

Nickel Catalyzed C–S Bond Formation and Activation

Dissertation

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Preface

This cumulative thesis presents five research projects focused on the formation and activation of C–S bonds. It is organized into a general introduction covering the relevant background and concepts, followed by the presentation and discussion of published studies. Where applicable, unpublished results are also included. The appendix contains the published articles.

This work was conducted at the Institute of Organic Chemistry at the University of Tübingen, Germany, from December 2022 to May 2026 under the supervision of Prof. Dr. Ivana Fleischer.

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Abbreviations

4CzIPN	2,4,5,6-Tetrakis(9 <i>H</i> -carbazol-9-yl)isophthalonitrile
AE	Atom Economy
API	Active Pharmaceutical Ingredient
BAr _F	Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
BHT	Dibutylhydroxytoluene
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Boc	<i>tert</i> -Butyloxycarbonyl
cod	1,4-cyclooctadiene
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
diglyme	Bis(2-methoxyethyl)ether
DMA	<i>N,N</i> -Dimethylacetamide
DME	Dimethoxyethane
DMF	<i>N,N</i> -Dimethylformamide
DMPU	<i>N,N'</i> -Dimethylpropyleneurea
DMSO	Dimethylsulfoxide
dppbz	1,2-Bis(diphenylphosphino)benzene
DPEphos	Bis[(2-diphenylphosphino)phenyl]ether
dppf	1,1'-Bis(diphenylphosphino)ferrocene
DSC	Differential Scanning Calorimetry
dtbbpy	4,4'-Di- <i>tert</i> -butyl-2,2'-bipyridine
FID	Flame-Ionization-Detector
GC	Gas Chromatography
HPLC	High-Performance-Liquid-Chromatography
HRMS	High-Resolution Mass Spectrometry
IM	Intermediate
IR	Infrared
IRC	Intrinsic Reaction Coordinate

KIE	Kinetic Isotope Effect (p = primary, s = secondary)
L	Ligand
LAG	Liquid-Assisted-Grinding
MS	Mass Spectrometry
NHC	<i>N</i> -Heterocyclic carbene
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
OA	Oxidative addition
OAC	Oxidative addition complex
OMs/Mesylate	Methanesulfonate
ORTEP	Oak Ridge Thermal Ellipsoid Plot
OTf/Triflate	Trifluoromethanesulfonate
PEPPSI	Pyridine-Enhanced Precatalyst Preparation, Stabilization and Initiation
PMI	Process Mass Intensity
RME	Reaction Mass Efficiency
ROESY	Rotating-frame nuclear Overhauser Effect correlation Spectroscopy
SET	Single Electron Transfer
SS	Stainless Steel
TCD	Thiol Coordination and Deprotonation
TEMPO	2,2,6,6-Tetramethylpiperidin-1-oxyl
^{tbu} stb	4,4'-Di- <i>tert</i> -butylstilbene
THF	Tetrahydrofuran
TM	Transition Metal
TMEDA	<i>N,N,N,N</i> -Tetramethylethylenediamine
TMS	Trimethylsilyl
TS	Transition State
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XEC	Cross-Electrophile-Coupling
XRD	X-Ray Diffraction

Summary

Recent advances in nickel catalysis have significantly expanded the synthetic toolbox for carbon–heteroatom and carbon–carbon bond formation. In this work, five studies collectively demonstrated how catalyst design, mechanochemical activation, and mechanistic understanding can be integrated to overcome longstanding limitations in transition-metal-catalyzed synthesis. A central theme in this thesis is the development of efficient nickel-catalyzed transformations under mild and operationally simple conditions while simultaneously providing insight into catalyst activation and speciation.

One major focus is the development of general and robust protocols for nickel-catalyzed formation of C–S bonds. One particular challenging class of substrates are sterically demanding aryl electrophiles. The use of a flexible bidentate phosphine ligand enabled efficient coupling of hindered aryl electrophiles with alkyl thiols, affording products with high efficiency and broad functional-group tolerance. Computational studies revealed a dynamic coordination mode of the bidentate ligand, facilitating substrate access to the metal center.

In further work, the efficiency of nickel precatalysts in the context of C–S coupling was investigated with respect to the counterion. New synthetic routes towards nickel precatalysts of the general formula $(L)Ni(o\text{-tolyl})X$ were explored and the corresponding new complexes were fully characterized, including by X-Ray diffraction. Evaluation in catalysis revealed that the activation time is directly linked to the nature of the counterion on nickel, revealing the triflate anion as optimal choice.

Another key contribution was the implementation of mechanochemistry as a more convenient activation platform for nickel catalysis. By replacing conventional solvent-based conditions with ball-milling techniques, a new methodology for thioether synthesis under solvent-minimized conditions was developed. This mechanochemical approach provided high efficiency and robustness while operating under air without exclusion of ambient atmosphere, thereby improving operational simplicity and reducing cost. Detailed mechanistic studies revealed initial catalyst deactivation and explored the reactivity of the formed nickel-thiolate clusters.

Additionally, mechanochemical approaches for nickel-catalyzed cross-electrophile coupling of thioesters with alkyl bromides were explored. Here, thioesters served as versatile and benchstable acyl donors in synthesis of ketones under reductive conditions, avoiding the

use of stoichiometric organometallic reagents and eliminating the need for Schlenk techniques. Mechanistic evidence supported the involvement of radical intermediates.

Finally, synthetically valuable 1,4-dicarbonyl compounds were obtained *via* nickel-catalyzed hydroacylation of activated alkenes using water as hydrogen source under mechanochemical conditions. This concept was extended to deuterioacylation using deuterium oxide, enabling efficient synthesis of deuterated 1,4-ketoesters. In-depth mechanistic studies, including kinetic isotope effects, Hammett analysis and DFT calculations provided insight into oxidative addition of thioesters to nickel, as well as the C–C bond forming step, which was proposed to proceed *via* migratory insertion of the alkene into a Ni–acyl bond.

Taken together, these contributions illustrated the growing versatility of nickel catalysis at the interface of organometallic chemistry, readily applicable synthetic protocols, and mechanistic research, offering valuable design principles for future developments in reductive and mechanochemical catalysis.

Zusammenfassung

Neuere Fortschritte in der Nickelkatalyse haben den synthetischen Werkzeugkasten für die Bildung von C–C- und C–Heteroatom-Bindungen erheblich erweitert. In dieser Arbeit werden fünf Studien zusammengeführt, die zeigen, wie sich Katalysatordesign, mechanochemische Aktivierung und mechanistisches Verständnis zusammenfügen lassen, um lang bestehende Einschränkungen in der Übergangsmetall-katalysierten Synthese zu überwinden. Ein zentrales Thema dieser Dissertation ist die Entwicklung effizienter nickelkatalysierter Transformationen unter milden und operativ einfachen Bedingungen bei gleichzeitiger Aufklärung der katalytisch aktiven Spezies, sowie deren Deaktivierung und Regenerierung.

Ein wesentlicher Schwerpunkt liegt auf der nickelkatalysierten Bildung von C–S-Bindungen unter generell und breit anwendbaren Bedingungen. Insbesondere sterisch anspruchsvolle Substrate galten bislang unter thermischer Nickelkatalyse als herausfordernd. Der Einsatz eines flexiblen, bidentaten Phosphinliganden ermöglichte die effiziente Kupplung gehinderter Aryl-Elektrophile mit Alkylthiolen, wobei Produkte in hoher Effizienz und mit breiter Verträglichkeit funktioneller Gruppen erhalten wurden. DFT-Rechnungen zeigten ein dynamisches Koordinationsverhalten des bidentaten Liganden, das den Zugang der Substrate zum Metallzentrum erleichtert.

