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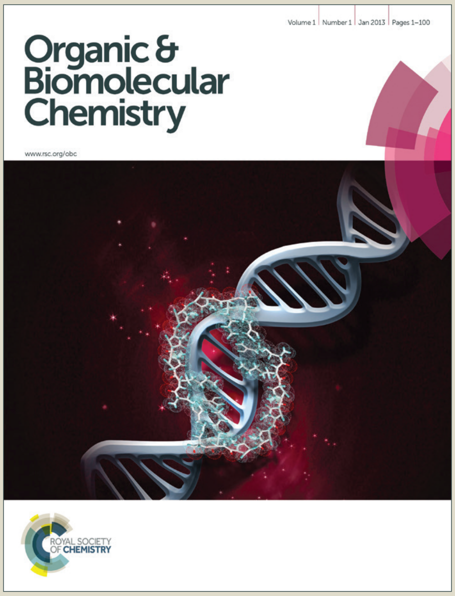

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A diphenyl ether derived bidentate secondary phosphine oxide as a preligand for nickel-catalyzed C–S cross-coupling reactions†

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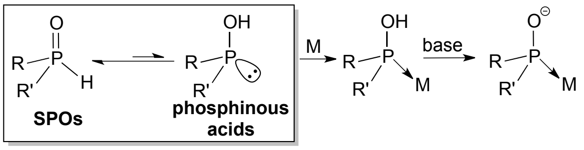
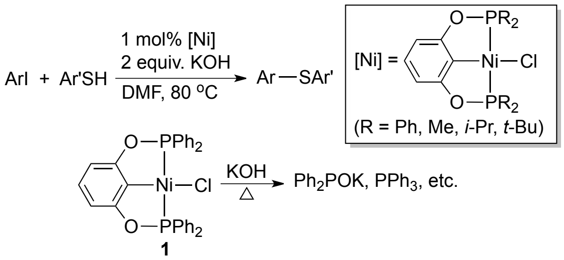
A new bidentate secondary phosphine oxide (SPO) was synthesized from diphenyl ether via *ortho*-lithiation, phosphorylation with $PhP(Cl)NEt_2$, and hydrolysis in an acidic medium. Nickel(0) species ligated with this new SPO was established as a more effective catalyst than Ni(0)-$Ph_2P(O)H$ for the cross-coupling of aryl iodides with aryl thiols.

Secondary phosphine oxides (SPOs) have become increasingly important for transition-metal-catalyzed reactions.[1] They are often described as preligands because upon mixing with a metal complex or salt, the tautomeric equilibria between SPOs and phosphinous acids are usually shifted to the trivalent-phosphorus compounds, resulting in the formation of *P*-bound complexes (Scheme 1). In rare cases, however, SPOs can coordinate to a metal via the oxygen lone pair without isomerization to the phosphinous acids.[2] The attractiveness of using SPOs for catalysis stems from the fact that they are generally air and moisture stable. For reactions under basic conditions, the coordinated phosphinous acids can be deprotonated, which may provide additional benefits, especially for catalytic reactions requiring an electron-rich metal center. The calculated Tolman's electronic parameters for *O*-anionic phosphinito ligands[3] have suggested that these ligands are more donating than many trialkylphosphines.[4] In the early 2000's, Li and co-workers first demonstrated the success of SPOs such as $(t\text{-Bu})_2P(O)H$ in promoting palladium- or nickel-catalyzed C–C, C–N and C–S cross-coupling reactions.[5] Since then, many new SPOs have been developed as preligands for cross-coupling reactions[6] and other catalytic processes.[7-10]



Scheme 1 Tautomeric equilibria of SPOs and their *P*-bound complexes.

We became interested in SPOs several years ago when we were exploring catalytic applications of nickel POCOP-pincer complexes for C–S cross-coupling reactions (Scheme 2).[11] Our mechanistic investigation focusing on catalyst **1** showed that, under the catalytic conditions, the pincer scaffold was degraded to Ph_2POK, PPh_3 and other phosphorus-containing products. The true catalytically active species was proposed to be an SPO-ligated Ni(0) complex based on the observation that $Ni(COD)_2$-$Ph_2P(O)H$ exhibited similar catalytic activity. $Ph_2P(O)H$, though effective, was shown to react with KOH at 80 °C to yield PPh_3 and some unidentified species, which compromised its ability to promote the catalytic reactions.



Scheme 2 Reactivity of nickel POCOP-pincer complexes in C–S cross-coupling reactions.

