Challenging Nickel-Catalyzed Cross-Couplings Enabled by Ligand Design

by

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Abstract

Carbon-nitrogen linkages are highly prevalent in bioactive molecules, and as such, the development of sustainable methodologies for their formation is of immense importance to both the pharmaceutical and agricultural industries. Within this realm, the advent of homogeneous transition metal catalysis has allowed significant progress to be made in the development of routes toward the formation of these linkages, encompassing a wide range of different carbon and nitrogen-containing organic reagents. Specifically, the development of Pd-catalyzed C(sp^2)-N (herein, C-N) cross-coupling (i.e. Buchwald-Hartwig-Amination, BHA) has transformed the way chemists approach solving synthetic problems. Indeed, research efforts in BHA over the past 25 years have allowed for the development of several catalytic systems, encompassing a large array of both (hetero)aryl (pseudo)halide and NH-bearing substrates. Successes in BHA can be largely attributed to the rational design of ancillary ligands, which are able to dramatically influence the reactive properties of Pd through a combination of steric and electronic effects. Despite the utility of BHA, researchers have now turned to more Earth-abundant sources for effecting these transformations, including the implementation of Cu for improved versions of well-known Ullmann-coupling, and the implementation of Ni, both as alternatives to precious Pd. In this thesis, my contributions toward the rational design, syntheses and use of appropriate ancillary ligands for enabling Ni-catalyzed C-N cross-coupling are described. Included are the development of new phosphonite/phosphine ligands such as Phen-DalPhos and related variants, along with the application of Ni-based pre-catalysts for the cross-coupling of ammonia, (hetero)anilines, indoles, sulfonamides, fluoroalkylamines and amides with (hetero)aryl (pseudo)halides under unprecedently mild conditions in Ni-based catalysis.

List of Abbreviations Used

API	active pharmaceutical ingredient
Ar	aryl
bpy	bipyridine
BHA	Buchwald-Hartwig amination
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthalene
CgP	1,3,5,7-tetramethyl-2,4,8-trioxa-6-phosphaadamantane
δ	chemical shift
Cp	cyclopentadienyl
CyPF-Cy	(R)-(-)-1-[(S)-2-(Dicyclohexylphosphino)ferrocenyl]ethyldicyclohexylphosphine
CyPF-*t*Bu	(R)-(-)-1-[(S)-2-(Dicyclohexylphosphino)ferrocenyl]ethyldi-tbutylphosphine
CPME	cyclopentyl methyl ether
dme	1,2-dimethoxyethane
dppe	1,2-bis(diphenylphosphino)ethane
dtbbpy	4,4’-di-*tert*-butyl-2,2’-dipyridyl
d	doublet
DPPF	1,1′-ferrocenediyl-bis(diphenylphosphine)
ESI	electrospray ionization
GC	gas chromatography
HRMS	high-resolution mass spectrometery
IPr	1,3-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene
IMes	1,3-bis-(1,3,5-trimethylphenyl)imidazol-2-ylidene
J	scalar coupling constant
L	neutral 2-electron donor ligand
M	mol / L
m	multiplet
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
phen	phenanthroline

PS	polystyrene
PTFE	poly(tetrafluoroethylene)
rt	room-temperature
SET	single electron transfer
THF	tetrahydrofuran
TLC	thin layer chromatography
X	halide substituent or anionic ligand
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

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Firstly, sincere recognition is extended to my supervisor Dr. Mark Stradiotto who I consider to be an important role model to me. Mark has helped me to better both my research and life skills, by providing continual mentorship, motivation and enthusiasm throughout my studies. Appreciation is also extended to members of the Stradiotto group (both past and present) including Jillian Clark, Chris Lavoie, Joseph Tassone, Alex Gatien, Preston MacQueen, Julia Paffile, Kathleen Morrison, Connor Simon, Josh MacMillan, Travis Lundrigan, Nicholas Bode, Casper MacAulay, Karlee Bamford and Melody Shen, all of whom have been a pleasure to work with.

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1. Introduction

1.1 Thesis overview

Homogeneous transition metal catalysis is a useful method for facilitating organic reactions that will not proceed otherwise.[1] Catalyst design of this type is now a fundamental component of organic synthesis, and often involves the rational design or selection of ancillary ligands that can dramatically influence the reactive properties of a given transition metal through a combination of steric and electronic effects.[2,3] The importance of ligand design in enabling transition metal catalyzed reactions is demonstrated in cross-coupling reactions involving C-X bond formation (X = C, N, O, S, P, etc.), which are of immense importance given their utility in the preparation of pharmaceuticals.[4] Indeed, transition metal catalyzed cross-coupling methodology has wide-reaching applications in the pharmaceutical and agricultural industries, by providing research chemists with a synthetic toolkit in the small-scale syntheses of diverse arrays of bio-active molecules, and then in the process stage involving the large scale syntheses of active pharmaceutical ingredients.[4,5]

Significant interest lies in the design of practical ways to facilitate C(sp^2)-N bond formation giving rise to hetero(aniline) derivatives, as the aniline motif is widespread among bio-active molecules and functional materials.[6] Traditional methods for synthesizing (hetero)anilines include nucleophilic aromatic substitution (S_NAr) on appropriately substituted (hetero)aryl halides,[7] and nitration/reduction sequences,[8] both methods of which pose limitations especially when considered in the late-stage functionalization of drug-like molecules, given that both methods often require elevated temperatures and strongly basic/acidic conditions. The development of the Pd-catalyzed C-N cross-coupling between NH substrates and (hetero)aryl (pseudo)halides (i.e., Buchwald Hartwig Amination, BHA)

represents a major advancement in the syntheses of (hetero)aniline derivatives, with several key advancements being made over the past quarter century in terms of reaction development enabling an extensive substrate scope.[6,9] Despite these successes, however, key drawbacks such as the scarcity and resultant cost of Pd has caused a widespread shift in research focus, mainly toward Earth-abundant base metals such as Ni[10] and Cu[11] (i.e. Ullmann-coupling). Both metals have proven to be competent in achieving analogous reactivity to varying degrees, and in some cases even offering unique reactivity that is superior to analogous BHA methods.[12]

1.2 Buchwald Hartwig Amination

In 1995, the research groups of Stephen L. Buchwald and John F. Hartwig independently reported the first Pd-catalyzed cross-coupling of aryl bromides with aliphatic amines, which would later become known as the BHA reaction.[13,14] Since then, several research groups have contributed in the optimization of this reaction, with some of the biggest contributions arguably falling in the category of ancillary ligand design.[2,9,15] The relative ease by which mechanistic details of the BHA reaction could be studied allowed for research groups to optimize reaction conditions by designing ligands to help facilitate rate-limiting steps pertaining to the commonly accepted Pd(0)/Pd(II) cycle, where the oxidative addition of C(sp^2)-X (X = Br, Cl, etc.) bonds can often be rate-limiting.[2,15] For this reason, effective ligands in BHA often meet the criteria of being both electronically rich and sterically encumbering as to favour oxidative addition and to prevent bis-ligation in cases where it may be deleterious to catalytic performance.[2,15]

Some premier ligands featured in useful BHA chemistry are shown below in Figure 1.1; included are those developed by the Buchwald group including **JohnPhos**, **RuPhos**,

BrettPhos, and **XPhos** – all of which feature a relatively strongly electron-donating phosphine unit connected to a biphenyl backbone.[15] Although the ligands displayed in Figure 1.1 are very different in structure, it is evident that bulky phosphines have emerged as the premier ligand class for effecting the BHA reaction, along with NHCs such as **IPr** and **IMes**.[16,17] In addition to Buchwald's biphenyl-based monophosphine ligands, other monophosphines such as **P(*t*Bu)$_3$** and **BippyPhos**, have emerged as prominent ligands in BHA, the latter of which has proven to accommodate a remarkably extensive range of C-N substrates leading to a diverse array of (hetero)aniline products.[18] Large bite-angle bisphosphines such as **DPPF**,[19] **XantPhos**,[20] **BINAP**[21] and the **JosiPhos**[22] ligand family are also among the top-performing ligands in BHA, all of which adhere to the design criteria in terms of steric bulk and relative electronic richness.[2]

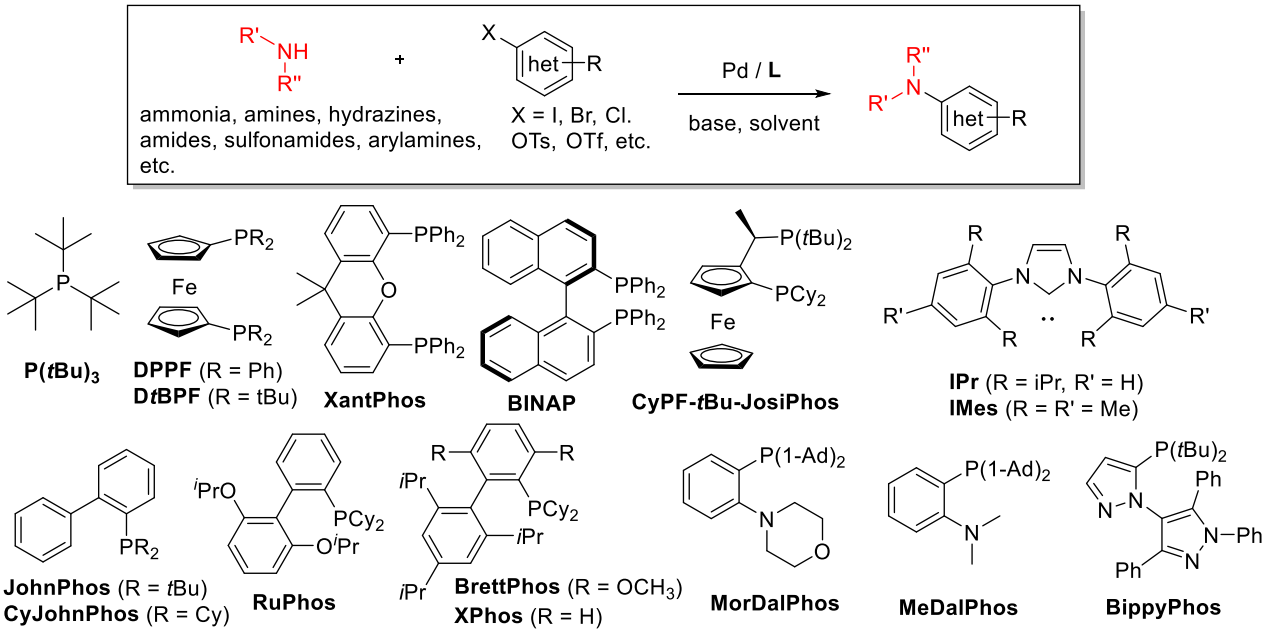


Figure 1.1 The Buchwald-Hartwig Amination reaction, featuring some useful ligands.

The Stradiotto group has also developed the mixed P-N donor ligands **MorDalPhos** and **MeDalPhos** as useful for implementation in BHA, the former of which was utilized in

the first reported monoarylation of hydrazine with aryl halides.[23] This reaction represents a remarkable advance in the preparation of phenylhydrazines, which in turn can easily be converted into indoles via the Fischer indole synthesis, developed by the Nobel Prize winning Emil Fischer in 1883.[24]

Since the advent of BHA in 1995, the reaction has become both a reliable and versatile tool for the construction of C-N bonds at both the academic and industrial levels.[9] The reaction has been performed on the benchtop in both the syntheses of optoelectronics and in the total syntheses of natural products.[6] Perhaps more noteworthy however, is the transferability of BHA protocols to the industrial scale, with several industrial processes operating successfully on the kilogram scale.[9] Indeed, several biologically relevant compounds have been prepared on the kilogram scale utilizing BHA methodology including anti-leukemia agents **Venetoclax**[25] and **AMG 925**[26] as well as the fungicide, **Sedaxane**[9] (Figure 1.2).

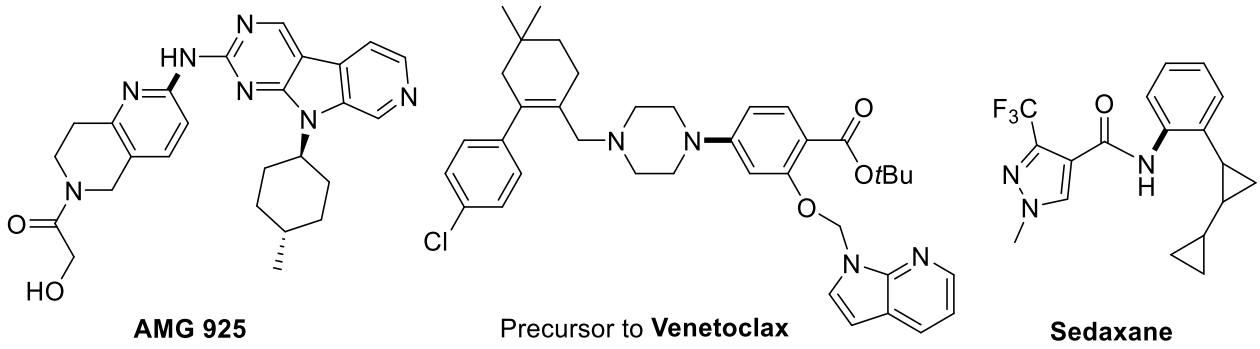


Figure 1.2 Industrially relevant compounds that featured a BHA step performed on kg scale. Bolded bonds represent those of which were constructed using BHA methodology.

Despite the obvious utility of BHA, the cost and scarcity of Pd motivates researchers to look for other methods to affect the same chemical transformations.[12,27] For instance, each of Ni,[10,12] Cu[11] and Cu/Fe[28] have been demonstrated to be effective in metal-catalyzed C-N

cross-coupling. Furthermore, in the ongoing quest for expanded reactivity, other metals are likely to perform successfully in situations where Pd struggles, such as in the oxidative addition of phenol-derived ArX substrates (X = OR, OMs, OTs, OTf, $OCONR_2$, OSO_2NR_2, etc.).[12]

1.3 Cu-catalyzed C-N cross-coupling

In an effort to seek more Earth-abundant sources to affect difficult C-N cross-coupling reactions, several research groups have resorted to Cu as an alternative in place of Pd.[11] The cross-coupling of hetero(aryl) iodides and bromides with NH substrates (i.e. Ullmann-Coupling) has been known for over 100 years, and has indeed proven to be a useful route in synthesizing (hetero)anilines.[11] Despite the successes, however, Ullmann-Coupling involving (hetero)aryl chlorides has proven to be difficult, accommodating a relatively small substrate scope and involving high reaction temperatures (>110 ˚C).[29,30] In the interest of addressing some of the challenges associated with Ullmann-Coupling, several research groups have turned to Ni as a group 10 base-metal alternative to Pd, offering similar redox properties to Pd allowing for the accommodation of (hetero)aryl chloride based substrates, in addition to inherently different reactivity which is likely to be useful in the quest for an expanded substrate scope.[12]

1.4 Ni-catalyzed C-N cross-coupling

1.4.1 Overview of Ni-catalyzed C-N cross-coupling

Perhaps the most promising alternative to Pd for use in C-N cross-coupling is that of Ni, with Ni-based catalysts having already been shown to couple a broad scope of NH partners with a broad scope of (hetero)aryl (pseudo)halides, including (hetero)aryl chlorides that are often difficult substrates in BHA and Ullmann-Coupling.[12,31] However, contrary to

Pd-catalyzed C-N cross-coupling where a generally accepted Pd(0)/Pd(II) mechanism is likely responsible for product turnover, the mechanism of Ni-catalyzed C-N cross-coupling is significantly more complex despite the fact that both metals share group 10 of the periodic table.[12] Indeed, existing evidence suggests that Ni can operate in both Ni(0)/Ni(II)[32,33] and Ni(I)/Ni(III)[34] cycles in such reactions, where the product-forming mechanism is not always clear as seen in Figure 1.3. Furthermore, Ni is more likely to participate in single-electron transfer (SET) mechanisms such as comproportionation and disproportionation, both of which may link the two catalytic manifolds in a single operative process.[12,33]

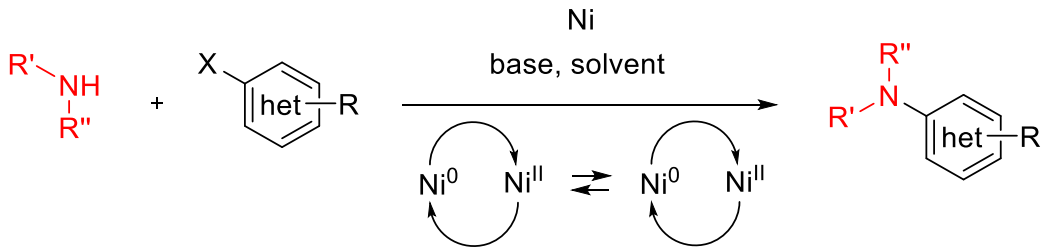


Figure 1.3 General scheme of Ni-catalyzed C-N cross-coupling, where the product forming mechanism is often unclear.

Further divergence between Ni and Pd can be observed when comparing the electronegativities of each group 10 metal, the latter of which is more electronegative, a feature that may account for the difficulty associated with the oxidative addition step in Pd-catalyzed C-N cross-coupling whereas the oxidative addition step in analogous Ni chemistry can occur more readily.[27] Due to these and other chemical differences, careful considerations must be taken when designing catalytic systems involving Ni to truly exploit ability of Ni to function catalytically. Within the realm of homogeneous Ni-catalyzed C-N cross-coupling, research groups haven taken two general approaches which involve either redox-enabled processes,[35,36] or ligand-enabled processes,[12] both methods of which have been shown to have strengths and limitations which will be discussed herein.

1.4.2 Redox-enabled Ni-catalyzed C-N cross-coupling

In redox-enabled Ni-catalyzed C-N cross-coupling, electrochemical[36] or photochemical[35] stimuli can be applied in order to facilitate catalytic turnover, both of which often exploit the characteristic behaviour of Ni to engage in SET processes. Both electrochemical and photochemical methods commonly utilize relatively inexpensive $Ni(II)X_2$ salts in conjunction with relatively simple chelating N,N-donor ligands such as 2,2'-bipyridine,[35,36] although in some cases ligand-free conditions have also proven feasible.[35]

In electrochemically induced Ni-catalyzed C-N cross-coupling, popularized by Phil S. Baran and co-workers, electrolysis allows for simultaneous oxidation and reduction to occur to facilitate catalytic turnover.[36] The key proposed elementary steps induced by electrochemical voltage involve the cathodic reduction of a $Ni(II)X_2$ pre-catalyst to furnish a Ni(I)X salt, and the anodic oxidation of a Ni(II)(Ar)NRR' complex to a Ni(III)X(Ar)NRR' complex which can undergo facile reductive elimination to generate aniline product.[36]

In photochemically induced Ni-catalyzed C-N cross-coupling, popularized by David W. C. MacMillan and co-workers, catalytic cycles involving oxidation states Ni(0), Ni(I), Ni(II) and Ni(III) are commonly invoked.[35] The invoked mechanism operates via the catalytic reduction of a $Ni(II)X_2$ pre-catalyst by Ir(II), eventually generating Ni(0), which can then undergo oxidative addition of ArBr followed by single-electron oxidation via photoexcited $*Ir(III)^{+}$, generating Ni(III)X(Ar)NRR' which can then undergo reductive elimination to furnish aniline product.[35]

In both redox-facilitated approaches, however, reactor designs are often complicated, involving setups that may not be practical in particular industrial settings.[35,36] Precious metal additives such as the Ir photocatalysts used in photochemically mediated catalysis also

present sustainability and cost issues, which may offset the potential benefits of using base-metal catalysis to facilitate reactions of this type. Furthermore, (hetero)aryl (pseudo)halides such as aryl chlorides and those that are phenol derived (i.e. mesylates, tosylates, triflates, etc.) are often incompatible substrates in redox-mediated methods, constituting a major design flaw given the prevalence of aryl chlorides when compared to the analogous aryl bromides.[31] For these reasons, researchers including the Stradiotto group have turned to ligand-enabled Ni-catalyzed methodology to avoid complicated reactor setups, and to help address outstanding reactivity challenges in the realm of C-N cross-coupling.

1.4.3 Ligand-enabled Ni-catalyzed C-N cross-coupling

Contrary to the limitations of redox-enabled Ni-catalyzed C-N cross-coupling, ligand-enabled protocols have proven to be superior thus far in the accommodation of a broad scope of (hetero)aryl (pseudo)halides including chlorides, mesylates, tosylates, triflates, carbamates, pivalates and sulfamates - while also accommodating a broad scope of NH partners.[12] Noteworthy is the fact that while Pd-catalyzed BHA methods have been employed with success with aryl sulfonates, these methods have not been shown to be generally compatible with alternative phenol derived aryl electrophile classes[37] (ethers, pivalates, carbamates, sulfamates) – showcasing the true potential of Ni-catalyzed C-N cross-coupling in enabling a broader substrate scope.[27] When comparing Pd and Ni in analogous chemistry, however, mechanistic complexities arise in Ni-catalyzed C-N cross-coupling due to a wide range of possible Ni oxidation states (i.e. Ni(0)-Ni(III)) when compared to BHA where a Pd(0)/Pd(II) cycle is generally accepted; as a result, ligand design criteria in Ni-catalyzed C-N cross-coupling has proven to not be as straightforward thus far.[12,33] The repurposing of prominent ancillary ligands in BHA for use in analogous Ni chemistry has had some

successes.[38–41] However, due to the inherently different reactivity of Ni versus Pd including the relatively more complex mechanistic landscape associated with Ni, it has recently become clear that ligands specifically tailored for use in Ni-catalysis, such as the **PAd-DalPhos**[42] ligand family and related variants (i.e. **ThioPAd-DalPhos**,[43] **NHP-DalPhos**[44]) developed by Stradiotto and co-workers, have generally been more useful (Figure 1.4).[12] For example, ligands such as **DPPF**,[41] **BINAP**[39] and the **JosiPhos**[38] ligand family have proven to be effective ligands for use in both BHA as well as in analogous Ni chemistry, whereas Buchwald's state-of-the-art biphenylene-based monophosphines (i.e. **JohnPhos**, **RuPhos**, **XPhos**, etc.) and Stradiotto's P-N donating **MorDalPhos** and **MeDalPhos** have generally proven ineffective in enabling analogous Ni-catalyzed amination chemistry.[12]

When considering effective ancillary ligands for implementation in Ni-catalyzed C-N cross-coupling, certain criteria seem to be important despite mechanistic complications relative to Pd. Firstly, when designing ligands, it is important to consider the oxidation state of the implemented Ni pre-catalyst source - some possible oxidation state choices are represented in Figure 1.4. An important discovery was made by Lavoie, Stradiotto, and co-workers in 2017 when it was found that (**DPPF**)$Ni^{I}Cl$ out-performed (**DPPF**)Ni^{II}(*o*-tolyl)Cl in the cross-coupling of benzamide with 4-chlorobenzonitrile whereas (**PAd-DalPhos**)Ni^{II}(*o*-tolyl)Cl was found to perform generally superior to (**PAd-DalPhos**)$Ni^{I}Cl$ in related cross-couplings.[33] For these reasons, sterically encumbering ancillary ligands such as bulky bisphosphines and NHCs may be advantageous as they likely help to minimize comproportionation/disproportionation reactions, thereby minimizing deleterious off-cycle reactions.[12] Even still, it can sometimes remain unclear as to which mechanism is responsible for product-formation, so choosing the appropriate ligand/Ni oxidation state is not as trivial

as in BHA chemistry where electron-rich phosphine ligands are likely to help facilitate potentially rate-limiting oxidative addition.[27] When assuming a Ni(0)/Ni(II) cycle is dominant, it may be wise to implement ligands that are sterically encumbering as well as relatively electron-deficient as experimental evidence suggests that reductive elimination to afford a ligand stabilized Ni(0) species may be rate-limiting, whereas in a presumptive Ni(I)/Ni(III) cycle, the oxidative addition step is likely to be rate-limiting and relatively more electron-rich ligands may well facilitate better catalytic performance (Figure 1.5).[12]

The Stradiotto-developed **PAd-DalPhos** family of ligands were designed to function within a Ni(0)/Ni(II) regime, as they all feature the sterically encumbering yet relatively electron-deficient 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phosphaadamantane (CgP) group, which presumably helps in facilitating the potentially rate-limiting reductive elimination step in a Ni(0)/Ni(II) cycle.[42] Indeed, when utilizing ligands of the **PAd-DalPhos** family in Ni-catalyzed C-N cross-coupling, better catalytic performance is typically observed when utilizing either Ni(0) or Ni(II) based pre-catalyst types such as either $Ni(COD)_2$ or LNi(Ar)X, lending credence toward a product-forming Ni(0)/Ni(II) mechanism.[33]

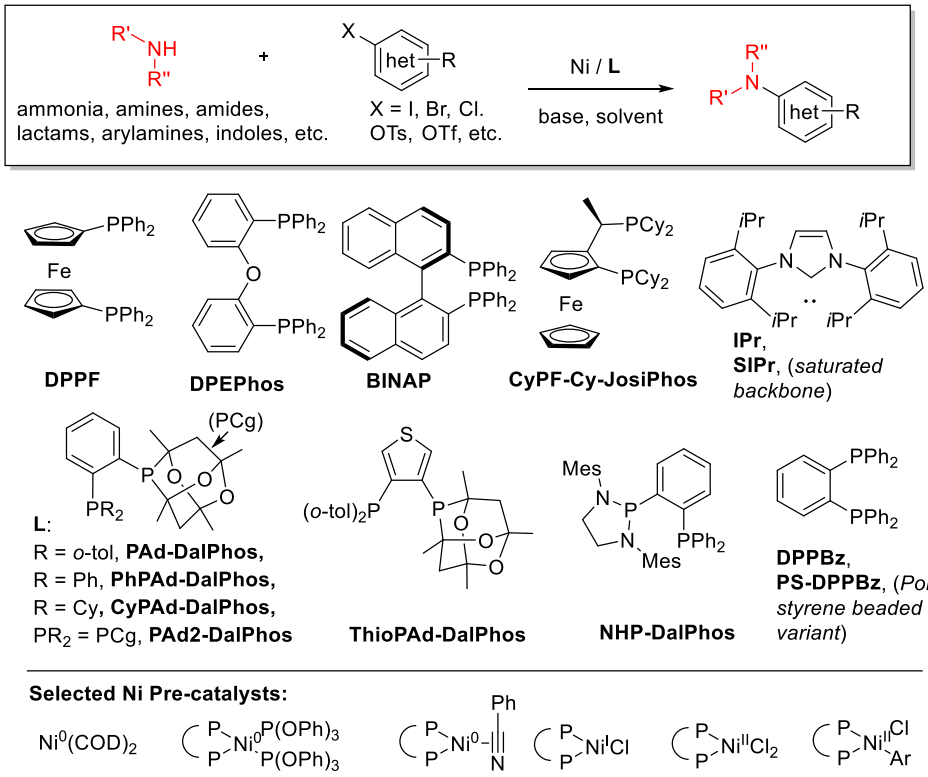


Figure 1.4 Ligand-enabled Ni-catalyzed C-N cross-coupling, featuring some prominent ligands and pre-catalyst types.[12,33,45]

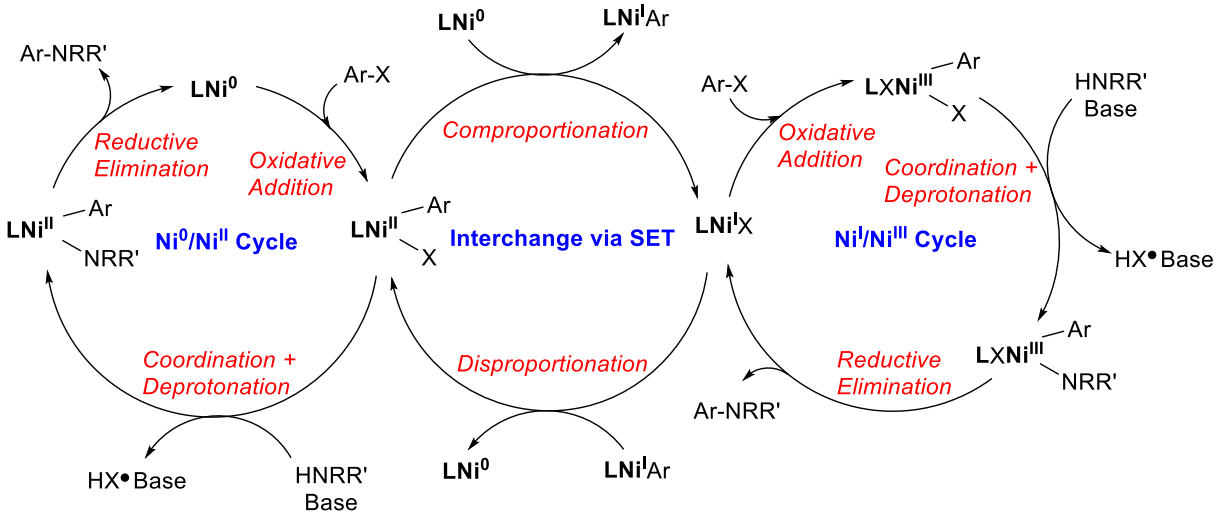


Figure 1.5 Proposed mechanisms for Ni-catalyzed C-N cross-coupling involving Ni(0)/Ni(II) and Ni(I)/Ni(III) cycles in which comproportionation and disproportionation may allow for interchange between respective cycles.

1.4.4 Current scope and limitations in Ni-catalyzed C-N cross-coupling

Due to the combined efforts of several research groups, ligand-enabled Ni-catalyzed C-N cross-coupling now enables a broad scope of transformations involving the use of several NH nucleophile classes and a range of (hetero)aryl (pseudo)halides.[11] Indeed, nucleophilic NH partners such as ammonia,[38,42] secondary amines,[46] primary amines,[42,44,47,48] anilines,[46] (hetero)arylamines,[49] amides,[50] lactams[50] and heteroarenes[40] (i.e. indole, carbazole, etc.) are all accommodated with a range of (hetero)aryl (pseudo)halides as seen in Figure 1.6. For a comprehensive review of Ni-catalyzed C-N cross-coupling, Lavoie and Stradiotto have recently provided a literature analysis that details the substrate scope.[12] Despite key advances in ligand-enabled Ni-catalyzed C-N cross-coupling, however, several unmet challenges exist that provide motivation for continued research in this area. Furthermore, given the relatively few ligands developed specifically for use with Ni when compared to those developed for Pd (BHA), it is likely that the true potential of Ni-catalysis has not yet been reached.[12]

With regard to specific limitations in Ni-catalyzed C-N cross-coupling, the use of relatively high temperatures to facilitate C-N cross-coupling reactions involving hetero(arene) and (hetero)arylamine (80-110 ˚C) nucleophilic NH partners presents potential issues, in that several bio-active molecules posses functional groups which may be unstable above physiological temperatures.[40] Indeed, the issue of functional group stability becomes particularly important when considering the common requirement of strong bases such as MO*t*Bu (M = Na, Li) in facilitating difficult C-N cross-coupling reactions, as the combination of elevated temperature and strong base is likely to cause deleterious side-reactivity when using complex functional-group bearing substrates. Unlike in BHA where Lundgren and

Stradiotto developed the first Pd-catalyzed C-N cross-coupling of hydrazines,[23] no known Ni-catalyzed route exists for coupling hydrazines with aryl halides, although one report details the Ni-catalyzed cross-coupling of benzophenone hydrazine with aryl bromides.[51] Deactivated (hetero)aryl chlorides including substituted 3-chloropyridines and electron-rich aryl halides such as 4-chloroanisole remain challenging substrates in Ni-catalyzed C-N cross-coupling, specifically when paired with NH substrates such as amides[50] and heteroarylamines.[49]

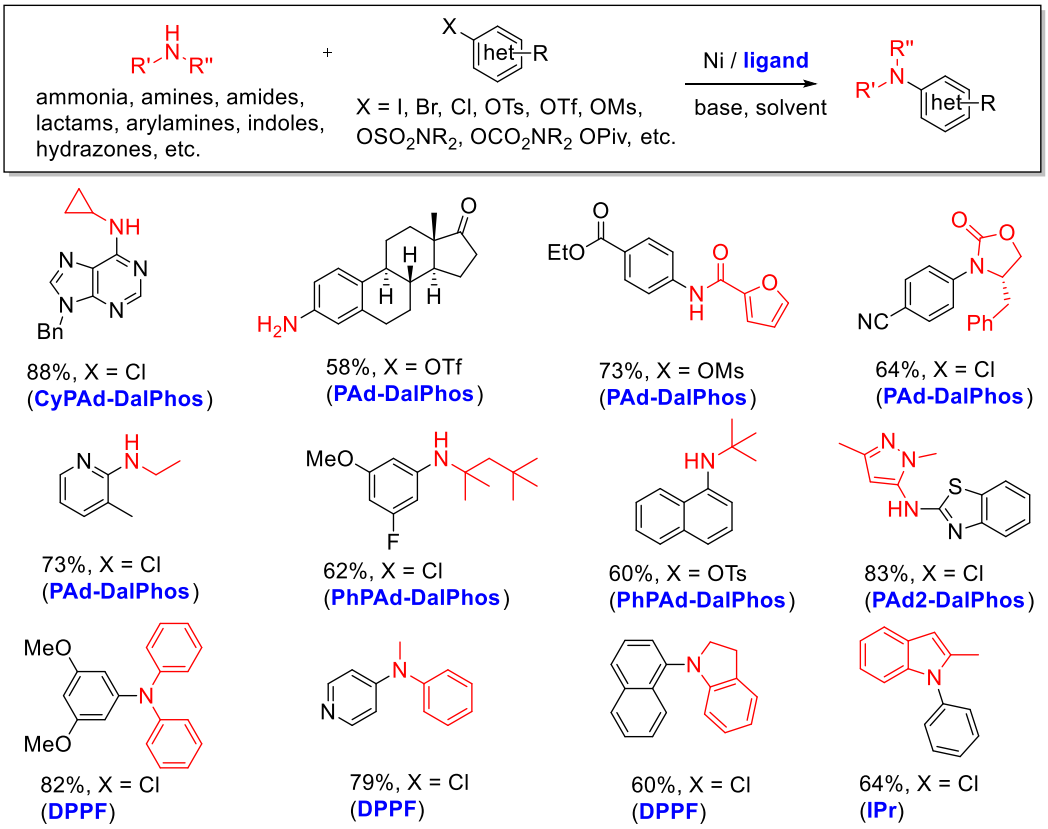


Figure 1.6 Current scope of ligand-enabled Ni-catalyzed C-N cross-coupling featuring some selected substrate pairings.[12,48,49]

Given that unique challenges in Ni-catalyzed C-N cross-coupling are still prevalent, this thesis aims to address said challenges in achieving more sustainable routes toward

(hetero)aniline derivatives by implementing ancillary ligand design. Furthermore, this work aims to design Ni-catalysts that are not only competitive with catalytic systems involving precious metals such as Pd, but will even provide new beneficial reactivity owing to inherent chemical differences.[27] The presented work also aims to contribute in advancing the fundamental understanding of ancillary ligation effects in Ni catalysis, extending to potential applications beyond those of which are presented herein.

2. Bulky 1,1′-Ferrocenyl Ligands Featuring Phosphonite Donor Fragments: Catalytic Screening in Nickel-Catalyzed C-N Cross-Coupling

2.1 Research overview and contribution report

This author wishes to clarify his contributions to the research described in Chapter 2 of this Thesis document. This chapter describes the design and application of 1,1'-ferrocenyl ligands featuring dioxaphosphepine donor fragments in Ni-catalyzed C-N cross-coupling. Ligands **L1** and **L1**^{SS} were synthesized in high yield and were applied successfully to several different test Ni-catalyzed C-N cross-coupling reactions, proving useful for enabling the monoarylation of both amines and indoles with (hetero)aryl chlorides. The catalytic performance of *rac* and *meso*-**L1** were compared amongst different substrate pairings, and it was found that *meso*-**L1** generally outperformed *rac*-**L1** except for in the cross-coupling of indole and 4-chlorobenznitrile.

My contributions to the study included synthesizing **L1** and **L1**^{SS}, growing crystals of *meso*-**L1** that were suitable for X-ray crystallography, and developing the substrate scope of reactivity. Alexandre V. Gatien and Melody Yue Shen were responsible for synthesizing and characterizing the diazaphospholene containing ferrocenyl based **L2** that is mentioned in this chapter for comparative purposes, and growing crystals for X-ray crystallography. Dr. Michael J. Ferguson carried out X-ray diffraction analysis of both *rac*-**L1** and **L2.** Dr. Jillian S. K. Clark and Dr. Mark Stradiotto helped in mentoring myself as well as providing advice throughout the project.

Reference: McGuire, R. T.; Clark, J. S. K.; Gatien, A. V.; Shen, M. Y.; Ferguson, M. J.; Stradiotto, M. Bulky 1,1'-Ferrocenyl Ligands Featuring Diazaphospholene or Dioxaphosphepine Donor Fragments: Catalytic Screening in Nickel-Catalyzed C-N Cross-Coupling. *Eur. J. Inorg. Chem.* **2019**, 38, 4112-4116.

2.2 Introduction

In the interest of expanding the substrate scope in Ni-catalyzed C-N cross-coupling, this research seeks to rationally design new ancillary ligands that feature what are envisioned to be key ligand criteria for facilitating difficult steps within a presumptive Ni(0)/Ni(II) catalytic cycle.[12,42] Given the evident successes had by the Stradiotto group in the development of the sterically encumbering yet moderately electron-donating **PAd-DalPhos**[42] ligand family, and the prominence of ferrocenyl-based ligands (i.e. **DPPF**,[41] **JosiPhos**[38]) for use in Ni-catalyzed C-N cross-coupling, this works seeks to merge aspects of both ligand structures in the design and application of new 1,1'-ferrocenyl ligands featuring relatively electron-deficient, yet sterically encumbering dioxaphosphepine (**L1**) or diazaphospholene (**L2**) fragments as seen in Figure 2.1.

For the sake of completeness, **L2** is depicted in Figure 2.1 although it will not be discussed further given that its synthesis and characterization were not completed as part of my thesis research. This chapter will thus focus on the synthesis and application of the ferrocenyl-based, phosphonite-containing **L1** ligand in facilitating Ni-catalyzed C-N cross coupling reactions involving NH nucleophiles such as primary amines, secondary amines and indoles.

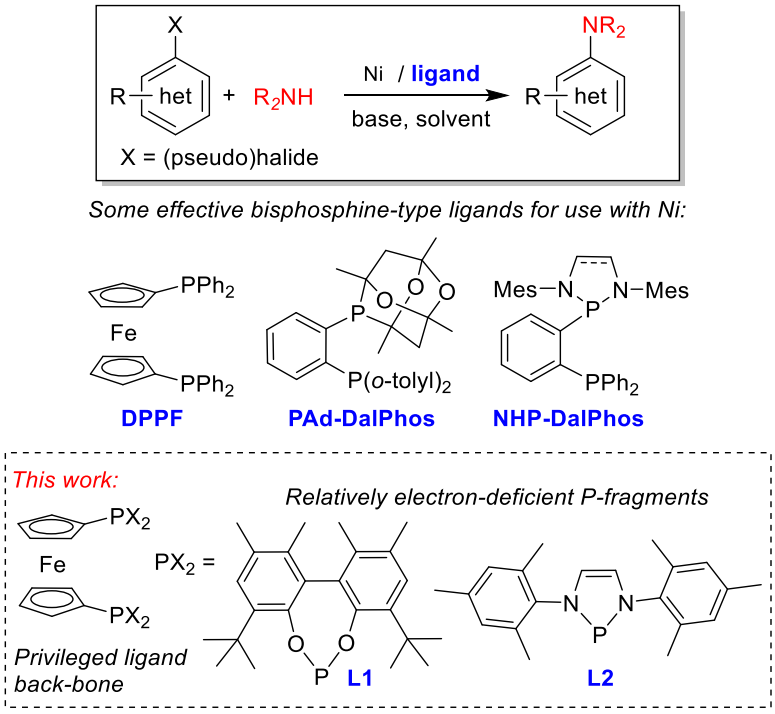


Figure 2.1 New ancillary ligands **L1** and **L2** designed based on previous successful ligands (i.e. **PAd-DalPhos**, **DPPF**) in Ni-catalyzed C-N cross-coupling.

2.3 Results and discussion

*2.3.1 Synthesis of **L1** and **L1**^{SS}*

In synthesizing **L1**, an initial approach involved the adaptation of a literature preparation for the synthesis of **DPPF** analogues,[41] whereby the lithiation of ferrocene (1 equiv.) with *n*BuLi (2.1 equiv.) in the presence of TMEDA (2.1 equiv.) allows for the in situ generation of a 1,1'-dilithioferrocene species which is stabilized by ligand chelation of TMEDA.[52] The generated 1,1'-dilithioferrocene species can then be quenched when adding 2 equiv. of PR_2Cl, or in the case of the synthesis of **L1**, when adding 2 equiv. of (BIPHEN)PCl[53] (shown in Figure 2.2). In following this procedure, a significant amount of generated **L1** product was observable via $^{31}P\{^1H\}$ NMR, however, minor unidentifiable impurities possessing similar solubility properties to that of **L1** made early attempts at purification difficult given that the phosphonite motif is especially prone to

hydrolysis/oxidation in the presence of water and oxygen, thereby limiting purification efforts to those of which could be conducted within an inert glove-box environment. It should be noted that a racemic mixture of chiral-at-phosphorus (BIPHEN)PCl was employed in the initial synthesis, which generates {R,R}, {S,S} and {R,S/S,R} isomers of **L1**, thus presenting the challenge of isolating diastereomers which will inherently have different physical properties. For this reason, synthetic efforts were directed toward identifying reaction conditions that facilitated near quantitative product conversion, eliminating potential issues in isolating a diastereomeric product mixture of **L1**. Optimal conditions were eventually identified of which closely resemble my initial attempt at the synthesis of **L1**, key differences being the isolation of the 1,1'-dilithioferrocene-TMEDA adduct,[52] and the application of elevated temperature (110 ˚C) in the (BIPHEN)PCl quenching step as seen in Figure 2.2, ultimately leading to a 90% isolated yield of **L1**. Indeed, the isolation of the 1,1'-dilithioferrocene-TMEDA adduct minimized the formation of undesirable side-products, allowing for easy purification of a 1:1 mixture consisting of *homochiral*-**L1** (i.e. {R,R}, {S,S}) and *heterochiral*-**L1** (i.e. {R,S/S,R}) diastereomers as estimated on the basis of $^{31}P\{^{1}H\}$ NMR and ^{1}H NMR integrations.

In following an analogous procedure to that outlined in Figure 2.2, enantiopure **L1*SS*** was synthesized in similarly high yield (88% isolated) by implementing enantiopure (*S*)-(BIPHEN)PCl in place of (*rac*)-(BIPHEN)PCl.

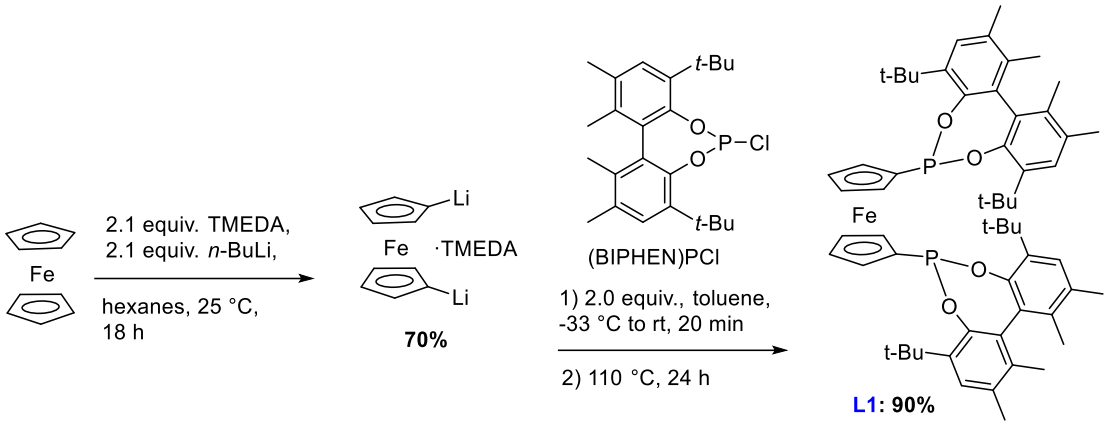


Figure 2.2 Optimized synthesis of **L1**, involving the synthesis and isolation of 1,1'-dilithioferrocene-TMEDA intermediate and subsequent treatment with (BIPHEN)PCl at 110 ˚C in toluene.

*2.3.2 Characterization of **L1** and **L1^{SS}***

When utilizing (*rac*)-(BIPHEN)PCl in the synthesis of **L1**, all possible stereoisomers of **L1** are generated, as evidenced by both $^{31}P\{^{1}H\}$ NMR and ^{1}H NMR data. Two signals are visible in the resulting $^{31}P\{^{1}H\}$ NMR spectrum at 180.7 (s) and 180.3 (s) ppm which can be attributed to *homochiral*-**L1** (i.e. {R,R}, {S,S}; *rac*-**L1**), and heterochiral-**L1** (i.e. {R,S/S,R}; *meso*-**L1**) isomers respectively, as seen in Figure 2.3 (c). These NMR assignments can be confirmed through the selective crystallization of *meso*-**L1** through vapour-diffusion, allowing for NMR spectroscopic and X-ray crystallographic characterization as seen in Figures 2.3 and 2.4. Furthermore, **L1^{SS}** (representative of *rac*-**L1**) can be independently synthesized in high yield and purity by implementing (*S*)-(BIPHEN)PCl, thus allowing for NMR spectroscopic characterization of both *meso* and *rac*-**L1** independently of each other.

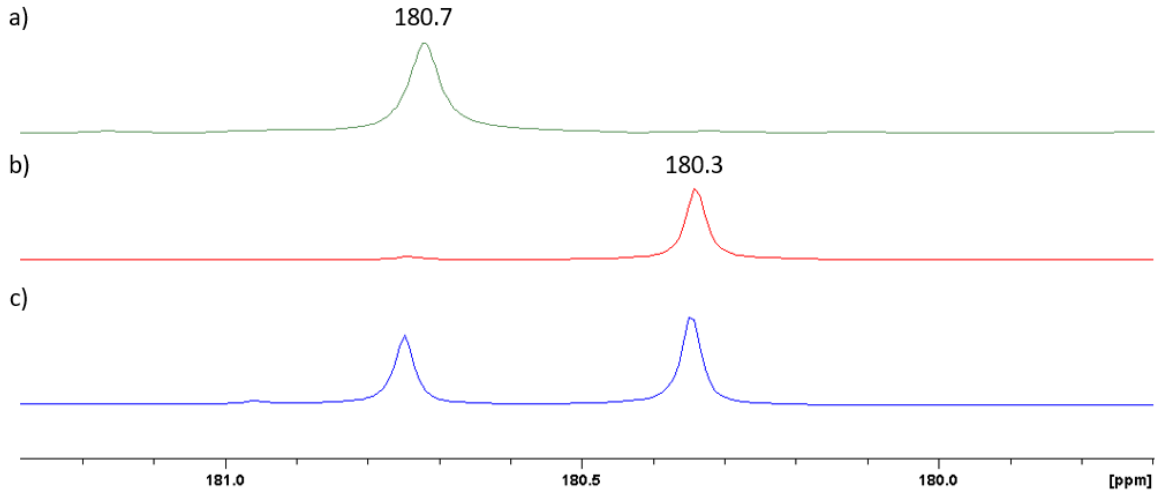


Figure 2.3 $^{31}P\{^{1}H\}$ NMR (202.5 MHz, $CDCl_3$) spectra of **L1**, displaying signals at 180.7 (s) and 180.3 (s) ppm, corresponding to *rac* and *meso* isomers of **L1** respectively. a) **L1**^{SS}; b) crystallized *meso*-**L1**; c) **L1** as a 1:1 mixture of *rac* and *meso* isomers as obtained in the synthesis of **L1** utilizing (*rac*)-(BIPHEN)PCl.

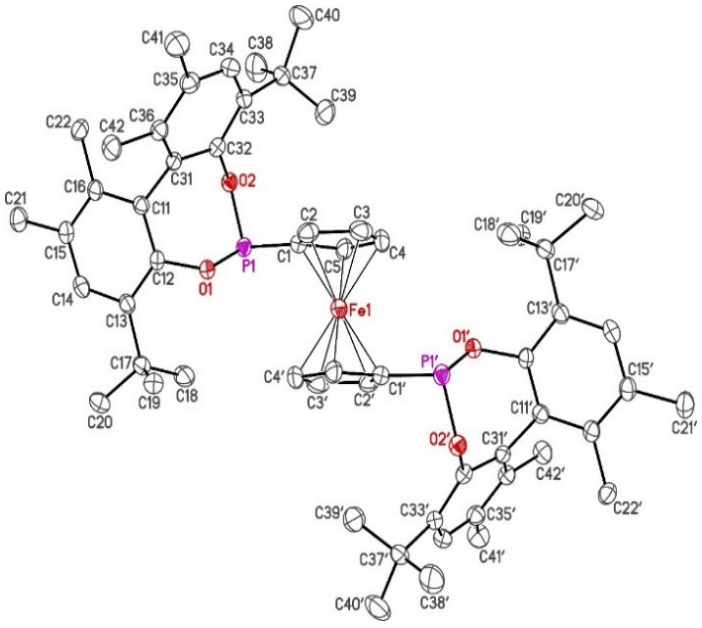


Figure 2.4 Single-crystal X-ray structure of *meso*-**L1** shown with 30 % displacement ellipsoids and with hydrogen atoms and solvate omitted for clarity. Primed atoms are generated via crystallographic symmetry (inversion center at 0.5, 0.5, 0.5).

The reason for the observation of two distinct singlets in the resulting $^{31}P\{^{1}H\}$ NMR spectrum of **L1** (one for each of *rac* and *meso* isomers) is due to internal symmetry properties, with the two phosphorus units in each respective diastereomer being related by either a C_2 (*rac*-**L1**) or a C_s (*meso*-**L1**) symmetry element. In crystallizing *meso*-**L1** through vapour-diffusion of pentane into THF, single crystals suitable for X-ray diffraction analysis can be obtained; the crystal structure of *meso*-**L1** is presented in Figure 2.4, allowing for further confirmation of absolute stereochemistry and calculated interatomic distances.

*2.3.3 Application of **L1** and **L1^{SS}** in Ni-catalyzed C-N cross-coupling*

With both **L1** and **L1^{SS}** in hand, the performance of each was tested in known, representative Ni-catalyzed C-N cross-coupling reactions involving the arylation of both primary amines, secondary amines, and indoles with (hetero)aryl chlorides as seen in Figure 2.5. It is important to note that although the C(sp^2)-N cross-coupling reaction is achiral in nature, it is to be expected that *rac*-**L1** and *meso*-**L1** will have unique catalytic performance given that they are diastereomers. Although I was unable to isolate a significant amount of pure *meso*-**L1** for catalytic testing, I sought to compare the catalytic performance of *rac*-**L1** and *meso*-**L1** indirectly by testing **L1** which consists of a 1:1 mixture of both *rac* and *meso* isomers, versus **L1^{SS}** which represents *rac*-**L1** in this achiral transformation.

Synthetic attempts at making **L1**$NiCl_2$ and **L1**NiCl(*o*-tolyl) pre-catalysts were unsuccessful when following literature preparations for related bisphosphine ligands,[42] and therefore catalytic testing was limited to *in situ* testing whereby **L1** and $Ni(COD)_2$ were added in order to generate a ligand-bound Ni(0) pre-catalyst. As seen in Figure 2.5, **L1** proved competent in enabling the Ni-catalyzed cross-coupling of a diverse array of nucleophilic NH substrates (primary amines, morpholine and indole) with activated

(hetero)aryl chlorides. Importantly, the catalytic performance of **L1** and **L1**^{SS} was differentiated in the cross-couplings of both indole and morpholine with 4-chlorobenzonitrile. Indeed, **L1** emerged as superior in the morpholine transformation (79% vs 37% product conversion), whereas **L1**^{SS} proved to be superior in the indole transformation (63% vs 36% product conversion). Noteworthy is the fact that the newly synthesized **L2** ligand failed to provide any substantial product conversion in all of the reactions shown in Figure 2.5. Although both **L1** and **L1**^{SS} proved to be competent in the exemplified Ni-catalyzed C-N cross-coupling reactions, efforts to conduct these reactions at room temperature were unsuccessful, as was the incorporation of other (hetero)aryl chlorides such as the challenging ortho-methyl hindered 2-chloro-3-methylpyridine. Furthermore, the incorporation of other challenging NH nucleophile classes such as (hetero)anilines and ammonia were also unsuccessful. Despite the unsuccessful application of phosphonite-containing **L1** and **L1**^{SS} in these selected challenging Ni-catalyzed cross-couplings, the synthesis of **L1** and **L1**^{SS} served as a starting point in developing synthetic routes toward the new phosphonite-containing **Phen-DalPhos** ligand class as highlighted in Chapter 3 of this

work, where **Phen-DalPhos** was successful in achieving this challenging yet desirable reactivity.

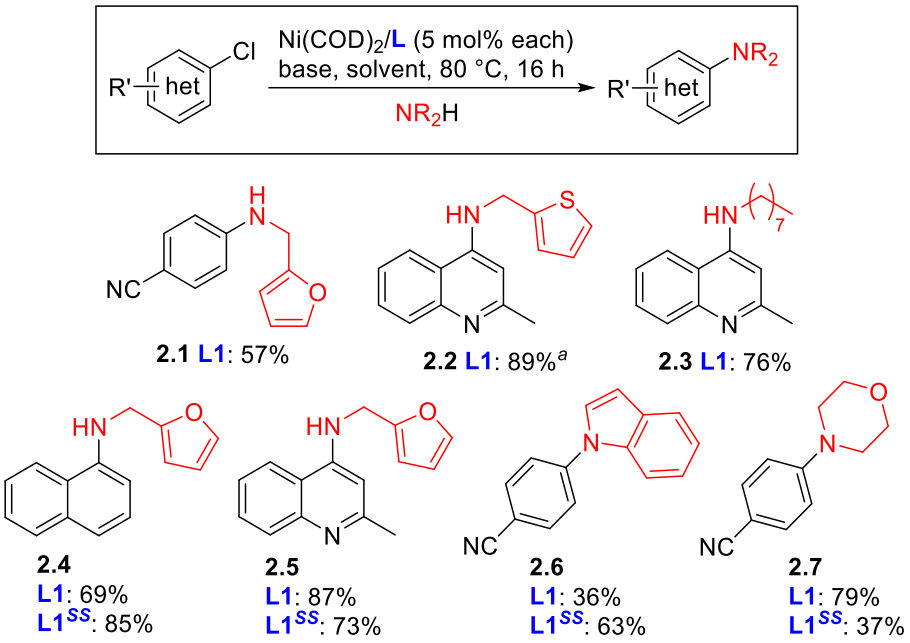


Figure 2.5 Reaction screening involving **L1** (*meso* + *rac* mixture) and **L1**^{SS} in selected Ni-catalyzed C–N cross-couplings, with conversion to the product given on the basis of calibrated GC data employing authentic products. [a]Isolated yield.

2.3.4 Summary

Although this study confirmed that the newly synthesized ferrocenyl-based ancillary **L1** and **L1**^{SS} ligand species are competent in Ni-catalyzed C-N cross-coupling, the ligands failed to enable more challenging transformations. Indeed, although the ligands developed in this chapter are inferior to ferrocenyl-based **DPPF** (and related analogues) in the applications presented herein,[33c] the identification of **L1** and **L1**^{SS} as competent ancillary ligands serves to expand the "tool-box" for synthetic chemists in the quest to solve unmet challenges in Ni-catalyzed cross-coupling and beyond.

2.4 Experimental

2.4.1 General considerations

Unless otherwise indicated, all experimental procedures were conducted in a nitrogen-filled, inert atmosphere glovebox using oven-dried glassware and purified solvents, with the exception of the workup of catalytic reaction mixtures, which was conducted on the benchtop in air using unpurified solvents. For solvents used within the glovebox, the following purification methods were used: toluene and pentane were deoxygenated by sparging with nitrogen gas followed by passage through a double column solvent purification system packed with alumina and copper-Q5 reactant and storage over activated 4 Å molecular sieves; tetrahydrofuran was dried over Na/benzophenone followed by distillation under an atmosphere of nitrogen gas; and *tert*-butanol was dried over CaH_2 followed by distillation under an atmosphere of dinitrogen. Solvents used within the glovebox were stored over activated 4 Å molecular sieves. All other commercial solvents, reagents, and materials were used as received. The 1,1'-dilithioferrocene-tetramethylethylenediamine adduct was prepared according to an existing literature protocol.[52] GC data were obtained on an instrument equipped with an SGE BP-5 column (30 m, 0.25 mm i.d.). Flash column chromatography was carried out using Silicycle Siliaflash 60 silica (particle size 40−63 μm; 230−400 mesh). All ^{1}H NMR (500 and 300 MHz), $^{13}C\{^{1}H\}$ NMR (125.8 and 75.4 MHz), and $^{31}P\{^{1}H\}$ NMR (202.5 and 121.5 MHz) spectra were recorded at 300 K and were referenced to residual protio solvent peaks (^{1}H), deuterated solvent peaks ($^{13}C\{^{1}H\}$), or external 85% H_3PO_4 ($^{31}P\{^{1}H\}$). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. All coupling constants (J) are reported

in Hertz (Hz). Mass spectra were obtained using ion trap (ESI) instruments operating in positive mode.

*2.4.2 Procedure for the synthesis of **L1** and **L1^{SS}***

In a dinitrogen filled glovebox, a Schlenk flask containing a magnetic stir bar was charged with 1,1'-dilithioferrocene-tetramethylethylenediamine adduct (933 mg, 2.97 mmol) and toluene (10 mL), and was cooled to -33 ˚C. A separate vial containing a magnetic stir bar was charged with (*rac*)-(BIPHEN)PCl (2.49 g, 5.94 mmol) and toluene (18 mL), and magnetic stirring was initiated to dissolve (*rac*)-(BIPHEN)PCl, followed by cooling to -33 ˚C. To the stirring solution of dilithioferrocene was added, the solution of (*rac*)-(BIPHEN)PCl dropwise, and the resulting mixture was allowed to reach room temperature before the flask was taken out of the glove-box and heated at 110 ˚C for 24 h. The flask was then brought back into the glove-box and was cooled to -33 ˚C for 30 minutes. The resulting mixture was filtered through celite and concentrated *in vacuo* to afford **L1** in a 1:1 ratio of *rac*-**L1** : *meso*-**L1** as estimated on the basis of both $^{31}P\{^{1}H\}$ NMR and ^{1}H NMR spectra (2.55 g, 90%). In synthesizing **L1^{SS}**, an analogous procedure was followed implementing enantiopure (*S*)-(BIPHEN)PCl, giving rise to a similarly high yield of **L1^{SS}** (88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (s, 2H, ArH), 6.86 (s, 2H, ArH), 4.60 (s, 2H, CpH), 4.50, (s, 2H, CpH), 4.40 (s, 2H, CpH), 3.61 (s, 2H, CpH), 2.25 (s, 6H, CH_3), 2.19 (s, 6H, CH_3), 1.81 (s, 6H, CH_3), 1.70 (s, 6H, CH_3), 1.51 (s, 18H, $C(CH_3)_3$), 1.00 (s, 18H, $C(CH_3)_3$). $^{13}C\{^{1}H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 148.0 (ArC), 145.9 (d, $J_{C\text{-}P}$ = 5.8 Hz, ArC), 138.1 (ArC), 137.2 (ArC), 135.0 (ArC), 133.7 (ArC), 133.3 (d, $J_{C\text{-}P}$ = 5.3 Hz, ArC), 132.4 (ArC), 131.4 (d, $J_{C\text{-}P}$ = 2.3 Hz, ArC), 131.2 (ArC), 128.4 (ArC), 127.9 (ArC), 74.4 (d, $J_{C\text{-}P}$ = 40.8 Hz, CpC), 71.7 (CpC), 71.3 (d, $J_{C\text{-}P}$ = 7.5 Hz, CpC), 70.7 (CpC), 35.0 ($C(CH_3)_3$), 34.9

($C(CH_3)_3$), 32.3 ($C(CH_3)_3$), 31.4 (d, $J_{C\text{-}P}$ = 4.8 Hz, ($C(CH_3)_3$), 20.8 (CH_3), 20.5 (CH_3), 16.7 (CH_3), 16.5 (CH_3). $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$): δ 180.7 (s). Diastereomerically pure crystals of *meso*-**L1** (*confirmed through X-ray crystallographic analysis*) were obtained through vapor diffusion using a mixture of tetrahydrofuran-acetonitrile, allowing for full NMR characterization. ^1H NMR (500 MHz, $CDCl_3$): δ 7.16 (s, 2H, ArH), 6.89 (s, 2H, ArH), 4.57 (s, 2H, CpH), 4.52 (s, 2H, CpH), 4.40 (s, 2H, CpH), 3.87 (s, 2H, CpH), 2.26 (s, 6H, CH_3), 2.24 (s, 6H, CH_3), 1.89 (s, 6H, CH_3), 1.73 (s, 6H, CH_3), 1.54 (s, 18H, $C(CH_3)_3$), 1.00 (s, 18H, $C(CH_3)_3$). $^{13}C\{^1H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 148.0 (ArC), 145.7 (d, $J_{C\text{-}P}$ = 5.6 Hz, ArC), 138.1 (d, $J_{C\text{-}P}$ = 2.4 Hz, ArC), 137.2 (ArC), 135.1 (ArC), 133.8 (ArC), 133.3 (d, $J_{C\text{-}P}$ = 5.0 Hz, ArC), 132.4 (ArC), 131.5 (d, $J_{C\text{-}P}$ = 2.9 Hz, ArC), 131.3 (ArC), 128.5 (ArC), 127.9 (ArC), 79.0 (d, $J_{C\text{-}P}$ = 38.8 Hz, CpC), 74.6 (d, $J_{C\text{-}P}$ = 40.3 Hz, CpC), 71.7 (CpC), 71.4 (d, $J_{C\text{-}P}$ = 7.3 Hz, CpC), 70.4 (CpC), 35.0 ($C(CH_3)_3$, two overlapping resonances) 32.3 ($C(CH_3)_3$), 31.5 (d, $J_{C\text{-}P}$ = 4.9 Hz, $C(CH_3)_3$), 20.8 (CH_3), 20.6 (CH_3), 16.9 (CH_3), 16.5 (CH_3). $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$): δ 180.3 (s). HRMS *m/z* ESI^+ found 973.4114 $[M+Na]^+$ calculated for $C_{58}H_{72}FeNaO_4P_2$ 973.4147.

2.4.3 Procedure for the monoarylation of primary amines and indoles with aryl chlorides

For primary amines: Within a dinitrogen filled glovebox, **L1** (0.05 equiv.), NaO*t*Bu (2.0 equiv.), and aryl chloride (1.0 equiv.) were added to a screw capped vial containing a magnetic stir bar, followed by the addition of bis(cyclooctadiene)-nickel(0) (0.05 equiv.) dissolved in toluene (0.12 M aryl halide). To this solution was added furfurylamine (1.1 equiv.), and the vial was sealed with a cap containing a PTFE septum, removed from the glovebox and placed in a temperature-controlled aluminum heating block set to the stated temperature for 16 h under the influence of magnetic stirring. For indoles: Analogous

conditions were followed except LiO*t*Bu (1.5 equiv.) was utilized as base, and indole was added just prior to the addition of bis(cyclooctadiene)-nickel(0) solution. After cooling to room-temperature, either dodecane or 1-phenyldodecane (0.12 mmol) was added to the reaction mixture as an internal standard, so that the resulting mixtures could be quantitatively analyzed using GC methods.

2.4.4 Procedure for the N-arylation of morpholine with aryl chlorides

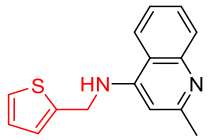
Within a dinitrogen filled glovebox, **L1** (0.05 equiv.), LiO*t*Bu (1.5 equiv.), and aryl chloride (1.0 equiv.) were added to a screw capped vial containing a magnetic stir bar, followed by the addition of bis(cyclooctadiene)-nickel(0) (0.05 equiv.) dissolved in CPME (0.5 M aryl halide). To this solution was added morpholine (1.5 equiv.), and the vial was sealed with a cap containing a PTFE septum, removed from the glovebox and placed in a temperature-controlled aluminum heating block set to the stated temperature for 16 h under the influence of magnetic stirring. After cooling to room-temperature, dodecane (0.12 mmol) was added to the reaction mixture as an internal standard, so that the resulting mixture could be quantitatively analyzed using GC methods.

2.4.5 Preparation of GC samples

Following the procedures outlined above (Sections 2.4.3 and 2.4.4, employing 0.12 mmol aryl halide) the reaction mixture was diluted using ethyl acetate and was passed through a Kimwipe filter containing Celite and silica gel, with the eluent collected in a GC vial. Calibrated GC estimates are given on the basis of data obtained from authentic materials using dodecane or 1-phenyldodecane as internal standards.

