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High yield thiolation of iodobenzene catalyzed by the phosphinite nickel PCP pincer complex: [NiCl{C_6H_3-2,6-($OPPh_2)_2$}]

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Abstract—[NiCl{C_6H_3-2,6-($OPPh_2)_2$}] efficiently catalyzes the thiolation of iodobenzene with a broad scope of disulfides in the presence of zinc, the coupled products are obtained in excellent and in many cases nearly quantitative yields.

The increasing interest in the use and applications of diarylthioethers and alkylarylthioethers has in recent years lead to the design of efficient and high yield methods for their synthesis.[1] Moreover, the scope and application of organosulfur chemistry in organic synthetic reactions has increased tremendously since sulfur-containing groups serve as an important auxiliary function in synthetic sequences,[2] for instance, in the reversing of the polarity (Umpolong), the enhancement of the acidity of C–H bonds, and the transfer of chirality from sulfur to carbon.[3] Additionally, arylsulfides are a common functionality found in a number of drugs commonly used for the treatment of diabetes, Alzheimer's, and Parkinson's diseases.[4] On the other hand, transition metal complex-catalyzed reactions have made a great contribution to the recent growth of organic synthesis.[5] However, transition metal complex-catalyzed synthetic reactions using sulfur-containing compounds remain a fertile field of study, since this sort of complexes have long been known to act as catalyst poisons often rendering the catalytic reaction totally ineffective.[6] However, in recent years several useful transformations of sulfur containing compounds using transition metal catalysts have been developed.[7] In the particular case of arylsulfides, their metal-catalyzed synthesis has included the cross coupling of thiols with aryl halides using copper compounds under basic conditions or palladium catalyst.[8] Nevertheless, the metal catalyzed thiolation of arylhalides with disulfides has been scarcely studied.[9]

We believe that a robust complex used as catalyst may render a better performance in the alkyl and aryl thiolation of halobenzenes. Thus we have previously reported the use of fluorinated bis-imino nickel(II) NNN pincer complexes [$NiCl_2${C_5H_3N-2,6-($CHNAr_f)_2$}] as efficient and selective catalysts for the cross coupling of $(RS)_2$ and halobenzenes attaining yields as high 90% of methyl phenyl sulfide from the reaction of iodobenzene and MeS–SMe.[10] However this system affords lower yields as the substituent in the disulfide increases in size, thus the lower yields employing the diimino system were only of 60% for di-*tert*-butyl disulfide.[10] Additionally, we have previously synthesized the PCP pincer ligand precursor [C_6H_4-1,3-($OPPr^i_2)_2$] (**1**).[11] And reported on the use of its palladium PCP pincer complex [PdCl{C_6H_3-2,6-($OPPr^i_2)_2$}] (**2**) for the efficient, high yield C–C coupling reaction of a wide variety of chlorobenzenes.[12] It was therefore of interest to synthesize an analogous nickel complex [NiCl{C_6H_3-2,6-($OPR_2)_2$}] in an effort to obtain an efficient, cheap, and easy to synthesize system for the thiolation of iodobenzene using disulfides. Hence, we synthesized the NiPCP phosphinite pincer complex [NiCl{C_6H_3-2,6-($OPPh_2)_2$}] (**3**). Complex **3** was obtained in a very facile manner and quantitative yield as an olive green microcrystalline powder by

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Keywords: C–S cross-coupling; Phosphinite ligands; Homogeneous catalysis; Nickel; Pincer complexes; Thiolation.

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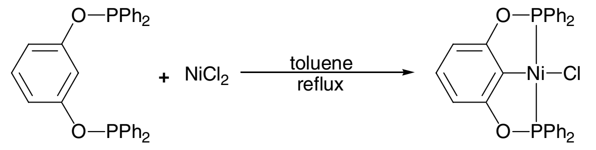
C–H activation from the reaction of the ligand [C_6H_4-1,3-$OPPh_2)_2$][13] and $NiCl_2$.[14]



(**3**)