To develop a more efficient catalytic system, we shifted our attention to bidentate SPOs under the premise that chelating ligands would be less likely to dissociate from metals to provide the opportunity for a base to decompose the ligands. It should be mentioned that two mono SPOs can coordinate to the same metal, and with the loss of proton(s), can be tethered together by hydrogen bonding (structure **A** in Fig. 1),[5,6k,7a-e,12] or via electrostatic interactions with an alkali ion (structure **B**),[4] thus mimicking a bidentate SPO ligand. For bidentate ligands with a covalent backbone, we are aware of only one study in which a ferrocene unit was used to link two SPOs (ligand **2**).[13] Our design of new bidentate SPO ligands was inspired by van Leeuwen's DPEphos, which was prepared from diphenyl ether[14] and successfully employed in cross-coupling reactions.[15] Recently, we sought to prepare the analogous

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SPO ligand **3**, guided by the hypothesis that the large bite angle and the central oxygen atom might be particularly beneficial for the reductive elimination of ArSAr'.[16]

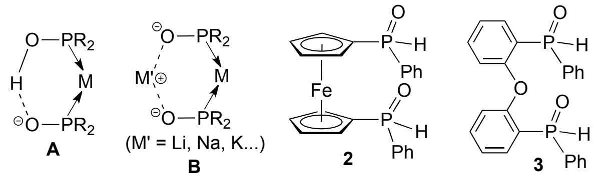
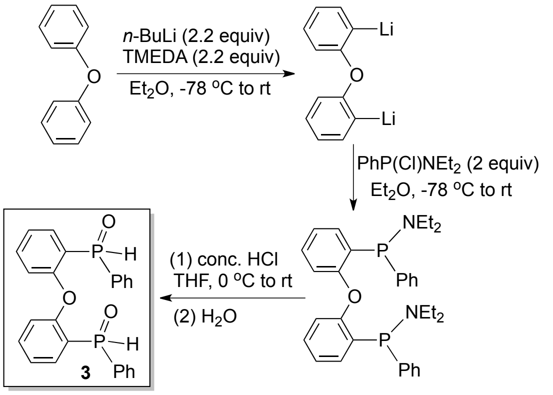


Fig. 1 Complexes bearing a pseudo bidentate SPO (**A** and **B**, charge-localized forms) and SPOs with a covalent backbone.

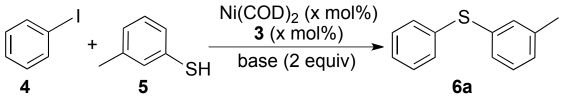
Synthesis of the targeted ligand **3** was accomplished in three steps as illustrated in Scheme 3. Slow addition of PhP(Cl)NEt_2 to the lithiated diphenyl ether was necessary for obtaining a good product yield. The final hydrolysis step had to be carried out using a concentrated HCl solution.[17] Other standard methods for preparing SPOs from RP(R')NEt_2 (e.g., hydrolysis on silica gel[13] or with Amberlyst-15®,[18] or conversion to RP(R')H using $LiAlH_4$ or $LiBEt_3H$[19] followed by air oxidation) proved to be unsuccessful here. Analytically pure **3** was obtained from recrystallization of the crude product in ethyl acetate at –5 °C, which resulted in 46% overall isolated yield starting from diphenyl ether. The $^{31}P\{^1H\}$ NMR spectrum of **3** in $CDCl_3$ showed two singlets at 13.75 and 13.87 ppm with an integration ratio of 28 : 72. This is due to fact that there are two (*meso* and *racemic*) diastereomers of **3**. The presence of a diastereomeric mixture was further confirmed by ^1H NMR spectroscopy, which gave the same ratio for the P*H* and aromatic resonances. The one-bond coupling constant $^1J_{P\text{-}H}$ was measured to be 503 Hz from the proton-coupled ^{31}P NMR spectrum. The IR spectrum of **3** revealed a characteristic band at 2333 cm^{-1} for the P–H bond stretch.[20] Separation of the two diastereomers was not attempted, and the isomeric mixture described above was used directly for the C–S cross-coupling study.



Scheme 3 A synthetic route to **3**.