2.4.6 Characterization data for isolated products

2-methyl-*N*-(2-thienylmethyl)- 4-quinolinamine (**2.2**)



The title compound was synthesized from the corresponding aryl chloride (1.0 mmol) according to Section 2.4.3, conducted at 80°C using 5 mol% catalyst loading. The reaction mixture was diluted with ethyl acetate (20 mL) and washed with brine (3 x 20 mL), and the organic layer was dried over sodium sulfate. The solvent was removed *in vacuo* and the compound was purified by flash column chromatography on silica gel using a trimethylamine/ethyl acetate eluent gradient (4% triethylamine) which afforded the title product in 89% isolated yield (226 mg, 0.89 mmol) as an off-white solid. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.93 (m, 1H), 7.69 (m, 1H), 7.61 (m, 1H), 7.38 (m, 1H), 7.29 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.2), 7.10 (m, 1H), 7.02 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.5), 6.46 (s, 1H), 5.22 (br. s, 1H), 4.70 (d, 2H, J = 5.2 Hz), 2.63 (s, 3H). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 160.0, 149.3, 148.7, 141.0, 129.7, 129.5, 127.5, 126.4, 125.7, 124.5, 119.4, 117.7, 100.1, 43.0, 26.2. HRMS *m/z* ESI$^+$ found 255.0957 $[M+H]^+$ calculated for $C_{15}H_{15}N_2S$ 255.0950.

3. Ni-Catalyzed C-N Cross-Coupling of Ammonia, (Hetero)anilines and Indoles with Activated (Hetero)aryl Chlorides Enabled by Ligand Design

3.1 Research overview and contribution report

This author wishes to clarify his contributions to the research described in Chapter 3 of this Thesis document. This chapter describes the synthesis and application of the new phosphonite bearing **Phen-DalPhos** ancillary ligand and the corresponding air-stable (**Phen-DalPhos**)Ni(*o*-tolyl)Cl pre-catalyst in the Ni-catalyzed C-N cross-coupling of both (hetero)arylamines and ammonia with (hetero)aryl chlorides, under mild conditions (25 ˚C, 0.5 mol % Ni). Also described herein is the application of ancillary **PAd2-DalPhos** in the N-arylation of indoles under mild conditions (25 ˚C, 0.25 mol % Ni), offering orthogonal chemoselectivity versus **Phen-DalPhos** when cross-coupling substrates featuring contending aniline and indole NH functionalities.

My contributions to the study included developing synthetic routes toward new phosphonite-bearing phenylene bisphosphine ligands and corresponding Ni pre-catalysts, (including **Phen-DalPhos** and the related (**Phen-DalPhos**)Ni(*o*-tolyl)Cl pre-catalyst), growing crystals of Ni complexes suitable for X-ray diffraction analysis, and developing the substrate scope for all of the isolated aniline, ammonia and indole coupled products. During this project, I was also responsible for the mentorship of an undergraduate student (Julia F. J. Paffile) who assisted in screening C-N cross-coupling reactions and in isolating C-N cross-coupled products. Yuqiao Zhou carried out the X-ray diffraction analysis of (**Phen-DalPhos**)Ni(*o*-tolyl)Cl. Dr. Mark Stradiotto helped in mentoring myself as well as providing advice throughout the project.

Reference: McGuire, R. T.; Paffile, J. F. J.; Zhou, Y.; Stradiotto, M. Nickel-Catalyzed C-N Cross-Coupling of Ammonia, (Hetero)anilines, and Indoles with Activated (Hetero)aryl Chlorides Enabled by Ligand Design. *ACS Catal.* **2019**, 9, 9292-9297.

3.2 Introduction

Given the successes had with the application of relatively electron-deficient ancillary bisphosphines such as the **PAd-DalPhos** ligand class, as well as with phosphonite-containing **L1** and **L1**^{SS} as disclosed in Chapter 2 for applications in Ni-catalyzed C-N cross-coupling chemistry, attention was turned to the design and application of new 1,2-disubstituted phenylene-based phosphine-phosphonite hybrid ligands such as **Phen-DalPhos**, in related applications (Figure 3.1). Despite the potential promise associated with ligands of this type, this ligand class has received no prior attention in Ni-catalyzed cross-coupling chemistry prior to this work.

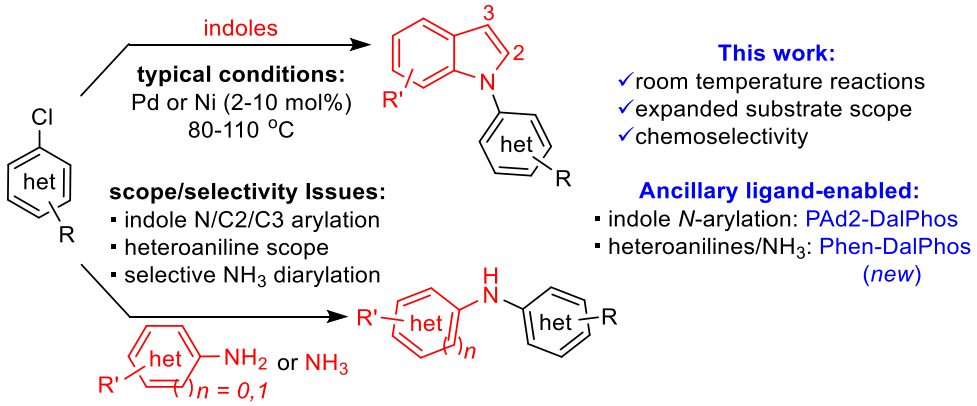


Figure 3.1 Summary of Ni-catalyzed C-N cross-coupling reactivity challenges addressed in this chapter.

As described herein, the newly synthesized ancillary **Phen-DalPhos** ligand was applied successfully in the difficult Ni-catalyzed cross-coupling of both ammonia and (hetero)anilines with (hetero)aryl chlorides to afford both symmetric and asymmetric

di(hetero)anilines, under unprecedentedly mild conditions. Also reported in this chapter is the identification of the previously disclosed **PAd2-DalPhos**[49] ligand for use in effecting the Ni-catalyzed cross-coupling of indoles with (hetero)aryl chlorides, also under unprecedently mild conditions.

3.3 Results and discussion

3.3.1 Ligand syntheses

In devising synthetic routes toward the targeted 1,2-disubstituted phenylene-based phosphine-phosphonite hybrid ligands **Phen-DalPhos** and **L3**-**L5**, as shown in Figure 3.2, initial synthetic conditions were adapted from previous literature methods toward the syntheses of 1,2-disubstituted bisphosphine ligands, such as **PAd-DalPhos** and related variants.[42] In the documented syntheses of **PAd-DalPhos** variants, (2-bromophenyl)PCg (1.0 equiv.) is lithiated upon the addition of *n*BuLi (1.5 equiv., 2.5 M in hexanes) at -33 ˚C, and the resulting lithio-benzene intermediate is subsequently quenched when adding 1.2 equiv. of the appropriate PR_2Cl species. In targeting the syntheses of **Phen-DalPhos** and related variants (**L3**-**L5**), this literature procedure was followed closely, except for starting with 1.0 equiv. of (2-bromophenyl)diphenylphosphine or (2-bromophenyl)di(*o*-tolyl)phosphine instead of (2-bromophenyl)PCg, and adding the appropriate $P(OR)_2Cl$ species (1.2 equiv.) instead of chlorophosphine as was done in the syntheses of **PAd-DalPhos** variants. In all cases, the resulting product mixtures appeared quite complex on the basis of $^{31}P\{^1H\}$ NMR data, with several signals appearing that were not attributed to target products or starting materials. It was speculated that the resultant complex reaction mixtures were generated as a result of the potential for P-O bond-cleavage, whereby both excess *n*BuLi and the generated lithio-benzene species can nucleophilically attack the $P(OR)_2Cl$ species several times

whereby Cl and OR act as leaving groups, leading to a diverse mixture of potential products. For these reasons, a two-pronged approach was taken in improving the syntheses of these ligands. Firstly, it was speculated that the isolation of generated lithio-benzene species[54] would minimize the potential for side-reactivity as the residual excess *n*BuLi would be unable to compete as a nucleophile toward $P(OR)_2Cl$ species. Secondly, in circumventing the possibility for generated lithio-benzene species to add multiple times to $P(OR)_2Cl$ species, relative reaction concentrations were considered, and the order of addition was reversed from the literature preparation for **PAd-DalPhos** variants. Indeed, upon isolation of lithio-benzene intermediates, and adding these dropwise (toluene solutions) to stirring solutions of $P(OR)_2Cl$ species, clean reactivity was observed to the desired products in the cases of **Phen-DalPhos** and (**L3**-**L5**), with only a small amount of starting material observable through $^{31}P\{^1H\}$ NMR analysis of the product mixtures.

A final synthetic improvement was made by employing TMEDA as a stabilizing agent in the syntheses of BIPHEN-derived ligands **Phen-DalPhos** and **L3**, which helped to allow the reactions to proceed in higher conversion to product. As seen in Figure 3.2, final optimized conditions allowed for the successful syntheses of **Phen-DalPhos** and **L3**-**L5** as LiCl adduct salts in synthetically useful yields (49-75% isolated yields). It should be noted that of these synthesized ligands, only **L4** is known,[55] with **Phen-DalPhos** along with **L3** and **L5** representing new ancillary ligands.

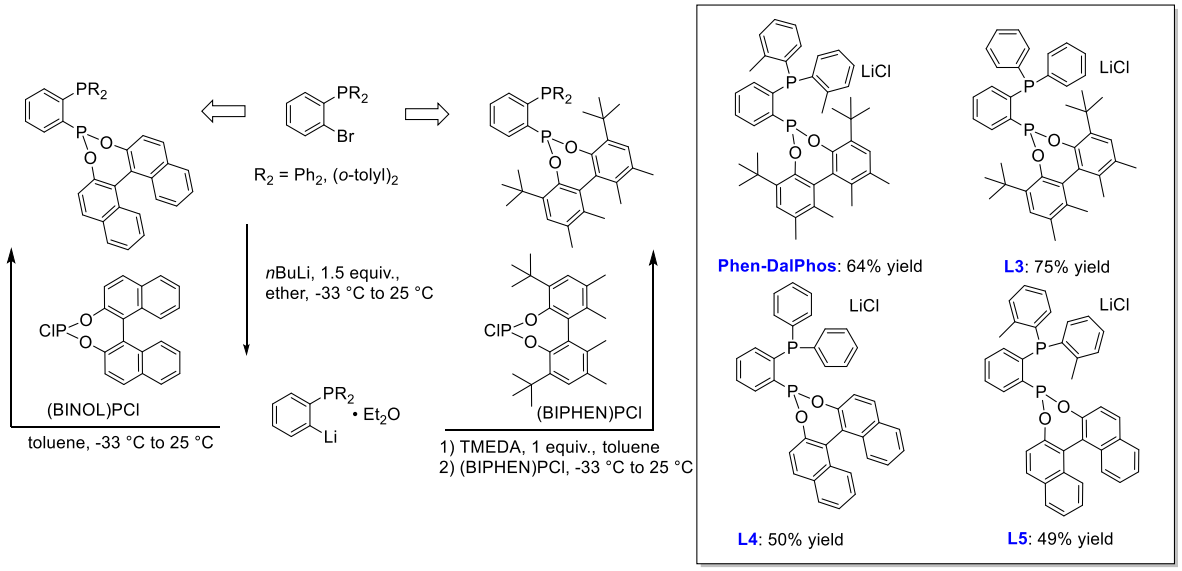


Figure 3.2 New synthetic routes toward 1,2-disubstituted phenylene-based phosphine-phosphonite hybrid ligands **Phen-DalPhos**, and **L3-L5**.

3.3.2 Preliminary ligand / Ni(COD)$_2$ screens

With ancillary ligands **Phen-DalPhos** and **L3-L5** in hand, the next step involved evaluating their catalytic performance in Ni-catalyzed C-N cross-coupling chemistry through preliminary reaction screening employing Ni(COD)$_2$ as the Ni source. Some known test reactions involving traditionally difficult NH partners such as ammonia and benzamide were performed to gauge the general effectiveness of the newly synthesized ligand variants, as seen in Figure 3.3.[42,50] In the Ni-catalyzed cross-coupling of ammonia with 1-chloronaphthalene, only **Phen-DalPhos** facilitated satisfactory product conversion (85%) to the monoarylated product, while **L3** facilitated some product conversion (45%), but a significant amount of higher molecular weight by-product (likely attributed to diarylation of ammonia) was detected by GC analysis. Both **L4** and **L5** provided no significant amount of product conversion (<5%) and a significant amount of aryl chloride starting material was detected in each case. In the cross-coupling of benzamide with 4-chlorobenzonitrile, once

again only **Phen-DalPhos** provided satisfactory product conversion (90%), while all the other variants tested (**L3**-**L5**) proved incompetent in this reaction with a significant amount of aryl chloride starting material remaining in each case. Having identified **Phen-DalPhos** as an effective ligand for facilitating difficult Ni-catalyzed cross-coupling reactions, it was decided that more rigorous catalytic testing should be conducted focusing predominately on this new ligand variant.

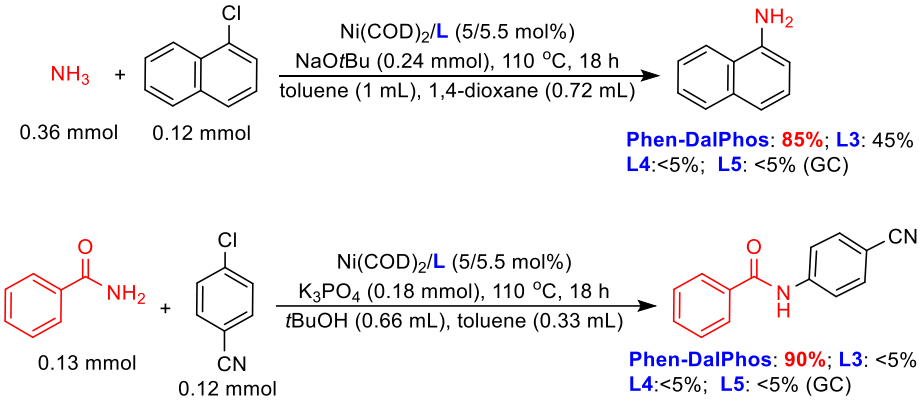


Figure 3.3 Ligand / $Ni(COD)_2$ screens demonstrating the superiority of **Phen-DalPhos** in facilitating difficult Ni-catalyzed C-N cross-couplings involving ammonia and benzamide, when compared to ligand variants **L3**-**L5**. Estimated conversions based on GC data (monitoring consumption of aryl chloride and formation of products).

In applying **Phen-DalPhos** to the cross-coupling of benzamide with other (hetero)aryl chlorides such as 4-chloroquinaldine, 1-chloronaphthalene, 4-chloroanisole and 2-chloro-*p*-xylene under similar conditions to those outlined in Figure 3.3 for the cross-coupling of benzamide and 4-chlorobenzonitrile, unsatisfactory product conversions were observed via GC analysis in all cases (<30%). Due to these shortcomings, **Phen-DalPhos** was then applied to alternative difficult transformations involving ammonia as an NH partner, under similar conditions to those outlined in Figure 3.3 for the cross-coupling of ammonia with 1-chloronaphthalene. Indeed, cross-couplings of ammonia with 4-chloroquinaldine, 4-chlorobenzonitrile, 4-chloroanisole and 2-chloro-*p*-xylene were all tested, and the results

were more interesting than in the case of the benzamide reactions. It was found that only in the cross-coupling of ammonia and 2-chloro-*p*-xylene did **Phen-DalPhos** facilitate high conversion to the monoarylated product (80%) as estimated by GC analysis. In the cross-coupling of ammonia with 4-chloroanisole, negligible turnover was observed, and the remaining mass balance corresponded to a large amount of unconsumed aryl chloride starting material, likely owing to the deactivated nature of this electrophile in being relatively electron-rich, and thus less prone to engaging in oxidative addition. In the cross-couplings of ammonia with 4-chloroquinaldine and 4-chlorobenzonitrile, nearly quantitative conversion to the diarylated product (>95%) was ascertained in each case by GC analysis, suggesting that the (hetero)aniline formed in the initial monoarylation is a competitive nucleophile versus ammonia in coupling to the (hetero)aryl chloride partner.

Although we were initially targeting the monoarylation of ammonia with (hetero)aryl chloride partners, the apparent selectivity for the diarylation product facilitated by the ancillary **Phen-DalPhos** ligand was intriguing. For these reasons, along with the fact that **PAd-DalPhos** had previously been disclosed as an effective ancillary ligand for the monoarylation of ammonia with (hetero)aryl chlorides, the diarylation of ammonia, along with the monoarylation of (hetero)anilines with (hetero)aryl chlorides was explored further with **Phen-DalPhos**. It should be noted at this time that although **L3** provided some conversion to the presumptive diarylated product in the reaction of ammonia with 1-chloronaphthalene as seen in Figure 3.3, **L3** proved generally less effective in affording ammonia diarylated products, as well as ammonia monoarylated products in other reactions, including in the reaction of ammonia with 4-chloroquinaldine whereby only 45% diarylated product conversion (~55% remaining ArCl) was detected versus the >95% diarylated product

detected when employing **Phen-DalPhos** in the same transformation. Furthermore, **L3** also proved ineffective in the Ni-catalyzed cross-coupling of 4-aminoquinalidne with 2-chloro-3-methyl pyridine, offering <5% product versus the 90% product detected when employing **Phen-DalPhos**, suggesting that **Phen-DalPhos** is a superior ligand for facilitating reactions involving both ammonia and (hetero)aniline NH partners.

3.3.3 Pre-catalyst syntheses and preliminary screening

Although the ability of **Phen-DalPhos** to operate as an effective ligand when employing ligand/Ni(COD)$_2$ mixtures was satisfying, improved catalytic performance was sought by attempting to synthesize a pre-catalyst incorporating the new **Phen-DalPhos** ligand. The LNiCl(*o*-tolyl) pre-catalyst type is commonly used in Ni-catalyzed C-N cross-coupling, owing to several reactivity benefits versus commonly implemented ligand/Ni(COD)$_2$ systems; LNiCl(*o*-tolyl) pre-catalysts are generally air-stable and are typically synthesized using Ni(II) salts, which are significantly cheaper than Ni(0) sources such as air-sensitive Ni(COD)$_2$.[56] Furthermore, on top of having the ligand already bound prior to addition, LNiCl(*o*-tolyl) species are commonly invoked catalytic intermediates in Ni-catalyzed C-N cross-coupling.[12,33] Given the established benefits in using Ni(II) pre-catalysts as opposed to the reliance on generating catalytically active ligand-bound Ni species in solution from a Ni(0) source, the synthesis of (**Phen-DalPhos**)NiCl(*o*-tolyl) was pursued as seen in Figure 3.4. As shown in Figure 3.4, crystallographically characterized (**Phen-DalPhos**)NiCl(*o*-tolyl) was synthesized in an 86% overall yield when starting from **Phen-DalPhos**·LiCl and performing a two-step protocol involving a ligand substitution on (DME)NiCl$_2$ to afford the synthetic intermediate (**Phen-DalPhos**)NiCl$_2$, (92% isolated yield) and subsequent Grignard addition of (*o*-tolyl)MgCl (2.5 equiv. 1.0 M in THF). With (**Phen-**

DalPhos)NiCl(*o*-tolyl) in hand, more rigorous catalytic screening began in testing the cross-coupling of both (hetero)anilines and ammonia with (hetero)aryl chlorides.

Given the apparent selectivity of **Phen-DalPhos** in enabling the diarylation of ammonia with (hetero)aryl chlorides in preliminary $Ni(COD)_2$ screens, including when an excess of ammonia (3.0-10.0 equiv.) was delivered relative to (hetero)aryl chloride, it was speculated that the catalyst was particularly selective for cross-coupling of the aniline NH. For these reasons, the unprecedented chemoselective cross-coupling of 5-aminoindole with 2-chloroquionoline was tested at room temperature using (**Phen-DalPhos**)NiCl(*o*-tolyl) and a series of other prominent pre-catalysts of the type LNiCl(*o*-tolyl) for comparison, as seen in Figure 3.5. When employing (**Phen-DalPhos**)NiCl(*o*-tolyl), nearly exclusive coupling of the aniline NH occurred, affording high conversion to the product **3.1** (>95% by GC), whereas when using (**PAd2-DalPhos**)NiCl(*o*-tolyl), orthogonal chemoselectivity was observed in the near-exclusive generation of the indole N-arylated product **3.17** in high conversion (>95% by GC). Other established ligands for Ni-catalyzed C-N cross-coupling proved generally ineffective, with the "DalPhos" ligands **PAd-DalPhos** (for ammonia and 1˚ amine arylation[42] and **PhPAd-DalPhos** (for bulky 1˚ amine and bulky aniline arylation[48]) both affording a mixture of products, and **DPPF** (for 2˚ amine and indole arylation[41]) generating insignificant amounts of C-N cross-coupled product.

Given the unprecedented ability of **Phen-DalPhos** to selectively cross-couple the aniline NH when in the presence of either ammonia or indole NH functionalities, and the ability of **PAd2-DalPhos** to provide complimentary unprecedented reactivity in selectively cross-coupling the indole NH of 5-aminoindole at room temperature, it was decided that the

true scope of reactivity with regards to these reaction classes be demonstrated through the development of a substrate scope survey.

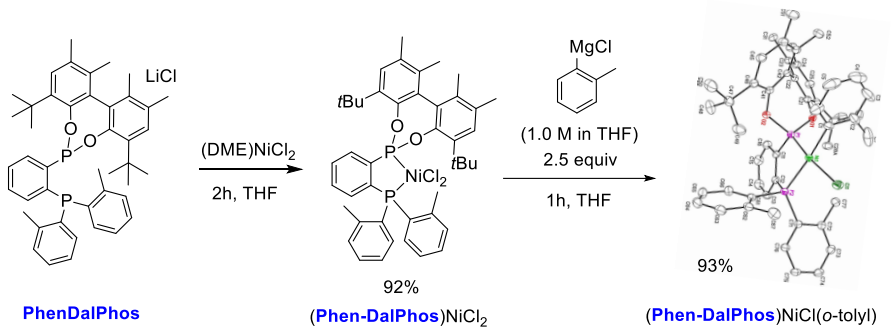
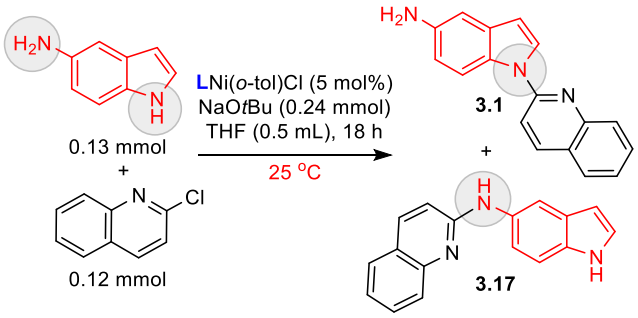


Figure 3.4 Synthesis of (**Phen-DalPhos**)NiCl(*o*-tolyl). For the single-crystal X-ray structure of (**Phen-DalPhos**)NiCl(*o*-tolyl), 30% thermal ellipsoids are shown, and selected H atoms have been omitted.



	Calibrated GC analysis		
L:	**3.1**	**3.17**	higher MW
Phen-DalPhos	>95%	<5%	<5%
PAd-DalPhos	47%	21%	~30%
PhPAd-DalPhos	27%	22%	~25%
PAd2-DalPhos	<5%	>95%	<5%
DPPF[a]	<5%	<5%	<5%

Figure 3.5 Chemoselective screening of 5-aminoindole with 2-chloroquinoline employing several LNiCl(*o*-tolyl) pre-catalysts including newly synthesized (**Phen-DalPhos**)NiCl(*o*-tolyl). Conversions to product are reported on the basis calibrated GC data using authentic products **3.1** and **3.17**.[a] >95% ArCl starting material remains as evidenced by GC analysis.

3.3.4 Scope of reactivity enabled by LNiCl(o-tolyl) pre-catalysts

In exploring the scope of cross-couplings involving (hetero)anilines paired with (hetero)aryl chlorides enabled by (**Phen-DalPhos**)NiCl(*o*-tolyl), it was found that all of 5-aminoindole, 6-aminoindole, 2-aminopyridine, aminopyrazine, 2-aminopyrimidine, 4-aminoquinaldine, and 2-aminobenzothiazole NH partners were successful substrates in conjunction with (hetero)aryl chlorides derived from quinoline, pyridine, quinaldine, and quinoxaline cores, as seen in Figure 3.6. Ironically, while our groups reported (**PAd2-**

DalPhos)NiCl(*o*-tolyl) pre-catalyst was previously disclosed as the state-of-the-art in achieving such transformations involving hetero-atom dense anilines and aryl chlorides (5 mol% Ni, 80 ˚C), the new **Phen-DalPhos** system offers several benefits including room-temperature reactivity in several cases, chemoselectivty versus indole NHs, and the ability to cross-couple ortho-methyl hindered aryl chlorides with (hetero)anilines.[49] Indeed, as seen in Figure 3.6, in the cross-coupling of 2-aminobenzothiazole with 6-chloroquinoxaline as well as in the cross-coupling of 2-aminopyrimidine with 4-chloroquinaldine, <25% conversion to product was detected when employing (**PAd2-DalPhos**)NiCl(*o*-tolyl) in both cases. Despite the clear advantages in using the new **Phen-DalPhos** system for the cross-couplings of (hetero)anilines with (hetero)aryl chlorides, limitations to this methodology include the unsuccessful cross-couplings of electron-rich aryl chlorides such as 4-chloroanisole, and the unsuccessful cross-couplings of 3-chloropyridines.

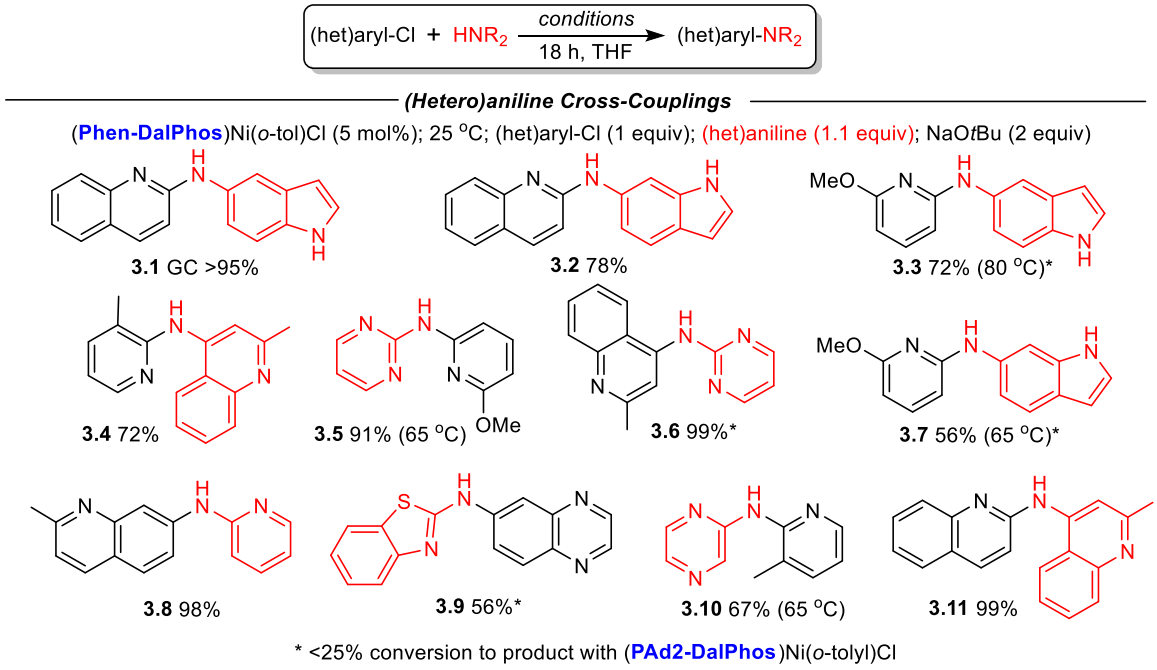


Figure 3.6 Substrate scope for the cross-coupling of (hetero)anilines with (hetero)aryl chlorides to afford asymmetric di(hetero)aniline products, enabled by (**Phen-DalPhos**)NiCl(*o*-tolyl). Isolated yields are reported. In all cases, <10% conversion to

product observed under the reported conditions in the absence of (**Phen-DalPhos**)NiCl(*o*-tolyl) on the basis of calibrated GC data, except for **3.6** where 20% conversion was noted.

In further extending the scope of reactivity enabled by the use of (**Phen-DalPhos**)NiCl(*o*-tolyl), the ability of this catalyst to enable the diarylation of ammonia with (hetero)aryl chlorides to afford symmetric di(hetero)anilines was explored. The preparation of symmetric di(hetero)anilines is traditionally achieved through BHA using elevated temperatures (>90 ˚C) and the Pd-catalyzed cross-coupling of heteroaryl bromides with the corresponding heteroaniline.[57] In utilizing (**Phen-DalPhos**)NiCl(*o*-tolyl), the previously unreported diarylation of ammonia with (hetero)aryl chlorides was successfully performed at room temperature, accommodating a range of (hetero)aryl chlorides including those based on pyridine, quinoline, quinoxaline and quinaldine core structures as seen in Figure 3.7. As in the case of the **Phen-DalPhos** enabled Ni-catalyzed cross-coupling of (hetero)anilines with (hetero)aryl chlorides, the inclusion of 3-chloropyridines and electronically rich (hetero)aryl chloride based substrates (such as 4-chloranisole) in the diarylation of ammonia was met with negligible success.

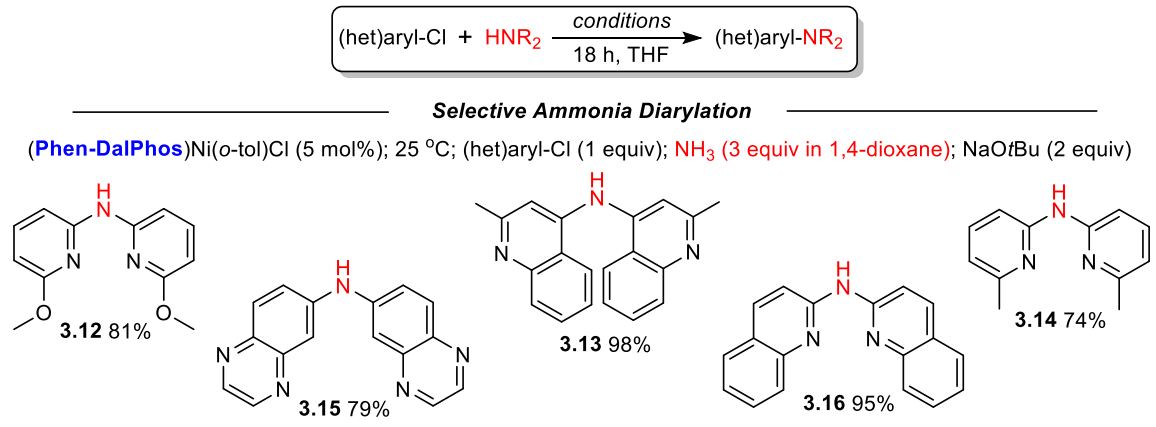


Figure 3.7 Substrate scope for the diarylation of ammonia with (hetero)aryl chlorides to afford symmetric di(hetero)aniline products, enabled by (**Phen-DalPhos**)NiCl(*o*-tolyl). Isolated yields are reported. In all cases, <10% conversion to product observed under the reported conditions in the absence of (**Phen-DalPhos**)NiCl(*o*-tolyl) on the basis of calibrated GC data.

The previously reported state-of-the-art in Ni-catalyzed indole N-arylation was reported in 2015 by Nicasio and co-workers, whereby the cross-coupling of (hetero)aryl chlorides and indoles is made possible through the implementation of (**IPr**)Ni(styrene)$_2$ as a pre-catalyst.[40] Despite the successful inclusion or heteroaryl chloride electrophiles reported by Nicasio and co-workers, relatively forcing conditions (10 mol% Ni, 110 ˚C) were required. In seeking to improve upon this work, we were inspired to test our previously reported **PAd2-DalPhos** ancillary ligand in such reactions, given that excellent chemoselectivty is observed for indole N-arylation in the cross-coupling of 2-chloroquinoline with 5-aminoindole at room temperature (5 mol% Ni). As seen in Figure 3.8, when utilizing (**PAd2-DalPhos**)NiCl(*o*-tolyl) in affecting the N-arylation of indoles with (hetero)aryl chlorides, several improvements can be observed when compared to previous work, including the compatibility of ortho-methyl-hindered (hetero)aryl chlorides (entry **3.22**), the ability to perform reactions at room-temperature (entries **3.17**-**3.18**, **3.20**), and the ability to cross-couple indoles bearing competitive NH groups (entries **3.17**-**3.18**).

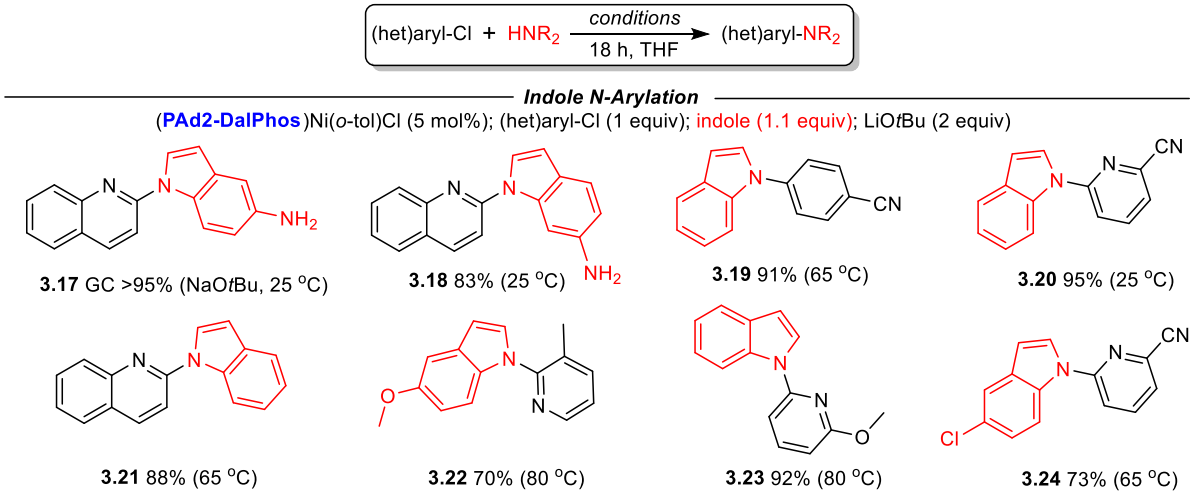


Figure 3.8 Substrate scope for the N-arylation of indoles with (hetero)aryl chlorides, enabled by (**PAd2-DalPhos**)NiCl(*o*-tolyl). Isolated yields are reported. In all cases, <10% conversion to product observed under the reported conditions in the absence of (**PAd2-DalPhos**)NiCl(*o*-tolyl) on the basis of calibrated GC data.

Although the **PAd2-DalPhos**-based catalyst system for the Ni-catalyzed N-arylation of indoles offers significant improvements upon previously reported methodology, the compatibility of electron-rich and deactivated aryl chlorides such as 4-chloroanisole and 3-chloropyridine was proven to be unsuccessful, and the developed methodology was limited to the inclusion of activated aryl chlorides such as 4-chlorobenzonitrile, 2-chloropyridnes and 2-chloroquinoline. In attempting to extend this methodology to the N-arylation of electron-rich indoles (i.e. 5-methoxyindole) and heteroarenes such as 7-azaindole, benzimidazole and indazole with heteroaryl chlorides such as 2-chloroquinoxaline and 2-chlorobenzothiophene, it was found that efficient product generation was detected in the absence of added Ni catalyst. Indeed, as seen in Figure 3.9, control experiments proved to be crucial in assessing the true contribution of (**PAd2-DalPhos**)NiCl(*o*-tolyl) in affecting product conversion, as apparent background S_NAr reactivity was evident in all (entries **3.25**-**3.29**), with (**PAd2-DalPhos**)NiCl(*o*-tolyl) only providing any significant reactivity benefit in the N-arylation of indazole with 2-chloroquinoxaline (entry **3.27**).

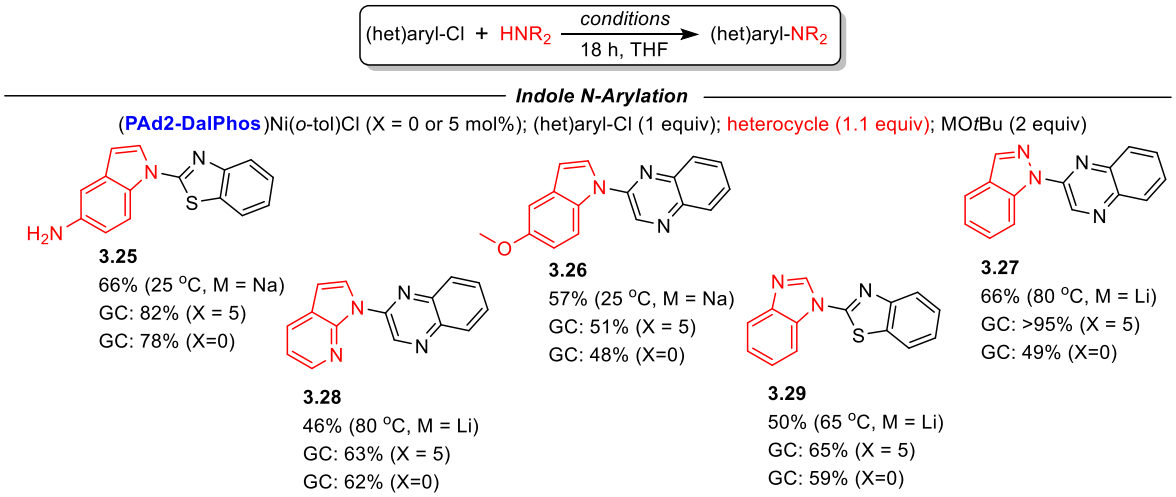


Figure 3.9 Substrate scope for the N-arylation of heterocycles with (hetero)aryl chlorides, enabled by strong-base conditions. Isolated yields reported for reactions employing (**PAd2-DalPhos**)NiCl(*o*-tolyl).

Having established both the new **Phen-DalPhos** and **PAd2-DalPhos** catalyst systems as efficient in affecting unique Ni-catalyzed cross-coupling reactions, the two catalyst systems were tested in the room-temperature cross-coupling of 5-aminoindole with 2-chloroquinoline in experiments involving low catalyst loadings and reduced reaction times. As seen in Figure 3.10, when utilizing (**Phen-DalPhos**)NiCl(*o*-tolyl) to affect this transformation, >95% conversion to the aniline coupled product **3.1** was observed at 0.5 mol% Ni, whereas when utilizing (**PAd2-DalPhos**)NiCl(*o*-tolyl), 91% conversion to the indole coupled product **3.17** was observed at 0.25 mol% Ni. In extending these reactions to the gram-scale, it was found that **3.1** could be synthesized using 0.5 mol% (**Phen-DalPhos**)NiCl(*o*-tolyl) on a 4.8 mmol scale in a 92% isolated yield, whereas **3.17** could be synthesized using 0.25 mol% (**PAd2-DalPhos**)NiCl(*o*-tolyl) on a 4.8 mmol scale in a 75% isolated yield. Particularly interesting is that after just 30 minutes of reaction time when utilizing 0.25 mol% (**PAd2-DalPhos**)NiCl(*o*-tolyl), 63% conversion to product **3.17** can be detected by GC analysis, making this catalyst system the most active catalyst system known (TOF ~ 500 h^{-1}) for indole N-arylation involving (hetero)aryl chlorides.

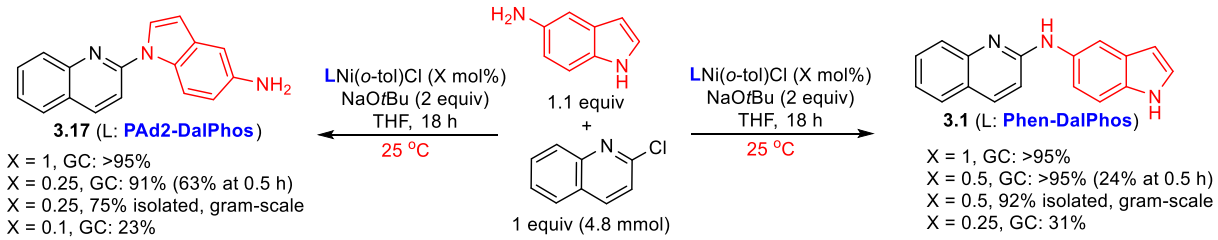


Figure 3.10 Low loading, gram-scale, room temperature, chemoselective Ni-catalyzed C–N cross-couplings leading to **3.1** and **3.17**. Conversions to product are reported on the basis calibrated GC data using authentic products **3.1** and **3.17**.

3.3.5 Summary

In conclusion, the newly synthesized **Phen-DalPhos** ligand and corresponding (**Phen-DalPhos**)NiCl(*o*-tolyl) pre-catalyst have proven effective in the Ni-catalyzed cross-coupling of both (hetero)anilines and ammonia with (hetero)aryl chlorides, affording a diverse array of di(hetero)aniline products under unprecedently mild conditions (0.5-5 mol% Ni, 25-80 ˚C), with examples proceeding chemoselectively. Furthermore, the previously disclosed **PAd2-DalPhos** ligand and corresponding (**PAd2-DalPhos**)NiCl(*o*-tolyl) pre-catalyst have been identified as being effective in enabling the Ni-catalyzed N-arylation of indoles under unprecedently mild conditions (0.25-5 mol% Ni, 25-80 ˚C) with examples proceeding with orthogonal chemoselectivty versus the **Phen-DalPhos** catalyst system. This study reaffirms the notion that rational ligand design is an effective strategy for facilitating difficult organic reactions, and specifically that the newly applied phosphine-phosphonite motif in **Phen-DalPhos** offers superior reactivity versus ancillary bisphosphines such as **PAd-DalPhos** in select cases.

3.4 Experimental

3.4.1 General considerations

Unless otherwise indicated, all experimental procedures were conducted in a nitrogen-filled, inert atmosphere glovebox using oven-dried glassware and purified solvents, except for the workup of catalytic reaction mixtures, which was conducted on the benchtop in air using unpurified solvents. For solvents used within the glovebox, the following purification methods were used: toluene and pentane were deoxygenated by sparging with nitrogen gas followed by passage through a double column solvent purification system packed with alumina and copper-Q5 reactant and storage over activated 4 Å molecular sieves;

tetrahydrofuran was dried over Na/benzophenone followed by distillation under an atmosphere of nitrogen gas; and tert-butanol was dried over CaH_2 followed by distillation under an atmosphere of dinitrogen. Solvents used within the glovebox were stored over activated 4 Å molecular sieves. (BINOL)PCl,[58] (BIPHEN)PCl,[53] and 1-P(*o*-tol)$_2$-2-bromobenzene[43] were prepared according to literature procedures. All other commercial solvents, reagents, and materials were used as received. GC data were obtained on an instrument equipped with an SGE BP-5 column (30 m, 0.25 mm i.d.). Flash column chromatography was carried out using silica (Silicycle Siliaflash 60 silica, particle size 40 - 63 μm; 230-400 mesh), alumina (activated, neutral Brockmann I), or by use of reverse-phase silica-based Silicycle SiliaSep C_{18} (17%) mono, 40 g (particle size 40−63 μm; pore size 60 Å). All ^{1}H NMR (500 and 300 MHz), ^{13}C{^{1}H} NMR (125.8 and 75.4 MHz), and ^{31}P{^{1}H} NMR (202.5 and 121.5 MHz) spectra were recorded at 300 K and were referenced to residual protio solvent peaks (^{1}H), deuterated solvent peaks (^{13}C{^{1}H}), or external 85% H_3PO_4 (^{31}P{^{1}H}). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. All coupling constants (J) are reported in Hertz (Hz). Mass spectra were obtained using either APCI or ion trap (ESI) instrumental methods operating in positive mode.

3.4.2 Procedure for the syntheses of ligands and Ni pre-catalysts

General procedure for synthesis of (**Phen-DalPhos**)·LiCl and **L3**·LiCl-**L5**·LiCl. In a nitrogen filled glovebox, a vial containing a magnetic stir bar was charged with the appropriate 1-PR$_2$-2-bromobenzene (1.0 equiv., R = o-tol for **Phen-DalPhos** and **L5**, R = Ph for **L3**-**L4**) in diethyl ether (0.3 M). The vial was then cooled to -33 ˚C for 1 h at which point *n*-BuLi (1.5 equiv., 2.5 M in hexanes) was added dropwise and the reaction mixture was

allowed to warm to ambient temperature with continued stirring. After 20 h, the reaction mixture was dried in vacuo and washed with pentane until any residual color was removed. The mixture was then dried in vacuo to afford (*o*-$PR_2(C_6H_4)$)Li·Et_2O by analogy with literature methods.[54] A new vial containing a magnetic stir bar was charged with isolated (*o*-$PR_2(C_6H_4)$)Li·Et_2O (1.0 equiv.) as noted above, toluene (0.1 M), and TMEDA (1.0 equiv., only in the synthesis of **Phen-DalPhos** or **L3**) before being cooled to -33 ˚C for 1 h. Simultaneously, a separate vial containing a magnetic stir bar was charged with (BIPHEN)PCl (for **Phen-DalPhos** and **L3**) or (BINOL)PCl (for **L4**-**L5**) (1.0 equiv.) and toluene (0.15 M) before being cooled to -33 ˚C for 1 h. The mixture containing (*o*-$PR_2(C_6H_4)$)Li·Et_2O was then added dropwise to the stirring solution of chlorophosphonite in toluene and the resulting mixture was allowed to stir for 20 h at ambient temperature before being dried in vacuo to afford a crude off-white residue. The residue was then washed with diethyl ether until the color was removed, affording the desired L·LiCl adducts: **Phen-DalPhos**·LiCl (64% based on (BIPHEN)PCl, 2.37 g, 3.31 mmol); **L3**·LiCl (75% based on (BIPHEN)PCl, 0.320 g, 0.465 mmol); **L4**·LiCl (50% based on (BINOL)PCl, 0.167g, 0.270 mmol) **L5**·LiCl (54% based on (BINOL)PCl, 0.201 g, 0.281 mmol). Given that our efforts to obtain ligands rigorously free of the generated LiCl were unsuccessful, leading to non-stoichiometric amounts of coordinated LiCl, we opted to employ all ligands in the form of the as-prepared LiCl adducts in subsequent catalyst screening and in the preparation of (**Phen-DalPhos**)NiCl(*o*-tolyl).

Data for **Phen-DalPhos**·LiCl. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25-7.17 (m, 5H, overlapping ArHs); 7.08-7.01 (m, 5H, overlapping ArHs; 6.78 (m, 4H, overlapping ArHs); 2.45 (s, 3H, CH_3); 2.39 (s, 3H, CH_3); 2.30 (s, 3H, CH_3); 2.23 (s, 3H, CH_3); 1.91 (s, 3H, CH_3);

1.79 (s, 3H, CH_3); 1.00 (s, 9H, $C(CH_3)_3$); 0.97 (s, 9H, $C(CH_3)_3$). ^{13}C UDEFT NMR (125.8 MHz, $CDCl_3$): δ 147.8 (s, ArC), 145.4 (d, J_{PC} = 6.2 Hz, ArC), 143.1-142.2 (m, overlapping ArCs), 138.0 (d, J_{PC} = 2.5 Hz, ArC), 137.7 (s, ArC), 136.3 (d, J_{PC} = 8.2 Hz, ArC), 134.9 (s, ArCH), 134.7-134.6 (m, overlapping ArCs), 134.0 (s, ArC), 133.8 (d, J_{PC} = 2.0 Hz, ArCH), 132.6 (d, J_{PC} = 5.9 Hz, ArC), 132.2 (s, ArC), 132.0 (d, J_{PC} = 6.0 Hz, ArCH), 131.5 (s, ArCH), 131.3 (d, J_{PC} = 2.8 Hz, ArC), 131.2 (s, ArC), 130.5-130.4 (m, overlapping ArCs), 130.0-129.9 (m, overlapping ArCs), 128.7 (s, ArCH), 128.6 (s, ArC), 128.0 (s, ArC), 127.9 (s, ArC), 126.4 (s, ArC), 126.1 (s, ArCH), 34.6 (s, $\underline{C}(CH_3)_3$), 34.3 (s, $\underline{C}(CH_3)_3$), 31.3 (s, $C(\underline{C}H_3)_3$), 30.8 (d, J_{PC} = 4.9 Hz, $C(\underline{C}H_3)_3$), 21.6 (d, J_{PC} = 21.1 Hz, CH_3), 21.1 (d, J_{PC} = 22.8 Hz, CH_3), 20.4 (s, CH_3), 20.3 (s, CH_3), 16.6 (s, CH_3), 16.2 (s, CH_3). $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$): δ 162.4 (d, J_{PP} = 244.1 Hz), - 26.9 (d, J_{PP} = 244.1 Hz). HRMS *m/z* APCl found 673.3368 $[M + H]^+$ calculated for $C_{44}H_{51}O_2P_2$ 673.3364.

Data for **L3**·LiCl. ^1H NMR (500 MHz, $CDCl_3$): δ 7.34-7.30 (m, overlapping ArHs, 8H); 7.25-7.22 (m, overlapping ArHs, 3H); 7.08 (s, ArH, 1H); 7.04 (apparent t, ArH, 1H); 7.00 (s, ArH, 1H); 6.88-6.83 (m, overlapping ArHs, 2H); 2.29 (s, CH_3, 3H); 2.24 (s, CH_3, 3H); 1.92 (s, CH_3, 3H); 1.80 (s, CH_3, 3H); 1.06 (s, $C(CH)_3$, 9H), 1.01 (s, $C(CH)_3$, 9H). ^{13}C UDEFT NMR (125.8 MHz, $CDCl_3$): δ 147.9 (s, ArC), 145.6 (d, J_{PC} = 6.4 Hz, ArC), 144.2-143.3 (m, overlapping ArCs), 138.0 (d, J_{PC} = 2.4 Hz, ArC), 137.7 (s, ArC), 137.1-136.9 (m, overlapping ArCs), 134.8 (s, ArC), 134.5-134.1 (m, overlapping ArCs), 132.8 (d, J_{PC} = 5.7 Hz, ArC), 132.5-132.4 (m, overlapping ArCs), 131.8 (s, ArCH), 131.6 (d, J_{PC} = 2.5 Hz, ArC), 131.3 (s, ArCH), 130.1 (m, ArCH), 128.8 (s, ArCH), 128.7-128.6 (m, overlapping ArCs), 128.2 (s, ArCH), 128.0 (d, J_{PC} = 6.0 Hz, ArCH), 34.9 (s, $\underline{C}(CH_3)_3$), 34.6 (s, $\underline{C}(CH_3)_3$), 31.3 (s, $C(CH_3)_3$), 31.1 (d, J_{PC} = 5.1 Hz, $C(CH_3)_3$), 20.6 (s, CH_3), 20.5 (s, CH_3), 16.8 (s, CH_3),

16.4 (s, CH_3). HRMS *m/z* APCl found 645.3066 $[M + H]^+$ calculated for $C_{42}H_{47}O_2P_2$ 645.3046.

Data for **L4**·LiCl. NMR data are in agreement with literature.[55] HRMS *m/z* APCl found 577.1483 $[M + H]^+$ calculated for $C_{38}H_{27}O_2P_2$ 577.1481.

Data for **L5**·LiCl. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.8 Hz, 1H, ArH); 7.92 (d, *J* = 8.2 Hz, 1H, ArH); 7.82 (d, *J* = 8.1 Hz, 1H, ArH); 7.56 (apparent d, *J* = 8.8 Hz, 2H, overlapping ArHs); 7.43-7.38 (m, 3H, overlapping ArHs); 7.35- 7.28 (m, 6H, overlapping ArHs); 7.25- 7.22 (m, 3H, overlapping ArHs); 7.18-7.05 (m, 4H, overlapping ArHs); 7.00-6.98 (m, 1H, ArH); 6.86-6.83 (m, 1H, ArH); 6.28 (d, *J* = 8.8 Hz, 1H, ArH); 2.56 (s, 3H, CH_3); 2.40 (s, 3H, CH_3). ^{13}C UDEFT NMR (125.8 MHz, $CDCl_3$): δ 150.2 (s, ArC), 143.4 (d, J_{PC} = 5.3 Hz, ArC), 143.1 (s, ArC), 142.4 (s, ArC), 135.0 (s, ArC), 134.6 (ArCH), 134.2-134.1 (m, overlapping ArCs), 133.1 (s, ArCH), 132.9 (s, ArC), 132.5 (s, ArC), 131.5 (s, ArCH), 131.4 (s, ArC), 130.9 (s, ArC), 130.5-130.4 (m, overlapping ArCs), 130.2 (d, J_{PC} = 4.7 Hz, ArCH), 129.2-129.0 (m, overlapping ArCs), 128.7 (s, ArCH), 128.3 (s, ArCH), 128.2 (s, ArCH), 126.8 (s, ArCH), 126.1-126.0 (m, overlapping ArCs), 125.8 (s, ArC), 125.3 (s, ArC), 124.8 (s, ArCH), 124.6)s, ArC), 122.2 (s, ArCH), 121.7 (s, ArCH), 21.6 (d, J_{PC} = 3.5 Hz, CH_3), 21.4 (s, CH_3). ^{31}P{^{1}H} NMR (202.5 MHz, $CDCl_3$): δ 174.1 (d, J_{PP} = 216.5 Hz); -34.0 (d, J_{PP} = 216.4 Hz). HRMS *m/z* APCl found 605.1794 $[M + H]^+$ calculated for $C_{40}H_{31}O_2P_2$ 605.1799.

Procedure for the synthesis of (**Phen-DalPhos**)NiCl(*o*-tolyl). In a dinitrogen filled glovebox, a vial containing a magnetic stir bar was charged with **Phen-DalPhos-**LiCl (2.37 g, 3.32 mmol, 1.1 equiv.), $NiCl_2$(DME) (0.66 g, 3.01 mmol, 1.0 equiv.) and THF (22 mL, 0.14 M). The resulting mixture was stirred magnetically at room temperature for 2 h. Within

the dinitrogen filled glovebox, pentane was added (50 mL) to generate further precipitate and the product was washed with a 1:3 THF-pentane solution (4 x 15 mL) prior to isolation *via* suction filtration to afford the putative (**Phen-DalPhos**)$NiCl_2$ salt as an orange solid. The putative (**Phen-DalPhos**)$NiCl_2$ (1.0 equiv.) was then transferred to a vial containing a magnetic stir bar, followed by the addition of THF (30 mL, 0.1 M). The mixture was then cooled to -33 ˚C for 0.5 h, followed by the addition of precooled (*o*-tol)MgCl (-33 ˚C, 1.0 M in THF, 2.5 equiv.); the mixture was allowed to warm to room temperature under the influence of magnetic stirring. After 1.5 h, the reaction was treated with anhydrous MeOH (4 mL) and the resulting contents were dried *in vacuo*. The resulting material was washed with anhydrous MeOH (2 x 6 mL) followed by pentane (2 x 10 mL). The solid was further dried *in vacuo* to afford (**Phen-DalPhos**)NiCl(*o*-tolyl) as a yellow solid (2.39 g, 2.79 mmol, 92%). Please note that (**Phen-DalPhos**)NiCl(*o*-tolyl) was isolated as a mix of isomers in a relative ratio of 8:1 as estimated on the basis of both ^{1}H and $^{31}P\{^{1}H\}$ NMR data. When possible, ^{1}H NMR signals were only assigned and integrated in the case of the major isomer. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.50-7.47 (m, overlapping isomers), 7.40-7.30 (m, overlapping isomers), 7.20-7.13 (m, overlapping isomers), 7.09-7.00 (m, overlapping isomers), 6.68-6.67 (m, overlapping isomers), 6.60-6.58 (m, 1H), 6.55-6.52 (m, 1H), 6.41-6.39 (m, overlapping isomers), 5.91-5.88 (m, 1H), 5.75-5.72 (m, 1H), 3.07 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 2.78 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.15 (s, 9H, $C(CH_3)_3$), 1.10 (s, 9H, $C(CH_3)_3$). $^{31}P\{^{1}H\}$ NMR (202.5 MHz, $CDCl_3$): δ 156.3 (d, J = 10.0 Hz, major isomer), 154.9 (d, J = 12.5 Hz, minor isomer), 31.4 (d, J = 9.9 Hz, major isomer), 30.8 (d, J = 12.3 Hz, minor isomer). Anal. Calculated for $C_{51}H_{57}ClNiO_2P_2$ C, 71.34; H, 6.70. Found: C, 71.42; H, 6.80. A single crystal suitable for X-

ray diffraction analysis was prepared by slow evaporation of pentane into a solution of THF at - 33˚C.

3.4.3 Procedure for the monoarylation of heteroarylamines and indoles with (hetero)aryl halides.

Unless otherwise indicated in the text, solid (**Phen-DalPhos**)NiCl(*o*-tolyl) or (**PAd2-DalPhos**)NiCl(*o*-tolyl) (5 mol%), NaOtBu or LiOtBu (2.0 equiv.), (hetero)aryl halide (0.48 mmol, 1.0 equiv.), heteroarylamine or indole (1.1 equiv.) and THF (0.24 M (hetero)aryl halide) were added to a screw-capped vial containing a magnetic stir bar. In the case of experiments conducted at lower catalyst loadings (all 0.30 mmol scale in (hetero)aryl halide), the pre-catalyst was delivered from stock solutions in THF so that the final concentration of (hetero)aryl halide remained 0.24 M. The vial was sealed with a cap containing a PTFE septum, was removed from the glovebox and placed in a temperature-controlled aluminum heating block set at the specified temperature and was allowed to react under the influence of magnetic stirring for 18 h (unoptimized).

3.4.4 Procedure for the selective diarylation of ammonia with (hetero)aryl halides

Unless otherwise indicated in the text, solid (**Phen-DalPhos**)NiCl(*o*-tolyl) (5 mol%), NaOtBu (2.0 equiv.), (hetero)aryl halide (0.8 mmol, 1.0 equiv.), ammonia (0.5 M in dioxane, 3.0 equiv.) and THF (6.666 mL) were added to a screw-capped vial containing a magnetic stir bar. The vial was sealed with a cap containing a PTFE septum, was removed from the glovebox and placed in a temperature-controlled aluminum heating block set at the specified temperature and was allowed to react under the influence of magnetic stirring for 18 h (unoptimized).

3.4.5 Procedure for the preparation of GC samples

Following *3.4.3* or *3.4.4* (0.12 mmol scale in (hetero)aryl halide), at room temperature the reaction mixture was diluted using an 8:1:1 ethyl acetate/methanol/NEt_3 mixture and was passed through a Kimwipe filter containing Celite and silica gel, with the eluent collected in a GC vial. Calibrated GC estimates are given on the basis of data obtained from authentic materials using dodecane as an internal standard.

3.4.6 Purification of heteroarylamines and (hetero)arylindoles via reverse-phase chromatography

Following *3.4.3* or *3.4.4*, the resultant mixture was cooled to room temperature (if needed) before adsorption onto silica and subsequent elution through a silica/celite frit employing an 8:1:1 ethyl acetate/methanol/NEt_3 mixture as eluent (~30-100 mL). The resulting solution was then dried *in vacuo* to afford a crude residue which was dissolved in DMSO before being loaded onto a 40g reverse-phase silica-based Silicycle SiliaSep C_{18} column cartridge. The product was then purified using the following gradient of acetonitrile/water, where the water contains 3 mL of a 28% NH_3 in H_2O solution per 1000 mL of water (total volume) as the eluent: 0% acetonitrile (8CV), 0-100% (18CV), 100% (6CV). The relevant UV-active column fractions were combined and lyophilized to afford the target product in each case.

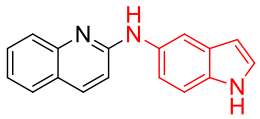
3.4.7 Purification of heteroarylamines and (hetero)arylindoles via normal-phase chromatography

Following *3.4.3* or *3.4.4*, the resultant mixture was cooled to room temperature (if needed) before adsorption onto silica and subsequent elution through a silica/celite frit employing an 8:1:1 ethyl acetate/methanol/NEt_3 mixture as eluent (~30-100 mL). The

solvent was removed in vacuo and the compound was purified by use of flash column chromatography on either alumina or silica gel.

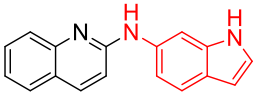
3.4.8 Characterization data for isolated products

N-(1H-indol-5-yl)quinolin-2-amine (**3.1**)



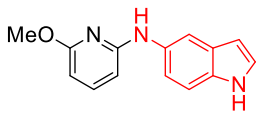
The title compound was synthesized from the corresponding aryl chloride (4.8 mmol) according to *3.4.3*, conducted at 25 °C using 0.5 mol% (**Phen-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.6* which afforded the title compound in a 92% isolated yield (1.145 g, 4.416 mmol). ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 10.83 (br, 1H), 9.01 (d, J = 1.0 Hz, 1H), 7.89 (d, J = 9.0 Hz, 1H), 7.63-7.62 (m, 2H, overlapping Hs), 7.51-7.48 (m, 1H), 7.39-7.37 (m, 1H), 7.34-7.32 (m, 1H), 7.24-7.23 (m, 1H), 7.20-7.17 (m, 1H), 7.00 (d, J = 9.0 Hz, 1H), 6.83 (br, 1H). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, DMSO-d_6): δ 155.4, 147.9, 136.6, 133.7, 132.5, 129.4, 128.2, 127.7, 126.4, 125.7, 123.7, 122.1, 116.0, 114.1, 111.5, 110.9, 101.4. HRMS-ESI (*m*/*z*): Calc'd for $C_{17}H_{14}N_3$ $[M+H]^+$: 260.1182. Found: 260.1193.

N-(1H-indol-6-yl)quinolin-2-amine (**3.2**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *3.4.3*, conducted at 25 °C using 5 mol% (**Phen-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.6* which afforded the title compound in a78% isolated yield (0.097 g, 0.374 mmol) as a brown solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.34 (br, 1H), 7.86 (d, J = 9.0 Hz, 1H), 7.79-7.76 (m, 2H, overlapping Hs), 7.64-7.56 (m, 3H, overlapping Hs), 7.29-7.26 (m, 1H), 7.18-7.17 (m, 1H), 7.06-7.04 (m, 1H), 6.97-6.93 (m, 2H, overlapping Hs), 6.54-6.53 (m, ^{1}H). ^{13}C{1H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ155.6, 147.9, 137.6, 136.4, 134.7, 129.7, 127.5, 126.3, 124.9, 124.2, 124.0, 122.7, 121.2, 116.0, 111.3, 104.8, 102.6. HRMS-ESI (m/z): Calc'd for $C_{17}H_{14}N_3$[M+H]+: 260.1182. Found: 260.1181.

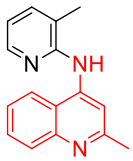
N-(6-methoxypyridin-2-yl)-1H-indol-5-amine (**3.3**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *3.4.3*, conducted at 80 °C using 5 mol% (**Phen-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.6* which afforded the title compound in a 72% isolated yield (0.083 g, 0.346 mmol) as a light brown solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.13 (br, 1H), 7.60

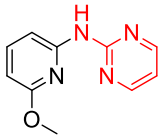
(s, 1H), 7.37-7.32 (m, 2H, overlapping Hs), 7.23-7.22 (m, 1H), 7.14 (dd, J = 8.6, 1.5 Hz, 1H), 6.52 (s, 1H), 6.32 (br, 1H), 6.27 (d, J = 7.9 Hz, 1H), 6.12 (d, J = 7.9 Hz, 1H), 3.91 (s, 3H, CH_3). $^{13}C\{^1H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 163.7, 156.7, 140.1, 133.2, 132.9, 128.5, 125.0, 119.2, 114.9, 111.4, 102.6, 98.8, 98.2, 53.2. HRMS-ESI (*m*/*z*): Calc'd for $C_{14}H_{14}N_3O_1$ $[M+H]^+$: 240.1131. Found: 240.1130.

2-methyl-N-(3-methylpyridin-2-yl)quinolin-4-amine (**3.4**)



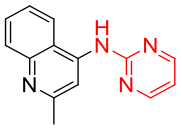
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *3.4.3*, conducted at 25 °C using 5 mol% (**Phen-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.7*. Purified by flash column chromatography on alumina gel using a 1:2:7 NEt_3/ethyl acetate/hexanes eluent, which afforded the title compound in a 72% isolated yield (0.086 g, 0.346 mmol) as a beige solid. ^1H NMR (500.1 MHz, $CDCl_3$): δ 8.30 (d, J = 4.3 Hz, 1H), 8.11 (s, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.69-7.66 (m, 1H), 7.53-7.48 (m, 2H, overlapping Hs), 7.06 (br, 1H), 6.93 (dd, J = 7.3, 5.0 Hz, 1H), 2.71 (s, 3H, CH_3), 2.40 (s, 3H, CH_3). $^{13}C\{^1H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 160.0, 152.7, 148.7, 145.8, 143.4, 138.7, 129.8, 129.0, 124.9, 120.7, 118.8, 118.7, 117.6, 107.1, 26.0, 17.4. HRMS-ESI (*m*/*z*): Calc'd for $C_{16}H_{16}N_3$ $[M+H]^+$: 250.1339. Found: 250.1349.

