

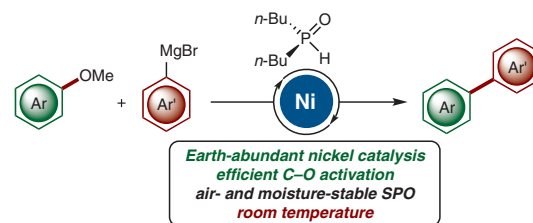
# Air-Stable Secondary Phosphine Oxides for Nickel-Catalyzed Cross-Couplings of Aryl Ethers by C–O Activation

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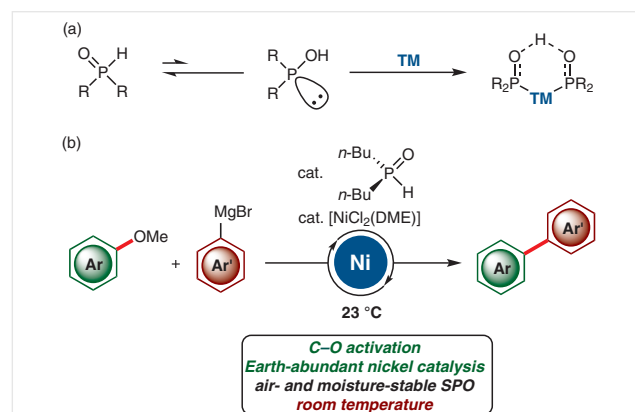
**Abstract** Air- and moisture-stable secondary phosphine oxides (SPOs) enabled nickel-catalyzed Kumada–Corriu cross-couplings of various arylmethyl ethers at room temperature by challenging C–O activation.

**Key words** C–O activation, arylation, cross-coupling, secondary phosphine oxide, nickel

Transition-metal-catalyzed cross-coupling reactions have emerged as a uniquely powerful tool for the assembly of substituted biaryl motifs.<sup>1</sup> Thus far, these cross-couplings have heavily relied on aryl halides as electrophilic coupling reagents. In contrast, easily accessible phenol-based electrophiles have recently undergone a renaissance as attractive alternatives.<sup>2</sup> On the basis of Wenkert's early studies from 1979,<sup>3</sup> the considerable potential of phenol-derived substrates has only recently been fully recognized. Thus, versatile cross-couplings have been realized with challenging carbamates, carbonates, sulfamates, silyloxyarenes, esters and ethers, among others, prominently featuring nickel catalysis.<sup>4</sup> Generally, these nickel catalysts largely require electron-rich tertiary phosphines as stabilizing ligands to guarantee efficacy in the key C–O bond scission.<sup>4</sup> Unfortunately, these electron-rich tertiary phosphines are usually highly air-sensitive, with a documented half-life for the aerobic oxidation of tri-*t*-butyl-phosphine of a few minutes.<sup>5</sup>

The (heteroatom-substituted) secondary phosphine oxides (HA)SPOs represent uniquely powerful ancillary preligands for metal catalysis because of their unique features, including the air- and moisture-stable nature, among oth-

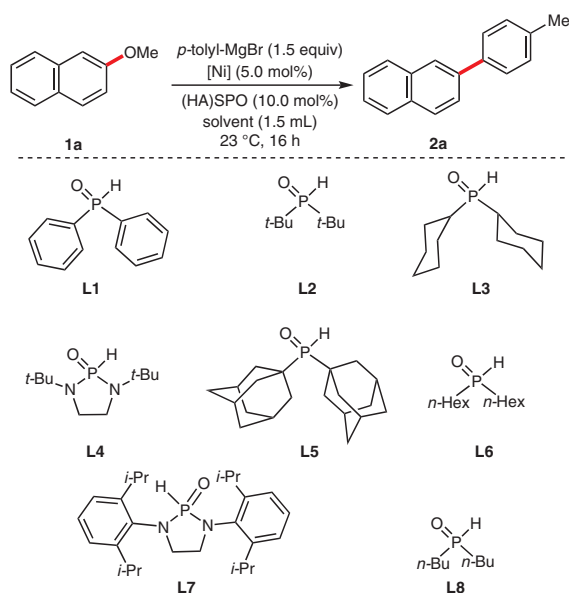
ers.<sup>6</sup> Notably, air-stable SPOs undergo a self-assembly process in the presence of transition metals to generate a monoanionic bidentate chelate coordination environment (Scheme 1, a).<sup>6</sup> While Ackermann and others have unraveled the considerable potential of SPO complexes towards a wealth of efficient cross-coupling reactions with various aryl halides,<sup>7</sup> the possibility of employing air-stable SPO preligands for more challenging C–O activations with aryl ethers has thus far proven elusive. Within our program on sustainable transition-metal-catalyzed transformations<sup>8</sup> and selective C–O activation,<sup>9</sup> we hence became attracted to probing the unprecedented use of air-stable SPOs preligands for cross-couplings with easily available aryl ethers, the result of which we report herein. Notable features of our findings include (i) air- and moisture-stable SPOs for efficient C–O activations, (ii) earth-abundant nickel catalysis, and (iii) exceedingly mild reaction conditions at room temperature (Scheme 1, b).



