Transition-Metal-Free Homocoupling of Organomagnesium Compounds†

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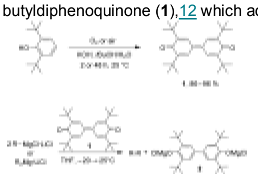
- biaryls; C—C coupling; dienes; diynes; Grignard reagents

C—C coupling reactions are among the most powerful tools in modern organic chemistry.[1, 2] For most types of cross-couplings, transition metals are required as mediators or catalysts.[3] Usually Cu^I salts[4] (for Ullmann-type coupling reactions[5]), $TiCl_4$,[6] or the addition of catalytic amounts of other transition metals is needed.[2, 7] The importance of finding new catalytic systems[8] and using atmospheric oxygen[9] or its derivatives[10] for the performance of oxidation reactions is well-recognized. However, such oxidations are often unselective since they are governed by the chemistry of high-energy zwitterions, (di)radicals, or by electron-transfer reactions without stereochemical control.

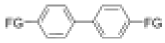
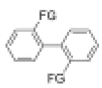
Herein, we report a new concept which allows the performance of coupling reactions by using only main-group-metal derivatives. We have envisioned that the coordination of a main-group-metal center with a readily reducible ligand would function as an electron shuttle and would allow a reductive coupling to take place. Thus, the organic oxidant (Ox) converts the intermediate **A** to the key intermediate **B**, which can undergo an intramolecular redox process leading to C—C bond formation (oxidative coupling) and reduction of the ligand Ox, which is thereby converted into the reduced ligand (Red) by accepting two electrons (Scheme 1). The main-group metal keeps the same oxidation state during the entire process.

Scheme 1. Coupling reactions of Mg^{II} reagents.

Thus, mono- and diorganomagnesium reagents that are complexed with lithium chloride[11] can be efficiently coupled by treatment with readily available 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone (**1**),[12] which acts as a two-electron acceptor (Scheme 2 and Table 1).



Scheme 2. Coupling of organomagnesium reagents with **1**.

Entry	Grignard reagent	Biaryl (4)	Yield [%][a]
			
1	**3 a**: FG=H, X=Br	**4 a**: FG=H	96
2	**3 b**: FG=MeO, X=Br	**4 b**: FG=MeO	94
3	**3 c**: FG=CF_3, X=Cl	**4 c**: FG=CF_3	92
4	**3 d**: FG=CN, X=Cl	**4 d**: FG=CN	96
5	**3 e**: FG=CO_2Et, X=Cl	**4 e**: FG=CO_2Et	93
			
6	**3 f**: FG=CN	**4 f**: FG=CN	85
7	**3 g**: FG=CO_2Et	**4 g**: FG=CO_2Et	88
8	**3 h**: FG=*t*Bu	**4 h**: FG=*t*Bu	83

1. [a] Yield of isolated, analytically pure product.

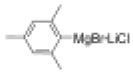
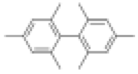
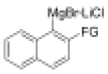
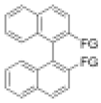
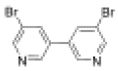
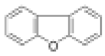
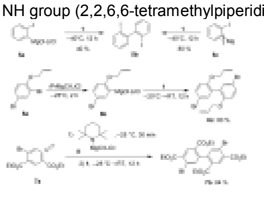
Entry	Grignard reagent	Biaryl (4)	Yield [%][a]
			
9	**3 i**	**4 i**	88
			
10	**3 j**: FG=H	**4 j**: FG=H	99
11	**3 k**: FG=OMe	**4 k**: FG=OMe	90
			
12	**3 l**	**4 l**	80
			
13	**3 m**	**4 m**	96

Table 1. Formation of biaryls.

The resulting biphenyldiolate **2** can be easily separated (>90 % yield) from the reaction mixture by the addition of pentane and subsequent filtration. By oxidation of **2** with air, **1** can be recovered in nearly quantitative yield,13 which makes this methodology especially attractive from ecological and economical standpoints.