Unlike 1,3-bis(phos**phino**)benzenes, the 1,3-bis(phos**phinite**)benzene [C_6H_4-1,3-$OPPh_2)_2$] can be conveniently prepared in 95% yield from the reaction of inexpensive precursors (resorcinol and chlorodiphenylphosphine)[13] and more important, this ligand is not sensitive to oxygen, thus it can be easily handled in the open air. Crystals of **3** suitable for single crystal X-ray diffraction analysis were obtained from a CH_2Cl_2/MeOH solvent system, showing the nickel center to be into a slightly distorted square planar environment with the phosphinite ligand being coordinated in a tridentate PCP pincer fashion having one chloride completing the coordination sphere (Fig. 1).[15]

The results of our studies on the catalytic activity of **3** are summarized in Table 1. In order to optimize the efficiency of the catalytic system, we initially examined the coupling reaction of iodobenzene and MeS–SMe by **3** under a variety of reaction conditions[19] and analyzed the product mixtures through GC–MS techniques. We found the reactions uniformly affording >99% yields of the corresponding asymmetric sulfide when carried out in DMF, in the presence of zinc powder as a necessary ingredient. Using the same combination of reagents in a preparative scale experiment, we were able to isolate the coupled product in nearly quantitative yield. At 110 °C, a reaction time of 24 h is required to achieve this high conversion.

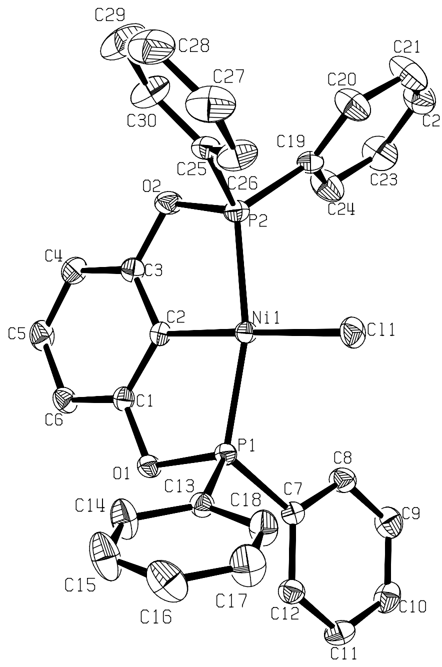
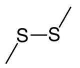
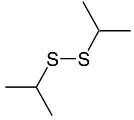
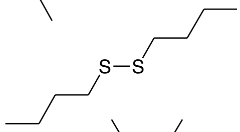
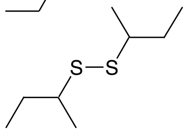
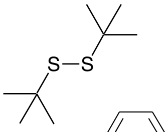
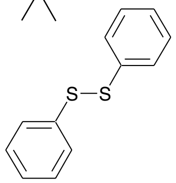


Figure 1. Thermal ellipsoid (50% probability) drawing of NiCl{C_6H_3-2,6-$(OPPh_2)_2$} (**3**). Hydrogen atoms have been omitted for clarity. Selected bond distances (Å) and angles (°): Ni(1)–C(2) 1.879(2), Ni(1)–P(1) 2.1556(6), Ni(1)–P(2) 2.1582(7), Ni(1)–Cl(1) 2.1880(6), C(2)–Ni(1)–P(1) 81.98(7), C(2)–Ni(1)–P(2) 82.31(7), P(1)–Ni(1)–P(2) 164.16(2), C(2)–Ni(1)–Cl(1) 178.43(7), P(1)–Ni(1)–Cl(1) 97.24(2), P(2)–Ni(1)–Cl(1) 98.51(3).

Table 1. Alkyl- and arylthiolation of iodobenzene by [NiCl{C_6H_3-1,3-$(OPPh_2)_2$}] (**3**)

Entry	RS–SR	Yield[a] (%)
1		>99
2		>99
3		>99
4		>99
5		49[b]
6		86[c]

