CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.201300491

Transition-Metal-Free One-Pot Synthesis of Biaryls from Grignard Reagents and Substituted Cyclohexanones

Feng Zhou, Marc-Oliver Simon, and Chao-Jun Li*[a]

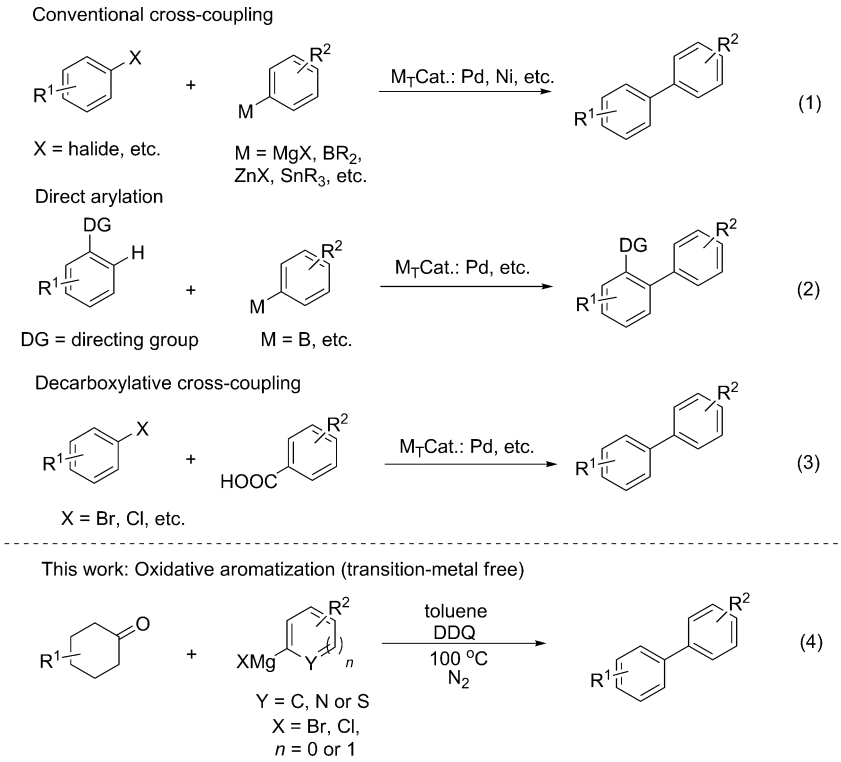
Dedicated to Professor Irina Petrovna Beletskaya

Abstract: A new strategy for the construction of biaryls by a transition-metal-free process is presented. A sequence of a Grignard reaction, dehydration, and oxidative aromatization affords the desired products in a one-pot fashion.

Keywords: biaryls · cyclohexanone · Grignard reaction · one-pot process · transition-metal free

Introduction

The synthesis of biaryl scaffolds, which are widely occurring subunits in a variety of compounds such as biologically active molecules,[1] natural products,[2] polymers, advanced materials, and liquid crystals (LCD),[3] has attracted persistent interest from the chemistry community. Over the past decades, a large number of methods[4] have been developed, among which the most reliable and widely applicable are the transition-metal-catalyzed cross-coupling reactions [Eq. (1), Scheme 1]. These reactions include the Kumada,[5] Suzuki,[6] Negishi,[7] and Stille couplings,[8] along with further refinements thereof. Alternative methods, such as arylation through C–H bond activation [Eq. (2), Scheme 1],[9] have emerged in the past few years. In such processes, the regioselectivity of C–H bond functionalization is the primary challenge. Although this may be accomplished by using a directing group, additional synthetic steps are often required to both install the directing group into the substrate and to manipulate it after the functionalization. A third interesting approach involving a decarboxylative step between an aryl halide and an arene carboxylic acid [Eq. (3), Scheme 1] has recently been established.[10] However, for all of the methods mentioned above, it is essential to utilize transition metals to catalyze the transformations, which may be undesirable. We are particularly interested in exploring the potential of transition-metal-free systems, which might provide an alternative approach for the construction of biaryls.