The reaction of phenylmagnesium bromide with 0.5 equivalents of **1** at −20 °C led to the formation of biphenyl (**4 a**; Table 1, entry 1) in quantitative yield. The reaction proceeded well with electron-rich (**3 b**) and electron-poor (**3 c**) arylmagnesium halides and afforded the corresponding biaryls **4 b** and **4 c**, respectively, in high yields (Table 1, entries 2 and 3). At low reaction temperature functionalized organomagnesium compounds that bear a nitrile (**3 d**) or an ester group (**3 e**) could be coupled in excellent yields (**4 d** and **4 e**; Table 1, entries 4 and 5). Functional groups in the *ortho* position do not disturb the reaction, and the corresponding *ortho,ortho*′-disubstituted biaryls **4 f** and **4 g** were formed in 85 and 88 % yield, respectively (Table 1, entries 6 and 7). Even the sterically hindered *ortho*-*tert*-butyl- (**3 h**) and mesitylmagnesium (**3 i**) derivatives gave biaryls **4 h** and **4 i** in 83 and 88 % yield, respectively (Table 1, entries 8 and 9). 1-Naphthylmagnesium reagents **3 j** and **3 k** are also suitable substrates and afforded the corresponding binaphthyls **4 j** and **4 k,**respectively, in good yields (Table 1, entries 10 and 11). Heterocyclic organomagnesium reagents could also be coupled by **1**. Thus, 5-bromopyridin-3-ylmagnesium chloride led to the corresponding dipyridine **4 l** in 80 % yield (Table 1, entry 12). The organomagnesium reagent **3 m**, which was generated from 1,1′-oxybis(2-iodobenzene), underwent selective intramolecular coupling with quantitative formation of dibenzofuran (**4 m**; Table 1, entry 13).

Although coupling of the *ortho*-iodophenyl Grignard reagent **5 a** led only to a moderate yield of biaryl **5 b**, compound **5 b** was obtained in 80 % yield when the diorganomagnesium reagent **5 c** was used (Scheme 3). Coupling of the allyloxy-substituted organomagnesium reagent**6 b**, which was prepared by selective Br/Mg exchange from the corresponding dibromide **6 a** and *i*PrMgCl·LiCl,14 gave rise to biaryl **6 c**. We did not observe any ring-closure products arising from radical cyclization. The diester **7 a** could be selectively deprotonated with the mixed Mg/Li base **8**15 and coupled to form the highly substituted biaryl **7 b**. This example shows that the presence of an NH group (2,2,6,6-tetramethylpiperidine) is tolerated.

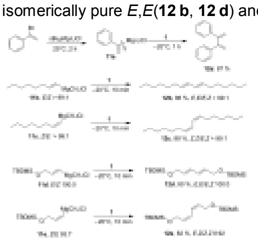


Scheme 3. Formation of biaryls.

We have also examined the coupling of alkynylmagnesium compounds, which are easily available by deprotonation of the corresponding acetylenes with *i*PrMgCl·LiCl. Although the Glaser coupling,16 the Eglinton procedure,17 and modifications thereof18 are well-known, each of them necessitates the addition of a transition metal (usually Cu^{I}) that requires subsequent recycling or disposal. Reactions of alkynylmagnesium reagents with **1** proceed cleanly with the formation of only the desired diacetylenes and easily recyclable **2**. Thus, phenyl- (**9 a**), *n*-hexyl- (**9 b**), trimethylsilyl- (**9 c**), and cyclohexenylethynylmagnesium chloride (**9 d**) react with **1** within 12 hours at 25 °C to give the corresponding diynes **10 a**–**d** in 80–90 % yield (Scheme 4).

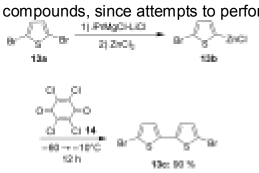
Scheme 4. Formation of diynes.

