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Gandrath Dayaker,† Floris Chevallier,† Philippe C. Gros,‡ and Florence Mongin*,†

† Chimie et Photonique Moléculaires, UMR 6510 CNRS, Université de Rennes 1, Bâtiment 10A, Case 1003, Campus Scientifique de Beaulieu, 35042 Rennes, France, ‡ SOR, SRSMC, CNRS, Nancy Université, Boulevard des Aiguillettes, 54506 Vandœuvre-les-Nancy, France

* To whom correspondence should be addressed. E-mail: florence.mongin@univ-rennes1.fr. Phone: +33 2 2323 6931. Fax: +33 2 2323 6955.
Abstract:
The deprotonation of anisole was attempted using different homo- and heteroleptic TMP/Bu mixed lithium-cobalt combinations. Using iodine to intercept the metalated anisole, an optimization of the reaction conditions showed that in THF at room temperature 2 equiv of base were required to suppress the formation of the corresponding 2,2'-dimer. The origin of the dimer was not identified, but its formation was favored with allyl bromide as electrophile. The metalated anisole was efficiently trapped using iodine, anisaldehyde, and chlorodiphenylphosphone, and moderately employing benzophenone, and benzoyl chloride. 1,2-, 1,3- and 1,4-dimethoxybenzene were similarly converted regioselectively to the corresponding iodides. It was observed that 2-methoxy- and 2,6-dimethoxypyridine were more prone to dimerization than the corresponding benzenes when treated similarly. Involving ethyl benzoate in the metalation-iodination sequence showed the method was not suitable to functionalize substrates bearing reactive functions.

Keywords:
bimetallic bases, deprotonative metalation, aromatic compounds, lithium, cobalt

Introduction
The deprotonative metalation using lithium bases has been widely used as a powerful method for the regioselective functionalization of aromatic compounds. The use of metal additives in order to get more efficient or more chemoselective bases (synergic superbases) is a challenging field. Pioneer studies, respectively carried out in the groups of Schlosser and Lochmann with LIC-KOR, mixture of butyllithium (LIC) and potassium tert-butoxide (KOR), and by Caubère, Gros and Fort in the pyridine series with BuLi-LiDMAE (DMAE = 2-dimethylaminoethoxide) and Me₃SiCH₂Li-LiDMAE merged alkyllithiums and alkali-metal alkoxides. More recently, the use of other (R)n(R’)_n-MLi-type bases, with M being different from an alkali-metal (e.g. M = Mg, Al, Cr, Mn, Cu, Zn), has been described by different groups for their ability to deprotonate aromatic compounds, and notably anisole. In 2009, Klett, Mulvey and co-workers showed that it is possible to design sodium-iron(II) bases, and extended
the ability to deprotonate to group 8 ate compounds. The same year, Wunderlich and Knochel showed that ferration can be achieved using salt-solubilized (TMP)$_2$Fe·2MgCl$_2$·4LiCl (TMP = 2,2,6,6-tetramethylpiperidino).

We recently accomplished the room temperature deproto-metalation of a large range of substrates including sensitive heterocycles and functionalized benzenes using newly developed lithium-zinc, lithium-cadmium, and lithium-copper(I) combinations, in situ prepared from MCl$_2$·TMEDA (M = Zn, Cd or Cu, TMEDA = $N,N',N''$-tetramethylethlenediamine) and lithium reagents (alkyllithiums or lithium amides). The studies performed using lithium-zinc and lithium-cadmium combinations have notably shown that the more efficient bases were obtained by mixing the metal salt with 3 equiv of LiTMP. A main drawback of the methods developed being the lack of reactivity of such generated arylmetals in direct trapping with electrophiles, we turned to other bimetallic combinations in order to identify candidates able to perform efficient deprotonations, but also to allow direct functionalizations. We here describe the first aromatic deproto-metalations using lithium-cobalt combinations.

**Results and Discussion**

The synthesis of organocobalt ate compounds is well-documented in the literature. They are in general obtained by transmetalation of organolithium or -magnesium reagents with cobalt(II) halides. Examples are Me$_3$CoLi, Me$_4$CoLi$_2$(TMEDA)$_2$ and (R$_3$SiCH$_2$)$_4$Co(MgCl)$_2$ (R$_3$Si = Me$_3$Si, MePh$_2$Si, BuMe$_2$Si). The access to mixed lithium-cobalt amides is far less documented, but seems possible similarly. We first consider the use of CoCl$_2$·TMEDA chelate in order to manipulate a salt less hygroscopic than CoCl$_2$, but attempts to prepare it failing in giving good microanalyses, we turned to CoBr$_2$. We prepared different lithium-cobalt combinations by mixing the cobalt salt with 3 or 4 equiv of a lithium compound, either LiTMP or mixtures with butyllithium, at 0 °C. We chose anisole (1) as substrate to check the ability to deprotonate of the mixtures (Table 1).