In weiterführenden Arbeiten wurde die Effizienz von Nickel-Präkatalysatoren im Kontext der C–S-Kupplung in Abhängigkeit vom Gegenion untersucht. Die Entwicklung neuer Syntheserouten zu Nickel-Präkatalysatoren der allgemeinen Formel (L)Ni(*o*-tolyl)X ermöglichte die Isolation und umfassende Charakterisierung der entsprechenden Komplexe, einschließlich Einkristall-Röntgenstrukturanalyse. Die Evaluation unter katalytischen Bedingungen zeigte, dass die Aktivierungszeit direkt von der Art des Nickel-Gegenions abhängt, wobei das Triflat-Anion als optimale Wahl identifiziert wurde.

Weitere zentrale Beiträge konnten durch die Kombination von Nickelkatalyse mit Mechanochemie erreicht werden. Durch den Ersatz konventioneller lösungsmittelbasierter Bedingungen durch Kugelmöhlen-Techniken wurde eine neue Methodik zur Thioether-Synthese unter lösungsmittelarmen Bedingungen entwickelt. Dieser mechanochemische Ansatz zeichnet sich durch hohe Effizienz und Robustheit aus und verläuft unter Luft ohne Ausschluss der Atmosphäre, wodurch die operative Simplizität erhöht und Kosten reduziert werden. Durch detaillierte mechanistische Studien konnte die anfänglich beobachtete Katalysatordeaktivierung erklärt und die Reaktivität der gebildeten Nickel-Thiolat-Cluster untersucht werden.

Darüber hinaus wurden mechanochemische Ansätze für die nickelkatalysierte Kreuz-Elektrophil-Kupplung von Thioestern mit Alkylbromiden untersucht. Dabei dienen Thioester als vielseitige und stabile Acyldonoren in der Ketonsynthese unter reduktiven Bedingungen, wodurch der Einsatz stöchiometrischer metallorganischer Reagenzien sowie Schlenk-Techniken vermieden werden konnten. Mechanistische Befunde unterstützen die Beteiligung radikalischer Zwischenstufen.

Schließlich wurden synthetisch wertvolle 1,4-Dicarbonylverbindungen über eine nickelkatalysierte Hydroacylierung aktivierter Alkene unter Verwendung von Wasser als Hydridquelle unter mechanochemischen Bedingungen erhalten. Dieses Konzept wurde auf die Deuteroacylierung unter Einsatz von Deuteriumoxid erweitert, wodurch selektiv deuterierte 1,4-Ketoester zugänglich wurden. Umfassende mechanistische Studien, einschließlich kinetischer Isotopeneffekte, Hammett-Analysen und DFT-Rechnungen, lieferten Einblicke in die oxidative Addition von Thioestern an Nickel sowie in den C–C-Bindungsbildungsschritt, der über eine migratorische Insertion des Alkens in eine Ni–Acyl-Bindung erfolgt.

Zusammenfassend zeigen diese Arbeiten die zunehmende Vielseitigkeit der Nickelkatalyse an der Schnittstelle von metallorganischer Chemie, anwendungsorientierter Synthesemethodik und mechanistischer Forschung und liefern wertvolle Designprinzipien für zukünftige Entwicklungen in der reduktiven und mechanochemischen Katalyse.

Publications

A) Publications incorporated into this thesis

A1. Nickel Catalyzed C–S Cross Coupling of Sterically Hindered Substrates Enabled by Flexible Bidentate Phosphines.

Ivo H. Lindenmaier, Robert C. Richter and Ivana Fleischer.

Org. Chem. Front. **2024**, *11*, 2485–2493.

DOI 10.1039/D4QO00260A

A2. Influence of the Counterion on the Activation of Nickel(σ -Aryl) Precatalysts.

Ivo H. Lindenmaier, Anna S. Harzer, Markus Ströbele and Ivana Fleischer.

Organometallics **2025**, *44*, 4, 595–605.

DOI 10.1021/acs.organomet.4c00498

A3. Nickel-Catalyzed C–S Cross-Coupling Enhanced by Mechanochemistry.

Ivo H. Lindenmaier, Robert C. Richter, Marius Schier, Markus Ströbele and Ivana Fleischer.

ACS Catal. **2025**, *15*, 21, 17871–17881.

DOI 10.1021/acscatal.5c04516

A4. Nickel-catalyzed Cross-Electrophile-Coupling of Thioesters with Alkyl Bromides to Form Ketones Under Mechanochemical Conditions.

Ivo H. Lindenmaier, Robert C. Richter, Liesa Renz, Mattis T. Vochezer, Marius Schier, Pascal Faßnacht, Markus Ströbele and Ivana Fleischer.

Chem. Comm. **2026**, *62*, 5284–5288.

DOI 10.1039/d6cc00297h

A5. Nickel-Catalyzed Hydro- and Deuteroacylation of Acrylates using Water as Hydrogen Source.

Ivo H. Lindenmaier, Fabian Bölzle and Ivana Fleischer.

Chem. Sci. **2026**.

DOI 10.1039/d6sc04272d

B) Publications with minor contributions

B1. Stereoselective [2 + 2 + 2] Cycloaddition of Benzocyclobutanones and Norbornadienes through Nickel-Catalyzed C–C Bond Activation.

Robert C. Richter, Ivo H. Lindenmaier, David Schray, Markus Ströbele and Ivana Fleischer.

Org. Lett. **2025**, 27, 21, 5385–5389.

DOI 10.1021/acs.orglett.5c01324

Personal Contributions

Paper A1

Personal Contribution: 80%.

Development and optimization of the catalytic system as well as substrate synthesis was carried out by myself. Experiments for evaluation of the substrate scope and mechanistic studies were designed, conducted and interpreted by myself. DFT calculations were carried out by Dr. Robert C. Richter. Analytical data were obtained by myself, excluding HRMS analyses, which were conducted by the analytical department of the University of Tübingen. The crystal structure was measured and resolved by Dr. Cécilia Maichle-Mössmer. I compiled the results and wrote the manuscript with support from Prof. Dr. Ivana Fleischer.

Paper A2

Personal Contribution: 80%.

Conceptualization and exploration of synthetic routes was carried out by myself. Evaluation of nickel complexes in C–S and C–N coupling, as well as competition experiments were conducted by myself. Evaluation in C–C coupling was performed by Anna S. Harzer. NMR spectra were obtained by myself. HRMS analyses were conducted by the analytical department of the University of Tübingen. Crystal structures were measured and resolved by Dr. Markus Ströbele. Elemental analysis was conducted by Mohammad Ghani. I compiled the results and wrote the manuscript with support from Prof. Dr. Ivana Fleischer.

Paper A3

Personal Contribution: 80%.

Development and optimization of the catalytic system was carried out by myself. Substrate synthesis and evaluation of the substrate scope was conducted by myself, with exception of aryl triflates, which were evaluated by Marius Schier. Mechanistic experiments were conducted by myself and Dr. Robert C. Richter. Analytical data were obtained by myself, excluding HRMS analyses, which were conducted by the analytical department of the University of Tübingen. Crystal structures were measured and resolved by Dr. Markus

Ströbele. Elemental analysis was conducted by Mohammad Ghani. I compiled the results and wrote the manuscript with support from Prof. Dr. Ivana Fleischer.

Paper A4

Personal Contribution: 50%.

Conceptualization and supervision were carried out by myself and Dr. Robert C. Richter. Optimization of the catalytic system was carried out by Pascal Faßnacht with help of myself and Dr. Robert C. Richter. Substrate synthesis and evaluation of the substrate scope was conducted by Marius Schier, Mattis Vochezer and Liesa Renz. Mechanistic experiments were designed and interpreted by myself and conducted by Liesa Renz. Analytical data were obtained by myself, excluding HRMS analyses, which were conducted by the analytical department of the University of Tübingen. The crystal structure were measured and resolved by Dr. Markus Ströbele. Elemental analysis was conducted by Mohammad Ghani. I compiled the results and wrote the manuscript with support from Dr. Robert C. Richter and Prof. Dr. Ivana Fleischer.