Alkenylmagnesium reagents also could be coupled in this way. Bis(α-styryl)magnesium (**11 a**) reacted with **1** to afford 2,3-diphenyl-1,3-butadiene (**12 a**) in 87 % yield. Stereoselective couplings of terminal alkenes are of great interest since the resulting isomerically pure 1,3-dienes cannot be prepared by conventional Wittig reactions.[19] This methodology allows the coupling of *E*- (**11 b**, **11 d**) or *Z*-alkenylmagnesium reagents (**11 c**, **11 e**) with complete retention of the double-bond stereochemistry to afford the isomerically pure *E*,*E*(**12 b**, **12 d**) and *Z*,*Z* dienes (**12 c**, **12 e**), respectively (Scheme 5).



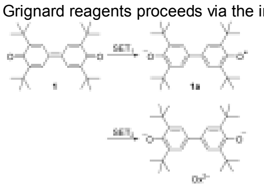
Scheme 5. Stereoselective coupling of alkenylmagnesium reagents; TBDMS=*tert*-butyldimethylsilyl.

Interestingly, the coupling reaction could also be performed by using organozinc reagents. Thus, the reaction of 2,5-dibromothiophene (**13 a**) with *i*PrMgCl·LiCl (25 °C, 1 h) and subsequent transmetalation with $ZnCl_2$ produced the zinc reagent **13 b**. The reaction of this thiophene–zinc species with chloranil (**14**, 1.05 equiv, −60 °C→ −10 °C, 12 h) afforded the expected dimer **13 c** in 90 % yield (Scheme 6). The use of the zinc reagent in association with chloranil is complementary to the homocoupling of Grignard compounds, since attempts to perform the coupling with the Grignard reagent corresponding to **13 b** and **1** did not lead to **13 c**.



Scheme 6. Coupling of an organozinc compound.

The mechanism of this reaction is still under investigation. By using a stopped-flow instrument with a UV/Vis detector, we were able to show that the interaction of **1** with Grignard reagents proceeds via the intermediate radical anion **1 a** (Scheme 7).



Scheme 7. Stepwise reduction of **1** in the course of homocoupling of Grignard reagents; SET=single-electron transfer.

When **1** was mixed with a large excess of mesitylmagnesium bromide **3 i**, the UV/Vis spectrum, which was taken 7 ms after mixing of the reagents, showed the complete consumption of **1** (λ_{max}=423 nm, Figure 1 b). A new species with an absorption maximum at λ_{max}=459 nm had appeared, which is assigned to **1 a** (Scheme 7). Treatment of **1** with sodium metal in THF gave a green solution with a UV/Vis spectrum (Figure 1 c) that was identical to that from the reaction of **1** with organomagnesium reagents (compare Figures 1 a and 1 c). Since both **1** and **1 a** have previously been reported to have very similar absorption coefficients at λ_{max},[20] one can conclude that immediately after mixing, the concentration of **1 a** is similar to the initial concentration of **1**.

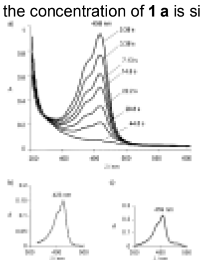
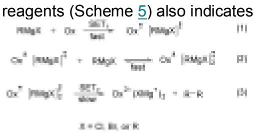


Figure 1. a) UV/Vis monitoring of the interaction of mesitylmagnesium bromide (c=0.079 M) with **1** (c=1.25×10^{-5} M). b) UV/Vis spectrum of **1**(c=2.01×10^{-6} M). c) UV/Vis spectrum of **1 a**, obtained from the reduction of **1**(c=5.12×10^{-6} M) with Na in THF.

In all cases studied, the formation of **1 a** proceeded faster than the mixing of the reagents in the stopped-flow instrument. Assuming that the mixing time of the stopped-flow system (ca. 7 ms) corresponds to more than three half-lives of the substrate **1** in the presence of 0.08 M Grignard reagent, the pseudo-first-order rate constant for SET_1 must be greater than 300 s^{-1}, thus corresponding to a second-order rate constant of greater than 3700 M^{-1} s^{-1}. The consumption of **1 a** is much slower and can be followed photometrically (Figure 1 a). It was not possible, however, to find a simple rate law which describes SET_2 (Scheme 7).