Using LiTMP (1 equiv) or (TMP)$_2$Co (1 equiv, in situ generated from CoBr$_2$ and 2 equiv of LiTMP) in tetrahydrofuran (THF) at room temperature for 2 h, and then iodine, anisole (1) was converted into
the 2-iodo derivative 2a in 9 or 0% yield, respectively. In contrast, when treated with an in situ prepared mixture of CoBr₂ (1 equiv) and LiTMP (3 equiv) at 25 °C for 2 h, anisole (1) was readily ortho-metalated, a result evidenced with the formation of 2a in 54% yield after purification (Entry 1). Lowering the reaction temperature to 0 °C resulted in a low conversion, even after 4 h reaction time (Entries 2 and 3). When performed at 45 °C, the metalation step worked as at 25 °C, affording 2a in 50% yield (Entry 4). It is known that labile ligands can play a role on the course of reactions.⁹ To check a possible effect, the reaction was performed at room temperature in the presence of 1 equiv of TMEDA; the 39 and 59% yields respectively obtained with and without TMEDA indicates the deleterious influence of this ligand, uninteresting in this case (Entry 5). The impact of the reaction time was next considered. It was observed that reducing the reaction time to 30 min resulted in a lower 43% yield (Entry 6). Extending the reaction time to 4 h did not bring any improvement (Entry 7), but after 20 h the yield was significantly reduced to 38% (Entry 8). The effect of the base amount was then studied. Using 0.5 equiv of CoBr₂ and 1.5 equiv of LiTMP led to low conversions, whatever the reaction time (Entry 9). It was possible to find again the 54% yield already obtained Entry 1 by using 1.5 equiv of CoBr₂ and 4.5 equiv of LiTMP, and a 30 min reaction time (Entry 10). The best result (93% yield) was obtained using 2 equiv of CoBr₂ and 6 equiv of LiTMP (Entry 11), allowing to reduce the reaction time to 30 min (Entry 12).

As previously noted in a lesser extent in other bimetallic series,⁹d,¹⁰g putative Bu₃CoLi·2LiBr (Entry 13), Bu₂Co(TMP)Li·2LiBr (Entry 14), and BuCo(TMP)₂Li·2LiBr (Entry 15) alkyl/amino combinations are not able to deprotonate anisole (1). Higher-order ate compounds being in general more reactive than lower-order ones,¹⁷ reactions were attempted using putative Bu₃Co(TMP)Li₂·2LiBr (Entry 16), Bu₂Co(TMP)₂Li₂·2LiBr (Entry 17), and BuCo(TMP)₃Li₂·2LiBr (Entry 18). The iodide 2a was only isolated in 19% yield in the last reaction, due to the competitive formation of 2,2′-dimethoxybiphenyl (3) in 35% yield.
The formation of the dimer 3 has been observed in all the experiments where metalation took place, but in various yields. Its formation does not seem to depend on the deprotonation temperature (Entries 1-4), but seems to be favored with long contact times (Entry 8). In addition, it is clear that the use of 2 equiv of base prevents its formation (Entries 11 and 12), as if it formed intramolecularly. Using water instead of iodine to trap the metalated anisole derivative also resulted in the formation of 3 in a similar 14% yield (Entry 19). Thus, if cross-coupling with the iodide 2,12c,18 and iodine-mediated oxidation19 can be proposed to explain the formation of 3, alternatives ways without recourse to them exist. A possible in situ partial reduction of Co(II) species to Co(I) due to the presence of metal amides is possible,20 but would not lead to a dimer in the absence of an halide.21 Even if the use of degassed THF did not change significantly the result (Entry 19),22 a possible role of dissolved oxygen cannot be ruled out.19 An alternative explanation could be the presence of a metal impurity in CoBr2 for which the corresponding diaryl metal ate compounds is prone to dimerization. Using allyl bromide instead of iodine (or water) to quench the metalated anisole derivative produced the dimer 3 in 38% yield, and 2-allylanisole (2b) in 6% yield besides (Entry 20). One-electron transfers from cobalt(II) ate compounds to allyl bromide are possible pathways,23 and dimerization from the generated Co(III) species bearing two aryl groups18a appears as a possible pathway to explain the formation of 3 in this case (Scheme 1). Other electrophiles favor the dimerization. For example, the use of 2-bromopyridine in order to convert the metalated anisole into the cross-coupling product 2c was similarly threatened by a significant formation of 3 (Entry 21).

**SCHEME 1. Possible pathway for the formation of 3 from the metalated anisole derivative.**

![Diagram of anisole and metlated product]

