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

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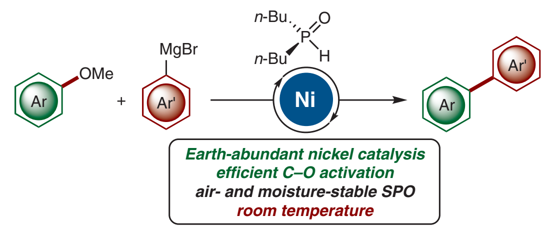

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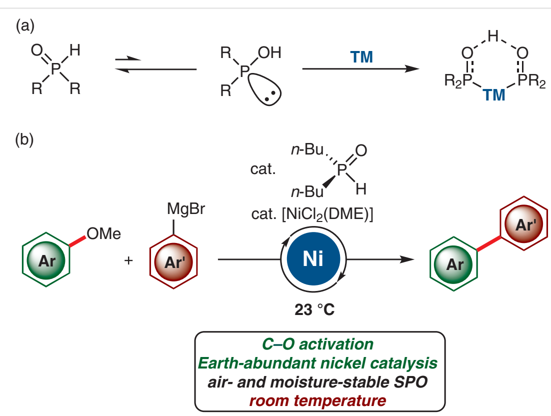
Abstract Air- and moisture-stable secondary phosphine oxides (SPOs) enabled nickel-catalyzed Kumada–Corriu cross-couplings of various arylmethyl ethers at room temperature by challenging C–O activation.

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.[1] 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.[2] On the basis of Wenkert's early studies from 1979,[3] 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.[4] Generally, these nickel catalysts largely require electron-rich tertiary phosphines as stabilizing ligands to guarantee efficacy in the key C–O bond scission.[4] 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.[5]

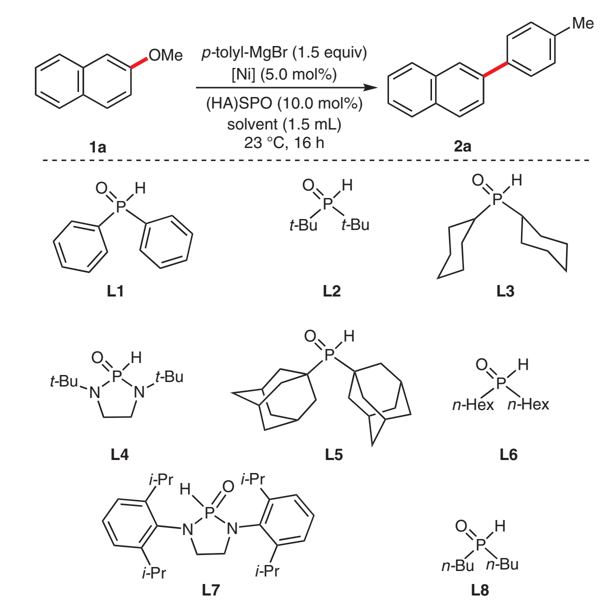
The (heteroatom-substituted) secondary phosphine oxides (HA)SPOs represent uniquely powerful ancillary preligands for metal catalysis because of their unique features, including the air- and moisture-stable nature, among others.[6] Notably, air-stable SPOs undergo a self-assembly process in the presence of transition metals to generate a monoanionic bidentate chelate coordination environment (Scheme 1, a).[6] While Ackermann and others have unraveled the considerable potential of SPO complexes towards a wealth of efficient cross-coupling reactions with various aryl halides,[7] 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[8] and selective C–O activation,[9] 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 $Ni(acac)_2$ and $Ph_2P(O)H$ (**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 $(n\text{-}Bu)_2P(O)H$ (**L8**) and THF gave optimal results, respectively (entries 2–13). $NiCl_2(DME)$ 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).

