Organic LETTERS

Letter

Cite This: *Org. Lett.* XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

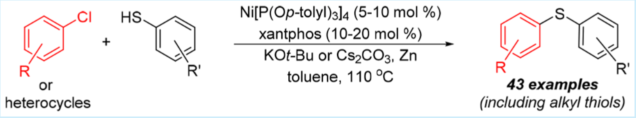
Nickel Phosphite/Phosphine-Catalyzed C−S Cross-Coupling of Aryl Chlorides and Thiols

Kieran D. Jones,[†,‡] Dennis J. Power,[†] Donald Bierer,[‡] Kersten M. Gericke,[‡] and Scott G. Stewart[*,†]

[†]School of Molecular Sciences, The University of Western Australia (M310), 35 Stirling Highway, Crawley WA 6009, Australia
[‡]Bayer AG, Pharmaceuticals Division, Drug Discovery, Aprather Weg 18a, Elberfeld, 42096 Wuppertal, Germany

Supporting Information

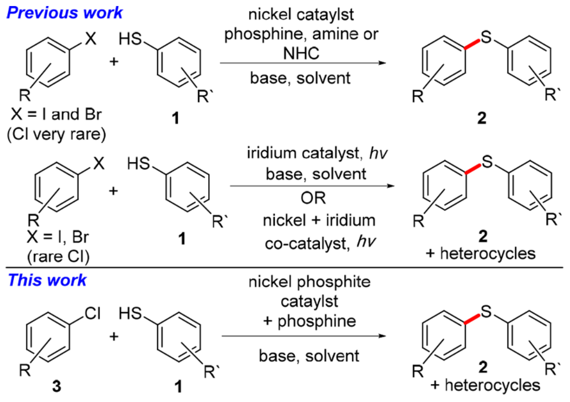
ABSTRACT: A method for the coupling of aryl chlorides and thiophenols using an air-stable nickel(0) catalyst is described. This thioetherification procedure can be effectively applied to a range of electronically diverse aryl/heteroaryl chlorides without more expensive metal catalysts such as palladium, iridium, or ruthenium. This investigation also illustrates both, a variety of thiol coupling partners and, in certain cases, the use of Cs_2CO_3.



Nickel-catalyzed cross-coupling reactions are a rapidly growing field in synthetic chemistry, and recent publications in this area have reported efficient processes for C−C and C−heteroatom bond formation.[1] These couplings have been achieved by development of the catalysts and catalyst precursors Ni(cod)$_2$,[2−4] Ni(II) precatalysts,[3,5] Ni−*N*,*N*,*N*−pincer complexes,[6] and nickel phosphine/phosphite systems,[7] among others.[8]

The development of C−S bond forming processes involving nickel has been achieved with aryl-iodides and bromides under moderate to harsh conditions (Scheme 1).[6,9] These investigations have also included intramolecular C−S bond forming methods.[10] More recently, aryl iodide substrates have been used in C−S bond forming reactions with thiyl radicals in an Ir/Ni dual-catalytic photoredox system.[11] A second photoredox system was also reported and used Ni/Ru for the coupling of aryl bromides.[12] Many of these processes are carried out on expensive precursors or using solvents like DMF that are not suitable for industrial synthesis. Thioethers are also becoming more prevalent structural motifs in pharmaceuticals. Examples include axitinib (a tyrosine kinase inhibitor), albendazole (a treatment for parasitic worm infestations), vortioxetine (an antidepressant), and fenticonazole (an antifungal).

Scheme 1. Modern Thioetherification Reactions



Aryl chlorides in nickel-catalyzed C−S cross-coupling reactions are generally either unreactive or result in impractical yields.[9h,l] Some reactive, electronically poor aryl chlorides have been described, but invariably, these systems do not allow for the coupling of substrates containing electron donating substituents.[9j,k] Interestingly, in this field, a Ni(cod)$_2$/dppf catalytic system with $(Me_4N)SCF_3$ has been used to incorporate a SCF_3 groups into aryl chlorides.[13] A nickel catalyst for the coupling of Ar−Cl substrates was reported using NaOH and DMF, but this catalyst system was inconsistent with our modern industrial requirements.[14] Most recently, an iridium photoredox system has been applied at room temperature for C−S bond formation (Scheme 1).[15]