Cross-coupling of iodobenzene (**4**) with 3-methylbenzenethiol (**5**) was selected for the optimization of the reaction conditions (Table 1). In order to use the catalytic system $Ni(COD)_2$-$Ph_2P(O)H$ (1 : 2) as a benchmark, substrate concentrations, the amount of base (2 equiv of KOH with respect to **5**), solvent (DMF) and temperature (80 °C) were initially kept the same as those used in our previous study with the mono SPO.[11] A series of experiments with variable amounts of catalyst (entries 1-4) showed that a catalyst loading as low as 0.5 mol% was sufficient for obtaining a nearly quantitative GC yield of the sulfide **6a**, in which case the cross-coupling reaction was completed in 1 h (entry 3). By comparison, the reaction catalyzed by $Ni(COD)_2$-$Ph_2P(O)H$ needed 2 h and 1 mol% catalyst. As expected, control experiments without using $Ni(COD)_2$ or **3** or both under otherwise the same conditions showed a negligible amount of product formed, confirming that both nickel and the ligand are required. At room temperature, almost no sulfide product was detected (entry 5). Unlike the mono SPO system,[11] weaker bases such as K_3PO_4 (entry 6) and Na_2CO_3 (entry 7) could be used here in place of KOH without affecting the GC yield of **6a**. Interestingly, NaOH, which was shown to be as effective as KOH in the mono SPO system, was an inferior base for the new catalytic system, giving a noticeably lower product yield (entry 8). Both catalytic systems suffered low yields when Cs_2CO_3 (entry 9) or NaOMe (entry 10) was used as the base, or when the reaction was carried out in THF (entry 11) or toluene (entry 12). Although using a large excess of KOH may not be a concern for the synthesis, the amount could be reduced from 2 to 1.1 equiv with limited impact on the yield (entry 13). Under such catalytic conditions, replacing **3** by DPEphos afforded **6a** in only 45% yield (entry 14), suggesting that the SPO moiety is critical to the success of the reaction.

Table 1 Optimization of the catalytic conditions[a]

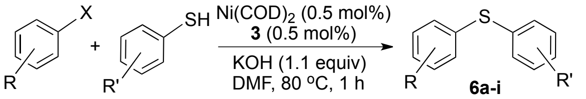


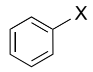
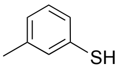
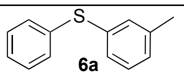
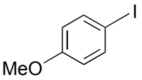
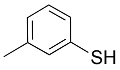
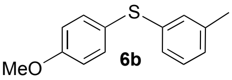
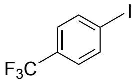
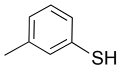
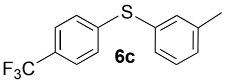
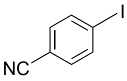
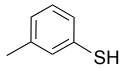
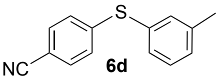
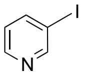
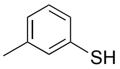
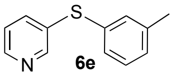
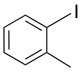
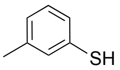
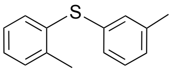
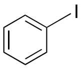
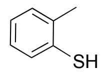
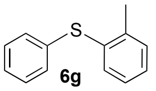
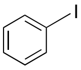
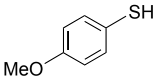
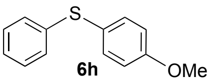
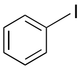
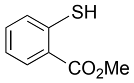
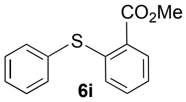
Entry	x	Temp. (°C)	Time (h)	Solvent	Base	GC yield (%)[b]
1	5	80	0.5	DMF	KOH	>99
2	1	80	1	DMF	KOH	>99
3	0.5	80	1	DMF	KOH	99
4	0.25	80	24	DMF	KOH	59
5	0.5	23	24	DMF	KOH	trace
6	0.5	80	1	DMF	K_3PO_4	>99
7	0.5	80	1	DMF	Na_2CO_3	98
8	0.5	80	1	DMF	NaOH	87
9	0.5	80	1	DMF	Cs_2CO_3	10
10	0.5	80	1	DMF	NaOMe	6
11	0.5	80	1	THF	KOH	6
12	0.5	80	1	Toluene	KOH	trace
13	0.5	80	1	DMF	KOH	95[c]
14	0.5	80	1	DMF	KOH	45[c,d]

[a] Reaction conditions: 1.1 mmol of **4**, 1.0 mmol of **5**, 2.0 mmol of base (except entries 13 and 14), $Ni(COD)_2$-**3** (variable), and 1.0 mmol *n*-decane (GC internal standard) in 6 mL of solvent. [b] Average of three runs. [c] 1.1 equiv of KOH was used. [d] **3** was replaced by DPEphos.