Paper A5

Personal Contribution: 80%.

Development and optimization of the catalytic system was carried out by myself. Substrate synthesis and evaluation of the substrate scope was conducted by myself. Mechanistic experiments were designed, conducted and interpreted by myself. DFT calculations were performed by Fabian Bölzle. Analytical data were obtained by myself, excluding HRMS analyses, which were conducted by the analytical department of the University of Tübingen. I compiled the results and wrote the manuscript with support from Prof. Dr. Ivana Fleischer.

Paper B1

Personal Contribution: 10%.

Synthesis of benzocyclobutanones was conducted by myself and Dr. Robert C. Richter. All other experimental results were obtained by Dr. Robert C. Richter. The manuscript was written by Dr. Robert C. Richter with support from Prof. Dr. Ivana Fleischer.

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INTRODUCTION

1. Introduction

1.1. Homogenous Catalysis in Modern Organic Chemistry

The emergence and evolution of homogeneous transition metal catalysis represent one of the most profound paradigm shifts in modern chemistry.¹ Over the past five decades, catalytic methodologies based on soluble transition metal complexes have fundamentally altered how chemists conceptualize bond construction, enabling transformations that were once considered impractical, inefficient, or altogether impossible.²⁻³ Among these, cross-coupling reactions, and particularly palladium-catalyzed processes,⁴⁻⁶ have redefined synthetic strategy in both academic and industrial contexts.⁷⁻¹⁰ The development of these reactions has not only expanded the synthetic chemist's toolbox¹¹ but has also reshaped the economic, environmental, and technological landscape of the chemical and pharmaceutical industries.¹²⁻¹⁴

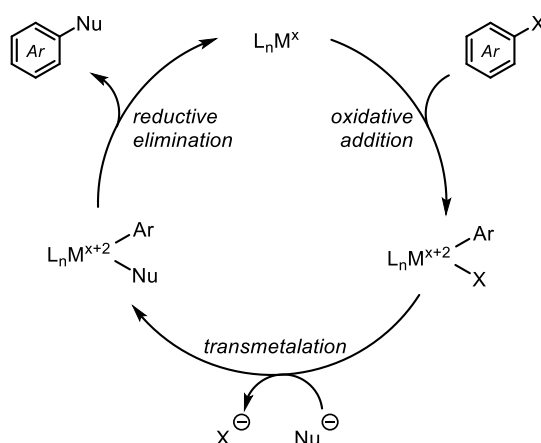
At the heart of cross-coupling reactions lies the unique ability of transition metals to mediate bond formation *via* accessible oxidation states, tunable coordination environments, and well-defined mechanistic pathways. Homogeneous catalysis, in contrast to its heterogeneous counterpart, allows for precise ligand design and mechanistic control, enabling chemists to fine-tune reactivity, selectivity, and substrate scope at an unprecedented level.¹⁵⁻¹⁶ The interplay between metal centers and tailored ligands has thus become a central design principle in modern synthetic chemistry, giving rise to a diverse array of catalytic systems that underpin contemporary research and industrial production.

Development of Homogenous Catalysis

The roots of homogeneous transition metal catalysis can be traced back to the first half of the 20th century,¹⁷⁻²⁰ but its explosive growth began in the 1970s and 1980s with the development of cross-coupling reactions. Landmark contributions by pioneers such as Suzuki,²¹ Heck,²² and Negishi²³ established general strategies for carbon–carbon bond formation *via* transition metal catalysis.²⁴ This work was ultimately recognized with the 2010 Nobel Prize in chemistry for some of the most versatile and widely adopted reactions in organic synthesis.²⁵

Mechanistically, the Suzuki–Miyaura reaction resembles the canonical catalytic cycle of oxidative addition, transmetalation, and reductive elimination (Scheme 1).²⁶ The ability to

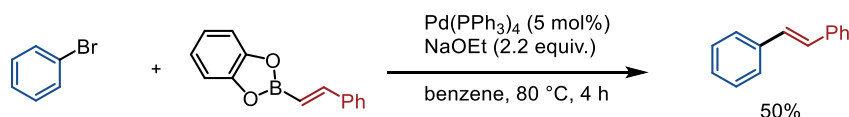
modulate each of these steps through ligand design has been a major driver of innovation in the field. The success and efficiency of cross-coupling reactions likely arise from a continuous interplay between mechanistic understanding and methodological innovation: increasingly detailed insight into reaction mechanisms has not only deepened fundamental knowledge but also informed the rational design of next-generation catalysts, enabling expansion of substrate scope and functional group tolerance.²⁷⁻³⁰



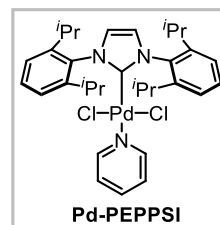
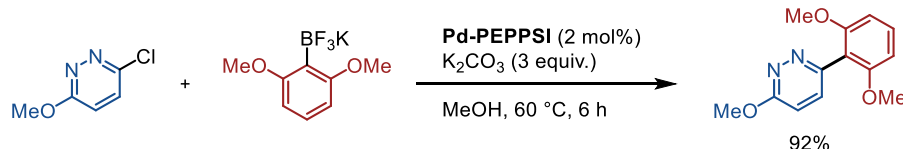
Scheme 1. General catalytic cycle of a transition-metal-catalyzed cross-coupling reaction.²⁶

Phosphine ligands, for example, have been extensively optimized to enhance catalytic activity and enable challenging substrate combinations,³¹⁻³³ demonstrating how ligand engineering can directly influence reaction efficiency and scope. This progress can be exemplified by directly comparing two methods for C–C-bond formation, one according to the original publication from Suzuki, and the other with a more contemporary palladium-NHC catalyst featuring the “pyridine-enhanced precatalyst preparation stabilization and initiation” (PEPPSI) system (Scheme 2).^{21, 30} The Pd-PEPPSI catalyst not only required lower catalyst loading and employed milder conditions, but efficiently coupled two challenging substrates in excellent yield, while the original procedure resulted in modest yield even for simple substrates.

A) Suzuki & Miyaura, 1979:



B) Organ, 2006:

**Scheme 2.** Comparison of old and modern methods for Suzuki cross-coupling.^{21, 30}

Following the initial success of palladium-catalyzed cross-coupling reactions, the field rapidly diversified, enabling the extension of cross-coupling methodologies to a broader range of substrates, including aryl chlorides,³⁴⁻³⁵ heterocycles,³⁶ and complex functionalized molecules.³⁷ Next to C–C cross-coupling, C–Heteroatom bond formation reactions have been developed, most prominently C–N³⁸⁻⁴⁰ and C–O⁴¹⁻⁴² cross-coupling. One of the key advantages of palladium-catalyzed C–X cross-coupling reactions in industrial contexts is its operational simplicity and robustness, tolerating a wide range of functional groups, minimizing number of steps and the need for protecting groups. Moreover, strict exclusion of air and moisture is not always required; in fact, many Suzuki coupling protocols employ water as (co-)solvent.⁴³⁻⁴⁴ These advantages translate directly into cost savings and improved process efficiency. While the development of palladium-catalyzed cross-coupling reactions largely matured in the 2000s, harnessing the more challenging reactivity of nickel remains an active area of research.⁴⁵⁻⁴⁸