N-(6-methoxypyridin-2-yl)pyrimidin-2-amine (**3.5**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *3.4.3*, conducted at 65 °C using 5 mol% (**Phen-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.6* which afforded the title compound in a 91% isolated yield (0.089 g, 0.44 mmol) as a light yellow solid. ^1H NMR (500.1 MHz, $CDCl_3$): δ 8.49-8.48 (m, 2H, overlapping Hs), 7.92 (d, J = 7.9 Hz, 1H), 7.78 (br, 1H, NH), 7.60-7.57 (m, 1H), 6.80-6.78 (m, 1H), 6.39 (d, J = 8.0 Hz, 1H), 3.89 (s, 3H, CH_3) $^{13}C\{^1H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 162.9, 159.2, 157.9, 157.9, 140.5, 113.2, 103.8, 103.6, 53.3. HRMS-ESI (*m*/*z*): Calc'd for $C_{10}H_{11}N_4O$ $[M+H]^+$: 203.0927. Found: 203.0920.

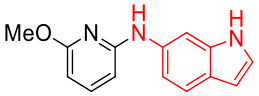
2-methyl-N-(pyrimidin-2-yl)quinolin-4-amine (**3.6**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *3.4.3*, conducted at 25 °C using 5 mol% (**Phen-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.6* which afforded the title compound in a 99% isolated yield (0.111 g, 0.47 mmol) as an off-white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.57 (m, 2H, overlapping Hs), 8.44 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.95-7.93 (m, 2H, overlapping Hs), 7.70-7.67 (m, 1H), 7.53-7.50 (m, 1H), 6.91-6.89 (m, 1H), 2.76 (s, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 159.9, 159.7, 158.1, 158.1, 148.5, 141.9, 129.6, 129.2, 125.2, 119.1, 118.4, 114.2, 108.5, 25.9. HRMS-ESI (*m/z*): Calc'd for $C_{14}H_{13}N_4$ $[M+H]^+$: 237.1135. Found: 237.1137.

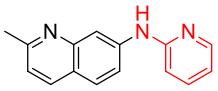
N-(6-methoxypyridin-2-yl)-1H-indol-6-amine (**3.7**)

The title compound was synthesized from the corresponding aryl chloride (0.48 mmol)



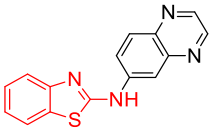
according to *3.4.3*, conducted at 65 °C using 5 mol% (**Phen-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.6* which afforded the title compound in a 56% isolated yield (0.065 g, 0.269 mmol) as a light brown solid.^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.08 (br, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.50 (br, 1H), 7.39-7.35 (m, 1H), 7.17-7.16 (m, 1H), 7.01 (dd, J = 8.4, 1.9 Hz, 1H), 6.53-6.52 (m, 1H), 6.38-6.36 (m, 2H, overlapping Hs), 6.15 (d, J = 7.9 Hz, 1H), 2.97 (s, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 163.7, 155.7, 140.1, 136.3, 135.4, 124.3, 123.9, 121.1, 115.8, 103.9, 102.7, 99.2, 98.9, 53.3. HRMS-ESI (m/z): Calc'd for $C_{14}H_{14}N_3O$[M+H]+: 240.1131. Found: 240.1140.

2-methyl-N-(pyridin-2-yl)quinolin-7-amine (**3.8**)



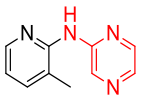
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *3.4.3*, conducted at 25 °C using 5 mol% (**Phen-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.6* which afforded the title compound in a 98% isolated yield (0.111 g, 0.47 mmol) as an off-white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.28 (d, J = 4.9 Hz, 1H), 8.00 (d, J = 1.7 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.70 (d, J = 8.7 Hz, 1H), 7.58-7.54 (m, 1H), 7.41 (dd, J = 8.7, 2.1 Hz, 1H), 7.16-7.12 (m, 2H, overlapping Hs), 6.87 (br, 1H), 6.83-6.81 (m, 1H), 2.72 (s, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 159.5, 154.9, 149.2, 148.5, 141.8, 137.8, 135.7, 128.4, 122.4, 120.1, 120.0, 116.0, 114.0, 109.5, 25.4. HRMS-ESI (*m/z*): Calc'd for $C_{15}H_{14}N_3$ $[M+H]^+$: 236.1182. Found: 236.1190.

N-(quinoxalin-6-yl)benzo[d]thiazol-2-amine (**3.9**)



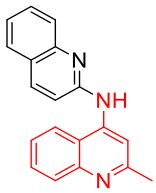
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *3.4.3* (*with an additional 0.5 mL of toluene to aid in solubility*), conducted at 25 °C using 5 mol% (**Phen-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.6* which afforded the title compound in a 56% isolated yield (0.075 g, 0.269 mmol) as an off-white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.77 (s, 2H, overlapping Hs), 7.91 (d, J = 8.9 Hz, 1H), 7.66 (d, J = 7.7 Hz, 1H), 7.61-7.58 (m, 1H), 7.45-7.43 (m, 2H, overlapping Hs), 7.36 (dd, J = 8.9, 2.1 Hz, 1H), 7.22-7.19 (m, 1H). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 145.6, 144.6, 143.2, 141.5, 140.3, 138.7, 138.1, 132.8, 130.3, 128.2, 124.6, 124.6, 115.8, 115.2, 109.8. HRMS-ESI (*m*/*z*): Calc'd for $C_{15}H_{10}N_4S_1Na$ $[M+Na]^+$: 301.0518 Found: 301.0508.

N-(3-methylpyridin-2-yl)pyrazin-2-amine (**3.10**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *3.4.3*, conducted at 65 °C using 5 mol% (**Phen-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.6* which afforded the title compound in a 67% isolated yield (0.060 g, 0.322 mmol) as a brown solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 9.77 (s, 1H), 8.20 (d, J = 4.7 Hz, 1H), 8.17 (s, 2H, overlapping Hs), 7.45 (d, J = 7.3 Hz, 1H), 6.97 (br, 1H), 6.86 (dd, J = 7.3, 5.0 Hz, 1H), 2.32 (s, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 151.6, 150.3, 145.4, 141.8, 138.4, 137.2, 136.2, 118.9, 117.2, 17.2. HRMS-ESI (*m*/*z*): Calc'd for $C_{10}H_{11}N_4$ $[M+H]^+$: 187.0978. Found: 187.0971.

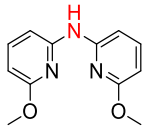
N-(2-methylquinolin-4-yl)quinolin-2-amine (**3.11**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *3.4.3*, conducted at 25 °C using 5 mol% (**Phen-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.6* which afforded the title compound in a 99% isolated yield (0.136 g, 0.47 mmol) as a yellow solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.17 (s, 1H), 8.08 (d, J = 8.8 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 7.9 Hz, 1H), 7.71-7.67 (m, 2H, overlapping Hs), 7.51-7.48 (m, 2H, overlapping Hs),

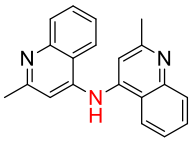
7.44-7.40 (m, 1H), 7.23 (d, J = 8.8 Hz, 1H), 2.75 (s, 3H, CH_3). $^{13}C\{^1H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 159.8, 153.0, 148.8, 147.4, 143.4, 138.2, 130.2, 129.6, 129.4, 127.5, 127.3, 125.2, 124.8, 124.5, 119.5, 119.2, 113.0, 108.1, 25.9. HRMS-ESI (m/z): Calc'd for $C_{19}H_{16}N_3$ $[M+H]^+$: 286.1339. Found: 286.1332.

bis(6-methoxypyridin-2-yl)amine (**3.12**)



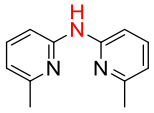
The title compound was synthesized from the corresponding aryl chloride (0.8 mmol) according to *3.4.4*, conducted at 25 °C using 5 mol% (**Phen-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.6* which afforded the title compound in an 81% isolated yield (0.075 g, 0.324 mmol) as an off-white solid. ^1H NMR (500.1 MHz, $CDCl_3$): δ 7.51-7.48 (m, 2H), 7.06 (d, J = 7.9 Hz, 2H), 7.00 (br, 1H, NH), 7.30 (d, J = 8.0 Hz, 2H), 3.93 (s, 6H, CH_3). $^{13}C\{^1H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 163.2, 152.0, 140.1, 102.6, 101.6, 53.4. HRMS-ESI (m/z): Calc'd for $C_{12}H_{14}N_3O_2$ $[M+H]^+$: 232.1081. Found: 232.1072.

bis(2-methylquinolin-4-yl)amine (**3.13**)



The title compound was synthesized from the corresponding aryl chloride (0.8 mmol) according to *3.4.4*, conducted at 25 °C using 5 mol% (**Phen-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.6* which afforded the title compound in a 98% isolated yield (0.118 g, 0.392 mmol) as an off-white solid. ^1H NMR (500.1 MHz, $CDCl_3$): δ 8.06 (d, J = 8.2 Hz, 2H), 7.96 (d, J = 8.3 Hz, 2H), 7.74-7.71 (m, 2H), 7.51-7.48 (m, 2H), 7.10 (s, 2H), 7.06 (br, 1H, NH), 2.66 (s, 6H, CH_3). $^{13}C\{^1H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 159.6, 149.2, 145.2, 129.9, 129.6, 125.4, 120.2, 119.9, 108.9, 25.6. HRMS-ESI (m/z): Calc'd for $C_{20}H_{18}N_3$ $[M+H]^+$: 300.1495. Found: 300.1489.

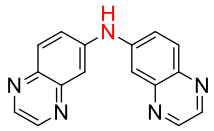
bis(6-methylpyridin-2-yl)amine (**3.14**)



The title compound was synthesized from the corresponding aryl chloride (0.8 mmol) according to *3.4.4*, conducted at 25 °C using 5 mol% (**Phen-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.6* which afforded the title compound in a 74% isolated yield (0.059 g, 0.296 mmol) as an off-white solid. ^1H NMR (500.1 MHz, $CDCl_3$): δ 7.50-7.46 (m, 2H), 7.36 (d, J = 8.3 Hz, 2H), 7.14 (br, 1H, NH), 6.69 (d, J = 7.3 Hz, 2H), 2.47 (s, 6H, CH_3).

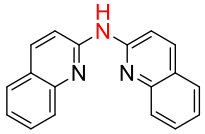
$^{13}C\{^{1}H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 156.7, 153.4, 137.9, 115.9, 108.2, 24.3. HRMS-ESI (*m/z*): Calc'd for $C_{12}H_{14}N_3$ $[M+H]^+$: 200.1182. Found: 200.1175. Spectral data are in agreement with literature.[57]

di(quinoxalin-6-yl)amine (**3.15**)



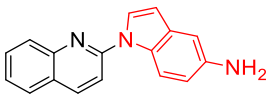
The title compound was synthesized from the corresponding aryl chloride (0.8 mmol) according to *3.4.4* (*without the addition of THF*), conducted at 25 °C using 5 mol% (**Phen-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.7*. Purified by flash column chromatography on alumina gel using an eluent gradient of 8:2 ethyl acetate/hexanes (300 mL), ethyl acetate (300 mL) followed by 1:9 methanol/ethyl acetate (200 mL) which afforded the title compound in a 79% isolated yield (0.087 g, 0.316 mmol) as a yellow solid. ^{1}H NMR (500.1 MHz, THF-d_8): δ 8.69 (d, J = 3.1, 2H), 8.60 (d, J = 3.1 Hz, 2H), 8.58 (br, 1H, NH), 7.98 (d, J = 15.1 Hz, 2H), 7.82 (d, J = 4.2 Hz, 2H), 7.67 (dd, J = 15.1, 4.2 Hz, 2H). $^{13}C\{^{1}H\}$ UDEFT NMR (125.8 MHz, THF-d_8): δ 145.4, 144.8, 143.8, 142.4, 139.5, 130.4, 123.5, 111.7. HRMS-APCI (*m/z*): Calc'd for $C_{16}H_{12}N_5$ $[M+H]^+$: 274.1087. Found: 274.1087.

di(quinolin-2-yl)amine (**3.16**)



The title compound was synthesized from the corresponding aryl chloride (0.8 mmol) according to *3.4.4*, conducted at 25 °C using 5 mol% (**Phen-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.6* which afforded the title compound in a 95% isolated yield (0.103 g, 0.380 mmol) as an off-white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.11-8.09 (m, 3H, overlapping Hs), 8.02 (d, J = 8.9 Hz, 2H), 7.87 (d, J = 8.5 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H), 7.66-7.63 (m, 2H), 7.40-7.37 (m, 2H). $^{13}C\{^{1}H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 152.7, 147.1, 138.0, 129.8, 127.5, 127.1, 125.0, 123.9, 114.1. HRMS-ESI (*m/z*): Calc'd for $C_{18}H_{14}N_3$ $[M+H]^+$: 272.1182. Found: 272.1182.

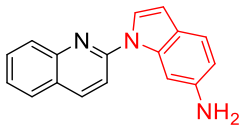
1-(quinolin-2-yl)-1H-indol-5-amine (**3.17**)



The title compound was synthesized from the corresponding aryl chloride (4.8 mmol) according to *3.4.3*, conducted at 25 °C using 0.25 mol% (**PAd2-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.6* which afforded the title compound in a 75% isolated yield (0.944 g, 3.629 mmol) as a light yellow solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.50 (d, J = 8.8 Hz,

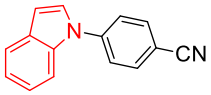
1H), 8.21 (d, *J* = 8.9 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.80 (d, *J* = 10.0 Hz, 1H), 7.76 (d, *J* = 3.5 Hz, 1H), 7.74-7.70 (m, 1H), 7.60 (d, *J* = 8.9 Hz, 1H), 7.49-7.46 (m, 1H), 6.96 (d, *J* = 2.2 Hz, 1H), 6.80 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.59 (d, *J* = 3.4 Hz), 3.62 (br, 2h, NH_2). $^{13}C\{^1H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 151.3, 147.3, 141.2, 138.5, 131.8, 130.2, 130.1, 128.4, 127.4, 125.9. 125.7, 125.3, 115.3, 113.5, 113.4, 105.8, 105.6. HRMS-ESI (*m/z*): Calc'd for $C_{17}H_{14}N_3$ $[M+H]^+$: 260.1182. Found: 260.1185.

1-(quinolin-2-yl)-1H-indol-6-amine (**3.18**)



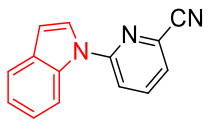
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *3.4.3*, conducted at 25 °C using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.6* which afforded the title compound in an 83% isolated yield (0.103 g, 0.398 mmol) as a brown solid.^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.8 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 2.0 Hz, 1H), 7.82-7.80 (m, 1H), 7.75-7.72 (m, 1H), 7.61-7.59 (m, overlapping Hs, 2H), 7.51-7.48 (m, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 6.69 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.64 (d, *J* = 3.3 Hz, 1H), 3.76 (br, 2H, NH_2).$^{13}C\{^1H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 151.6, 147.3, 143.4, 138.6, 136.8, 130.2, 128.4, 127.5, 125.7, 125.4, 123.7, 123.6, 121.5, 113.9, 111.9, 106.4, 100.4. HRMS-ESI (m/z): Calc'd for $C_{17}H_{14}N_3$[M+H]+: 260.1182. Found: 260.1177.

4-(1H-indol-1-yl)benzonitrile (**3.19**)



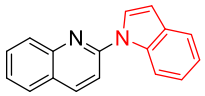
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *3.4.3*, conducted at 65 °C using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.7*. Purified by flash column chromatography on silica gel using a 1:3:6 NEt_3/ethyl acetate/hexanes eluent which afforded the title compound in a 91% isolated yield (.095 g, 0.437 mmol) as a light brown solid. . ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.82-7.80 (d, *J* = 8.6 Hz, 2H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.35 (d, *J* = 3.4 Hz, 1H), 7.30-7.22 (m, 2H), 6.76 (d, *J* = 3.4 Hz, 1H). $^{13}C\{^1H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 143.8, 135.4, 134.0, 130.2, 127.3, 124.1, 123.4, 121.8, 121.6, 118.6, 110.6, 109.6, 106.0. Spectral data are in agreement with literature.[41]

6-(1H-indol-1-yl)picolinonitrile (**3.20**)



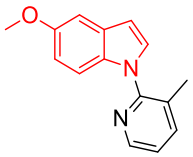
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *3.4.3*, conducted at 25 °C using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.6* which afforded the title compound in a 95% isolated yield (0.099 g, 0.456 mmol) as a beige solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.35 (d, J = 8.4 Hz, 1H), 7.93-7.90 (m, 1H), 7.70-7.68 (m, 2H, overlapping Hs), 7.66 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 7.4 Hz, 1H), 7.37-7.34 (m, 1H), 7.28-7.25 (m, 1H), 6.76 (d, J = 3.6 Hz, 1H). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 153.2, 139.3, 135.0, 132.5, 130.7, 125.0, 124.0, 123.9, 122.3, 121.3, 117.0, 116.9, 113.9, 107.5. HRMS-ESI (*m*/*z*): Calc'd for $C_{14}H_9N_3Na$ $[M+Na]^+$: 242.0689. Found: 242.0691.

2-(1H-indol-1-yl)quinoline (**3.21**)



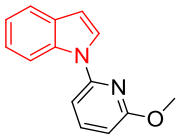
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *3.4.3*, conducted at 65 °C using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.7*. Purified by flash column chromatography on alumina gel using a 1:9 NEt_3/hexanes eluent which afforded the title compound in an 88% isolated yield (.103 g, 0.422 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.60 (d, J = 8.4 Hz, 1H), 8.27 (d, J = 8.9 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.85-7.83 (m, 2H, overlapping Hs), 7.77-7.73 (m, 1H), 7.69-7.66 (m, 2H, overlapping Hs), 7.53-7.50 (m, 1H), 7.38-7.35 (m, 1H), 7.27-7.24 (m, 1H), 6.77 (d, J = 3.5 Hz, 1H). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 151.3, 147.3, 138.7, 135.5, 130.6, 130.3, 128.5, 127.5, 125.9, 125.8, 125.6, 123.4, 121.6, 121.0, 114.1, 114.0, 106.2. HRMS-ESI (*m*/*z*): Calc'd for $C_{17}H_{13}N_2$ $[M+H]^+$: 245.1073. Found: 245.1076. Spectral data are in agreement with literature.[40]

5-methoxy-1-(3-methylpyridin-2-yl)-1H-indole (**3.22**)



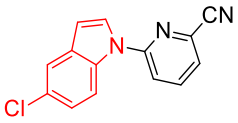
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *3.4.3*, conducted at 80 °C using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.6* which afforded the title compound in a 70% isolated yield (0.080 g, 0.336 mmol) as a beige solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.46-8.45 (m, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 3.3 Hz, 1H), 7.28-7.26 (m, 1H), 7.17 (d, J = 3.9 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 6.86 (dd, J = 8.9, 2.5 Hz, 1H), 6.62 (d, J = 3.3 Hz, 1H), 3.87 (s, 3H, CH_3), 2.24 (s, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 154.6, 151.1, 146.9, 140.5, 131.4, 129.4, 128.6, 128.0, 122.6, 112.5, 112.1, 103.4, 102.8, 55.8, 18.0. HRMS-ESI (*m*/*z*): Calc'd for $C_{15}H_{14}N_2ONa$ $[M+Na]^+$: 261.0998. Found: 261.1000.

1-(6-methoxypyridin-2-yl)-1H-indole (**3.23**)



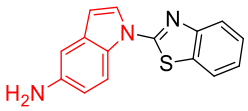
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *3.4.3*, conducted at 80 °C using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.6* which afforded the title compound in a 92% isolated yield (0.099 g, 0.442 mmol) as an off-white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.28 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 3.5 Hz, 1H), 7.71-7.68 (m, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.31-7.28 (m, 1H), 7.22-7.19 (m, 1H), 7.04 (d, J = 7.7 Hz, 1H), 6.70 (d, J = 3.4 Hz, 1H), 6.62 (d, J = 8.1 Hz, 1H), 4.06 (s, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 163.6, 150.6, 140.5, 135.1, 130.4, 126.0, 123.0, 121.1, 121.0, 113.4, 106.4, 105.8, 105.3, 53.8. HRMS-ESI (*m*/*z*): Calc'd for $C_{14}H_{12}N_2ONa$ [M+Na]$^{+}$: 247.0842. Found: 247.0837.

6-(5-chloro-1H-indol-1-yl)picolinonitrile (**3.24**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *3.4.3*, conducted at 65 °C using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.6* which afforded the title compound in a 73% isolated yield (0.089 g, 0.350 mmol) as an off-white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.34 (d, J = 8.9 Hz, 1H), 7.96-7.93 (m, 1H), 7.69 (d, J = 3.6 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.61 (d, J = 2.0 Hz, 1H), 7.54, (d, J = 7.5 Hz, 1H), 7.31 (dd, J = 8.9, 2.0 Hz, 1H), 6.70 (d, J = 3.6 Hz, 1H). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 152.9, 139.5, 133.4, 132.4, 131.8, 127.9, 126.0, 124.2, 124.2, 120.7, 116.8, 115.4, 106.9, (1 quaternary carbon unresolved). HRMS-ESI (*m*/*z*): Calc'd for $C_{14}H_8ClN_3Na$ [M+Na]$^{+}$: 276.0299. Found: 276.0300.

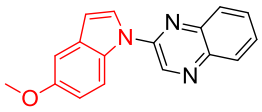
1-(benzo[d]thiazol-2-yl)-1H-indol-5-amine (**3.25**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *3.4.3*, conducted at 25 °C using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.6* which afforded the title compound in a 66% isolated yield (0.084 g, 0.317 mmol) as a beige solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.40 (d, J = 8.7 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 3.5 Hz, 1H), 7.48-7.45 (m, 1H), 7.32-7.29 (m, 1H), 6.92 (s, 1H), 6.83-6.81 (m, 1H), 6.59 (d, J = 3.5 Hz, 1H), 3.66 (br,

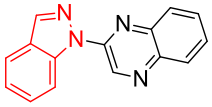
2H, NH_2). $^{13}C\{^1H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 158.9, 151.4, 142.2, 131.5, 131.4, 129.9, 126.7, 126.5, 124.0, 121.8, 121.0, 115.1, 114.0, 107.6, 106.1. HRMS-ESI (*m*/*z*): Calc'd for $C_{15}H_{12}N_3S$ $[M+H]^+$: 266.0746. Found: 266.0752.

2-(5-methoxy-1H-indol-1-yl)quinoxaline (**3.26**)



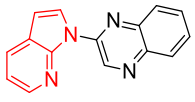
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *3.4.3*, conducted at 25 °C using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.7*. Purified by flash column chromatography on silica gel using a 1:3:6 NEt_3/ethyl acetate/hexanes eluent which afforded the title compound in a 57% isolated yield (0.076 g, 0.274 mmol) as a light yellow solid. ^1H NMR (500.1 MHz, $CDCl_3$): δ 9.15 (s, 1H), 8.62 (d, *J* = 9.1 Hz, 1H), 8.08 (dd, *J* = 12.0, 8.3 Hz, 1H), 7.85 (d, *J* = 3.5 Hz, 1H), 7.80-7.77 (m, 1H), 7.70-7.67 (m, 1H), 7.14 (d, *J* = 2.5 Hz, 1H), 7.03 (dd, *J* = 9.1, 2.6 Hz, 1H), 6.76 (d, *J* = 3.5 Hz, 1H), 3.90 (s, 3H, CH_3). $^{13}C\{^1H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 155.8, 146.6, 140.9, 139.7, 137.9, 131.4, 130.9, 130.4, 129.1, 128.2, 128.2, 125.1, 115.7, 113.3, 107.6, 103.4, 55.7. HRMS-APCI (*m*/*z*): Calc'd for $C_{17}H_{14}N_3O$ $[M+H]^+$: 276.1131. Found: 276.1124. Spectral data are in agreement with literature.[40]

2-(1H-indazol-1-yl)quinoxaline (**3.27**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *3.4.3*, conducted at 80 °C using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.7*. Purified by flash column chromatography on alumina gel using a 1:9 ethyl acetate/hexanes eluent which afforded the title compound in a 93% isolated yield (0.110 g, 0.446 mmol) as a light orange solid. ^1H NMR (500.1 MHz, $CDCl_3$): δ 9.80 (s, 1H), 9.05 (d, *J* = 8.5 Hz, 1H), 8.31 (s, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.80-7.77 (m, 1H), 7.71-7.68 (m, 1H), 7.64-7.61 (m, 1H), 7.39-7.36 (m, 1H). $^{13}C\{^1H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 147.7, 140.2, 140.0, 139.1, 138.9, 138.4, 130.6, 129.3, 128.6, 128.2, 128.2, 126.3, 123.6, 121.1, 115.6. HRMS-ESI (*m*/*z*): Calc'd for $C_{15}H_{10}N_4Na$ $[M+Na]^+$: 269.0798. Found: 269.0787.

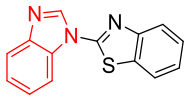
2-(1H-pyrrolo[2,3-b]pyridin-1-yl)quinoxaline (**3.28**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *3.4.3*, conducted at 80 °C using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tolyl), and

purified according to *3.4.7*. Purified by flash column chromatography on alumina gel using a 1:9 ethyl acetate/hexanes eluent which afforded the title compound in a 46% isolated yield (0.054 g, 0.221 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.51 (d, J = 3.9 Hz, 1H), 8.46 (dd, J = 4.7, 1.4 Hz, 1H), 8.15 (d, J = 8.2 Hz, 1H), 8.02 (dd, J = 8.4, 0.8 Hz, 1H), 7.98 (dd, J = 7.8, 1.5 Hz, 1H), 7.77-7.75 (m, 1H), 7.72-7.68 (m, 1H), 7.23 (dd, J = 7.8, 4.7 Hz, 1H), 6.76 (d, J = 3.9 Hz, 1H). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 147.9, 145.6, 143.7, 140.9, 140.7, 140.6, 130.4, 129.3, 129.2, 128.3, 128.2, 125.9, 123.3, 117.9, 104.8. HRMS-ESI (*m*/*z*): Calc'd for $C_{15}H_{10}N_4Na$ $[M+Na]^+$: 269.0798. Found: 269.0789.

2-(1H-benzo[d]imidazol-1-yl)benzo[d]thiazole (**3.29**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *3.4.3*, conducted at 65 °C using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tolyl), and purified according to *3.4.6* which afforded the title compound in a 50% isolated yield (0.061 g, 0.240 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.34 (d, J = 8.2 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H), 7.89-7.88 (m, 2H, overlapping Hs), 7.57-7.55 (m, 1H), 7.52-7.49 (m, 1H), 7.45-7.41 (m, 2H, overlapping Hs). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 155.6, 150.5, 144.4, 141.3, 132.0, 131.8, 127.1, 125.3, 125.3, 124.5, 122.8, 121.5, 121.0, 113.2. HRMS-ESI (*m*/*z*): Calc'd for $C_{14}H_{10}N_3S$ $[M+H]^+$: 252.0590. Found: 252.0582.

4. Nickel-Catalyzed Cross-Coupling of Sulfonamides with (Hetero)aryl Chlorides

4.1 Research overview and contribution report

This author wishes to clarify his contributions to the research described in Chapter 4 of this Thesis document. This chapter describes the application of both **PhPAd-DalPhos** and **PAd2-DalPhos** in the Ni-catalyzed C-N cross-coupling of primary and secondary sulfonamides respectively. The catalytic transformations presented herein represent state-of-the-art amongst all nickel-based catalysts for the cross-coupling of aryl chlorides and aryl phenol derivatives.

My contributions to the study included optimizing catalytic conditions, developing a substrate scope based on both primary and secondary aryl sulfonamide N-arylation, performing competition experiments to gauge catalyst selectivity, and mentoring Connor M. Simon. Connor M. Simon was responsible for developing a substrate scope based on primary and secondary alkyl sulfonamide N-arylation, Dr. Arun Yadav was responsible for conceptual input in the early stages of the project, while Dr. Mark Stradiotto helped in mentoring myself as well as providing advice throughout the project.

Reference: McGuire, R. T.; Simon, C. M.; Yadav, A. A.; Ferguson, M. J.; Stradiotto, M. Nickel-Catalyzed Cross-Coupling of Sulfonamides with (Hetero)aryl Chlorides. *Angew. Chem. Int. Ed.* **2020**, 59, 8952-8956.

4.2 Introduction

The sulfonamide core, despite not occurring in nature, is a prominent biologically active synthon that can be found in several blockbuster pharmaceuticals, including in

celecoxib (primary sulfonamide), tipranavir (secondary sulfonamide), and sildenafil (tertiary sulfonamide).[59,60] In addition to being remarkably stable in metabolic environments,[60] secondary N-(hetero)aryl sulfonamides in particular can serve as bio-isosteres for carboxylic acids, whereby the N-H acidity can be modulated by choice of the N-(hetero)aryl group.[61]

Traditional routes toward accessing secondary N-(hetero)aryl sulfonamides rely on the reaction of sulfonyl chlorides with primary (hetero)anilines, the former of which is often genotoxic and requires harsh conditions to prepare, including strongly acidic and oxidizing synthetic sequences.[62] With these issues in mind, along with the ever-expanding desire to identify new disconnection strategies for organic synthesis, we sought to utilize a base-metal catalyzed route for forging secondary N-(hetero)aryl sulfonamides.[63–65]

While the metal-catalyzed C(sp^2)-N cross-coupling of sulfonamides with (hetero)aryl halides is known to be accomplished with palladium,[62,66–70] base metal-catalyzed routes which accommodate (hetero)aryl chlorides (and phenol derivatives), the most difficult and abundant electrophile class, remain elusive.[71] Indeed, Cu-catalyzed approaches are limited to the incorporation of just (hetero)aryl bromides and iodides,[72–75] while a recently published nickel-iridium photocatalytic method is limited solely to the incorporation of (hetero)aryl bromides (Figure 4.1).[76]

This work focuses on the application of a DalPhos ligand-enabled nickel-catalyzed approach toward the cross-coupling of both primary and secondary sulfonamides with (hetero)aryl (pseudo)halides, including chlorides, tosylates, and carbamates – all of which were previously unreported transformations in the context of base metal catalysis (Figure 4.1). The application of nickel pre-catalysts derived from **PhPAd-DalPhos** and **PAd2-DalPhos** for primary and secondary sulfonamide N-arylation respectively was key to the

successes achieved herein. Competition experiments were also conducted to gauge catalyst selectivity in various Ni-catalyzed amination systems.

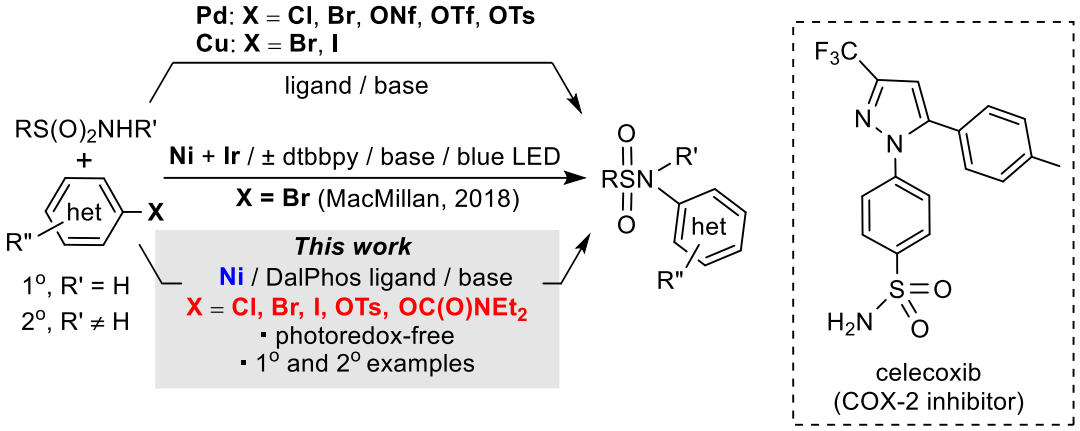


Figure 4.1 Summary of work conducted on the metal-catalyzed N-arylation of sulfonamides.

4.3 Results and discussion

4.3.1 Preliminary ligand / Ni(COD)$_2$ screening

In an attempt to identify catalytic conditions for the N-arylation of primary sulfonamides with (hetero)aryl chlorides, an initial test ligand screen was performed in the reaction of *p*-toluenesulfonamide and 1-chloronaphthalene in the presence of Ni(COD)$_2$ and NaO*t*Bu. In testing several different DalPhos ligands, as well as other superior ligands for various Ni-catalyzed C-N cross-coupling reactions, it was found that **PhPAd-DalPhos** easily distinguished itself as a successful ligand candidate for the N-arylation of primary sulfonamides, providing 70% product formation in this model reaction as determined by GC analysis. Strikingly, of the other ligands tested, only **CyPAd-DalPhos** provided >5% conversion (10%) to the desired product, emphasizing the notion that seemingly very small perturbations in ligand steric and electronic factors can have profound effects on the governed reactivity.

In the case of secondary sulfonamide N-arylation, a similar ligand / $Ni(COD)_2$ test reaction screen was conducted between the substrates N-methyl-*p*-toluenesulfonamide and 2-chloro-6-methoxypyridine in the presence of NaO*t*Bu, and in this case **PAd2-DalPhos** emerged as the best catalytic performer, furnishing 35% of the desired product as determined by GC analysis (Figure 4.2).

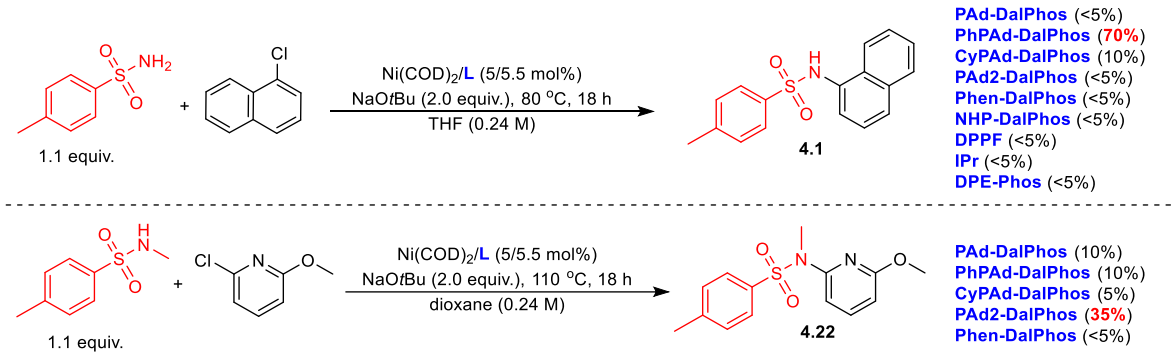


Figure 4.2 Ligand / $Ni(COD)_2$ screens demonstrating the superiority of **PhPAd-DalPhos** and **PAd2-DalPhos** in facilitating difficult Ni-catalyzed C-N cross-couplings involving primary and secondary sulfonamide N-arylation respectively. Estimated product conversions based on GC data (monitoring consumption of aryl chloride and formation of products).

4.3.2 Primary sulfonamide N-arylation scope

In utilizing the (**PhPAd-DalPhos**)Ni(*o*-tolyl)Cl pre-catalyst derived from **PhPAd-DalPhos**, a wide range of both primary sulfonamides and (hetero)aryl (pseudo)halides could be successfully cross-coupled in moderate to high yields (Figure 4.3). Indeed, all of electron-rich (**4.11**, **4.21**), electron-neutral (**4.1-4.10**), and electron-poor (**4.13-4.15**) primary aryl sulfonamides could be successfully N-arylated, as could alkyl sulfonamides (**4.17-4.19**). The inclusion of a broad scope of tolerable (hetero)aryl (pseudo)halide electrophile classes (X = Cl, Br, I, OTs, $OC(O)NEt_2$) is unprecedented in sulfonamide N-arylation chemistry when using any metal catalyst.[66,72,76] While (hetero)aryl chloride electrophiles featuring electron-withdrawing and electron-neutral substituents were coupled with success, the coupling of electron-rich (hetero)aryl chlorides such as 4-chloroanisole and 3-chloropyridine was

unsuccessful. Primary sulfonamides and (hetero)aryl (pseudo)halides containing a diverse range of functionality (ie. ethers, nitriles, trifluoromethyls, pinacolatoboron, ketones) were all successfully cross-coupled, as were electrophiles based on quinaldine, quinoline and pyridyl core structures. Challenging *ortho*-hindered electrophiles (**4.3**, **4.4**, **4.7**, **4.20**, **4.21**) were successfully coupled using this methodology, including in the first reported N-arylation of celecoxib, the latter transformation of which demonstrates the applicability of the methodology toward late-stage functionalization of complex biologically relevant target molecules.

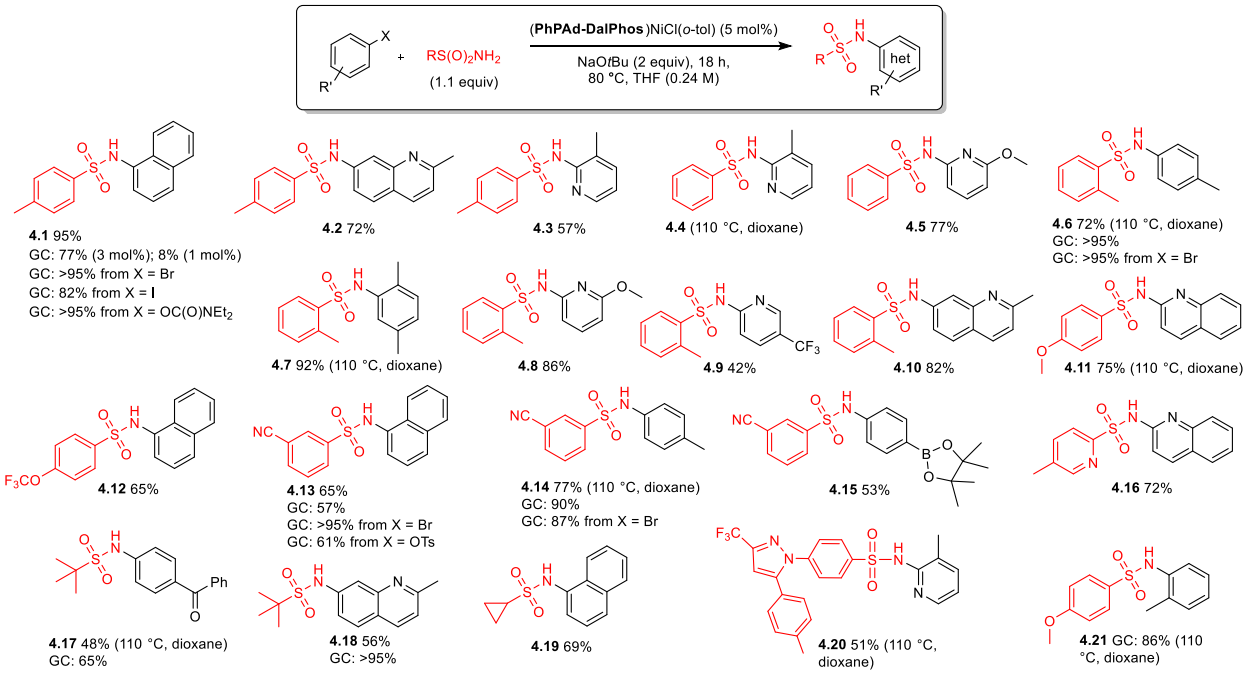


Figure 4.3 Substrate scope for the cross-coupling of primary sulfonamides with (hetero)aryl (pseudo)halides, enabled by (**PhPAd-DalPhos**)NiCl(*o*-tolyl). Isolated yields are reported from X = Cl unless noted otherwise. Yields reported from reactions conducted on 0.48 mmol scale in aryl halide, except for GC yields for which reactions were performed on 0.12 mmol scale in aryl halide. GC yields reported based on response-factor calibrated data using dodecane as an internal standard.

4.3.3 Secondary sulfonamide N-arylation scope

While not the main focus of this work, it was found that (**PAd2-DalPhos**)NiCl(*o*-tolyl) could be successfully applied to the Ni-catalyzed N-arylation of secondary sulfonamides under similar conditions to those for primary sulfonamide N-arylation, albeit at slightly higher temperature (110 ˚C) and with dioxane instead of THF. Indeed, the N-arylation of N-Methyl sulfonamides proceeded with several different (hetero)aryl chlorides including those based on both quinolone (**4.23**) and pyridyl (**4.22, 4.25-4.26**) backbones. Particularly intriguing was that the coupling of 2-chloro-3-methyl pyridine proceeded in high yield when paired with secondary N-methyl sulfonamide leading to product **4.25**; this entry demonstrating the robustness of the methodology toward the accommodation of sterically encumbered substrates.

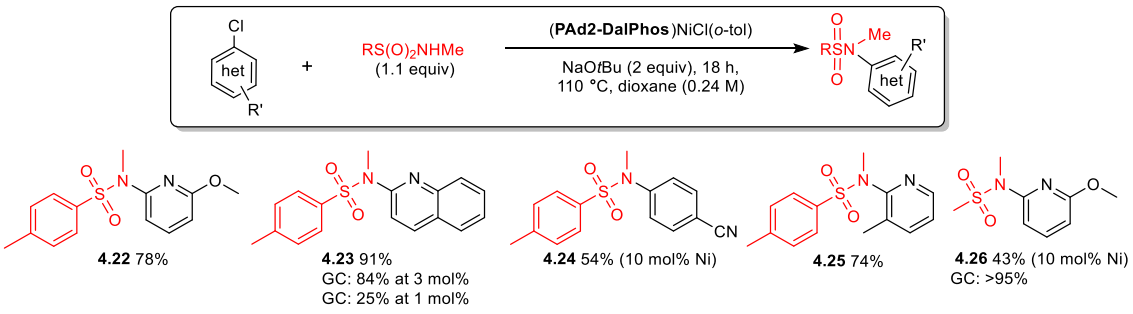


Figure 4.4 Substrate scope for the cross-coupling of secondary sulfonamides with (hetero)aryl (pseudo)halides, enabled by (**PhPAd-DalPhos**)NiCl(*o*-tolyl). Isolated yields are reported from X = Cl unless noted otherwise. Yields reported from reactions conducted on 0.48 mmol scale in aryl halide, except for GC yields for which reactions were performed on 0.12 mmol scale in aryl halide. GC yields reported based on response-factor calibrated data using dodecane as an internal standard.

Efforts to extend this methodology to cross-couple secondary sulfonamides possessing other N-substituted groups such as N-cyclohexyl and N-phenyl were met with limited success, as in some cases complex reaction mixtures were obtained where the presumptive product could not be isolated cleanly.

4.3.4 Competition experiments

Given that **PhPAd-DalPhos** and **PAd2-DalPhos** had been previously disclosed by the Stradiotto to group to be particularly effective for the N-arylation of bulky alkylamines[48] and indoles (see Chapter 3 of this thesis) respectively with (hetero)aryl chlorides, competition experiments were performed to gauge the catalyst selectivity for preferential uptake of NH nucleophiles in the presence of a primary or secondary sulfonamide. Interestingly, the competitive Ni-catalyzed C-N cross-coupling of *p*-toluenesulfonamide (1.1 equiv) versus *t*BuNH$_2$ (3 equiv) with 7- chloroquinaldine (1 equiv) using NaO*t*Bu (2 equiv) and (**PhPAd-DalPhos**)NiCl(o-tol) (5 mol%) under the conditions outlined in Figure 4.5 afforded high conversion of the electrophile and produced the primary sulfonamide-derived product preferably (circa 3:1) relative to the alkylamine product, despite the relative excess of tBuNH$_2$ that was used in an effort to compensate for the volatility of this amine. However, in analogous experiments conducted using 2.2 equiv of *p*-toluenesulfonamide without *t*BuNH$_2$, no conversion was observed. These two experiments highlight the favourability of *p*-toluenesulfonamide over *t*BuNH$_2$ as a nucleophile for Ni-catalyzed C-N cross-couplings under these conditions, while also underscoring the possible inhibitory effect of excess primary sulfonamide and/ or the need to employ excess base relative to sulfonamide in order to achieve conditions favoring catalysis. In the competitive cross-coupling of N-methyl-*p*-toluenesulfonamide (1.1 equiv) versus indole (1.1 equiv) with 2-chloroquinoline (1 equiv) using NaO*t*Bu (2 equiv) and (**PAd2-DalPhos**)NiCl(o-tol) (5 mol%) as depicted in Figure 4.5, exclusive indole N-arylation is observed. Although a control experiment determined that 43% conversion to the N-heteroaryl indole product was observed by GC analysis even in the

absence of (**PAd2-DalPhos**)NiCl(o-tol), the selectivity for indole N-arylation versus secondary N-methyl sulfonamide N-arylation induced by **PAd2-DalPhos** remains apparent.

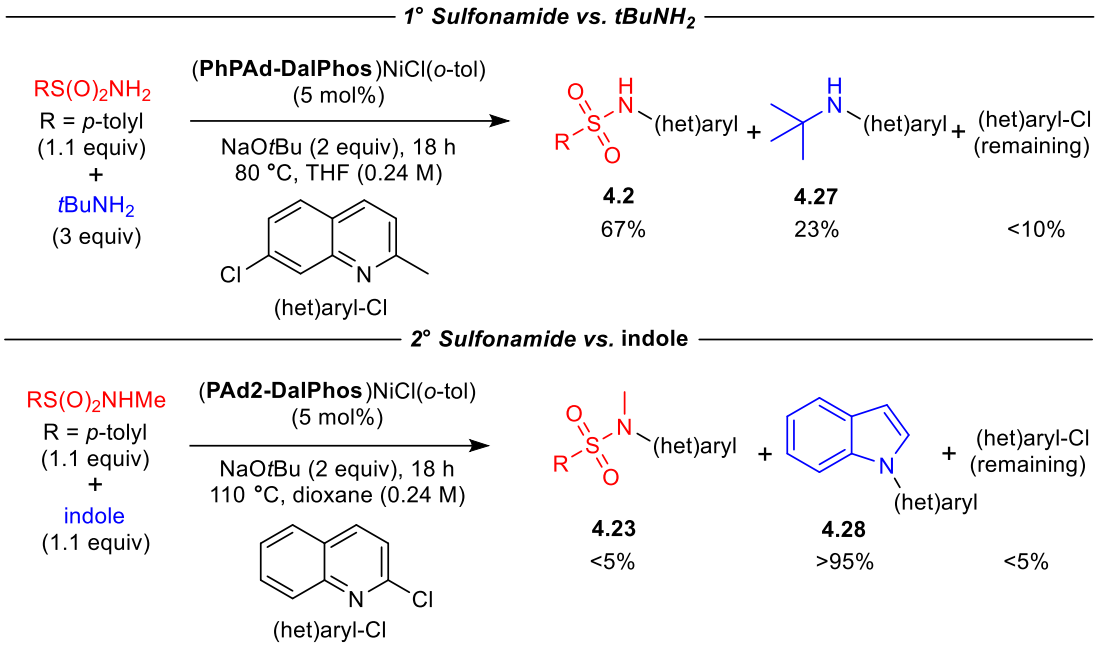


Figure 4.5 Nucleophile competition experiments. Conversion to products determined on the basis of response-factor calibrated GC data using authentic material. In the absence of added (*p*-tolyl)S(O)$_2$NHMe and Ni pre-catalyst, 43% conversion to N-heteroaryl indole and about 60% remaining (hetero)aryl chloride observed.

4.3.5 Summary

The N-arylation of both primary and secondary sulfonamides has been accomplished through the application of nickel pre-catalysts derived from **PhPAd-DalPhos** and **PAd2-DalPhos** respectively, offering a competitive alternative to related Pd and Cu-catalyzed approaches. Indeed, the scope of compatible (hetero)aryl chlorides and other (hetero)aryl (pseudo)halide electrophiles (X = I, Br, OTs, OC(O)NR$_2$) is unprecedented in any base metal-catalyzed sulfonamide N-arylation chemistry.

4.4 Experimental

4.4.1 General considerations

Unless otherwise indicated, all experimental procedures were conducted in a nitrogen-filled, inert atmosphere glovebox using oven-dried glassware and purified solvents, with the exception of the workup of catalytic reaction mixtures, which was conducted on the benchtop in air using unpurified solvents. For solvents used within the glovebox, the following purification methods were used: toluene and pentane were deoxygenated by sparging with nitrogen gas followed by passage through a double column solvent purification system packed with alumina and copper-Q5 reactant and storage over activated 4 Å molecular sieves; tetrahydrofuran was dried over Na/benzophenone followed by distillation under an atmosphere of nitrogen gas; and *tert*-butanol was dried over CaH_2 followed by distillation under an atmosphere of nitrogen. Solvents used within the glovebox were stored over activated 4 Å molecular sieves. DalPhos ligands were prepared according to literature procedures.[42,49] All other commercial solvents, reagents, and materials were used as received. GC data were obtained on an instrument equipped with an SGE BP-5 column (30 m, 0.25 mm i.d.). Automated flash column chromatography was carried out using a normal-phase Biotage SNAP KP-Sil 10 g column cartridge. All ^{1}H NMR (500 and 300 MHz), $^{13}C\{^{1}H\}$ NMR (125.8 and 75.4 MHz), and $^{31}P\{^{1}H\}$ NMR (202.5 and 121.5 MHz) spectra were recorded at 300 K and were referenced to residual protio solvent peaks (^{1}H), deuterated solvent peaks ($^{13}C\{^{1}H\}$), or external 85% H_3PO_4 ($^{31}P\{^{1}H\}$). Splitting patterns are indicated as follows: br, broad; *s*, singlet; *d*, doublet; *t*, triplet; *q*, quartet; *m*, multiplet. All coupling constants (*J*) are reported in Hertz (Hz). Mass spectra were obtained using either APCI or ion trap (ESI) instruments operating in positive mode.

4.4.2 Procedure for the N-arylation of primary sulfonamides with (hetero)aryl (pseudo)halides

Unless otherwise indicated in the text, solid (**PhPAd-DalPhos**)NiCl(*o*-tol) (5 mol%), NaO*t*Bu (2.0 equiv.), (hetero)aryl halide (0.48 mmol, 1.0 equiv.), primary sulfonamide (1.1 equiv.) and THF or dioxane (0.24 M (hetero)aryl halide) were added to a screw-capped vial containing a magnetic stir bar. In the case of experiments conducted at lower catalyst loadings (all 0.25 mmol scale in (hetero)aryl halide), the pre-catalyst was delivered from stock solutions in THF so that the final concentration of (hetero)aryl halide remained 0.24 M. In the case of $Ni(COD)_2$ / ligand screens, reactions were carried out on 0.12 mmol scale (aryl halide) and the $Ni(COD)_2$ was delivered from stock solutions in THF so that the final concentration of aryl halide remained 0.24 M. The vial was sealed with a cap containing a PTFE septum, was removed from the glovebox and placed in a temperature-controlled aluminum heating block set at the specified temperature and was allowed to react under the influence of magnetic stirring for 18 h (unoptimized).

4.4.3 Procedure for the N-arylation of secondary sulfonamides with (hetero)aryl chlorides

Unless otherwise indicated in the text, solid (**PAd2-DalPhos**)NiCl(*o*-tol) (5 mol%), NaO*t*Bu (2.0 equiv.), (hetero)aryl halide (0.48 mmol, 1.0 equiv.), primary sulfonamide (1.1 equiv.) and dioxane (0.24 M (hetero)aryl halide) were added to a screw-capped vial containing a magnetic stir bar. In the case of experiments conducted at lower catalyst loadings (all 0.25 mmol scale in (hetero)aryl halide), the pre-catalyst was delivered from stock solutions in THF so that the final concentration of (hetero)aryl halide remained 0.24 M. In the case of $Ni(COD)_2$ / ligand screens, reactions were carried out on 0.12 mmol scale (aryl halide) and the $Ni(COD)_2$ was delivered from stock solutions in dioxane so that the final

concentration of aryl halide remained 0.24 M. The vial was sealed with a cap containing a PTFE septum, was removed from the glovebox, and placed in a temperature-controlled aluminum heating block set at the specified temperature and was allowed to react under the influence of magnetic stirring for 18 h (unoptimized).

4.4.4 Procedure for competition experiments

In a nitrogen-filled glovebox, precatalyst (**PhPAd-DalPhos**)NiCl(*o*-tol) or (**PAd2-DalPhos**)NiCl(*o*-tol) (5 mol %), NaO*t*Bu (2.0 or 3.0 equiv.), nucleophilic NH coupling partners (1.1, 2.2, or 3.0 equiv.), (hetero)aryl halide (0.12 mmol, 1.0 equiv) and THF or dioxane (0.5 mL) were added to a 1 dram, screw capped vial, followed by a magnetic stir bar. The vial was then sealed with a cap containing a PTFE septum, removed from the glovebox, and placed in a temperature-controlled aluminum heating block set to 80 °C or 110 °C, as appropriate. The mixture was stirred at this temperature for 18 h (unoptimized), after which time the vial was removed from the heat source and cooled to room temperature. Either dodecane, hexadecane, or phenyldocecane (1.0 equiv.) was then added as an internal standard for calibration against authentic products in each case. Subsequently, an aliquot of the reaction mixture was filtered through a short Celite/silica plug, diluted with EtOAc (~1.5 mL), and subjected to GC analysis.

4.4.5 Procedure for the preparation of GC samples

Following *4.4.2* or *4.4.3* (0.12 mmol scale in (hetero)aryl halide), at room temperature the reaction mixture was quenched with 2 drops of methanol and diluted using ethyl acetate and was passed through a Kimwipe filter containing Celite and silica gel, with the eluent collected in a GC vial. Calibrated GC estimates are given on the basis of data obtained from

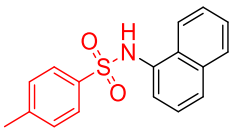
authentic materials using either dodecane, phenyldodecane, or hexadecane as internal standards.

4.4.6 Purification of N-aryl sulfonamides vis flash chromatography

Following *4.4.2* or *4.4.3*, the resultant mixture was cooled to room temperature before adsorption onto silica and subsequent elution through a silica/Celite frit employing ethyl acetate as an eluent (~30-100 mL). The resulting solution was then dried *in vacuo* to afford a crude residue which was dissolved in a hexanes-ethyl acetate mixture before being loaded onto either a silica-based flash column, or a 10 g normal-phase Biotage SNAP KP-Sil column cartridge. The product was then purified using a hexanes-ethyl acetate eluent mixture in each case. The relevant UV-active column fractions were combined and dried *in vacuo* to afford the target product in each case.

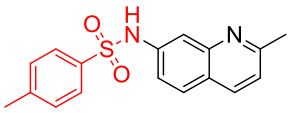
4.4.7 Characterization data for isolated products

4-methyl-N-(naphthalen-1-yl)benzenesulfonamide (**4.1**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *4.4.2*, conducted at 80 °C in THF using 5 mol% (**PhPAd-DalPhos**)NiCl(*o*-tol), and purified according to Workup Method B. Purified by flash column chromatography on silica using an eluent consisting of 20% ethyl acetate in hexanes which afforded the title compound in a 95% isolated yield (0.135 g, 0.456 mmol) as a white solid. The title compound was also synthesized analogously on a 4.8 mmol scale in a 56% isolated yield (0.799 g , 2.688 mmol) despite the reaction having an estimated product conversion which was similar (> 90% by GC) to when performed on 0.48 mmol scale. (^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.83-7.80 (m, 2H, overlapping Hs), 7.71 (dd, J = 6.7, 2.6 Hz, 1H), 7.63 (d, J = 8.3 Hz, 2H), 7.47-7.41 (m, 2H, overlapping Hs), 7.38-7.35 (m, 2H, overlapping Hs), 7.16 (d, J = 8.1 Hz, 2H), 6.83 (br, 1H, NH). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 143.8, 136.4, 134.2, 131.4, 129.5, 128.9, 128.4, 127.3, 127.2, 126.6, 126.3, 125.4, 122.7, 121.4, 21.5. HRMS-ESI (*m*/*z*): Calc'd for $C_{17}H_{15}NO_2SNa$ $[M+Na]^+$: 320.0716. Found: 320.0712.

4-methyl-N-(2-methylquinolin-7-yl)benzenesulfonamide (**4.2**)

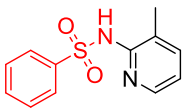


The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *4.4.2*, conducted at 80 °C in THF using 5 mol% (**PhPAd-DalPhos**)NiCl(*o*-tol), and purified according to *4.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-60% ethyl acetate in hexanes (12 CV) followed by 60% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 72% isolated yield (0.108 g, 0.346 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.94 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.7 Hz, 1H), 7.55 (d, J = 1.9 Hz, 1H), 7.42 (dd, J = 8.7, 2.2 Hz, 1H), 7.39 (br, 1H, NH), 7.19-7.17 (m, 3H, overlapping Hs), 2.67 (s, 3H, CH_3,), 2.32 (s, 3H, CH_3,). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 160.0, 148.2, 144.0, 137.9, 136.1, 135.8, 129.7, 128.8, 127.2, 123.8, 121.4, 120.1, 117.8, 25.3, 21.5. HRMS-ESI (*m*/*z*): Calc'd for $C_{17}H_{17}N_2O_2S$ $[M+H]^+$: 313.1005. Found: 313.1006.

4-methyl-N-(3-methylpyridin-2-yl)benzenesulfonamide (**4.3**)

The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *4.4.2*, conducted at 80 °C in THF using 5 mol% (**PhPAd-DalPhos**)NiCl(*o*-tol), and purified according to *4.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-40% ethyl acetate in hexanes (12 CV) followed by 40% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 57% isolated yield (0.072 g, 0.274 mmol) as an off-white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 12.43 (br, 1H, NH), 7.87 (d, J = 8.2 Hz, 2H), 7.47-7.46 (m, 1H), 7.43 (d, J = 7.0 Hz, 1H), 7.24 (d, J = 8.1 Hz, 2H), 6.53 (apparent t, J = 6.6 Hz, 1H), 2.38 (s, 3H, CH_3), 2.18 (s, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 153.5, 142.2, 140.7, 139.8 129.2 (overlapping ArCs), 126.1, 111.6, 21.4, 17.8. HRMS-ESI (*m*/*z*): Calc'd for $C_{13}H_{14}N_2O_2SNa$ $[M+Na]^+$: 285.0668. Found: 285.0666.

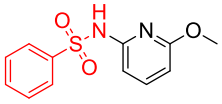
N-(3-methylpyridin-2-yl)benzenesulfonamide (**4.4**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *4.4.2*, conducted at 110 °C in dioxane using 5 mol% (**PhPAd-DalPhos**)NiCl(*o*-

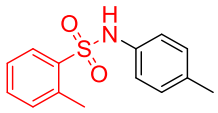
tol), and purified according to *4.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 20% ethyl acetate in hexanes (4 CV), 20-80% ethyl acetate in hexanes (10 CV) followed by 80% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 65% isolated yield (0.077 g, 0.312 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 12.3 (br, 1H, NH), 7.99-7.97 (m, 2H, overlapping Hs), 7.50-7.42 (m, 5H, overlapping Hs), 6.54 (apparent t, J = 6.7 Hz, 1H), 2.18 (s, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 153.6, 143.7, 140.0, 131.6, 128.6 (overlapping ArCs), 126.0, 111.6, 17.8. HRMS-ESI (*m*/*z*): Calc'd for $C_{12}H_{12}N_2O_2SNa$ $[M+Na]^+$: 271.0512. Found: 271.0513.

N-(6-methoxypyridin-2-yl)benzenesulfonamide (**4.5**)



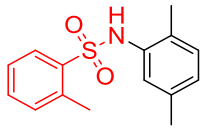
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *4.4.2*, conducted at 80 °C in THF using 5 mol% (**PhPAd-DalPhos**)NiCl(*o*-tol), and purified according to *4.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 10% ethyl acetate in hexanes (4 CV), 10-45% ethyl acetate in hexanes (12 CV) followed by 45% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 77% isolated yield (0.098 g, 0.370 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.95-7.94 (m, 2H, overlapping Hs), 7.57-7.54 (m, 1H), 7.49-7.45 (m, 3H, overlapping Hs), 6.79 (d, J = 7.8 Hz, 1H), 6.39 (d, J = 8.1 Hz, 1H), 3.73 (s, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 163.4, 148.3, 140.7, 139.6, 133.2, 129.0, 127.3, 105.7, 103.3, 53.5. HRMS-ESI (*m*/*z*): Calc'd for $C_{12}H_{12}N_2O_3SNa$ $[M+Na]^+$: 287.0461. Found: 287.0460.

2-methyl-N-(p-tolyl)benzenesulfonamide (**4.6**)



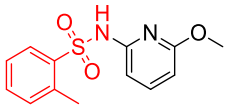
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *4.4.2*, conducted at 110 °C in dioxane using 5 mol% (**PhPAd-DalPhos**)NiCl(*o*-tol), and purified according to *4.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (2 CV), 0-30% ethyl acetate in hexanes (14 CV) followed by 30% ethyl acetate in hexanes (6 CV) which afforded the title compound in an 72% isolated yield (0.090 g, 0.346 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.93-7.92 (m, 1H), 7.43-7.40 (m, 1H), 7.28-7.24 (m, 2H, overlapping Hs), 7.00 (d, J = 8.3 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 6.61 (br, 1H, NH), 2.64 (s, 3H, CH_3), 2.25 (s, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 137.5, 137.1, 135.2, 133.6, 133.0, 132.5, 130.0, 129.9, 126.2, 121.6, 20.8, 20.4. HRMS-ESI (*m*/*z*): Calc'd for $C_{14}H_{15}NO_2SNa$ $[M+Na]^+$: 284.0716. Found: 284.0714.

N-(2,5-dimethylphenyl)-2-methylbenzenesulfonamide (**4.7**)



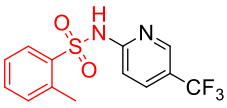
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *4.4.2*, conducted at 110 °C in dioxane using 5 mol% (**PhPAd-DalPhos**)NiCl(*o*-tol), and purified according to *4.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-15% ethyl acetate in hexanes (12 CV) followed by 15% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 92% isolated yield (0.121 g, 0.442 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.92 (d, J = 7.8 Hz, 1H), 7.46-7.43 (m, 1H), 7.29-7.27 (m, 2H, overlapping Hs), 7.70 (d, J = 7.7 Hz, 1H), 6.92 (s, 1H), 6.85 (d, J = 7.7 Hz, 1H), 6.32 (s, 1H), 2.60 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.08 (s, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 138.1, 137.3, 136.7, 134.2, 133.0, 132.6, 130.6, 129.8, 127.5, 126.6, 126.2, 124.0, 20.9, 20.5, 17.1. HRMS-ESI (*m*/*z*): Calc'd for $C_{15}H_{17}NO_2SNa$ $[M+Na]^+$: 298.0872. Found: 298.0878.

N-(6-methoxypyridin-2-yl)-2-methylbenzenesulfonamide (**4.8**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *4.4.2*, conducted at 80 °C in THF using 5 mol% (**PhPAd-DalPhos**)NiCl(*o*-tol), and purified according to *4.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (2 CV), 0-30% ethyl acetate in hexanes (12 CV) followed by 30% ethyl acetate in hexanes (6 CV) which afforded the title compound in an 86% isolated yield (0.115 g, 0.413 mmol) as an off-white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.10 (dd, J = 7.9, 1.1 Hz, 1H), 7.44-7.39 (m, 3H, overlapping Hs), 7.31-7.27 (m, 2H, overlapping Hs), 6.62 (d, J = 7.8 Hz, 1H), 6.36 (d, J = 8.1 Hz, 1H), 3.74 (s, 3H, CH_3), 2.71 (s, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 163.4, 148.2, 140.6, 137.6, 137.2, 133.2, 132.6, 130.2, 126.1, 105.5, 102.9, 53.5, 20.2. HRMS-ESI (*m*/*z*): Calc'd for $C_{13}H_{14}N_2O_3SNa$ $[M+Na]^+$: 301.0617. Found: 301.0622.

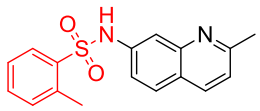
2-methyl-N-(5-(trifluoromethyl)pyridin-2-yl)benzenesulfonamide (**4.9**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *4.4.2*, conducted at 80 °C in THF using 5 mol% (**PhPAd-DalPhos**)NiCl(*o*-tol),

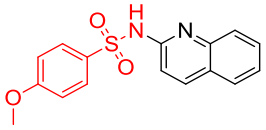
and purified according to *4.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 20% ethyl acetate in hexanes (4 CV), 20-60% ethyl acetate in hexanes (12 CV) followed by 60% ethyl acetate in hexanes (6 CV) which afforded the title compound in an 42% isolated yield (0.064 g, 0.202 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 11.1 (br, 1H, NH), 8.70 (s, 1H), 8.13 (d, J = 7.6 Hz, 1H), 7.80 (dd, J = 8.9, 2.1 Hz, 1H), 7.51-7.48 (m, 1H), 7.38-7.30 (m, 3H, overlapping Hs), 2.63 (2, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 153.9, 145.0, 137.5, 137.2, 136.6-136.5 (m), 133.7, 133.0, 129.8, 126.4, 123.2 (q, J_{FC} = 269.9 Hz), 121.4 (q, J_{FC} = 33.9 Hz), 111.2, 20.2. ^{19}F NMR (470.6 MHz, $CDCl_3$): δ -62.1. HRMS-ESI (*m*/*z*): Calc'd for $C_{13}H_{11}N_2O_2F_3SNa$ $[M+Na]^+$: 339.0386. Found: 339.0379.