The substrate scope of the new catalytic system was subsequently examined using the optimized conditions (0.5 mol% catalyst in DMF, 1.1 equiv of KOH, 80 °C, 1 h). As shown in Table 2, the bidentate SPO-ligated nickel catalyst was effective for the C–S coupling of aryl iodides, but not aryl bromides (entry 2) and chlorides (entry 3). Functional groups such as OMe, CF_3, CN and pyridyl groups (entries 4-7) were tolerated under the reaction conditions. In general, a slight excess of aryl iodide was employed to ensure that all the thiols were fully converted. Because of the foul odor, even a trace amount of unreacted thiol could make the work-up process unpleasant. However, in the case of 4-iodobenzonitrile (entry 6), an exact 1 : 1 mixture of aryl iodide and aryl thiol was used because separating the leftover 4-iodobenzonitrile from **6d** proved to be challenging. Sterically crowded substrates (entries 8, 9 and 11) required a higher catalyst loading (1 or 5 mol%) to achieve synthetically useful yields, and so did electron-rich thiols such as the one in entry 10. Despite rigorous exclusion of oxygen from the reagents and solvent, disulfides (ArS–SAr) were observed as the byproducts along with **6f-i**. In the event that separating the disulfide from the desired sulfide became problematic (entries 8 and 9), $NaBH_4$ was added to the crude product prior to purification by column chromatography (see ESI for details). The borohydride could effectively remove the disulfides; however, it also eroded the sulfide yields.

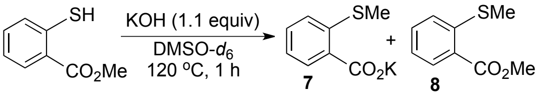
Table 2 Nickel-catalyzed thiolation of aryl halides[a]



Entry	Aryl halide	Aryl thiol	Product	Yield[b] (%)
			 6a	
1	(X = I)			86
2	(X = Br)			33[c]
3	(X = Cl)			2[c]
4			 6b	89
5			 6c	90
6			 6d	86[d]
7			 6e	94
8			 6f	58[e]
9			 6g	37(85)[e,f]
10			 6h	91[e]
11			 6i	77[g]

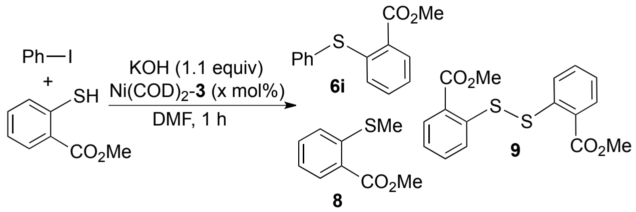
[a] Reaction conditions: 1.1 mmol of aryl halide, 1.0 mmol of aryl thiol, 1.1 mmol KOH and $Ni(COD)_2$-**3** (0.5 mol%) in 6 mL of DMF at 80 °C. [b] Isolated yield unless otherwise mentioned. [c] GC yield determined using 1.0 mmol of *n*-decane as an internal standard. [d] 1.0 mmol of aryl iodide was used. [e] 1 mol% catalyst loading. [f] NMR yield (in parenthesis) determined using 0.33 mmol of mesitylene as the internal standard. [g] 5 mol% catalyst loading.

It is noted that only a handful of studies have included alkyl thiosalicylates as substrates for cross-coupling reactions.[21] In DMSO-d_6,[22] methyl thiosalicylate was shown to react with KOH to afford methyl aryl sulfides **7** and **8** (5 : 1) as a result of intra- and intermolecular nucleophilic attack of the methyl group by the thiolate (eqn (1)). Therefore, it was not too surprising that with a low catalyst loading, methyl aryl sulfide **8** was the main isolated product (entries 1 and 2, Table 3).[23] However, when the catalyst loading was increased to 5 mol%, the cross-coupling reaction became more competitive than the uncatalyzed reactions depicted in eqn (1), providing diaryl sulfide **6i** as the major product (entry 3).