Scheme 1. Strategies for the synthesis of biaryls.

Recently, our group reported the synthesis of aromatic ethers[11] and amines[12] from non-aromatic precursors by ox-

[a] Dr. F. Zhou, M.-O. Simon, Prof. Dr. C.-J. Li
Department of Chemistry, McGill University
Montreal, QC, H3A 0B8 (Canada)
Fax: (+1) 514-398-3797
E-mail: cj.li@mcgill.ca

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201300491.

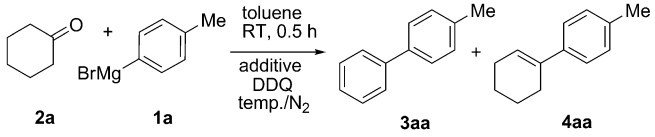
idative aromatization, for which the copper and palladium, respectively, were used as the catalysts. We envisaged that the even more valuable biaryls might also be accessed by using a similar strategy.[13] Herein, we describe a transition-metal-free oxidative aromatization based on a sequential process in one pot, employing a Grignard reagent as the nucleophile, cyclohexanone as the source of one aromatic ring, and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as a hydrogen abstractor [Eq. (4), Scheme 1].

Results and Discussion

We started the investigation by examining the reaction of *para*-tolylmagnesium bromide (**1a**) with cyclohexanone (**2a**). Toluene was selected as the reaction medium because it has been shown to be the most effective solvent for aerobic aromatization.[11,12] DDQ is a well-known oxidant in organic chemistry.[14] For many years, it has been used for the oxidation of allylic and benzylic alcohols[15] as well as allylic ethers[16] to the corresponding carbonyl compounds. Therefore, we decided to use it as the oxidant in the present studies.

The reaction of **1a** and **2a** in the presence of DDQ (2.2 equiv) under a nitrogen atmosphere afforded the expected product **3aa** in 60% yield. Furthermore, an alkene byproduct, **4aa**, which is the hypothetical reaction intermediate (see the Supporting Information), was generated in 30% yield (Table 1, entry 1). We suspected that the dehydration step might not have been efficient enough under these reaction conditions. In an attempt to overcome this, we added 5 mol% *p*-TsOH to improve the efficiency of the dehydration; however, no clear improvement was observed (Table 1, entry 2). Indeed, the yield of byproduct **4aa** decreased to 17%. We then focused our attention on the dehydrogenation and increased the amount of DDQ to 3.5 equivalents. Under these conditions, the desired product **3aa** was obtained in almost quantitative yield (Table 1, entry 3). The

Table 1. Reaction optimization for the transition-metal-free synthesis of biaryls from a Grignard reagent and cyclohexanone.[a]



2a 1a 3aa 4aa

Entry	DDQ [equiv]	Additive	Temp. [°C]	Yield [%][b] (**3aa**/**4aa**)
1	2.2	–	100	60:30
2	2.2	*p*-TsOH (5 mol%)	100	61:17
3	3.5	–	100	99:0
4	3.5	–	50	81:0
5	3.5	–	RT	0:13

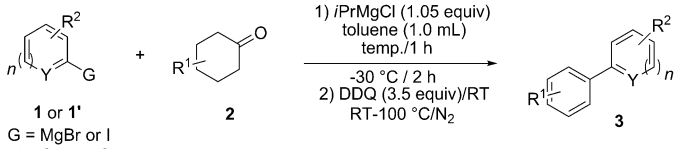
[a] The reaction was conducted under the following conditions: **1a** (0.22 mmol, 1.0 M in THF), **2a** (0.2 mmol), and DDQ in toluene (1.0 mL) under N_2 were heated in a sealed tube at the indicated temperature for 40 h (DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; *p*-TsOH = *para*-toluenesulfonic acid). [b] Yield of the isolated product.