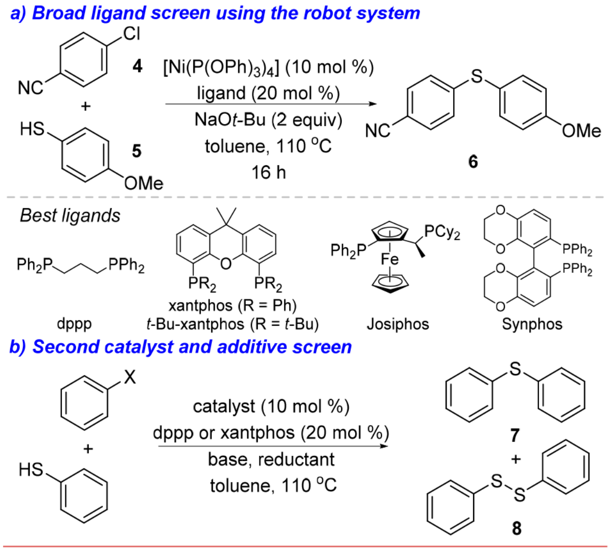
In our study, we sought to develop a nickel catalyst system with a substrate scope that includes a wide range of aryl chlorides (**3**) with a variety electronic demands. Additionally, if a relatively benign solvent and base system could be used, it would simplify the transition of the system to industrial processes. Nickel phosphites and nickel phosphites/phosphines have been shown to catalyze a range of cross-couplings, and the cheap, air-stable nickel(0) species $Ni[P(OPh)_3]_4$ was selected as the starting point for our investigations.[7,16]

The activated cross-coupling between electron-poor 4-chlorobenzonitrile (**4**) and *p*-methoxythiophenol (**5**) to generate *bis*-aryl thioether **6** was initially tested under dilute conditions (0.02 M), using a robotic screening system (Scheme 2a), to gauge the reactivity of a library of bidentate phosphines with $Ni[P(OPh)_3]_4$. The ligand screening system, contained in a glovebox under an argon atmosphere, consists of X, Y, Z, *α*-robotics with a tool−exchange interface. Reactions were carried out at 0.036 mmol, and the outcomes were determined by GCMS analysis (see Supporting Information, SI).