2-methyl-N-(2-methylquinolin-7-yl)benzenesulfonamide (**4.10**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *4.4.2*, conducted at 80 °C in THF using 5 mol% (**PhPAd-DalPhos**)NiCl(*o*-tol), and purified according to *4.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 20% ethyl acetate in hexanes (4 CV), 20-60% ethyl acetate in hexanes (12 CV) followed by 60% ethyl acetate in hexanes (6 CV) which afforded the title compound in an 82% isolated yield (0.123 g, 0.394 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.04 (dd, J = 8.6, 1.5 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.51 (d, J = 2.1 Hz, 1H), 7.41-7.37 (m, 1H), 7.36 (dd, J = 8.8, 2.3 Hz, 1H), 7.26-7.24 (m, 2H, overlapping Hs), 7.18 (d, J = 8.4 Hz, 1H), 7.05 (br, 1H, NH), 2.70 (s, 3H, CH_3), 2.68 (s, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 159.8, 148.0, 138.4, 137.6, 137.2, 136.0, 133.0, 132.6, 129.8, 128.7, 126.2, 123.4, 121.2, 119.2, 116.2, 25.0, 20.3. HRMS-ESI (*m*/*z*): Calc'd for $C_{17}H_{17}N_2O_2S$ $[M+H]^+$: 313.1005. Found: 313.0995.

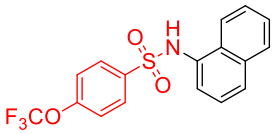
4-methoxy-N-(quinolin-2-yl)benzenesulfonamide (**4.11**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *4.4.2*, conducted at 110 °C in dioxane using 5 mol% (**PhPAd-DalPhos**)NiCl(*o*-tol), and purified according to *4.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 15% ethyl acetate in hexanes (4 CV), 15-55% ethyl acetate in hexanes (12 CV) followed by 55% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 75% isolated yield (0.113 g, 0.360 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 11.80 (br, 1H, NH), 7.95 (d, J = 8.8 Hz, 2H), 7.84 (d, J = 9.4 Hz, 1H), 7.62-7.59 (m, 2H, overlapping Hs), 7.43 (d, J = 8.1 Hz, 1H), 7.34 (apparent t, J = 7.5 Hz, 1H), 6.96-6.93 (m, 3H, overlapping Hs), 3.83 (s, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ

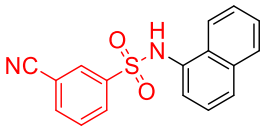
162.5, 154.1, 140.6, 136.6, 134.7, 131.6, 128.4, 128.1, 124.6, 121.4, 120.9, 117.5, 114.0, 55.5. HRMS-ESI (*m/z*): Calc'd for $C_{16}H_{14}N_2O_3SNa$ $[M+Na]^+$: 337.0617. Found: 337.0612.

N-(naphthalen-1-yl)-4-(trifluoromethoxy)benzenesulfonamide (**4.12**)



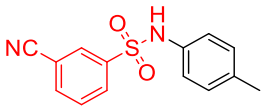
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *4.4.2*, conducted at 80 °C in THF using 5 mol% (**PhPAd-DalPhos**)NiCl(*o*-tol), and purified according to *4.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-25% ethyl acetate in hexanes (12 CV) followed by 25% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 65% isolated yield (0.115 g, 0.312 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.83 (d, J = 8.1 Hz, 1H), 7.77-7.74 (m, 3H, overlapping Hs), 7.70 (d, J = 8.5 Hz, 1H), 7.47-7.44 (m, 1H), 7.42-7.38 (m, 3H, overlapping Hs), 7.17 (d, J = 8.2 Hz, 2H), 6.91 (br, 1H, NH). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 152.3, 137.6, 134.3, 130.8, 129.4, 129.0, 128.5, 127.9, 126.8, 126.4, 125.4, 123.8, 121.1, 120.8, 120.1 (q, J_{FC} = 257.8 Hz). HRMS-ESI (*m/z*): Calc'd for $C_{17}H_{12}NO_3F_3SNa$ $[M+Na]^+$: 390.0382. Found: 390.0377.

3-cyano-N-(naphthalen-1-yl)benzenesulfonamide (**4.13**)



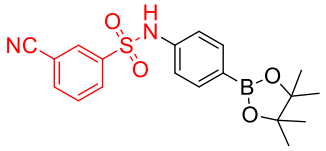
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *4.4.2*, conducted at 80 °C in THF using 5 mol% (**PhPAd-DalPhos**)NiCl(*o*-tol), and purified according to *4.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% ethyl acetate (4 CV), 0-25% ethyl acetate in hexanes (12 CV) followed by 25% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 65% isolated yield (0.096 g, 0.312 mmol) as an off-white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.91-7.89 (m, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.80-7.78 (m, 1H), 7.75-7.73 (m, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.49-7.46 (m, 2H, overlapping Hs), 7.44-7.41 (m, 3H, overlapping Hs), 6.97 (br, 1H, NH). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 141.0, 136.0, 134.3, 131.2, 130.8, 130.2, 129.9, 129.0, 128.7, 128.3, 127.0, 126.6, 125.5, 124.1, 120.9, 116.9, 113.5. HRMS-ESI (*m/z*): Calc'd for $C_{17}H_{12}N_2O_2SNa$ $[M+Na]^+$: 331.0512. Found: 331.0510.

3-cyano-N-(p-tolyl)benzenesulfonamide (**4.14**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *4.4.2*, conducted at 110 °C in dioxane using 5 mol% (**PhPAd-DalPhos**)NiCl(*o*-tol), and purified according to *4.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 5% ethyl acetate in hexanes (4 CV), 5-25% ethyl acetate in hexanes (14 CV) followed by 25% ethyl acetate in hexanes (6 CV) which afforded the title compound in an 77% isolated yield (0.100 g, 0.370 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.95-7.94 (m, 1H), 7.81-7.80 (m, 1H), 7.58 (apparent t, J = 7.9 Hz, 1H), 7.07 (d, J = 8.2 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 6.80 (br, 1H, NH), 2.30 (s, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 140.8, 136.6, 136.0, 132.6, 131.2, 130.8, 130.2, 130.0, 123.0, 117.1, 113.6, 20.9. HRMS-ESI (*m/z*): Calc'd for $C_{14}H_{12}N_2O_2SNa$ $[M+Na]^+$: 295.0512. Found: 295.0511.

3-cyano-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzenesulfonamide (**4.15**)



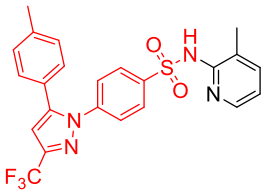
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *4.4.2*, conducted at 80 °C in THF using 5 mol% (**PhPAd-DalPhos**)NiCl(*o*-tol), and purified according to *4.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-30% ethyl acetate in hexanes (12 CV) followed by 30% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 53% isolated yield (0.098 g, 0.254 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.97-7.95 (m, 1H), 7.81-7.80 (m, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.57 (apparent t, J = 7.9 Hz, 1H), 7.07 (d, J = 8.4 Hz, 2H), 6.68 (br, 1H, NH), 1.32 (s, 12H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 140.7, 138.0, 136.3, 136.2, 131.1, 130.7, 130.1, 120.2, 116.9, 113.8, 84.0, 24.8. HRMS-ESI (*m/z*): Calc'd for $C_{19}H_{21}N_2O_4BSNa$ $[M+Na]^+$: 407.1207. Found: 407.1203.

5-methyl-N-(quinolin-2-yl)pyridine-2-sulfonamide (**4.16**)

The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *4.4.2*, conducted at 80 °C in THF using 5 mol% (**PhPAd-DalPhos**)NiCl(*o*-tol), and purified according to *4.4.6*. Purified by flash column chromatography on silica using a 60% ethyl acetate in hexanes eluent mixture which afforded the title compound in a 72% isolated yield (0.103 g, 0.346 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 12.56 (br, 1H, NH), 8.45 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 9.3 Hz, 1H), 7.72-7.70 (m, 1H), 7.67-7.64 (m, 2H, overlapping Hs), 7.54 (d, J = 8.6 Hz, 1H), 7.39 (apparent t, J = 7.9 Hz, 1H), 6.95 (d, J = 9.3 Hz, 1H), 2.40 (s, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz,

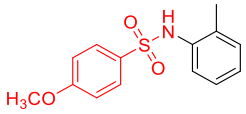
$CDCl_3$): δ 156.6, 154.8, 149.4, 140.6, 138.6, 137.0, 136.4, 131.7, 128.1, 124.9, 122.1, 121.6, 121.5, 117.3, 18.5. HRMS-ESI (*m/z*): Calc'd for $C_{15}H_{13}N_3O_2SNa$ $[M+Na]^+$: 322.0621. Found: 322.0618.

N-(3-methylpyridin-2-yl)-4-(5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide (**4.20**)



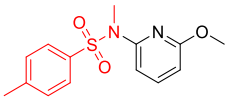
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *4.4.2*, conducted at 110 °C in dioxane using 5 mol% (**PhPAd-DalPhos**)NiCl(*o*-tol), and purified according to *4.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 20% ethyl acetate in hexanes (4 CV), 20-60% ethyl acetate in hexanes (12 CV) followed by 60% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 51% isolated yield (0.116 g, 0.245 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 12.23 (br, 1H, NH), 7.96-7.94 (m, 2H), 7.49-7.48 (m, 1H), 7.44-7.43 (m, 1H), 7.40-7.38 (m, 2H), 7.16-7.15 (m, 2H), 7.11-7.10 (m, 2H), 6.72 (s, 1H), 6.59 (apparent t, J = 6.7 Hz, 1H), 2.37 (s, 3H, CH_3), 2.17 (s, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 153.6, 145.1, 143.8 (q, J_{FC} = 38.3 Hz), 143.3, 141.7, 140.4, 139.6, 131.6, 130.9, 129.7, 128.7, 127.1, 125.8, 125.2, 121.1 (q, J_{FC} = 269.4), 111.9, 106.0, 21.3, 17.7. ^{19}F NMR (470.6 MHz, $CDCl_3$): δ -62.4. HRMS-ESI (*m/z*): Calc'd for $C_{23}H_{19}N_4O_2F_3SNa$ $[M+Na]^+$: 495.1073. Found: 495.1067.

4-methoxy-N-(o-tolyl)benzenesulfonamide (**4.21**)



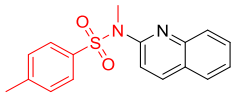
The title compound was synthesized from the corresponding aryl chloride (0.12 mmol) according to *4.4.2*, conducted at 120 °C in dioxane using 30 mol% (**PhPAd-DalPhos**)NiCl(*o*-tol), and purified according to *4.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 5% ethyl acetate in hexanes (4 CV), 5-30% ethyl acetate in hexanes (12 CV) followed by 30% ethyl acetate in hexanes (4 CV) which afforded the title compound in a 70% isolated yield (0.026 g, 0.092 mmol) as a white solid. Note that in this case, the yield was based off added primary sulfonamide (1.1 equiv. 0.132 mmol) as the catalyst activation product is also **2u** (30 mol%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.68-7.65 (m, 2H), 7.31 (d, J = 8.0 Hz, 1H), 7.15-7.12 (m, 1H), 7.09-7.06 (m, 2H, overlapping Hs), 6.89-6.87 (m, 2H), 6.50 (br, 1H, NH), 3.83 (s, 3H, CH_3), 2.03 (s, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 163.1, 134.6, 131.3 (overlapping ArCs), 129.3, 126.9, 126.1, 124.3, 114.1, 55.6, 17.6. HRMS-ESI (*m/z*): Calc'd for $C_{14}H_{15}NO_3SNa$ $[M+Na]^+$: 300.0665. Found: 300.0663.

N-(6-methoxypyridin-2-yl)-N,4-dimethylbenzenesulfonamide (**4.22**)



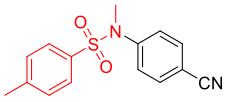
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *4.4.3*, conducted at 110 °C in dioxane using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *4.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-15% ethyl acetate in hexanes (12 CV) followed by 15% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 78% isolated yield (0.109 g, 0.374 mmol) as an off-white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.56 (apparent t, J = 7.9 Hz, 1H), 7.52 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 7.7 Hz, 1H), 6.52 (d, J = 8.1 Hz, 1H), 3.65 (s, 3H, CH_3), 3.28 (s, 3H, CH_3), 2.39 (s, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 162.7, 151.3, 143.6, 140.0, 134.9, 129.3, 127.5, 111.8, 107.1, 53.2, 35.4, 21.5. HRMS-ESI (*m*/*z*): Calc'd for $C_{14}H_{16}N_2O_3SNa$ $[M+Na]^+$: 315.0774. Found: 315.0768.

N,4-dimethyl-N-(quinolin-2-yl)benzenesulfonamide (**4.23**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *4.4.3*, conducted at 110 °C in dioxane using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *4.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-15% ethyl acetate in hexanes (12 CV) followed by 15% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 91% isolated yield (0.136 g, 0.437 mmol) as an off-white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.10 (d, J = 8.9 Hz, 1H), 7.93 (d, J = 8.9 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.64-7.61 (m, 1H), 7.54 (d, J = 8.3 Hz, 2H), 7.49-7.46 (m, 1H), 7.19 (d, J = 8.2 Hz, 2H), 3.44 (s, 3H, CH_3), 2.36 (s, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 152.9, 146.6, 143.9, 137.3, 134.6, 129.6, 129.5, 128.5, 127.5, 127.3, 126.1, 125.9, 118.5, 35.3, 21.5. HRMS-ESI (*m*/*z*): Calc'd for $C_{17}H_{16}N_2O_2SNa$ $[M+Na]^+$: 335.0825. Found: 335.0811.

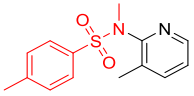
N-(4-cyanophenyl)-N,4-dimethylbenzenesulfonamide (**4.24**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *4.4.3*, conducted at 110 °C in dioxane using 10 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *4.4.6*. Purified by flash column chromatography on silica using

an eluent gradient of 5% ethyl acetate in hexanes (4 CV), 5-40% ethyl acetate in hexanes (12 CV) followed by 40% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 54% isolated yield (0.074 g, 0.259 mmol) as an off-white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.60 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.3 Hz, 2H), 7.28-7.25 (m, 4H, overlapping Hs), 3.18 (s, 3H, CH_3), 2.42 (s, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 145.7, 144.3, 133.1, 132.8, 129.6, 127.6, 126.0, 118.2, 110.3, 37.4, 21.5. HRMS-ESI (*m*/*z*): Calc'd for $C_{15}H_{14}N_2O_2SNa$ $[M+Na]^+$: 309.0668. Found: 309.0666.

N,4-dimethyl-N-(3-methylpyridin-2-yl)benzenesulfonamide (**4.25**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *4.4.3*, conducted at 110 °C in dioxane using 5 mol% (***meso*-PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *4.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-35% ethyl acetate in hexanes (12 CV) followed by 35% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 74% isolated yield (0.098 g, 0.355 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.18-8.17 (m, 1H), 7.64-7.63 (m, 1H), 7.59 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.17-7.14 (m, 1H), 3.08 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 2.43 (s, 3H, CH_3). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 153.5, 146.1, 143.5, 140.0, 134.3, 134.1, 129.3, 128.6, 123.3, 36.9, 21.6, 18.4. HRMS-ESI (*m*/*z*): Calc'd for $C_{14}H_{16}N_2O_2SNa$ $[M+Na]^+$: 299.0825. Found: 299.0827.

5. Nickel-Catalyzed N-Arylation of Fluoroalkylamines

5.1 Research overview and contribution report

This author wishes to clarify his contributions to the research described in Chapter 5 of this Thesis document. This chapter describes the application of **PAd2-DalPhos** in the Ni-catalyzed N-arylation of fluoroalkylamines. The catalytic transformations presented herein represent state-of-the-art amongst all nickel-based catalysts for the cross-coupling of aryl chlorides and aryl phenol derivatives.

My contributions to the study included optimizing catalytic conditions, developing a substrate scope based on both linear and branched fluoroalkylamine N-arylation, developing soluble organic dual-base conditions for the cross-coupling of aryl (pseudo)halides possessing base-sensitive functional groups, and performing competition experiments to gauge catalyst selectivity. Dr. Arun Yadav was responsible for conceptual input in the early stages of the project, while Dr. Mark Stradiotto helped in mentoring myself as well as providing advice throughout the project.

Reference: McGuire, R. T.; Yadav, A. A.; Stradiotto, M. Nickel-Catalyzed N-Arylation of Fluoroalkylamines. *Angew. Chem. Int. Ed.* **2021**, 60, 4080-4084.

5.2 Introduction

The importance of strategies for accessing fluorinated functional groups cannot be overstated, especially in the context of preparing active pharmaceutical agents (APIs), given that fluorinated API analogues are often more robust to various metabolic pathways, and posses other distinct physicochemical properties versus non-fluorinated analogues.[77–80] Specifically, β-fluoroalkylamino substructures are important analogues of alkylamines that

can serve as bio-isosteres of biologically important amide and sulfonamide functionalities amongst others, while offering distinct properties.[78] Surprisingly, given the obvious advantages of incorporating β-fluoroalkylamino fragments, along with the prevalence of anilines in top-selling pharmaceuticals, relatively few commercial APIs contain N-(β-fluoroalkyl)aniline substructures.[77] One possible explanation for this is that the formation of N-(β-fluoroalkyl)anilines from the corresponding aryl (pseudo)halides and β-fluoroalkylamines is particularly troublesome when considering both S_NAr and BHA type approaches.[80] Francotte and co-workers reported on S_NAr reactivity using $CH_3CH_2NH_2$ as a nucleophile and it was found that reactions typically required forcing conditions (160 ºC, 50 h) as well as appropriately substituted electron-poor chloroarenes.[80] More recently, researchers like the Hartwig and Hu groups have turned to BHA approaches for affecting these transformations, using Pd[81] and Cu[82] respectively (Figure 5.1). While useful, limitations in both methods exist, namely in the case for Pd, the use of elevated temperature as well as the requirement for commercially unavailable KOPh as a base both pose drawbacks in that fluoroalkylamines typically boil at very low temperatures (i.e. 37 ºC for $CH_3CH_2NH_2$), and the stoichiometric non-volatile organic by-product phenol can contribute to purification difficulties in isolating the desired products.[81] Although the use of Cu for promoting reactions of this type is attractive given its Earth-abundance, drawbacks in using Cu include the requirement for elevated reaction temperatures (110-120 ºC) and high Cu loadings (10-40 mol%), along with the incompatibility of (hetero)aryl (pseudo)halides including aryl chlorides, with the methodology being limited to the inclusion of just (hetero)aryl bromide electrophiles.[82] Indeed, a more general approach for solving these highlighted issues would utilize a catalyst system that can operate at room temperature, with commercially available reagents, and is compatible with (hetero)aryl (pseudo)halide electrophiles, especially aryl

chlorides and phenol derivatives which constitute the vast majority of commercially available electrophiles in this class.

In this chapter, the Ni-catalyzed N-arylation of β-fluoroalkylamines with (hetero)aryl (pseudo)halides is reported for the first time, enabled by use of the air-stable (**PAd2-DalPhos**)Ni(o-tolyl)Cl pre-catalyst in combination with commercially available NaO*t*Bu as the base at room temperature, or in combination with the soluble organic dual-base system (comprised of DBU and NaOTf) at 100 ºC. These homogeneous reaction conditions allow for the compatibility of (hetero)aryl (pseudo)halides (het-ArX where X = Cl, Br, I, and phenol derived electrophiles for the first time) under unprecedently mild conditions, encompassing base-sensitive substrates along with enantioretentive transformations (Figure 5.1).

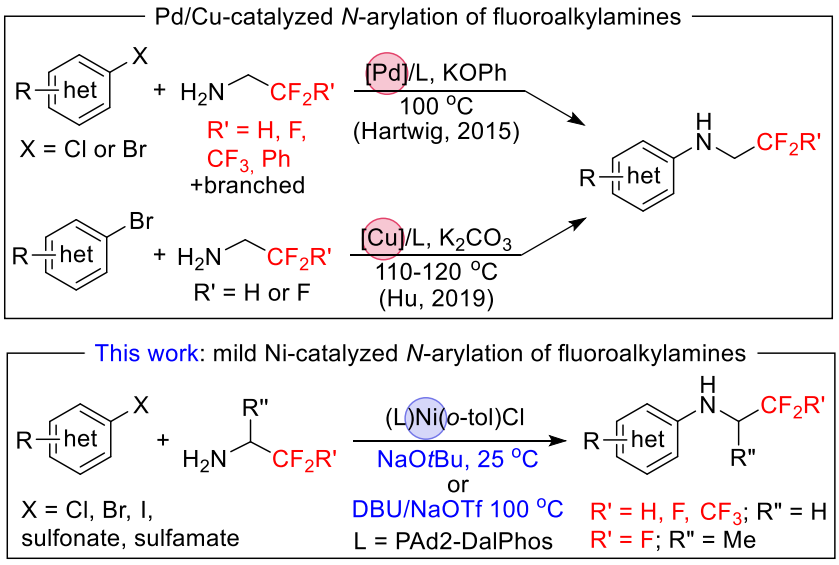


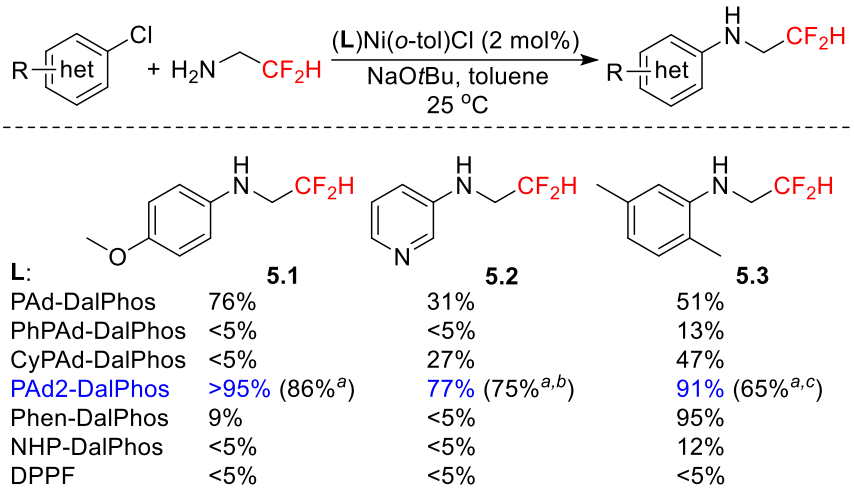
Figure 5.1 Summary of work conducted on the metal-catalyzed N-arylation of fluoroalkylamines, including this work.

5.3 Results and discussion

5.3.1 Preliminary pre-catalyst screening

In a quest to identify optimal catalytic conditions for enabling the Ni-catalyzed N-arylation of β-fluoroalkylamines with (hetero)aryl (pseudo)halides, initial screening commenced with the deployment of known and air-stable Ni pre-catalysts of the type (**L**)Ni(o-tolyl)Cl, in conjunction with the commercially available base, NaO*t*Bu, in room temperature reactions where toluene was the solvent (Figure 5.2). The choice of NaO*t*Bu for enabling these reactions is somewhat non-intuitive in that Hartwig and co-workers found in their analogous Pd-catalyzed approach that the product N-(β-fluoroalkyl)anilines decomposed under the conditions required to affect catalytic turnover (i.e. 100 ºC) when in the presence of NaO*t*Bu.[81] Gratifyingly, when performing reactions with DalPhos derived pre-catalysts, conversion to the desired N-(β-fluoroalkyl)aniline products (**5.1-5.3**) proceeded especially efficiently when using (**PAd2-DalPhos**)Ni(o-tolyl)Cl which offered >75% conversion to product (based on calibrated GC data) in cases involving electron-rich (**5.1**), heteroaryl (**5.2**), and sterically hindered (**5.3**) aryl chlorides (Figure 5.2).

In performing the reactions at room-temperature, less equivalents of the volatile 2,2-difluoroethylamine nucleophile were required relative to in the analogous Pd-catalyzed reactions (1.2 equiv. versus 2.0 equiv.), and the use of soluble NaO*t*Bu instead of KOPh posed no issues in the product purification as the by-product *tert*-butanol is volatile.[81]



L:	5.1	5.2	5.3
PAd-DalPhos	76%	31%	51%
PhPAd-DalPhos	<5%	<5%	13%
CyPAd-DalPhos	<5%	27%	47%
PAd2-DalPhos	>95% (86%[a])	77% (75%[a,b])	91% (65%[a,c])
Phen-DalPhos	9%	<5%	95%
NHP-DalPhos	<5%	<5%	12%
DPPF	<5%	<5%	<5%

Figure 5.2 Pre-catalyst screen for the Ni-catalyzed N-arylation of fluoroalkylamines. Reactions were conducted at 0.12 mmol scale (aryl halide, 0.24 M in toluene), with NaOtBu (1.1 equiv), and 2,2-difluoroethylamine (1.2 equiv) for 18 h (unoptimized). Reported GC yields determined on the basis of response-factor calibrated GC data using authentic material, with the mass balance corresponding to unreacted starting material. [a]Isolated yield; [b]3mol%; [c]volatile product.

5.3.2 Primary fluoroalkylamine N-arylation scope

Given that (**PAd2-DalPhos**)Ni(o-tolyl)Cl was successful in enabling the N-arylation of 2,2-difluoroethylamine with electron-rich (**5.1**), heteroaryl (**5.2**), and sterically hindered (**5.3**) aryl chlorides at room temperature, a more general substrate scope was probed involving linear primary fluoroalkylamines paired with various (hetero)aryl (pseudo)halide electrophiles. The application of **PAd2-DalPhos** was successful in enabling a vast array of transformations of this type, including most notably, the first examples of β-fluoroalkylamine N-arylation with aryl pseudohalides derived from phenols, including aryl tosylates (**5.4, 5.20-5.21**) and aryl triflates (**5.4, 5.19**) (Figure 5.3). Indeed, a wide range of heterocyclic electrophiles were tolerated in these reactions, including those based on pyridine (**5.5, 5.22**), quinoline (**5.6**), benzothiophene (**5.9**), benzothiazole (**5.10**), quinaldine (**5.11, 5.18**), and quinoxaline (**5.16**) core structures. These reaction conditions were also tolerant to a range of

functional groups including methoxy (**5.1, 5.13, 5.15, 5.20, 5.23**), nitrile (**5.12, 5.24, 5.26**), fluoroaryl (**5.13**), boronic acid (**5.14**), and secondary amine (**5.17**) groups. The chemoselective cross-coupling of N-methyl-3-chloroaniline with a cyclobutane-derived γ-fluoroalkylamine to give **5.17**, as well as the successful cross-coupling of 3,3,3-trifluoropropylamine leading to **5.18**, establishes the viability of using such γ-fluoroalkylamines in this chemistry. Unfortunately, the reactions were unable to be extended to (hetero)aryl chloride electrophiles featuring 5-membered rings, such 2-chlorobenzothiazole and 2-chlorobenzoxazole.

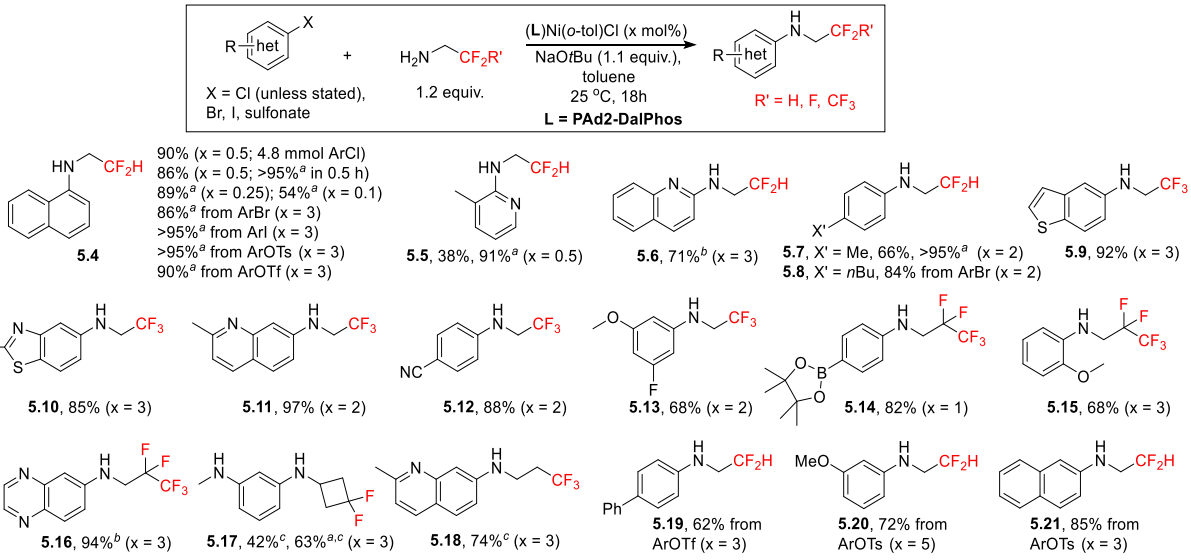


Figure 5.3 Substrate scope for the cross-coupling of primary fluoroalkylamines with (hetero)aryl (pseudo)halides, enabled by (**PAd2-DalPhos**)NiCl(*o*-tolyl). Isolated yields are reported from X = Cl unless noted otherwise. Yields reported from reactions conducted on 0.48 mmol scale in aryl halide, except for GC yields for which reactions were performed on 0.12 mmol scale in aryl halide. GC yields reported based on response-factor calibrated data using dodecane or phenyldodecane as internal standards. [a]calibrated GC yield; [b]3.0 equiv. amine; [c]amine added as HCl salt and 2.3 equiv. NaO*t*Bu used.

Amongst the successful inclusion of a wide range of various aryl chloride electrophiles, aryl bromides (**5.4, 5.8**) and iodides (**5.4**) were unsurprisingly also accommodated successfully. To gauge the catalytic activity in this system, a catalyst loading

drop was performed in the reaction of 2,2-difluoroethylamine with 1-chloronaphthalene and it was found that reactions could still proceed efficiently with a Ni loading of just 0.25 mol% (89% **5.4** by calibrated GC). The reaction of 2,2-difluoroethylamine with 1-chloronaphthalene was also successfully conducted on gram-scale (4.8 mmol ArCl), affording **5.4** in 90% isolated yield when using just 0.5 mol% Ni.

5.3.3 Enantio-retentive fluoroalkylamine N-arylation scope

Given the successful inclusion of linear fluoroalkylamines in this chemistry, we opted to extend the developed methodology to bulkier branched fluoroalkylamine N-arylation chemistry. This proved fruitful, and it was found that in the N-arylation of 1,1,1-trifluoro-2-propanamine with electron-rich (**5.23**), electron-poor (**5.24**), ortho-substituted (**5.25**), and heterocyclic (**5.22**) aryl chlorides, no detectable racemization was observed at the α-carbon position when starting with enantioenriched nucleophile (er > 99:1) and the reactions proceeded with useful product yields (> 70% isolated yields), except for in the case of **5.25**, where the product volatility caused an abnormally poor isolated yield of 19% (Figure 5.4). To reflect the true catalytic performance in the formation of **5.25**, a GC calibrated yield was taken prior to reaction work-up which showed > 95% conversion to the desired product **5.25**. The volatility of the product N-(β-fluoroalkyl)anilines was also noted by Hartwig and co-workers in some of their examples.[81] Although **PAd2-DalPhos** was unable to promote the cross-coupling of secondary 2-(trifluoromethyl)pyrrolidine with 4-chlorobenzonitile leading to **5.26**, the application of **DPPF** was successful in enabling this Ni-catalyzed transformation in good yield (96%).

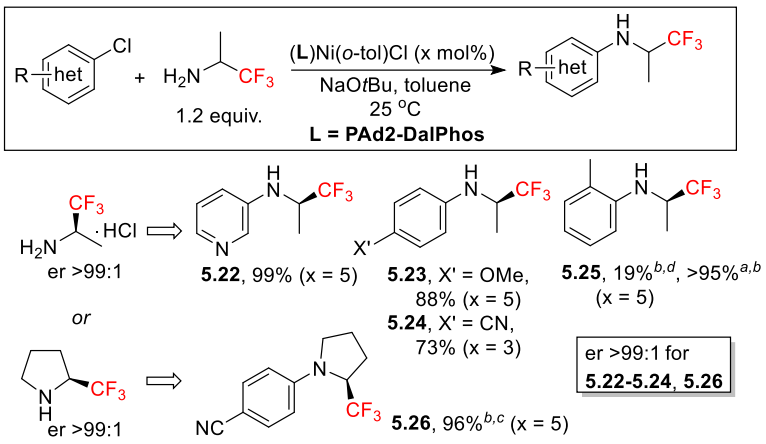


Figure 5.4 Substrate scope for the cross-coupling of branched fluoroalkylamines with (hetero)aryl chlorides, enabled by (**PAd2-DalPhos**)NiCl(o-tolyl). Isolated yields reported from reactions conducted on 0.48 mmol scale in aryl halide, except for GC yields for which reactions were performed on 0.12 mmol scale in aryl halide. GC yields reported based on response-factor calibrated data using dodecane or phenyldodecane as internal standards. [a]calibrated GC yield; [b]65 C; [c]**L = DPPF**; [d]unable to obtain sufficient chiral resolution to determine unequivocal retention of stereochemistry.

5.3.4 Fluoroalkylamine N-arylation scope involving base-sensitive (pseudo)halides

Having established the utility of the (**PAd2-DalPhos**)NiCl(*o*-tolyl) pre-catalyst in enabling both the N-arylation of linear and branched primary fluoroalkylamines with (hetero)aryl (pseudo)halides when using soluble NaO*t*Bu as a base, we postulated as to whether a milder combination of soluble bases could enable the N-arylation of more base-sensitive (hetero)aryl (pseudo)halides. Inspired by previous work involving the use of the organic dual-base system comprised of DBU and NaX (X = TFA, OTf) for Pd catalysis[83,84] we sought to deploy this system in enabling the Ni-catalyzed N-arylation of base-sensitive (hetero)aryl (pseudo)halides possessing functional groups such as aldehydes, ketones and esters – all functional groups of which led to complicated reaction mixtures when utilized in the aforementioned NaO*t*Bu enabled couplings involving linear primary fluoroalkylamines. We were pleased to find that the application of 2.0 equiv. of both DBU and NaOTf enabled synthetically useful yields in the Ni-catalyzed N-arylation of 2,2-difluoroethylamine with a

range aryl (pseudo)halides possessing base-sensitive functional handles including ketones (**5.27, 5.31**), esters (**5.28-5.29**) and aldehydes (**5.30**) upon increasing the reaction temperature to 100 ºC as seen in Figure 5.5.

Furthermore, it was found that base-sensitive aryl triflates, sulfamates and mesylates were also compatible electrophiles in this chemistry when utilizing the milder organic dual-base conditions, demonstrating the capacity of this developed methodology for accommodating a range of phenol-derived electrophiles.

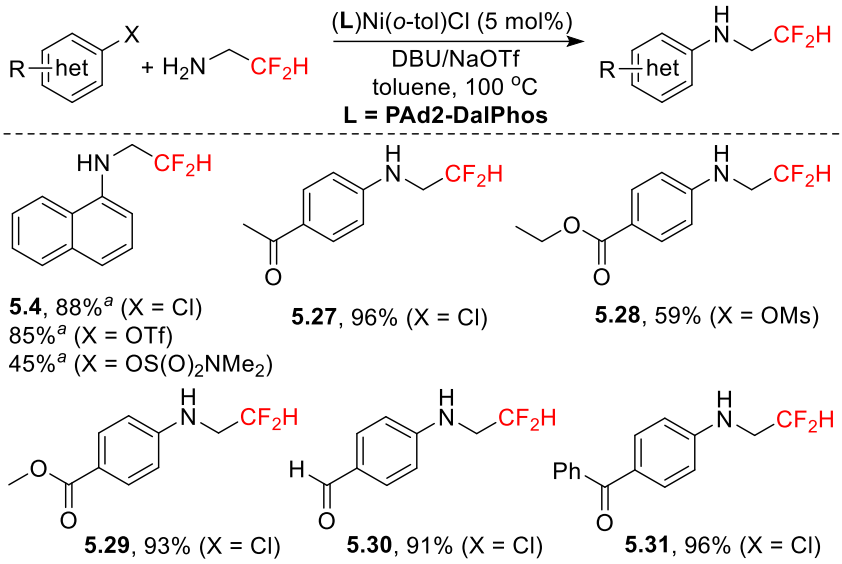


Figure 5.5 Substrate scope for the cross-coupling of fluoroalkylamines with base-sensitive aryl (pseudo)chlorides, enabled by (**PAd2-DalPhos**)NiCl(*o*-tolyl) with dual organic base. Isolated yields reported from reactions conducted on 0.48 mmol scale in aryl halide, except for GC yields for which reactions were performed on 0.12 mmol scale in aryl halide. GC yields reported based on response-factor calibrated data using dodecane or phenyldodecane as internal standards. [a]calibrated GC yield.

5.3.5 Competition experiments

To gain insights into the reactivity preferences of the (**PAd2-DalPhos**)Ni(o-tol)Cl pre-catalyst in room temperature cross-couplings of β-fluoroalkylamines employing NaO*t*Bu, some competition studies were conducted. While (hetero)aryl chlorides, bromides,

and phenol derivatives such as tosylates each independently proved to be viable electrophiles in this chemistry, the competition results presented in Figure 5.6 establish the Cl > Br > OTs reactivity trend in sterically and electronically similar substrates. In a complementary competition employing the nucleophiles 2,2-difluoroethylamine, furfurylamine, and 2-aminopyridine with 1-chloronaphthalene, preferential formation of the pyridine-derived aniline product (**5.33**) over both the alkylamine (**5.32**) and the β-fluoroalkylamine (**5.4**) derivatives was noted. The **5.4**:**5.32** ratio (1.3:1) indicated a modest preference for the fluorinated versus the nonfluorinated alkylamine nucleophile (Figure 5.6), in contrast to competition studies reported by Hu and co-workers focusing on Cu-catalyzed C-N cross-coupling of an aryl bromide, whereby the alkylamine was preferred (3.1:1) over the β-fluoroalkylamine.[82] The competitive formation of **5.4** and **5.32** herein also contrasts the results of studies focusing on the AdBippyPhos/Pd system, in which *p*-toluidine and *n*-butylamine nucleophiles were cross-coupled preferentially, with no conversion of the contending pentafluoropropylamine.[81] While many factors are likely to contribute to our observed selectivity, the favorable nature of 2-aminopyridine as a nucleophile in C-N cross-couplings employing (**PAd2-DalPhos**)Ni(o-tol)Cl was noted in our previous studies. Furthermore, the apparent observed selectivity for **PAd2-DalPhos** in enabling N-arylation of the more acidic NH position was also noted previously in the chemoselective N-arylation of 5-aminoindole with 2-chloroquinoline, giving rise to the indole N-arylated product. Although it is unclear as to why **PAd2-DalPhos** selects generally for N-arylating at the more acidic NH position, and we are hesitant to make any definitive claims in this respect; one possibility could be that the off-cycle deprotonation occurs more readily with the more acidic NH nucleophiles, and the electrophilicity of (**PAd2-DalPhos**)Ni(Ar)X species intercepts formally anionic nucleophilic partners more readily than neutral NH partners.

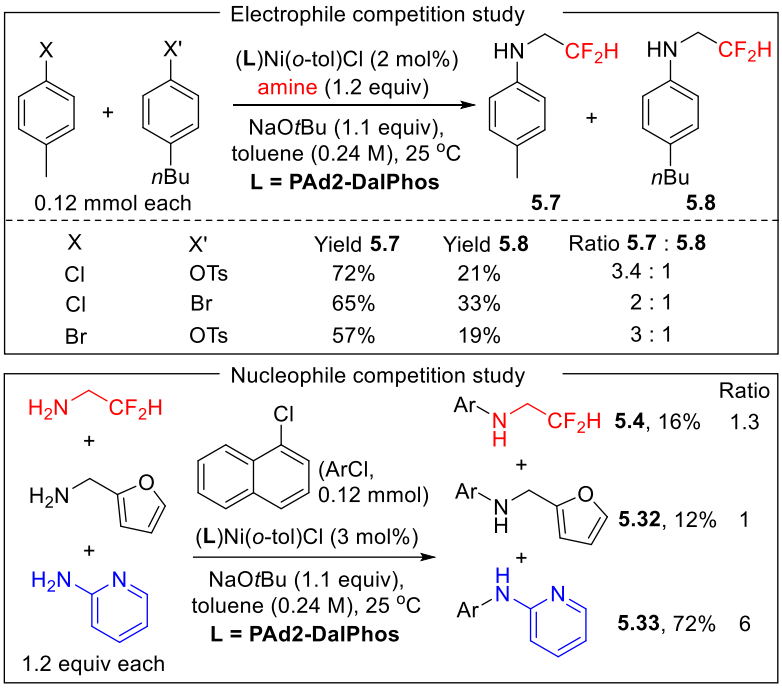


Figure 5.6 Electrophilic and nucleophilic competition experiments. Conversion to products determined on the basis of response-factor calibrated GC data using authentic material.

5.3.6 Summary

In summary, we have developed a mild Ni-catalyzed route toward the cross-coupling of β-fluoroalkylamines with a vast array of (hetero)aryl (pseudo)halides, including phenol derivatives for the first time. The transformations accommodate both linear and branched β-fluoroalkylamines, including enantio-retentive examples, and are enabled by use of the air-stable (**PAd2-DalPhos**)Ni(o-tol)Cl pre-catalyst in conjunction with either NaOtBu (25 ºC) or with DBU/NaOTf (110 ºC) for base-sensitive aryl (pseudo)halides. Competition experiments show a mild preference for the coupling of aryl chloride electrophiles versus aryl bromides, and the reactivity of more acidic NH nucleophiles is generally favored.

5.4 Experimental

5.4.1 General considerations

Unless otherwise indicated, all experimental procedures were conducted in a nitrogen-filled, inert atmosphere glovebox using oven-dried glassware and purified solvents, with the exception of the workup of catalytic reaction mixtures, which was conducted on the benchtop in air using unpurified solvents. Toluene was deoxygenated by sparging with nitrogen gas followed by passage through a double column solvent purification system packed with alumina and copper-Q5 reactant and storage over activated 4 Å molecular sieves. Solvents used within the glovebox were stored over activated 4 Å molecular sieves. (*p*-*n*Bu-C_6H_4)OTs,[47] (**PAd2-DalPhos**)NiCl(*o*-tol),[49] and (**DPPF**)NiCl(*o*-tol)[85] were prepared as described previously. All other commercial solvents, reagents, and materials were used as received. GC data were obtained on an instrument equipped with an SGE BP-5 column (30 m, 0.25 mm i.d.). Automated flash column chromatography was carried out using a normal-phase Biotage SNAP KP-Sil 10 g column cartridge. All ^{1}H NMR (500 and 300 MHz), ^{13}C NMR (125.8 and 75.4 MHz), ^{19}F NMR (470.6 MHz) and ^{31}P NMR (202.5 and 121.5 MHz) spectra were recorded at 300 K and were referenced to residual protio solvent peaks (^{1}H), deuterated solvent peaks (^{13}C), external 0.5% (CF_3)C_6H_5 in $CDCl_3$ at -63.7 ppm (^{19}F), or external 85% H_3PO_4 (^{31}P). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. All coupling constants (J) are reported in Hertz (Hz). Mass spectra were obtained using either APCI or ion trap (ESI) instruments operating in positive mode. Enantiopurity was assessed by use of chiral phase HPLC methods.

5.4.2 Procedure for the N-arylation of primary fluoroalkylamines with (hetero)aryl halides

Unless otherwise indicated in the text, solid (**PAd2-DalPhos**)NiCl(*o*-tol) or (**DPPF**)NiCl(*o*-tol) (1-5 mol%), NaO*t*Bu (1.1 equiv. or 2.3 equiv. when amine delivered as HCl salt), (hetero)aryl halide (0.48 mmol, 1.0 equiv.), fluoroalkylamine (1.2 equiv. or 3.0 equiv.) and toluene (0.24 M (hetero)aryl halide) were added to a screw-capped vial containing a magnetic stir bar. In the case of experiments conducted at lower catalyst loadings (<1 mol%), the pre-catalyst was delivered from stock solutions in toluene so that the final concentration of (hetero)aryl halide remained 0.24 M. The vial was sealed with a cap containing a PTFE septum, was removed from the glovebox and placed in a temperature-controlled aluminum heating block set at the specified temperature (25 ˚C or 65 ˚C) and was allowed to react under the influence of magnetic stirring for 18 h (unoptimized).

5.4.3 Procedure for the N-Arylation of fluoroalkylamines with base-sensitive (hetero)aryl halides

Unless otherwise indicated in the text, solid (**PAd2-DalPhos**)NiCl(*o*-tol) (5 mol%), NaOTf (2.0 equiv.), DBU (2.0 equiv.), (hetero)aryl halide (0.48 mmol, 1.0 equiv.), fluoroalkylamine (2.0 equiv.) and toluene (0.24 M (hetero)aryl halide) were added to a screw-capped vial containing a magnetic stir bar. Pre-catalyst was delivered from stock solutions in toluene so that the final concentration of (hetero)aryl halide remained 0.24 M. The vial was sealed with a cap containing a PTFE septum, was removed from the glovebox and placed in a temperature-controlled aluminum heating block set at the specified temperature (100 ˚C) and was allowed to react under the influence of magnetic stirring for 18 h (unoptimized).

5.4.4 Procedure for competition experiments

Unless otherwise indicated in the text, NaO*t*Bu (1.1 equiv.), (hetero)aryl halide(s) (0.12 mmol, 1.0 equiv.), and nucleophilic NH coupling partner(s) (1.2 equiv.) were added to a screw capped vial, followed by a magnetic stir bar. Pre-catalyst (**PAd2-DalPhos**)NiCl(*o*-tol) (2 or 3 mol%) was then delivered from a stock solution in toluene so that the final concentration of (hetero)aryl halide remained 0.24 M. The vial was then sealed with a cap containing a PTFE septum, removed from the glovebox, and placed in a temperature-controlled aluminum heating block set to 25 ˚C. The mixture was stirred at this temperature for 18 h (unoptimized), after which time either dodecane, hexadecane, or phenyldocecane (1.0 equiv.) was then added as an internal standard for calibration against authentic products in each case. Subsequently, an aliquot of the reaction mixture was filtered through a short Celite/silica plug, diluted with EtOAc (~1.5 mL), and subjected to GC analysis.

5.4.5 Procedure for the preparation of GC samples

Following *5.4.2* or *5.4.3* (0.12 mmol scale in (hetero)aryl halide), at room temperature the reaction mixture was diluted using ethyl acetate and was passed through a Kimwipe filter containing Celite and silica gel, with the eluent collected in a GC vial. Calibrated GC estimates are given on the basis of data obtained from authentic materials using either dodecane, phenyldodecane, or hexadecane as internal standards.

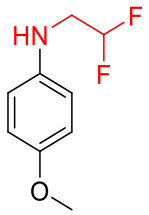
5.4.6 Purification of N-Aryl fluoroalkylamine products via flash chromatography.

Following *5.4.2* or *5.4.3*, the resultant mixture was cooled to room temperature if necessary before adsorption onto silica and subsequent elution through a silica/celite frit employing ethyl acetate as an eluent (~30-50 mL). The resulting solution was then dried *in vacuo* to afford a crude residue which was dissolved in a hexanes-ethyl acetate mixture before

being loaded onto either a silica-based flash column, or a 10 g normal-phase Biotage SNAP KP-Sil column cartridge. The product was then purified using a hexanes-ethyl acetate eluent mixture in each case. The relevant UV-active column fractions were combined and dried *in vacuo* to afford the target product in each case. The abbreviation CV is column volume.

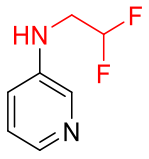
5.4.7 Characterization data for isolated N-(β-fluoroalkyl)anilines

N-(2,2-difluoroethyl)-4-methoxyaniline (**5.1**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 2 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-15% ethyl acetate in hexanes (12 CV) followed by 15% ethyl acetate in hexanes (4 CV) which afforded the title compound in an 86% isolated yield (77.6 mg, 0.413 mmol) as a brown oil. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 6.82-6.79 (m, 2H), 6.65-6.62 (m, 2H), 5.91 (tt, J = 56.2 Hz, 1H), 3.76 (s, 3H), 3.61 (br, 1H), 3.51-3.45 (m, 2H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -122.8. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 153.0, 140.8, 115.0, 114.7 (t, J = 241.8 Hz), 114.6, 55.7, 47.6 (t, J = 26.0 Hz). HRMS-ESI (*m*/*z*): Calc'd for $C_9H_{11}F_2NO$ $[M+H]^+$: 188.0881. Found: 188.0881. Data in agreement with literature.[S4]

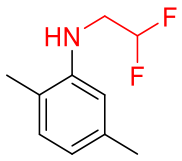
N-(2,2-difluoroethyl)pyridin-3-amine (**5.2**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 3 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 20% ethyl acetate in hexanes (4 CV), 20-70% ethyl acetate in hexanes (12 CV) followed by 70% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 75% isolated yield (57.2 mg, 0.360 mmol) as a brown oil. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.10-8.04 (m, 2H, overlapping Hs), 7.14-7.11 (m, 1H), 6.97-6.95 (m, 1H), 5.92 (tt, J = 55.8, 4.0 Hz, 1H), 3.98 (br, 1H), 3.60-3.52 (m, 2H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -122.7.

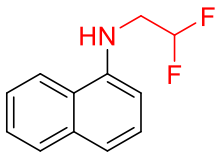
$^{13}C\{^{1}H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 142.9, 140.1, 136.2, 123.8, 119.0, 114.3 (t, J = 242.3 Hz), 46.0 (t, J = 26.0 Hz). HRMS-ESI (m/z): Calc'd for $C_7H_8F_2N_2$ $[M+H]^+$: 159.0728. Found: 159.0732. Data in agreement with literature.[81]

N-(2,2-difluoroethyl)-2,5-dimethylaniline (**5.3**)



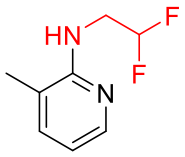
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 2 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (6 CV), 0-7% ethyl acetate in hexanes (10 CV) followed by 7% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 65% isolated yield (57.6 mg, 0.312 mmol) as a clear oil. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 6.97 (d, J = 7.5 Hz, 1H), 6.56 (d, J = 7.5 Hz, 1H), 6.47 (s, 1H), 5.95 (tt, J = 52.0, 4.3 Hz, 1H), 3.69 (br, 1H), 3.61-3.56 (m, 2H), 2.30 (s, 3H), 2.13 (s, 3H). $^{19}F\{^{1}H\}$ NMR (470.6 MHz, $CDCl_3$): δ -122.6. $^{13}C\{^{1}H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 144.6, 136.9, 130.4, 119.7, 118.9, 114.5 (t, J = 241.7 Hz), 110.8, 46.4 (t, J = 26.2 Hz), 21.5, 16.9. HRMS-ESI (m/z): Calc'd for $C_{10}H_{13}F_2N$ $[M+H]^+$: 186.1089. Found: 186.1088.

N-(2,2-difluoroethyl)naphthalen-1-amine (**5.4**)



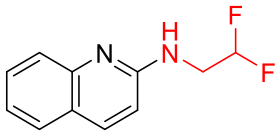
The title compound was synthesized from the corresponding aryl chloride on 4.8 mmol scale according to *5.4.2*, conducted at 25 °C in toluene using 0.5 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6***.** Purified by flash column chromatography on silica (25 g normal-phase Biotage SNAP KP-Sil column cartridge) using an eluent gradient of 100% hexanes (6 CV), 0-10% ethyl acetate in hexanes (12 CV) followed by 10% ethyl acetate in hexanes (4 CV) which afforded the title compound in a 90% isolated yield (892 mg, 4.30 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.84-7.81 (m, 2H, overlapping Hs), 7.50-7.47 (m, 2H, overlapping Hs), 7.38-7.33 (m, 2H, overlapping Hs), 6.69-6.67 (m, 1H), 6.08 (tt, J = 56.2, 4.3 Hz, 1H), 4.53 (br, 1H), 3.76-3.69 (m, 2H). $^{19}F\{^{1}H\}$ NMR (470.6 MHz, $CDCl_3$): δ -122.2. $^{13}C\{^{1}H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 142.0, 134.4, 128.7, 126.2, 126.0, 125.2, 123.7, 119.8, 119.0, 114.5 (t, J = 241.6 Hz), 104.9, 46.7 (t, J = 26.2 Hz). HRMS-ESI (m/z): Calc'd for $C_{12}H_{11}F_2N$ $[M+H]^+$: 208.0932. Found: 208.0933.

N-(2,2-difluoroethyl)-3-methylpyridin-2-amine (**5.5**)



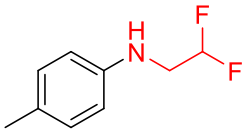
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 0.5 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-10% ethyl acetate in hexanes (12 CV) followed by 10% ethyl acetate in hexanes (4 CV) which afforded the title compound in a 38% isolated yield (31.0 mg, 0.182 mmol) as a clear oil. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.00-7.99 (m, 1H), 7.24 (m, 1H), 6.59 (dd, *J* = 7.1, 5.1 Hz, 1H), 6.02 (tt, *J* = 57.0, 4.4 Hz, 1H), 4.37 (br, 1H), 3.93-3.85 (m, 2H), 2.11 (s, 3H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -123.4. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 155.7, 145.3, 137.3, 116.8, 114.4 (t, *J* = 240.9 Hz), 113.9, 43.8 (t, *J* = 26.9 Hz), 16.7. HRMS-ESI (*m*/*z*): Calc'd for $C_8H_{10}F_2N_2$ $[M+H]^+$: 173.0885. Found: 173.0889.

N-(2,2-difluoroethyl)quinolin-2-amine (**5.6**)



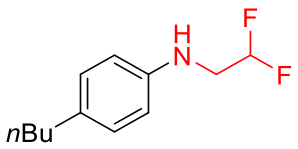
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 3 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-10% ethyl acetate in hexanes (12 CV) followed by 10% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 71% isolated yield (70.5 mg, 0.341 mmol) as a brown oil. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.9 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.62 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.59-7.55 (m, 1H), 7.29-7.27 (m, 1H), 6.68 (d, *J* = 8.9 Hz, 1H), 6.11 (tt, *J* = 56.9, 4.4 Hz, 1H), 5.13 (br, 1H), 4.01-3.92 (m, 2H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -123.1. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 155.5, 146.8, 138.0, 129.9, 127.5, 126.1, 123.6, 123.0, 114.2 (t, *J* = 241.0 Hz), 111.6, 43.7 (t, *J* = 27.0 Hz). HRMS-ESI (*m*/*z*): Calc'd for $C_{11}H_{10}F_2N_2$ $[M+H]^+$: 209.0885. Found: 209.0882.

N-(2,2-difluoroethyl)-4-methylaniline (**5.7**)



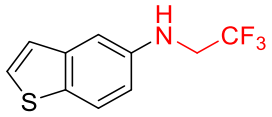
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 2 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6***.** Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-5% ethyl acetate in hexanes (12 CV) followed by 5% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 66% isolated yield (54.2 mg, 0.317 mmol) as a clear oil. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.03-7.02 (m, 2H), 6.62 (d, J = 8.4 Hz, 2H), 5.93 (tt, J = 56.0, 4.3 Hz, 1H), 4.16 (br, 1H), 3.51 (td, J = 14.3, 4.3 Hz, 2H), 2.26 (s, 3H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -122.6. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 144.1, 130.0, 128.4, 114.4 (t, J = 242.2 Hz), 113.5, 47.0 (t, J = 26.2 Hz), 20.3. HRMS-ESI (*m*/*z*): Calc'd for $C_9H_{11}F_2N$ $[M+H]^+$: 172.0932. Found: 172.0935.

4-butyl-N-(2,2-difluoroethyl)aniline (**5.8**)



The title compound was synthesized from the corresponding aryl bromide (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 2 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-5% ethyl acetate in hexanes (12 CV) followed by 5% ethyl acetate in hexanes (6 CV) which afforded the title compound in an 84% isolated yield (86.4 mg, 0.403 mmol) as a yellow oil. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.04-7.03 (m, 2H), 6.64-6.62 (m, 2H), 5.93 (tt, J = 56.2, 4.3 Hz, 1H), 4.19 (br, 1H), 3.51 (td, J = 14.4, 4.3 Hz, 2H), 2.52 (t, J = 7.8 Hz, 2H), 1.58-1.52 (m, 2H), 1.38-1.31 (m, 2H), 0.092 (t, J = 7.4 Hz, 3H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -122.5. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 144.1, 133.7, 129.3, 114.5 (t, J = 241.8 Hz), 113.5, 47.0 (t, J = 26.5 Hz), 34.7, 33.9, 22.3, 13.9. HRMS-ESI (*m*/*z*): Calc'd for $C_{12}H_{17}F_2N$ $[M+H]^+$: 214.1402. Found: 214.1404.

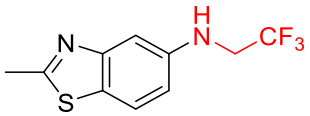
N-(2,2,2-trifluoroethyl)benzo[b]thiophen-5-amine (**5.9**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 3 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (6 CV), 0-10% ethyl acetate in hexanes (10 CV) followed by 10% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 92% isolated yield (102 mg, 0.442 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.67 (d, J = 8.7 Hz, 1H), 7.41 (d, J = 5.4 Hz, 1H), 7.20-7.19 (m, 1H), 7.09 (d, J = 2.3 Hz, 1H), 6.78 (dd, J = 8.7, 2.3, 1H), 3.96 (br, 1H), 3.86-3.79 (m, 2H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -72.1. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 143.7, 140.9, 130.9, 127.4, 125.1 (q, J

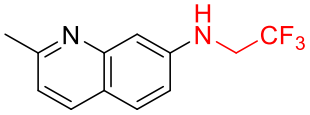
= 280.5 Hz), 123.3, 123.1, 113.7, 105.7, 46.7 (q, J = 33.4 Hz). HRMS-ESI (m/z): Calc'd for $C_{10}H_8F_3NS$ $[M+H]^+$: 232.0402. Found: 232.0406.

2-methyl-N-(2,2,2-trifluoroethyl)benzo[d]thiazol-5-amine (**5.10**)



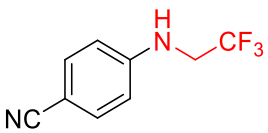
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 3 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 5% ethyl acetate in hexanes (4 CV), 5-30% ethyl acetate in hexanes (12 CV) followed by 30% ethyl acetate in hexanes (6 CV) which afforded the title compound in an 85% isolated yield (101 mg, 0.408 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.59 (d, J = 8.6 Hz, 1H), 7.25 (d, J = 2.3 Hz, 1H), 6.76 (dd, J = 6.2, 2.4, 1H), 4.07 (br, 1H), 3.86-3.79 (m, 2H), 2.79 (s, 3H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -72.1. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 168.1, 154.9, 145.3, 125.9, 125.0 (q, J = 280.4 Hz), 121.8, 113.2, 105.1, 46.4 (q, J = 33.5 Hz), 20.2. HRMS-ESI (m/z): Calc'd for $C_{10}H_9F_3N_2S$ $[M+H]^+$: 247.0511. Found: 247.0507. Data in agreement with literature.[81]

2-methyl-N-(2,2,2-trifluoroethyl)quinolin-7-amine (**5.11**)



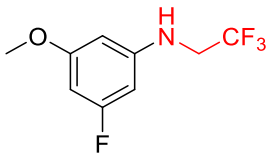
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 2 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 15% ethyl acetate in hexanes (6 CV), 15-60% ethyl acetate in hexanes (12 CV) followed by 60% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 97% isolated yield (112 mg, 0.466 mmol) as an off-white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.87 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.14-7.13 (m, 1H), 7.06 (d, J = 8.3 Hz, 1H), 6.90 (dd, J = 6.3, 2.4 Hz, 1H), 4.31 (br, 1H), 3.93-3.87 (m, 2H), 2.68 (s, 3H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -72.0. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 159.5, 149.6, 147.1, 135.7, 128.6, 124.9 (q, J = 280.0 Hz), 120.7, 119.0, 116.9, 106.1, 45.6 (q, J = 33.9), 25.3. HRMS-ESI (m/z): Calc'd for $C_{12}H_{11}F_3N_2$ $[M+H]^+$: 241.0947. Found: 241.0947.

4-((2,2,2-trifluoroethyl)amino)benzonitrile (**5.12**)



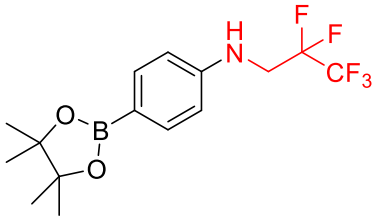
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 2 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6***.** Purified by flash column chromatography on silica using an eluent gradient of 10% ethyl acetate in hexanes (4 CV), 10-30% ethyl acetate in hexanes (10 CV) followed by 30% ethyl acetate in hexanes (4 CV) which afforded the title compound in an 88% isolated yield (84.1 mg, 0.422 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.50-7.47 (m, 2H), 6.71-6.68 (m, 2H), 4.45 (br, 1H), 3.83-3.81 (m, 2H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -72.1. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 149.5, 133.8, 124.6 (q, J = 280.3 Hz), 119.6, 112.8, 101.4, 45.1 (q, J = 34.4 Hz). HRMS-ESI (*m*/*z*): Calc'd for $C_9H_7F_3N_2$ [M+Na]$^{+}$: 223.0454. Found: 223.0452.

3-fluoro-5-methoxy-N-(2,2,2-trifluoroethyl)aniline (**5.13**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 2 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-10% ethyl acetate in hexanes (10 CV) followed by 10% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 68% isolated yield (72.9 mg, 0.326 mmol) as a brown oil. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 6.11-6.09 (m, 1H), 6.03-6.00 (m, 2H, overlapping Hs), 3.93 (br, 1H), 3.76-3.70 (m, 5H, overlapping Hs). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -72.3, -111.1. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 164.7 (d, J = 241.9 Hz), 161.8 (d, J = 13.7 Hz), 148.3 (d, J = 13.5 Hz), 124.7 (q, J = 280.1 Hz), 95.1, 93.2 (d, J = 26.2 Hz), 92.2 (d, J = 25.8 Hz), 55.4, 45.9 (q, J = 34.0 Hz). HRMS-ESI (*m*/*z*): Calc'd for $C_9H_9F_4NO$ [M-H]$^{-}$: 222.0548. Found: 222.0541.

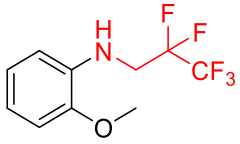
N-(2,2,3,3,3-pentafluoropropyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**5.14**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 1 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6***.** Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (6 CV), 0-20% ethyl acetate in hexanes (12 CV) followed by 20% ethyl acetate in hexanes (6 CV) which afforded the title compound in an 82% isolated yield (138 mg, 0.394 mmol) as a brown solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.67 (d, J = 8.5 Hz, 2H), 6.66 (d, J = 8.5 Hz, 2H), 4.04 (br, 1H), 3.88-3.81 (m, 2H), 1.32 (s, 12H). ^{19}F{^{1}H}

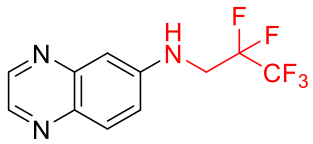
NMR (470.6 MHz, $CDCl_3$): δ -83.9, -121.8. $^{13}C\{^1H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 148.8, 136.4, 120.3-111.6 (m, overlapping Cs), 112.2, 83.4, 43.6 (t, J = 24.1 Hz), 24.8. *Quaternary carbon undiscernible by $^{13}C\{^1H\}$ UDEFT NMR at solution concentration.* HRMS-ESI (*m*/*z*): Calc'd for $C_{15}H_{19}BF_5NO_2$ $[M+H]^+$: 352.1502. Found: 352.1513.

2-methoxy-N-(2,2,3,3,3-pentafluoropropyl)aniline (**5.15**)



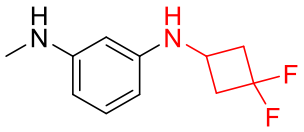
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 3 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6***.** Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-5% ethyl acetate in hexanes (12 CV) followed by 5% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 68% isolated yield (83.1 mg, 0.326 mmol) as a clear oil. ^1H NMR (500.1 MHz, $CDCl_3$): δ 6.91-6.88 (m, 1H), 6.83-6.81 (m, 1H), 6.79-6.75 (m, 1H), 6.69 (d, J = 7.8 Hz, 1H), 3.87 (s, 3H), 3.83 (t, J = 14.9 Hz, 2H). $^{19}F\{^1H\}$ NMR (470.6 MHz, $CDCl_3$): δ -84.0, -121.8. $^{13}C\{^1H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 147.0, 136.4, 130.9-111.8 (m, overlapping Cs), 121.2, 118.3, 110.2, 110.0, 55.5, 44.0 (t, J = 24.0). HRMS-APCI (*m*/*z*): Calc'd for $C_{10}H_{10}F_5NO$ $[M+H]^+$: 256.0755. Found: 256.0758.