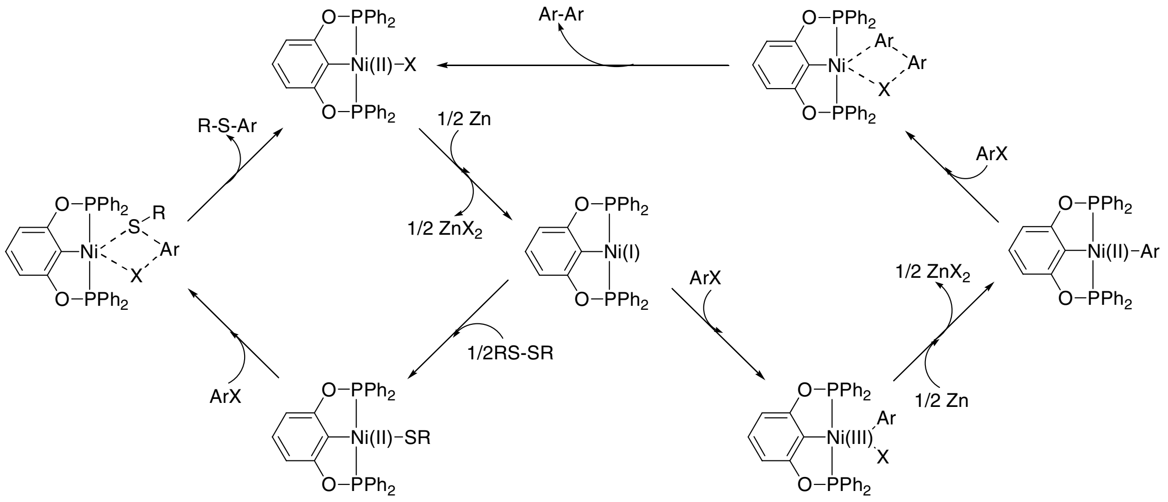
[a] Yields were determined by GC–MS and related to C_6H_5I.

[b] Formation of biphenyl is observed with a 35% yield.

[c] Formation of biphenyl is observed with an 8% yield.

The reactivities of a variety of disulfides were examined under the optimized conditions and uniformly showed >99% selective for the corresponding asymmetric sulfide, except for the cases of di-*tert*-butyldisulfide and diphenyldisulfide (entries 5 and 6, respectively, in Table 1) where the yields for the desired product are reduced by the formation of biphenyl, product of the C–C homo-coupling of iodobenzene. This fact, being probably due to steric effects due to the larger size of the substituents in these disulfides.

In order to verify that the high catalytic activity of the present system requires the presence of both the phosphinite PCP pincer complex [NiCl{C_6H_3-2,6-$(OPPh_2)_2$}] (**3**) and zinc, we carried out control experiments excluding complex **3** and zinc powder, respectively, obtaining no conversion at all in both experiments. Similarly, other reducing agents such as magnesium and tin powder were employed under the same reaction conditions, however the effect of both metals is negligible in comparison with that of zinc.



Scheme 1. Proposed reaction mechanism for the thiolation of iodobenzene with disulfides.

It has been proposed that these reactions using nickel catalysts must proceed through a Ni(0)/Ni(II) intermediates.[20] So, it is possible to conceive a similar mechanism to be involved in the present case (Scheme 1), although alternative routes cannot be ruled out. Thus, one of the first steps would be the reduction of the complex [Ni^{II}PCP(Cl)] by metallic zinc, further activation by this new complex [Ni^{I}PCP] of the disulfide RS–SR would lead to the cleavage of the S–S bond by oxidative addition to afford the thiolate species [Ni^{II}PCP(SR)]. It is worth to note, that as the size of the substituent in the thiolate increases the complex [Ni^{II}PCP(SR)] becomes more stable.[21] This fact would explain the lower yields attained with sterically hindered disulfides, since the resulting intermediate would prefer to stay as a thiolate species rather than react further. The nickel thiolate complex [Ni^{II}PCP(SR)] will then undergo, in a concerted manner, the addition of iodobenzene and further elimination of the C–S cross coupled product Ar–S–R, to yield the [Ni^{II}PCP(X)] species that after a new reduction with more metallic zinc would restart the catalytic cycle all over again (Scheme 1). Additionally, a parasite side mechanism can be invoked to explain the formation of biphenyl in the case of entries 5 and 6 in Table 1, this side reaction must be favored due to the steric hindrance of these particular disulfides (Bu^tS–SBu^t and PhS–SPh respectively) resulting easier the oxidative addition of iodobenzene and thus eventually leading to the formation of the C–C coupling product. This theory is currently being investigated in our research group by synthesizing analogous pincer ligands with larger byte angles in order to evaluate the cavity size.

