Synlett R. S. Sawatzky et al. Letter

# Thieme Chemistry Journals Awardees – Where Are They Now? Efficient Cross-Coupling of Secondary Amines/Azoles and Activated (Hetero)Aryl Chlorides Using an Air-Stable DPEPhos/Nickel Pre-Catalyst

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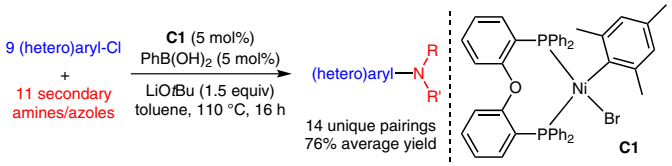



Received: 14.03.2017
Accepted after revision: 31.03.2017
Published online: 02.05.2017
DOI: 10.1055/s-0036-1588806; Art ID: st-2017-r0188-l

**Abstract** Synthesis and characterization of the new air-stable pre-catalyst (DPEPhos)Ni(2-mesityl)Br (C1) is reported, along with the application of this pre-catalyst in the cross-coupling of secondary amines/azoles with activated (hetero)aryl chlorides to afford tertiary (hetero)anilines. The performance of C1 in these cross-couplings is competitive with some of the best and/or most widely employed nickel catalysts for such transformations.

**Key words** nickel, DPEPhos, C–N cross-coupling, anilines, secondary amines, azoles

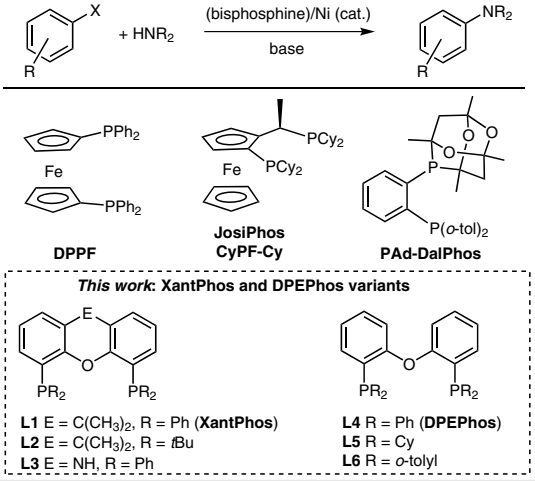
The tertiary (hetero)aniline motif is found in a range of pharmaceuticals and agrochemicals, as well as conjugated organic materials;[1] as such there is considerable interest in establishing efficient methods for their synthesis. As a complement to more conventional methods,[2] the metal-catalyzed cross-coupling of NH substrates and (hetero)aryl (pseudo)halides has emerged as a useful approach to C($sp^2$)–N bond formation, including for the assembly of tertiary (hetero)anilines. Whereas such cross-couplings employing the relatively inexpensive base metal copper are well-established,[3] they are generally limited to (hetero)aryl bromides and iodides and require relatively high temperatures and catalyst loadings. Conversely, the use of palladium catalysts (i.e., Buchwald–Hartwig amination,[4] BHA) enables a wider spectrum of coupling partners, including (hetero)aryl chlorides, under more mild conditions. Beyond the inherent reactivity differences that exist between copper and palladium, the latter exhibits a particular affinity for phosphine and N-heterocyclic carbene ligation; variation of the steric and electronic properties of such ligands has been exploited as a means of tuning the reactivity of palladium catalysts in C($sp^2$)–N cross-couplings, with bulky and electron-rich ligands that promote otherwise challenging C($sp^2$)–Cl oxidative additions proving particularly effective.

**Mark Stradiotto** received his BSc (Hons.) in Applied Chemistry (1995) and PhD in Organometallic Chemistry (1999) from McMaster University, the latter under the supervision of Profs. M. A. Brook and M. J. McGlinchey. After conducting research as an NSERC PDF at the University of California at Berkeley with Prof. T. D. Tilley (1999–2001), he moved to the Department of Chemistry at Dalhousie University where he is now the Alexander McLeod Professor of Chemistry. His research focus is on developing new ancillary ligands–metal complexes that exhibit interesting and unusual reactivity patterns, with the goal of incorporating such reactivity into synthetically useful catalytic substrate transformations. Mark received the Thieme Chemistry Journals Award in 2009.