Looking forward, several trends are likely to shape the future of the field. The development of earth-abundant metal catalysts, the integration of catalysis with automation and artificial intelligence, and the continued emphasis on green chemistry principles will likely play a central role.^{5, 12-13, 49}

1.2. C–S Cross-Coupling: Synthesizing Thioethers

Carbon–sulfur (C–S) cross-coupling reactions have emerged as a critical extension of the transition metal-catalyzed bond-forming paradigm, complementing the extensively developed C–C, C–N and C–O coupling methodologies.^{50–51} The formation of C–S bonds is of substantial importance due to the prevalence of thioethers and related sulfur-containing motifs in biologically active compounds,^{52–53} functional materials,^{54–55} and agrochemicals.⁵⁶ In the pharmaceutical industry in particular, sulfur-containing moieties are frequently encountered in drug candidates in various oxidation states (Figure 1).⁵² In fact, one third of the top 200 drugs by retail sales in 2024 contained at least one sulfur atom,⁵⁷ rendering sulfur the third most abundant heteroatom in APIs, following nitrogen and oxygen.⁵⁸

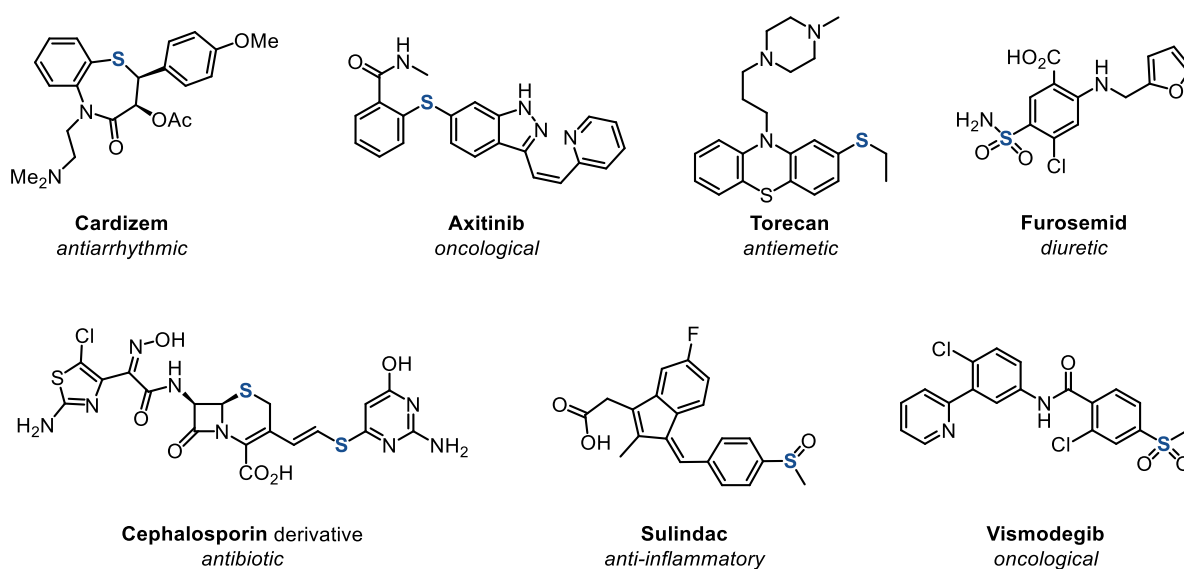


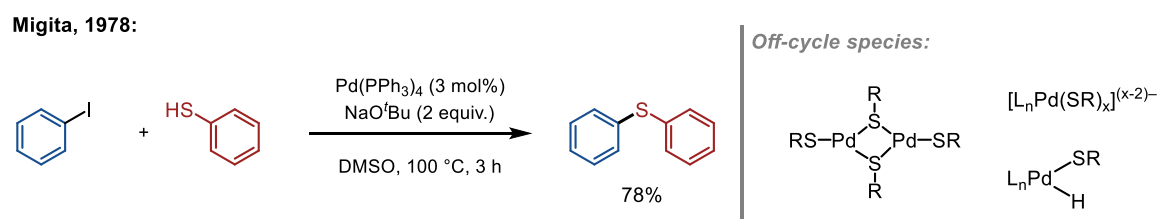
Figure 1. Sulfur containing scaffolds in pharmaceutically active ingredients (APIs).⁵²

Among the diverse functional groups implemented in drug molecules, thioethers stand out as versatile targets, as they offer easy access to higher oxidation state functional groups.^{59–60} One reason for the prevalence of sulfur in biologically active compounds is their increased lipophilicity compared to their oxygen counterparts, possibly influencing cell permeability and bioavailability,⁶¹ and thus leading to improved pharmacokinetic and pharmacodynamic profiles.^{62–65} Consequently, the development of efficient, selective, and scalable C–S cross-coupling reactions has become a key objective in both academic and industrial research.

Historically, the synthesis of aryl sulfides relied on nucleophilic (aromatic) substitution involving thiols and alkyl or activated aryl halides,^{66–70} often suffering from limited substrate scope and harsh conditions. However, an emerging trend, especially in drug discovery, is the application of cross-coupling for late-stage functionalization. The ability to introduce sulfur-

containing groups into complex molecules at a late stage of synthesis allows for rapid diversification of lead compounds and fine-tuning of pharmacological properties. This strategy is increasingly important in modern medicinal chemistry, where speed and flexibility are critical to the drug development process.⁷¹

The advent of transition metal-catalyzed C–S coupling, particularly palladium-catalyzed systems in the late 20th century, represented a major breakthrough. Seminal work from Migita first introduced the palladium-catalyzed coupling of aryl iodides with thiols (Scheme 3).^{72–73} However, C–S coupling posed unique challenges that slowed its initial development and broader adoption. One of the primary difficulties in C–S cross-coupling arises from the strong affinity of sulfur for late transition metals.⁷⁴ Thiols and thiolates can coordinate strongly to palladium and other metal centers, leading to catalyst poisoning and deactivation,⁷⁵ often necessitating high reaction temperatures and long reaction times to regenerate catalytically active species. Additionally, thiols are prone to oxidation to disulfides under reaction conditions,^{76–77} which can compete with the desired coupling pathway and reduce yields. These intrinsic reactivity issues have historically limited the efficiency and generality of early catalytic systems.



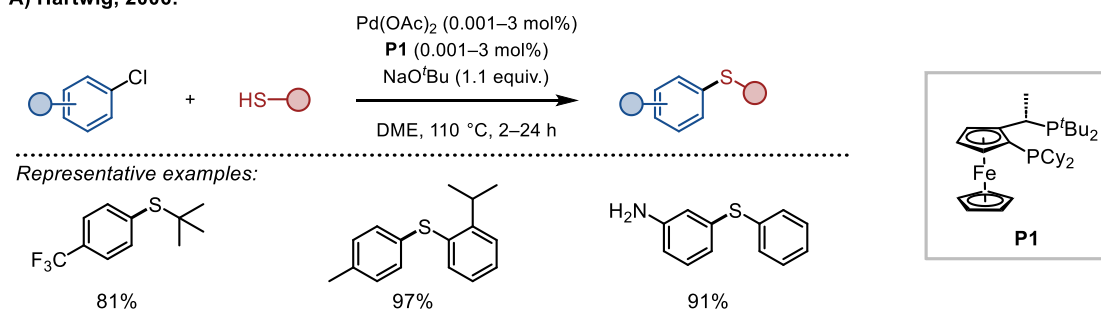
Scheme 3. First report of palladium-catalyzed C–S cross-coupling.^{72–73}