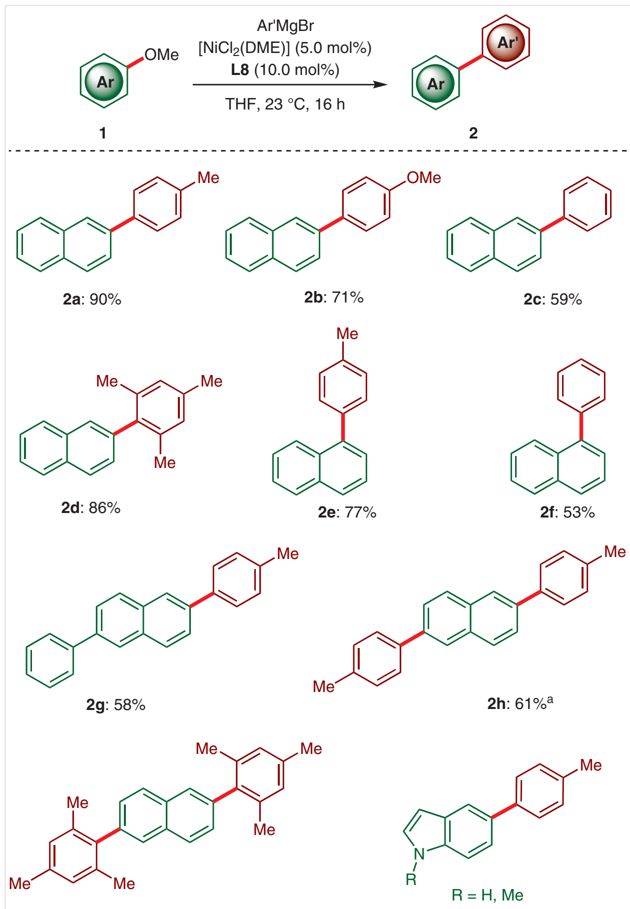
Table 1 Optimization of the Nickel/SPO-Catalyzed C–O Activation of Ether **1a**[a]



Entry	Ni Catalyst	SPO	Solvent	Yield (%)
1	$Ni(acac)_2$	**L1**	toluene	10
2	$Ni(acac)_2$	**L2**	toluene	12
3	$Ni(acac)_2$	**L3**	toluene	25
4	$Ni(acac)_2$	**L4**	toluene	35
5	$Ni(acac)_2$	**L5**	toluene	23
6	$Ni(acac)_2$	**L6**	toluene	50
7	$Ni(acac)_2$	**L6**	THF	64
8	$Ni(acac)_2$	**L1**	THF	15
9	$Ni(acac)_2$	**L5**	THF	21
10	$Ni(acac)_2$	**L3**	THF	60
11	$Ni(acac)_2$	**L4**	THF	48
12	$Ni(acac)_2$	**L7**	THF	69
13	$Ni(acac)_2$	**L8**	THF	83
14	$Ni(OTf)_2$	**L8**	THF	53
15	$NiBr_2$	**L8**	THF	n.r.
16	**$NiCl_2(DME)$**	**L8**	**THF**	**90**
17	$NiCl_2(DME)$	**L8**	THF	68[b]
18	$NiCl_2(DME)$	dppp	THF	39[c]
19	–	**L8**	THF	n.r.

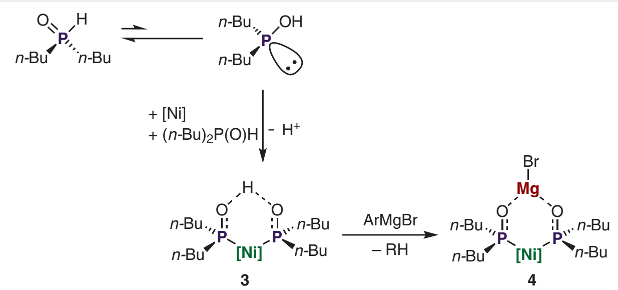
[a] Reaction conditions: **1a** (0.50 mmol), *p*-TolMgBr (0.75 mmol), [Ni] (5.0 mol%), (HA)SPO (10 mol%), solvent (1.5 mL), 23 °C, 16 h; yield of isolated product given; n.r. = no reaction.
[b] SPO **L8** (5.0 mol%).
[c] dppp (5.0 mol%).

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; [a] with $NiCl_2(DME)$ (10 mol%) and **L8** (20 mol%)

Based on our previous literature reports,[6c–d,10] 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.[11] Thus, in situ generated nickel catalysts enabled efficient Kumada–Corriu arylations of naphthyl ethers at room temperature, even when using sterically hindered aryl nucleophiles.

Funding Information

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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), [$NiCl_2$(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_2. 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_2SO_4 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^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 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). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.5 (C_q), 138.3 (C_q), 137.2 (C_q), 133.8 (C_q), 132.5 (C_q), 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_3). MS (EI): *m*/*z* (relative intensity) = 218 [M]$^+$ (100), 217 (41), 202 (35). HRMS (EI): *m*/*z* [M]$^+$ calcd for $[C_{17}H_{14}]^+$: 218.1096; found: 218.1094.