Indeed, many of the breakthroughs that have been achieved in BHA chemistry can be attributed directly to advances in rational ancillary ligand design.[5]

The quest to identify base metal catalysts that offer competitive or even enhanced reactivity profiles relative to more rare and expensive palladium catalysts has contributed to the resurgence in nickel-catalyzed C($sp^2$)–N cross-coupling chemistry[6] and beyond.[7] However, in contrast to palladium-catalyzed BHA chemistry, for which both a detailed understanding of the reaction mechanism and optimal ancillary ligand design strategies are known,[4b] guiding ancillary ligand-design principles for use in promoting related nickel-catalyzed transformations have not yet been established. Given the greater propensity for C($sp^2$)–Cl oxidative additions to phosphine-ligated Ni(0) versus Pd(0),[8] it follows that phosphine ancillary ligands that promote C($sp^2$)–N reductive elimination (i.e., sterically demanding, relatively electron-poor, and/or possessing a wide bite angle[9]) may be well suited for use in nickel-catalyzed C($sp^2$)–N cross-coupling chemistry.

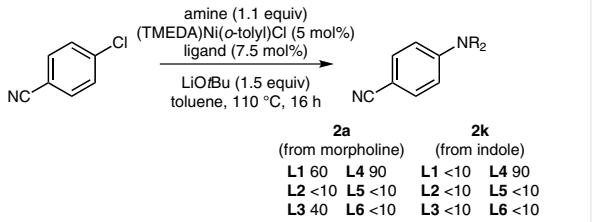
In keeping with this idea, some bisphosphine ligands that comprise one or more of the aforementioned design features have indeed proven to be useful in nickel-catalyzed C($sp^2$)–N cross-coupling chemistry; a selection of prominent examples are presented in Scheme 1. The use of DPPF was featured in the pioneering report by Wolfe and Buchwald[10] on the cross-coupling of (hetero)aryl chlorides with mainly secondary alkyl/aryl amines; this ligand, and related variants, have proven to be particularly useful for the synthesis of tertiary (hetero)anilines.[11] Other bisphosphine-ligated nickel catalysts have been identified,[12] including but not limited to those featuring JosiPhos variants (e.g., CyPF-Cy[11i,12d]) and PAd-DalPhos,[11i,12c,f] that offer complementary nucleophile scope versus DPPF in enabling the selective monoarylation of ammonia, primary alkyl/aryl amines, or primary amides/lactams.[13]




**Scheme 1** Some effective bisphosphine ligands in nickel-catalyzed C($sp^2$)–N cross-coupling, and the XantPhos and DPEPhos variants examined herein

In an effort to explore further the landscape of ancillary ligation in nickel-catalyzed C($sp^2$)–N cross-coupling chemistry, we turned our attention to the study of XantPhos and DPEPhos, as well as some of their structural relatives (Scheme 1). Despite the established utility of these wide bite-angle ancillary ligands in homogeneous catalysis,[14] including both in nickel-catalyzed C–C cross-couplings[15] and in BHA,[16] to the best of our knowledge, their application in nickel-catalyzed C($sp^2$)–N cross-coupling chemistry has not been examined. We disclose herein that the new crystallographically characterized air-stable pre-catalyst (DPEPhos)Ni(2-mesityl)Br (**C1**) is particularly effective for the cross-coupling of secondary amines/azoles with activated (hetero)aryl chlorides to afford tertiary (hetero)anilines, with the demonstrated scope of nucleophile reactivity being competitive with some of the best nickel catalysts known for such transformations.

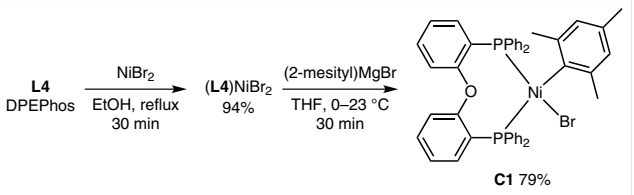
We initiated our evaluation of **L1**–**L6** in nickel-catalyzed C($sp^2$)–N cross-coupling chemistry leading to tertiary (hetero)anilines by exploring the cross-coupling of 4-chlorobenzonitrile with morpholine to give **2a** (Scheme 2). In the presence of **L**/(TMEDA)Ni(*o*-tolyl)Cl[11h,13l] pre-catalyst mixtures, negligible conversion of the starting materials was achieved when using **L2**, **L5**, or **L6**, and only moderate conversion into **2a** was achieved when using **L1** and **L3**. Conversely, high conversion into **2a** was achieved with **L4** (i.e., DPEPhos). The superiority of **L4** was also noted in test transformations involving indole. Whereas high conversion into the target product **2k** was achieved by use of **L4**, negligible conversion of the starting materials was observed with each of the other ancillary ligands in our screen. Efforts to apply **L1**–**L6** in the selective monoarylation of ammonia or octylamine were unsuccessful. In such transformations, poor conversion of the starting materials and/or undesired side reactions, including hydrodehalogenation, were observed.