<table>
<thead>
<tr>
<th>entry</th>
<th>Li/Co base (x)</th>
<th>conditions</th>
<th>electrophile (3x or 4x)</th>
<th>2 (E), yield</th>
<th>yield of 3&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>CoBr&lt;sub&gt;2&lt;/sub&gt; (1) + LiTMP (3)</td>
<td>25 °C, 2 h</td>
<td>I&lt;sub&gt;2&lt;/sub&gt; (3)</td>
<td>2a (I), 54%</td>
<td>17%</td>
</tr>
<tr>
<td>2</td>
<td>CoBr&lt;sub&gt;2&lt;/sub&gt; (1) + LiTMP (3)</td>
<td>0 °C, 2 h</td>
<td>I&lt;sub&gt;2&lt;/sub&gt; (3)</td>
<td>2a (I), 12%</td>
<td>5%</td>
</tr>
<tr>
<td>3</td>
<td>CoBr&lt;sub&gt;2&lt;/sub&gt; (1) + LiTMP (3)</td>
<td>0 °C, 4 h</td>
<td>I&lt;sub&gt;2&lt;/sub&gt; (3)</td>
<td>2a (I), 13%</td>
<td>24%</td>
</tr>
<tr>
<td>4</td>
<td>CoBr&lt;sub&gt;2&lt;/sub&gt; (1) + LiTMP (3)</td>
<td>45 °C, 2 h</td>
<td>I&lt;sub&gt;2&lt;/sub&gt; (3)</td>
<td>2a (I), 49%</td>
<td>20%</td>
</tr>
<tr>
<td>5</td>
<td>CoBr&lt;sub&gt;2&lt;/sub&gt; (1) + LiTMP (3)</td>
<td>rt,&lt;sup&gt;c&lt;/sup&gt; 2 h</td>
<td>I&lt;sub&gt;2&lt;/sub&gt; (3)</td>
<td>2a (I), 59%&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>CoBr&lt;sub&gt;2&lt;/sub&gt; (1) + LiTMP (3)</td>
<td>rt, 30 min</td>
<td>I&lt;sub&gt;2&lt;/sub&gt; (3)</td>
<td>2a (I), 43%</td>
<td>21%</td>
</tr>
<tr>
<td>7</td>
<td>CoBr&lt;sub&gt;2&lt;/sub&gt; (1) + LiTMP (3)</td>
<td>rt, 4 h</td>
<td>I&lt;sub&gt;2&lt;/sub&gt; (3)</td>
<td>2a (I), 57%</td>
<td>-&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>CoBr&lt;sub&gt;2&lt;/sub&gt; (1) + LiTMP (3)</td>
<td>rt, 20 h</td>
<td>I&lt;sub&gt;2&lt;/sub&gt; (3)</td>
<td>2a (I), 38%</td>
<td>34%</td>
</tr>
<tr>
<td>9</td>
<td>CoBr&lt;sub&gt;2&lt;/sub&gt; (0.5) + LiTMP (1.5)</td>
<td>rt, 2 to 20 h</td>
<td>I&lt;sub&gt;2&lt;/sub&gt; (1.5)</td>
<td>2a (I), -</td>
<td>-&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>CoBr&lt;sub&gt;2&lt;/sub&gt; (1.5) + LiTMP (4.5)</td>
<td>rt, 30 min</td>
<td>I&lt;sub&gt;2&lt;/sub&gt; (4.5)</td>
<td>2a (I), 54%</td>
<td>16%</td>
</tr>
<tr>
<td>11</td>
<td>CoBr&lt;sub&gt;2&lt;/sub&gt; (2) + LiTMP (6)</td>
<td>rt, 2 h</td>
<td>I&lt;sub&gt;2&lt;/sub&gt; (6)</td>
<td>2a (I), 93%</td>
<td>-&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td>CoBr&lt;sub&gt;2&lt;/sub&gt; (2) + LiTMP (6)</td>
<td>rt, 30 min</td>
<td>I&lt;sub&gt;2&lt;/sub&gt; (6)</td>
<td>2a (I), 93%</td>
<td>5%</td>
</tr>
<tr>
<td>13</td>
<td>CoBr&lt;sub&gt;2&lt;/sub&gt; (1) + BuLi (3)</td>
<td>rt, 2 h</td>
<td>I&lt;sub&gt;2&lt;/sub&gt; (3)</td>
<td>2a (I), 0%</td>
<td>0%</td>
</tr>
<tr>
<td>14</td>
<td>CoBr&lt;sub&gt;2&lt;/sub&gt; (1) + LiTMP (1) + BuLi (2)</td>
<td>rt, 2 h</td>
<td>I&lt;sub&gt;2&lt;/sub&gt; (3)</td>
<td>2a (I), 0%</td>
<td>0%</td>
</tr>
<tr>
<td>15</td>
<td>CoBr&lt;sub&gt;2&lt;/sub&gt; (1) + LiTMP (2) + BuLi (1)</td>
<td>rt, 2 h</td>
<td>I&lt;sub&gt;2&lt;/sub&gt; (3)</td>
<td>2a (I), 0%</td>
<td>0%</td>
</tr>
<tr>
<td>16</td>
<td>CoBr&lt;sub&gt;2&lt;/sub&gt; (1) + LiTMP (1) + BuLi (3)</td>
<td>rt, 2 h</td>
<td>I&lt;sub&gt;2&lt;/sub&gt; (4)</td>
<td>2a (I), 0%</td>
<td>0%</td>
</tr>
<tr>
<td>17</td>
<td>CoBr&lt;sub&gt;2&lt;/sub&gt; (1) + LiTMP (2) + BuLi (2)</td>
<td>rt, 2 h</td>
<td>I&lt;sub&gt;2&lt;/sub&gt; (4)</td>
<td>2a (I), 0%</td>
<td>0%</td>
</tr>
<tr>
<td>18</td>
<td>CoBr&lt;sub&gt;2&lt;/sub&gt; (1) + LiTMP (3) + BuLi (1)</td>
<td>rt, 2 h</td>
<td>I&lt;sub&gt;2&lt;/sub&gt; (4)</td>
<td>2a (I), 19%</td>
<td>35%</td>
</tr>
<tr>
<td>19</td>
<td>CoBr&lt;sub&gt;2&lt;/sub&gt; (1) + LiTMP (3)</td>
<td>rt, 2 h</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O (3)</td>
<td>1 (H), -</td>
<td>14%&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>20</td>
<td>CoBr&lt;sub&gt;2&lt;/sub&gt; (1) + LiTMP (3)</td>
<td>rt, 2 h</td>
<td>BrCH&lt;sub&gt;2&lt;/sub&gt;CH=CH&lt;sub&gt;2&lt;/sub&gt; (3)</td>
<td>2b (CH&lt;sub&gt;2&lt;/sub&gt;CH=CH&lt;sub&gt;2&lt;/sub&gt;, 6%&lt;sup&gt;h&lt;/sup&gt;)</td>
<td>38%</td>
</tr>
<tr>
<td>21</td>
<td>CoBr&lt;sub&gt;2&lt;/sub&gt; (1) + LiTMP (3)</td>
<td>rt, 2 h</td>
<td>Br&lt;sup&gt;Br&lt;/sup&gt;N&lt;sub&gt;Me&lt;/sub&gt; (3)</td>
<td>2c (14% (16%)&lt;sup&gt;i&lt;/sup&gt;)</td>
<td>19% (26%)&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> The rest is in general anisole. <sup>b</sup> 9 and 0% yield using LiTMP and (TMP)<sub>2</sub>Co, respectively, under the same reaction conditions. <sup>c</sup> Between 17 and 23 °C. <sup>d</sup> 39% yield in the presence of 1 equiv of TMEDA. <sup>e</sup> Not quantified. <sup>f</sup> Low conversion and significant formation of dimer. <sup>g</sup> 12% using degassed THF. <sup>h</sup> The high volatility of the compound could be partly responsible for the low yield obtained. <sup>i</sup> Trapping step performed at 50 °C instead of rt.
The optimized conditions in hands, the use of different electrophiles was attempted (Table 2). Anisaldehyde led to the corresponding alcohol 2d in a satisfying yield (Entry 2). The alcohol 2e and ketone 2f were produced in moderate yields upon interception with benzophenone and benzoyl chloride, respectively (Entries 3 and 4). The phosphine 2g was obtained satisfactorily using chlorodiphenylphosphine, but the cross-coupled derivative 2c was isolated in a low 25% yield due to a significant formation of 3 (Entry 6).

