Transition-Metal-Free Homocoupling of Organomagnesium Compounds

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Article first published online: 3 JUL 2006
DOI: 10.1002/anie.200600772
Angewandte Chemie International Edition
Volume 45, Issue 30, pages 5010–5014, July 24, 2006

Keywords:
- 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 salts4 (for Ullmann-type coupling reactions5), TiCl4,6 or the addition of catalytic amounts of other transition metals is needed.2 The importance of finding new catalytic systems8 and using atmospheric oxygen9 or its derivatives10 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 MgII reagents.

Thus, mono- and diorganomagnesium reagents that are complexed with lithium chloride11 can be efficiently coupled by treatment with readily available 3,3',5,5'-tetra-tert-butyldiphenyloquinone (1),12 which acts as a two-electron acceptor (Scheme 2 and Table 1).

Scheme 2. Coupling of organomagnesium reagents with 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Grignard reagent</th>
<th>Biaryl (4)</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FG=H, X=Br</td>
<td>FG=Br</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>FG=MeO, X=Br</td>
<td>FG=MeO</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>FG=CF3, X=Cl</td>
<td>FG=CF3</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>FG=CN, X=Cl</td>
<td>FG=CN</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>FG=CO2Et, X=Cl</td>
<td>FG=CO2Et</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>FG=tBu</td>
<td>FG=tBu</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>FG=CO2Et</td>
<td>FG=CO2Et</td>
<td>88</td>
</tr>
<tr>
<td>8</td>
<td>FG=tBu</td>
<td>FG=tBu</td>
<td>83</td>
</tr>
</tbody>
</table>
corresponding diynes requires subsequent recycling or disposal. Reactions of alkynylmagnesium reagents with the Glaser coupling, Scheme 3.

NH group (2,2,6,6-tetramethylpiperidine) is tolerated.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Grignard reagent</th>
<th>Biaryl (4)</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>3 i</td>
<td>4 i</td>
<td>88</td>
</tr>
<tr>
<td>10</td>
<td>3 j FG=H</td>
<td>4 j FG=H</td>
<td>99</td>
</tr>
<tr>
<td>11</td>
<td>3 k FG=OMe</td>
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<td>90</td>
</tr>
<tr>
<td>12</td>
<td>3 l</td>
<td>4 l</td>
<td>80</td>
</tr>
<tr>
<td>13</td>
<td>3 m</td>
<td>4 m</td>
<td>96</td>
</tr>
</tbody>
</table>

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, 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 PrMgClLiCl, 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 PrMgClLiCl. Although the Glaser coupling, 16 the Eglinton procedure, 17 and modifications thereof 18 are well-known, each of them necessitates the addition of a transition metal (usually Cu) 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 cyclohexenylmethylene-magnesium 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-styrylmagnesium) (11a) reacted with 1 to afford 2,3-diphenyl-1,3-butadiene (12a) 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. This methodology allows the coupling of E- (11b, 11d) or Z-alkenylmagnesium reagents (11c, 11e) with complete retention of the double-bond stereochemistry to afford the isomerically pure E,E (12b, 12d) and Z,Z dienes (12c, 12e), 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 (13a) with iPrMgCl·LiCl (25°C, 1 h) and subsequent transmetalation with ZnCl₂ produced the zinc reagent 13b. The reaction of this thiophene–zinc species with chloranil (14, 1.05 equiv, −60°C→−10°C, 12 h) afforded the expected dimer 13c 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 13b and 1 did not lead to 13c.

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 1a (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 31, the UV/Vis spectrum, which was taken 7 ms after mixing of the reagents, showed the complete consumption of 1 (λmax=423 nm, Figure 1b). A new species with an absorption maximum at λmax=459 nm had appeared, which is assigned to 1a (Scheme 7). Treatment of 1 with sodium metal in THF gave a green solution with a UV/Vis spectrum (Figure 1c) that was identical to that from the reaction of 1 with organomagnesium reagents (compare Figures 1a and 1c). Since both 1 and 1a have previously been reported to have very similar absorption coefficients at λmax, one can conclude that immediately after mixing, the concentration of 1a is similar to the initial concentration of 1.
The coupling of alkenylmagnesium reagents proceeds with high stereoselectivity. All of the reactions take place within a convenient range of temperatures (−30 to +20 °C). It is likely that the transfer of the R group to the radical center of the reduced carbonyl group or form stable dimeric dications that contain two ketyl molecules as counterions. Furthermore, it was reported that exchange of ligands in these intermediates (analogous to Eq. (2)) is fast and precedes the product-determining step.

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 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.

The species that are formed by fast transfer of an electron from RMgX (or RMg) to 1 (Eq. (1)) can be formally considered as radicals R 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. These highly reactive species were reported to effect transfer of the R group to a radical center of the reduced carbonyl group or form stable dimeric dications that contain two ketyl molecules as counterions. Furthermore, it was reported that exchange of ligands in these intermediates (analogous to Eq. (2)) is fast and precedes the product-determining step.

It is likely that the transfer of the R group to the radical center of 1a is hindered by the α-tether butyl groups. This hindrance may favor the consumption of the radical species through oxidative dimerization (SET, Eq. (3)). Similar dimerization pathways that give rise to the formation of biaryls or biaryl anion radicals are known.

In conclusion, we have shown that the use of 3,3′,5,5′-tetra-t-butyl-diphenonone (1) as an electron acceptor allows a simple, high-yield preparation of a broad range of functionalized biaryls, diynes, and dienes through coupling of readily available organomagnesium reagents. The coupling of organomagnesium reagents proceeds with high stereoselectivity. All of the reactions take place within a convenient range of temperatures (−20 to +20 °C) 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 5) and further such investigations are currently underway.

### Experimental Section

Representative procedure: Synthesis of 4a: 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 iPrMgCl-LiCl (2 mL, 1.05 M in THF, 2.1 mmol) was added dropwise. After 20 min at −20 °C, the iMg-e-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/CH2Cl2, 1:1) yielded 4a (184 mg, 93 %) as white crystals.

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


Recently, we have found that mono- and diorganomagnesium reagents that are complexed with lithium chloride show exceptional reactivity towards electrophiles and can easily be prepared by I/Mg- or Br/Mg-exchange reactions; see:

11d H. Ren, A. Krasovskiy, P. Knochel, Org. Lett. 2004, 6, 4215;

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