Received: November 16, 2017

DOI: 10.1021/acs.orglett.7b03560

Scheme 2. Initial Screening Reactions

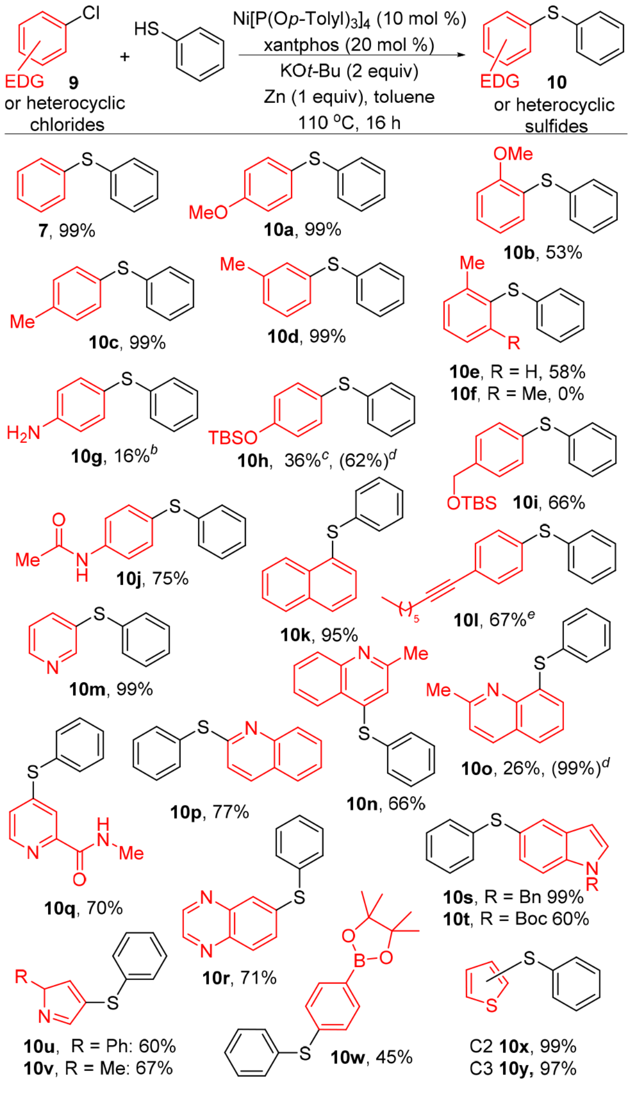


The most promising ligands from our extensive screening were dppp, xantphos, *t*-Bu-xantphos, Josiphos, and Synphos. We disregarded Josiphos, Synphos, and *t*-Bu-xantphos due to their high retail prices and focused our attention on dppp and xantphos.

In a series of control experiments, the two ligand candidates were further investigated in the comparatively less reactive C−S cross-coupling reaction between various halobenzenes and thiophenol (Scheme 2b, also see SI). In this series of reactions, a group of inexpensive Ni-catalysts was examined, including Ni[P(OPh)$_3$]$_4$ and nickel(II) catalysts along with the in-house-developed (dppf)Ni[P(OPh)$_3$]$_2$[7] and (dppf)Ni[P(O*p*-tolyl)$_3$]$_2$. This study highlighted the advantages of *para*-tolyl phosphite ligands, which eventually led to us choosing air-stable Ni[P(O*p*-tolyl)$_3$]$_4$ for further studies.[17] It was assumed, based on our previous investigations, that the two phosphite ligands are exchanged with the bidentate ligand additive leading to a catalytically active species precursor. While dppp proved to be efficient at promoting C−S cross-coupling using iodobenzene as the substrate, it was ineffective at facilitating the reaction using chlorobenzene. Xantphos, which has a large bite angle and higher backbone rigidity compared with dppp, was required to promote reactions with chlorobenzene. The detection of disulfide **8** prompted us to include a reductant; zinc was the reductant of choice due to its use in early examples of C−S cross-coupling reactions.[9b,d] Following this modification, less disulfide **8** was produced, and a large increase in production of sulfide **7** was often observed in these test trials (Scheme 2b). When investigating bases, KO*t*-Bu was shown to improve yields, while the weaker bases such as Cs$_2$CO$_3$ afforded high yields in cases in which electron-poor aryl chlorides were involved. This discovery is unique in nickel-catalyzed C−S coupling with aryl chlorides. Ultimately, the catalytic system of Ni[P(O*p*-Tolyl)$_3$]$_4$ (5 mol %), xantphos (10 mol %), KO*t*-Bu (2 equiv), and zinc (1 equiv) in toluene was selected at 110 °C (see SI). Under these conditions, the coupling of chlorobenzene and thiophenol afforded diphenyl sulfide (**7**) in 96% yield.

As nickel-catalyzed C−S cross-coupling of aryl chlorides containing electron-donating substituents **9** are extremely uncommon in the literature, these transformations were an important focus of our study. The initially selected 5:10 mol %, catalyst/ligand loading produced a sluggish reaction for these more challenging substrates; however, increased loading was found to be more effective. Initially, we were encouraged to find a 99% yield for the coupling of 4-chloroanisole (see Scheme 3). Similar quantitative to excellent yields were also observed for the reaction of 4-chlorotoluene and 3-chlorotoluene, leading to sulfides **10c** and **10d**, respectively.

Scheme 3. Nickel-Catalyzed C−S Coupling: Scope of Aryl Chlorides (ED Substituents) and Heterocycles[a]