**TABLE 2. Electrophilic Trapping of Metalated Anisole.**

<table>
<thead>
<tr>
<th>entry</th>
<th>electrophile</th>
<th>2, yield</th>
<th>yield of 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I₂</td>
<td>2a, 93%</td>
<td>5%</td>
</tr>
<tr>
<td>2</td>
<td>4-MeOC₆H₄CHO</td>
<td>2d, 84%</td>
<td>15%</td>
</tr>
<tr>
<td>3</td>
<td>PhC(O)Ph</td>
<td>2e, 45%</td>
<td>10%</td>
</tr>
<tr>
<td>4</td>
<td>PhC(O)Cl</td>
<td>2f, 30%</td>
<td>16%</td>
</tr>
<tr>
<td>5</td>
<td>Ph₂PCl</td>
<td>2g, 82%</td>
<td>15%</td>
</tr>
<tr>
<td>6</td>
<td>Cl-N</td>
<td>2c, 25%</td>
<td>b</td>
</tr>
</tbody>
</table>

* Using 1 equiv of base.

---

The method was then extended to other aromatic substrates (Table 3). Starting from 1,4-dimethoxybenzene (4) and using iodine as electrophile, the expected derivative 5a was obtained in a correct yield provided that 2 equiv of base were used (Entries 1-3). It was noted that a longer reaction time favored the co-formation of
diiodides. Trapping with allyl bromide resulted in a significant formation of the dimer 6 whereas the expected allylated compound 5b was isolated in a low 6% yield (Entry 4). These results are similar to those obtained from anisole (1). Benefiting from a greater activation, 1,3-dimethoxybenzene (7) was quantitatively converted to the iodide 8a (Entry 5). Using allyl bromide instead of iodine yielded the derivative 8b in a low yield due to a significant recovery of starting material; in this case, the corresponding dimer 9 was isolated in a low 6% yield (Entry 6). The behavior of 1,2-dimethoxybenzene (10) is similar to that of 1,4-dimethoxybenzene (4); the formation of the corresponding dimer 12 was suppressed by reducing the reaction time to 30 min (Entries 7 and 8). Trapping using allyl bromide led to a significant formation of the dimer 12, limiting the yield of the allylated derivative 11b to 23% (Entry 9). 1,2,3-Trimethoxybenzene (13) led to the expected iodide 14 in a moderate 33% yield, due to a significant recovery of starting material (Entry 10). Performed with 2-methoxypyridine (15), the reaction led to a more important formation of dimer than starting from methoxybenzenes. The iodide resulting from a regioselective metalation next to the methoxy group was isolated in a moderate 43% yield (Entries 11 and 12). Except an increased conversion, a similar result was observed from 2,6-dimethoxypyridine (18) (Entry 13). The method is not suitable to functionalize substrates bearing reactive functions. Indeed, using ethyl benzoate (21), side reactions with the ester function only allowed the expected iodide 22 to be obtained in maximum 22% yield (Entries 14 and 15). A deprotonative metalation followed by a cross-coupling reaction was carried out from thiophene. Using 1 equiv of base (in order to avoid 2,5-dideprotonation), the expected cross-coupled compound was isolated, but in a low 19% yield (Entry 16).