**Scheme 1** (a) Self-assembly with SPOs, (b) nickel/SPO-catalyzed C–O activation

We initiated our studies by probing reaction conditions for the envisioned cross-coupling of ether **1a** with Ni(acac)<sub>2</sub> and Ph<sub>2</sub>P(O)H (**L1**) in toluene at a room temperature of 23 °C (Table 1, entry 1). Among a variety of preligands and solvents, the electron-rich HASPO **L7** as well as (*n*-Bu)<sub>2</sub>P(O)H (**L8**) and THF gave optimal results, respectively (entries 2–13). NiCl<sub>2</sub>(DME) proved to be most effective (entries 14–17). It is noteworthy that under otherwise identical reaction conditions, the bidentate ligand dppp featured a significantly inferior performance (entry 18). A control experiment verified the essential role of the nickel catalyst (entry 19).

**Table 1** Optimization of the Nickel/SPO-Catalyzed C–O Activation of Ether **1a**<sup>a</sup>



| Entry | Ni Catalyst           | SPO       | Solvent | Yield (%) |
|-------|-----------------------|-----------|---------|-----------|
| 1     | Ni(acac) <sub>2</sub> | <b>L1</b> | toluene | 10        |
| 2     | Ni(acac) <sub>2</sub> | <b>L2</b> | toluene | 12        |
| 3     | Ni(acac) <sub>2</sub> | <b>L3</b> | toluene | 25        |
| 4     | Ni(acac) <sub>2</sub> | <b>L4</b> | toluene | 35        |
| 5     | Ni(acac) <sub>2</sub> | <b>L5</b> | toluene | 23        |
| 6     | Ni(acac) <sub>2</sub> | <b>L6</b> | toluene | 50        |
| 7     | Ni(acac) <sub>2</sub> | <b>L6</b> | THF     | 64        |
| 8     | Ni(acac) <sub>2</sub> | <b>L1</b> | THF     | 15        |
| 9     | Ni(acac) <sub>2</sub> | <b>L5</b> | THF     | 21        |
| 10    | Ni(acac) <sub>2</sub> | <b>L3</b> | THF     | 60        |
| 11    | Ni(acac) <sub>2</sub> | <b>L4</b> | THF     | 48        |
| 12    | Ni(acac) <sub>2</sub> | <b>L7</b> | THF     | 69        |
| 13    | Ni(acac) <sub>2</sub> | <b>L8</b> | THF     | 83        |
| 14    | Ni(OTf) <sub>2</sub>  | <b>L8</b> | THF     | 53        |
| 15    | NiBr <sub>2</sub>     | <b>L8</b> | THF     | n.r.      |

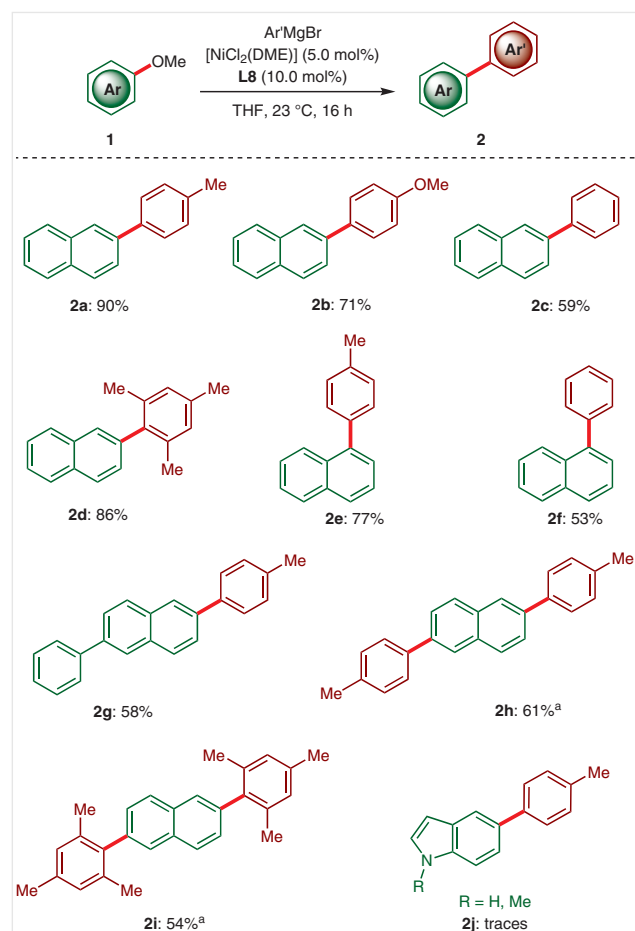
| Entry     | Ni Catalyst                  | SPO       | Solvent    | Yield (%)       |
|-----------|------------------------------|-----------|------------|-----------------|
| <b>16</b> | <b>NiCl<sub>2</sub>(DME)</b> | <b>L8</b> | <b>THF</b> | <b>90</b>       |
| 17        | NiCl <sub>2</sub> (DME)      | <b>L8</b> | THF        | 68 <sup>b</sup> |
| 18        | NiCl <sub>2</sub> (DME)      | dppp      | THF        | 39 <sup>c</sup> |
| 19        | –                            | <b>L8</b> | THF        | n.r.            |

<sup>a</sup> Reaction conditions: **1a** (0.50 mmol), *p*-TolMgBr (0.75 mmol), [Ni] (5.0 mol%), (HA)SPO (10 mol%), solvent (1.5 mL), 23 °C, 16 h; yield of isolated product given; n.r. = no reaction.