N-(2,2,3,3,3-pentafluoropropyl)quinoxalin-6-amine (**5.16**)



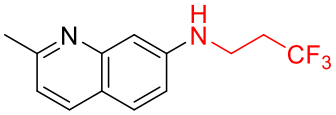
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 3 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6***.** Purified by flash column chromatography on silica using an eluent gradient of 20% ethyl acetate in hexanes (4 CV), 20-60% ethyl acetate in hexanes (10 CV) followed by 60% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 94% isolated yield (125 mg, 0.451 mmol) as a bright yellow solid. ^1H NMR (500.1 MHz, $CDCl_3$): δ 8.69 (d, J = 1.7 Hz, 1H), 8.59 (d, J = 1.7 Hz, 1H), 7.92 (d, J = 9.1 Hz, 1H), 7.21 (dd, J = 6.4, 2.7 Hz, 1H), 7.14 (d, J = 2.5 Hz, 1H), 4.48 (br, 1H), 4.03-3.95 (m, 2H). $^{19}F\{^1H\}$ NMR (470.6 MHz, $CDCl_3$): δ -83.9, -121.6. $^{13}C\{^1H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 147.4, 145.3, 144.9, 141.6, 138.5, 130.6, 122.3-111.8 (m, overlapping Cs), 121.5, 105.4, 43.7 (t, J = 24.0 Hz). HRMS-ESI (*m*/*z*): Calc'd for $C_{11}H_8F_5N_3$ $[M+H]^+$: 278.0711. Found: 278.0710.

N^1-(3,3-difluorocyclobutyl)-N^3-methylbenzene-1,3-diamine (**5.17**)



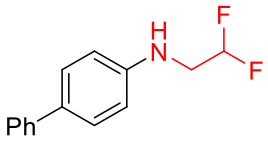
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 3 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6***.** Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-30% ethyl acetate in hexanes (12 CV) followed by 30% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 42% isolated yield (43.1 mg, 0.202 mmol) as a brown oil. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.03-7.00 (m, 1H), 6.11-6.09 (m, 1H), 5.97-5.95 (m, 1H), 5.83-5.82 (m, 1H), 3.88-3.75 (m, 3H, overlapping Hs), 3.07- 3.00 (m, 2H), 2.82 (s, 3H), 2.47-2.37 (m, 2H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -83.3 (d, J = 197.3 Hz), -95.6 (d, J = 197.3 Hz). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 150.4, 147.6, 130.1, 119.1 (dd, J = 282.8, 271.9 Hz), 103.7, 103.1, 97.3, 43.7-43.3 (m), 38.2 (dd, J = 15.9, 7.3 Hz), 30.8. HRMS-ESI (*m/z*): Calc'd for $C_{11}H_{14}F_2N_2$ $[M+H]^+$: 213.1198. Found: 213.1191.

2-methyl-N-(3,3,3-trifluoropropyl)quinolin-7-amine (**5.18**)



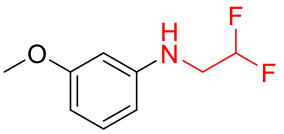
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 3 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6***.** Purified by flash column chromatography on silica using an eluent gradient of 15% ethyl acetate in hexanes (4 CV), 15-80% ethyl acetate in hexanes (12 CV) followed by 80% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 74% isolated yield (89.8 mg, 0.355 mmol) as a yellow solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.87 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 8.7 Hz, 1H), 7.04-7.02 (m, 2H, overlapping Hs), 6.83 (dd, J = 8.8, 2.4 Hz, 1H), 4.22 (br, 1H), 3.61-3.57 (m, 2H), 2.69 (s, 3H), 2.55-2.46 (m, 2H). ^{19}F NMR (470.6 MHz, $CDCl_3$): δ -64.9 (t, J = 10.8 Hz). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 159.1, 149.6, 148.0, 136.0, 128.6, 126.5 (q, J = 276.9 Hz), 120.3, 118.4, 117.6, 104.5, 36.8 (m), 33.1 (q, J = 27.6 Hz), 25.1. HRMS-ESI (*m/z*): Calc'd for $C_{13}H_{13}F_3N_2$ $[M+H]^+$: 255.1104. Found: 255.1115.

N-(2,2-difluoroethyl)-[1,1'-biphenyl]-4-amine (**5.19**)



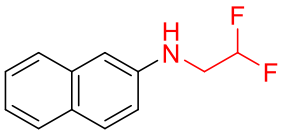
The title compound was synthesized from the corresponding aryl triflate (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 3 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6***.** Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (6 CV), 0-10% ethyl acetate in hexanes (12 CV) followed by 10% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 62% isolated yield (69.2 mg, 0.298 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.54-7.53 (m, 2H), 7.50-7.47 (m, 2H), 7.42-7.39 (m, 2H), 7.30-7.27 (m, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.99 (tt, *J* = 56.0, 4.3 Hz, 1H), 4.88 (br, 1H), 3.60 (td, *J* = 14.3, 4.3 Hz, 2H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -122.4. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 145.3, 140.8, 132.5, 128.7, 128.2, 126.5, 126.4, 114.2 (t, *J* = 242.2 Hz), 114.0, 46.9 (t, *J* = 26.5 Hz). (HRMS-APCI (*m*/*z*): Calc'd for $C_{14}H_{13}F_2N$ $[M+H]^+$: 234.1089. Found: 234.1088.

N-(2,2-difluoroethyl)-3-methoxyaniline (**5.20**)



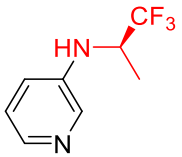
The title compound was synthesized from the corresponding aryl tosylate (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6***.** Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (6 CV), 0-15% ethyl acetate in hexanes (12 CV) followed by 15% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 72% isolated yield (64.6 mg, 0.346 mmol) as a clear oil. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.12 (t, *J* = 8.1 Hz, 1H), 6.38-6.36 (m, 1H), 6.31-6.29 (m, 1H), 6.25-6.24 (m, 1H), 5.93 (tt, *J* = 56.1, 4.3 Hz, 1H), 4.22 (br, 1H), 3.78 (s, 3H), 3.53 (td, *J* = 14.4, 4.3 Hz, 2H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -122.6. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 160.9, 147.8, 130.3, 114.3 (t, *J* = 241.9 Hz), 106.3, 104.1, 99.6, 55.1, 46.6 (t, *J* = 26.3 Hz). HRMS-APCI (*m*/*z*): Calc'd for $C_9H_{11}F_2NO$ $[M+H]^+$: 188.0881. Found: 188.0886.

N-(2,2-difluoroethyl)naphthalen-2-amine (**5.21**)



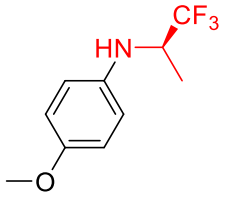
he title compound was synthesized from the corresponding aryl tosylate (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 3 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6***.** Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (6 CV), 0-15% ethyl acetate in hexanes (12 CV) followed by 15% ethyl acetate in hexanes (6 CV) which afforded the title compound in an 85% isolated yield (84.3 mg, 0.408 mmol) as a yellow oil. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.71-7.64 (m, 3H, overlapping Hs), 7.42-7.38 (m, 1H), 7.28-7.25 (m, 1H), 6.96-6.94 (m, 2H, overlapping Hs), 6.03 (tt, *J* = 56.0, 4.3 Hz, 1H), 4.62 (br, 1H), 3.66 (td, *J* = 14.3, 4.3 Hz, 2H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -122.4. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 144.3, 134.9, 129.4, 128.1, 127.6, 126.6, 126.1, 122.7, 117.7, 114.4 (t, *J* = 242.0 Hz), 105.2, 46.5 (t, *J* = 26.4 Hz). HRMS-ESI (*m*/*z*): Calc'd for $C_{12}H_{11}F_2N$ $[M+H]^+$: 208.0932. Found: 208.0924.

(R)-N-(1,1,1-trifluoropropan-2-yl)pyridin-3-amine (**5.22**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 20% ethyl acetate in hexanes (4 CV), 20-70% ethyl acetate in hexanes (12 CV) followed by 70% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 99% isolated yield (90.2 mg, 0.475 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.16-8.03 (m, 2H, overlapping Hs), 7.16 (br, 1H), 7.01-7.00 (m, 1H), 4.05-3.97 (m, 2H, overlapping Hs), 1.44 (d, J = 6.5 Hz, 3H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -77.3. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 142.5, 139.2, 135.9, 126.0 (q, J = 283.2 Hz), 124.0, 119.7, 51.1 (q, J = 30.9 Hz), 15.0. HRMS-ESI (*m/z*): Calc'd for $C_8H_9F_3N_2$ $[M+H]^+$: 191.0791. Found: 191.0797. The ratio of enantiomers was assessed by chiral phase HPLC using a CHIRALPAK AD-H column, eluting with 10% IPA in hexanes. No signal at the retention time for the minor enantiomer was observed in the HPLC trace of the product obtained from the reaction with enantioenriched amine. HPLC retention times: (*R*)-**5.22**: 7.5 minutes; (*S*)-**5.22**: 6.7 minutes. Data in agreement with literature.[81]

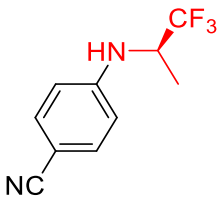
(R)-4-methoxy-N-(1,1,1-trifluoropropan-2-yl)aniline (**5.23**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-10% ethyl acetate in hexanes (12 CV) followed by 10% ethyl acetate in hexanes (6 CV) which afforded the title compound in an 88% isolated yield (92.1 mg, 0.422 mmol) as a clear oil. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 6.80-6.78 (m, 2H), 6.67-6.65 (m, 2H), 3.93-3.87 (m, 1H), 3.75 (s, 3H), 1.38 (d, J = 6.8 Hz, 3H). *NH signal undiscernible by ^{1}H NMR at solution concentration.* ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -77.2. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 153.4, 139.5, 126.3 (q, J = 283.3 Hz), 115.7, 114.9, 55.7, 52.9 (q, J = 28.8 Hz), 15.0. HRMS-ESI (*m/z*): Calc'd for $C_{10}H_{12}F_3NO$ $[M+H]^+$: 220.0944. Found: 220.0951. The ratio of enantiomers was assessed by chiral phase HPLC using an ASTEC Cellulose DMP column, eluting with a mixture of 0.1% cyclohexylamine, 10% IPA, and 90% hexanes. No signal at the retention time for the minor enantiomer was observed in the HPLC trace of the product obtained from the reaction with

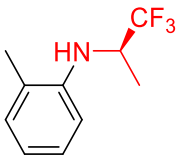
enantioenriched amine. HPLC retention times: (*R*)-**5.23**: 8.8 minutes; (*S*)-**5.23**: 12.8 minutes. Data in agreement with literature.[81]

(R)-4-((1,1,1-trifluoropropan-2-yl)amino)benzonitrile (**5.24**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.2*, conducted at 25 °C in toluene using 3 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-20% ethyl acetate in hexanes (12 CV) followed by 20% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 73% isolated yield (75.4 mg, 0.350 mmol) as a clear oil. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.48-7.45 (m, 2H), 6.66 (d, J = 8.8 Hz, 2H), 4.09 (br, 2H, overlapping Hs), 1.44 (d, J = 5.4 Hz, 3H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -77.3. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 149.2, 133.8, 125.7 (q, J = 283.0), 119.7, 113.0, 101.0, 50.5 (q, J = 31.2 Hz), 15.0. HRMS-ESI (*m*/*z*): Calc'd for $C_{10}H_9F_3N_2$ $[M+Na]^+$: 237.0610. Found: 237.0615. The ratio of enantiomers was assessed by chiral phase HPLC using an ASTEC Cellulose DMP column, eluting with 10% IPA in hexanes. No signal at the retention time for the minor enantiomer was observed in the HPLC trace of the product obtained from the reaction with enantioenriched amine. HPLC retention times: (*R*)-**5.24**: 12.1 minutes; (*S*)-**5.24**: 22.8 minutes. Data in agreement with literature.[81]

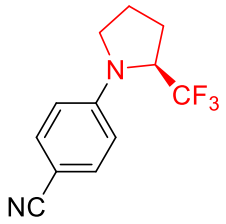
(R)-2-methyl-N-(1,1,1-trifluoropropan-2-yl)aniline (**5.25**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.2*, conducted at 65 °C in toluene using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6*. Purified by flash column chromatography on silica using an eluent of 100% hexanes (16 CV) which afforded the title compound in a 19% isolated yield (18.5 mg, 0.091 mmol) as a clear oil. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.15-7.12 (m, 1H), 7.09-7.08 (m, 1H), 6.74-6.70 (m, 2H, overlapping Hs), 4.11-4.06 (m, 1H), 2.18 (s, 3H), 1.43 (d, J = 6.8 Hz, 3H). *NH signal undiscernible by ^{1}H NMR at solution concentration.* ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -77.4. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 143.9, 130.6, 127.2, 126.3 (q, J = 282.8), 122.4, 118.5, 110.9, 51.2 (q, J = 30.4 Hz), 17.4, 15.5. HRMS-APCI (*m*/*z*): Calc'd for $C_{10}H_{12}F_3N$ $[M+H]^+$: 204.0995. Found: 204.0995. We were unable, under a range of HPLC conditions, to obtain sufficient resolution of the racemate so

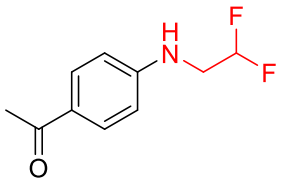
as to enable unequivocal determination of enantioretention when using enantioenriched 1,1,1-trifluoro-2-propanamine. Data in agreement with literature.[81]

(S)-1-(4-methoxyphenyl)-2-(trifluoromethyl)pyrrolidine (**5.26**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.2*, conducted at 65 °C in toluene using 5 mol% (**DPPF**)NiCl(*o*-tol), and purified according to *5.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-20% ethyl acetate in hexanes (12 CV) followed by 20% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 96% isolated yield (111 mg, 0.461 mmol) as a clear oil. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.52-7.50 (m, 2H), 6.75 (d, J = 8.9 Hz, 2H), 4.33-4.27 (m, 1H), 3.68-3.64 (m, 1H), 3.33-3.28 (m, 1H), 2.32-2.22 (m, 2H, overlapping Hs), 2.15-2.08 (m, 2H, overlapping Hs). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -73.4. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 150.0, 133.4, 126.3 (q, J = 284.8), 120.0, 113.1, 100.1, 59.5 (q, J = 30.9 Hz), 49.4, 26.7, 23.0. HRMS-ESI (*m*/*z*): Calc'd for $C_{12}H_{11}F_3N_2$ [M+Na]$^{+}$: 263.0767. Found: 263.0761. The ratio of enantiomers was assessed by chiral phase HPLC using an ASTEC Cellulose DMP column, eluting with a mixture of 0.1% cyclohexylamine, 10% IPA, and 89.9% hexanes. No signal at the retention time for the minor enantiomer was observed in the HPLC trace of the product obtained from the reaction with enantioenriched amine. HPLC retention times: (*S*)-**5.26**: 11.0 minutes; (*R*)-**5.26**: 12.5 minutes. Data in agreement with literature.[81]

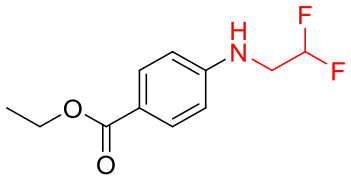
1-(4-((2,2-difluoroethyl)amino)phenyl)ethan-1-one (**5.27**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.3*, conducted at 100 °C in toluene using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-20% ethyl acetate in hexanes (12 CV) followed by 20% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 96% isolated yield (91.5 mg, 0.461 mmol) as a clear oil. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.87-7.84 (m, 2H), 6.66-6.63 (m, 2H), 5.93 (tt, J = 55.8, 4.0 Hz, 1H), 3.62 (td, J = 14.5, 4.0 Hz, 2H), 2.51 (s, 3H). *NH signal undiscernible by ^{1}H NMR at solution concentration.* ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -122.6. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 196.3, 150.8, 130.8,

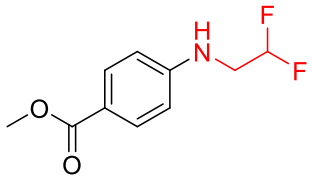
128.1, 114.0 (t, J = 242.5 Hz), 111.8, 45.7 (t, J = 26.2 Hz), 26.0. HRMS-APCI (*m/z*): Calc'd for $C_{10}H_{11}F_2NO$ $[M+H]^+$: 200.0881. Found: 200.0875.

Ethyl 4-((2,2-difluoroethyl)amino)benzoate (**5.28**)



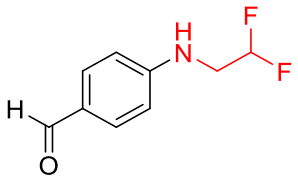
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.3*, conducted at 100 °C in toluene using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-25% ethyl acetate in hexanes (12 CV) followed by 25% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 59% isolated yield (65.3 mg, 0.283 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.91-7.89 (m, 2H), 6.64-6.62 (m, 2H), 5.92 (tt, J = 55.8, 4.1 Hz, 1H), 4.34-4.30 (m, 3H, overlapping Hs), 3.60 (td, J = 14.5, 4.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -122.6. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 166.6, 150.6, 131.6, 120.4, 114.1 (t, J = 242.3 Hz), 111.8, 60.4, 45.8 (t, J = 26.2 Hz), 14.4. HRMS-APCI (*m/z*): Calc'd for $C_{11}H_{13}F_2NO_2$ $[M+H]^+$: 230.0987. Found: 230.0989.

Methyl 4-((2,2-difluoroethyl)amino)benzoate (**5.29**)



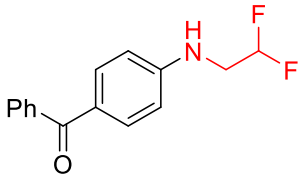
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.3*, conducted at 100 °C in toluene using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6***.** Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-25% ethyl acetate in hexanes (12 CV) followed by 25% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 93% isolated yield (95.9 mg, 0.446 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.89 (d, J = 8.8 Hz, 2H), 6.63 (d, J = 8.8 Hz, 2H), 5.92 (tt, J = 55.8, 4.0 Hz, 1H), 4.05 (br, 1H), 3.86 (s, 3H), 3.60 (td, J = 14.5, 4.1 Hz, 2H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -122.6. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 167.0, 150.6, 131.6, 120.0, 114.1 (t, J = 242.4), 111.8, 51.6, 45.8 (t, J = 26.2 Hz). HRMS-APCI (*m/z*): Calc'd for $C_{10}H_{11}F_2NO_2$ $[M+H]^+$: 216.0831. Found: 216.0834.

4-((2,2-difluoroethyl)amino)benzaldehyde (**5.30**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.3*, conducted at 100 °C in toluene using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-30% ethyl acetate in hexanes (12 CV) followed by 30% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 91% isolated yield (81.1 mg, 0.437 mmol) as a yellow oil. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 9.77 (s, 1H), 7.74 (d, J = 8.7 Hz, 2H), 6.71 (d, J = 8.6 Hz, 2H), 5.94 (tt, J = 55.6, 3.9 Hz, 1H), 4.53 (br, 1H), 3.68-3.60 (m, 2H). ^{19}F {1H} NMR (470.6 MHz, $CDCl_3$): δ -122.5. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 190.3, 152.0, 132.3, 127.9, 113.9 (t, J = 242.5 Hz), 112.2, 45.6 (t, J = 26.2 Hz). HRMS-ESI (*m*/*z*): Calc'd for $C_9H_9F_2NO$ $[M+Na]^+$: 208.0544. Found: 208.0548.

(4-((2,2-difluoroethyl)amino)phenyl)(phenyl)methanone (**5.31**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *5.4.3*, conducted at 100 °C in toluene using 5 mol% (**PAd2-DalPhos**)NiCl(*o*-tol), and purified according to *5.4.6*. Purified by flash column chromatography on silica using an eluent gradient of 100% hexanes (4 CV), 0-25% ethyl acetate in hexanes (12 CV) followed by 25% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 96% isolated yield (121 mg, 0.461 mmol) as a yellow solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.77-7.76 (m, 2H), 7.73-7.71 (m, 2H), 7.56-7.52 (m, 1H), 7.47-7.44 (m, 2H), 6.68-6.66 (m, 2H), 5.95 (tt, J = 55.7, 4.0 Hz, 1H), 4.08 (br, 1H), 3.63 (td, J = 14.5, 4.0 Hz, 2H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -122.5. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 150.7, 138.8, 132.9, 131.5, 129.5, 128.1, 127.6, 114.1 (t, J = 242.5), 111.7, 45.7 (t, J = 26.1 Hz). HRMS-APCI (*m*/*z*): Calc'd for $C_{15}H_{13}F_2NO$ $[M+H]^+$: 262.1038. Found: 262.1046.

6. Mapping 'Dual-Base'-Enabled Ni-Catalyzed Aryl Amidations: Application in the Synthesis of 4-Quinolones

6.1 Research overview and contribution report

This author wishes to clarify his contributions to the research described in Chapter 6 of this Thesis document. This chapter describes the Ni-catalyzed C-N cross-coupling of amides with 2'-(pseudo)halide-substituted acetophenones, with scope that exceeds that established by use of Pd or Cu-based catalysts, and which is made possible by use of a new pre-catalyst supported by **PAd2-DalPhos** in combination with the DBU/NaTFA dual-base system; subsequent exposure to Camps cyclization conditions affords 4-quinolones that are sought-after for their biological properties. Also reported is our stoichiometric and experimental examination of the elementary steps that comprise the putative Ni(0/II) C-N cross-coupling cycle, including assessing the potential involvement of Ni(I) species, and a focus on surveying the role of the dual-base system. The results of this stoichiometric reactivity study provided the rationale for our successful demonstration of unprecedented room-temperature amide cross-couplings.

My contributions to the study included optimizing catalytic conditions for the N-arylation of amides with 2'-(pseudo)halide-substituted acetophenones as well as optimizing conditions for the subsequent one-pot Camps Cyclization event, synthesizing and characterizing relevant organo-Ni species, and performing stoichiometric and mechanistic probing experiments to map the catalytic cycle (including identifying the role of both DBU and NaTFA in enabling productive catalysis). Dr. Arun Yadav was responsible for conceptual input in the early stages of the project, while Dr. Mark Stradiotto helped in mentoring myself as well as providing advice throughout the project. Dr. Travis Lundrigan

also helped in identifying optimal catalytic conditions for the amide cross-coupling, as well in isolating the overwhelming majority of the N-aryl amide products. Josh W. M. MacMillan synthesized (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl for the first time. Kathy N. Robertson was responsible for carrying out X-ray diffraction experiments to determine the molecular connectivity of the various organo-Ni species presented herein.

Reference: McGuire, R. T.; Lundrigan, T.; MacMillan, J. W. M.; Robertson, K. N.; Yadav, A. A.; Stradiotto, M. Mapping 'Dual-Base'-Enabled Ni-Catalyzed Aryl Amidations: Application in the Synthesis of 4-Quinolones. *Submitted to Nat. Catal. on Sept. 27th, 2021.* NatCatal-21096161.

6.2 Introduction

The 4-quinolone core structure is found contained within a variety of APIs including ciprofloxacin (antibiotic) and ivacaftor (cystic fibrosis), and methods for the construction of such motifs are of undeniable utility.[86] The Buchwald[87] and Huang[88] groups have reported on the syntheses of 4-Quinolones starting from 2'-X-substituted acetophenones (X = Br, I) and performing Cu and Pd based catalytic amidations respectively, followed by a subsequent Camps Cyclization in each case (Figure 6.1a). Despite these important contributions, the syntheses of 4-Quinolones from corresponding 2'-(pseudo)halide-substituted acetophenones, where the (pseudo)halide is a chloride or phenol derivative, remains an unsolved challenge. Furthermore, the Cu and Pd-based approaches rely on the use of insoluble inorganic bases (eg. K_2CO_3 or Cs_2CO_3), rendering the scalability of these processes as questionable given that homogeneity issues can quickly arise due to unequal particle distribution in larger reaction vessels.[84] Indeed, with the increasing uptake and utilization of High-Throughput-Experimentation (HTE) techniques in screening reactions for method development, the

utilization of soluble, liquid organic bases makes for markedly increased efficiency in this regard, especially with regard to reaction homogeneity and ease of liquid dispensing in HTE setup.[83] To address these outlined limitations, we sought to deploy Ni-DalPhos catalysts in conjunction with the dual-base system, comprised of DBU/NaTFA, in enabling these difficult transformations (Figure 6.1a).

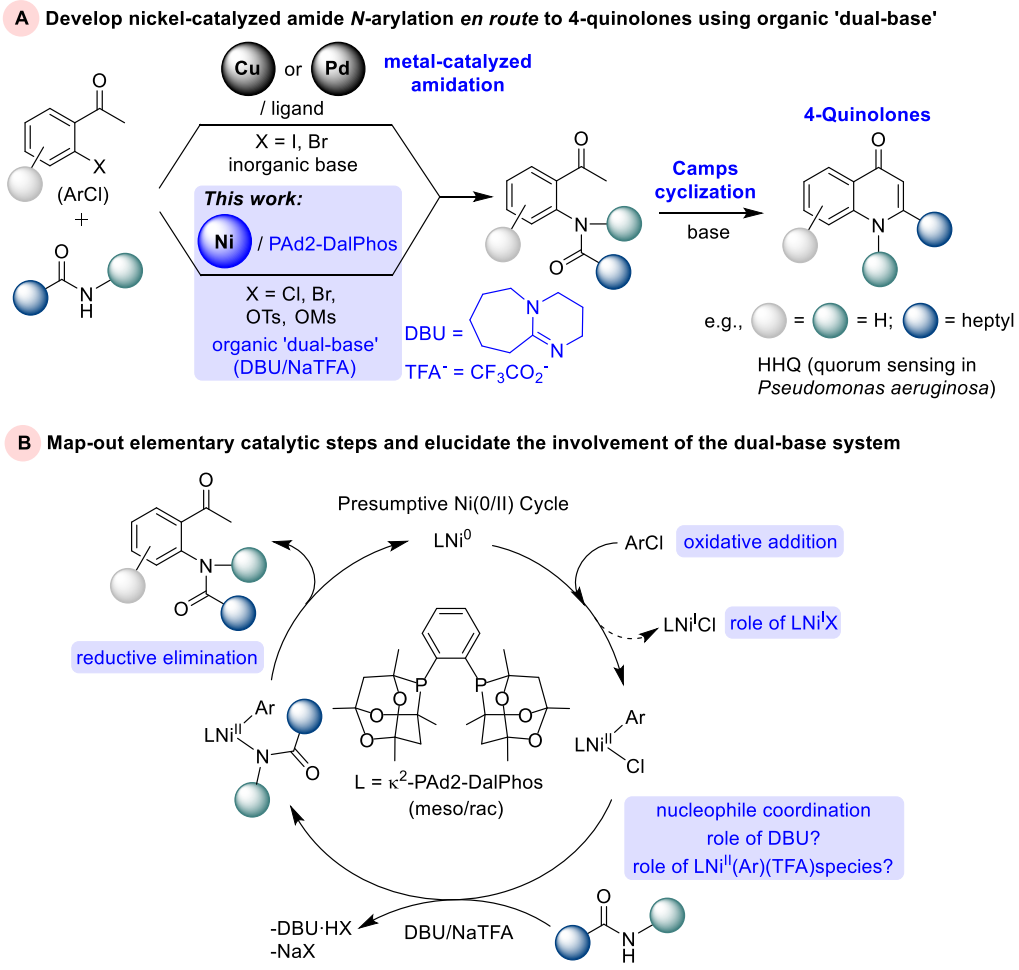


Figure 6.1 Summary of work conducted on the metal-catalyzed N-arylation of amides with 2'-halide-substituted acetophenones leading to 4-quinolones, including this newly reported Ni-catalyzed approach enabled by the mechanistically distinct dual-base mediated approach.

In addition to addressing challenges within the preparation of bio-relevant 4-quinolones, it was speculated that this would be a good opportunity to look more closely into the role of the dual-base system in affecting amination reactions of this type, especially given

that use of the dual-base system is relatively new in amination reactions involving either Pd[83,84,89] or Ni (see Chapter 5 of this thesis) catalyst systems, and no prior report clearly establishes the mechanistic interplay of the reagents under catalytic conditions. The use of organic bases in enabling Ni-catalyzed amination reactions is not new, however, as range of redox-enabled approaches exist including those involving the use of electrochemistry,[36] photochemistry[35] and heterogeneous reductants to modulate the Ni oxidation state and allow for catalyst turnover.[90] However, these approaches are limited in substrate scope, typically involving reactions mechanisms based on Ni(I)/(III) manifolds, and struggle with the inclusion of aryl chloride and aryl (pseudo)halide electrophiles, often being limited to the inclusion of just activated aryl bromide electrophiles. Recently, the Buchwald group reported on the mechanistically distinct organic base enabled Ni-catalyzed N-arylation of anilines with aryl triflates and found experimentally that triethylamine was especially useful in enabling these transformations, while the computationally predicted coordinating and inhibitory nature of less sterically hindered amine bases, such as DBU, was reason for the observed inferior performance of such bases in enabling the aforementioned transformations.[91] Noteworthy is that the Buchwald report is mechanistically different from the redox-enabled approaches, where they use a bisphosphine ligand in contrast to the bipyridine ligands typically employed in redox-enabled Ni-aminations, and the suggested mechanism proceeds through a computationally predicted Ni(0)/(II) manifold, which in part allows them to access aryl triflate electrophiles.[91] Notwithstanding these important contributions, absent from all the mentioned reports is the general inclusion of (hetero)aryl chloride and other phenol based (hetero)aryl electrophiles.

While the use of organic amine bases in thermally promoted (P_2)Ni-catalyzed C-N cross-couplings merge some of the best features of existing Ni catalyst methodologies (i.e., mild homogeneous base and diverse substrate scope), a dearth of mechanistic information regarding such catalytic protocols exists. The preponderance of evidence regarding related cycles that use inorganic bases supports a 'Pd-like' (P_2)Ni(0/II) cycle,[12] with the following elementary steps having been examined across different P_2 ligands and coupling partners: aryl-X oxidative addition of (P_2)Ni(0) to give (P_2)Ni(aryl)X;[92] overall nucleophile coordination with base/NHR_2 to give (P_2)Ni(aryl)(NR_2); and product-forming C-N reductive elimination[93,94] leading to the reforming of the key (P_2)Ni(0) intermediate.[12]

With regard to the use of organic amine bases, mechanistic observations are limited to the aforementioned report from Buchwald and co-workers,[91] who identified the importance of both P_2 ligand design and choice of organic amine base to avoid catalyst inhibition via binding to [(P_2)Ni(aryl)]$^+$OTf$^-$ intermediates within a Ni(0/II) cycle. However, no experimental study mapping the key elementary reaction steps that comprise a putative Ni(0/II) C-N cross-coupling cycle for a P_2-ligated species has been reported, and the involvement of dual-base (DBU/NaX) systems in such Ni (or Pd[84]) catalytic cycles has also not been elucidated.

6.3 Results and discussion

6.3.1 Preliminary pre-catalyst screening

We envisioned that optimization of our conditions for the C-N cross-coupling of primary amides with DBU/NaTFA (5 mol% $Ni(COD)_2$/**CyPAd-DalPhos**, toluene, 110 ºC) would provide a useful base-metal catalyst system for the amidation of 2'-(pseudo)halide-substituted acetophenones *en route* to 4-(1*H*)-quinolones.[95] We sought a Ni catalyst that

would allow use of inexpensive (hetero)aryl chloride and phenol-derived electrophiles that were not described in reports involving Cu- or Pd-based catalysts with inorganic bases (Figure 1).[87,88] Our survey involved the C-N cross-coupling of 2'-chloroacetophenone and 3,5-bis(trifluoromethyl)benzamide to give **6.1** (Figure 6.2a), employing ligands having proven utility in Ni-catalyzed C-N cross-couplings (Figure 6.2b). Under these conditions our $Ni(COD)_2$/**CyPAd-DalPhos** catalyst system performed poorly versus catalysts featuring some other DalPhos ligands (entries 1-6), with **PAd2-DalPhos** (~1:1 mixture of meso/rac isomers, entry 4) providing optimal conversion to **6.1**. Negligible conversion was achieved with IPr, DPE-Phos, or DPPF (entries 7-9). The feasibility of using more air-stable Ni sources (i.e., stilbene-Ni(0) pre-catalysts[96] with **PAd2-DalPhos**, or (**PAd2-DalPhos**)Ni(*o*-tol)Cl was also demonstrated (entries 10-12). Given the utility of (P_2)Ni(4-CN-Ph)Cl pre-catalysts in Ni-catalyzed C-N cross-couplings[97] , we prepared, characterized, and confirmed the catalytic utility (entry 13) of the new air-stable pre-catalyst (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl (mixture of meso/rac isomers approximately corresponding to the isomeric composition of **PAd2-DalPhos**, Figure 6.2c). In cross-couplings employing **PAd2-DalPhos**-derived catalysts involving the more electron-rich 4-methoxybenzamide leading to **6.2** (entries 14-18), (**PAd2-DalPhos**)Ni(aryl)Cl pre-catalysts proved superior.

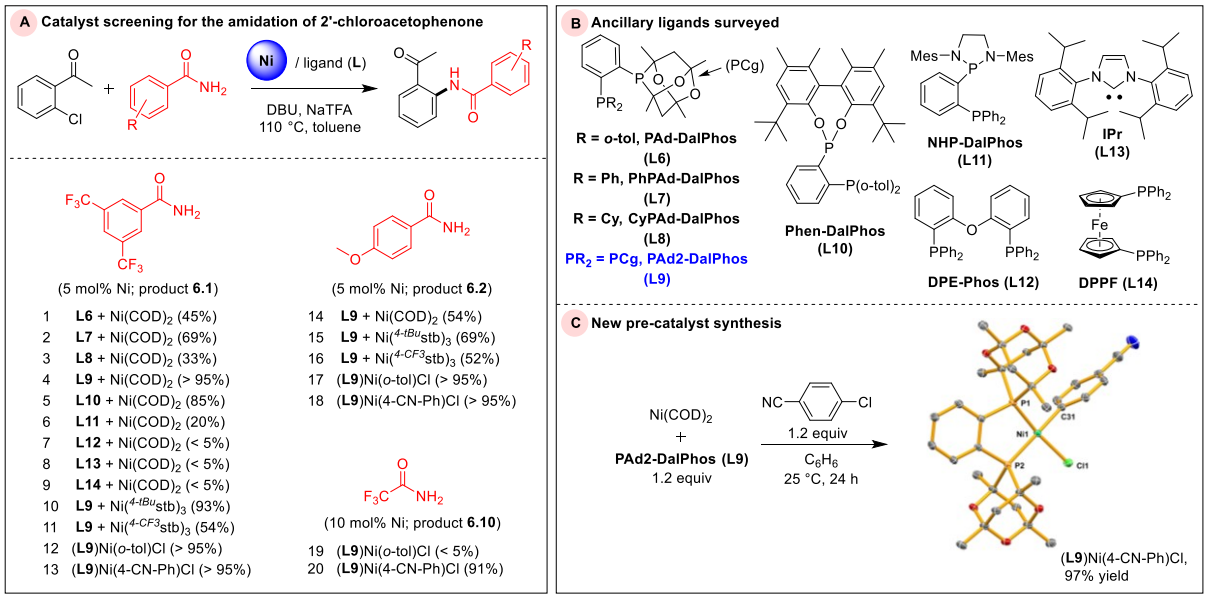


Figure 6.2 Ligand screening and pre-catalyst optimization. GC yields were determined on the basis of response-factor calibrated data, in reactions conducted on 0.12 mmol scale in ArCl (0.12 M) using amide (1.1 equiv), DBU (2.0 equiv), and NaTFA (2.0 equiv) in toluene for 18 h (mass balance corresponds primarily to unreacted starting material). Single-crystal X-ray structure of *meso*-(**PAd2-DalPhos**)Ni(4-CN-Ph)Cl shown with 50% probability ellipsoids, and with H-atoms and solvates omitted for clarity.

The use of trifluoroacetamide as a nucleophile in the reaction cascade featured in Figure 1 was not disclosed in leading reports by Buchwald (Cu[87]) and Huang (Pd[88]), and we have found its use to be challenging in Ni-catalyzed C-N cross-couplings. While (**PAd2-DalPhos**)Ni(*o*-tol)Cl proved ineffective in the formation of **6.10** (Figure 6.2a, entry 19), high conversion was achieved by use of (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl (91%, entry 20), possibly owing to more facile catalyst activation and/or nitrile stabilization afforded by the latter. Having established the superiority of (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl in the formation of **6.1**, **6.2**, and **6.10** (Figure 6.2a), we proceeded to explore the substrate scope enabled by this newly synthesized pre-catalyst.

6.3.2 Substrate scope for the N-arylation of amides en route to 4-quinolones

The cross-coupling leading to **6.1** was successfully extended to include other (pseudo)halide variants (X = Br, OTs, and OMs; also see **6.16**-**6.18**), establishing expanded electrophile scope versus that featured in pioneering reports by Buchwald (Cu[87]) and Huang (Pd[88]). Beyond the formation of **6.1**, a broad collection of electron-rich, electron-poor, and hindered benzamide derivatives were coupled successfully with 2'-chloroacetophenone, leading to **6.2**-**6.8**; in these transformations methoxy (**6.2**), nitrile (**6.4**), polyfluoro (**6.5**, **6.6**), trifluoromethyl (**6.7**) and pinacolatoboron (**6.8**) functional groups were tolerated (Figure 6.3a). Formamide and trifluoroacetamide also proved to be compatible nucleophiles, affording **6.9** and **6.10**. Indeed, our Ni-catalyzed C-N protocol proved compatible with a range of pairings leading to structurally diverse *N*-(ketoaryl)-amides, encompassing: cyclopropylamide (where no ring-opening was observed), thiophene (**6.14**), furan (**6.15**), anisolyl (**6.16**), and 2-oxazolidinone (**6.18**) amide structures; and (pseudo)halide electrophiles featuring trifluoromethyl (**6.11**, **6.12**), (poly)fluoro (**6.13**-**6.16**), methyl (**6.13**, **6.14**, **6.17**), and methoxy (**6.18**) substituents. The ability of these *N*-(ketoaryl)-amides to serve as precursors to 4-quinolones was also confirmed (Figure 6.3b). Representative 'one-pot' reactions in which the *N*-(ketoaryl)-amide intermediate generated via C-N cross-coupling was directly cyclized to the 4-quinolone, as well as protocols where such intermediates were isolated prior to Camps cyclization, each afforded synthetically useful yields of the target 4-quinolone.

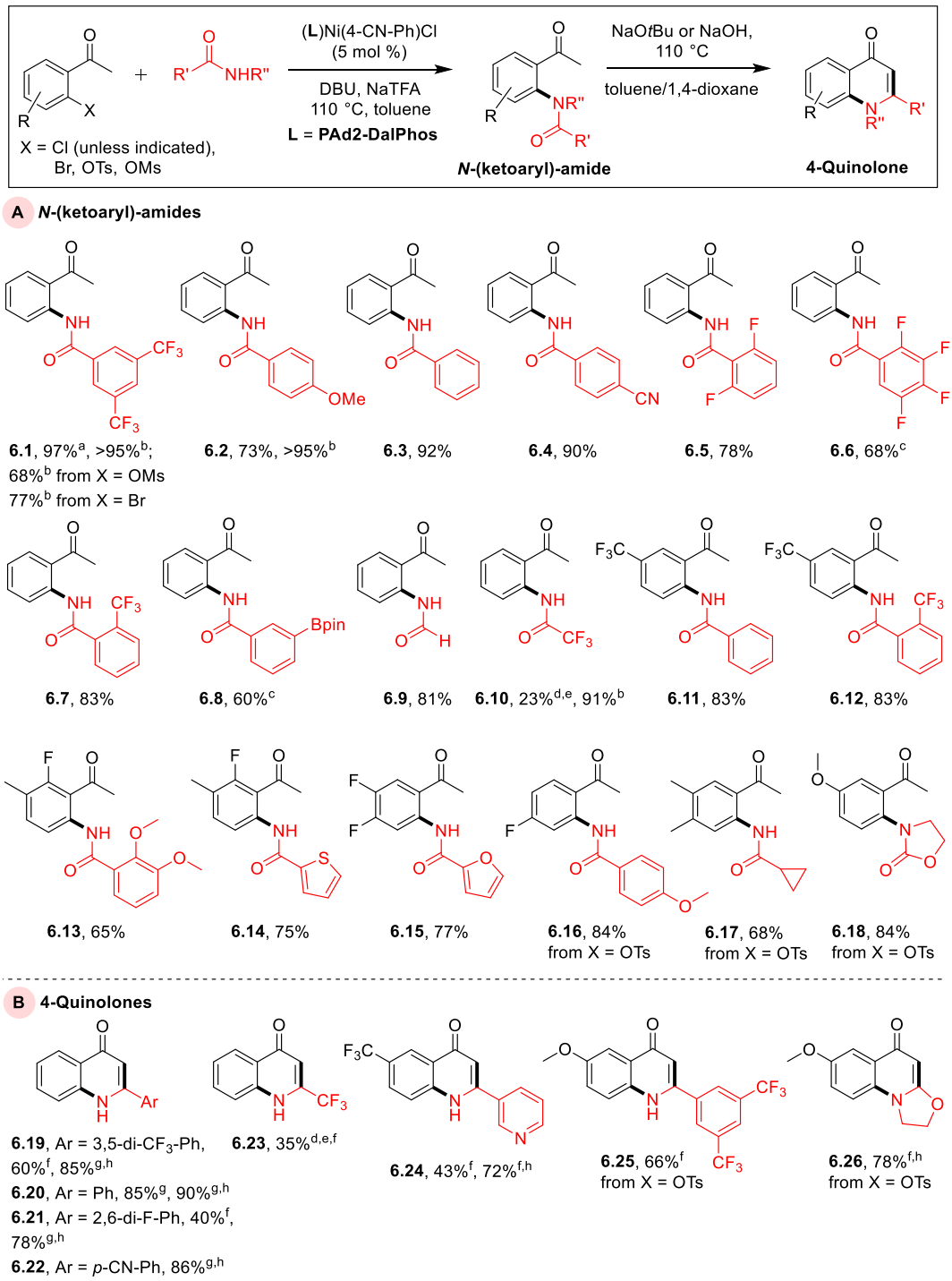


Figure 6.3 Substrate scope for the Ni-catalyzed *N*-arylation of amides with 2'-(pseudo)haloacetophenones. Unless otherwise indicated, isolated yields of amides are reported from reactions conducted on 0.48 mmol scale in ArX (0.12 M) using amide (1.1 equiv), DBU (2.0 equiv), and NaTFA (2.0 equiv) in toluene for 18 h (mass balance corresponds primarily to unreacted starting material). Except where noted, 'one-pot' Camps cyclization to afford the 4-quinolone product were conducted in the same reaction vessel by addition of base (NaO*t*Bu or NaOH, 2.0-3.0 equiv) and 1,4-dioxane (final solution 1:1

toluene:1,4-dioxane, 0.06 M) directly following the amide C-N cross-coupling step. [a]1 mmol scale ArCl. [b]GC yield determined on the basis of response-factor calibrated data. [c]7.5 mol% Ni and using 1,1,3,3-tetramethylguanidine (TMG, 2.0 equiv) instead of DBU. [d]10 mol% Ni and using TMG (2.0 equiv) instead of DBU (low isolated yield due to product volatility/instability). [e]0.24 mmol scale ArCl. [f]Camps cyclization with NaO*t*Bu. [g]Camps cyclization with NaOH. [h]Yield of the Camps cyclization 4-quinolone product starting from the corresponding isolated amide.

6.3.3 Syntheses of mechanistically relevant Ni(0, I, II) species

Given that no experimental studies probing the roles of DBU/NaTFA in enabling Ni or Pd-catalyzed C-N dual-base cross-couplings have been published, we became interested in studying the viability of an operative Ni(0/II) cycle in the chemistry reported herein. Although Ni(0/II) cycles are generally invoked for thermal (P_2)Ni-catalyzed C-N cross-couplings, the preponderance of literature evidence supports a Ni(I/III) cycle when using organic amine bases under photoredox/electrochemical/reductant conditions, thereby rendering the mechanistic scenario in the present case less obvious. Furthermore, a report documenting [(AlPhos)Pd^{II}(aryl)(DBU)]$^{+}OTf^{-}$ as the resting state in the Pd-catalyzed C-N cross-coupling of anilines with aryl triflates,[98] along with the experimentally computed inhibitory nature of DBU in related transformations utilizing Ni,[91] both highlight the possible role of DBU as a ligand under such conditions. We also postulated as to whether some form of a LNi(TFA) intermediate was necessary to facilitate amide binding and subsequent deprotonation, analogously to how LM(OR) intermediates are often necessary in related catalytic transformations involving Pd.[99]

Our initial efforts focused on the study of Ni(0, I, and II) species of potential mechanistic relevance to the Ni-catalyzed amide *N*-arylation chemistry reported herein (Figure 4). Treating **PAd2-DalPhos** with $Ni(COD)_2$ (C_6H_6, 80 ºC, 0.5 h) afforded (**PAd2-DalPhos**)Ni(COD) as a ~1:1 meso/rac mixture in 69% isolated yield (Figure 6.4a);

crystallographic analysis of *rac*-(**PAd2-DalPhos**)Ni(COD) confirmed the pseudo-tetrahedral structure of this complex. While the formation of (**PAd2-DalPhos**)Ni(COD) was slow at 25 ºC and did not proceed to completion, ^{31}P NMR monitoring revealed that after 1 h only trace *rac*-(**PAd2-DalPhos**)Ni(COD) was observable, along with substantial amounts of *meso*-(**PAd2-DalPhos**)Ni(COD), unreacted *rac*-**PAd2-DalPhos**, and remaining *meso*-**PAd2-DalPhos** (~1:2:1), suggesting that *meso*-**PAd2-DalPhos** is more efficient at displacing COD in this transformation.

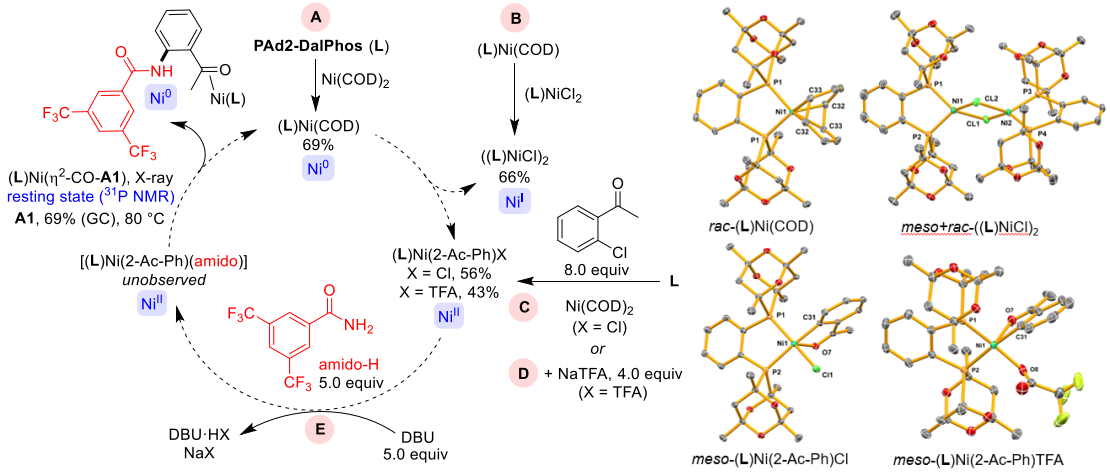


Figure 6.4 The pursuit of putative species within a Ni(0/II) catalytic cycle of relevance to dual-base-enabled aryl amidations. Isolated yields of nickel complexes reported. Single-crystal X-ray structures shown with 50% probability ellipsoids, and with H-atoms and solvates omitted for clarity.

The putative Ni(II) oxidative addition intermediate (**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl was prepared in 56% isolated yield via combination of **PAd2-DalPhos**, Ni(COD)$_2$, and excess 2'-chloroacetophenone (C_6H_6, 25 ºC, 2 h; Figure 6.4c). As prepared and isolated herein, (**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl exists based on ^{1}H and ^{31}P NMR data as a mixture of isomers (~10:2:1, major *meso*-**PAd2-DalPhos**, minor *rac*-**PAd2-DalPhos**, minor *meso*-**PAd2-DalPhos**) arising from the meso/rac composition of **PAd2-DalPhos** and hindered Ni-aryl rotation arising from carbonyl coordination (*vide infra*). The composition of this mixture

is consistent with the unconsumed *rac*-**PAd2-DalPhos** that is observed in the crude reaction mixture (^{31}P NMR) prior to workup. The identification of meso versus rac isomers of (**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl was corroborated by reactions conducted using isolated *rac*-**PAd2-DalPhos**, whereby NMR analysis of the crude reaction mixture allowed for the assignment of signals arising from *rac*-**PAd2-DalPhos** ligated species. The crystallographic characterization of *meso*-(**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl (Figure 6.4) confirmed the five-coordinate nature of this complex, with k^2-C,O coordination of the aryl electrophile moiety.

In early attempts to synthesize (**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl, minor amounts of the paramagnetic Ni(I) dimer ((**PAd2-DalPhos**)NiCl)$_2$ were co-crystallized, suggesting that ((**PAd2-DalPhos**)NiCl)$_2$ can likely arise from comproportionation of (**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl and (**PAd2-DalPhos**)Ni(COD). In an effort to deliberately synthesize and characterize ((**PAd2-DalPhos**)NiCl)$_2$, we reacted (**PAd2-DalPhos**)Ni(COD) and (**PAd2-DalPhos**)NiCl$_2$ (C_6H_6, 25 ºC, 3 h) which afforded the paramagnetic Ni(I) dimer ((**PAd2-DalPhos**)NiCl)$_2$ in 66% isolated yield; we were successful in crystallographically characterizing both the *meso*+*rac*-((**PAd2-DalPhos**)NiCl)$_2$ (Figure 6.4b) and *rac*+*rac*-((**PAd2-DalPhos**)NiCl)$_2$ isomers (Figure 6.4).

As mentioned previously, one viable mechanistic scenario for the catalysis documented herein involves the formation of (**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl via oxidative addition of 2'-chloroacetophenone to a (**PAd2-DalPhos**)Ni(0) species, followed by anion metathesis involving NaTFA leading to (**PAd2-DalPhos**)Ni(2-Ac-Ph)TFA. This latter species was prepared by using the general conditions outlined for the synthesis of (**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl, with inclusion of excess NaTFA (C_6H_6, 25 ºC, 4 h; Figure 6.4d). Unlike the multiple isomeric forms of (**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl that were obtained,

under the synthetic/workup conditions employed herein *meso*-(**PAd2-DalPhos**)Ni(2-Ac-Ph)TFA was isolated as the only NMR-detectable isomer in 43% yield. The crystal structure of *meso*-(**PAd2-DalPhos**)Ni(2-Ac-Ph)TFA (Figure 6.4) features a five-coordinate complex featuring a k^1-O TFA ligand and a k^2-C,O coordinated aryl electrophile. No reaction was observed (^{31}P NMR) upon treatment of (**PAd2-DalPhos**)Ni(2-Ac-Ph)X (X = Cl or TFA) with 4-methoxybenzamide (5.0 equiv, C_6D_6, 25 ºC, 1 h), suggesting that anion displacement by amide to give [(**PAd2-DalPhos**)Ni(2-Ac-Ph)(amide)]$^+X^-$ is not facile in the present catalytic system.

We next turned our attention to examining C-N bond reductive elimination involving the putative Ni(II) intermediate (**PAd2-DalPhos**)Ni(2-Ac-Ph)(amido) to give **6.1** (Figure 6.4e). Exposure of (**PAd2-DalPhos**)Ni(2-Ac-Ph)X (X = Cl or TFA) to 3,5-bis(trifluoromethyl)benzamide and DBU (5.0 equiv each in C_6H_6, 25 ºC, 1 h) afforded clean conversion to what we assign as a ~3:2 mixture of **PAd2-DalPhos**-ligated complexes on the basis of ^{31}P{^{1}H} NMR data collected from the reaction mixture prior to workup (202.5 MHz, C_6D_6: δ 36.2, d, J_{PP} = 76.0 Hz, complex-I; 34.2, d, J_{PP} = 84.9 Hz, complex-II; 23.7, d, J_{PP} = 84.9 Hz, complex-II; 23.1, d, J_{PP} = 76.0 Hz, complex-I; Figure 6.5). Heating of this reaction mixture afforded substantial conversion to **6.1** (69% GC yield, 80 ºC, 0.5 h). Moreover, ^{31}P NMR monitoring of catalytic reactions conducted at 25 ºC using 10 mol% (**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl as a pre-catalyst revealed after 0.75 h, at which point 30% conversion to **6.1** was confirmed on the basis of GC data, complex-I and II as the only observable phosphorus-containing species. These observations support the intermediacy of complex-I and II on the path to the cross-coupling product **6.1**. These results also confirm that (**PAd2-DalPhos**)Ni(2-Ac-Ph)TFA is not a required intermediate *en route* to product **6.1**,

meaning that amide binding and subsequent deprotonation can indeed occur without the on-cycle transmetalation of Cl for TFA.

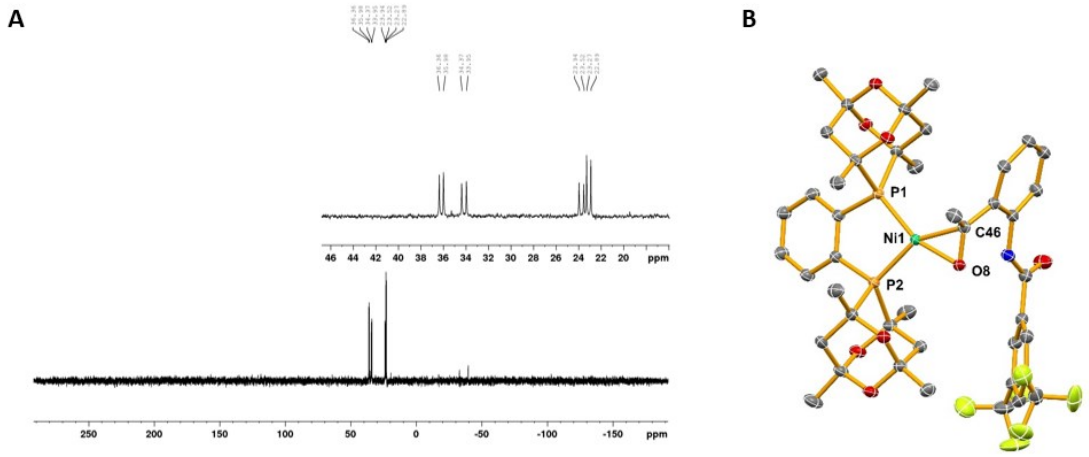


Figure 6.5 A) $^{31}P\{^{1}H\}$ NMR spectrum (202.5 MHz, C_6D_6) upon exposure of (**PAd2-DalPhos**)Ni(2-Ac-Ph)X (X = Cl or TFA) to 3,5-bis(trifluoromethyl)benzamide and DBU (5.0 equiv in C_6H_6, 25 ºC, 1 h); B) Single-crystal X-ray structure of *meso*-(**PAd2-DalPhos**)Ni(η^2-CO-**6.1**) (CCDC 2102674) shown with 50% probability ellipsoids, and with H-atoms omitted for clarity.

The magnitudes of the observed J_{PP} for complex-I and II (76.0 and 84.9 Hz) differ significantly from those of the (**PAd2-DalPhos**)Ni^{II}(aryl)X compounds (<15 Hz) reported herein, and are consistent[100] with (**PAd2-DalPhos**)Ni(0) species arising from (**PAd2-DalPhos**)Ni(2-Ac-Ph)(amido). While all efforts to workup these reactions afforded intractable product mixtures comprising substantial amounts of **6.1**, in one instance we fortuitously isolated a few crystals that were identified on the basis of X-ray analysis as *meso*-(**PAd2-DalPhos**)Ni(k^2-CO-**6.1**), which can be viewed as arising from C-N bond reductive elimination from (**PAd2-DalPhos**)Ni(2-Ac-Ph)(amido) (Figure 6.5b). Efforts to rationally generate (**PAd2-DalPhos**)Ni(L') (L' = **6.1** or DBU) via treatment of (**PAd2-DalPhos**)Ni(COD) with L' (10.0 equiv, C_6D_6, 100 ºC) resulted in no discernable conversion. Nonetheless, it is feasible that *meso*-(**PAd2-DalPhos**)Ni(k^2-CO-**6.1**) represents one of

complex-I or II as outlined above, with the other possibly corresponding to products arising from differing coordination modes of **6.1** to (**PAd2-DalPhos**)Ni(0), or (**PAd2-DalPhos**)Ni(L') species (L' = solvent, DBU, or another Lewis base). Our observation that the same mixture of complex-I and II is formed when starting from *meso*-(**PAd2-DalPhos**)Ni(2-Ac-Ph)TFA suggests that *rac*-(**PAd2-DalPhos**)Ni(k^2-CO-**6.1**) is not formed in substantial quantities under these conditions. The collective observations presented herein show that C-N bond reductive elimination from putative (**PAd2-DalPhos**)Ni(2-Ac-Ph)(amido) is facile, even at 25 ºC.

6.3.4 Catalytic competence experiments and room-temperature amide cross-couplings

With some mechanistic insight gained from the aforementioned stoichiometric experiments, we sought to learn more about the roles of various reaction components and Ni intermediates by performing a range of mechanistically relevant catalytic experiments (Figure 6.6a). Under the standard conditions (5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, toluene, 110 ºC, 18 h), > 95% conversion to **6.2** was observed; the addition of excess 4-methoxybenzamide or **6.1** did not result in diminished conversion to **6.2**, and using (**PAd2-DalPhos**)Ni(2-Ac-Ph)X (X = Cl or TFA) as pre-catalysts similarly resulted in > 95% conversion (Figure 6.6a, entries 1-5). In contrast, only 37% conversion to **6.2** was achieved using ((**PAd2-DalPhos**)$NiCl)_2$ (5 mol% Ni, entry 6), thereby suggesting that this Ni(I) species does not contribute importantly to the observed catalytic production of **6.2**. The inhibiting nature of COD is evidenced by the diminished yield of **6.2** with added COD (entries 7-9). The importance of NaTFA (entry 10) and necessity of DBU (entry 11) in enabling high conversion to **6.2** was also confirmed. Although our stoichiometric reactivity studies (*vide supra*) suggest that anion exchange involving (**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl

and NaTFA is not a requirement for catalytic turnover, inhibition by DBU·HCl (entries 12-13) supports the role of NaTFA in sequestering chloride off-cycle, as suggested by Simmons and co-workers[84] in Pd catalysis. Similar trends were observed when employing 3,5-bis(trifluoromethyl)benzamide to give **6.1**: added **6.1** had negligible impact on catalysis (entry 19); NaTFA and crucially DBU were required to achieve optimal turnover (entries 20-21); and DBU·HCl was observed to have an inhibitory effect on catalysis (entries 22-23).

On the basis of our observed stoichiometric reactivity, we posited that catalytic turnover should be feasible at 25 ºC and/or below 5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl – this proved to be the case (Figure 6.6a). In the formation of **6.1** (entry 24) and **6.2** (entry 15) at 25 ºC and using only 3 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, > 80% conversion to product was observed. We are unaware of any catalyst system (Pd, Ni, or other) that is capable of operating under such mild conditions for amide *N*-arylation. Efforts to drop the loading to 1 mol% Ni afforded inferior results (entries 16 and 25), and neither excess DBU (3.0 equiv total) nor added **6.1** (2.0 equiv) was found to significantly inhibit catalysis leading to **6.1** (5 mol% Ni, 25 ºC, 18 h). A brief substrate scope examination (≤ 5 mol%, 25 ºC; Figure 6.6b) confirmed the applicability of such mild conditions for a range of Ni-catalyzed amide *N*-arylations with 2'-chloroacetophenone, including a gram-scale reaction leading to **6.1**. Also demonstrated is the inferior performance of both (**PAd2-DalPhos**)Ni(*o*-tol)Cl (especially in the formation of **6.1**) and ((**PAd2-DalPhos**)NiCl)$_2$ at the 5 mol% Ni loading level in comparison to (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl.

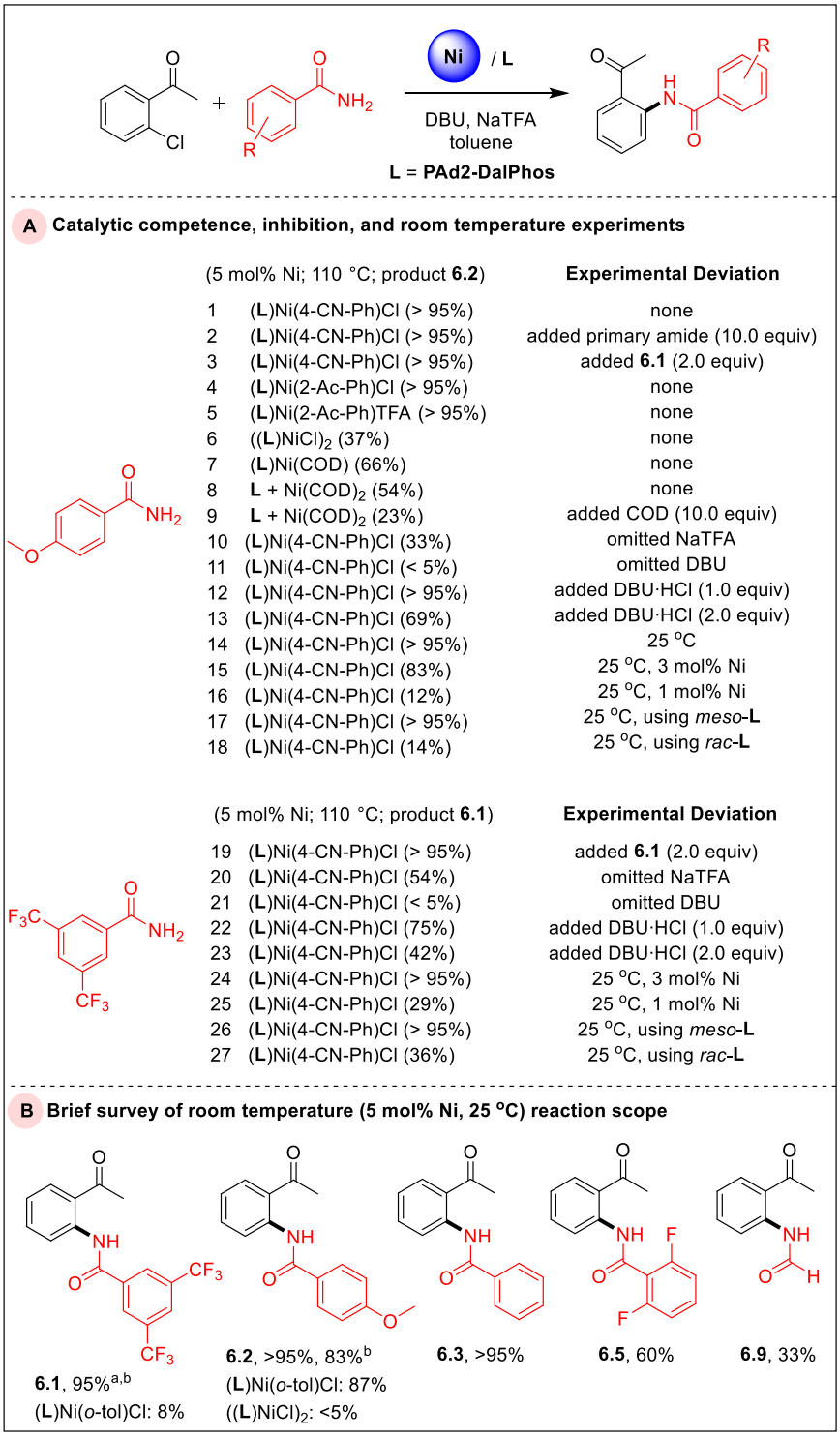


Figure 6.6 Probing reaction variables in dual-base-enabled Ni-catalyzed aryl amidations involving 2'-chloroacetophenone. Unless stated otherwise, GC yields reported on the basis of response-factor calibrated data, in reactions conducted on 0.12 mmol scale in ArCl (0.12 M) using amide (1.1 equiv), DBU (2.0 equiv), and NaTFA (2.0 equiv) in toluene for 18 h (mass balance corresponds primarily to unreacted starting material). [a]Isolated yield (6.5 mmol ArCl scale). [b]3 mol% Ni.

The ligand **PAd2-DalPhos**, as-prepared using literature methods or purchased from commercial sources, is obtained as a ~1:1 mixture of meso and rac isomers, which can be separated chromatographically.[49] In probing whether one of these diastereomers might be superior in terms of enabling the transformations herein, we examined cross-couplings leading to **6.1** and **6.2** (5 mol%, 25 ºC). In both transformations, *meso*-(**PAd2-DalPhos**)Ni(4-CN-Ph)Cl significantly out-performed *rac*-(**PAd2-DalPhos**)Ni(4-CN-Ph)Cl (Figure 6.6a; entries 17 and 18, entries 26 and 27). These observations are consistent with the aforementioned stoichiometric experiments where it was found that ligand substitution and oxidative addition of 2′-chloroacetophenone to afford *rac*-(**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl proceeded markedly less efficiently than in the case of the preparation of *meso*-(**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl.