Despite these challenges, significant progress has been made through ligand and catalyst design (Scheme 4). The development of bulky, electron-rich phosphine ligands enabled palladium-catalyzed cross-coupling at extremely low Pd-loadings (Scheme 4, A),⁷⁸ while *N*-heterocyclic carbenes (NHCs) have proven particularly effective in promoting reactivity of sterically⁷⁹ or electronically⁸⁰ challenging substrates (Scheme 4, B). Likewise, bidentate phosphine ligands, derived from BINAP,⁸¹ dppf,⁸² and Xantphos,^{83–84} have been shown to be effective. One of the state-of-the-art works was published by the group of Buchwald, who reported the coupling of (hetero)aryl bromides with alkyl and aryl thiols at low Pd-loadings at room temperature, affording high yields even when more complex substrates were used (Scheme 4, C).⁸⁵ The mild and soluble base Et₃N tolerated acidic functional groups and prevented generation of bulk inorganic waste. Despite the advances in this field, the

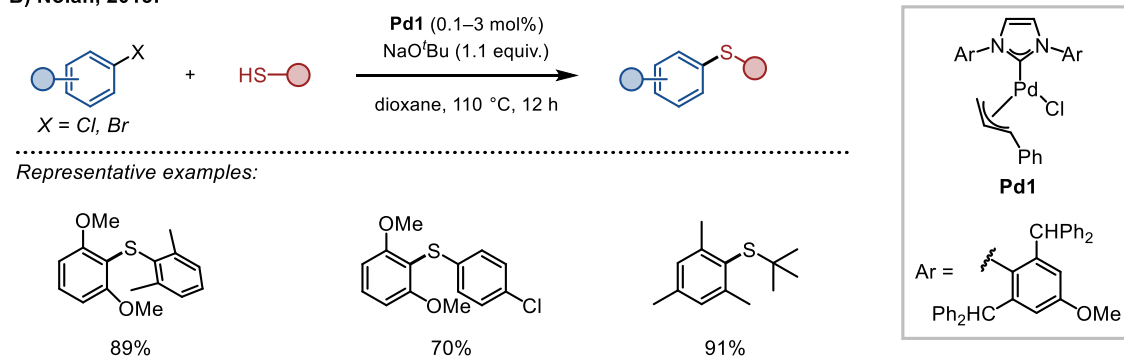
1. Introduction

sophisticated ligands necessary for these transformations pose severe disadvantages for applications.

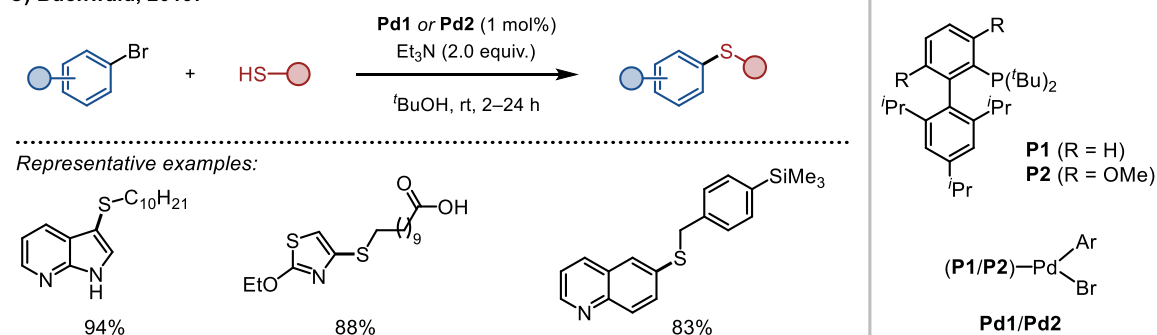
A) Hartwig, 2006:



B) Nolan, 2013:



C) Buchwald, 2019:



Scheme 4. Overview over selected Pd-catalyzed C–S cross-coupling methodologies independently reported by Hartwig,⁷⁸ Nolan⁷⁹ and Buchwald.⁸⁵

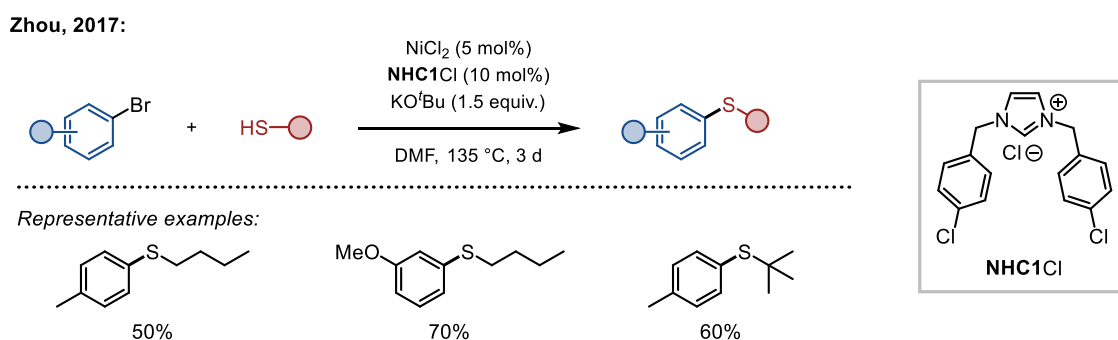
Parallel advances in copper-^{77,86–88} and nickel-catalyzed systems have also expanded the methodological landscape, offering more cost-effective alternatives to palladium and enabling complementary reactivity profiles.

Nickel-Catalyzed C–S Cross-Coupling

Nickel-catalyzed C–S cross-coupling has emerged as a strategically important subfield within transition metal catalysis, driven by the need for more sustainable and cost-effective alternatives to palladium-based systems.^{77, 89} Despite these advantages, several challenges continue to limit the widespread adoption of nickel-catalyzed C–S coupling, particularly in

industrial settings. Nickel catalysts are often more sensitive to air and moisture than their palladium counterparts,⁹⁰ and their propensity for off-cycle pathways can reduce efficiency and reproducibility. Nonetheless, the continued development of robust ligand frameworks, including NHCs and bidentate phosphines, as well as the integration of nickel catalysis with photoredox and electrochemical methods, is steadily addressing these limitations.

A representative example is the use of nickel(II) *N*-heterocyclic carbene (NHC) complexes, which showed coupling across a range of substrates (Scheme 5).⁹¹ Even for rather simple substrates, high temperatures and long reaction times were required, while delivering only moderate to good yields. Similar results for NHC-derived ligands were reported by groups of Nicasio and Nolan.⁹²⁻⁹³ Nitrogen ligands can also be effective in nickel-catalyzed C–S cross-coupling, although typically not suitable for less reactive electrophiles.⁹⁴⁻⁹⁶



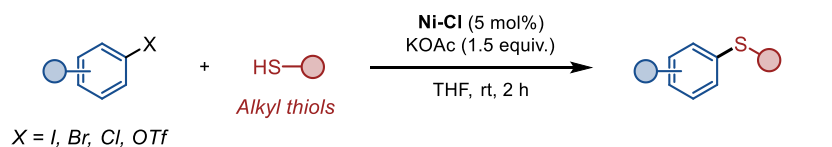
Scheme 5. Ni/NHC-catalyzed C–S coupling by Zhou *et al.*⁹¹

More recent advances have significantly expanded the scope and practicality of nickel-catalyzed C–S cross-coupling. Monodentate phosphines are more rarely employed in this context, although appropriate design, e.g. sterically demanding terphenyl motifs, can lead to high yields, including aryl chlorides and heterocyclic electrophiles.⁹⁷

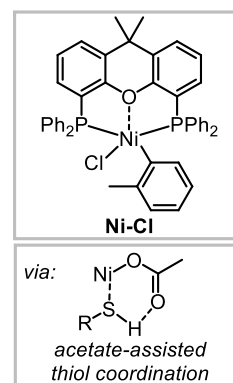
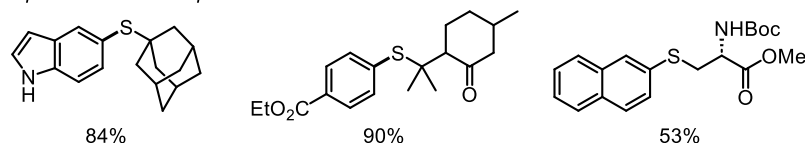
Next to others,⁹⁸ the Fleischer group has contributed to this field with reports featuring the bidentate phosphine ligand Xantphos (Scheme 6).⁹⁹⁻¹⁰⁰ Crucially, the choice of base played an important role next to ligand selection. Indeed, selecting KOAc as base enabled fast C–S coupling of traditionally more unreactive aryl chlorides, as well as bromides, iodides, and triflates at room temperature, proposedly *via* a concerted metalation-deprotonation pathway. While this protocol featured a broad scope and high yields, an important limitation imposed the use of aromatic thiols that resulted in complete inhibition of the coupling reaction. Still, this work represents a state-of-the-art method for nickel-catalyzed thioetherification.