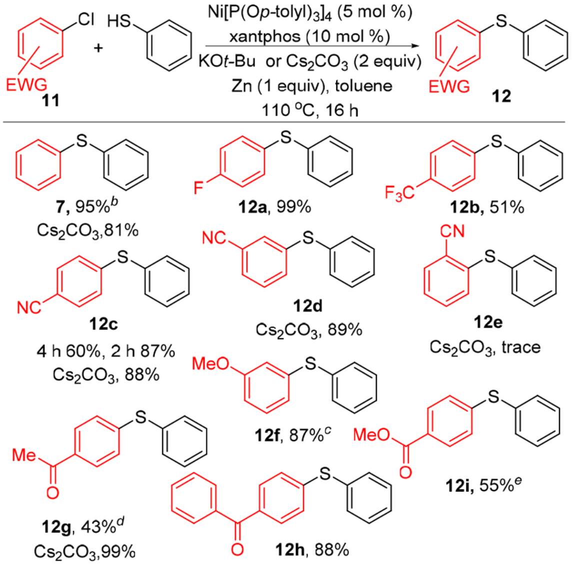


[a] All reactions were carried out using aryl chloride (0.5 mmol), thiophenol (0.6 mmol), Ni[P(O*p*-tolyl)$_3$]$_4$ (0.05 mmol), xantphos (0.1 mmol), zinc (0.5 mmol), KO*t*-Bu (1.0 mmol), toluene (2 mL), 110 °C, 16 h. [b] Three equivalents of base used. [c] Four hour reaction time. [d] Based on recovered starting material. [e] Two hour reaction time.

Electron-rich *ortho*-substituted substrates afforded the corresponding products in more moderate yields of 53% (**10b**) and 58% (**10e**); however, these yields were slightly higher than those recently reported in an iridium photocatalyzed system with the same substrate (40%, *o*-OMe).[15] Although 2-chloro-1,3-dimethylbenzene was not reactive under these conditions, the sulfide product **10f** could easily be prepared by reversing the substrate and the coupling partner (see Scheme 5). The phenoxysilane moiety degraded in the described reaction conditions over long periods (ca. 16 h). This result is consistent with a recent report highlighting nickel-catalyzed reductions of silyloxyarenes.[18] Reducing the reaction time allowed the formation of **10h** (36%) with significant amounts of starting material recovered. Other silyl ethers were more robust in our conditions (see **10i**). Competing coordination was thought to be the cause of the low yields of aniline **10g**; however, protecting the aniline substrate with acetate eliminated these problems. Reducing the reaction time allowed for the effective coupling of an alkyne substituted substrate leading to compound **10l**. Importantly, a range of *N*-heteroaryl chlorides, including pyridines, indoles, quinolones, and pyrazine, were also coupled with thiophenol under our conditions (see Scheme 3). The lesser known pyrazole chlorides successfully led to the formation of the thioethers **10u** and **10v**. To highlight the chemoselectivity of this reaction, an aryl chloride substrate bearing a *p*-boronic ester substituent was coupled in 45% yield. The coupling of 2- or 3-chlorothiophene efficiently led to sulfides **10x** and **10y**, respectively, in excellent yields.

Given nickel-catalyzed couplings of aryl chloride substrates containing electron-poor substituents have previously been reported and are more activated,[9j,k] we decided to halve the catalyst and ligand for these reactions. Under these conditions, simple thiophenol could be readily coupled with chlorobenzene and its fluorinated counterparts (see Scheme 4).

Scheme 4. Nickel-Catalyzed C−S Coupling: Scope of Aryl Chlorides (EW Substituents)[a]

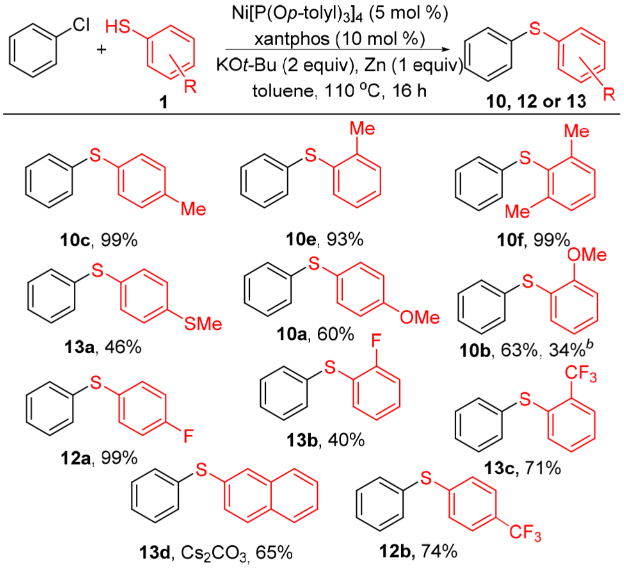


[a] All reactions were carried out as Scheme 3, except for $Ni[P(Op\text{-}tolyl)_3]_4$ 5 mol % and xantphos 10 mol %. [b] One mmol scale. [c] Ten mol % catalyst used. [d] Starting material reduced to 1-(4-chlorophenyl)-ethanol, isolated 57%. [e] KHMDS (2 equiv) and $MgCl_2$ (1.1 equiv), 2 h, were used.