6.3.5 Mechanistic explanation

Our observations support a Ni(0/II) catalytic cycle for the *N*-arylation of amides with 2'-(pseudo)haloacetophenones leading to 4-quinolones, employing (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl under dual-base (DBU/NaTFA) conditions (Figure 6.7). Activation of the pre-catalyst, presumably by an amide coordination/deprotonation/elimination sequence, likely affords (**PAd2-DalPhos**)Ni(L)$_n$, where L is a Lewis base present in the reaction mixture (Figure 6.7a). Inhibition by COD provides indirect evidence that loss of L from (**PAd2-DalPhos**)Ni(L)$_n$ may be important in facilitating aryl electrophile oxidative addition, and catalytic turnover. Although we have no direct evidence of DBU functioning as a ligand, and observe catalyst inhibition by DBU·HCl but not by increasing amounts of DBU, we cannot rule out the involvement of (**PAd2-DalPhos**)Ni(DBU)$_n$ species. Oxidative addition of 2'-chloroacetophenone to (**PAd2-DalPhos**)Ni(L')$_n$ affords (**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl

(Figure 6.7b), and in the presence of NaTFA, on-cycle anion exchange can occur to give (**PAd2-DalPhos**)Ni(2-Ac-Ph)TFA (Figure 6.7c); however, this is not required for catalytic turnover. Instead, the observation that DBU·HCl inhibits catalysis suggests that the key function of NaTFA may be to sequester chloride via off-cycle anion exchange (Figure 6.7c′). Our work establishes the viability of ((**PAd2-DalPhos**)NiCl)$_2$ formed via comproportionation of (**PAd2-DalPhos**)Ni(II) and (**PAd2-DalPhos**)Ni(0); however, the generally poor catalytic performance observed for this dinuclear (**PAd2-DalPhos**)Ni(I) species, versus (**PAd2-DalPhos**)Ni(aryl)X complexes, suggests that ((**PAd2-DalPhos**)NiCl)$_2$ is not likely a key intermediate in the dominant productive catalytic cycle.

In probing nucleophile coordination (Figure 6.7d), we found no evidence of amide displacement of X in (**PAd2-DalPhos**)Ni(2-Ac-Ph)X (X = Cl or TFA) in the absence of DBU. In the presence of DBU such complexes are transformed into (**PAd2-DalPhos**)Ni(L)$_n$ that could not be isolated (Figure 6.7e); these appear to be the resting state of the catalyst system at 25 ºC on the basis of NMR spectroscopic analysis. The high conversion to the target product **6.1** on heating, and crystallographic evidence for the formation of (**PAd2-DalPhos**)Ni(η^2-CO-**6.1**) in these reaction mixtures, are in keeping with the generation of the unobserved intermediate (**PAd2-DalPhos**)Ni(2-Ac-Ph)(amido), from which (**PAd2-DalPhos**)Ni(η^2-CO-**6.1**) and **6.1** are likely generated via C-N bond reductive elimination. The efficiency of the aforementioned elementary steps at 25 ºC was reflected in catalytic turnover under mild conditions (as low as 3 mol% Ni, 25 ºC), and *meso*-(**PAd2-DalPhos**)Ni(4-CN-Ph)Cl out-performed *rac*-(**PAd2-DalPhos**)Ni(4-CN-Ph)Cl in terms of overall catalytic output.

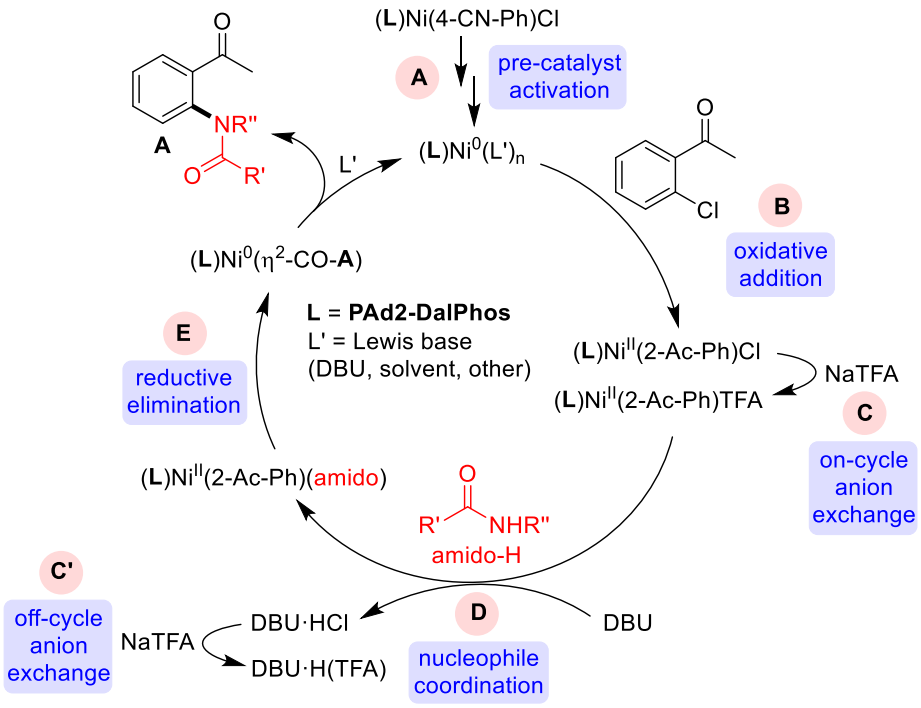


Figure 6.7 Proposed Ni(0/II) mechanism for dual-base-enabled (**PAd2-DalPhos**)Ni-catalyzed aryl amidations involving 2'-chloroacetophenone. **A** = N-(ketoaryl)-amide.

6.3.6 Summary

In summary, this chapter discloses the first in depth study on the mechanistic mapping of dual-base enabled metal-catalyzed amidation chemistry, in this case with the application in preparing bio-relevant 4-quinolones via sequential Camps Cyclization of the generated *N*-(ketoaryl)-amides, which are prepared for the first time from corresponding 2'-(pseudo)halide-substituted acetophenones. The findings herein ultimately lead us to successfully conduct the first examples of room-temperature amide N-arylations of this type, enabled by deployment of our newly reported air-stable (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl pre-catalyst. Beyond providing a useful base-metal catalyzed route to *N*-(ketoaryl)-amides and derived 4-quinolones from inexpensive and abundant reagents, we believe our findings illuminate the mechanistic underpinnings of Ni-catalyzed C(sp^2)-N bond formation using

organic amine bases, thereby supporting the continued evolution and diversification of these useful transformations.

6.4 Experimental

6.4.1 General considerations

Unless otherwise indicated, all experimental procedures were conducted in a nitrogen-filled, inert atmosphere glovebox using oven-dried glassware and purified solvents, with the exception of the workup of catalytic reaction mixtures, which were conducted on the benchtop in air using unpurified solvents. Toluene was deoxygenated by sparging with nitrogen gas followed by passage through a double column solvent purification system packed with alumina and copper-Q5 reactant and storage over activated 4 Å molecular sieves. Each of pentane, $CDCl_3$, C_6H_6, and C_6D_6 when used with nickel complexes were deoxygenated by sparging with nitrogen gas followed by storage over activated 4 Å molecular sieves. All aforementioned DalPhos ligands were prepared according to literature methods.[42,49] All other chemicals were obtained from commercial sources and were used as received. GC data were obtained on an instrument equipped with an SGE BP-5 column (30 m, 0.25 mm i.d.). Automated flash column chromatography was carried out using a normal-phase Biotage SNAP KP-Sil 10 g column cartridge or a reverse-phase silica-based Silicycle SiliaSep C_{18} (17%) mono, 40 g (particle size 40−63 μm; pore size 60 Å). All ^{1}H NMR (500 and 300 MHz), $^{13}C\{^{1}H\}$ NMR (125.8 and 75.4 MHz), and $^{31}P\{^{1}H\}$ NMR (202.5 and 121.5 MHz) spectra were recorded at 300 K and were referenced to residual protio solvent peaks (^{1}H), deuterated solvent peaks ($^{13}C\{^{1}H\}$), external 0.5% $(CF_3)C_6H_5$ in $CDCl_3$ at -63.7 ppm (^{19}F), or external 85% H_3PO_4 ($^{31}P\{^{1}H\}$). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. All coupling constants (*J*) are reported

in Hertz (Hz). Mass spectra were obtained using either APCI or ion trap (ESI) instruments. Elemental analysis data were obtained from Galbraith Laboratories, Inc.

6.4.2 General procedure for the N-arylation of amides with (hetero)aryl (pseudo)halides

Unless otherwise indicated in the text, solid (**Pad2-DalPhos**)Ni(4-CN-Ph)Cl, NaTFA (2.0 equiv), DBU (2.0 equiv), (hetero)aryl (pseudo)halide (0.48 mmol, 1.0 equiv), amide (1.1 equiv) and toluene (0.12 M (hetero)aryl (pseudo)halide) were added to a screw-capped vial containing a magnetic stir bar. The vial was sealed with a cap containing a PTFE septum, removed from the glovebox, placed in a temperature-controlled aluminum heating block set at the specified temperature, and was allowed to react under the influence of magnetic stirring for 18 h (unoptimized).

6.4.3 General procedure for the one-pot syntheses of 4-quinolones

Following *6.4.2*, the vial was allowed to cool to room temperature, and brought back into the glovebox. Base (NaO*t*Bu or NaOH, 2.0-3.0 equiv) and 1,4-dioxane (final solution 1:1 toluene:1,4-dioxane, 0.06 M) were added directly following the amide C-N cross-coupling step. The resultant mixture was then re-sealed with a cap containing a PTFE septum, removed from the glovebox, placed in a temperature-controlled aluminum heating block set at 110 ˚C, and was allowed to react under the influence of magnetic stirring for 18 h (unoptimized).

6.4.4 General procedure for the cyclization of N-(ketoaryl)-amides to 4-quinolones

Unless otherwise indicated in the text, the corresponding *N*-(ketoaryl)-amide**,** NaOH (3.0 equiv.), and 1,4-dioxane (0.12 M in *N*-(ketoaryl)-amide) were added to a screw-capped vial containing a magnetic stir bar. The vial was sealed with a cap containing a PTFE septum,

removed from the glovebox, placed in a temperature-controlled aluminum heating block set at the specified temperature, and was allowed to react under the influence of magnetic stirring for 18 h (unoptimized).

6.4.5 General procedure for the synthesis of aryl tosylates

The aryl sulfonates used herein were prepared according to published procedures and afforded characterization data that were in agreement with literature;[101] these protocols were also employed in the synthesis of other aryl tosylate reagents used herein. To a flask containing a magnetic stir bar and the corresponding 2-acetylphenol (1.0 equiv) in THF (1.5 M) was added a solution of K_2CO_3 (1.0 equiv.) in distilled water (0.67 M) under the influence of magnetic stirring. The resultant mixture was cooled to 0 ˚C. A separate flask was then charged with 4-toluenesulfonyl chloride in THF (0.67 M), and this solution was then added dropwise to the stirring 2-acetylphenol/K_2CO_3 mixture. After addition, the resultant mixture was allowed to warm to room temperature with continued stirring over the course of 4 h. The reaction mixture was then extracted with ethyl acetate (~30 mL) followed by drying over Na_2SO_4 and filtration to remove the drying agent. The resultant ethyl acetate solution was then concentrated in vacuo to dryness, and the residue was washed with 10% ethyl acetate in hexanes (3 x 5 mL, if necessary) to remove excess starting material, yielding the desired aryl sulfonate.

6.4.6 Procedure for the preparation of GC samples

Following *6.4.2* (0.12 mmol scale in (hetero)aryl halide), the reaction mixture was cooled to room temperature if necessary, diluted using ethyl acetate (~1-2 mL), and was passed through a Kimwipe filter containing Celite and silica gel, with the eluent collected in

a GC vial. Calibrated GC conversions are given on the basis of data obtained from authentic materials using either dodecane, phenyldodecane, or hexadecane as an internal standard.

6.4.7 Purification of N-aryl amide products via normal-phase chromatography

Following *6.4.2*, the resultant mixture was cooled to room temperature if necessary, followed by adsorption onto silica and subsequent elution through a silica/Celite frit employing ethyl acetate as an eluent (~30-50 mL). The resulting solution was then dried *in vacuo* to afford a crude residue that was dissolved in a hexanes-ethyl acetate mixture before being loaded onto either a silica-based flash column, or a 10 g normal-phase Biotage SNAP KP-Sil column cartridge. The product was then purified using a hexanes-ethyl acetate eluent mixture in each case. The relevant UV-active column fractions were combined and dried *in vacuo* to afford the target product in each case.

6.4.8 Purification of 4-quinolone products

Following *6.4.3* or *6.4.4*, the resultant mixture was cooled to room temperature if necessary and concentrated via rotary evaporation. The crude residue was then dissolved in methanol (~3-5 mL) and neutralized with concentrated HCl. The resulting solution was then dried *in vacuo* to afford a crude residue, which could then be subjected to chromatographic conditions for separation. In the case of normal-phase separations, chromatographic conditions analogous to those in *6.4.7* were employed. In the case of reverse-phase separations, the crude residue was dissolved in DMSO before being loaded onto a 40 g reverse-phase silica-based Silicycle SiliaSep C_{18} column cartridge. The product was then purified using the following gradient of acetonitrile/water: 0% acetonitrile (8 column volumes, CV), 0-100% (18CV), 100% (6CV). The relevant UV-active column fractions were combined and lyophilized to afford the target product in each case.

6.4.9 Nickel complexes: Synthesis and characterization

Procedure for the synthesis of (**PAd2-DalPhos**)Ni(4-CNPh)Cl. In a nitrogen-filled glovebox, **PAd2-DalPhos** (0.300 g, 0.592 mmol, 1.2 equiv; ~1.2:1 meso:rac **PAd2-DalPhos** used in this representative synthesis) and benzene (5 mL) were added to a screw-capped vial containing a magnetic stir bar. Magnetic stirring was initiated and continued until the mixture was homogeneous. Solid $Ni(COD)_2$ (0.136 g, 0.494 mmol, 1.0 equiv) was then added and the mixture was stirred until homogeneous, at which point solid 4-chlorobenzonitrile (0.0815 g, 0.592 mmol, 1.2 equiv) was added under the influence of continued stirring. Once a homogeneity was again obtained, stirring was halted and the magnetic stir bar was removed. The vial was sealed with a cap containing a PTFE septum and was allowed to stand at ambient temperature for 24 h; during this time the target product precipitated as a red solid, which was isolated by suction filtration (0.336 g, 0.494 mmol, 97%). The product was obtained as a ~1.4:1 mixture of meso and rac isomers of (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl. The identification of NMR signals attributable to the meso and rac isomers was made possibly by employing isomerically pure (meso or rac) **PAd2-DalPhos** in the above synthesis; due to the significant overlap of these resonances, integrations are not provided. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (br s, overlapping isomers), 8.53 (br s, 1H, rac isomer), 8.30 (br s, overlapping isomers), 7.82 – 7.73 (m, 1H, rac isomer), 7.72 – 7.50 (m, overlapping isomers), 7.38 (s, 2H, meso isomer), 7.34 – 7.29 (m, 1H, rac isomer), 7.25 – 7.09 (m, overlapping isomers), 3.95 (dd, J = 13.5, 3.8 Hz, 1H, rac isomer), 3.74 (dd, J = 13.4, 4.2 Hz, 1H, meso isomer), 2.46 – 2.35 (m, overlapping isomers), 2.26 (d, J = 13.6 Hz, 1H, meso isomer), 2.12 (d, J = 13.8 Hz, 1H, rac isomer), 2.08 – 1.97 (m, 3H, meso isomer), 1.97 – 1.64 (m, overlapping isomers), 1.63 – 1.35 (m, overlapping isomers), 1.34 – 1.16 (m, overlapping isomers), 1.16 – 1.08 (m,

overlapping isomers), 0.67 (dd, J = 13.8, 2.8 Hz, 1H, meso isomer), 0.55 (dd, J = 13.9, 2.8 Hz, 1H, rac isomer). $^{31}P\{^{1}H\}$ NMR (122 MHz, $CDCl_3$): δ 32.4 (d, J_{PP} = 7.5 Hz, meso isomer), 31.9 (d, J_{PP} = 10.6 Hz, rac isomer), 19.0 (d, J_{PP} = 7.6 Hz, meso isomer), 17.6 (d, J_{PP} = 10.6 Hz, rac isomer). Due to the poor solubility of *rac*-(**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, efforts to obtain suitably intense/resolved $^{13}C\{^{1}H\}$ NMR spectra were unsuccessful. $^{13}C\{^{1}H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$) for *meso*-(**PAd2-DalPhos**)Ni(4-CN-Ph)Cl: δ 170.4 (m), 169.6 (m), 142.4 (m), 140.6 (br m), 139.4 (m), 135.0 (m), 133.2 (br m), 132.1, 131.7, 129.6 (br m), 128.5, 128.0 (br m), 120.5, 105.7, 97.6, 96.7 (m), 75.5 (m), 41.6 (m), 39.5 (m), 30.0 (m), 28.7 (m), 27.9, 27.6, 26.8-26.6 (overlapping signals), 25.0 (m). Anal. Calculated for $C_{33}H_{40}ClNNiO_6P_2$ C, 56.40; H, 5.74; N, 1.99. Found: C, 56.12; H, 5.69; N, 2.15. A single crystal of *meso*-(**PAd2-DalPhos**)Ni(4-CNPh)Cl suitable for X-ray diffraction analysis was grown from a solution of (**PAd2-DalPhos**)Ni(4-CNPh)Cl in dichloromethane (CCDC 2102678).

Procedure for the synthesis of (**PAd2-DalPhos**)Ni(COD). In a nitrogen-filled glovebox, **PAd2-DalPhos** (0.064 g, 0.126 mmol, 1.05 equiv), $Ni(COD)_2$ (0.033 g, 0.12 mmol, 1.0 equiv), and benzene (1 mL) were added to a screw-capped vial containing a magnetic stir bar. The vial was sealed with a cap containing a PTFE septum, was removed from the glovebox, placed in a temperature-controlled aluminum heating block set at 80 ˚C, and was allowed to react under the influence of magnetic stirring for 30 minutes. The vial was then allowed to cool to room temperature before being brought back into the glovebox. The solvent was then removed *in vacuo* and the resulting crude residue was washed with 1 mL of cold (-33 ˚C) pentane. The residue was then dried *in vacuo* yielding (**PAd2-DalPhos**)Ni(COD) as an orange solid (0.056 g, 0.083 mmol, 69%). The product was isolated

as a ~1:1 mixture of isomers corresponding to meso and rac (**PAd2-DalPhos**)Ni(COD). ^{1}H NMR data collected in C_6D_6 (300-330 K) for the mixture of rac and meso isomers of (**PAd2-DalPhos** Ni(COD) appeared broad, likely due to various dynamic processes, and thus definitive assignments could not made; the ^{1}H NMR spectrum is provided for completeness (Figure S98). $^{13}C\{^{1}H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 146.7 (m), 145.3 (m), 133.0-132.8 (overlapping signals), 128.4-128.1 (overlapping signals), 97.1 (d, J = 34.0 Hz), 95.8 (d, J = 27.7 Hz), 86.3, 84.8, 80.8, 80.4, 75.9 (m), 75.0 (m), 74.4 (m), 43.9 (overlapping signals), 39.6, 39.1, 30.8 (m), 30.2, 28.6 (m), 27.9 (m), 25.6-24.8 (overlapping signals). $^{31}P\{^{1}H\}$ NMR (202.5 MHz, C_6D_6): δ 35.3 (s, rac), 33.0 (s, meso). Anal. Calculated for $C_{34}H_{48}NiO_6P_2$ C, 60.64; H, 7.18. Found: C, 60.87; H, 6.91. A single crystal of *rac*-(**PAd2-DalPhos**)Ni(COD) suitable for X-ray diffraction analysis was grown from a solution of (**PAd2-DalPhos**)Ni(COD) in a mixture of C_6H_6 and $CDCl_3$ (CCDC 2102676).

Procedure for the synthesis of ((**PAd2-DalPhos**)$NiCl)_2$. In a nitrogen-filled glovebox, **PAd2-DalPhos** (0.018 g, 0.036 mmol, 1.02 equiv), $Ni(COD)_2$ (0.010 g, 0.035 mmol, 1.0 equiv), and benzene (0.24 mL) were added to a screw-capped vial containing a magnetic stir bar. The vial was sealed with a cap containing a PTFE septum, was removed from the glovebox, placed in a temperature-controlled aluminum heating block set at 80 ˚C, and was allowed to react to form (**PAd2-DalPhos**)Ni(COD) under the influence of magnetic stirring for 30 minutes. The vial was then allowed to cool to room temperature before being brought back into the glovebox. A separate vial containing a magnetic stir bar was then charged with (**PAd2-DalPhos**)$NiCl_2$ (0.022 g, 0.035 mmol, 1.0 equiv). The solution of generated (**PAd2-DalPhos**)Ni(COD) was then added to the vial containing (**PAd2-DalPhos**)$NiCl_2$, stirring was initiated, and the resultant mixture was left to stir at room-temperature for 3 h. The

mixture was then filtered over Celite, eluted with benzene (~5 mL), and the eluent was then collected and dried *in vacuo*. The resultant crude residue was then washed with minimal cold (-33 ˚C) pentane (2 x 2 mL). The residue was then dried *in vacuo* yielding ((**PAd2-DalPhos**)$NiCl)_2$ as an orange, dinuclear, paramagnetic (NMR-silent) solid (0.028 g, 0.023 mmol, 66%). Anal. Calculated for $C_{26}H_{36}ClNiO_6P_2$ C, 51.99; H, 6.04. Found: C, 52.18; H, 6.17. Single crystals of both *meso*+*rac*-((**PAd2-DalPhos**)$NiCl)_2$ (CCDC 2102681) and *rac*+*rac*-((**PAd2-DalPhos**)$NiCl)_2$ (CCDC 2102679) suitable for X-ray diffraction analysis were grown by way of vapor diffusion of pentane into a benzene solution of ((**PAd2-DalPhos**)$NiCl)_2$.

Procedure for the synthesis of (**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl. In a nitrogen-filled glovebox, a vial containing a magnetic stir bar was charged with **PAd2-DalPhos** (0.182 g, 0.36 mmol, 1.2 equiv), $Ni(COD)_2$ (0.083 g, 0.300 mmol, 1.0 equiv), and benzene (2 mL). The resulting mixture was stirred magnetically at room temperature for five minutes before 2-chloroacetophenone (311 µL, 2.4 mmol, 8.0 equiv) was added. The resulting mixture was then stirred magnetically at room temperature for 2 h, after which pentane (6 mL) was added, forming an insoluble suspension. The filtrate was decanted off, and the crude residual solid was further washed (2 x 3 mL) with a 1:4 benzene-pentane mixture. The resultant material was then dried *in vacuo* to afford (**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl as an orange solid (0.120 g, 0.167 mmol, 56%). As noted in the text, (**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl as prepared and isolated exists, based on ^{1}H and ^{31}P NMR data, as a mixture of isomers (~10:2:1, major *meso*-**PAd2-DalPhos**, minor *rac*- **PAd2-DalPhos**, minor *meso*- **PAd2-DalPhos**) arising from the meso/rac composition of **PAd2-DalPhos** and hindered Ni-aryl rotation arising from carbonyl coordination. Where appropriate, NMR signals were assigned and integrated primarily in the

case of the major isomer. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.65 (m, 1H), 8.42 (m, 1H), 7.88-7.86 (m, 1H), 7.59-7.56 (m, overlapping isomers), 7.12-7.09 (m, 1H), 6.90-6.87 (m, 1H), 3.56 (dd, *J* = 13.3, 4.1 Hz, 1H), 2.61 (s, 3H), 2.37-2.31 (m, 2H), 1.94-1.44 (m, overlapping isomers), 0.98-0.91 (m, overlapping isomers). $^{13}C\{^{1}H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 204.3, 172.0 (m), 143.7 (m), 142.4, 140.8 (m), 135.1 (m), 131.3-130.6 (overlapping signals), 121.8, 97.4, 96.7-96.2 (overlapping signals), 76.5 (m), 75.5 (m), 74.5 (m), 42.0 (m), 41.4 (m), 39.6 (m), 29.7 (m), 28.9 (m), 28.2, 27.7, 26.9, 26.7, 25.6 (m), 25.1 (m). $^{31}P\{^{1}H\}$ NMR (202.5 MHz, $CDCl_3$): δ 25.6 (d, J_{PP} = 11.9 Hz, minor meso), 23.2 (d, J_{PP} = 14.0 Hz, minor rac), 22.5-22.3 (second order m, major meso), 19.7 (d, J_{PP} = 13.9 Hz, minor rac), 17.0 (d, J_{PP} = 11.9 Hz, minor meso). Anal. Calculated for $C_{34}H_{43}ClNiO_7P_2$ C, 56.73; H, 6.02. Found: C, 56.55; H, 5.83. A single crystal of *meso*-(**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl suitable for X-ray diffraction analysis was grown by way of vapor diffusion of pentane into a benzene solution of (**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl (CCDC 2102680).

Procedure for the synthesis of *meso*-(**PAd2-DalPhos**)Ni(2-Ac-Ph)TFA. In a nitrogen-filled glovebox, a vial containing a magnetic stir bar was charged with **PAd2-DalPhos** (0.182 g, 0.36 mmol, 1.2 equiv.), $Ni(COD)_2$ (0.083 g, 0.30 mmol, 1.0 equiv), and benzene (2 mL). The resulting mixture was stirred magnetically at room temperature for five minutes before 2-chloroacetophenone (311 μL, 2.4 mmol, 8.0 equiv) and NaTFA (0.163 g, 1.2 mmol, 4.0 equiv) were added. The resulting mixture was stirred magnetically at room temperature for 4 hours, after which pentane (6 mL) was added, to form an insoluble suspension. The filtrate was decanted off, and the crude residue was further washed (2 x 3 mL) with a 1:4 benzene-pentane mixture. The residue was then taken up in CH_2Cl_2 (10 mL) and the mixture was filtered over Celite. The filtrate was collected and dried *in vacuo* to

afford exclusively *meso*-(**PAd2-DalPhos**)Ni(2-Ac-Ph)TFA as an orange solid (0.102 g, 0.128 mmol, 43%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.60-8.58 (m, 1H), 8.28-8.26 (m, 1H), 8.02-8.00 (m, 1H), 7.63-7.61 (m, 1H), 7.58-7.55 (m, 1H), 7.08-7.05 (m, 1H), 6.96-6.93 (m, 1H), 2.81 (dd, *J* = 13.5, 4.4 Hz, 1H), 2.68 (s, 3H), 2.34-2.28 (m, 2H), 2.13 (d, *J* = 15.7 Hz, 3H), 1.94-1.84 (m, 2H), 1.82-1.78 (m, overlapping Hs), 1.71 (d, *J* = 13.9 Hz, 3H), 1.53 (s, 3H), 1.44 (s, 3H), 1.32 (s, 3H), 1.12 (dd, *J* = 23.1, 14.4, 1H), 0.97 (d, *J* = 14.3 Hz, 3H), 0.92 (s, 3H), 0.68 (dd, *J* = 13.4, 3.4, 1H). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 204.7 (two signals), 167.4 (m), 160.3 (m), 144.0, 143.5 (m), 140.8, 138.8 (m), 134.4 (m), 131.5-130.0 (overlapping signals), 128.3, 122.9, 97.4, 96.5-95.7 (overlapping signals), 76.1 (m), 75.0 (m), 41.9-41.1 (overlapping signals), 39.5, 28.9-27.5 (m), 26.6 (m), 25.1 (m), 24.9 (m). ^{31}P{^{1}H} NMR (202.5 MHz, $CDCl_3$): δ 26.6 (d, J_{PP} = 14.0 Hz), 24.7 (d, J_{PP} = 14.0 Hz). ^{31}P{^{1}H} NMR (202.5 MHz, C_6D_6): δ 26.6 (d, J_{PP} = 14.0 Hz), 24.5 (d, J_{PP} = 14.0 Hz). Anal. Calculated for $C_{36}H_{43}F_3NiO_9P_2$ C, 54.23; H, 5.44. Found: C, 54.26; H, 5.27. A single crystal of *meso*-(**PAd2-DalPhos**)Ni(2-Ac-Ph)TFA suitable for X-ray diffraction analysis was grown by way of vapor diffusion of pentane into a benzene solution of *meso*-(**PAd2-DalPhos**)Ni(2-Ac-Ph)TFA (CCDC 2102677).

6.4.10 Procedure for examining C-N bond reductive elimination

In a nitrogen-filled glovebox, (**PAd2-DalPhos**)Ni(2-Ac-Ph)X (X = Cl or TFA, 1.0 equiv), 3,5-bis(trifluoromethyl)benzamide (5.0 equiv), DBU (5.0 equiv), and benzene (0.015 M) were added to a screw-capped vial containing a magnetic stir bar. The vial was sealed with a cap containing a PTFE septum, magnetic stirring was initiated, and the reaction mixture was analyzed by use of ^{31}P{^{1}H} NMR methods (C_6H_6, 25 ºC, 1 h; 202.5 MHz, C_6D_6: δ 36.2, d, J_{PP} = 76.0 Hz, complex-I; 34.2, d, J_{PP} = 84.9 Hz, complex-II; 23.7, d, J_{PP} = 84.9

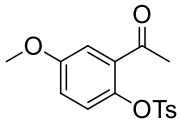
Hz, complex-II; 23.1, d, J_{PP} = 76.0 Hz, complex-I); a discussion of these results is provided in the text. Similar results were obtained under analogous conditions using 4-methoxybenzamide in place of 3,5-bis(trifluoromethyl)benzamide, whereby $^{31}P\{^{1}H\}$ NMR analysis revealed full conversion two new ligated (**PAd2-DalPhos**)Ni(0) species in a ~3:1 ratio (202.5 MHz, C_6D_6: δ 37.0 (d, J_{PP} = 83.4 Hz, minor), 32.6 (d, J_{PP} = 88.2 Hz, major), 23.1 (d, J_{PP} = 88.2 Hz, major), 20.9 (d, J_{PP} = 83.4 Hz, minor).

6.4.11 Procedure for conducting competition experiments

The favourability of 3,5-bis(trifluoromethyl)benzamide as a substrate over 4-methoxybenzamide was demonstrated in a cross-coupling competition experiment featuring these nucleophiles. (**PAd2-DalPhos**)NiCl(4-CN-Ph) (5 mol%), NaTFA (2.0 equiv), DBU (2.0 equiv), aryl chloride (0.12 mmol, 1.0 equiv), and primary amides (2.2 equiv) were added to a screw capped vial, followed by a magnetic stir bar and toluene so that the initial concentration of aryl chloride was 0.12 M. The vial was then sealed with a cap containing a PTFE septum, removed from the glovebox, and placed in a temperature-controlled aluminum heating block set to 25 ˚C. The mixture was stirred at this temperature for 18 h, after which time phenyldocecane (1.0 equiv) was then added as an internal standard for calibration against authentic products in each case. Subsequently, an aliquot of the reaction mixture was filtered through a short Celite/silica plug, diluted with EtOAc (~1.5 mL), and subjected to GC analysis. Full conversion of the electrophile was achieved leading to **6.1** and **6.2** in a ~6:1 ratio. While a number of variables are likely to contribute to this observed selectivity, it is plausible that more facile deprotonation by DBU of the more acidic 3,5-bis(trifluoromethyl)benzamide, versus 4-methoxybenzamide, is a contributing factor.

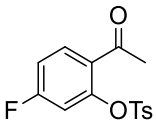
6.4.12 Characterization data for aryl tosylates and organic products

2-acetyl-4-methoxyphenyl 4-methylbenzenesulfonate



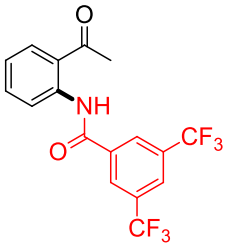
The title compound was synthesized and purified from the corresponding 2-acetylphenol (3 mmol), which afforded the title compound in a 66% isolated yield (0.638 g, 1.98 mmol).^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.66-7.65 (m, 2H), 7.32-7.30 (m, 2H), 7.11 (d, J = 3.0 Hz, 1H), 6.96-6.90 (m, 2H, overlapping Hs), 3.80 (s, 3H), 2.51 (s, 3H), 2.45 (s, 3H). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 197.7, 158.1, 145.8, 140.7, 134.6, 131.9, 129.9, 128.6, 124.6, 118.7, 113.9, 55.8, 30.4, 21.7. HRMS-ESI (*m*/*z*): Calc'd for $C_{16}H_{16}O_5SNa$ $[M+Na]^+$: 343.0616. Found: 343.0621.

2-acetyl-5-fluorophenyl 4-methylbenzenesulfonate



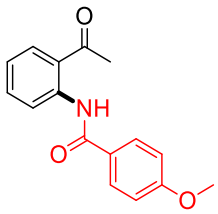
The title compound was synthesized and purified from the corresponding 2-acetylphenol (3 mmol), which afforded the title compound in a 94% isolated yield (0.638 g, 1.98 mmol).^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.73-7.69 (m, 3H, overlapping Hs), 7.35 (d, J = 8.0 Hz, 2H), 7.06-7.02 (m, 1H), 6.88 (dd, J = 9.0. 2.5 Hz, 1H), 2.49 (s, 3H), 2.47 (s, 3H). ^{19}F NMR (470.6 MHz, $CDCl_3$): δ -103.6 (m). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 196.3, 164.5 (d, J = 255.6), 148.5 (d, J = 11.2 Hz), 146.3, 132.1 (d, J = 10.1 Hz), 131.7, 130.1, 129.8 (d, J = 3.5 Hz), 128.5, 114.5 (d, J = 21.3 Hz), 111.0 (d, J = 25.2 Hz), 30.5, 21.8. HRMS-ESI (*m*/*z*): Calc'd for $C_{15}H_{13}FO_4SNa$ $[M+Na]^+$: 331.0411. Found: 331.0400.

N-(2-acetylphenyl)-3,5-bis(trifluoromethyl)benzamide (**6.1**)



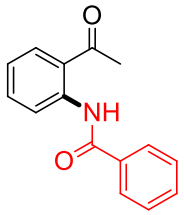
The title compound was synthesized from the corresponding aryl chloride (1.00 mmol) according to *6.4.2*, conducted at 110 °C in toluene using 5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, and purified according to *6.4.7*. Purified by flash chromatography on silica using an eluent gradient of 10% ethyl acetate in hexanes which afforded the title compound in an 97% isolated yield (386 mg, 0.97 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 13.02 (s, 1H), 8.90 (d, *J* = 8.5 Hz, 1H), 8.52 (s, 2H), 8.07 (s, 1H), 7.99 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.65 (td, *J* = 7.9, 1.3 Hz, 1H), 7.24-7.21 (m, 1H), 2.74 (s, 3H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -62.9. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 203.7, 163.0, 140.8, 137.2, 135.7, 132.6 (q, *J* = 34.1 Hz), 132.1, 127.91-127.89 (m), 125.54-125.48 (m), 123.5, 123.1 (q, *J* = 272.7 Hz), 122.3, 121.0, 28.6. HRMS-ESI (m/z): Calc'd for $C_{17}H_{11}F_6NO_2Na$ $[M+Na]^+$: 398.0586. Found: 398.0592.

N-(2-acetylphenyl)-4-methoxybenzamide (6.2)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *6.4.2*, conducted at 110 °C using 5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, and purified according to *6.4.7* using automated normal-phase chromatography with an eluent gradient of 100% hexanes (4 CV), 0-25% ethyl acetate in hexanes (12 CV) followed by 25% ethyl acetate in hexanes (4 CV) which afforded the title compound in a 73% isolated yield (0.0934 g, 0.350 mmol). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 12.6 (s, 1H), 8.98-8.96 (m, 1H), 8.06-8.03 (m, 2H), 7.96-7.94 (m, 1H), 7.62-7.59 (m, 1H), 7.15-7.12 (m, 1H), 7.03-7.00 (m, 2H), 3.88 (s, 3H), 2.72 (s, 3H). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 203.2, 165.7, 162.6, 141.7, 135.4, 131.8, 129.4, 127.2, 122.2, 121.9, 120.8, 114.0, 55.4, 28.6. HRMS-ESI (*m*/*z*): Calc'd for $C_{16}H_{15}NO_3Na$ $[M+Na]^+$: 292.0944. Found: 292.0941.

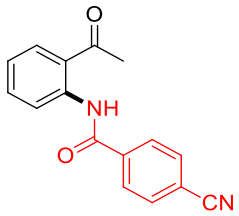
N-(2-acetylphenyl)benzamide (**6.3**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *6.4.2*, conducted at 110 °C in toluene using 5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, and purified according to *6.4.7*. Purified by flash chromatography on silica using an eluent gradient of 25% ethyl acetate in hexanes which afforded the title compound in an 92% isolated yield (106 mg, 0.442 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 12.69 (s, 1H), 8.99 (dd, *J* = 8.5, 0.9 Hz, 1H), 8.08-8.06 (m, 2H), 7.95 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.62

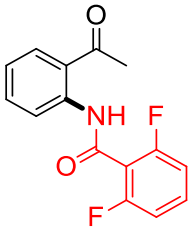
(ddd, J = 8.5, 7.3, 1.3 Hz, 1H), 7.57-7.50 (m, 3H), 7.17-7.14 (m, 1H), 2.71 (s, 3H). $^{13}C\{^{1}H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 203.3, 166.2, 141.5, 135.5, 134.9, 132.1, 131.9, 128.9, 127.6, 122.6, 122.1, 120.9, 28.7. HRMS-ESI (m/z): Calc'd for $C_{15}H_{13}NO_2Na$ $[M+Na]^+$: 262.0838. Found: 262.0849.

N-(2-acetylphenyl)-4-cyanobenzamide (**6.4**)



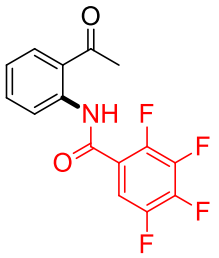
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *6.4.2*, conducted at 110 °C in toluene using 5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, and purified according to *6.4.7*. Purified by flash chromatography on silica using an eluent gradient of 15% ethyl acetate in hexanes which afforded the title compound in an 90% isolated yield (114 mg, 0.432 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 12.86 (s, 1H), 8.93 (d, J = 8.0 Hz, 1H), 8.16 (d, J = 8.4 Hz, 2H), 7.99 (d, J = 8.0, 1.3 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.67-7.63 (m, 1H), 7.23-7.20 (m, 1H), 2.73 (s, 3H). $^{13}C\{^{1}H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 203.8, 164.2, 141.0, 138.8, 135.7, 132.8, 132.1, 128.3, 123.3, 122.2, 121.0, 118.2, 115.6, 28.7. HRMS-ESI (m/z): Calc'd for $C_{16}H_{12}N_2O_2Na$ $[M+Na]^+$: 287.0791. Found: 287.0797.

N-(2-acetylphenyl)-2,6-difluorobenzamide (**6.5**)



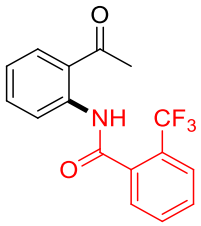
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *6.4.2*, conducted at 110 °C in toluene using 5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, and purified according to *6.4.7*. Purified by flash chromatography on silica using an eluent gradient of 15% ethyl acetate in hexanes which afforded the title compound in an 78% isolated yield (103 mg, 0.374 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 12.24 (s, 1H), 8.93 (d, J = 8.4 Hz, 1H), 7.94 (dd, J = 8.0, 1.4 Hz, 1H), 7.64-7.61 (m, 1H), 7.41 (tt, J = 8.5, 6.3 Hz, 1H), 7.22-7.18 (m, 1H), 7.00 (t, J = 8.1 Hz, 2H), 2.67 (s, 3H). $^{19}F\{^{1}H\}$ NMR (470.6 MHz, $CDCl_3$): δ -112.1. $^{13}C\{^{1}H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 202.9, 160.1 (dd, J = 252.6, 6.4 Hz), 159.4, 140.5, 135.4, 132.1 (t, J = 10.2 Hz), 131.8, 124.3, 122.3, 121.3, 115.3 (t, J = 19.5 Hz), 112.4-112.2 (m), 28.6. HRMS-ESI (m/z): Calc'd for $C_{15}H_{11}F_2NO_2Na$ $[M+Na]^+$: 298.0650. Found: 298.0651.

N-(2-acetylphenyl)-2,3,4,5-tetrafluorobenzamide (**6.6**)



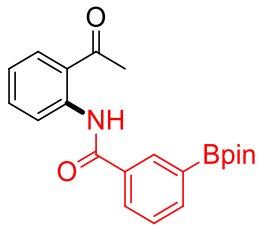
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *6.4.2*, conducted at 110 °C in toluene using 7.5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, and purified according to *6.4.7*. Purified by flash chromatography on silica using an eluent gradient of 15% ethyl acetate in hexanes which afforded the title compound in an 68% isolated yield (102 mg, 0.326 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 12.55 (s, 1H), 8.84 (d, *J* = 8.5 Hz, 1H), 7.96 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.72-7.68 (m, 1H), 7.64-7.61 (m, 1H), 7.24-7.21 (m, 1H), 2.70 (s, 3H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -137.1 (ddd, *J* = 21.3, 13.6, 2.9 Hz), -138.0 (ddd, *J* = 21.7, 13.9, 7.5 Hz), -149.0 (ddd, *J* = 21.3, 19.3, 7.2 Hz), -153.3 (ddd, *J* = 22.1, 19.0, 3.1 Hz). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 202.8, 159.8, 147.3 (dd, *J* = 248.5, 10.4 Hz), 146.1 (dd, *J* = 253.0, 10.1 Hz), 144.0-143.7 (m), 142.2-141.7 (m), 140.1, 135.3, 131.9, 123.7, 123.0, 121.8, 119.3-119.2 (m), 112.8 (d, *J* = 20.9 Hz), 28.6. HRMS-ESI (m/z): Calc'd for $C_{15}H_9F_4NO_2Na$ $[M+Na]^+$: 334.0462. Found: 334.0456.

N-(2-acetylphenyl)-2-(trifluoromethyl)benzamide (**6.7**)



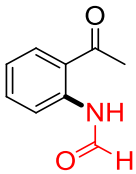
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *6.4.2*, conducted at 110 °C in toluene using 5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, and purified according to *6.4.7*. Purified by flash chromatography on silica using an eluent gradient of 15% ethyl acetate in hexanes which afforded the title compound in an 83% isolated yield (122 mg, 0.398 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 12.07 (s, 1H), 8.88 (d, *J* = 7.8 Hz, 1H), 7.93 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.68-7.57 (m, 4H), 7.21-7.17 (m, 1H), 2.64 (s, 3H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -58.9. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 203.0, 166.7, 140.7, 136.4, 135.4, 132.3, 131.8, 130.3, 128.4-127.5 (m), 128.2, 126.9 (q, *J* = 4.8 Hz), 124.8, 123.3, 122.3, 121.1, 28.6. HRMS-ESI (m/z): Calc'd for $C_{16}H_{12}F_3NO_2Na$ $[M+Na]^+$: 330.0712. Found: 330.0711.

N-(2-acetylphenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (**6.8**)



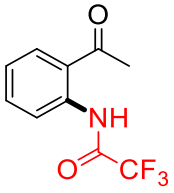
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *6.4.2*, conducted at 110 °C in toluene using 7.5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, and purified according to *6.4.7*. Purified by flash chromatography on silica using an eluent gradient of 15% ethyl acetate in hexanes which afforded the title compound in an 60% isolated yield (96.0 mg, 0.288 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 12.63 (s, 1H), 8.96 (d, J = 8.5 Hz, 1H), 8.51 (s, 1H), 8.11 (ddd, J = 7.8, 1.9, 1.2 Hz, 1H), 7.98 (d, J = 7.3 Hz, 1H), 7.94 (dd, J = 8.0, 1.4 Hz, 1H), 7.63-7.60 (m, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.15 (td, J = 7.6, 0.9 Hz, 1H), 2.71 (s, 3H), 1.37 (s, 12H). ^{11}B NMR (128 MHz, $CDCl_3$): δ 31.5 (br s). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 203.1, 166.5, 141.6, 138.3, 135.4, 134.5, 134.3, 131.8, 129.9, 128.2, 122.6, 122.3, 121.1, 84.2, 28.7, 25.0. HRMS-ESI (m/z): Calc'd for $C_{21}H_{24}BNO_4Na$ $[M+Na]^+$: 388.1691. Found: 388.1694.

N-(2-acetylphenyl)formamide (**6.9**)



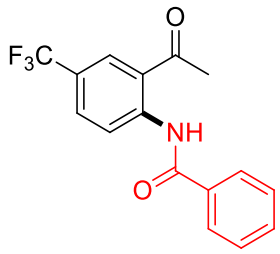
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *6.4.2*, conducted at 110 °C in toluene using 5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, and purified according to *6.4.2*. Purified by flash chromatography on silica using an eluent gradient of 15% ethyl acetate in hexanes which afforded the title compound in an 81% isolated yield (63.4 mg, 0.389 mmol) as a pale yellow solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 11.60 (s, 1H), 8.74 (d, J = 8.4 Hz, 1H), 8.49 (s, 1H), 7.92 (dd, J = 8.0, 1.5 Hz, 1H), 7.56 (t, J = 7.7 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 2.67 (s, 3H). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 202.9, 160.0, 140.0, 135.3, 131.8, 123.2, 122.1, 121.8, 28.7. HRMS-ESI (m/z): Calc'd for $C_9H_9NO_2Na$ $[M+Na]^+$: 186.0525. Found: 186.0522.

N-(2-acetylphenyl)-2,2,2-trifluoroacetamide (**6.10**)



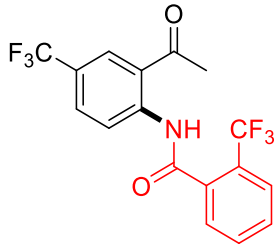
The title compound was synthesized from the corresponding aryl chloride (0.24 mmol) according to *6.4.2* using 2.0 equiv. of TMG instead of DBU, conducted at 110 °C using 10 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, and purified according to *6.4.7* using automated normal-phase chromatography with an eluent gradient of 100% hexanes (4 CV), 0-10% ethyl acetate in hexanes (16 CV) followed by 10% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 23% isolated yield (0.013 g, 0.055 mmol). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 12.91 (br, 1H), 8.69 (d, J = 8.4 Hz, 1H), 7.99 (dd, J = 8.0, 1.3 Hz, 1H), 7.66-7.63 (m, 1H), 7.31-7.27 (m, 1H), 2.71 (s, 3H). ^{19}F NMR (470.6 MHz, $CDCl_3$): δ -76.3 (br s). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 203.1, 155.7 (q, J = 37.7 Hz), 138.5, 135.4, 131.8, 124.6, 122.6, 121.1, 115.7 (q, J = 288.6 Hz), 28.3. HRMS-ESI (*m*/*z*): Calc'd for $C_{10}H_7F_3NO_2$ [M-H]$^-$: 230.0434. Found: 230.0432.

N-(2-acetyl-4-(trifluoromethyl)phenyl)benzamide (**6.11**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *6.4.2*, conducted at 110 °C in toluene using 5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, and purified according to *6.4.7*. Purified by flash chromatography on silica using an eluent gradient of 15% ethyl acetate in hexanes which afforded the title compound in an 83% isolated yield (122 mg, 0.397 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 12.80 (s, 1H), 9.14 (d, J = 8.9 Hz, 1H), 8.18 (s, 1H), 8.06 (d, J = 7.3 Hz, 2H), 7.84 (d, J = 8.9 Hz, 1H), 7.60-7.52 (m, 3H), 2.77 (s, 3H). ^{19}F{^{1}H} NMR (470.6 MHz, $CDCl_3$): δ -62.3. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 202.5, 166.4, 144.3, 134.3, 132.6, 131.94-131.92 (m), 129.1, 129.0-128.9 (m), 127.7, 124.4 (q, J = 33.4 Hz), 122.7, 121.5, 121.3, 28.7. HRMS-ESI (m/z): Calc'd for $C_{16}H_{12}F_3NO_2Na$ [M+Na]$^+$: 330.0712. Found: 330.0721.

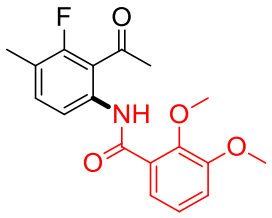
N-(2-acetyl-4-(trifluoromethyl)phenyl)-2-(trifluoromethyl)benzamide (**6.12**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *6.4.2*, conducted at 110 °C in toluene using 5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, and purified according to *6.4.7*. Purified by flash chromatography on silica using an eluent gradient of 15% ethyl acetate in hexanes which afforded the title compound in an 61% isolated yield (150 mg, 0.398 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 12.19

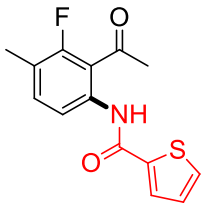
(s, 1H), 9.06 (d, J = 8.8, 1H), 8.17 (d, J = 1.0 Hz, 1H), 7.86 (dd, J = 8.9, 1.8 Hz, 1H), 7.78 (d, J = 7.7 Hz, 1H), 7.68-7.61 (m, 3H), 2.71 (s, 3H). $^{19}F\{^1H\}$ NMR (470.6 MHz, $CDCl_3$): δ -58.9, -62.4. $^{13}C\{^1H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 202.1, 167.0, 143.4, 135.8, 132.4, 131.9 (d, J = 3.3 Hz), 130.7, 128.8-128.7 (m), 128.2, 128.0 (q, J = 31.4 Hz), 127.1 (q, J = 5.3 Hz), 125.2 (q, J = 34.3 Hz), 124.7, 122.6 (d, J = 5.3 Hz), 121.8, 121.5, 28.6. HRMS-ESI (m/z): Calc'd for $C_{17}H_{11}F_6NO_2Na$ $[M+Na]^+$: 398.0586. Found: 398.0592.

N-(2-acetyl-3-fluoro-4-methylphenyl)-2,3-dimethoxybenzamide (**6.13**)



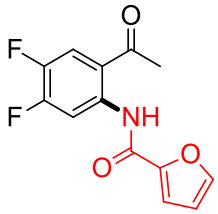
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *6.4.2*, conducted at 110 °C in toluene using 5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, and purified according to *6.4.7*. Purified by flash chromatography on silica using an eluent gradient of 20% ethyl acetate in hexanes which afforded the title compound in an 65% isolated yield (103 mg, 0.312 mmol) as a white solid. ^1H NMR (500.1 MHz, $CDCl_3$): δ 11.50 (s, 1H), 8.29 (d, J = 8.5 Hz, 1H), 7.67 (dd, J = 7.9, 1.6 Hz, 1H), 7.31 (t, J = 8.6 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.07 (dd, J = 8.1, 1.5 Hz, 1H), 4.05 (s, 3H), 3.90 (s, 3H), 2.63 (d, J = 6.1 Hz, 3H), 2.28 (d, J = 2.1 Hz, 3H). $^{19}F\{^1H\}$ NMR (470.6 MHz, $CDCl_3$): δ -112.3. $^{13}C\{^1H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 200.5, 164.4, 161.1, 159.1, 153.0, 148.0, 134.9 (d, J = 6.9 Hz), 127.4, 124.2, 122.9, 120.4 (d, J = 20.1 Hz), 118.8, 118.6, 116.0, 61.7, 56.2, 33.0, 14.2. HRMS-ESI (m/z): Calc'd for $C_{18}H_{18}FNO_4Na$ $[M+Na]^+$: 354.1112. Found: 354.1112.

N-(2-acetyl-3-fluoro-4-methylphenyl)thiophene-2-carboxamide (**6.14**)



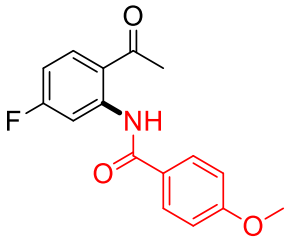
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *6.4.2*, conducted at 110 °C in toluene using 5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, and purified according to *6.4.7*. Purified by flash chromatography on silica using an eluent gradient of 15% ethyl acetate in hexanes which afforded the title compound in an 75% isolated yield (99.8 mg, 0.360 mmol) as a white solid. ^1H NMR (500.1 MHz, $CDCl_3$): δ 12.09 (s, 1H), 8.47 (m, 1H), 7.56 (m, 1H), 7.37 (m, 1H), 7.26 (m, 1H), 7.15 (m, 1H), 2.71 (d, J = 8.0 Hz, 3H), 2.28 (s, 3H). $^{19}F\{^1H\}$ NMR (470.6 MHz, $CDCl_3$): δ -107.5. $^{13}C\{^1H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ 202.2, 162.7, 160.6 (d, J = 9.7 Hz), 140.3, 139.2, 137.0 (d, J = 8.3 Hz), 131.5, 128.8, 128.1, 120.0 (d, J = 20.2 Hz), 116.5, 113.1 (d, J = 15.2 Hz), 33.9 (d, J = 12.3 Hz), 14.3 (d, J = 5.5 Hz). HRMS-ESI (m/z): Calc'd for $C_{14}H_{12}FNO_2SNa$ $[M+Na]^+$: 300.0465. Found: 300.0465.

N-(2-acetyl-4,5-difluorophenyl)furan-2-carboxamide (**6.15**)



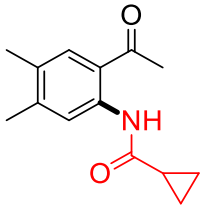
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *6.4.2*, conducted at 110 °C in toluene using 5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, and purified according to *6.4.7*. Purified by flash chromatography on silica using an eluent gradient of 20% ethyl acetate in hexanes which afforded the title compound in an 77% isolated yield (98.0 mg, 0.370 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 12.67 (s, 1H), 8.88 (dd, *J* = 13.4, 7.6 Hz, 1H), 7.72 (dd, *J* = 10.8, 8.5 Hz, 1H), 7.62 (s, 1H), 7.27 (s, 1H), 6.56 (dd, *J* = 3.5, 1.7 Hz, 1H), 2.66 (s, 3H). ^{19}F NMR (470.6 MHz, $CDCl_3$): δ -123.74, -123.78. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 200.7, 157.1, 154.0 (dd, *J* = 256.6, 12.5 Hz), 147.9, 145.4, 145.1 (dd, *J* = 246.6, 13.6 Hz), 138.8 (d, *J* = 12.4 Hz), 120.0 (d, *J* = 18.3 Hz), 118.5, 116.1, 112.6, 110.2 (d, *J* = 24.3 Hz), 28.7. HRMS-ESI (m/z): Calc'd for $C_{13}H_9F_2NO_3Na$ $[M+Na]^+$: 288.0443. Found: 288.0444.

N-(2-acetyl-5-fluorophenyl)-4-methoxybenzamide (**6.16**)



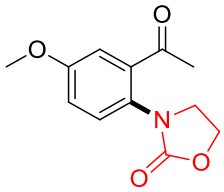
The title compound was synthesized from the corresponding aryl tosylate (0.48 mmol) according to *6.4.2*, conducted at 110 °C using 5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, and purified according to *6.4.7* using automated normal-phase chromatography with an eluent gradient of 100% hexanes (4 CV), 0-30% ethyl acetate in hexanes (12 CV) followed by 30% ethyl acetate in hexanes (6 CV) which afforded the title compound in an 84% isolated yield (0.116 g, 0.403 mmol). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 12.82 (s, 1H), 8.79 (dd, *J* = 12.2, 2.6 Hz, 1H), 8.04-8.02 (m, 2H), 7.95 (dd, *J* = 8.9, 6.3 Hz, 1H), 7.02-6.99 (m, 2H), 6.83-6.79 (m, 1H), 3.88 (s, 3H), 2.68 (s, 3H). ^{19}F NMR (470.6 MHz, $CDCl_3$): δ -99.2 (m). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, solvent): δ 201.8, 166.5 (d, *J* = 255.1 Hz), 165.8, 162.9, 144.3 (d, *J* = 13.5 Hz), 134.2 (d, *J* = 11.4 Hz), 129.5, 126.7, 118.4 (d, *J* = 2.4 Hz), 114.1, 109.4 (d, *J* = 22.7 Hz), 107.7 (d, *J* = 28.2 Hz), 55.4, 28.6. HRMS-ESI (*m/z*): Calc'd for $C_{16}H_{14}FNO_3Na$ $[M+Na]^+$: 310.0850. Found: 310.0839.

N-(2-acetyl-4,5-dimethylphenyl)cyclopropanecarboxamide (**6.17**)



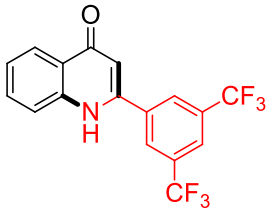
The title compound was synthesized from the corresponding aryl tosylate (0.48 mmol) according to *6.4.2*, conducted at 110 °C using 5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, and purified according to *6.4.7* using automated normal-phase chromatography with an eluent gradient of 100% hexanes (4 CV), 0-20% ethyl acetate in hexanes (12 CV) followed by 20% ethyl acetate in hexanes (6 CV) which afforded the title compound in a 68% isolated yield (0.0752 g, 0.326 mmol). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 11.9 (s, 1H), 8.55 (s, 1H), 7.61 (s, 1H), 2.64 (s, 3H), 2.29 (s, 3H), 2.26 (s, 3H), 1.66-1.61 (m, 1H), 1.08-1.05 (m, 2H), 0.87-0.84 (m, 2H). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 202.3, 172.9, 145.2, 139.3, 132.3, 130.3, 121.6, 119.6, 28.5, 20.5, 19.3, 16.7, 8.1. HRMS-ESI (*m*/*z*): Calc'd for $C_{14}H_{17}NO_2Na$ $[M+Na]^+$: 254.1151. Found: 254.1155.

3-(2-acetyl-4-methoxyphenyl)oxazolidin-2-onebenzamide (**6.18**)



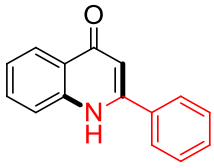
The title compound was synthesized from the corresponding aryl tosylate (0.48 mmol) according to *6.4.2*, conducted at 110 °C in toluene using 5 mol% ((**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, and purified according to *6.4.7*. Purified by flash chromatography on silica using an eluent gradient of 30% ethyl acetate in hexanes which afforded the title compound in an 84% isolated yield (94.8 mg, 0.403 mmol) as a white solid. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.21 (d, J = 8.7 Hz, 1H), 7.17 (d, J = 2.9 Hz, 1H), 7.01 (dd, J = 8.7, 2.9 Hz, 1H), 4.47 (t, J = 8.0 Hz, 2H), 3.97 (t, J = 8.0 Hz, 2H), 3.83 (s, 3H), 2.55 (s, 3H). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ 200.1, 158.7, 137.9, 133.3, 129.1, 128.2, 116.9, 115.1, 62.5, 55.9, 48.8, 28.8. HRMS-ESI (*m*/*z*): Calc'd for $C_{12}H_{13}NO_4Na$ $[M+Na]^+$: 258.0737. Found: 258.0729.

2-(3,5-bis(trifluoromethyl)phenyl)quinolin-4(1H)-one (**6.19**)



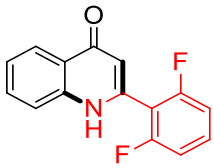
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *6.4.3*, conducted at 110 °C in toluene using 5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, and purified according to *6.4.8*. Purified by reverse phase column chromatography on a C-18 column which afforded the title compound in an 60% isolated yield (103 mg, 0.288 mmol) as a white solid. The title compound was also prepared and isolated analogously when starting from the corresponding amide coupled product **6.1** according to *6.4.4* and was isolated in an 85% yield. ^{1}H NMR (500.1 MHz, CD_3OD): δ 8.53 (s, 2H), 8.39 (d, J = 8.1 Hz, 1H), 8.29 (s, 1H), 7.99-7.93 (m, 2H), 7.68-7.65 (m, 1H), 7.02 (s, 1H). ^{19}F{^{1}H} NMR (470.6 MHz, CD_3OD): δ -64.3. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, CD_3OD): δ 176.5, 152.2, 142.0, 137.1, 135.4, 133.8 (q, J = 33.7 Hz), 130.1, 127.6, 126.0-125.9 (m), 125.6, 123.8, 123.4, 120.6, 108.0. HRMS-ESI (m/z): Calc'd for $C_{17}H_9F_6NONa$ $[M+Na]^+$: 380.0481. Found: 380.0472.

2-phenylquinolin-4(1H)-one (**6.20**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *6.4.3*, conducted at 110 °C in toluene using 5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, and purified according to *6.4.8*. Purified by reverse phase column chromatography on a C-18 column which afforded the title compound in an 85% isolated yield (97.6 mg, 0.408 mmol) as a white solid. The title compound was also prepared and isolated analogously when starting from the corresponding amide coupled product **6.3** according to *6.4.4* and was isolated in a 90% yield. ^{1}H NMR (500.1 MHz, CD_3OD): δ 8.27-8.25 (m, 1H), 7.80-7.78 (m, 2H), 7.77-7.70 (m, 2H), 7.58-7.57 (m, 3H), 7.43 (ddd, J = 8.2, 6.8, 1.4 Hz, 1H), 6.56 (s, 1H). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, CD_3OD): δ 180.7, 153.6, 142.0, 135.5, 133.7, 131.9, 130.3, 128.6, 126.0, 125.8, 125.4, 119.7, 108.5. HRMS-ESI (m/z): Calc'd for $C_{15}H_{12}NO$ $[M+H]^+$: 222.0913. Found: 222.0920.

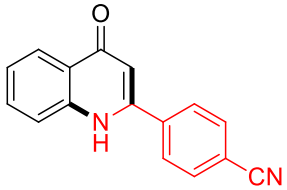
2-(2,6-difluorophenyl)quinolin-4(1H)-one (**6.21**)



The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *6.4.3*, conducted at 110 °C in toluene using 5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, and purified according to *6.4.8*. Purified by reverse phase column chromatography on a C-18 column which afforded the title compound in an 40% isolated yield (49.4 mg, 0.192 mmol) as a white solid. The title compound was also prepared and isolated analogously when starting from the corresponding amide coupled product **6.5** according to *6.4.4* and was isolated in a 78% yield. ^{1}H NMR (500.1 MHz, CD_3OD): δ 8.28 (dd, J = 8.2, 1.1 Hz, 1H), 7.74-7.71 (m, 1H), 7.63-7.57 (m, 2H), 7.46-7.43 (m, 1H), 7.18 (t, J = 8.2 Hz, 2H), 6.39 (s,

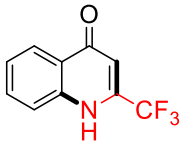
1H). $^{19}F\{^{1}H\}$ NMR (470.6 MHz, CD_3OD): δ -114.3. $^{13}C\{^{1}H\}$ UDEFT NMR (125.8 MHz, CD_3OD): δ 180.3, 161.3 (dd, J = 250.5, 5.9 Hz), 142.3, 142.0, 134.0 (t, J = 10.4 Hz), 133.9, 126.1, 125.8, 125.6, 119.6, 113.3, 113.1, 112.5. *The compound was unable to be detected via HRMS under a range of conditions involving various solvents.*

4-(4-oxo-1,4-dihydroquinolin-2-yl)benzonitrile (**6.22**)



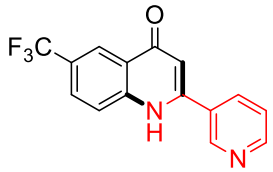
The title compound was synthesized from the corresponding coupled amide product (**6.4**, 0.36 mmol) according to *6.4.4* and purified according to *6.4.8*. Purified by reverse phase column chromatography on a C-18 column which afforded the title compound in an 86% isolated yield (76.2 mg, 0.310 mmol) as a pale yellow solid. ^{1}H NMR (500.1 MHz, CD_3OD): δ 8.26 (d, J = 8.1 Hz, 1H), 7.80-7.77 (m, 3H), 7.73 (t, J = 7.5 Hz, 1H), 7.58-7.56 (m, 3H), 7.43 (t, J = 7.3 Hz, 1H), 6.60 (s, 1H). $^{13}C\{^{1}H\}$ UDEFT NMR (125.8 MHz, CD_3OD): δ 180.1, 153.8, 141.9, 135.3, 133.8, 132.0, 130.7, 130.3, 129.4, 128.6, 125.9, 125.6, 119.8, 108.3. *The compound was unable to be detected via HRMS under a range of conditions involving various solvents.*

2-(trifluoromethyl)quinolin-4(1H)-one (**6.23**)



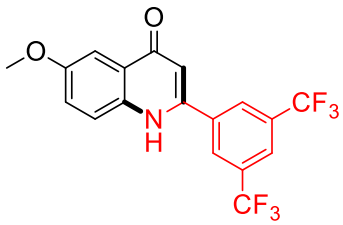
The title compound was synthesized from the corresponding aryl chloride (0.24 mmol) according to *6.4.3* (2.0 equiv. of 1,1,3,3-tetramethylguanidine used in place of DBU), conducted at 110 °C using 5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl and purified according to *6.4.8* using automated normal-phase chromatography with an eluent gradient of 100% hexanes (4 CV), 0-30% ethyl acetate in hexanes (14 CV) followed by 30% ethyl acetate in hexanes (4 CV) which afforded the title compound in a 35% isolated yield (0.018 g, 0.084 mmol). ^{1}H NMR (500.1 MHz, CD_3OD): δ 8.31 (d, J = 8.2 Hz, 1H), 7.89-7.88 (m, 1H), 7.85-7.82 (m, 1H), 7.58 (*t*, J = 7.6 Hz, 1H), 6.83 (br, 1H). *NH signal undiscernible by ^{1}H NMR at solution concentration.* $^{19}F\{^{1}H\}$ NMR (470.6 MHz, CD_3OD): δ -69.2. *Owing to the poor solubility of the title compound in a range of NMR solvents including CD_3OD, $CDCl_3$ and DMSO-d_6, efforts to obtain suitably intense/resolved $^{13}C\{^{1}H\}$ NMR spectra were unsuccessful.* HRMS-ESI (*m*/*z*): Calc'd for $C_{10}H_6F_3NONa$ $[M+Na]^+$: 236.0294. Found: 236.0292.