**Scheme 2** Screening of **L1**–**L6** in nickel-catalyzed C($sp^2$)–N cross-coupling; estimated conversion into product on the basis of GC-calibrated data

Having identified **L4** (i.e., DPEPhos) as being a useful ligand in enabling the nickel-catalyzed C($sp^2$)–N cross-coupling of secondary amines/azoles with activated (hetero)aryl chlorides, we turned our attention to the synthesis of a well-characterized (**L4**)Ni(aryl)X pre-catalyst. Preformed Ni(II) complexes of this type, including but not re-

stricted to $L_nNi(o\text{-tolyl})Cl$ variants,[6,11e,i,k,12c,17] are attractive as pre-catalysts in that they are often air-stable and commonly out-perform catalysts generated in situ upon combination of a nickel source and ancillary ligand (as in Scheme 2).[18] Our efforts to prepare (**L4**)Ni(*o*-tolyl)Cl by use of various established literature methods,[11e,1k,17] including treatment of (**L4**)$NiCl_2$ with (*o*-tolyl)MgCl, in each case initially afforded a crude orange solid in keeping with other $L_nNi(o\text{-tolyl})Cl$ complexes; however, in the course of attempting to further purify/characterize this material, decomposition to a dark, paramagnetic mixture was observed. Encouraged by a report from Jamison and co-workers,[17] whereby the incorporation of a 2-mesityl rather than *o*-tolyl group is shown to increase pre-catalyst stability, we turned our attention to the synthesis of (**L4**)Ni(2-mesityl)Br, as outlined in Scheme 3. We were pleased to find that the readily prepared intermediate (**L4**)$NiBr_2$ was efficiently transformed into (**L4**)Ni(2-mesityl)Br (i.e., **C1**) upon treatment with (2-mesityl)MgBr.




**Scheme 3** Synthesis of the air-stable pre-catalyst **C1** (isolated yields indicated)

Complex **C1** proved stable both to isolation and storage as a solid in air and was fully characterized. The solution $^{31}P\{^1H\}$ NMR spectrum of **C1** features two doublets, in keeping with the *cis*-chelated square-planar structure observed in the single-crystal X-ray structure of **C1** (P–Ni–P bite angle ca. 102°; Figure 1[19]). Whereas this *cis* geometry mirrors that of several reported $L_nNi(o\text{-tolyl})Cl$ complexes ($L_n$, P–Ni–P bite angles: DPPF,[11e] ca. 102°; CyPF-Cy,[11i] ca. 98°; BINAP, ca. 93°;[17] PAd-DalPhos,[12c] ca. 87°), *trans*-spanning bisphosphine ligation is observed in analogous DCPF[17] (ca. 144°), DiPPF[11k] (ca. 145°), and XantPhos[17] (ca. 156° and featuring $\kappa^3$-POP connectivity) complexes. At first glance it may be tempting to rationalize the superior catalytic abilities of **L4** relative to **L1**, especially in the cross-coupling of indole leading to **2k** (Scheme 2), on the basis of the *cis* versus *trans* bisphosphine ligating behavior of these ligands. However, this rationale is inconsistent with the excellent performance of nickel catalysts supported by *trans*-spanning DiPPF or DCPF in nickel-catalyzed $C(sp^2)$–N cross-couplings leading to **2k** under similar experimental conditions.[11k] It is feasible, however, that the shorter Ni–O distance in (**L1**)Ni(*o*-tolyl)Cl (ca. 2.54 Å)[17] relative to that in **C1** (ca. 3.36 Å) contributes to the inferior catalytic performance of the former in our preliminary catalytic screen (Scheme 2).