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Fleischer, 2022 & 2023:



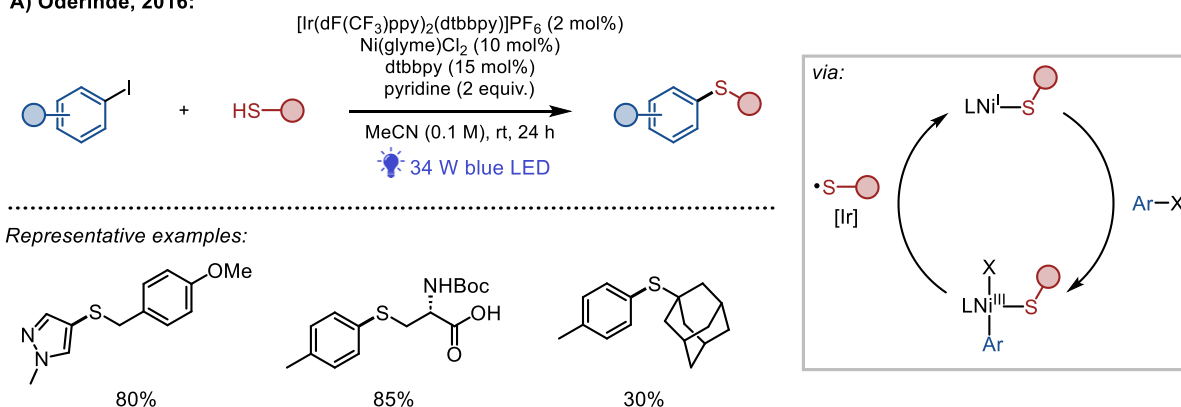
Representative examples:



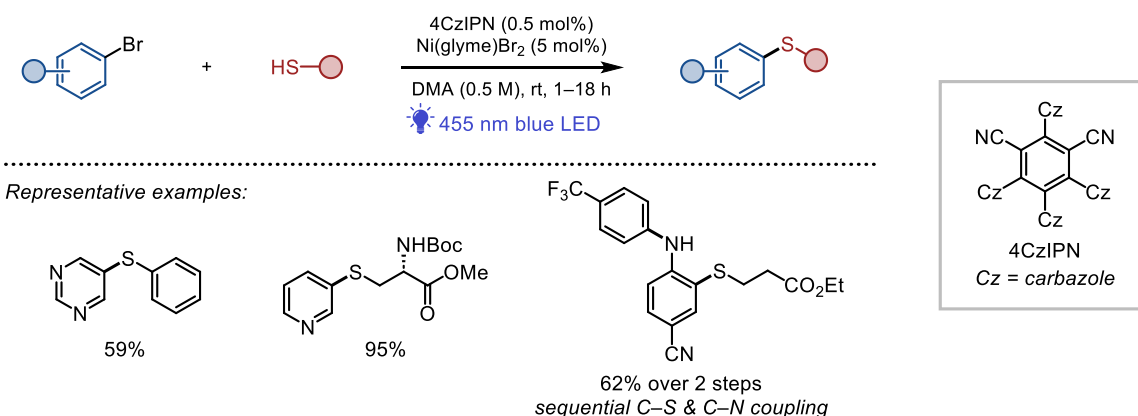
Scheme 6. Nickel/Xantphos-catalyzed C–S coupling by the Fleischer group.⁹⁹⁻¹⁰⁰

Interesting recent developments also included reports about base-free¹⁰¹ or even acidic C–S couplings,¹⁰² as well as C–S single-bond metathesis of thioethers,¹⁰³⁻¹⁰⁴ and decarbonylative approaches.¹⁰⁵⁻¹⁰⁷ Moreover, photochemically driven systems combining nickel catalysis with visible-light activation have enabled milder conditions and improved functional group tolerance (Scheme 7, A),¹⁰⁸⁻¹¹¹ illustrating the growing importance of dual catalytic strategies.

A) Oderinde, 2016:



B) König, 2023:



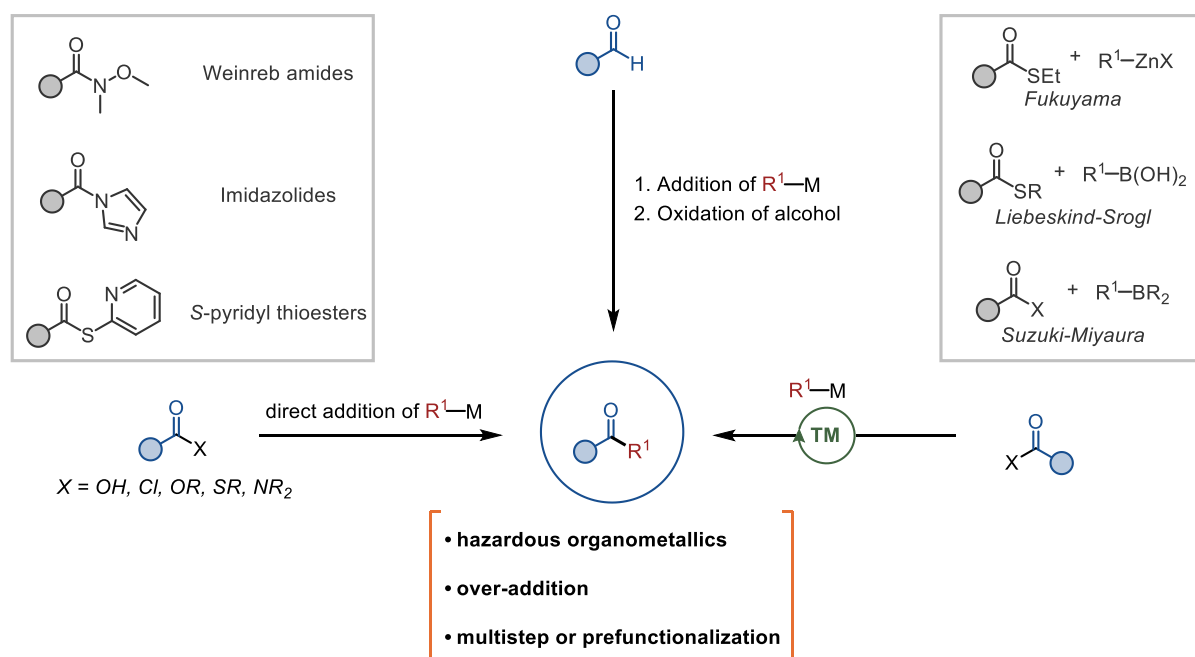
Scheme 7. Metallaphotoredox catalytic approach for C–S cross-coupling.¹¹¹

However, photochemical protocols without nickel¹¹² or any catalyst also exist.¹¹³ In metallaphotoredox C–S couplings, the generation of thiyl radicals is postulated to enable a Ni^I/Ni^{III} catalytic cycle. A powerful methodology was presented by König and co-workers, who established general C–X coupling conditions using metallaphotoredox catalysis, including examples for C–S coupling (Scheme 7, B).¹¹⁴ In this work, the thiol itself acts as the ligand, omitting the need for sophisticated external ligands and the applicability was demonstrated on numerous examples, often complex heterocyclic electrophiles. One frequently encountered drawback of photocatalytic approaches is the challenging activation of aryl chlorides and phenol-derived electrophiles, e.g. sulfonate esters.