results demonstrated that the amount of DDQ had not been sufficient in our initial studies (Table 1, entries 1 and 2), and presumably one equivalent of DDQ was decomposed[15b,17] by each equivalent of water formed during the reaction. We next examined the reaction at a lower temperature of 50°C, whereupon the yield was reduced to 81% (Table 1, entry 4). When the reaction was attempted at room temperature, none of the desired product **3aa** was detected and only the alkene byproduct **4aa** was obtained in 13% yield (Table 1, entry 5). Thus, *para*-tolylmagnesium bromide **1a** (1.1 equiv), cyclohexanone **2a** (1 equiv), and DDQ (3.5 equiv) in toluene at 100°C under a nitrogen atmosphere were identified as the optimized reaction conditions.

Having established the optimal conditions, the generality of this one-pot biaryl synthesis was explored and the results are summarized in Table 2. The biaryls were obtained very efficiently from the reactions of *para*-tolylmagnesium bromide (**1a**) or phenylmagnesium bromide (**1b**) with substituted cyclohexanones. With cyclohexanone, the reaction generated a 99% yield (Table 2, entry 1). The 4-methyl- and 3-methyl-substituted cyclohexanones (**2b**,**c**) also reacted smoothly to afford the corresponding products in 76–80% yields (Table 2, entries 2, 3, and 8). In the case of 2-methyl-substituted cyclohexanone **2d**, the yield dramatically decreased to 34%, presumably due to steric hindrance (Table 2, entry 4). The reaction of **2e**, bearing a 4-*tert*-butyl group, proceeded efficiently to furnish the product in 94% yield (Table 2, entry 5). Even better reactivity was observed when 4-phenyl-substituted substrate **2f** was used, and an almost quantitative yield of the product was obtained (Table 2, entry 6). However, 2,6-dimethylcyclohexanone **2g** did not afford the corresponding biaryl product, possibly because of the high degree of steric hindrance (Table 2, entry 7).

To further broaden the scope of the reaction, we turned our attention to various Grignard reagents generated in situ. Halogen–metal exchange[18] is a powerful tool for the preparation of functionalized organometallic species; therefore, we decided to prepare Grignard reagents with various functionalities by an iodine–magnesium exchange strategy.[19] It was anticipated that this strategy would be easier and more convenient than using pre-synthesized Grignard reagents. Thus, various aryl and heteroaryl iodides **1c′**–**k′** were converted into the corresponding organomagnesium compounds by treatment with 1.05 equivalents of *i*PrMgCl (2 M in THF) for 1 h at the indicated temperature (Table 2, entries 9–18). When cyclohexanone (**2a**) was added dropwise to a solution of the Grignard reagent generated in situ at −30°C, it reacted rapidly to produce the corresponding intermediate. The respective intermediates then underwent the sequential process in the presence of DDQ to afford a range of functionalized biaryls **3ca**–**ia**, **3ka**, and **3ih**. Substrates with either an electron-withdrawing group (**1c′**) or an electron-donating group (**1d′**–**f′**) reacted smoothly to provide the expected products in good to excellent yields (Table 2, entries 9–12). A 92% yield was obtained when a methoxy group was present at the *ortho*-position of the benzene ring

Table 2. Substrate scope of the transition-metal-free one-pot synthesis of biaryls.[a]