Reactions involving substrates containing reducible functional groups were carried out with the milder base Cs_2CO_3. In these cases the benzonitrile sulfides **12c** and **12d** were obtained, the former requiring shorter reaction times due to decomposition. A select group of nitriles have recently been used as leaving groups in combination with a $Ni(cod)_2$/dcype catalytic system, suggesting our catalytic system is milder.[19] Furthermore, the coupling of 4′-chloroacetophenone was more efficient with Cs_2CO_3 (**12g**, 99%). Similar substrates have also been used in visible-light-promoted C−S cross-coupling reactions.[20] The coupling of methyl 4-chlorobenzoate was initially problematic, in part due to transesterification; however, KHMDS and $MgCl_2$ with a shorter reaction time led to **12i** in modest yields (see SI).

In addition, our substrate exploration included a range of thiophenols (**1**, see Scheme 5). Interestingly, the coupling partners that contained more sterically encumbered sulfhydryl groups (such as 2,6-dimethylbenzenethiol) still led to excellent yields of the corresponding sulfides (i.e., **10f**, 99%). In general, aryl thiols containing either electron-donating and/or -withdrawing substituents were well tolerated and afforded the corresponding products in good to excellent yields.

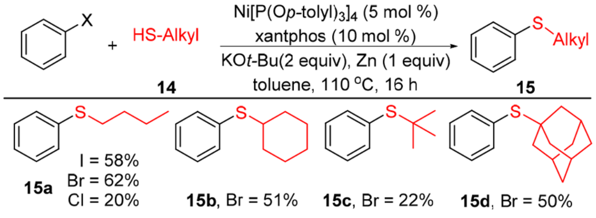
Scheme 5. Nickel-Catalyzed C−S Coupling: Scope of Thiophenols[a]



[a] All reactions were carried out on the same scale as Scheme 3. [b] $Ni[P(Op\text{-}tolyl)_3]_4$ 10 mol % and xantphos 20 mol % were used.

We also studied alkyl thiols **14** under the established catalytic conditions (see Scheme 6). We first tested butyl thiol as a model system and were pleased that coupling occurred with the aryl chloride (20%), as others have reported complete inactivity with this substrate.[21] The coupling of an aryl bromide with *n*-butanethiol was much more promising at 62% yield. Unfortunately, this yield could not be improved through increasing catalytic loading or modification of the ligand/complex ratio. Under these conditions, the cyclohexanethiol could be coupled in 51% yield (**15b**); however, the tertiary thiol was more challenging. Remarkably, the sterically demanding reaction leading to the adamantyl sulfide product **15d** was achieved in 50% yield.

Scheme 6. Nickel-Catalyzed C−S Coupling: Attempted Cross-Coupling of Alkyl Thiols[a]



[a] All reactions were carried out on the same scale as Scheme 4.

Although lower-yielding than the efficient system reported by Molander, we have avoided the use of a second catalyst and DMF to keep our system in line with industrial requirements.[12,14b]

In conclusion, we devised a nickel(0) catalytic system capable of cross-coupling normally unreactive aryl chlorides containing electron-donating substituents. This nickel-phosphite $\mathrm{Ni[P(O}p\text{-tolyl)}_3]_4$ and xantphos catalytic system can also be applied to a plethora of other aryl/heterocyclic chlorides. Importantly, the system can also be made milder by substituting KO*t*-Bu for Cs_2CO_3. This novel thioetherification protocol is also well suited to a range of electronic and sterically congested thiophenols and can be carried out in toluene, making it amenable to industrial applications.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03560.

Experimental procedures and spectra of new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: scott.stewart@uwa.edu.au.

ORCID

Scott G. Stewart: 0000-0002-7537-247X

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge the CMCA Research Facility at UWA. The authors would like to thank Prof. Reto Dorta and A/Prof. Keith Stubbs (UWA) for helpful discussion and several thiols. Further NMR assistance from Dr. Mark Howard and Dr. Gareth Nealon (UWA) is gratefully acknowledged. K.D.J. and D.J.P. are recipients of an APA and UWA, respectively.