Overall, nickel-catalyzed C–S cross-coupling represents a rapidly evolving area with significant implications for both academia and industry. Further increasing robustness as well as broader efforts toward sustainable chemistry could unlock its potential to replace precious metal catalysts in academic context as well as in process chemistry.

1.3. C–S-Bond Activation: Thioesters as Acyl Donors

Ketones constitute a ubiquitous and fundamentally important class of compounds in organic chemistry. Beyond their frequent occurrence in agrochemicals and pharmaceuticals,^{115–117} they serve as highly versatile intermediates in synthesis, enabling the construction of complex, natural product-inspired molecules through a broad array of classical transformations (Scheme 8).¹¹⁸ Numerous traditional strategies are available for the introduction of the ketone functionality, including the oxidation of secondary alcohols,¹¹⁹ Friedel–Crafts acylation,¹²⁰ and the reaction of carboxylic acid derivatives with organometallic reagents.^{121–124} However, the high reactivity of most organometallic reagents requires pre-functionalized acyl sources to prevent over-addition. Common acyl donors in such transformations comprise Weinreb amides,¹²⁵ Staab–Jost imidazolides,¹²⁶ and *S*-2-pyridyl thioesters.¹²⁷



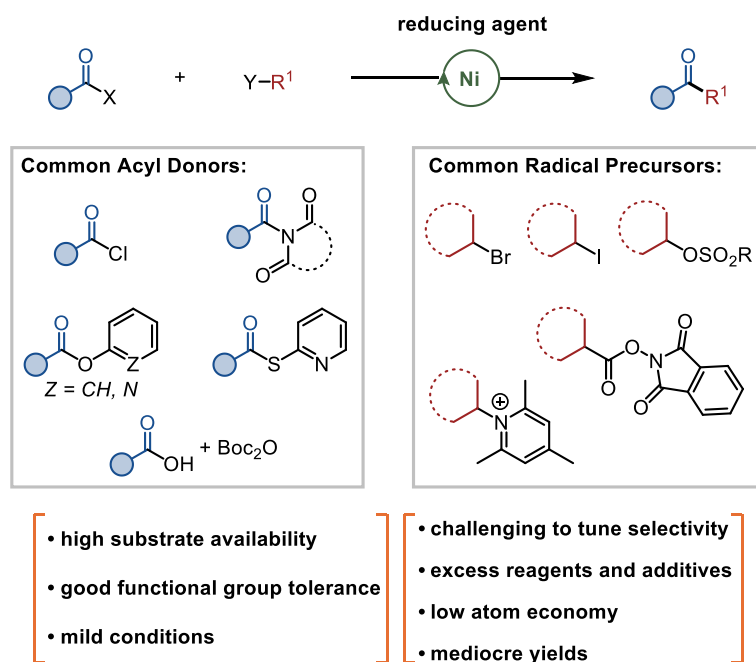
Scheme 8. Overview of traditional methods for ketone synthesis.

Among acyl donors, thioesters represent a unique functional group. Their reactivity in acyl substitution is usually more pronounced relative to oxoesters resulting from poor n - π^* -orbital overlap,¹²⁸ and can be compared to carboxylic acid anhydrides. The higher reactivity is also emphasized by weakened bond strength of the C–S-bond (ca. 74–78 kcal/mol) *versus* the C–O-bond in esters (ca. 80–100 kcal/mol)¹²⁹ and the better properties of thiolate as leaving group compared to alcoholates, as indicated by their respective basicity.¹³⁰ Meanwhile, thioesters are generally bench-stable, can be easily synthesized from the carboxylic acids and purified by

column chromatography, in contrast to more reactive acyl donors such as acyl chlorides.¹³¹ Moreover, the reactivity of thioesters can be fine-tuned by variation of the *S*-substituent.¹³²

In continuous efforts to circumvent the discussed disadvantages of direct addition of nucleophiles to acyl donors, both academic and industrial research have increasingly focused on the development of efficient and selective methodologies for ketone synthesis that deliver high yields while adhering to principles of sustainability. In this context, transition metal-catalyzed cross-coupling reactions have emerged as a key and rapidly evolving platform for ketone synthesis, complementing traditional methodologies (Scheme 8). Numerous protocols for the coupling of carboxylic acid derivatives with organometallic reagents under palladium or nickel catalysis have been reported,¹³³ with well-known reactions such as the Fukuyama-,¹³⁴⁻¹³⁵ Liebeskind-Srogl-¹³⁶⁻¹³⁷ and Suzuki-Miyaura-coupling¹³⁸⁻¹⁴⁰ as well as carbonylative approaches¹⁴¹⁻¹⁴² worth mentioning. It is well-known that thioesters can undergo oxidative addition to transition-metals, representing an ideal starting material for ketone synthesis. The Fleischer group has contributed to this field with several publications, combining thioesters with organomagnesium, -zinc and -manganese species.¹⁴³⁻¹⁴⁵

Still, these reactions exhibit severe drawbacks originating from the use of organometallic nucleophiles, that are usually less available, expensive, and exhibit toxic and hazardous properties. In contrast, cross-electrophile-coupling (XEC) offers an alternative approach towards ketones: By union of two electrophilic species under reductive conditions, the use of forementioned problematic reagents is circumvented. Moreover, typical electrophiles, such as alkyl and aryl halides, are usually more abundant and low-cost, rendering this approach attractive for large-scale applications. In seminal work, Mukaiyama¹⁴⁶ demonstrated the feasibility of this concept for ketone synthesis, while the basis for more contemporary conditions was independently presented by Weix¹⁴⁷ and Gong.¹⁴⁸ In this extensively investigated area, a carboxylic acid derivative is combined with an alkyl, or, more rarely, aryl electrophile,¹⁴⁹⁻¹⁵⁰ typically by nickel catalysis under reductive conditions (Scheme 9). Frequently used reductants include zinc or manganese metal, but electroreductive approaches offer attractive alternatives.^{149, 151} Regarding the acyl donor, most often acyl chlorides,^{147, 152-155} esters¹⁵⁶⁻¹⁵⁸ or twisted amides¹⁵⁹⁻¹⁶² have been utilized in previous approaches. In contrast, thioesters remained comparably limited to more reactive, but also more expensively prepared 2-pyridyl thioesters.¹⁶³⁻¹⁶⁵ A notable development is the direct use of carboxylic acids by *in situ* formation of an anhydride.^{148, 166-168}



Scheme 9. Overview of XEC for ketone synthesis.

Current methodologies for ketone synthesis *via* XEC are often limited by experimentally demanding protocols, largely stemming from intrinsic challenges in controlling selectivity. In many cases, competitive homocoupling occurs, necessitating the use of excess reagents and multiple additives to modulate reactivity and suppress side reactions. These requirements increase cost and waste generation, prolong reaction times, and complicate scalability. Moreover, the yields obtained are frequently only moderate, highlighting substantial room for improvement.

As a result, many existing XEC approaches remain misaligned with the principles of green chemistry. The implementation of alternative energy inputs, such as electro-, mechano- or photochemical activation, may help to address some of these limitations in the future. At the same time, achieving precise control over radical reactivity will be essential for the development of more efficient and selective coupling processes.