1 or **1'**
G = MgBr or I
Y = C, N or S
n = 0 or 1

2

3

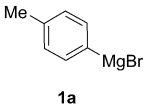
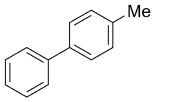
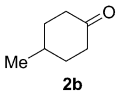
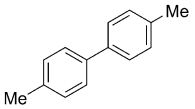
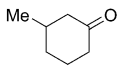
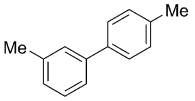
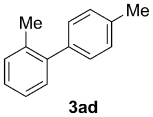
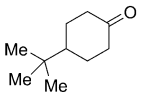
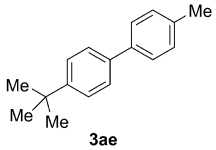
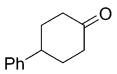
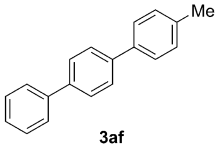
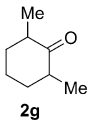
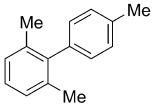
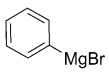
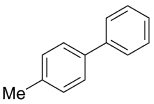
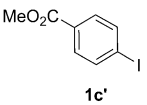
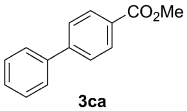
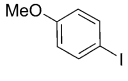
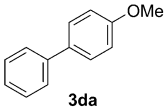
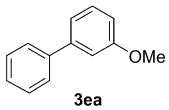
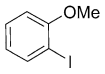
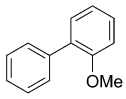
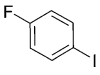
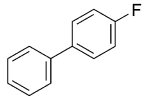
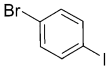
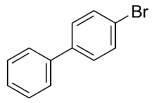
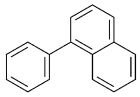
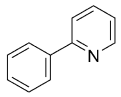
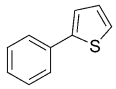
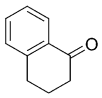
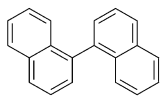
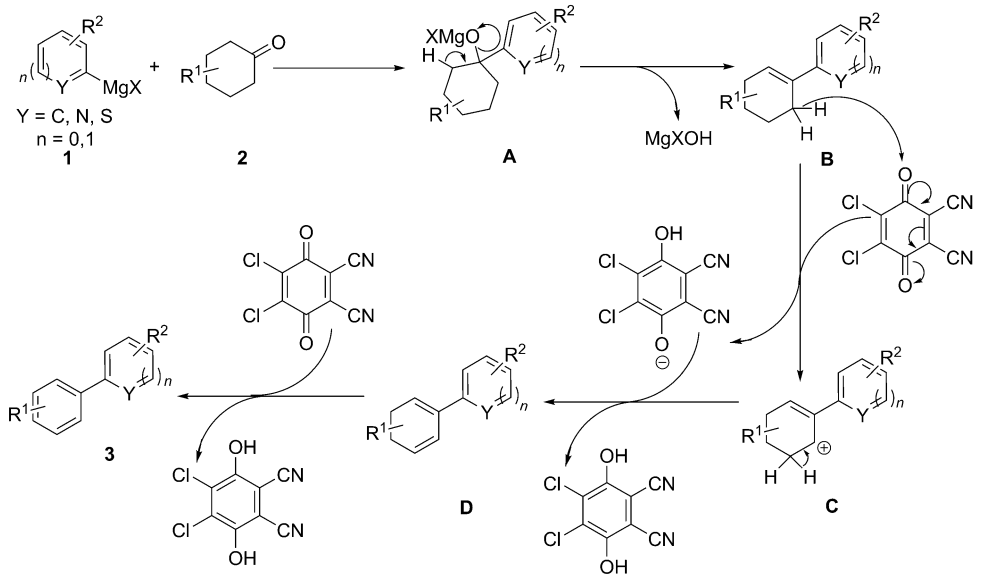
Entry	**1** or **1′**	**2**	**3**	Yield [%][b]
1	 **1a**	 **2a**	 **3aa**	99
2	**1a**	 **2b**	 **3ab**	80
3	**1a**	 **2c**	 **3ac**	76
4	**1a**	 **2d**	 **3ad**	34
5[c]	**1a**	 **2e**	 **3ae**	94
6	**1a**	 **2f**	 **3af**	99
7	**1a**	 **2g**	 **3ag**	0
8	 **1b**	**2b**	 **3bb**	76
9[d]	 **1c'**	**2a**	 **3ca**	86
10[e]	 **1d'**	**2a**	 **3da**	90