<sup>b</sup> SPO **L8** (5.0 mol%).

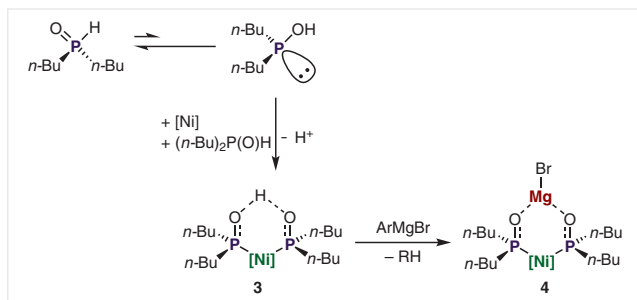
<sup>c</sup> dppp (5.0 mol%).

Having the optimized reaction conditions for the nickel/SPO-catalyzed C–O activation in hand, we tested its versatility with a representative set of ethers **1** (Scheme 2). Thus, a variety of naphthyl ethers **1** were identified as viable substrates for the Kumada–Corriu cross-coupling to deliver the desired products **2** with high catalytic efficacy. Notably, the nickel catalyst derived from the air-stable SPO **L8** even proved amenable to the chemoselective synthesis of biaryl **2b** and the sterically congested mesityl nucleophiles with comparable levels of activity (**2d** and **2i**).



**Scheme 2** Scope of SPO/nickel-catalyzed C–O activation; <sup>a</sup> with NiCl<sub>2</sub>(DME) (10 mol%) and **L8** (20 mol%)

Based on our previous literature reports,<sup>6c-d,10</sup> the working mode of the air-stable SPO-enabled C–O activation is suggested to initially involve the formation of complex **3** through self-assembly, along with the subsequent C–O activation by the key hetero-bimetallic intermediate **4** (Scheme 3).



**Scheme 3** Plausible working mode of SPOs for C–O activation

In summary, we have reported on the first use of air-stable secondary phosphine oxides (SPOs) for challenging cross-couplings of aryl ethers by C–O activation.<sup>11</sup> Thus, in situ generated nickel catalysts enabled efficient Kumada–Corriu arylations of naphthyl ethers at room temperature, even when using sterically hindered aryl nucleophiles.

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## Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1611663>.

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(11) **Representative Experimental Procedure and Characterization Data**

A mixture of 2-methoxynaphthalene (**1a**) (79 mg, 0.5 mmol), [NiCl<sub>2</sub>(DME)] (6.0 mg, 0.025 mmol, 5.0 mol%), and **L8** (8.0 mg, 0.05 mmol, 10.0 mol%) was stirred in THF (1.5 mL) for 2 min at ambient temperature under N<sub>2</sub>. Then, *p*-TolMgBr (1.0 M in THF, 0.75 mL, 0.75 mmol) was added, and the resulting solution was stirred for 16 h at ambient temperature. To the reaction was added aqueous HCl (1 M, 5 mL) and then EtOAc (5 mL), and the separated aqueous phase was extracted with EtOAc (2 × 5 mL).

The combined organic layers were dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The remaining residue was purified by column chromatography on silica gel (*n*-hexane) to yield **2a** (98 mg, 90%) as a colorless solid. Mp 93–95 °C. IR (ATR): 3054, 3024, 1501, 1351, 893, 856, 811, 748 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 8.14 (d, *J* = 1.4 Hz, 1 H), 8.03–7.93 (m, 3 H), 7.85 (dd, *J* = 8.5, 1.9 Hz, 1 H), 7.74 (d, *J* = 8.1 Hz, 2 H), 7.64–7.54 (m, 2 H), 7.40 (dd, *J* = 8.5, 0.6 Hz, 2 H), 2.53 (s, 3 H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 138.5 (C<sub>q</sub>), 138.3 (C<sub>q</sub>), 137.2 (C<sub>q</sub>), 133.8 (C<sub>q</sub>), 132.5 (C<sub>q</sub>), 129.6 (CH), 128.4 (CH), 128.2 (CH), 127.7 (CH), 127.3 (CH), 126.3 (CH), 125.8 (CH), 125.6 (CH), 125.5 (CH), 21.2 (CH<sub>3</sub>). MS (EI): *m/z* (relative intensity) = 218 [M]<sup>+</sup> (100), 217 (41), 202 (35). HRMS (EI): *m/z* [M]<sup>+</sup> calcd for [C<sub>17</sub>H<sub>14</sub>]<sup>+</sup>: 218.1096; found: 218.1094.