**TABLE 3. Extension to Other Aromatic Substrates Including Heterocycles.**

<table>
<thead>
<tr>
<th>entry</th>
<th>Ar-H</th>
<th>x</th>
<th>reaction time</th>
<th>electrophile</th>
<th>Ar-E (E), yield</th>
<th>Ar-Ar, yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4:</td>
<td>0.5</td>
<td>2 h</td>
<td>I₂</td>
<td>5a (I), 10%</td>
<td>6, 22%</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>1</td>
<td>2 h</td>
<td>I₂</td>
<td>5a (I), 45%</td>
<td>-a</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>2</td>
<td>30 min</td>
<td>I₂</td>
<td>5a (I), 76%</td>
<td>6, 10%</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>30 min</td>
<td>BrCH₂CH=CH₂</td>
<td>5b (CH₂CH=CH₂), 6%</td>
<td>6, 33%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>7:</td>
<td>2</td>
<td>30 min</td>
<td>I₂</td>
<td>8a (I), 97%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>2</td>
<td>30 min</td>
<td>BrCH₂CH=CH₂</td>
<td>8b (CH₂CH=CH₂), 14%</td>
<td>9, 6%</td>
</tr>
</tbody>
</table>
Conclusion

Like the other lithium-metal combinations, the mixture of CoBr$_2$ and 3 equiv of LiTMP behaves synergically, but compared with the previously described "all-TMP" lithium-zinc$^9$ and lithium-cadmium$^{10}$ combinations, the base obtained by combining CoBr$_2$ with 3 equiv of LiTMP is less efficient as far as both conversion and chemoselectivity are concerned. For example, starting from anisole (1), the iodide 2a was isolated in 84% and 75% yield using 0.5 equiv of the lithium-zinc and lithium-cadmium combinations, respectively, against 59% under the same conditions using 1 equiv of the lithium-cobalt one. Concerning the metalation of methoxybenzenes, its efficiency more looks like that of the reported "all-TMP" Gilman-type lithium-copper(I) combination.$^{11}$ Nevertheless, the reactivity exhibited by the generated arylmetal species has been improved using lithium-cobalt bases.

In conclusion, compared with the previously reported "all-TMP" reagents, the combination here presented allows more efficient direct trappings for the generated arylmetal compounds, but lacks both
efficiency and chemoselectivity. Studies are under development to identify more suitable lithium-metal systems.

**Experimental Section**

**General Procedure A (Deprotonation using 2 equiv CoBr₂ and 6 equiv LiTMP Followed by Trapping using I₂).** To a stirred cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (4.1 mL, 24 mmol) in THF (8 mL) were added BuLi (1.6 M hexanes solution, 24 mmol) and, 5 min later, CoBr₂ (1.7 g, 8.0 mmol). The mixture was stirred for 10 min at 0 °C before introduction of the substrate (4.0 mmol). After 2 h at room temperature, a solution of I₂ (6.1 g, 24 mmol) in THF (7 mL) was added. The mixture was stirred overnight before addition of an aq saturated solution of Na₂S₂O₃ (10 mL) and extraction with EtOAc (3 x 20 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure.

**2-Iodoanisole (2a).** 2a was obtained according to the general procedure A starting from anisole (0.44 mL), but reducing the metalation reaction time to 30 min, and was isolated after purification by flash chromatography on silica gel (eluent: heptane/CH₂Cl₂ 95/5) as a colorless oil (93% yield). The analyses are as described previously.¹⁰a

**2-Iodo-1,4-dimethoxybenzene (5a).** 5a was obtained according to the general procedure A starting from 1,4-dimethoxybenzene (0.55 g), but reducing the metalation reaction time to 30 min, and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 97/3) as a yellow solid (76% yield): mp < 50 °C; ¹H NMR (300 MHz, CDCl₃) δ 3.74 (s, 3H), 3.81 (s, 3H), 6.94 (d, 1H, J = 8.9 Hz), 6.85 (dd, 1H, J = 2.9 and 8.9 Hz), 7.33 (d, 1H, J = 2.9 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 154.2, 152.6, 124.7, 114.6, 111.5, 85.9, 56.9, 55.8. These data are analogous to those previously described.²⁴

**2,2',5,5'-Tetramethoxybiphenyl (6).** 6 was obtained according to the general procedure A starting from 1,4-dimethoxybenzene (0.55 g), but using 2,2,6,6-tetramethylpiperidine (1.0 mL, 6.0 mmol), BuLi
(6.0 mmol) and CoBr$_2$ (0.42 g, 2.0 mmol). It was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 88/12) as a red solid (22% yield): mp 94-95 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 3.73 (s, 6H), 3.78 (s, 6H), 6.83-6.88 (m, 4H), 6.91 (dd, 2H, $J = 1.0$ and 8.4 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 153.3 (2C), 151.1 (2C), 128.6 (2C), 117.1 (2C), 113.4 (2C), 112.4 (2C), 56.6 (2C), 55.7 (2C). These data are analogous to those previously described.$^{25}$

2-Iodo-1,3-dimethoxybenzene (8a). 8a was obtained according to the general procedure A starting from 1,3-dimethoxybenzene (0.55 g), but reducing the metalation reaction time to 30 min, and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 60/40) as a white solid (97% yield): mp 106 °C (lit.$^{26}$ 100 °C); $^1$H NMR (300 MHz, CDCl$_3$) δ 3.88 (s, 6H), 6.49 (d, 2H, $J = 8.2$ Hz), 7.25 (t, 1H, $J = 8.2$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 159.4 (2C), 129.7, 104.0 (2C), 77.5, 56.5 (2C).