Table 2. (Continued)

Entry	**1** or **1′**	**2**	**3**	Yield [%][b]
11[e]	 **1e'**	**2a**	 **3ea**	73
12[e]	 **1f'**	**2a**	 **3fa**	92
13[f]	 **1g'**	**2a**	 **3ga**	78
14[d]	 **1h'**	**2a**	 **3ha**	79
15[e]	 **1i'**	**2a**	 **3ia**	60
16[d,g]	 **1j'**	**2a**	 **3ja**	0
17[f]	 **1k'**	**2a**	 **3ka**	66
18[e]	**1i′**	 **2h**	 **3ih**	28

[a] Reaction conditions: **1a**,**b** (0.22 mmol, 1.0 M in THF) and **2a**–**g** (0.20 mmol; entries 1–8) or **1c′**–**k′** (0.2 mmol), *i*PrMgCl (0.21 mmol, 2.0 M in THF), and **2a**,**h** (0.22 mmol; entries 9–18) with DDQ (3.5 equiv) in toluene (1.0 mL) at 100 °C under N_2 for 40 h. For entries 1–8, Grignard reactions were carried out at room temperature for 0.5 h by using *para*-tolylmagnesium bromide (**1a**) or phenylmagnesium bromide (**1b**) directly; for entries 9–18, *i*PrMgCl was used to generate Grignard reagents in situ and the Grignard reactions were carried out at −30 °C for 2 h. [b] Yield of the isolated product. [c] 4.0 Equivalents of DDQ were used. [d] The Grignard reagents were generated in situ at −30 °C. [e] The Grignard reagents were generated in situ at room temperature. [f] The Grignard reagents were generated in situ at 0 °C. [g] The Grignard reagent was generated in situ at −78 °C.

(Table 2, entry 12), suggesting that once the Grignard reagent had been generated in situ, its addition to the cycloketone was very efficient. Halogenated substrates, bearing fluoro (**1g′**) or bromo substituents (**1h′**), were tolerated in this sequential process, furnishing the desired products in yields of 78 and 79%, respectively (Table 2, entries 13 and 14). When 1-iodonaphthalene (**1i′**) and cyclohexanone (**2a**) were subjected to the optimized reaction conditions, the cor-



Scheme 2. Tentative mechanism for the transition-metal-free formation of biaryls from Grignard reagents and cyclohexanones.

responding product was obtained in 60% yield (Table 2, entry 15). No reaction occurred in the case of 2-iodopyridine (**1j′**), presumably owing to the competitive homo-coupling[20] reaction of the pyridine Grignard reagent (Table 2, entry 16). Subjecting 1-iodothiophene (**1k′**) to the same reaction conditions gave the product in 66% isolated yield (Table 2, entry 17). Finally, the reaction of 1-iodonaphthalene (**1i′**) with 1-tetralone (**2h**) afforded 1,1′-binaphthalene in 28% yield (Table 2, entry 18).

A tentative mechanism that accounts for the formation of the biaryls is illustrated in Scheme 2. The Grignard reagent **1** was generated in situ by iodine–magnesium exchange[18] from the corresponding precursor aryl iodide **1′** and *i*PrMgCl, and then reacted with the requisite substituted cyclohexanone **2** to furnish the intermediate **A**. Subsequent elimination of MgXOH afforded the aryl-substituted alkene intermediate **B**. Transfer of a hydride ion from **B** to the oxygen atom of DDQ generated the intermediate **C**.[21] Abstraction of a proton by the resulting anionic oxygen of DDQ then provided the diene intermediate **D**, with reduction of DDQ to hydroquinone. The product was formed from the diene species **D** by using another equivalent of DDQ, which underwent the same process.

Conclusion

An efficient method for the construction of biaryls by a DDQ-mediated sequential process has been developed. This new method has several advantages: 1) no transition metal is needed, 2) the reaction is conducted in one pot, in which the Grignard reagent and cyclohexanone are either commercially available or easily prepared and 3) no additional reagent is required. An extension of this method to vinyl and alkyl Grignard reagents and its synthetic application are under investigation in our laboratory.