N-(2-acetyl-4-(trifluoromethyl)phenyl)nicotinamide (**6.24**)



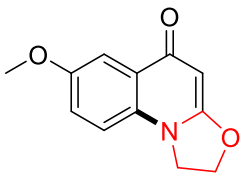
The title compound was synthesized from the corresponding aryl chloride (0.48 mmol) according to *6.4.3*, conducted at 110 °C using 5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl, and purified according to *6.4.8* using reverse-phase chromatography. This afforded the title compound in a 43% isolated yield (0.060 g, 0.207 mmol). ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 12.2 (br, 1H), 9.08 (m, 1H), 8.79-8.78 (m, 1H), 8.39 (m, 1H), 8.30-8.28 (m, 1H), 8.02-7.99 (m, 1H), 7.95-7.94 (m, 1H), 7.65-7.63 (m, 1H), 6.58 (s, 1H). ^{19}F{^{1}H} NMR (470.6 MHz, DMSO-d_6): δ -60.5. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, DMSO-d_6): δ 176.3, 151.8, 149.3, 148.7, 143.6, 135.7, 130.4, 128.3-123.6 (m, overlapping ArCs *complicated by ^{19}F splitting*), 122.8 (q, J = 4.1 Hz), 121.3, 109.2. HRMS-ESI (*m*/*z*): Calc'd for $C_{15}H_9F_3N_2ONa$ $[M+Na]^+$: 313.0559. Found: 313.0558.

2-(3,5-bis(trifluoromethyl)phenyl)-6-methoxyquinolin-4(1H)-one (**6.25**)



The title compound was synthesized from the corresponding aryl tosylate (0.48 mmol) according to *6.4.3*, conducted at 110 °C using 5 mol% (**PAd2-DalPhos**)Ni(4-CN-Ph)Cl and purified according to *6.4.8* using manual normal-phase chromatography eluting with a gradient of ethyl acetate in hexanes (20-80%). This afforded the title compound in a 66% isolated yield (0.122 g, 0.317 mmol). ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 8.63 (s, 2H), 8.02 (s, 1H), 7.61 (d, J = 9.0 Hz, 1H), 7.54 (d, J = 2.9 Hz, 1H), 7.09-7.07 (m, 1H), 6.67 (s, 1H), 4.20 (br, 1H), 3.83 (s, 3H). ^{19}F{^{1}H} NMR (470.6 MHz, DMSO-d_6): δ -61.3. ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, DMSO-d_6): δ 173.4, 154.7, 151.4, 145.9, 144.8, 130.6 (q, J = 32.6 Hz), 129.6, 128.5, 126.9, 124.2 (q, J = 272.6 Hz), 121.1, 120.0, 103.3, 103.2, 55.4. HRMS-ESI (*m*/*z*): Calc'd for $C_{18}H_{11}F_6NO_2Na$ $[M+Na]^+$: 410.0586. Found: 410.0571.

7-methoxy-1H-oxazolo[3,2-a]quinolin-5(2H)-one (**6.26**)



The title compound was synthesized from the corresponding coupled amide product (**6.18**, 0.36 mmol) according to *6.4.4* using NaO*t*Bu instead of NaOH and purified according to *6.4.8*. Purified by reverse phase column chromatography on a C-18 column which afforded the title compound in a 78% isolated yield (69 mg, 0.281 mmol). ^{1}H NMR (500.1 MHz, CD_3OD): δ 7.55 (d, *J* = 9.3 Hz, 1H), 7.47 (d, *J* = 3.0 Hz, 1H), 7.24 (dd, *J* = 9.3, 3.0 Hz, 1H), 5.98 (s, 1H), 4.39 (t, *J* = 6.5 Hz, 2H), 3.86 (s, 3H), 3.82 (t, *J* = 6.5 Hz, 2H). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, CD_3OD): δ 165.8, 163.6, 155.9, 135.2, 121.4, 118.8, 117.3, 105.9, 98.4, 60.4, 56.0, 45.0. *The compound was unable to be detected via HRMS under a range of conditions involving various solvents.*

7. Conclusion

7.1 Summary of work presented herein

In summary, my doctoral research has encompassed a range of Ni-catalyzed cross-coupling transformations including: the design, synthesis and application of ancillary phosphonite-phosphine ligands and derived pre-catalysts for enabling various Ni-catalyzed amination reactions (Chapters 2 and 3); the Ni-catalyzed N-arylation of sulfonamides and fluoroalkylamines with (hetero)aryl (pseudo)halides (Chapters 4 and 5 respectively); and the mechanistic mapping of dual-base mediated Ni-catalyzed amidation reactions for the syntheses of 4-quinolones (Chapter 6). The goals achieved in this work include addressing outstanding reactivity challenges through the design and application of sustainable base-metal catalysts, developing practical conditions for cross-coupling reactions, and understanding the mechanistic underpinnings of Ni-catalyzed reactions to inform future catalyst development. A graphical representation of the collective methodological work is presented in Figure 7.1.

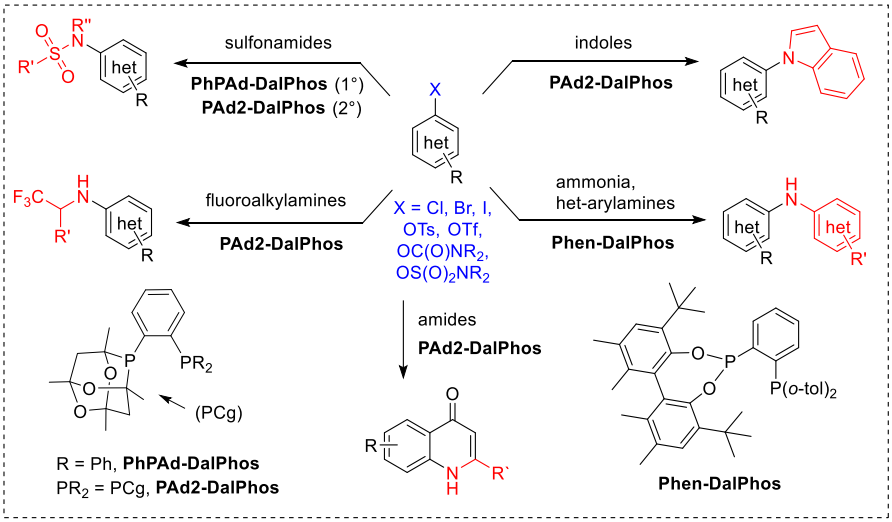


Figure 7.1 Summary of the various Ni-catalyzed N-arylations discussed herein.

Notwithstanding the successes had in the developed methodology in enabling a broad range of Ni-catalyzed N-arylation reactions, important limitations provide motivation for improvement as well as extension of the developed methodology to tackle other synthetic problems, including related cross-coupling reactions. The remainder of this chapter will thus discuss new avenues for which the developed methodology may be applicable, or avenues toward new catalyst development for facilitating more efficient catalytic performance in both the aforementioned, and related, catalytic transformations.

7.2 Future Work

7.2.1 Dual-base enabled Ni-catalyzed alpha-arylation of ketones

Given the successes in enabling various dual-base enabled N-arylations, both with Ni as mentioned in this thesis (Chapters 5 and 6) and with Pd[83,84,98], it stands to reason that this system might work in enabling various ketone alpha-arylations for which are known to proceed with inorganic bases using both Ni[102,103] and Pd.[104,105] Indeed, such a protocol (as seen in Figure 7.2) would be especially powerful given that organic bases are typically soluble in standard reaction solvents[83] (i.e. toluene, dioxane, THF, neat ketone) which is important for the scaling up of reactions where homogeneity issues and unequal particle distribution often plague the analogous inorganic base mediated approaches.[102] Specifically, the use of inorganic bases such as Cs_2CO_3 and CsF often necessitate intense reaction stirring (>750 RPM) without which product conversions are significantly hampered.[102] Furthermore, with the recent increased uptake of High-Throughput-Experimentation (HTE) methods,[66,83] the use of soluble liquid reagents allows for more facile and reliable reagent dispensing in that the reagents can be dispensed without relying on addition via slurry,[83] which is often the typical delivery method for insoluble inorganic bases; this method often leading to unequal

reagent distribution amongst reaction vials, and potentially, false negative reaction results in preliminary HTE screening.

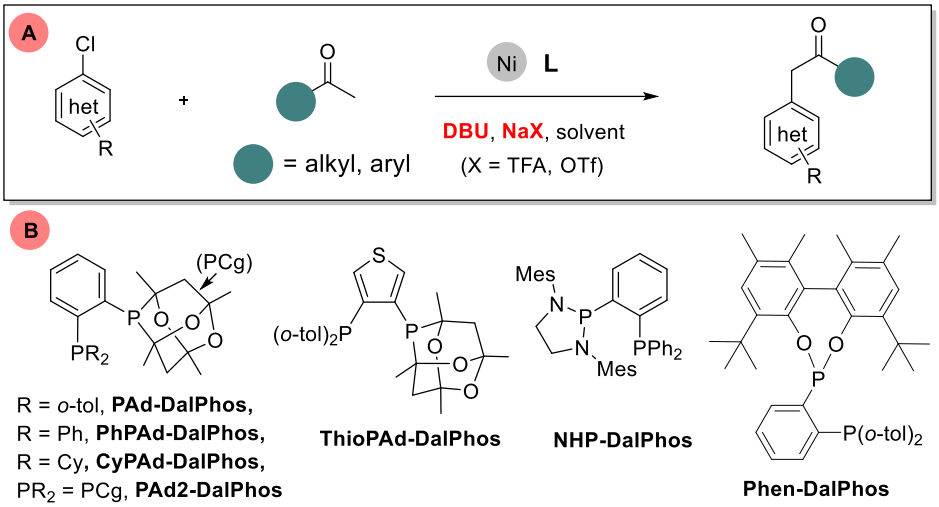


Figure 7.2 Proposed dual-base mediated Ni-catalyzed alpha-arylation of ketones enabled by DalPhos ligation.

In building off the inorganic base-mediated work of the Stradiotto group in developing the alpha-arylation of acetone catalyzed by Pd-**MorDalPhos**,[104] as well the very recent work reported by the Tlili group in the analogous Ni-**JosiPhos** catalyzed alpha-arylation of acetone,[102] this work would seek to utilize a Ni-DalPhos catalyst system in conjunction with an organic dual-base to enable the alpha-arylation of ketones under milder and more homogenous conditions which are likely to be more practical to end-users both in medicinal and process chemistry.

7.2.2 Ligand ideas for facilitating Ni-catalyzed reactions

The successes had with the Stradiotto-developed **PAd-DalPhos** ligands in enabling a diverse array of Ni-catalyzed C-N cross-coupling reactions has certainly helped to establish some ancillary ligand criteria for facilitating difficult transformations within this realm (i.e. moderately electron-donating, bulky bisphosphines). However, despite these successes, some

important questions remained unanswered, including the reason as to why relatively more electron-donating bisphosphines such as **CyPF-Cy** have also emerged as prominent ligands for facilitating reactions of this type.[38] It is important to note that as highlighted in Chapter 1, both Ni(0)/(II) and Ni(I)/Ni(III) cycles may or may not be operative at any given time, and clearly more mechanistic work must be conducted in this area before any clear ligand design criteria can be well defined.[33] Furthermore, as stated earlier in Section 1.4.4, Ni-catalyst systems that utilize the **PAd-DalPhos** ligand family typically struggle with the incorporation of electron rich (hetero)aryl chlorides as compatible substrate partners (i.e. 4-chloroanisole, 3-chloropyridine, etc.) and its noteworthy that perhaps the most electron rich member of the **PAd-DalPhos** ligand family (**CyPAd-DalPhos**) has shown to be the most effective in the cross-coupling of cyclopropylamine with 3-chloropyridine, while another similar ortho-phenylene bisphosphine ligand featuring di-*tert*-butylphophino and di-*ortho*-tolylphosphino fragments (i.e. **PAd-DalPhos** with P(*t*Bu)$_2$ in place of PCg) was superior in the cross-coupling of 4-chloroanisole with cyclopropylamine at room temperature.[47] Although I am hesitant to comment decisively on the reason for these observations given the mechanistic complexities associated with Ni-catalyzed C-N cross-coupling, it is clear that effective ligand criteria for facilitating difficult Ni-catalyzed C-N cross-coupling reactions remains ambiguous, and in cases involving deactivated aryl chlorides, more electron-donating bisphosphines are seemingly better at facilitating product formation. As is apparent in Chapters 2 and 3 of this document, when applying more electron deficient ligands containing phosphonite moieties to difficult Ni-catalyzed C-N cross-coupling reactions, the incorporation of deactivated (hetero)aryl chlorides was not possible.

In addressing certain challenges in Ni-catalyzed C-N cross-coupling through ancillary ligand design, including the incorporation of deactivated (hetero)aryl chloride based electrophiles, this proposed work seeks to build off of the success of ancillary bisphosphine ligation through the application of newly designed, electronically rich and sterically encumbering **PAd-DalPhos** ligand variants as seen in Figure 4.2. I envision that bisphosphines featuring di-alkylphosphino fragments based on tert-butyl, cycloheptyl, neopentyl, 2-methyl-2-phenylpropyl and 2-methylbenzyl "R" groups may provide the necessary steric bulk and electron richness needed to facilitate difficult Ni-catalyzed C-N cross-couplings involving deactivated (hetero)aryl (pseudo)halide electrophiles. Furthermore, both empirical and mechanistic observations seem to suggest that remote steric bulk may be advantageous in Ni catalysis,[106] suggesting that **PAd-DalPhos** variants which feature benzylic or neopentyl "R" groups may help to address outstanding challenges in Ni cross-coupling, particularly those which involve the coupling of bulkier substrates. Indeed, the syntheses of the proposed ligand variants as seen in Figure 4.2 rely on the synthetic feasibility of (2-dichlorophosphinophenyl)PCg as a viable synthon, although previous literature documentation on related compounds suggests that the synthesis of this compound will be feasible.[107]

Another remaining challenge within the field of Ni-catalyzed C-N cross-coupling is the monoarylation of hydrazine with (hetero)aryl (pseudo)halides, with only one relevant report that details the Ni-catalyzed cross-coupling of benzophenone hydrazone with aryl bromides to yield furnish products in generally poor isolated yields.[51] One significant issue in utilizing hydrazine as a cross-coupling partner is in its potential to act as a strong reducing agent, as upon its oxidation hydrazine yields dinitrogen and hydrogen gases as biproducts. In

attempting to circumvent these issues, the application of relatively more electron-donating bisphosphines such as those proposed in Figure 4.2 may help to minimize reduction by hydrazine at Ni, allowing for N-arylation to occur. The proposed ligands in Figure 4.2 may also aid in the selectivity for monoarylation, given that they are sterically encumbering as to prevent phenylhydrazine species (formed upon monarylation of hydrazine with aryl halides) from acting as competing NH substrates versus hydrazine.

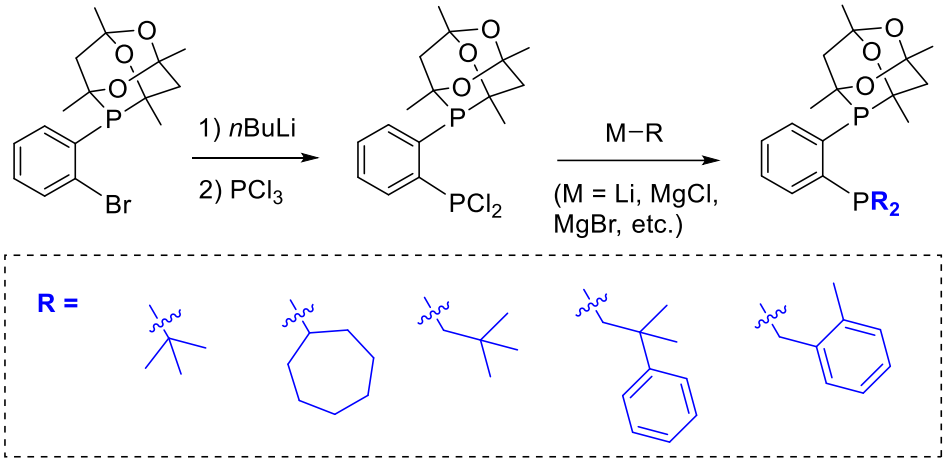


Figure 7.3 Proposed bulky electron-rich **PAd-DalPhos** ligand prototypes.

7.2.3 Halide selectivity in amination chemistry

One major challenge in metal-catalyzed N-arylation chemistry lies in the selective amination at one (pseudo)halide position when multiple competitive (pseudo)halide positions are available for coupling (Figure 7.4). The ability to reliably and consistently select for N-arylation at a given (pseudo)halide position would represent a remarkable advance in the field of Ni-amination chemistry, especially as it would pertain to the synthesis of complex APIs where additional functional handles could be installed later on in a synthesis at the untouched (pseudo)halide position. Indeed, only very recently, the Neufeldt group has shown that depending on the nature of the applied PR_3 ligand, selective oxidative addition into $L_nNi(0)$ can be achieved orthogonally for either an aryl chloride or an aryl tosylate, with most

PR_3 ligands preferentially oxidatively adding into the C-Cl bond, but with smaller PR_3 ligands (i.e. PMe_3, $PPhMe_2$) favoring oxidative addition into the C-O bond.[108] In extending this work, the Neufeldt group then showed that in Ni-catalyzed Suzuki cross-couplings where typical Ni catalysts cross-couple exclusively at the aryl chloride position when in the presence of an aryl tosylate, that they could provide orthogonal chemoselectivity in cross-coupling nearly exclusively (>88:2) at the aryl tosylate position when deploying dmpe as a ligand and using water as an additive.[109]

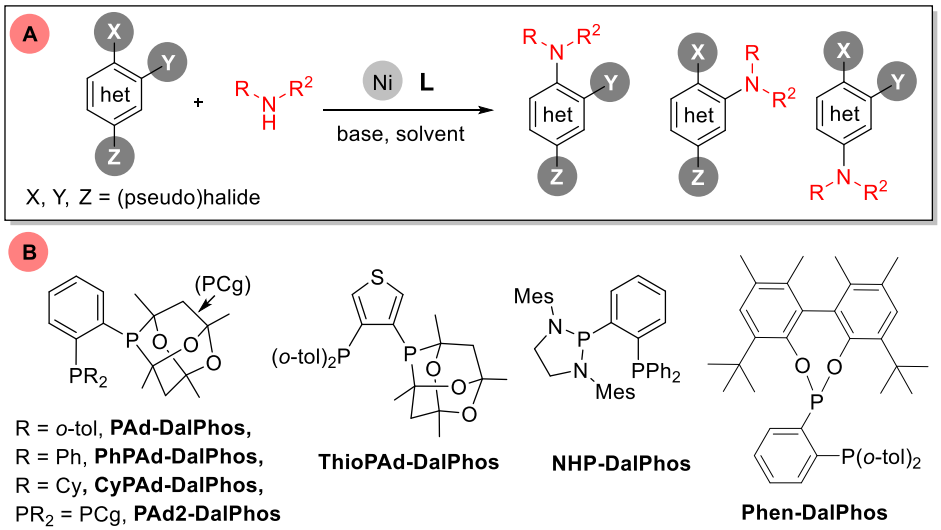


Figure 7.4 Proposed work on the chemoselective Ni-catalyzed N-arylation of specific (pseudo)halide positions.

Inspired by the work of Neufeldt and co-workers, and encouraged by the aforementioned results presented in Chapter 3 detailing the orthogonal chemoselectivity enabled by the application of **Phen-DalPhos** and **PAd2-DalPhos** in providing nearly exclusive cross-coupling at aniline and indole NH positions respectively, (see Chapter 3) along with the results presented in Chapter 5 where cross-coupling at the aryl tosylate position was at least competitive (~1:3) with cross-coupling at the aryl chloride position, the proposed work seeks to merge aspects of ligand design and reaction optimization to enable

orthogonally chemoselective N-arylation chemistry at various multi-(pseudo)halide-substituted aromatics. This work would serve not only to expand the toolkit available to synthetic chemists utilizing BHA chemistry, but also to improve the conceptual understanding of various reaction parameters which dictate catalyst selectivity.

7.3 Final remarks

In conclusion, the contributions made in this work have assisted in addressing a range of challenging C-N cross-couplings under mild conditions through the application of tailored ancillary ligation for Ni-based catalysts, including with the application of the newly synthesized **Phen-DalPhos** derived Ni pre-catalyst. Several pharmaceutically and agriculturally relevant C-N bond-constructions have been generated with success, including rare examples which proceed with near quantitative orthogonal chemoselectivity for the arylation of respective and competing indole and aniline NH handles, enabled solely by the choice of ancillary ligand. Preliminary mechanistic deductions into organic dual-base mediated Ni-catalyzed C-N cross-couplings are likely to provide researchers with a starting point for further catalyst development in this area, including in related cross-couplings involving non-nitrogenous nucleophiles such as in ketone alpha-arylation.

Although much work is to be done in advancing this work forward to make it amendable to implementation by end-users, including the commercialization of new ligands such as **Phen-DalPhos**, it is my hope that this thesis provides a guide in both academic and industrial settings for the construction of targeted bio-relevant C-N bonds, and for new avenues to continue research in the field of Ni-catalyzed cross-coupling.

8. References

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Appendix A. NMR Spectra

Figure A1. ^{1}H NMR Spectrum of *meso*+*rac* **L1** ($CDCl_3$, 500 MHz)

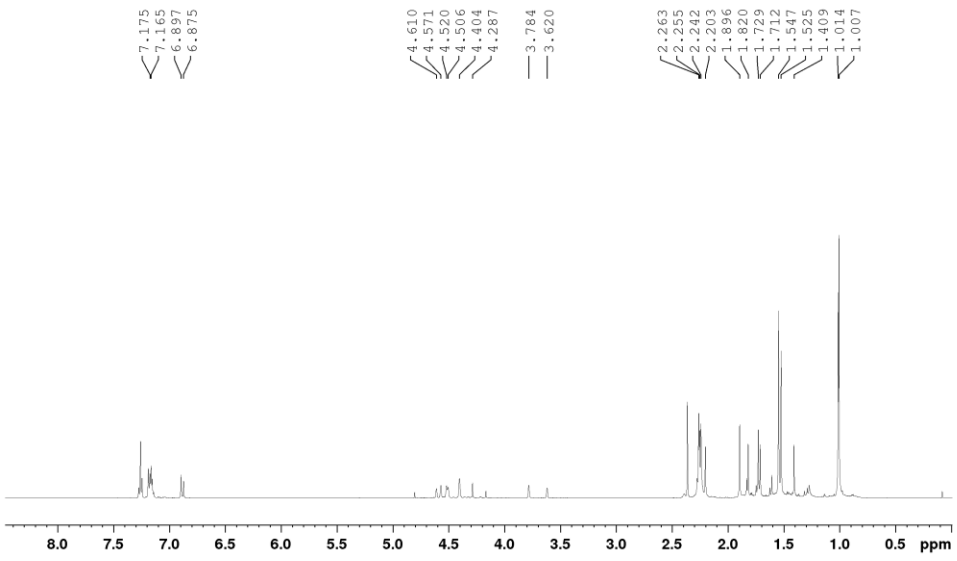


Figure A2. $^{31}P\{^{1}H\}$ NMR Spectrum of *meso*+*rac* **L1** ($CDCl_3$, 202.5 MHz)

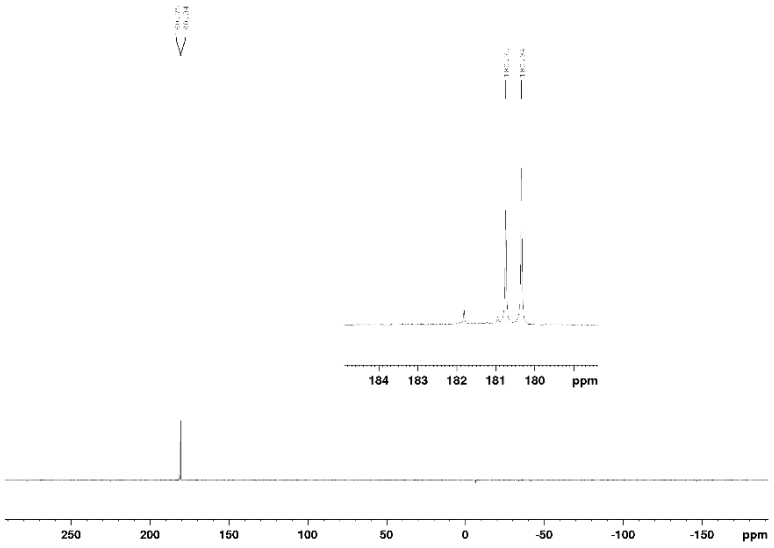


Figure A3. ^{1}H NMR Spectrum of **L1**^{SS} ($CDCl_3$, 500 MHz)

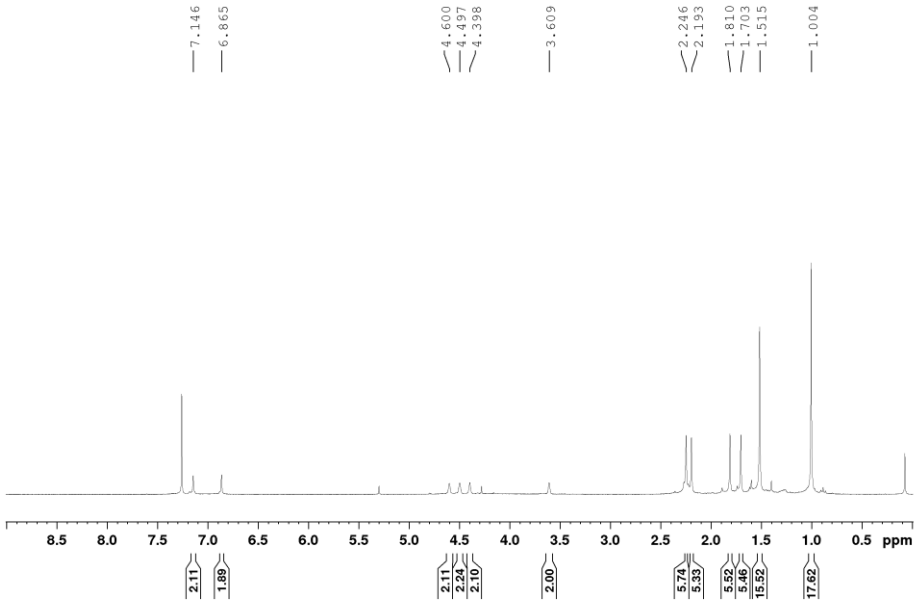


Figure A4. $^{13}C\{^{1}H\}$ UDEFT NMR Spectrum of **L1**^{SS} ($CDCl_3$, 125.8 MHz)

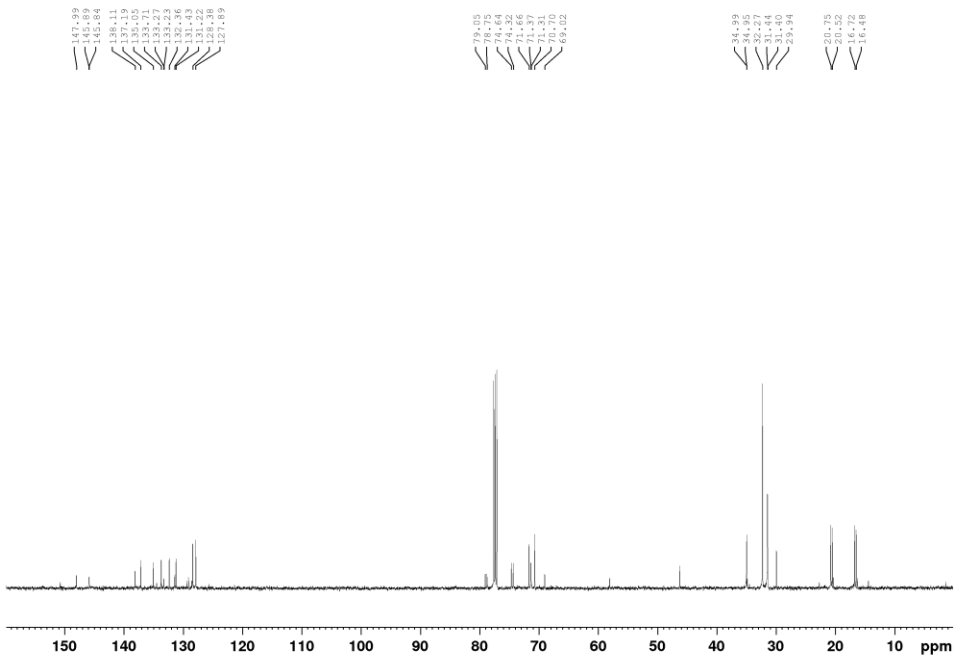


Figure A5. $^{31}P\{^{1}H\}$ NMR Spectrum of **L1*SS*** ($CDCl_3$, 202.5 MHz)

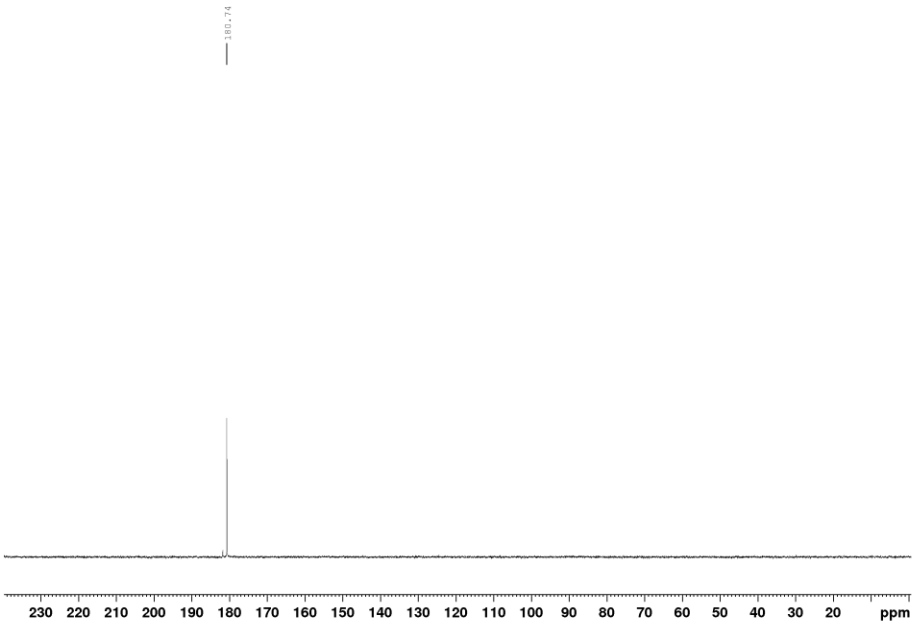


Figure A6. ^{1}H NMR Spectrum of *meso*-**L1** ($CDCl_3$, 500 MHz).

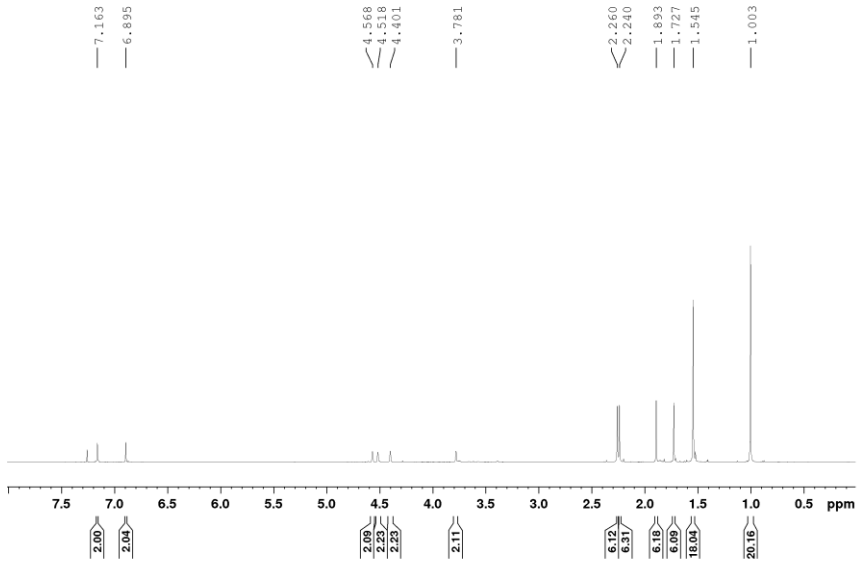


Figure A7. $^{13}C\{^{1}H\}$ UDEFT NMR Spectrum of *meso*-**L1** ($CDCl_3$, 125.8 MHz)

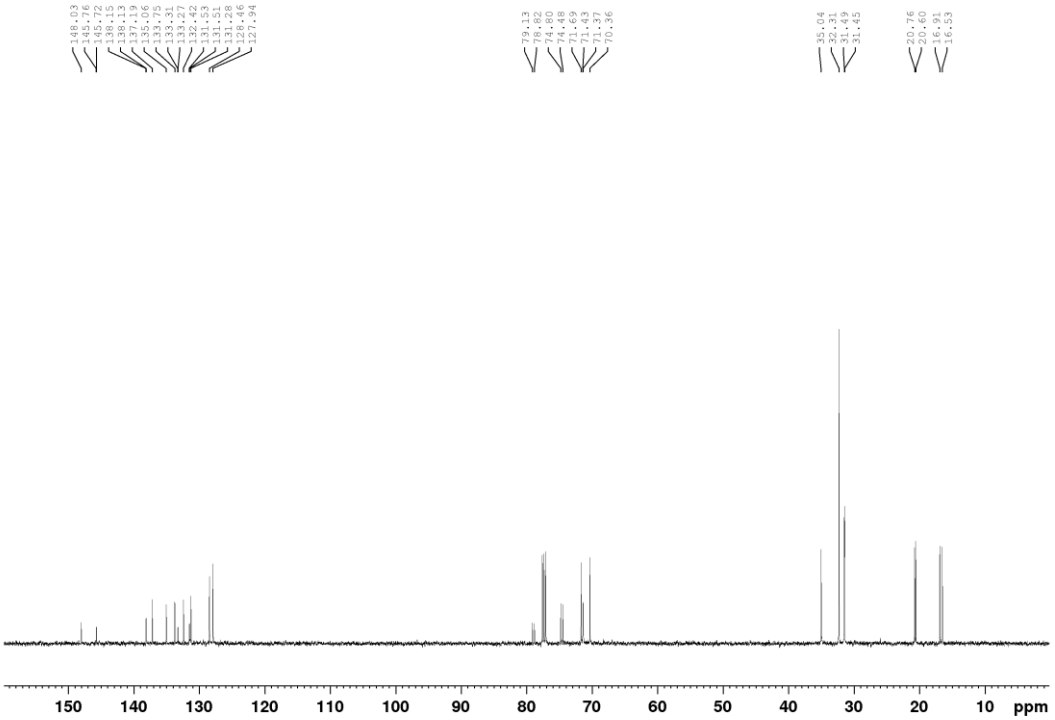


Figure A8. $^{31}P\{^{1}H\}$ NMR Spectrum of *meso*-**L1** ($CDCl_3$, 202.5 MHz)

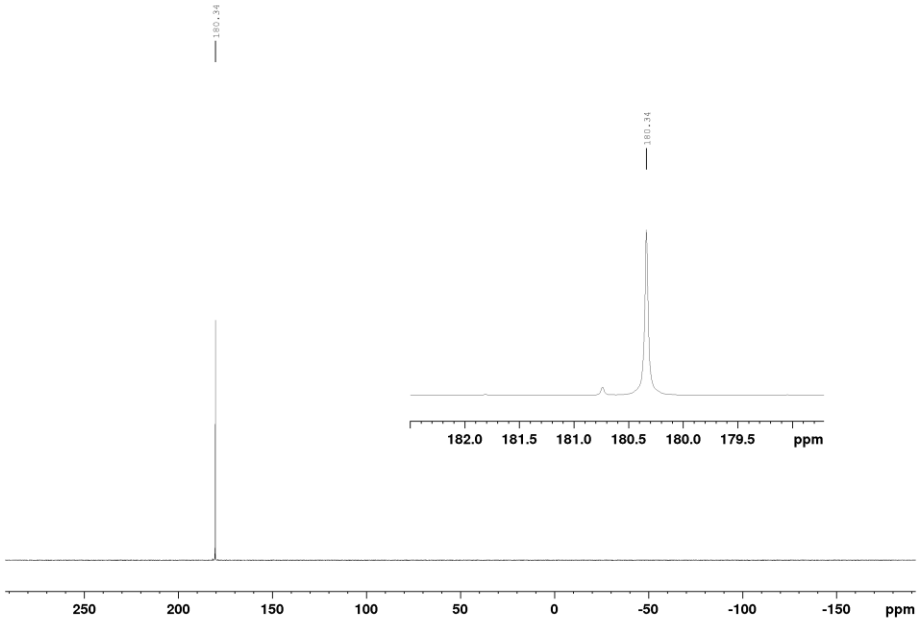
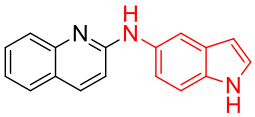


Figure A9. ^{1}H NMR Spectrum of **3.1** (500.1 MHz, DMSO-d_6)



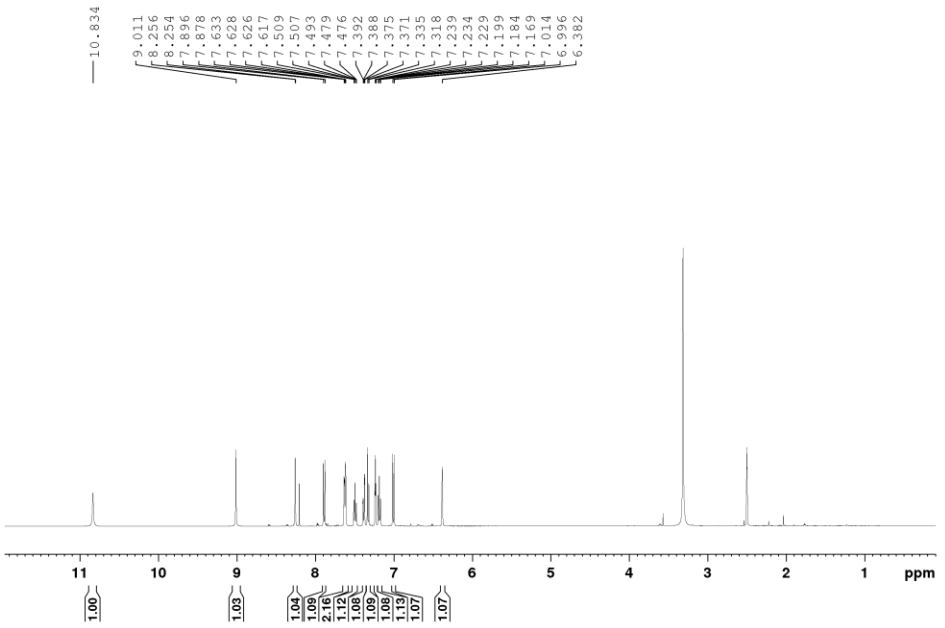


Figure A10. ^{13}C{^{1}H} UDEFT NMR of **3.1** (125.8 MHz, DMSO-d_6)

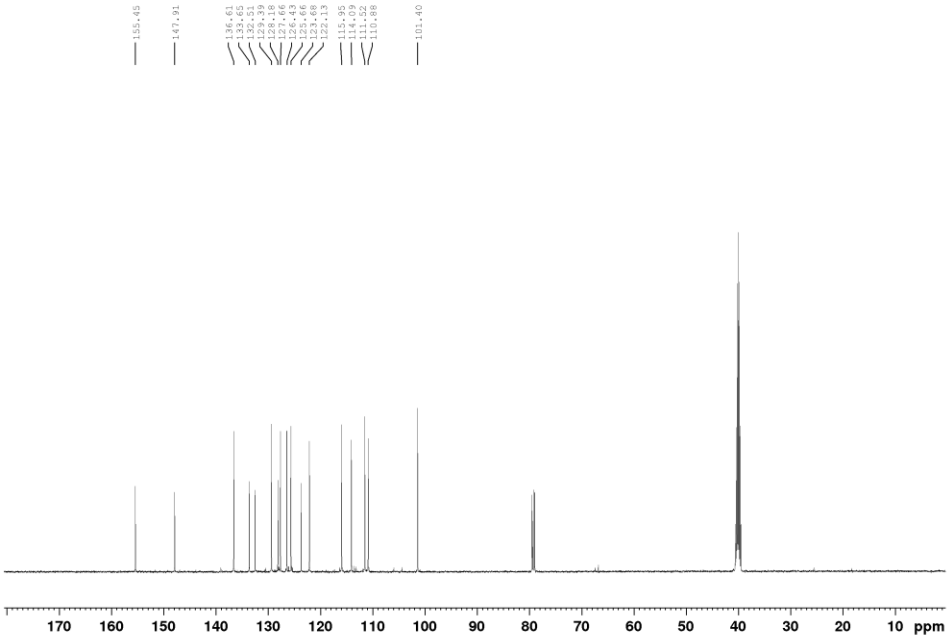
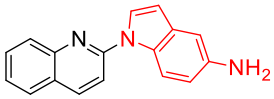


Figure A11. ^{1}H NMR Spectrum of **3.17** (500.1 MHz, $CDCl_3$)



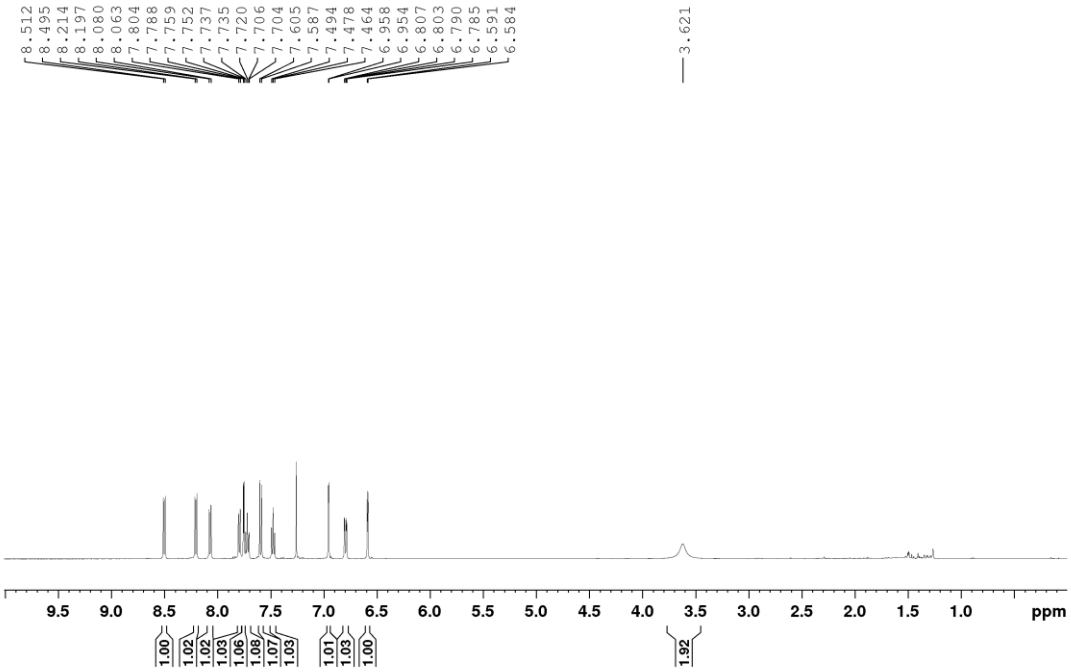


Figure A12. $^{13}C\{^{1}H\}$ UDEFT NMR of **3.17** (125.8 MHz, $CDCl_3$)

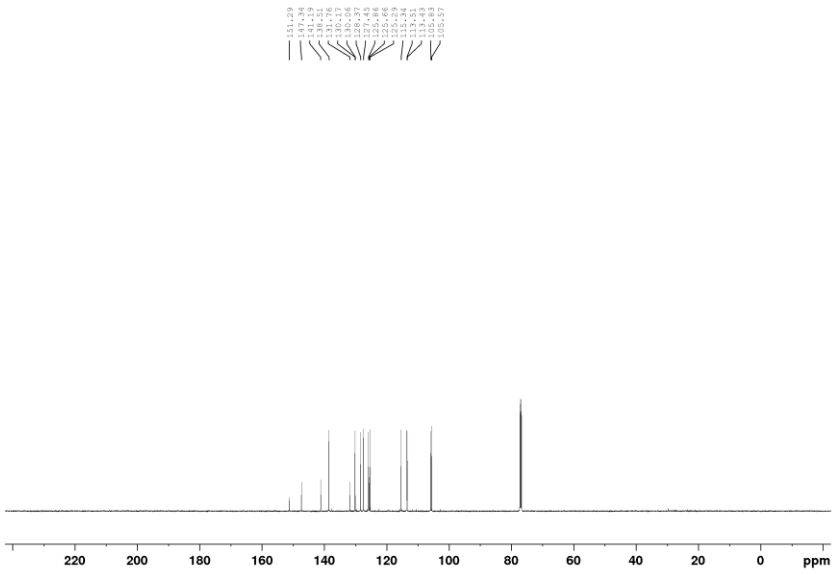
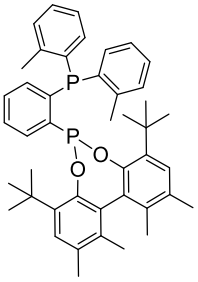


Figure A13. ^{1}H NMR Spectrum of **Phen-DalPhos** (500.1 MHz, $CDCl_3$)



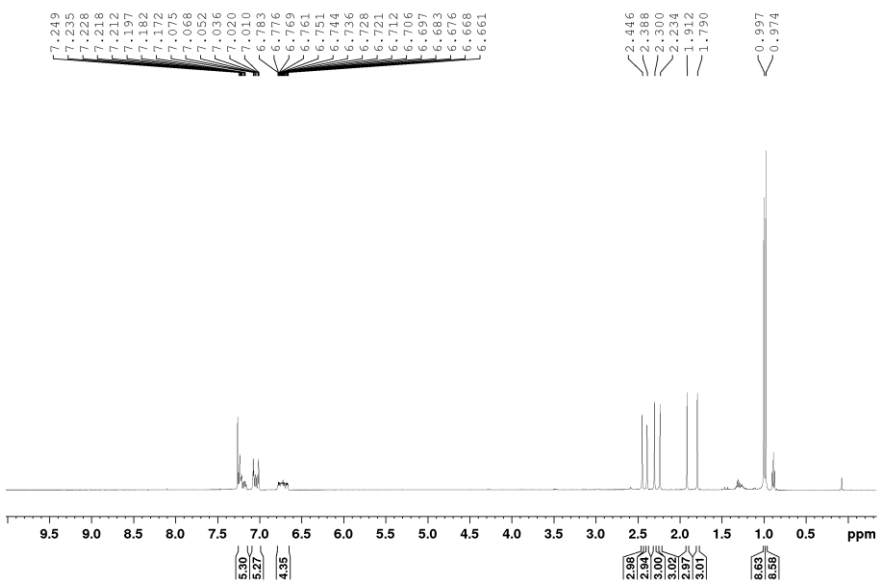


Figure A14. $^{13}C\{^{1}H\}$ UDEFT NMR Spectrum of **Phen-DalPhos** (125.8 MHz, $CDCl_3$)

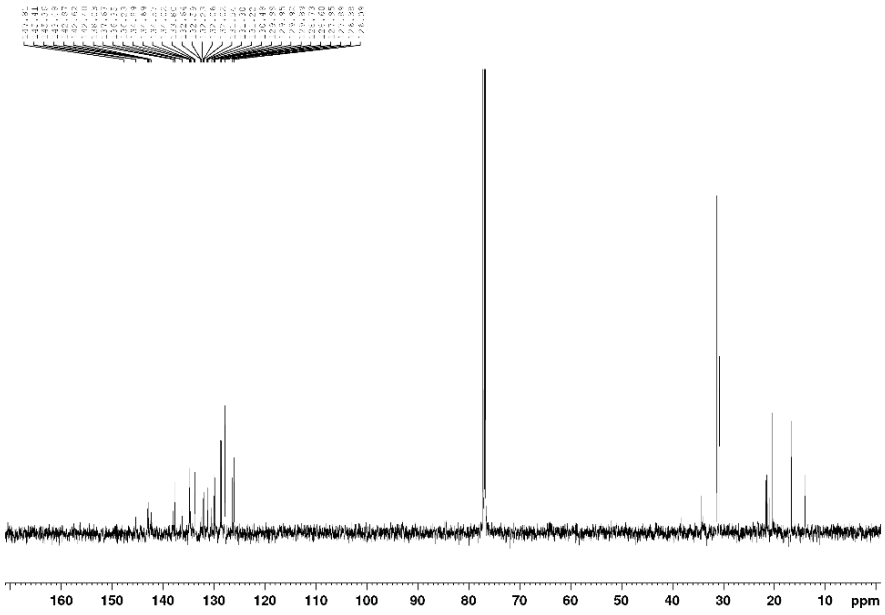
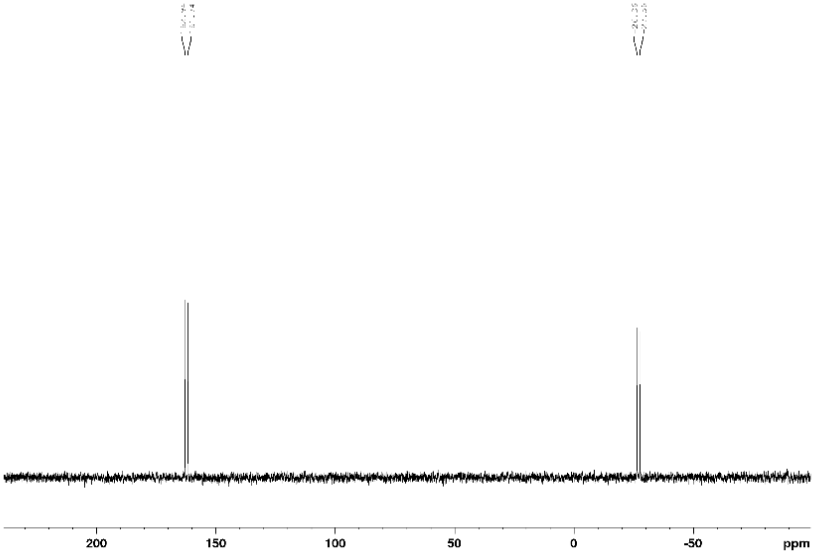


Figure A15. $^{31}P\{^{1}H\}$ NMR Spectrum of **Phen-DalPhos** ($CDCl_3$)



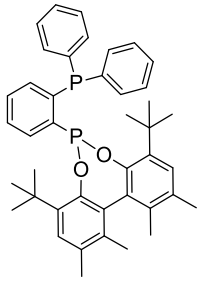


Figure A16. ^{1}H NMR Spectrum of **L3** ($CDCl_3$, 500 MHz)

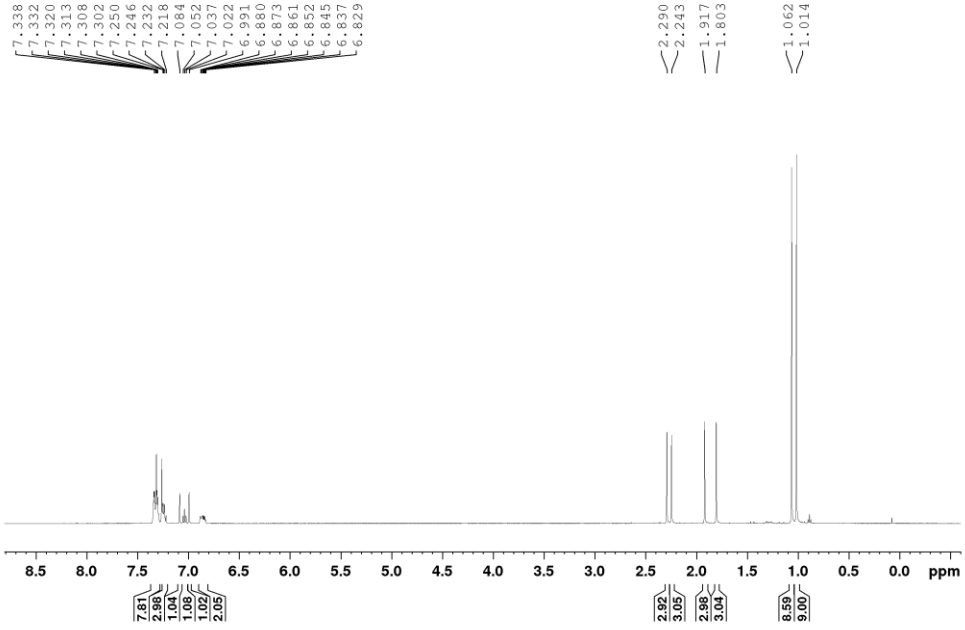


Figure A17. $^{13}C\{^{1}H\}$ UDEFT NMR Spectrum of **L3** ($CDCl_3$, 125.8 MHz)

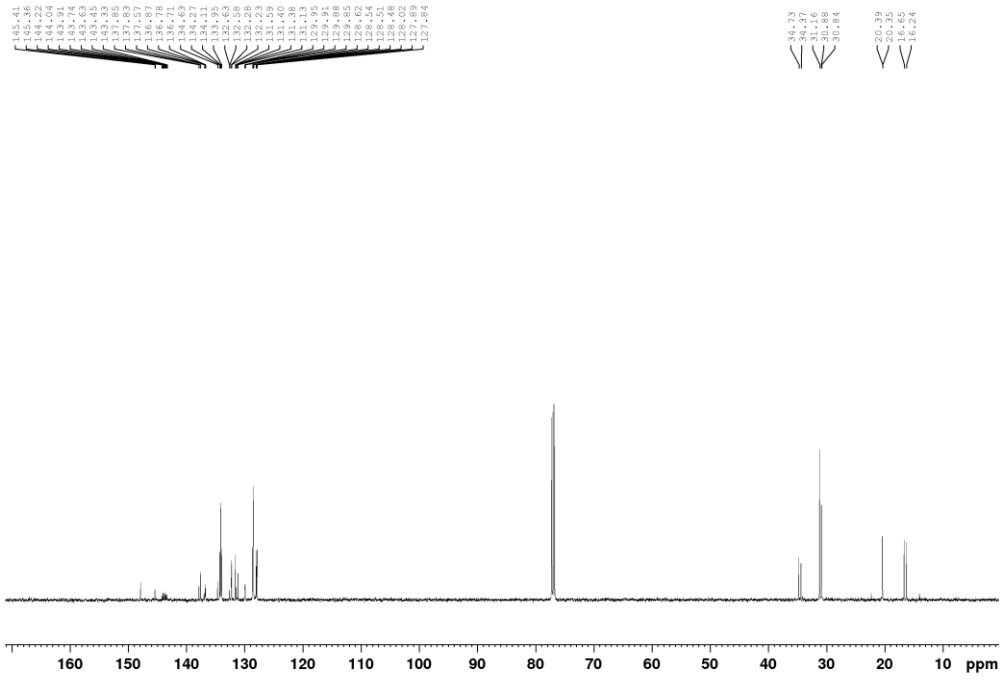


Figure A18. $^{31}P\{^{1}H\}$ NMR Spectrum of **L3** ($CDCl_3$, 202.5 MHz)

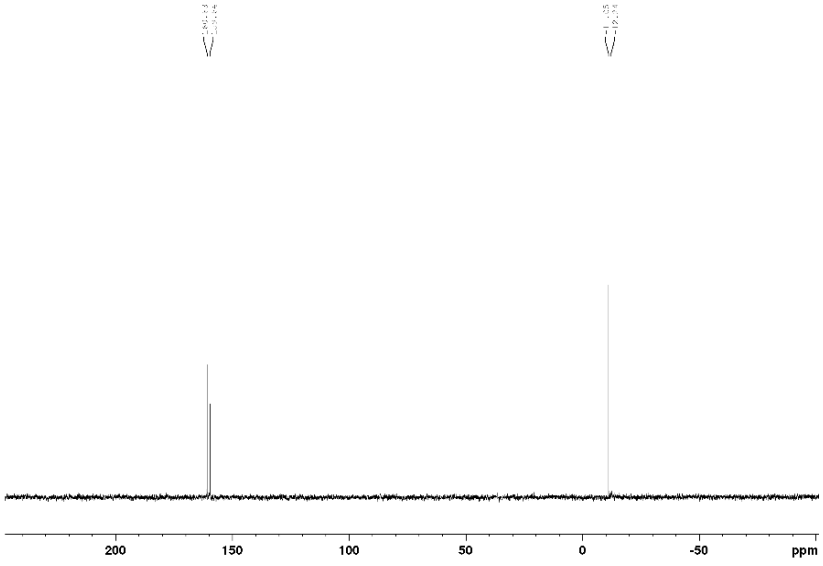
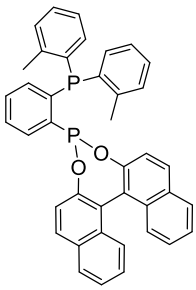


Figure A19. ^{1}H NMR Spectrum of **L5** (500.1 MHz, $CDCl_3$)



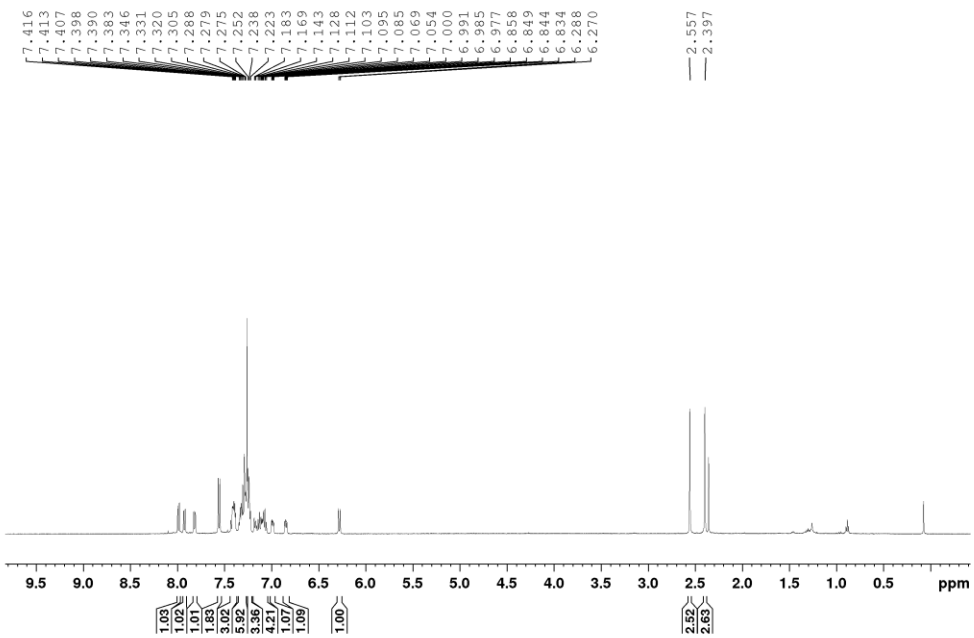


Figure A20. $^{13}C\{^{1}H\}$ UDEFT NMR Spectrum of **L5** (125.8 MHz, $CDCl_3$)

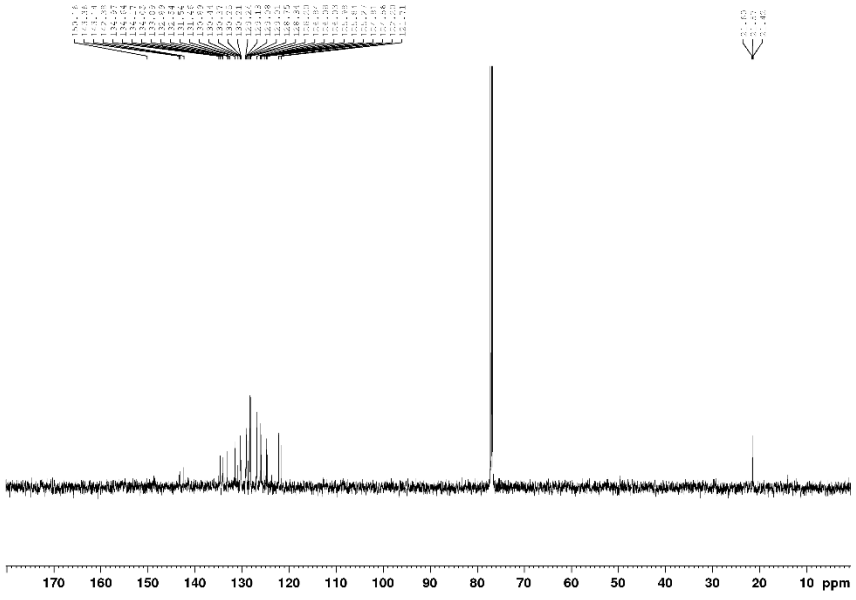


Figure A21. $^{31}P\{^{1}H\}$ NMR Spectrum of **L5** (202.5 MHz, $CDCl_3$)

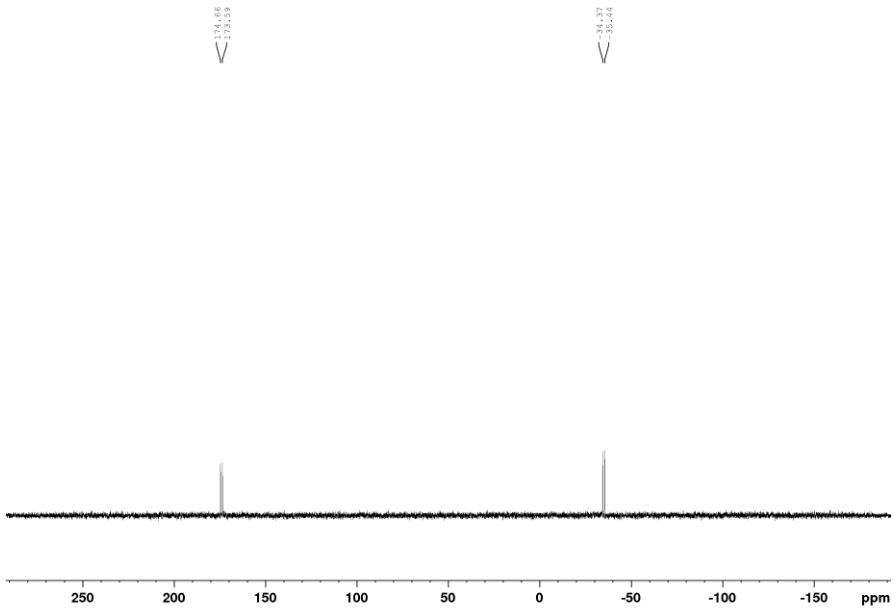


Figure A22. ^{1}H NMR Spectrum of (**Phen-DalPhos**)Ni(*o*-tolyl)Cl (500.1 MHz, $CDCl_3$)

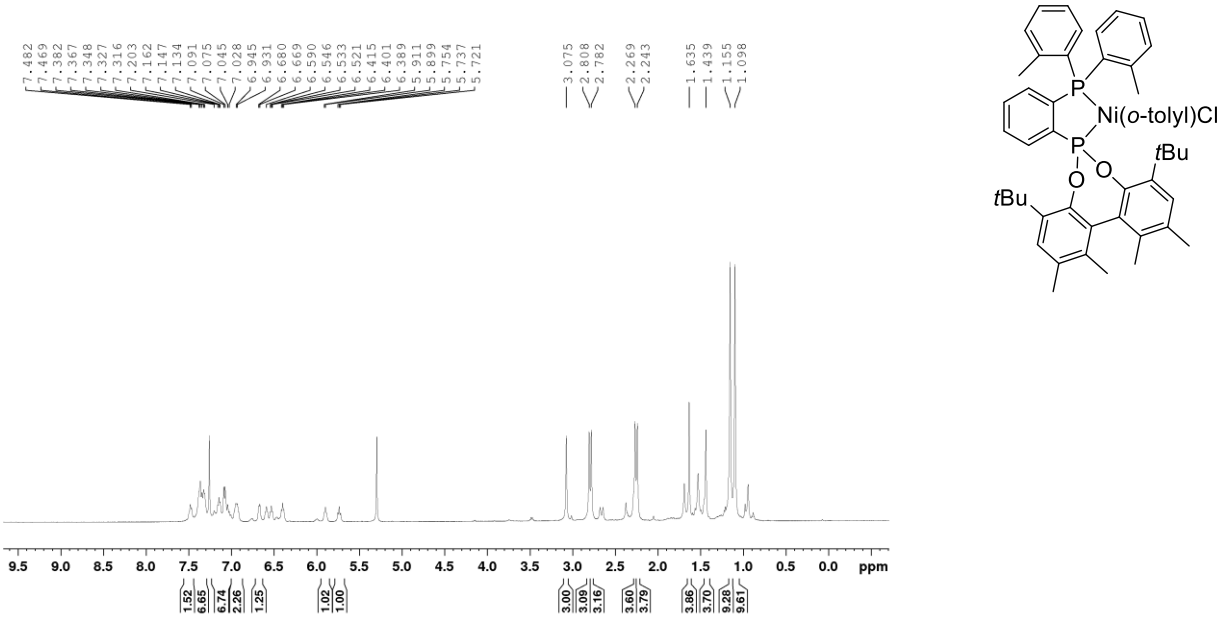


Figure A23. $^{13}C\{^{1}H\}$ UDEFT NMR Spectrum of (**Phen-DalPhos**)Ni(*o*-tolyl)Cl (125.8 MHz, $CDCl_3$)