1-Iodo-2,3-dimethoxybenzene (11a). 11a was obtained according to the general procedure A starting from veratrole (0.50 mL), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 98/2) as a yellow solid (76% yield). The analyses are as described previously.$^{10a}$

1-Iodo-2,3,4-trimethoxybenzene (14). 14 was obtained according to the general procedure A starting from 1,2,3-trimethoxybenzene (0.68 g), but reducing the metalation reaction time to 30 min, and was isolated after purification by flash chromatography on silica gel (eluent: heptane/CH$_2$Cl$_2$ 50/50) as a light yellow solid (33% yield): mp < 50 °C (lit.$^{27}$ 42 °C); $^1$H NMR (300 MHz, CDCl$_3$) δ 3.84 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 6.49 (d, 1H, $J = 8.8$ Hz), 7.40 (d, 1H, $J = 8.8$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 154.3, 153.3, 142.6, 132.5, 109.7, 81.2, 80.9, 60.8, 56.1.

3-Iodo-2-methoxypyridine (16). 16 was obtained according to the general procedure A starting from 2-methoxypyridine (0.42 mL), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/Et$_2$O 85/15) as a white solid (43% yield): mp 64 °C (lit.$^{28}$ 66 °C); $^1$H NMR (300 MHz,
CDCl₃ δ 3.98 (s, 3H), 6.64 (dd, 1H, J = 4.8 and 7.5 Hz) 8.02 (dd, 1H, J = 1.7 and 7.5 Hz), 8.11 (dd, 1H, 1.7 and 4.8 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 161.8, 147.9, 146.4, 118.1, 79.7, 54.6.

2,2'-Dimethoxybipyridine (17). 17 was obtained according to the general procedure A starting from 2-methoxypyridine (0.42 mL), but using 2,2,6,6-tetramethylpiperidine (2.0 mL, 12 mmol), BuLi (12 mmol) and CoBr₂ (0.84 g, 4.0 mmol). It was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 98/2) as a light yellow solid (19% yield): mp 104 °C (lit.²⁹ 139-140 °C); ¹H NMR (300 MHz, CDCl₃) δ 3.92 (s, 6H), 6.95 (dd, 2H, J = 5.0 and 7.2 Hz), 7.59 (dd, 2H, J = 1.9 and 7.2 Hz), 8.18 (dd, 2H, J = 1.9 and 5.0 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 161.1 (2C), 146.2 (2C), 139.5 (2C), 119.8 (2C), 116.4 (2C), 53.5 (2C).

3-Iodo-2,6-dimethoxypyridine (19).³⁰ 19 was obtained according to the general procedure A starting from 2,6-dimethoxypyridine (0.53 mL), but reducing the metalation reaction time to 30 min, and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 98/2) as a brown solid (64% yield): mp < 50 °C; ¹H NMR (300 MHz, CDCl₃) δ 3.88 (s, 3H), 3.95 (s, 3H), 6.13 (d, 1H, J = 8.2 Hz), 7.78 (d, 1H, J = 8.2 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 163.2, 160.5, 149.3, 103.4, 65.5, 54.3, 53.5; HRMS calcd for C₇H₈INO₂ [(M+Na)⁺] 287.9497 and C₇H₇INO₂ [(M+H)⁺] 265.9678, found 287.9492 and 265.9680, respectively.

2,2',6,6'-Tetramethoxy-3,3'-bipyridine (20).³⁰ 20 was obtained according to the general procedure A starting from 2,6-dimethoxypyridine (0.53 mL), but reducing the metalation reaction time to 30 min, and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 96/4) as a white solid (34% yield): mp 144.5 °C; ¹H NMR (300 MHz, CDCl₃) δ 3.92 (s, 6H), 3.94 (s, 6H), 6.36 (d, 2H, J = 8.0 Hz), 7.52 (d, 2H, J = 8.0 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 162.0 (2C), 159.6 (2C), 142.5 (2C), 110.5 (2C), 100.4 (2C), 53.4 (2C), 53.3 (2C); HRMS calcd for C₁₄H₁₆N₂NaO₄ [(M+Na)⁺] 299.1008 and C₁₄H₁₇N₂O₄ [(M+H)⁺] 277.1188, found 299.1007 and 277.1192, respectively.
Ethyl 2-iodobenzoate (22). 22 was obtained according to the general procedure A starting from ethyl benzoate (0.61 mL), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 98/2) as a yellow oil (22% yield): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.41 (t, 3H, $J = 7.1$ Hz), 4.39 (q, 2H, $J = 7.1$ Hz), 7.14 (td, 1H, $J = 1.7$ and 7.8 Hz), 7.39 (td, 1H, $J = 1.7$ and 7.9 Hz), 7.79 (dd, 1H, $J = 1.7$ and 7.8 Hz), 7.98 (dd, 1H, $J = 1.0$ and 7.9 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 166.5, 141.1, 135.4, 132.4, 130.7, 127.8, 93.9, 61.6, 14.1. These data are analogous to those previously described.$^{31}$

General Procedure B (Deprotonation using 2 equiv CoBr$_2$ and 6 equiv LiTMP Followed by Trapping with an electrophile $\neq$ I$_2$). To a stirred cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (4.1 mL, 24 mmol) in THF (8 mL) were added BuLi (1.6 M hexanes solution, 24 mmol) and, 5 min later, CoBr$_2$ (1.7 g, 8.0 mmol). The mixture was stirred for 10 min at 0 °C before introduction of the substrate (4.0 mmol). After 30 min at room temperature, the electrophile (24 mmol) was added. The mixture was stirred overnight before addition of H$_2$O (10 mL) and extraction with EtOAc (3 x 20 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated under reduced pressure.