■ REFERENCES

(1) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299.

(2) (a) Green, R. A.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2015**, *54*, 3768. (b) Muto, K.; Yamaguchi, J.; Lei, A.; Itami, K. *J. Am. Chem. Soc.* **2013**, *135*, 16384. (c) Ge, S.; Green, R. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 1617. (d) Gøgsig, T. M.; Kleimark, J.; Nilsson Lill, S. O.; Korsager, S.; Lindhardt, A. T.; Norrby, P.-O.; Skrydstrup, T. *J. Am. Chem. Soc.* **2012**, *134*, 443. (e) Ehle, A. R.; Zhou, Q.; Watson, M. P. *Org. Lett.* **2012**, *14*, 1202. (f) Borzenko, A.; Rotta-Loria, N. L.; MacQueen, P. M.; Lavoie, C. M.; McDonald, R.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 3773. (g) Lavoie, C. M.; MacQueen, P. M.; Rotta-Loria, N. L.; Sawatzky, R. S.; Borzenko, A.; Chisholm, A. J.; Hargreaves, B. K. V.; McDonald, R.; Ferguson, M. J.; Stradiotto, M. *Nat. Commun.* **2016**, *7*, 11073.

(3) Fine Nathel, N. F.; Kim, J.; Hie, L.; Jiang, X.; Garg, N. K. *ACS Catal.* **2014**, *4*, 3289.

(4) Iglesias, M. J.; Blandez, J. F.; Fructos, M. R.; Prieto, A.; Álvarez, E.; Belderrain, T. R.; Nicasio, M. C. *Organometallics* **2012**, *31*, 6312.

(5) (a) Shields, J. D.; Gray, E. E.; Doyle, A. G. *Org. Lett.* **2015**, *17*, 2166. (b) Standley, E. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2013**, *135*, 1585. (c) Park, N. H.; Teverovskiy, G.; Buchwald, S. L. *Org. Lett.* **2014**, *16*, 220. (d) Ge, S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 12837. (e) Gao, C.-Y.; Yang, L.-M. *J. Org. Chem.* **2008**, *73*, 1624.

(6) Baldovino-Pantaleón, O.; Hernández-Ortega, S.; Morales-Morales, D. *Adv. Synth. Catal.* **2006**, *348*, 236.

(7) (a) Kampmann, S. S.; Sobolev, A. N.; Koutsantonis, G. A.; Stewart, S. G. *Adv. Synth. Catal.* **2014**, *356*, 1967. (b) Kampmann, S. S.; Skelton, B. W.; Wild, D. A.; Koutsantonis, G. A.; Stewart, S. G. *Eur. J. Org. Chem.* **2015**, *2015*, 5995.

(8) Manolikakes, G.; Gavryushin, A.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 1429.

(9) (a) Cristau, H. J.; Chabaud, B.; Chêne, A.; Christol, H. *Synthesis* **1981**, *1981*, 892. (b) Takagi, K. *Chem. Lett.* **1987**, *16*, 2221. (c) Taniguchi, N. *J. Org. Chem.* **2004**, *69*, 6904. (d) Gendre, F.; Yang, M.; Diaz, P. *Org. Lett.* **2005**, *7*, 2719. (e) Baldovino-Pantaleón, O.; Hernández-Ortega, S.; Morales-Morales, D. *Inorg. Chem. Commun.* **2005**, *8*, 955. (f) Zhang, Y.; Ngeow, K. C.; Ying, J. Y. *Org. Lett.* **2007**, *9*, 3495. (g) Cao, Y. Q.; Zhang, Z.; Guo, Y. X.; Wu, G. Q. *Synth. Commun.* **2008**, *38*, 1325. (h) Jammi, S.; Barua, P.; Rout, L.; Saha, P.; Punniyamurthy, T. *Tetrahedron Lett.* **2008**, *49*, 1484. (i) Iglesias, M. J.; Prieto, A.; Nicasio, M. C. *Adv. Synth. Catal.* **2010**, *352*, 1949. (j) Zhang, J.; Medley, C. M.; Krause, J. A.; Guan, H. *Organometallics* **2010**, *29*, 6393. (k) Guan, P.; Cao, C.; Liu, Y.; Li, Y.; He, P.; Chen, Q.; Liu, G.; Shi, Y. *Tetrahedron Lett.* **2012**, *53*, 5987. (l) Martin, A. R.; Nelson, D. J.; Meiries, S.; Slawin, A. M. Z.; Nolan, S. P. *Eur. J. Org. Chem.* **2014**, *2014*, 3127. (m) Wellala, N. P. N.; Guan, H. *Org. Biomol. Chem.* **2015**, *13*, 10802. (n) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596. (o) Lee, C.-F.; Liu, Y.-C.; Badsara, S. S. *Chem. - Asian J.* **2014**, *9*, 706.

