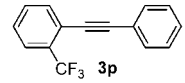
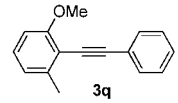
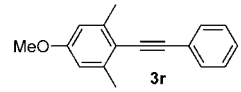
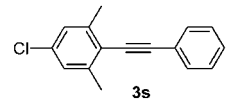
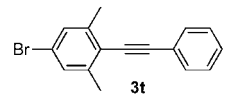
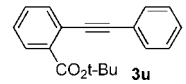
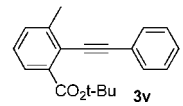
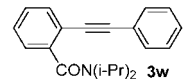
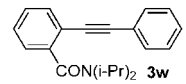
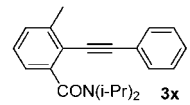
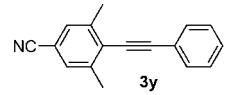
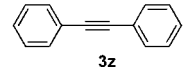
entry	product **3x**	time [h]	yield [%]
1	 **3b**	2.5	92
2	 **3c**	3	80
3	 **3d**	2.5	99
4	 **3e**	2.5	84
5	 **3f**	2.5	75
6	 **3g**	2.5	87
7	 **3h**	2.5	54
8	 **3i**	3	80
9	 **3j**	3	52
10	 **3k**	3	59
11	 **3l**	2.5	75

Table 3. Oxidative Coupling of Various Aryl Grignard Reagents (2.5 equiv) with **2a** by Using TEMPO (3.85 equiv) in THF

entry	product **3x**	temp [°C]	time [h]	yield [%]
1	 **3m**	66	2.5	91[a]
2	 **3n**	66	3	87
3	 **3o**	66	2.5	80
4[b]	 **3p**	66	2.5	84
5	 **3q**	66	3	80
6	 **3r**	66	3	95
7	 **3s**	66	2.5	95
8	 **3t**	66	2.5	92
9	 **3u**	25	24	94
10	 **3v**	25	18	99
11	 **3w**	25	2.5	75[c]
12	 **3w**	0	7.5	85[d]
13	 **3x**	25	2.5	93
14	 **3y**	25	2.5	99[d]
15	 **3z**	66	3	22[f]

[a] Isolated as a mixture with 9% of biaryl homocoupling product. [b] 4 equiv of aryl Grignard reagent was used. [c] 62% of biaryl product, which was readily separated, was formed. [d] The biaryl product was observed by TLC. [e] 3,5-Dimethyl cyano benzene derived from hydrolysis could not be separated from the product. [f] 44% of **4a** and 30% of biphenyl (yield calculated from used amount of phenyl Grignard reagent) were formed. Yield was determined by GC using decane as an internal standard.

Grignard reagents bearing electron-donating as well as electron-withdrawing substituents at the aryl moiety reacted with **1a** to give the cross coupling products **3b**−**e** with excellent yields and selectivities (Table 2, entries 1−4). None of the bisalkyne homocoupling products were identified in these and all following reactions. 1-Naphthylalkynyl and (6-methoxy-2-naphthyl)alkynyl Mg compounds underwent smooth transformation to internal alkynes **3f** and **3g** (entries 5 and 6). Also, heteroarenes were tolerated as shown for the cross coupling of the 2-pyridylalkynyl Grignard with **1a** to give **3h** (entry 7). Interestingly, magnesiated eneynes turned out to be good substrates for our oxidative cross coupling reaction as documented by the preparation of **3i** (80%, entry 8). Less reactive alkylalkynyl Grignard reagents afforded the corresponding cross coupling products **3j**,**k** in slightly lower yields (entries 9 and 10). However, with the benzyloxymethylalkynyl Mg derivative, a good yield for the cross coupling reaction was achieved (see **3l**, entry 11).

Reaction scope was further explored by testing a series of structurally and electronically diverse aryl Grignard reagents in the oxidative cross coupling with **2a**. In all cases, aryl Grignard reagents were generated from the corresponding aryl iodides via I−Mg-exchange reaction by using *i*-PrMgCl·LiCl (Table 3).[12] The 2-ethylphenyl Grignard compound underwent smooth cross coupling to provide **3m** with excellent yield (91%, Table 3, entry 1). Phenyl Grignards bearing the sterically more demanding 2-*tert*-butyl or two *ortho*-ethyl groups provided products **3n** and **3o** with 87% and 80% yield, respectively (entries 2 and 3). Phenyl Grignard reagents with an *ortho*-trifluoromethyl or *ortho*- or *para*-methoxy groups were also suitable coupling partners in the reaction with **2a** (entries 4−6). Sterically hindered aryl Grignards bearing a chloro or bromo substituent at the *para* position also underwent efficient cross coupling to provide **3s** and **3t** with 95% and 92% yield (entries 7 and 8).

Importantly, functionalized aryl Grignard reagents were also suitable candidates for our oxidative coupling reaction. These functional groups bearing aryl-Mg derivatives were generated at 0 °C, and cross coupling was performed at room temperature. Grignard reagents bearing an *ortho*-ester functionality underwent smooth transformation to **3u** and **3v** with excellent yields and selectivities (94 and 99%, entries 9 and 10).[14] With the phenyl Grignard reagent containing an *ortho*-amide functionality, a very fast cross coupling reaction with **2a** was achieved at room temperature providing a 75% yield of the desired alkyne **3w** (entry 11) besides the corresponding biaryl product derived from oxidative homocoupling of the aryl-Mg compound (62%). However, by conducting cross coupling at 0 °C, formation of biaryl could be largely suppressed, and the internal alkyne **3w** was isolated in 85% yield (entry 12). As expected, by installing a methyl group at the *ortho*′ position of the *ortho*-amide functionalized phenyl Grignard reagent, homocoupling of the aryl Grignard did not occur even at room temperature, and the targeted **3x** was isolated in excellent yield (93%, entry 13). A cyano group at the arene was also tolerated under our reaction conditions as shown for the preparation of **3y** which was formed in quantitative yield (entry 14). As expected, an *ortho* substituent is necessary to get high selectivity in these cross coupling processes as documented for the reaction of PhMgCl·LiCl with **2a** (entry 15). In that case, homocoupling of the phenyl-Mg derivative and **2a** was not suppressed.

In conclusion, we have described a highly efficient transition-metal-free cross coupling reaction between aryl and alkynyl Grignard reagents by using TEMPO as a mild organic oxidant. These coupling reactions can be performed on various aryl and alkynyl Grignard reagents. To suppress the unwanted oxidative homocoupling reaction of aryl Grignard reagents, substituents at the *ortho* position of the aryl-Mg derivative are installed. Importantly, functional groups such as esters, amides, and cyanides are tolerated. These reactions are very easy to perform, and products are obtained with high yields.

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Supporting Information Available: Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Reaction did not work on the corresponding methyl esters and for the aryl-Mg derivative derived from 4-iodo-3,5-dimethylphenylpivalate. This is probably due to the instability of the corresponding Ar−Mg species at room temperature.