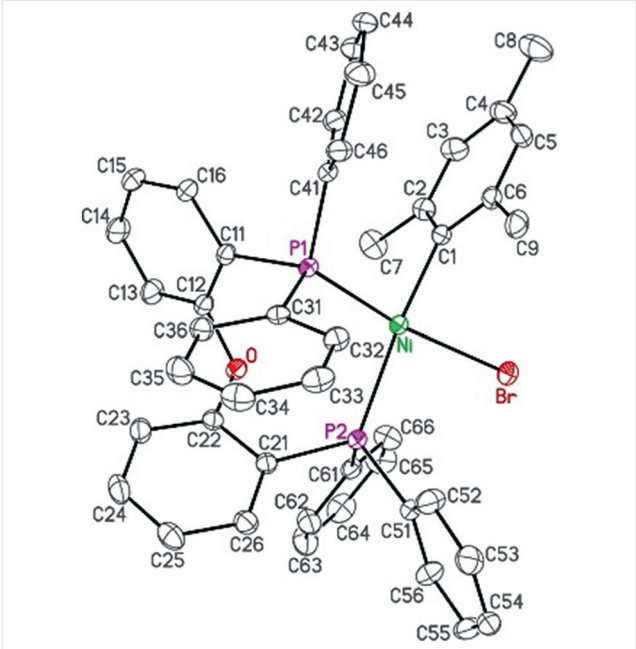


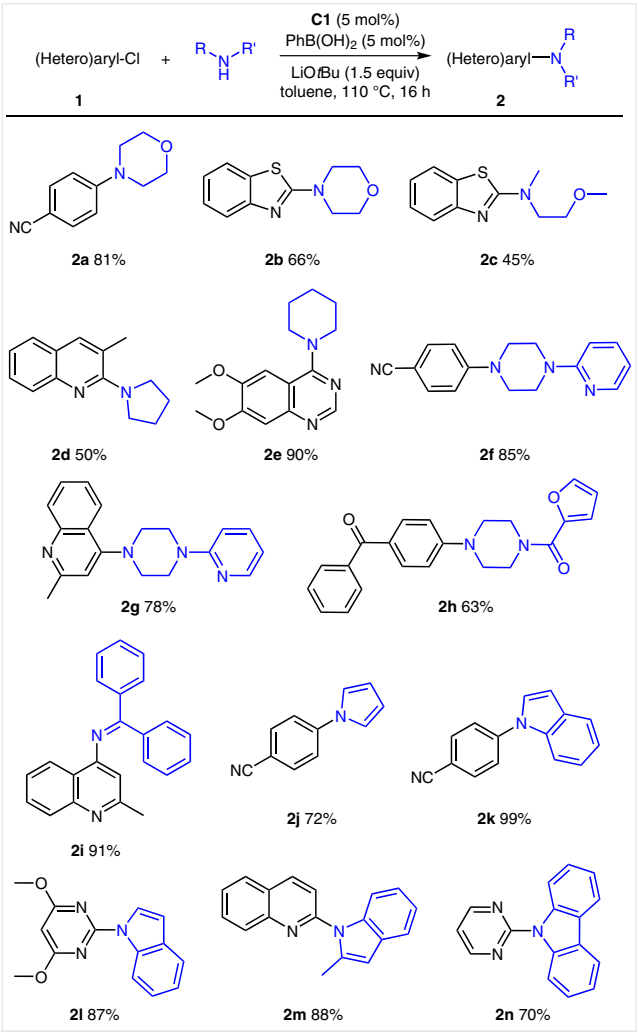

**Figure 1** Single-crystal X-ray structure of **C1**, depicted with 30% thermal ellipsoids and with hydrogen atoms omitted for clarity. Selected interatomic distances (Å): Ni–P1 2.1991(7), Ni–P2 2.2998(7), Ni–Br 2.3391(5), Ni–C1 1.935(2).

In an initial effort to test the efficacy of **C1** a pre-catalyst, we examined the transformations outlined in Scheme 2, under conditions where **L4**/(TMEDA)Ni(*o*-tolyl)Cl mixtures were successfully employed in cross-couplings leading to **2a** or **2k**. We were surprised to observe that comparatively poor conversion into the target products was achieved by use of **C1**, and postulated that the increased steric profile of the 2-mesityl group in **C1**, relative to *o*-tolyl, may inhibit catalyst activation that presumably occurs via net transmetalation involving the bulky secondary nitrogen nucleophile (i.e., morpholine or indole). This proposal is consistent with our observation that the addition of a catalytic quantity of $PhB(OH)_2$ to **C1** afforded high conversion into **2a** or **2k** in our test reaction.