Experimental Section

Typical procedure for the synthesis of biaryls by using *para*-tolylmagnesium bromide and substituted cyclohexanones: An oven-dried Biotage round-bottomed reaction vessel (10 mL) was charged with a magnetic stirring bar, evacuated, and refilled with nitrogen gas three times. Under an atmosphere of nitrogen, toluene (1.0 mL) was added, followed by *para*-tolylmagnesium bromide (**1a**; 0.22 mL, 0.22 mmol, 1.0 M in THF). Cyclohexanone (**2a**; 19.6 mg, 0.2 mmol) was then added dropwise to the solution at room temperature. The reaction mixture was stirred at room temperature for 0.5 h. DDQ (160 mg, 3.5 equiv) was then loaded into the vessel, which was sealed and placed in an oil bath. The reaction mixture was gradually heated from room temperature to 100 °C under vigorous stirring over a period of 40 h. After cooling to room temperature, it was filtered through a short column of silica gel, which was washed with ethyl acetate. The solvent was removed under vacuum, and the residue was purified by column chromatography on silica gel eluting with hexanes to afford the product 1-methyl-4-phenylbenzene **3aa** (33.2 mg, 99%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.63$ (d, $J = 8.5$ Hz, 2H), 7.55 (d, $J = 8.0$ Hz, 2H), 7.48 (t, $J = 8.0$ Hz, 2H), 7.37 (t, $J = 8.0$ Hz, 1H), 7.30 (d, $J = 7.5$ Hz, 2H), 2.45 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 141.1$, 138.3, 137.0, 129.5, 128.7, 127.0, 126.9, 21.1 ppm.

Typical procedure for the synthesis of biaryls by reacting Grignard reagents bearing functionalities (generated in situ) with cyclohexanone: An oven-dried Biotage round-bottomed reaction vessel (10 mL) was charged with a magnetic stirring bar, evacuated, and refilled with nitrogen gas three times. Under an atmosphere of nitrogen, a solution of methyl 4-iodobenzoate (**1c′**; 0.2 mmol) in toluene (1.0 mL) was cooled to −30 °C, whereupon *i*PrMgCl (0.11 mL, 0.21 mmol, 2.0 M in THF) was added dropwise. After the addition, the iodine–magnesium exchange reaction was kept at −30 °C for 1 h. Cyclohexanone (**2a**; 23 μL, 0.22 mmol) was then added dropwise to the reaction mixture, and stirring was continued for a further 2 h at −30 °C. After warming to room temperature, DDQ (160 mg, 3.5 equiv) was added and then the vessel was sealed and placed in an oil bath at 100 °C, stirring the contents vigorously for 40 h. After cooling to room temperature, the reaction mixture was filtered through a short column of silica gel, which was washed with ethyl acetate. The sol-

vent was removed under vacuum, and the residue was purified by column chromatography on silica gel eluting with hexanes/EtOAc (30:1) to give the product methyl 4-phenylbenzoate **3ca** (36.3 mg, 86%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.11$ (dd, $J = 6.4$, 1.6 Hz, 2H), 7.68–7.62 (m, 4H), 7.47 (t, $J = 8.0$ Hz, 2H), 7.40 (t, $J = 7.6$ Hz, 1H), 3.94 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 167.0$, 145.6, 140.0, 130.1, 128.9, 128.8, 128.1, 127.3, 127.0, 52.1 ppm.

Acknowledgements

We are grateful to the Canada Research Chair (Tier 1) Foundation (to C.-J. Li) and the NSERC for their support of our research.