The reaction of **1** (c=1.25×10^{-5} M) with 1-naphthylmagnesium bromide (c=0.042 M) also proceeded with immeasurably fast formation of **1 a**, which disappeared within 3 s, which is much faster than in the corresponding experiment with mesitylmagnesium chloride (Figure 1). Since **1 a**, generated from **1** and Na in THF, did not react with 1-naphthylmagnesium bromide, a mechanism in which the arylmagnesium reagents are oxidized by **1 a** can be ruled out.[21]

The oxidation of the organomagnesium reagents does not yield a significant amount of free radicals as only traces of by-products, which emerge from the abstraction of $H^{\cdot}$ from THF, are detected by GC–MS analysis of the crude reaction mixtures. Complete retention of the configuration of the C=C double bonds in the coupling of alkenylmagnesium reagents (Scheme 5) also indicates that free radicals are not involved in this homocoupling reaction. These findings are in line with the mechanism in Scheme 8.



Scheme 8. Mechanism of homocoupling of organomagnesium reagents; Ox=oxidizing agent, **1**.

The species that are formed by fast transfer of an electron from RMgX (or R_2Mg) to **1** ([Eq. (1)], Scheme 8) can be formally considered as radicals $R^{\cdot}$ that are bound to the cationic magnesium center. The formation of analogous intermediates, in which the C–Mg bond is retained, was proposed in reactions of organomagnesium reagents with benzophenones and benzils.[22] These highly reactive species were reported to effect transfer of the $R^{\cdot}$ group to a radical center of the reduced carbonyl group or form stable dimeric dications that contain two ketyl molecules as counterions.[23] Furthermore, it was reported that exchange of ligands in these intermediates (analogous to [Eq. (2)]) is fast and precedes the product-determining step.[24]

It is likely that the transfer of the $R^{\cdot}$ group to the radical center of **1 a** is hindered by the α-*tert*-butyl groups. This hindrance may favor the consumption of the radical species through oxidative dimerization (SET_2, [Eq. (3)]). Similar dimerization pathways that give rise to the formation of biaryls or biaryl anion radicals are known.[25]

In conclusion, we have shown that the use of 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone (**1**) as an electron acceptor allows a simple, high-yield preparation of a broad range of functionalized biaryls, diynes, and dienes through coupling reactions of readily available organomagnesium reagents. The coupling of alkenylmagnesium reagents proceeds with high stereoselectivity. All of the reactions take place within a convenient range of temperatures (−20 °C to room temperature) and can be easily extended to large-scale preparations. We have performed for the first time an effective transition-metal-free coupling of a broad range of organomagnesium reagents by using a conceptually new process (Scheme 1). Extension of this work to other organometallic compounds, such as zinc reagents, has already been demonstrated (Scheme 6), and further such investigations are currently underway.

Experimental Section

Representative procedure: Synthesis of **4 e**: A dry and argon-flushed flask (10 mL), equipped with a magnetic stirrer and a septum, was charged with ethyl 4-iodobenzoate (552 mg, 2.0 mmol) in THF (2 mL). The reaction mixture was cooled to −20 °C, and *i*PrMgCl·LiCl (2 mL, 1.05 M in THF, 2.1 mmol) was added dropwise. After 20 min at −20 °C, the I/Mg-exchange was complete (checked by GC analysis of reaction aliquots), and a solution of **1** (449 mg, 1.1 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred for 2 h at 0 °C. Conventional work up of the crude residue by flash chromatography (pentane/CH_2Cl_2 1:1) yielded **4 e** (184 mg, 93 %) as white crystals.

Dedicated to Professor Siegfried Hünig on the occasion of his 85th birthday

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