In summary, the relatively inexpensive, easy to prepare, air, and moisture stable nickel phosphinite PCP pincer complex [NiCl{C_6H_3-2,6-($OPPh_2)_2$}] (**3**) catalyzes the high yield C–S cross coupling (thiolation reaction) of a broad scope of disulfides using zinc as a necessary reducing agent. Thus, it should be possible to apply this catalytic system to the synthesis of commercially important, structurally complex fine chemicals containing thermally sensitive groups.

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14. Synthesis of $[NiCl\{C_6H_3\text{-}2,6\text{-}(OPPh_2)_2\}]$ (**3**). A solution of toluene (50 mL), $[C_6H_4\text{-}2,6\text{-}(OPPh_2)_2]$ (907 mg, 1.89 mmol), and $NiCl_2$ (450 mg, 1.89 mmol) were refluxed for 24 h. The solvent was evaporated under vacuum and the crude product isolated. Following recrystalization from diethyl ether, the purified product was obtained (yield 880 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.61$ (d, $^3J_{HH} = 8.0$ Hz, 2H, arom), 7.06 (t, $^3J_{HH} = 7.7$ Hz, 1H, arom), 7.45 (br m, 12H, arom), 7.99 (br m, 8H, arom); $^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$): $\delta = 141.52$ (s, 1P). Anal. calcd for $C_{30}H_{23}ClO_2P_2Ni$ (571.60) C, 63.04; H, 4.06. Found: C, 63.49; H, 4.15. MS-FAB$^+$ $[M^+] = 571$ *m/z*.
15. Data Collection and refinement for $[NiCl\{C_6H_3\text{-}2,6\text{-}(OPPh_2)_2\}]$ (**3**). A crystalline green prism of $[NiCl\{C_6H_3\text{-}2,6\text{-}(OPPh_2)_2\}]$ (**3**). The X-ray intensity data were measured at 291 K on a Bruker SMART APEX CCD-based X-ray diffractometer system equipped with a Mo-target X-ray tube ($\lambda = 0.71073$ Å). The detector was placed at a distance of 4.837 cm from the crystal. A total of 1800 frames were collected with a scan width of 0.3° in ω and an exposure time of 10 s/frame. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm. The integration of the data using a monoclinic unit cell yielded a total of 26,476 reflections to a maximum 2θ angle of 56.00° (0.93 Å resolution), of which 6284 were independent ($R_{int} = 5.05\%$, $R_{sig} = 5.47\%$) and 4566 were greater than $2\sigma(F^2)$. Analysis of the data showed negligible decay during data collection. The structure was solved by Patterson method using SHELXS-97 program.[16] The remaining atoms were located via a few cycles of least squares refinements and difference Fourier maps, using the space group $P2_1/c$, with $Z = 4$. The final cycle of refinement was carried out on all nonzero data using SHELXL-97[17] and anisotropic thermal parameters for all non-hydrogen atoms. The numbering of the atoms is shown in Figure 1 (ORTEP).[18] Supplementary data for complex **3** has been deposited at the Cambridge Crystallographic Data Centre. Copies of this information are available free of charge on request from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk) quoting the deposition number CCDC 298238.
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19. Thiolation of iodobenzene. Under an atmosphere of nitrogen, a solution of 4.9 mmol of iodobenzene, 2.45 mmol of methyl disulfide, 3.0 mg of catalyst **3** (0.0057 mmol) and 202 mg (0.924 mmol) of diethylene glycol di-*n*-butylether (internal standard) in 3.0 mL of DMF, was introduced into a Schlenk tube containing a magnetic stir bar and charged with 4.9 mmol of zinc dust. The tube was sealed and fully immersed in a 110 °C silicon oil bath. After 4 h, the reaction mixture was cooled to room temperature and, the organic phase analyzed by gas chromatography (Quantitative analyses were performed on a Agilent 6890N GC with a 30.0 m DB-1MS capillary column coupled to an Agilent 5973 inert mass selective detector).
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