2-Allylanisole (2b). 2b was obtained according to the general procedure B (in this case, an extended reaction time of 2 h was used, and the following amounts for 2,2,6,6-tetramethylpiperidine (4.1 mL, 24 mmol), BuLi (12 mmol) and CoBr$_2$ (0.84 g, 4.0 mmol) were used) starting from anisole (0.44 mL), and using allyl bromide (1.0 mL, 12 mmol). 2b was isolated after purification by flash chromatography on silica gel (eluent: heptane/CH$_2$Cl$_2$ 92/8) as a colorless oil (6% yield). The analyses are as described previously.$^{10e}$

2,2'-Dimethoxybiphenyl (3). 3 was obtained according to the general procedure B (in this case, an extended reaction time of 2 h was used, and the following amounts for 2,2,6,6-tetramethylpiperidine (2.0 mL, 12 mmol), BuLi (12 mmol) and CoBr$_2$ (0.84 g, 4.0 mmol) were used) starting from anisole (0.44 mL), and using allyl bromide (1.0 mL, 12 mmol). 3 was isolated after purification by flash
chromatography on silica gel (eluents: heptane/CH₂Cl₂ 50/50) as a white solid (38% yield): mp 158-160 °C; $^{1}H$ NMR (300 MHz, CDCl₃) δ 3.80 (s, 6H), 7.07-6.99 (m, 4H), 7.28 (dd, 2H, $J = 1.7$ and 7.4 Hz), 7.36 (td, 2H, $J = 1.7$ and 8.2 Hz); $^{13}C$ NMR (75 MHz, CDCl₃): δ 156.9 (2C), 131.4 (2C), 128.5 (2C), 127.7 (2C), 120.2 (2C), 111.0 (2C), 55.6 (2C). These data are analogous to those previously described.⁳²

(2-Methoxyphenyl)(4-methoxyphenyl)methanol (2d). 2d was obtained according to the general procedure B starting from anisole (0.44 mL), and using anisaldehyde (3.0 mL). It was isolated after purification by flash chromatography on silica gel (eluents: heptane/CH₂Cl₂ 40/60) as a light yellow oil (84% yield). The analyses are as described previously.⁹ᵈ

(2-Methoxyphenyl)diphenylmethanol (2e). 2e was obtained according to the general procedure B starting from anisole (0.44 mL), and using benzophenone (4.4 g). It was isolated after purification by flash chromatography on silica gel (eluents: heptane/Et₂O 90/10) as a white solid (45% yield): mp 114.5 °C (lit.³³ 111-113 °C); $^{1}H$ NMR (300 MHz, CDCl₃) δ 3.81 (s, 3H), 7.08-7.01 (m, 2H), 7.40-7.18 (m, 7H), 7.66-7.49 (m, 3H), 7.83-7.87 (m, 2H), OH not seen; $^{13}C$ NMR (75 MHz, CDCl₃): δ 156.9, 144.1, 131.3, 128.5 (4C), 128.5, 127.7, 127.1 (4C), 126.8, 120.2, 110.9, 82.9, 55.5.

2-Methoxybenzophenone (2f). 2f was obtained according to the general procedure B starting from anisole (0.44 mL), and using benzoyl chloride (2.8 mL). It was isolated after purification by flash chromatography on silica gel (eluents: heptane/CH₂Cl₂ 50/50) as a white solid (30% yield): mp < 50 °C (lit.³⁴ 35-37 °C); $^{1}H$ NMR (300 MHz, CDCl₃): δ 3.72 (s, 3H), 6.98-7.07 (m, 2H), 7.34-7.58 (m, 5H), 7.79-7.83 (m, 2H); $^{13}C$ NMR (75 MHz, CDCl₃): δ 196.4, 157.3, 137.7, 132.9, 131.8, 129.8 (2C), 129.5, 128.8, 128.1 (2C), 120.4, 111.4, 55.5.

(2-Methoxyphenyl)diphenylphosphine (2g). 2g was obtained according to the general procedure B starting from anisole (0.44 mL), and using chlorodiphenylphosphine (4.3 mL). Due to its suspected easy oxidation, all the solvents were degassed before use. It was isolated after purification by flash chromatography on silica gel (eluents: heptane/CH₂Cl₂ 85/15) as a white solid (82% yield): mp 123 °C.
1H NMR (300 MHz, CDCl$_3$) $\delta$ 3.76 (s, 3H), 6.69-6.73 (m, 1H), 6.86-6.95 (m, 2H), 7.28-7.39 (m, 11H); 13C NMR (75 MHz, CDCl$_3$): $\delta$ 161.0 (d, $J_P = 15$ Hz), 136.6 (d, 2C, $J_P = 10$ Hz), 133.8 (d, 4C, $J_P = 20$ Hz), 133.5 (d, $J_P = 0.7$ Hz), 130.2, 128.4 (2C), 128.3 (d, 4C, $J_P = 12$ Hz), 125.5 (d, $J_P = 12$ Hz), 120.9 (d, $J_P = 0.8$ Hz), 110.1 (d, $J_P = 1.7$ Hz), 55.5 (d, $J_P = 0.7$); 31P NMR (75 MHz, CDCl$_3$): $\delta$ -16.8; HRMS calcd for C$_{19}$H$_{17}$NaOP [(M+Na)$^{+}$] 315.0915 and C$_{19}$H$_{18}$OP [(M+H)$^{+}$] 293.1095, found 315.0913 and 293.1094, respectively.