Having established $PhB(OH)_2$-activated **C1** as an effective catalyst system for $C(sp^2)$–N cross-coupling chemistry, we set out to test the scope of reactivity with an array of (hetero)aryl chlorides and secondary amines/azoles (Scheme 4). A diversity of activated/heteroaryl electrophiles was accommodated in this chemistry including benzothiazole, quinoline, quinazoline, and pyrimidine derivatives. Conversely, reactions employing electron-neutral or electron-rich electrophiles (e.g., 1-chloronaphthalene) were unsuccessful. In terms of secondary amine scope, morpholine, (2-methoxyethyl)methylamine, pyrrolidine, piperidine, and N-substituted piperazines proved to be compatible substrates, leading to products **2a–h** (45–90%). To the best of our knowledge, the successful cross-coupling of 4-chloroquinaldine and benzophenone imine leading to **2i**

(91%) is the first reported cross-coupling of this nucleophile with a (hetero)aryl electrophile employing nickel catalysis. Benzophenone imine is an attractive coupling partner in that the corresponding primary aniline can be obtained via hydrolysis; as such, benzophenone imine can be used as an ammonia surrogate where direct ammonia coupling[20] is challenging. In further exploring the scope of nucleophile reactivity, N-arylated derivatives of pyrrole, indole, and carbazole were each successfully prepared via nickel-catalyzed C($sp^2$)–N cross-coupling employing pre-catalyst **C1**, affording **2j–n** in high isolated yield. Across the spectrum of cross-couplings examined herein, *ortho* substitution, ether, ketone, amide, furan, pyridine, and/or nitrile functionalities were well-tolerated. It is worthy of mention that the performance of **C1** in the transformation of (hetero)aryl chlorides is competitive both with DPPF/Ni catalyst systems that are employed widely in the cross-coupling of secondary amines,[11] as well as (IPr)Ni(styrene)$_2$ which represents the most effective nickel-based catalyst reported to date for the N-arylation of azoles.[13i]

In summary, following a preliminary screen of XantPhos and DPEPhos ligand variants, we developed an air-stable DPEPhos-ligated nickel pre-catalyst (i.e., **C1**) that is shown to be effective for the nickel-catalyzed C($sp^2$)–N cross-coupling of secondary amines/azoles and (hetero)aryl chlorides, leading to sought-after tertiary (hetero)anilines.[21–23] The identification of DPEPhos (**L4**) as being useful in this chemistry serves both to diversity the ligand 'toolbox' available to synthetic chemists in nickel-catalyzed C($sp^2$)–N cross-coupling chemistry, and to expand our appreciation of the ancillary ligand structures that give rise to efficient catalysts in such applications. Future work will involve the further development of new and effective ligands for these and related nickel-catalyzed cross-couplings.




**Scheme 4** Scope of C($sp^2$)–N cross-coupling using **C1**. All reactions were conducted using **1** (1 mmol), amine (1.1 mmol), **C1** (0.05 mmol), phenylboronic acid (0.05 mmol), LiO*t*-Bu (1.5 mmol), in toluene (10 mL), with isolated yields reported.

## Funding Information

Natural Sciences and Engineering Research Council of Canada (Discovery Grant RGPIN-2014-04807), (I2I Grant I2IPJ/485197-2015)

## Acknowledgment

We are grateful to the Natural Sciences and Engineering Research Council of Canada and Dalhousie University for their support of this work. Dr. Michael Lumsden (NMR-3, Dalhousie) is thanked for ongoing technical assistance in the acquisition of NMR data, and Mr. Xiao Feng (Maritime Mass Spectrometry Laboratories, Dalhousie) is thanked for technical assistance in the acquisition of mass spectrometric data.

## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588806.