[1] a) O. Baudoin, F. Guerite in *Studies in Natural Product Chemistry, Vol. 29* (Ed.: Atta-ur-Rahman), Elsevier, Amsterdam, **2003**, pp. 355–418; b) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893–930; c) P. J. Hajduk, M. Bures, J. Praestgaard, S. W. Fesik, *J. Med. Chem.* **2000**, *43*, 3443–3447; d) G. W. Bemis, M. A. Murcko, *J. Med. Chem.* **1996**, *39*, 2887–2893.

[2] a) G. Bringmann, C. Gunter, M. Ochse, O. Schupp, S. Tasler, in *Progress in the Chemistry of Organic Natural Products, Vol. 82* (Eds.: W. Herz, H. Falk, G. W. Kirby, E. Moore), Springer, New York, **2001**, pp. 1–249; b) K. C. Nicolaou, C. N. C. Boddy, S. Bräse, N. Winssinger, *Angew. Chem.* **1999**, *111*, 2230–2287; *Angew. Chem. Int. Ed.* **1999**, *38*, 2096–2152.

[3] E. Poetsch, *Kontakte (Darmstadt)* **1988**, *2*, 15–28.

[4] a) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1470; b) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651–2710.

[5] a) K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 4374–4376; b) M. Kumada, *Pure Appl. Chem.* **1980**, *52*, 669–679.

[6] a) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147–168; b) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483.

[7] a) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821–1823; b) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340–348.

[8] a) D. Milstein, J. K. Stille, *J. Am. Chem. Soc.* **1978**, *100*, 3636–3638; b) J. K. Stille, *Angew. Chem.* **1986**, *98*, 504–519; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524.

[9] a) K. Godula, D. Sames, *Science* **2006**, *312*, 67–72; b) L.-C. Campeau, K. Fagnou, *Chem. Commun.* **2006**, 1253–1264; c) L.-C. Campeau, M. Parisien, A. Jean, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 581–590; d) X. Wang, D. Leow, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 13864–13867; e) M. Wasa, B. T. Worrell, J.-Q. Yu, *Angew. Chem.* **2010**, *122*, 1297–1299; *Angew. Chem. Int. Ed.* **2010**, *49*, 1275–1277; f) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem.* **2012**, *124*, 10382–10401; *Angew. Chem. Int. Ed.* **2012**, *51*, 10236–10254; g) B. Li, Z.-H. Wu, Y.-F. Gu, C.-L. Sun, B.-Q. Wang, Z.-J. Shi, *Angew. Chem.* **2011**, *123*, 1141–1145; *Angew. Chem. Int. Ed.* **2011**, *50*, 1109–1113; h) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624–655.

[10] a) L. J. Gooßen, G. Deng, L. M. Levy, *Science* **2006**, *313*, 662–664; b) L. J. Gooßen, B. Zimmermann, T. Knauber, *Angew. Chem.* **2008**, *120*, 7211–7214; *Angew. Chem. Int. Ed.* **2008**, *47*, 7103–7106; c) P. Forgione, M.-C. Brochu, M. St. -Onge, K. H. Thesen, M. D. Bailey, F. Bilodeau, *J. Am. Chem. Soc.* **2006**, *128*, 11350–11351.

[11] a) M.-O. Simon, S. A. Girard, C.-J. Li, *Angew. Chem.* **2012**, *124*, 7655–7658; *Angew. Chem. Int. Ed.* **2012**, *51*, 7537–7540; b) for a leading reference on palladium-catalyzed oxidative aromatizations, see: Y. Izawa, D. Pun, S. S. Stahl, *Science* **2011**, *333*, 209–213.

[12] S. A. Girard, X. Hu, T. Knauber, F. Zhou, M.-O. Simon, G.-J. Deng, C.-J. Li, *Org. Lett.* **2012**, *14*, 5606–5609.

[13] The groups of Itami and Jasti used a similar strategy by employing the reaction of aryllithium reagents generated from *n*BuLi and an aryl halide with quinone as an initial step, which laid the foundation for the construction of carbon nanotubes. For the details, see: a) H. Omachi, Y. Segawa, K. Itami, *Acc. Chem. Res.* **2012**, *45*, 1378–1389; b) R. Jasti, J. Bhattacharjee, J. B. Neaton, C. R. Bertozzi, *J. Am. Chem. Soc.* **2008**, *130*, 17646–17647.