(1)

Table 3 Reaction of methyl thiosalicylate with iodobenzene

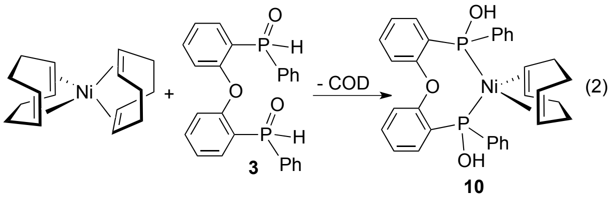


Entry	x	Temp. (°C)	Isolated yields for **6i**/**8**/**9** (%)
1	0.5	80	3/22/9
2	0.5	120	1/25/0
3	5	80	77/3/0

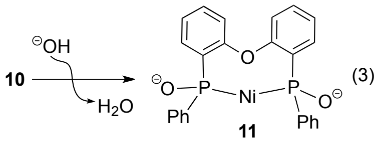
Yuan, Bolm and co-workers have demonstrated that it is possible to create a superbasic medium with KOH dissolved in DMSO, allowing the C–S bond formation between aryl halides and thiophenol to take place without using any metal catalyst.[24] Such a process operates at a more elevated temperature of 130 °C, and for a *para*-substituted aryl halide, often produces a mixture of regioisomers presumably via a benzyne intermediate. In our system, the cross-coupling reaction is clearly a nickel-catalyzed process, supported by the following two pieces of evidence: first, only one regioisomer was observed for the coupling of a *para*-substituted aryl iodide (entries 4-6, Table 2); and second, the control experiment in the absence of $Ni(COD)_2$ did not yield an appreciable amount of cross-coupling product.

We propose that in the present study, **3** first displaces one of the COD ligands from $Ni(COD)_2$, forming complex **10** as illustrated in eqn (2).[25] Isolation and full characterization of this particular nickel complex are ongoing in our laboratory. Monitoring the reaction in DMF by $^{31}P\{^1H\}$ NMR spectroscopy indicated that at room temperature, the ligand substitution process was completed within 3 h (see ESI). As the resonances of **3** started to diminish, two new resonances emerged at 88.64 and 90.98 ppm (with a 55 : 45 ratio), possibly due to the formation of a pair of diastereomeric *P*-bound complexes. IR spectrum of **10** further confirmed the absence of P–H bonds. The same reaction carried out in THF was slightly faster (completed within 2 h), producing a 59 : 41 mixture of isomers. In contrast, the reaction conducted in toluene was substantially slower, requiring more than 3 days to complete the substitution process. At the 3 h mark, about 40% of **3** was consumed and the ratio for the resultant two *P*-bound complexes was calculated to be 63 : 37.

These results suggest that the rate for the complexation of **3** with nickel and the product ratio of the reaction are solvent dependent. Increasing the temperature could potentially accelerate the ligand substitution process; however, Ni(COD)$_2$ is known to degrade rapidly above the ambient temperature.[26] For this reason, all the catalytic reactions described in this work employ Ni(COD)$_2$ and **3** that are pre-mixed at room temperature for 3 h.



In the presence of KOH, the phosphinous acid moieties of **10** are likely to be deprotonated, resulting in an *O*-anionic bis(phosphinite) Ni(0) complex **11** (eqn (3)), which may or may not have the central oxygen atom coordinated to the nickel. A similar palladium complex $[\kappa^P\text{-}\{(t\text{-Bu})_2PO\}_2Pd(0)]^{2-}$ has been proposed by Li and co-workers for cross-coupling reactions catalyzed by a palladium complex ligated with $(t\text{-Bu})_2P(O)H$ (two SPOs per palladium).[5b] How such a species affect the subsequent steps of the catalytic process (see ESI for a plausible mechanism,) will be the focus of our future study.



Conclusions

In conclusion, we have synthesized a new bidentate secondary phosphine oxide **3**, only the second of the kind bearing a covalent backbone. The 1 : 1 mixture of Ni(COD)$_2$ and **3** is a very effective catalyst for C–S coupling of aryl iodides with aryl thiols, including those with an OMe, CF$_3$, CN, pyridyl or ester group. Sterically crowded aryl iodides and aryl thiols are viable substrates, although higher catalytic loadings are required. Compared to our previously reported catalyst prepared from Ni(COD)$_2$ and Ph$_2$P(O)H,[11] the new catalytic system shows improvement, as measured by catalytic loading, reaction time and the amount of base used. It also compares favorably (in terms of catalyst loading and temperature) with other nickel-based catalytic systems for C–S bond formation reactions.[27] Our preliminary mechanistic study suggests that **3** binds to nickel via its phosphinous acid based tautomer. More detailed mechanistic investigations of the proposed catalytic species are currently in progress.

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