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(21) **General Ligand-Screening Procedure for the Formation of Aryl Amines (Scheme 2)**
In a nitrogen atmosphere glove box (TMEDA)Ni(*o*-tolyl)Cl (5 mol%, 0.015 mmol), ligand (7.5 mol%, 0.0225 mmol), LiO*t*-Bu (1.5 equiv, 0.45 mmol), 4-chlorobenzonitrile (1 equiv, 0.3 mmol), morpholine or indole (1.1 equiv, 0.33 mmol), and dry, degassed toluene (3 mL) were added to an oven-dried 1 dram vial containing a magnetic stir bar. The vial was sealed with a screw cap featuring a PTFE/silicone septum and removed from the glove box. The reaction mixture was magnetically stirred in a temperature-controlled aluminum heating block set to 110 °C for 16 h. The reaction mixture was then cooled to r.t. In air on the benchtop a 0.1 mL aliquot was taken, filtered, diluted with MeOH, and subjected to calibrated GC analysis.
(22) **General Catalytic Procedure (Scheme 4)**
In a nitrogen atmosphere glove box **C1** (5 mol%, 0.05 mmol), phenylboronic acid (5 mol%, 0.015 mmol), LiO*t*-Bu (1.5 mmol), (hetero)aryl chloride (1 mmol), amine/azole (1.1 mmol), and dry, degassed toluene (10 mL) were added to an oven-dried 4 dram vial containing a magnetic stir bar. The vial was sealed with a screw cap featuring a PTFE/silicone septum and removed from the glove box. The reaction mixture was magnetically stirred in a temperature-controlled aluminum heating block set to 110 °C for 16 h (unoptimized). The reaction mixture was then cooled to r.t., taken up in EtOAc (ca. 30 mL) and washed with brine (3 × 50 mL). The organic layer was separated, dried over $Na_2SO_4$, filtered, and concentrated with the aid of a rotary evaporator to afford the crude product, which was purified via chromatographic methods (see the Supporting Information for complete details).
(23) **Preparation of (L4)Ni(2-mesityl)Br (C1)**
Under nitrogen, $NiBr_2$ (6.0 mmol, 1.3 g) was added to an oven-dried 100 mL, two-necked round-bottom flask equipped with a magnetic stir bar and a reflux condenser that had previously been evacuated and back-filled with nitrogen. Absolute EtOH (60 mL) was added, and the reaction mixture was sparged with nitrogen for 0.5 h. DPEPhos (**L4**, 6.0 mmol, 3.2 g) was added in one portion under positive pressure counterflow of nitrogen. The flask was sealed and heated at reflux (78 °C) for 0.5 h. The

reaction mixture was then cooled to 0 °C in an ice bath and was subsequently subjected to suction filtration in air. The solids on the filter were washed with cold absolute EtOH (0 °C, 3 × 10 mL) and then $Et_2O$ (3 × 10 mL). The solid on the filter was then collected by dissolving/washing through with $CH_2Cl_2$; removal of the solvent from the collected $CH_2Cl_2$ eluent afforded a dark green solid (presumptively (**L4**)$NiBr_2$, 4.3 g 94% yield), a portion of which was used subsequently without further purification in the synthesis of **C1**. Under nitrogen, (**L4**)$NiBr_2$ (4.0 mmol, 3.0 g) and dry, degassed THF (40 mL) were added to an oven-dried 100 mL round-bottom flask equipped with a magnetic stir bar. The reaction mixture was cooled to 0 °C, stirring was initiated, and 2-mesitylmagnesium bromide (1 M in THF, 4.0 mmol, 3.9 mL) was added dropwise. Once the addition was complete, the reaction mixture was allowed to warm to r.t. over the course of 0.5 h. Subsequently the reaction flask was opened in air, and the THF was removed with the aid of a rotory evaporator. Cold MeOH (0 °C, 15 mL) was added, the reaction mixture was subjected to suction filtration, and the solids were washed with additional cold MeOH (0 °C, 3 × 15 mL) and hexanes (3 × 15 mL). The solid on the filter was then collected by dissolving/washing through with $CH_2Cl_2$; removal of the solvent from the collected $CH_2Cl_2$ eluent followed by extended drying in vacuo afforded **C1** as a light orange powder (2.5 g, 79% yield). $^1$H NMR (300 MHz, $CD_2Cl_2$): δ = 7.95 (br s, 4 H), 7.72–7.63 (m, 1 H), 7.57–7.39 (br m, 7 H), 7.22–7.12 (br m, 3 H), 7.08–6.84 (br m, 5 H), 6.71–6.64 (m, 1 H), 6.55–6.47 (m, 1 H), 6.31–6.07 (br m, 4 H), 5.35–5.34 (m, 4 H), 2.54 (br s, 6 H), 2.16 (s, 3 H). $^{31}$P{$^1$H} NMR (121.5 MHz, $CD_2Cl_2$): δ = 10.8 (d, *J* = 15 Hz), 5.5 (d, *J* = 15 Hz). Despite prolonged acquisition times satisfactory $^{13}$C{$^1$H} NMR data could not be obtained for **C1**, owing both to hindered rotation that is apparent in the $^1$H NMR spectrum, and slow decomposition to paramagnetic byproducts upon standing in solution for extended periods. Anal. Calcd for $C_{45}H_{39}O_1P_2Ni_1Br_1$: C, 67.85; H, 4.94. Found: C, 67.49; H, 4.81. Crystals of **C1** suitable for X-ray diffraction analysis were grown via slow evaporation of a $CH_2Cl_2$ solution.