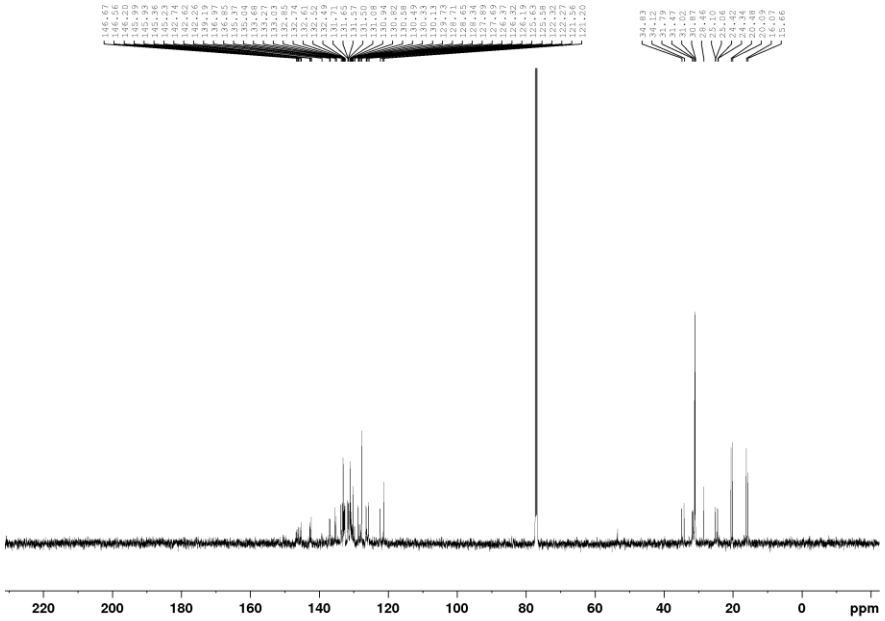


Figure A24. $^{31}P\{^{1}H\}$ NMR Spectrum of (**Phen-DalPhos**)Ni(*o*-tolyl)Cl (202.5 MHz, $CDCl_3$)

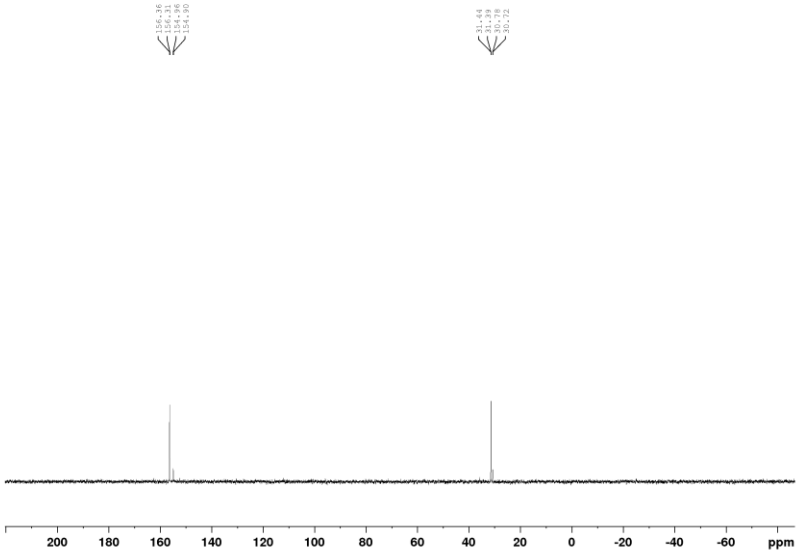


Figure A25. ^{1}H NMR Spectrum of (**PAd2-DalPhos**)Ni(4-CNPh)Cl (300 MHz, $CDCl_3$)

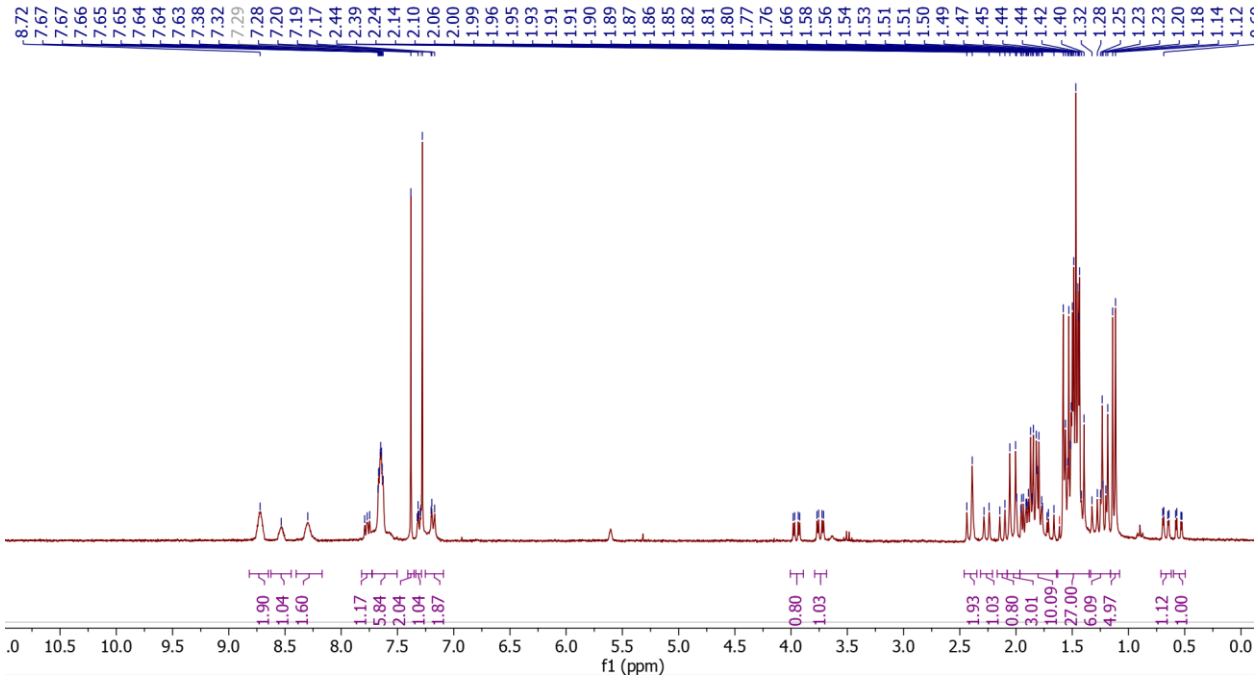


Figure A26. ^{31}P{^{1}H} NMR of (**PAd2-DalPhos**)Ni(4-CNPh)Cl (122 MHz, $CDCl_3$)

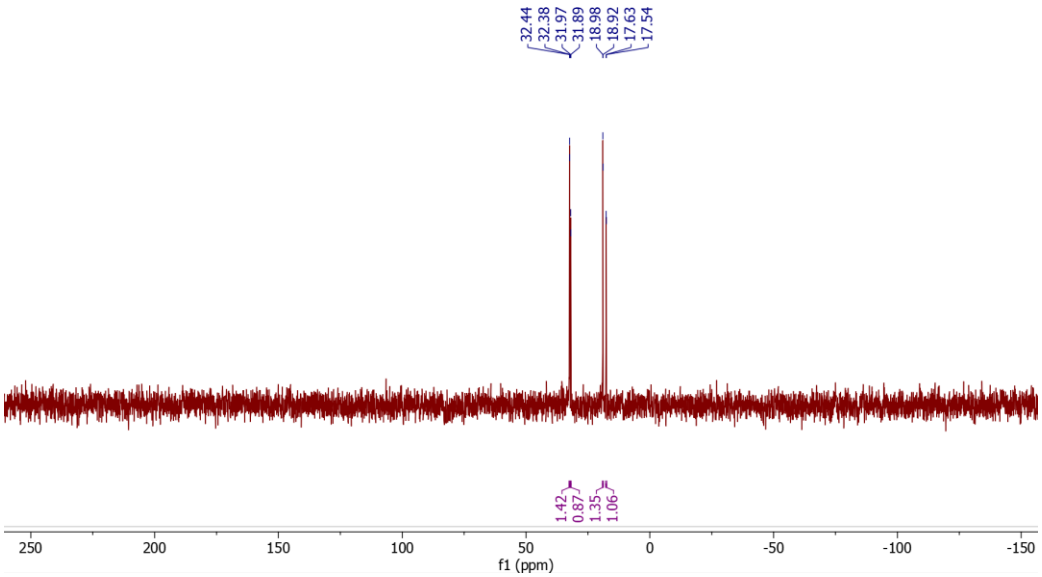


Figure A27. ^{1}H NMR Spectrum of *rac*-(**PAd2-DalPhos**)Ni(4-CNPh)Cl (500 MHz, $CDCl_3$)

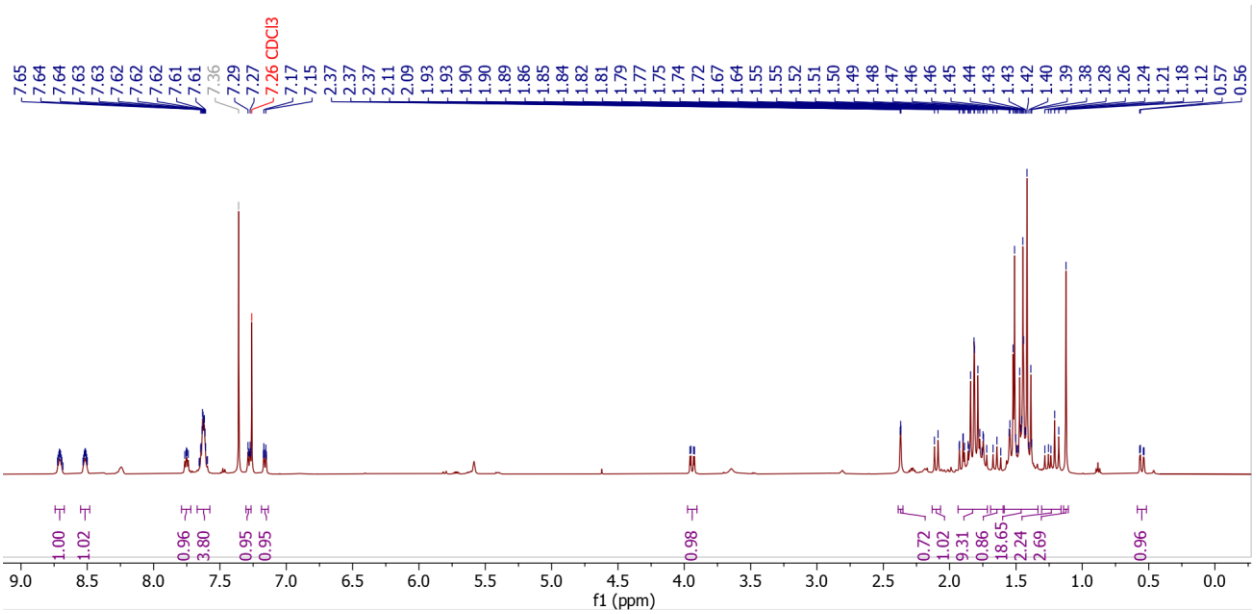


Figure A28. ^{31}P{^{1}H} NMR of *rac*-(**PAd2-DalPhos**)Ni(4-CNPh)Cl (202 MHz, $CDCl_3$)

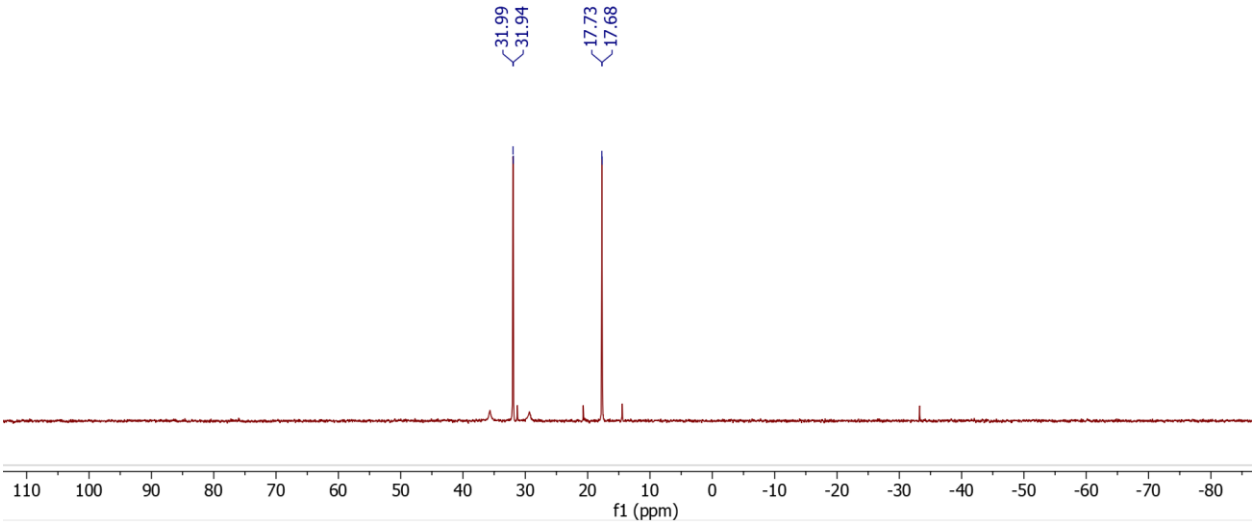


Figure A29. ^{1}H NMR Spectrum of *meso*-(**PAd2-DalPhos**)Ni(4-CNPh)Cl (500 MHz, $CDCl_3$)

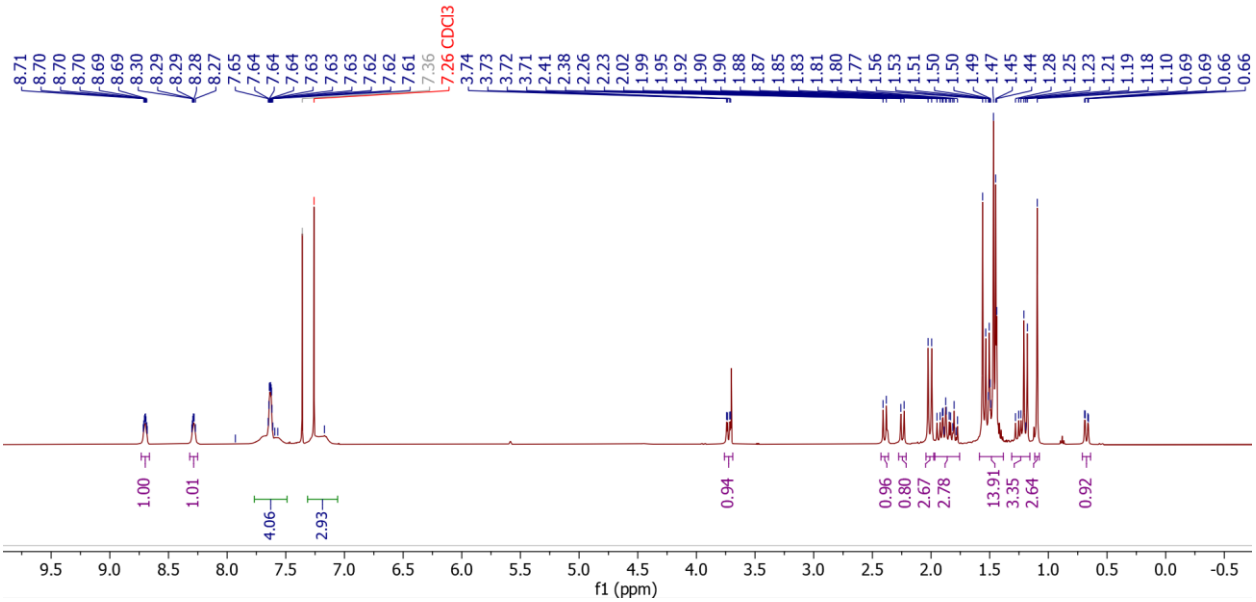


Figure A30. $^{31}P\{^{1}H\}$ NMR of *meso*-(**PAd2-DalPhos**)Ni(4-CNPh)Cl (202 MHz, $CDCl_3$)

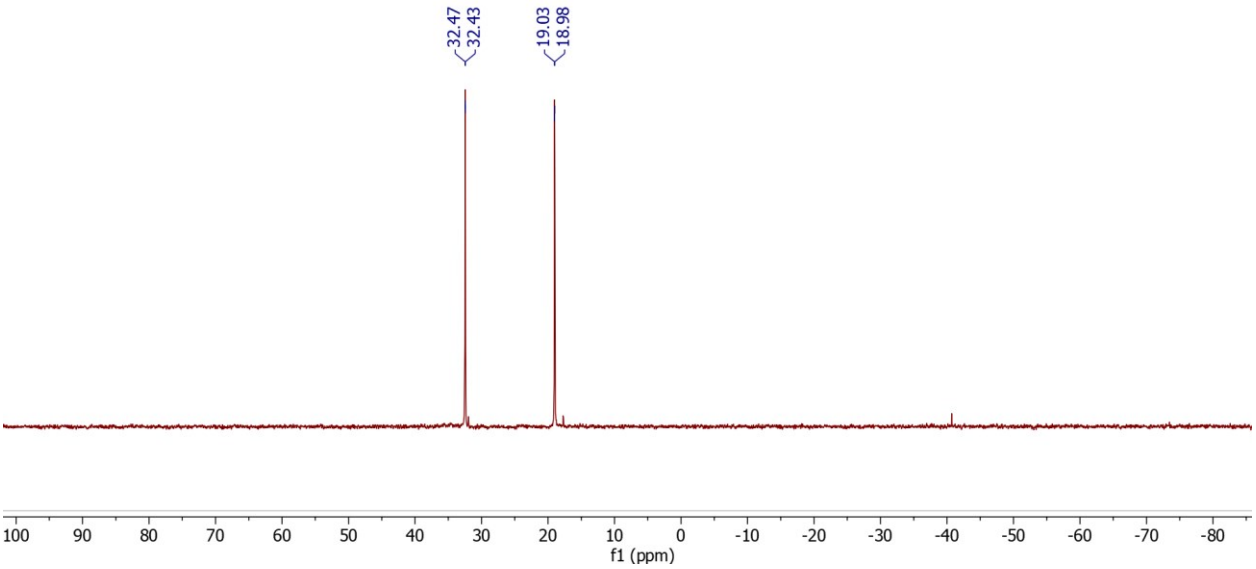


Figure A31. $^{13}C\{^{1}H\}$ UDEFT NMR Spectrum of *meso*-(**PAd2-DalPhos**)Ni(4-CNPh)Cl (125.8 MHz, $CDCl_3$)

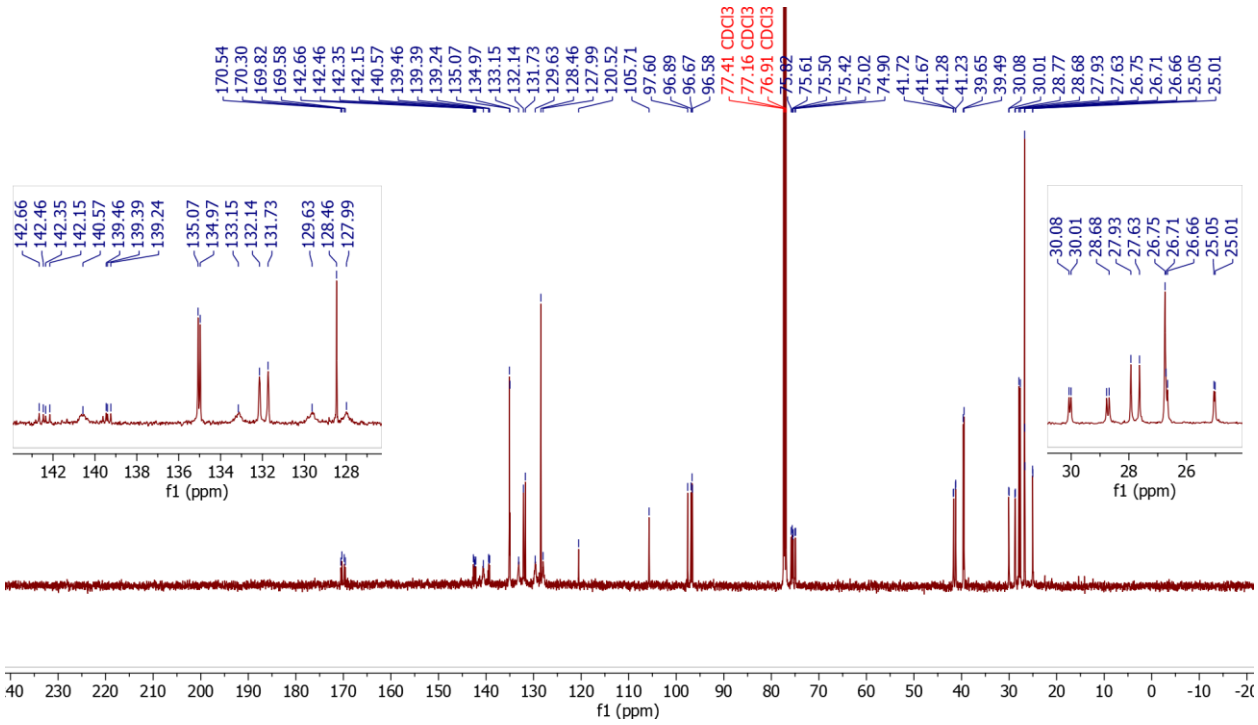


Figure A32. ^{1}H NMR Spectrum of (**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl (500.1 MHz, $CDCl_3$)

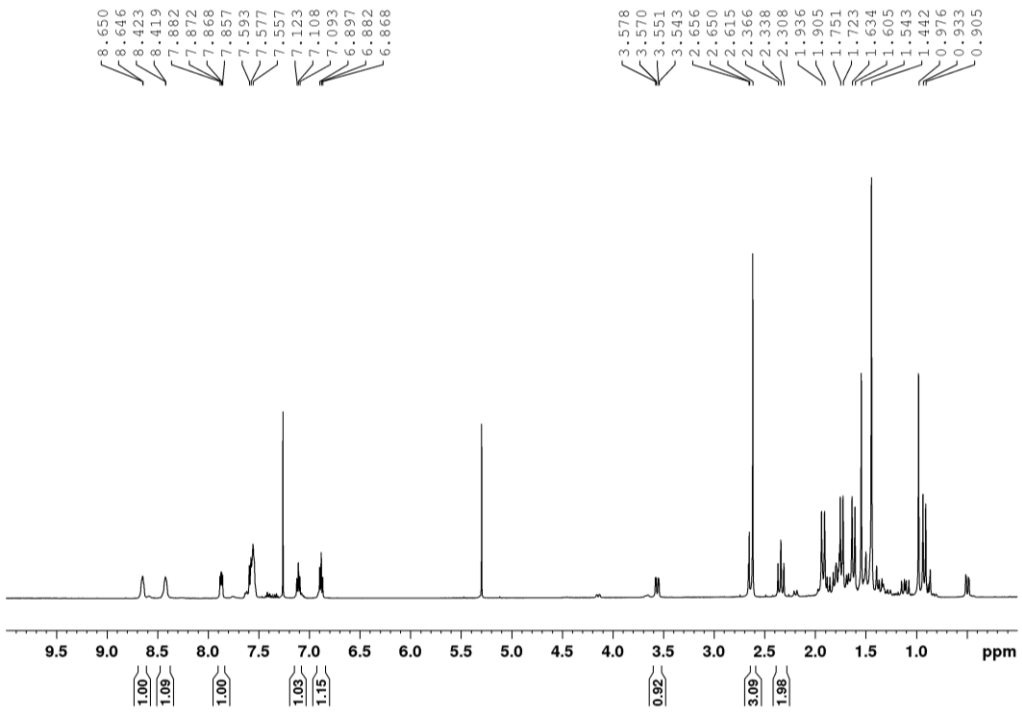


Figure A33. $^{13}C\{^{1}H\}$ UDEFT NMR Spectrum of (**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl (125.8 MHz, $CDCl_3$)

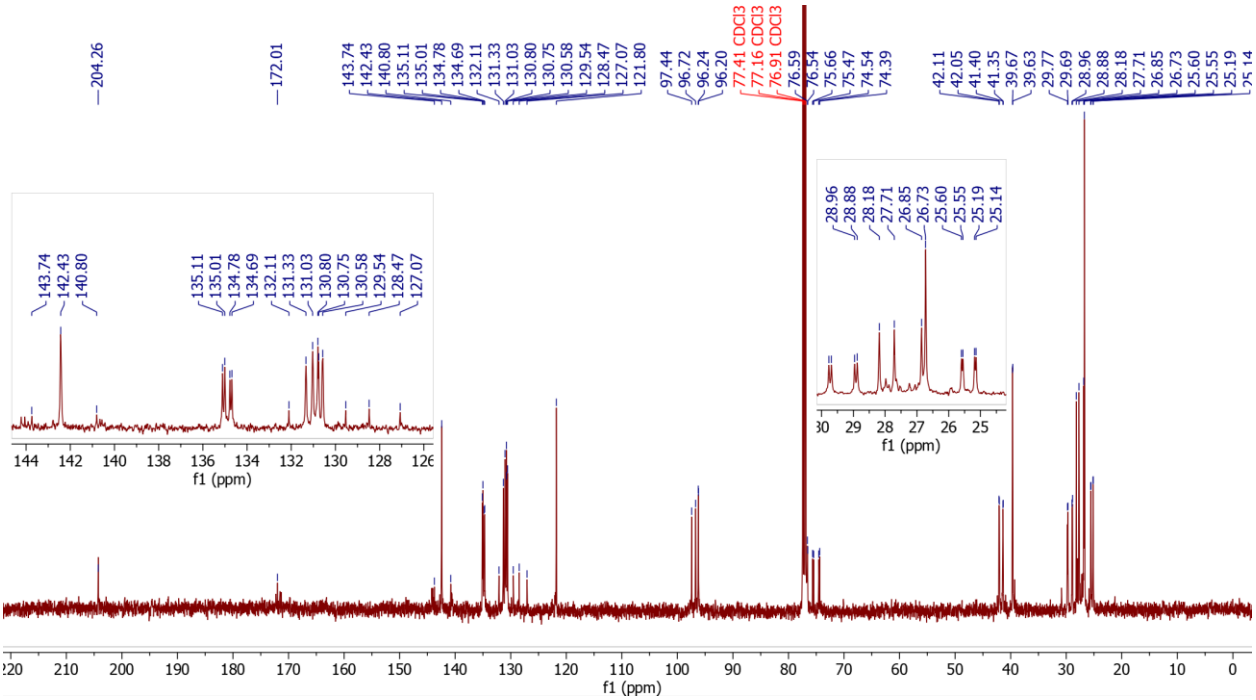


Figure A34. $^{31}P\{^{1}H\}$ NMR Spectrum of (**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl (202.5 MHz, $CDCl_3$)

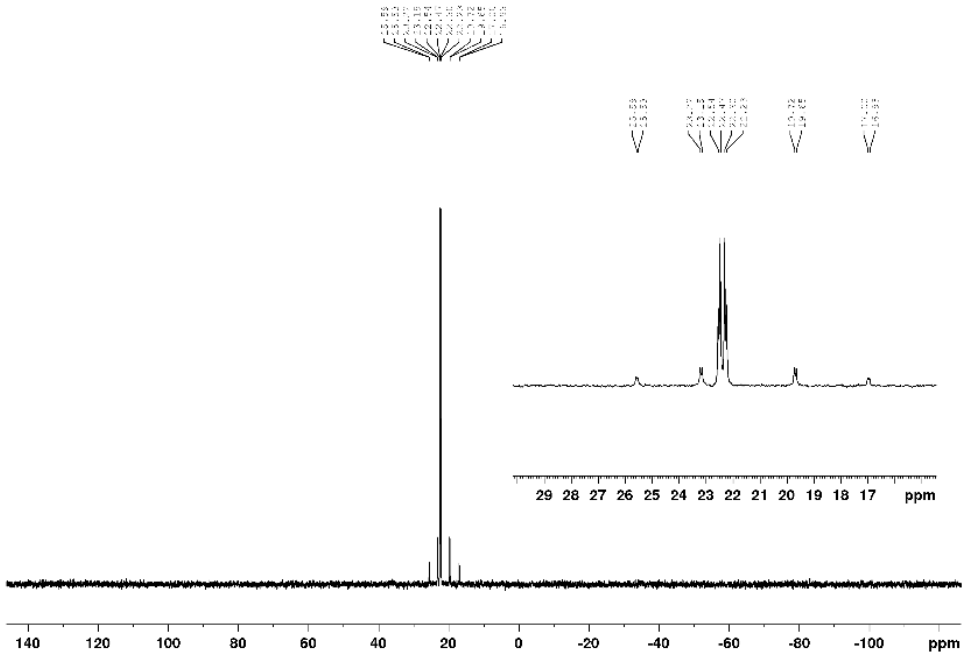


Figure A35. ^{1}H NMR Spectrum of *meso*-(**PAd2-DalPhos**)Ni(2-Ac-Ph)TFA (500.1 MHz, $CDCl_3$)

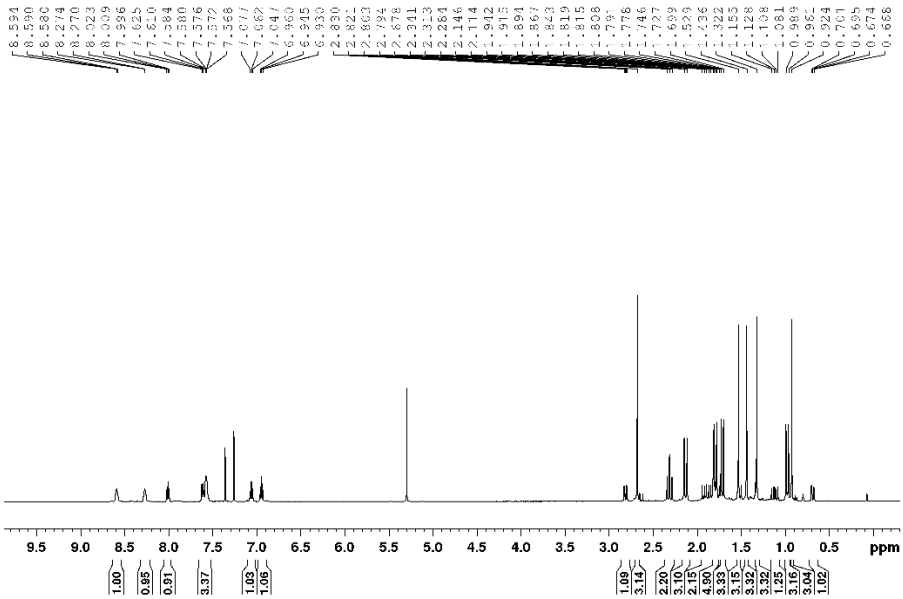


Figure A36. $^{13}C\{^{1}H\}$ UDEFT NMR Spectrum of *meso*-(**PAd2-DalPhos**)Ni(2-Ac-Ph)TFA (125.8 MHz, $CDCl_3$)

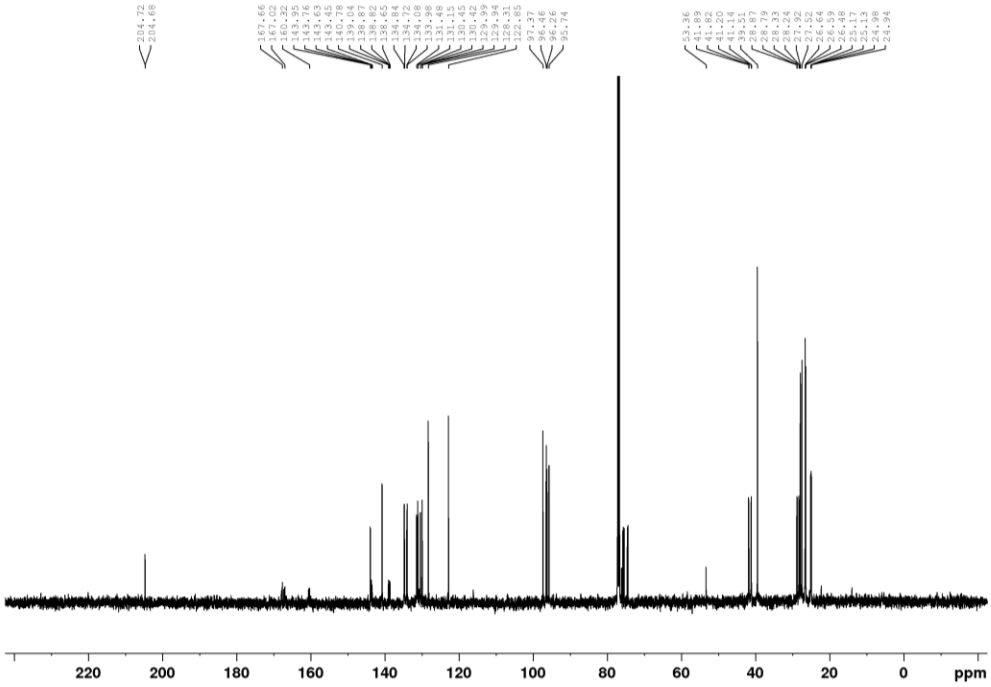


Figure A37. $^{31}P\{^{1}H\}$ NMR Spectrum of *meso*-(**PAd2-DalPhos**)Ni(2-Ac-Ph)TFA (202.5 MHz, $CDCl_3$)

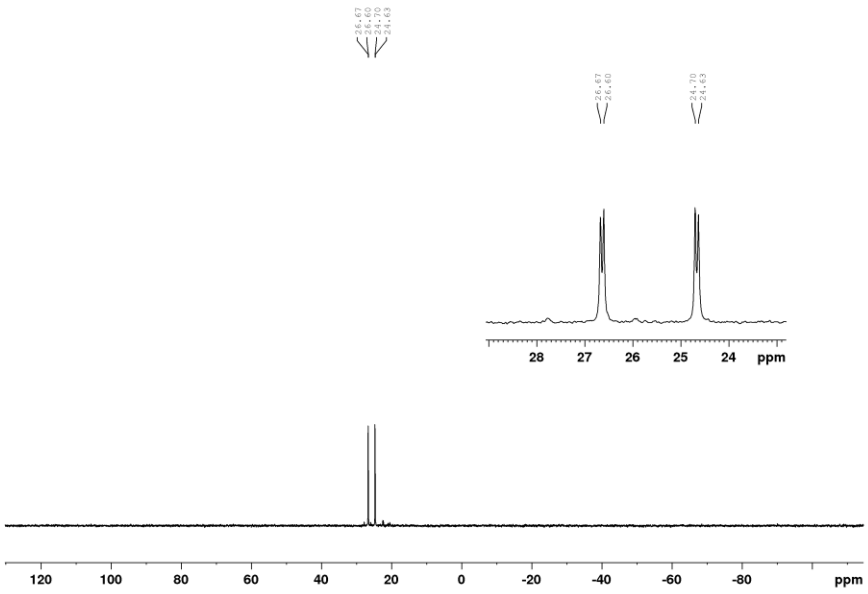


Figure A38. $^{19}F\{^{1}H\}$ NMR Spectrum of *meso*-(**PAd2-DalPhos**)Ni(2-Ac-Ph)TFA (470.6 MHz, $CDCl_3$)

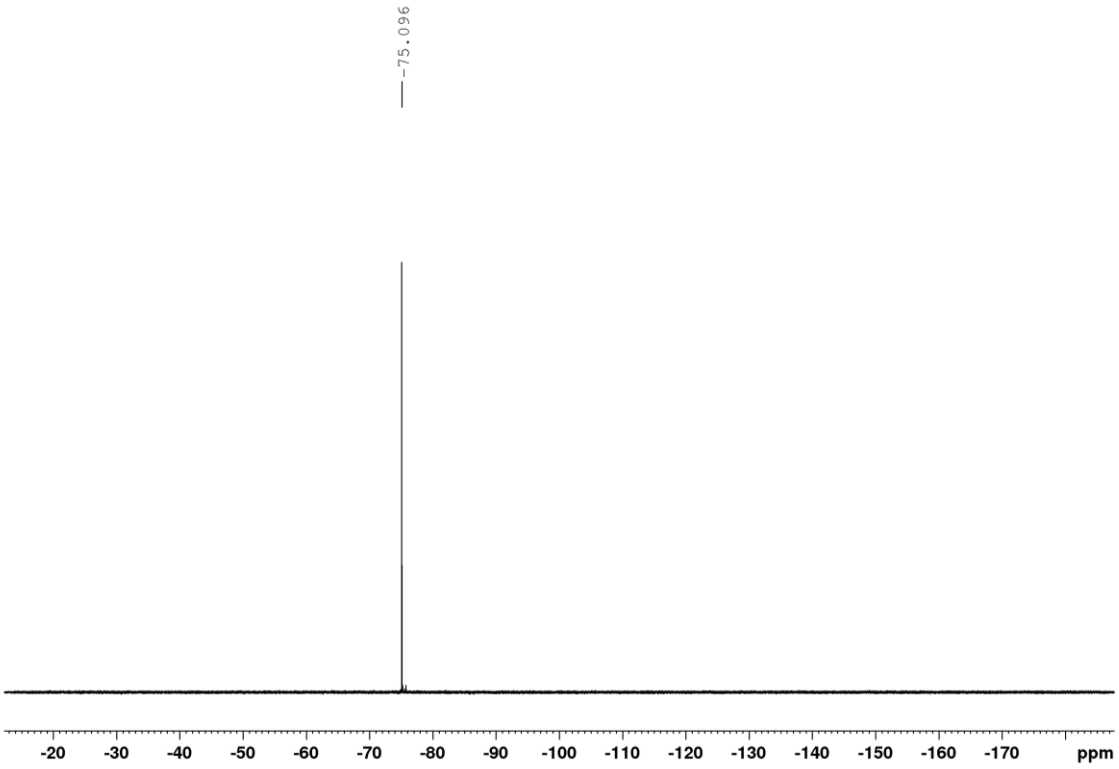


Figure A39. ^{1}H NMR Spectrum of (**PAd2-DalPhos**)Ni(COD) (500.1 MHz, C_6D_6)

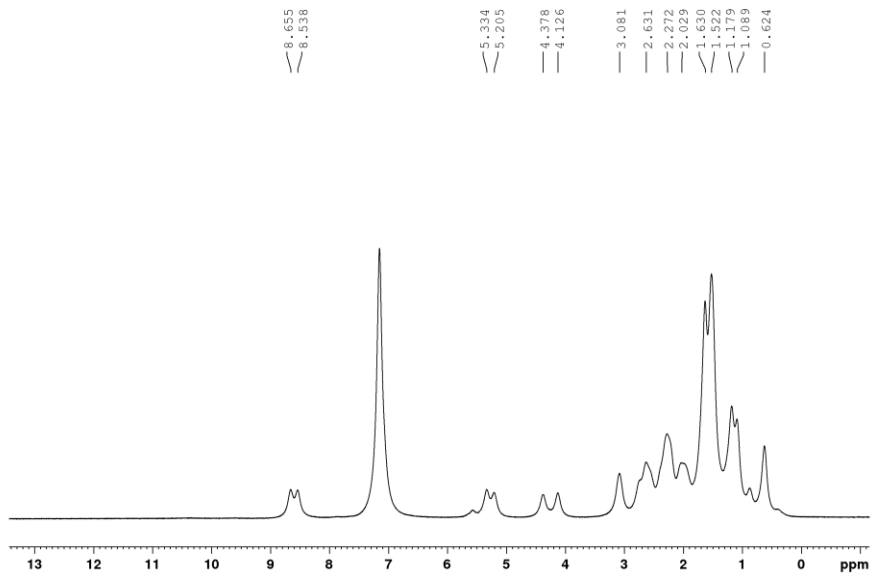


Figure A40. $^{13}C\{^{1}H\}$ UDEFT NMR Spectrum of (**PAd2-DalPhos**)Ni(COD) (125.8 MHz, C_6D_6)

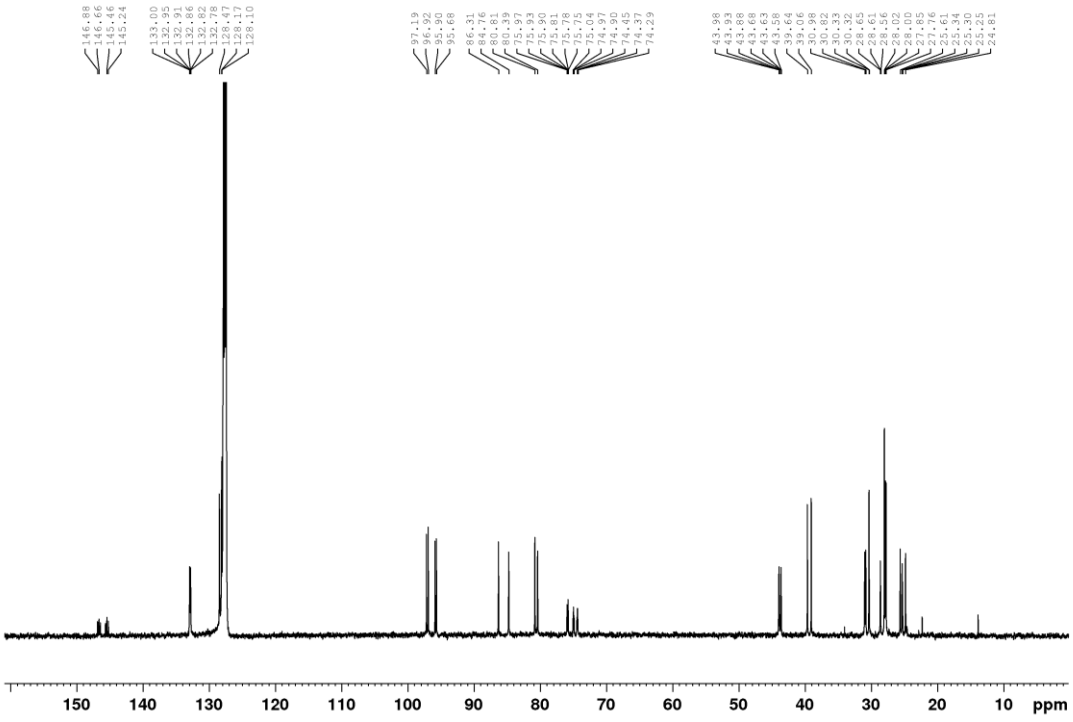


Figure A41. $^{31}P\{^{1}H\}$ NMR Spectrum of (**PAd2-DalPhos**)Ni(COD) (202.5 MHz, C_6D_6)

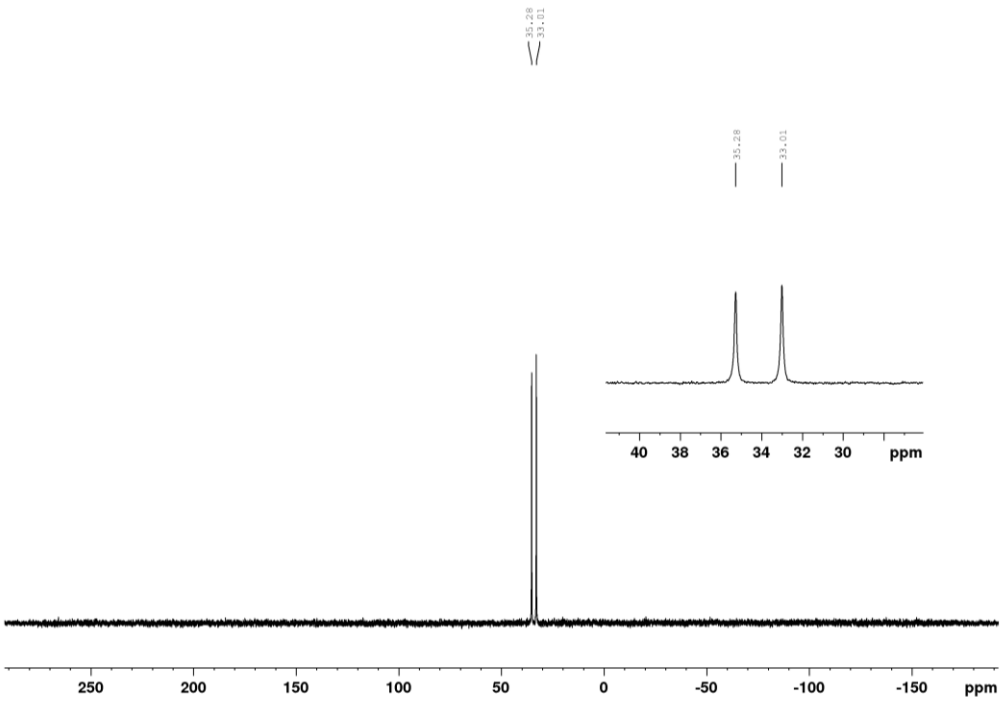


Figure A42. $^{31}P\{^{1}H\}$ NMR spectrum (202.5 MHz, C_6D_6) upon exposure of (**PAd2-DalPhos**)Ni(2-Ac-Ph)X (X = Cl or TFA) to 3,5-bis(trifluoromethyl)benzamide and DBU (5.0 equiv in C_6H_6, 25 ºC, 1 h).

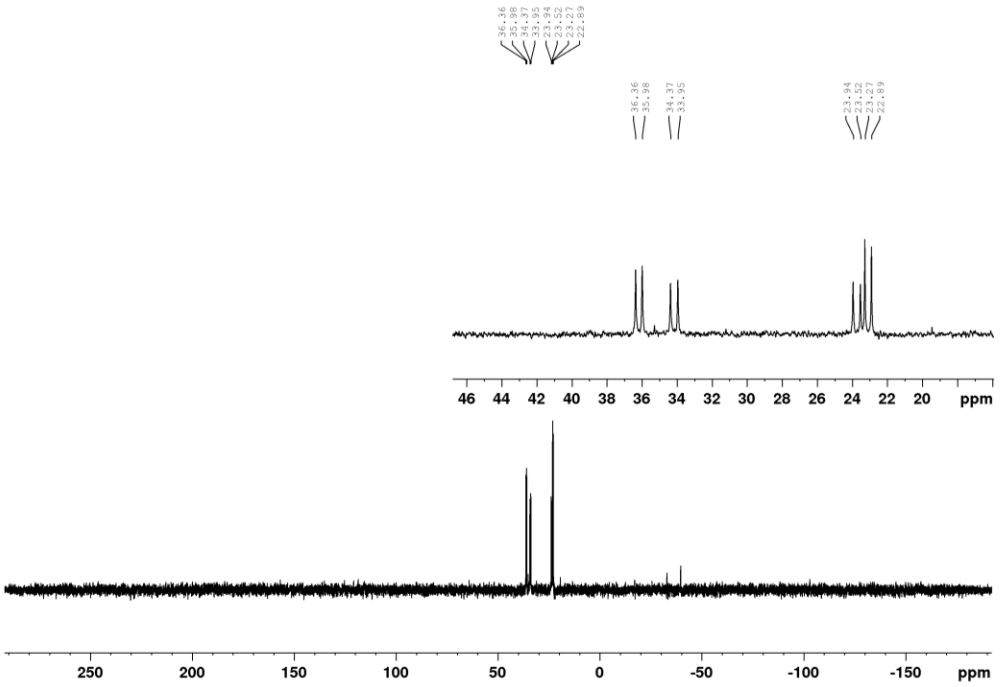
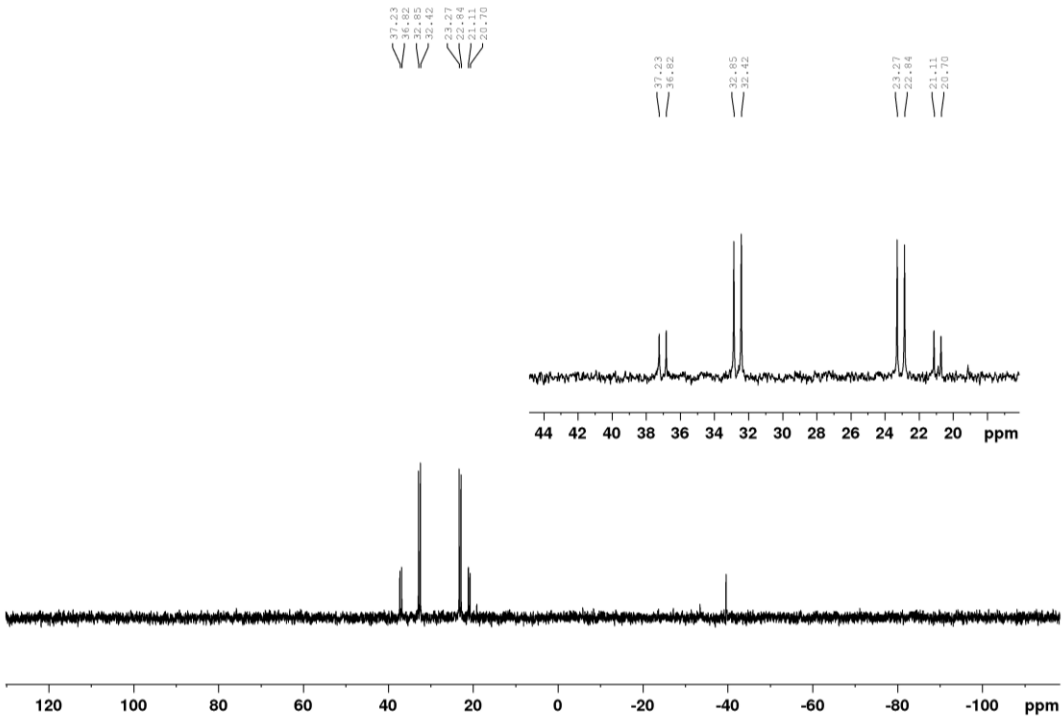


Figure A43. $^{31}P\{^{1}H\}$ NMR spectrum (202.5 MHz, C_6D_6) upon exposure of (**PAd2-DalPhos**)Ni(2-Ac-Ph)X (X = Cl or TFA) to 4-methoxybenzamide and DBU (5.0 equiv in C_6H_6, 25 ºC, 1 h).



Appendix B. X-ray Data

Crystallographic Solution and Refinement Details for Phen-DalPhosNiCl(*o*-tolyl) and L1:

Crystallographic solution and refinement details. Crystallographic data were obtained at 173(2) K on a Bruker D8/APEX II CCD diffractometer equipped with a CCD area detector, using Cu Kα (1.54178) (microfocus source) radiation and employing samples that were mounted in inert oil and transferred to a cold gas stream on the diffractometer. Data reduction, correction for Lorentz polarization, and absorption correction (Gaussian integration; face-indexed) were each performed. Structure solution by using intrinsic phasing was carried out, followed by least-squares refinement on F^2. All non-hydrogen atoms were refined with anisotropic displacement parameters, while all hydrogen atoms were added at calculated positions and refined by use of a riding model employing isotropic displacement parameters based on the isotropic displacement parameter of the attached atom.

Phen-DalPhosNiCl(*o*-tolyl) (CCDC 1935830)

Table A1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{51}H_{57}ClNiO_2P_2$
formula weight	858.06
crystal dimensions (mm)	0.34 x 0.34 x 0.23
crystal system	monoclinic
space group	$P2_1/n$ (an alternate setting of $P2_1/c$ [No. 14])
unit cell parameters[a]	
a (Å)	13.151(5)
b (Å)	15.965(6)

c (Å)	21.319(8)
b (deg)	91.921(6)
V (Å^3)	4474(3)
Z	4
r_{calcd} (g cm^{-3})	1.274
μ (mm^{-1})	0.604

B. Data Collection and Refinement Conditions

diffractometer	Bruker PLATFORM/APEX II CCD[b]
radiation (*l* [Å])	graphite-monochromated Mo K*a* (0.71073)
temperature (°C)	–80
scan type	*w* scans (0.3°) (10 s exposures)
data collection 2*q* limit (deg)	56.82
total data collected	130827 (-17 ≤ *h* ≤ 17, -21 ≤ *k* ≤ 21, -28 ≤ *l* ≤ 28)
independent reflections	11175 (R_{int} = 0.0552)
number of observed reflections (*NO*)	8901 [$F_o^2 \geq 2s(F_o^2)$]
structure solution method	intrinsic phasing (*SHELXT-2014*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–2017*[d])
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.9143–0.8151
data/restraints/parameters	11175 / 0 / 557
goodness-of-fit (*S*)[e] [all data]	1.047
final *R* indices[f]	
R_1 [$F_o^2 \geq 2s(F_o^2)$]	0.0421
wR_2 [all data]	0.1206
largest difference peak and hole	0.909 and –0.405 e Å^{-3}

[a]Obtained from least-squares refinement of 9935 reflections with $4.40° < 2\theta < 52.78°$.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c]Sheldrick, G. M. *Acta Crystallogr.* **2015**, *A71*, 3–8. (*SHELXT-2014*)

[d]Sheldrick, G. M. *Acta Crystallogr.* **2015**, *C71*, 3–8. (*SHELXL-2017*)

[e]$S = [\mathrm{S}w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [s^2(F_o^2) + (0.0686P)^2 + 1.5151P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[f]$R1 = \mathrm{S}||F_o| - |F_c||/\mathrm{S}|F_o|$; $wR2 = [\mathrm{S}w(F_o^2 - F_c^2)^2/\mathrm{S}w(F_o^4)]^{1/2}$.

Crystallographic Solution and Refinement Details for L1 (CCDC 1885150)

Table A2. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{60}H_{74}Cl_6FeO_4P_2$
formula weight	1189.68
crystal dimensions (mm)	0.28 × 0.14 × 0.05
crystal system	monoclinic
space group	*C*2/*c* (No. 15)
unit cell parameters[a]	
a (Å)	21.559(4)
b (Å)	10.331(2)
c (Å)	27.169(5)
β (deg)	95.473(3)
V (Å^3)	6024(2)
Z	4
ρ_{calcd} (g cm^{-3})	1.312
μ (mm^{-1})	0.614
bis{4,8-di-t-butyl-1,2,10,11-	
B. Data Collection and Refinement Conditions	
diffractometer	Bruker PLATFORM/APEX II CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–80
scan type	ω scans (0.3°) (20 s exposures)
data collection 2θ limit (deg)	51.39
total data collected	21274 (-26 ≤ *h* ≤ 26, -12 ≤ *k* ≤ 12, -33 ≤ *l* ≤ 33)
independent reflections	5731 (R_{int} = 0.0540)
number of observed reflections (*NO*)	4131 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	intrinsic phasing (*SHELXT-2014*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–2016*[d])
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.9901–0.9129
data/restraints/parameters	5731 / 51[e] / 372
goodness-of-fit (*S*)[f] [all data]	1.103
final *R* indices[g]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0633
wR_2 [all data]	0.1965
largest difference peak and hole	1.001 and –0.693 e Å^{-3}

[a]Obtained from least-squares refinement of 4614 reflections with $4.38° < 2\theta < 41.36°$.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c]Sheldrick, G. M. *Acta Crystallogr.* **2015**, *A71*, 3–8. (*SHELXT-2014*)

[d]Sheldrick, G. M. *Acta Crystallogr.* **2015**, *C71*, 3–8. (*SHELXL-2016*)

[e]The disordered solvent chloroform molecules were geometrically restrained to have approximately equal C–Cl distances. Additionally, the rigid bond restraint was applied to improve the anisotropic displacement parameters.

[f]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.1051P)^2 + 5.7068P]^{-1}$ where $P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3$).

[g]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Crystallographic Solution and Refinement Details for Relevant PAd2-DalPhos-ligated Ni Complexes:

The crystal chosen was attached to the tip of a MicroLoop with Paratone-N oil. Measurements were made on a Bruker D8 VENTURE diffractometer equipped with a PHOTON III CMOS detector using monochromated Mo Kα radiation (λ = 0.71073 Å) from an Incoatec micro-focus sealed tube at 125 K (Bruker, 2018, Bruker AXS Inc., Madison, Wisconsin, USA). The initial orientation and unit cell were indexed using a least-squares analysis of the reflections collected from a 180° phi-scan, 2 to 5 seconds per frame and 1° per frame. For data collection, a strategy was calculated to maximize data completeness and multiplicity, in a reasonable amount of time, and then implemented using the Bruker Apex 3 software suite (Bruker, 2018, Bruker AXS Inc., Madison, Wisconsin, USA). The crystal to detector distance was set to 4.0 cm and frames of appropriate time were collected. Cell refinement and data reduction were performed with the Bruker SAINT (Bruker, 2016, Bruker AXS Inc., Madison, Wisconsin, USA) software, which corrects for beam inhomogeneity, possible crystal decay, Lorentz and polarisation effects. A multi-scan absorption correction was applied (SADABS, Bruker, 2016, Bruker AXS Inc., Madison, Wisconsin, USA). The structure was solved using SHELXT-2014 (Sheldrick, G.M. (2015) *Acta Cryst*., A71, 3-8) and was refined using a full-matrix least-squares method on F^2 with SHELXL-2018 (Sheldrick, G.M. (2015) *Acta Cryst*., C71, 3-8.). The non-hydrogen atoms were refined anisotropically. The hydrogen atoms bonded to carbon were included at geometrically idealized positions and were not refined. The isotropic thermal parameters of these hydrogen atoms were fixed at $1.2U_{eq}$ of the parent carbon atom or $1.5U_{eq}$ for methyl hydrogens. The position of the hydrogen atoms bonded to nitrogen were located in near final Fourier

difference maps. They were allowed to refine isotropically with weak restraints applied if necessary.

Crystallographic data are available from the Cambridge Crystallographic Data Centre with the following codes: *meso*-(**PAd2-DalPhos**)Ni(4-CN-Ph)Cl (CCDC 2102678), *meso*+*rac*-((**PAd2-DalPhos**)NiCl)$_2$ (CCDC 2102681), *rac*+*rac*-((**PAd2-DalPhos**)NiCl)$_2$ (CCDC 2102679), *meso*-(**PAd2-DalPhos**)Ni(2-Ac-Ph)Cl (CCDC 2102680), *meso*-(**PAd2-DalPhos**)Ni(2-Ac-Ph)TFA (CCDC 2102677), *rac*-(**PAd2-DalPhos**)Ni(COD) (CCDC 2102676), *meso*-(**PAd2-DalPhos**)Ni(η^2-CO-**6.1**) (CCDC 2102674).

***meso*-(PAd2-DalPhos)Ni(4-CN-Ph)Cl (CCDC 2102678)**

$C_{33}H_{40}ClNNiO_6P_2 \cdot 2.5(CH_2Cl_2)$ 20 sec frames

Four reflections (1 1 1; -1 1 1; 0 0 2 and 0 2 4) were removed from the refinement because of poor agreement between F_{obs}^2 and F_{calc}^2, the former three because they were partially obscured by the beam stop. Data was collected to maximum resolution of 0.55 Å and integrated to a resolution of 0.50 Å. However, I/σ(I) was greater than 2 only to 0.55 Å and the data was limited to this resolution using a SHEL instruction during the refinement.

The molecule was found to crystallize in the centrosymmetric, monoclinic space group $P2_1/n$. The asymmetric unit was found to contain one complete molecule of the product plus "three" partially occupied molecules of dichloromethane solvent. Refinement of the occupancies of the atoms in the solvent molecules showed that the total solvent occupancy was less than 3. A free variable was assigned to the occupancies of the atoms in each solvent molecule (the same free variable for each atom in one molecule) and these were allowed to refine. The total solvent content refined to approximately 2.5 molecules, so the sum of the free variables was set to 2.5 molecules of dichloromethane total in each asymmetric unit,

using a SUMP command during the refinement. The occupancies of the solvent molecules refined to 0.868(2), 0.821(2) and 0.814(2) for molecules 1, 2 and 3, respectively.

At the end of the refinement there were no significant cif alerts generated on checking. However, it was clear from the final Fourier difference map that most of the residual density remaining unaccounted for was due to unresolved disorder caused by thermal motion in the solvent molecules.

***meso*+*rac*-((PAd2-DalPhos)NiCl)$_2$ (CCDC 2102681)**

$C_{52}H_{72}Cl_2Ni_2O_{12}P_4 \cdot 0.5(C_6H_6) \cdot 0.5(C_5H_{12})$ 10 sec frames

One reflection (2 0 0) was removed from the refinement as it was partially obscured by the beam stop. Data was collected to maximum θ angle of 47.23° (0.48 Å resolution). However, inspection of the collected reflections showed that $I/\sigma(I) < 2$ was reached at a relatively low θ value. The data was thus cut off at 0.70 Å (30.51°) during refinement using a SHEL instruction.

In this structure the asymmetric unit was found to contain one product molecule and disordered solvent. The best model that could be determined for the solvent included 0.5 molecules of benzene and 0.5 molecules of pentane in the asymmetric unit. The benzene was further modelled with a 2-part disorder with the occupancy of each part refined and the total occupancy set to 0.500 using a SUMP instruction. The occupancy of the pentane molecule was set to 0.500 and not refined (after initial refinement of all occupancies suggested the correct ratio to use). The geometries of the benzene rings were restrained to fit regular hexagons (AFIX 66) and the bond lengths in the pentane molecule were restrained to 1.54(2) Å. The thermal parameters of the carbon atoms in the benzene rings were restrained to be similar, as were those in the pentane molecule. The model used for the solvent was not

perfect. It was clear that there was residual electron density still present that has not been accounted for. More complicated solvent models were tried but with no greater success than the 3-part model provided.

***rac*+*rac*-((PAd2-DalPhos)NiCl)$_2$ (CCDC 2102679)**

$C_{52}H_{72}Cl_2Ni_2O_{12}P_4 \cdot 2.44(C_6H_6) \cdot 0.56(C_5H_{12})$ 10 sec frames

Three reflections were removed from the refinement as they were partially obscured by the beam stop. Data was integrated to a maximum θ angle of 36.28° (0.60 Å resolution) but the data was cut off at 0.75 Å (28.28°) during refinement using a SHEL instruction.

In this structure the asymmetric unit was found to contain one product molecule and disordered solvent. The best model that could be determined for the solvent included two ordered and fully occupied benzene molecules, one disordered and partially occupied benzene molecule, and one disordered and partially occupied pentane molecule in the asymmetric unit. The pentane was further modelled with a 2-part disorder with the occupancy of each part refined and the total occupancy, of pentane plus the partially occupied benzene, set to 1.000 using a SUMP instruction. The geometry of the partially occupied benzene ring was restrained to fit a regular hexagon (AFIX 66) and the bond lengths in the pentane molecule were restrained to 1.54(2) Å. The thermal parameters of the carbon atoms in the third benzene ring were restrained to be similar, as were those in the pentane molecule. The occupancies of the molecules refined to 0.44(1) for the partially occupied benzene, and 0.20(1) and 0.36(1) for the two parts of the pentane molecule, respectively.

***meso*-(PAd2-DalPhos)Ni(2-Ac-Ph)Cl (CCDC 2102680)**

$C_{34}H_{43}ClNiO_7P_2 \cdot 1.5(C_6H_6)$ 15 sec frames

Two reflections (1 0 0; -3 3 6) were removed from the refinement, the first as it was partially obscured by the beam stop and the second because of poor agreement. Data was collected to maximum θ angle of 45.65° (0.50 Å resolution). However, inspection of the collected reflections showed that $I/\sigma(I) < 2$ was reached at a θ value of 0.55 Å. The data was thus cut off at 0.55 Å (40.25°) during refinement using a SHEL instruction.

In this structure the asymmetric unit was found to contain one product molecule plus additional solvent. The solvent proved to be 1.5 molecules of well-ordered benzene per asymmetric unit.

***meso*-(PAd2-DalPhos)Ni(2-Ac-Ph)TFA (CCDC 2102677)**

$C_{36}H_{43}F_3NiO_9P_2 \cdot C_6H_6$ 20 sec frames

Two reflections (1 0 0; -3 3 6) were removed from the refinement, the first as it was partially obscured by the beam stop and the second because of poor agreement. Data was collected to maximum θ angle of 47.52° (0.48 Å resolution). However, inspection of the collected reflections showed that $I/\sigma(I) < 2$ was reached at a θ value of 0.75 Å. The data was thus cut off at 0.75 Å (28.28°) during refinement using a SHEL instruction.

In this structure the asymmetric unit was found to contain one product molecule plus additional solvent. The solvent proved to be one molecule of well-ordered benzene per asymmetric unit.

***rac*-(PAd2-DalPhos)Ni(COD) (CCDC 2102676)**

$C_{34}H_{48}NiO_6P_2 \cdot C_6H_6$ 10 sec frames

One reflection (-9 1 6) was removed from the refinement because of poor agreement between F_{obs}^2 and F_{calc}^2. Data was collected to maximum θ angle of 45.45° (0.50 Å resolution) and all of the collected data was used in the refinement of the structure.

The molecule was found to crystallize in the centrosymmetric, monoclinic space group *C*2/*c*. The asymmetric unit was found to contain one half of the product molecule plus one half of a molecule of well-ordered benzene solvent. The Ni atom of the main molecule lies on a special position, with the second half of the molecule related to the first by rotation about the C_2 axis it lies on. The second half of the benzene molecule is generated from the first by inversion.

***meso*-(PAd2-DalPhos)Ni(η^2-CO-A1) (CCDC 2102674)**

$C_{43}H_{47}F_6NNiO_8P_2$ 20 sec frames

Two reflections (-3 -3 6 and -12 3 2) were removed from the refinement because of poor agreement between F_{obs}^2 and F_{calc}^2. Data was collected to maximum resolution of 0.60 Å and integrated to a resolution of 0.53 Å. However, I/σ(I) was greater than 2 only to 0.60 Å and the data was limited to this resolution using a SHEL instruction during the refinement.