2-(2-Methoxyphenyl)pyridine (2c). 2c was obtained according to the general procedure B, but performing the trapping step at 50 °C, starting from anisole (0.44 mL), and using 2-chloropyridine (2.3 mL). It was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 90/10) as a yellow oil (25% yield). The analyses are as described previously.$^9d$

2-Allyl-1,4-dimethoxybenzene (5b). 5b was obtained according to the general procedure B starting from 1,4-dimethoxybenzene (0.55 g), and using allyl bromide (2.1 mL). It was isolated after purification by flash chromatography on silica gel (eluent: heptane/EtOAc 98/2) as a colorless oil (6% yield): 1H NMR (300 MHz, CDCl$_3$) $\delta$ 3.36 (d, 2H, $J = 6.6$ Hz), 3.76 (s, 3H), 3.78 (s, 3H), 5.01-5.14 (m, 2H), 6.10-5.90 (m, 1H), 6.92-6.68 (m, 3H); 13C NMR (75 MHz, CDCl$_3$): $\delta$ 153.5, 151.5, 136.7, 129.8, 116.1, 115.5, 111.4, 111.3, 56.0, 55.6, 34.2. The 1H NMR data are analogous to those described.$^{36}$

2-Allyl-1,3-dimethoxybenzene (8b).$^{37}$ 8b was obtained according to the general procedure B starting from 1,3-dimethoxybenzene (0.55 g), and using allyl bromide (2.1 mL). It was isolated after purification by flash chromatography on silica gel (eluent: heptane/CH$_2$Cl$_2$ 90/10) as a colorless oil (14% yield): 1H NMR (300 MHz, CDCl$_3$) $\delta$ 3.42 (dt, 2H, $J = 1.5$ and 6.1 Hz), 3.76 (s, 3H), 3.78 (s, 3H), 5.01-5.14 (m, 2H), 6.10-5.90 (m, 1H), 6.92-6.68 (m, 3H); 13C NMR (75 MHz, CDCl$_3$): $\delta$ 153.5, 151.5, 136.7, 129.8, 116.1, 115.5, 111.4, 111.3, 56.0, 55.6, 34.2. The 1H NMR data are analogous to those described.$^{36}$

2,2',6,6'-Tetramethoxybiphenyl (9). 9 was obtained according to the general procedure B starting from 1,3-dimethoxybenzene (0.55 g), and using allyl bromide (2.1 mL). It was isolated after purification by flash chromatography on silica gel (eluent: heptane/CH$_2$Cl$_2$ 30/70) as a white solid (6%
yield): mp 176 °C (lit.\textsuperscript{37} 174-175 °C); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 3.72 (s, 12H), 6.65 (d, 4H, \(J = 8.3\) Hz), 7.29 (t, 2H, \(J = 8.3\) Hz); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): \(\delta\) 158.3 (4C), 128.6 (2C), 112.5 (2C), 104.4 (4C), 56.1 (4C). These data are analogous to those previously described.\textsuperscript{38}

\textbf{1-Allyl-2,3-dimethoxybenzene (11b).}\textsuperscript{39} 11b was obtained according to the general procedure B starting from veratrole (0.50 mL), and using allyl bromide (2.1 mL). It was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 98/2) as a colorless oil (23% yield): \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 3.42 (d, 2H, \(J = 6.5\) Hz), 3.81 (s, 3H), 3.86 (s, 3H), 5.02-5.10 (m, 2H), 5.91-6.05 (m, 1H), 6.76-6.81 (m, 2H), 7.00 (t, 1H, \(J = 7.8\) Hz); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): \(\delta\) 152.7, 147.0, 137.2, 133.9, 123.8, 121.9, 115.4, 110.4, 60.5, 55.6, 33.9.

\textbf{2,2',3,3'-Tetramethoxybiphenyl (12).} 12 was obtained according to the general procedure B starting from veratrole (0.50 mL), and using allyl bromide (2.1 mL). It was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 88/12) as a white solid (62% yield): mp 106-108 °C (lit.\textsuperscript{40} 104-105 °C); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 3.65 (s, 6H), 3.90 (s, 6H), 6.87 (dd, 2H, \(J = 1.6\) and 7.6 Hz), 6.93 (dd, 2H, \(J = 1.6\) and 8.2 Hz), 7.08 (dd, 2H, \(J = 7.6\) and 8.2 Hz); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): \(\delta\) 152.7 (2C), 146.7 (2C), 132.8 (2C), 123.2 (2C), 123.2 (2C), 111.5 (2C), 60.5 (2C), 55.7 (2C); HRMS calcd for C\textsubscript{16}H\textsubscript{18}NaO\textsubscript{4} [(M+Na)+•] 297.1103 and C\textsubscript{16}H\textsubscript{18}K\textsubscript{O} \textsubscript{4} [(M+K)+•] 313.0842, found 297.1104 and 313.0854, respectively.

\textbf{2-(4-Methoxyphenyl)thiophene (24).} 24 was obtained according to the general procedure B starting from thiophene (0.32 g), but using 2,2,6,6-tetramethylpiperidine (2.0 mL, 12 mmol), BuLi (12 mmol) and CoBr\textsubscript{2} (0.84 g, 4.0 mmol). It was isolated after purification by flash chromatography on silica gel (eluent: heptane) as a yellow solid (19% yield). The analyses are as described previously.\textsuperscript{10e}

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References and Notes


(16) CoBr₂ more soluble than CoCl₂ was chosen to replace CoCl₂•TMEDA.


(21) The use of Zn as reductant did not change the yield of 3 either.

(22) The use of nitrobenzene or chloranil did not change the yield of 3 either.