(10) Xu, X.-B.; Liu, J.; Zhang, J.-J.; Wang, Y.-W.; Peng, Y. *Org. Lett.* **2013**, *15*, 550.

(11) Oderinde, M. S.; Frenette, M.; Robbins, D. W.; Aquila, B.; Johannes, J. W. *J. Am. Chem. Soc.* **2016**, *138*, 1760.

(12) (a) Jouffroy, M.; Kelly, C. B.; Molander, G. A. *Org. Lett.* **2016**, *18*, 876. (b) Vara, B. A.; Li, X.; Berritt, S.; Walters, C. R.; Petersson, E. J.; Molander, G. A. *Chem. Sci.* **2018**, DOI: 10.1039/C7SC04292B.

(13) (a) Kalvet, I.; Guo, Q.; Tizzard, G. J.; Schoenebeck, F. *ACS Catal.* **2017**, *7*, 2126. (b) Yin, G.; Kalvet, I.; Englert, U.; Schoenebeck, F. *J. Am. Chem. Soc.* **2015**, *137*, 4164.

(14) (a) Gogoi, P.; Hazarika, S.; Sarma, M. J.; Sarma, K.; Barman, P. *Tetrahedron* **2014**, *70*, 7484. (b) Øpstad, C. L.; Melø, T.-B.; Sliwka, H.-R.; Partali, V. *Tetrahedron* **2009**, *65*, 7616.

(15) Jiang, M.; Li, H.; Yang, H.; Fu, H. *Angew. Chem., Int. Ed.* **2017**, *56*, 874.

(16) (a) Kampmann, S. S.; Skelton, B. W.; Wild, D. A.; Koutsantonis, G. A.; Stewart, S. G. *Acta Crystallogr., Sect. C: Struct. Chem.* **2015**, *71*, 188. (b) Kampmann, S. S.; Man, N. Y. T.; McKinley, A. J.; Koutsantonis, G. A.; Stewart, S. G. *Aust. J. Chem.* **2015**, *68*, 1842. (c) Tolman, C. A.; Seidel, W. C.; Druliner, J. D.; Domaille, P. J. *Organometallics* **1984**, *3*, 33. (d) Arai, S.; Amako, Y.; Yang, X.; Nishida, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 8147. (e) Baker, M. J.; Harrison, K. N.; Orpen, A. G.; Pringle, P. G.; Shaw, G. *J. Chem. Soc., Chem. Commun.* **1991**, 803. (f) Wilting, J.; Janssen, M.; Müller, C.; Lutz, M.; Spek, A. L.; Vogt, D. *Adv. Synth. Catal.* **2007**, *349*, 350. (g) Falk, A.; Göderz, A.-L.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2013**, *52*, 1576. (h) Iyer, S.; Ramesh, C.; Ramani, A. *Tetrahedron Lett.* **1997**, *38*, 8533.

(17) The complex $\mathrm{Ni[P(O}p\text{-tolyl)}_3]_4$ was stable to at least 12 months in the fridge, under air, by ^{31}P, ^{1}H NMR analysis.

(18) Wiensch, E. M.; Todd, D. P.; Montgomery, J. *ACS Catal.* **2017**, *7*, 5568.

(19) Hanson, M. G.; Olson, N. M.; Yi, Z.; Wilson, G.; Kalyani, D. *Org. Lett.* **2017**, *19*, 4271.

(20) Liu, B.; Lim, C.-H.; Miyake, G. M. *J. Am. Chem. Soc.* **2017**, *139*, 13616−13619.

(21) Yatsumonji, Y.; Okada, O.; Tsubouchi, A.; Takeda, T. *Tetrahedron* **2006**, *62*, 9981.