[14] a) D. R. Buckle in *Encyclopaedia of Reagents for Organic Synthesis, Vol. 3* (Ed.: L. A. Paquette), Wiley, Chichester, **1995**, pp. 1699; b) D. Walker, J. D. Hiebert, *Chem. Rev.* **1967**, *67*, 153–195; c) Y. Zhang, C.-J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 4242–4243; d) B.-P. Ying, B. G. Trogden, D. T. Kohlman, S. X. Liang, Y.-C. Xu, *Org. Lett.* **2004**, *6*, 1523–1526; e) C. A. Correia, C.-J. Li, *Adv. Synth. Catal.* **2010**, *352*, 1446–1450.

[15] a) E. A. Braude, R. P. Linstead, K. R. Wooldridge, *J. Chem. Soc.* **1956**, 3070–3074; b) S. Cacchi, F. La Torre, G. Paolucci, *Synthesis* **1978**, 848–849.

[16] a) R. Caputo, A. Guaragna, G. Palumbo, S. Pedatella, *J. Org. Chem.* **1997**, *62*, 9369–9371; b) W. Wang, T. Li, G. Attardo, *J. Org. Chem.* **1997**, *62*, 6598–6602; c) O. Piva, A. c. Amougay, J.-P. Pete, *Tetrahedron Lett.* **1991**, *32*, 3993–3996; d) J. Muzart, *Synthesis* **1993**, 11–27; e) N. S. Narasimhan, C. P. Bapat, *J. Chem. Soc. Perkin Trans. 1* **1984**, 1435–1439; f) E. Lee-Ruff, F. J. Ablenas, *Can. J. Chem.* **1989**, *67*, 699–702.

[17] D. Walker, T. D. Waugh, *J. Org. Chem.* **1965**, *30*, 3240.

[18] P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem.* **2003**, *115*, 4438–4456; *Angew. Chem. Int. Ed.* **2003**, *42*, 4302–4320.

[19] a) L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem.* **1998**, *110*, 1801–1803; *Angew. Chem. Int. Ed.* **1998**, *37*, 1701–1703; b) P. Calí, M. Begtrup, *Synthesis* **2002**, 63–66.

[20] L. Bérillon, A. Leprêtre, A. Turck, N. Plé, G. Quéguiner, G. Cahiez, P. Knochel, *Synlett* **1998**, 1359–1360.

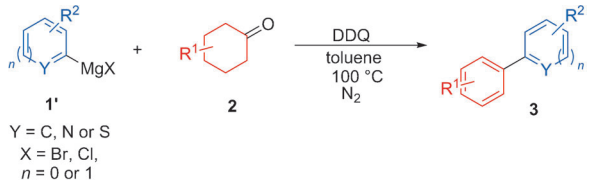
[21] a) E. A. Braude, L. M. Jackman, R. P. Linstead, *J. Chem. Soc.* **1954**, 3564–3568; b) V. K. Ahluwalia, R. K. Parashar, *Organic Reaction Mechanisms*, 2nd ed., Alpha Science International Ltd., Harrow, **2005**, p. 530.

Received: February 7, 2013
Published online: ■■ ■■, 0000

Biaryl synthesis

*F. Zhou, M.-O. Simon, C.-J. Li** ..... ▮▮▮▮–▮▮▮▮

Transition-Metal-Free One-Pot Synthesis of Biaryls from Grignard Reagents and Substituted Cyclohexanones



One-pot biaryl synthesis: An efficient method for the construction of biaryls based on a transition-metal-free process is presented (see scheme). Various functionalities are tolerated in this transformation, and the products can be generated in a one-pot fashion by a sequence of Grignard reaction, dehydration, and oxidative aromatization.