1.4. Mechanochemistry

Mechanochemistry describes the initiation and acceleration of chemical transformations through the direct application of mechanical energy rather than relying on more traditional sources of energy input, such as thermal energy, irradiation or electroreduction. In practice, reagents are activated by grinding, milling, shearing, or compressive forces that generate intimate contact between solids and create reactive interfaces.¹⁶⁹⁻¹⁷¹ Importantly, solvents are usually omitted or added in minimal amounts, also referred to as liquid-assisted grinding (LAG).¹⁷²⁻¹⁷³ In the context of organic synthesis and catalysis, this approach has developed into an important complementary strategy to conventional solution chemistry because it frequently enables reduced solvent consumption, shorter reaction times, simplified product isolation, and access to transformations involving poorly soluble or heterogeneous substrates. Moreover, mechanochemical activation can also provide altered reaction pathways, different selectivities,¹⁷⁴⁻¹⁷⁵ or reactivity patterns that are difficult to achieve under classical conditions.¹⁷⁶ Because solvents often dominate process mass intensity and waste streams,¹⁷⁷ mechanochemistry has become strongly associated with green and sustainable synthesis.¹⁷⁸⁻¹⁷⁹ Only within the past decade it became widely recognized that reactions traditionally considered to require rigorously inert conditions can, inside a ball mill, often be conducted without stringent exclusion of air or moisture.¹⁸⁰ This represents a significant opportunity for synthetic chemistry by reducing time, cost, and experimental complexity. For instance, the generation of organolithium compounds from lithium metal and their subsequent use in synthesis has been reported.¹⁸¹ One reason can be that gaseous oxygen and water diffuse inefficiently into solid reaction mixtures.¹⁸² Acknowledging the potential behind this technique for synthetic applications, IUPAC listed mechanochemistry as one of the “top 10 chemical innovations that will change our world” in 2019.¹⁸³

Although even simple tools such as mortar and pestle can be used for mechanochemistry in principle, more sophisticated devices are employed in modern laboratories (Figure 2). Most frequently used are ball mills, providing controlled and scalable conditions for mechanical activation.¹⁸⁴⁻¹⁸⁵ In mixer mills, a sealed jar containing the reactants and one or more milling balls oscillates rapidly, producing repeated impacts between the balls, jar walls, and reactants.^{169, 171} Planetary ball mills operate through simultaneous rotation of the jars around their own axes and around a central axis, resulting in strong centrifugal and sheering forces.¹⁸⁶

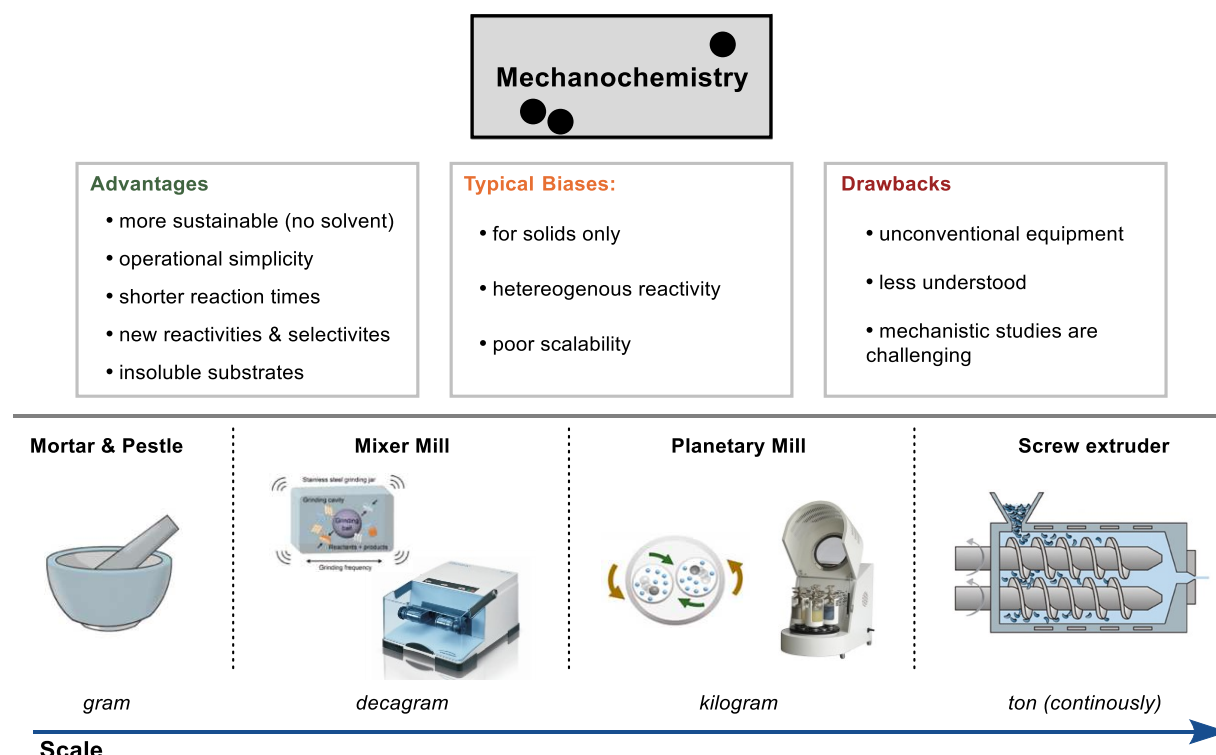


Figure 2. Features and typical devices in mechanochemistry. Portions adapted from ref. 171 (CC BY 4.0) and ref. 185 (Copyright © 2020 Elsevier, reproduced with permission).

Continuous mechanochemical processing can additionally be achieved by twin-screw extrusion, in which rotating screws convey reagents through a barrel while applying mixing, compression, and shear.¹⁸⁷ Extrusion has become especially significant in industrial settings because it offers a direct route toward continuous manufacturing and larger-scale synthesis.¹⁸⁸ Alternative agitation technologies, including resonant acoustic mixers, can also transfer mechanical energy without the use of milling media, thereby reducing abrasion and metal contamination.¹⁸⁹

Mechanistic Considerations

The mechanistic basis of mechanochemical reactivity is complex, difficult to investigate and, due to the current poor understanding, it remains widely discussed in the scientific community. However, several phenomena may contribute to observed mechanochemical reactivity:

- (i) Repeated impacts reduce particle size, continuously exposing fresh surfaces and increasing interfacial contact between reactants. Crystal lattices become disrupted, generating defects, dislocations, and amorphous regions that possess higher free energy and enhanced reactivity relative to ordered solids.^{171, 190}

- (ii) Intense mixing of organic compounds can result in the formation of eutectica, resulting in the formation of a melt phase.¹⁹¹
- (iii) Considerable attention has also been devoted to the concept of localized “hot spots”, transient microscopic regions generated during collisions where temperature and pressure rise briefly to levels significantly above the measured bulk temperature.¹⁹²⁻¹⁹³ Although difficult to quantify directly, hot-spots above 1000 K have been reported.¹⁹³⁻¹⁹⁵ These events are believed to explain bond activation, catalyst initiation, and accelerated kinetics.
- (iv) In some cases, mechanical strain was postulated to enable alternative pathways on the reaction coordinate, effectively lowering energy barriers.¹⁷¹
- (v) In many systems, liquid-assisted grinding further improves reactivity, possibly by enhancing diffusion-based mass transfer and altered reaction environment compared to fully solubilized species.¹⁹⁶

The relative importance of each of these factors remains unclear and may vary between systems, underscoring the need for further mechanistic investigations.

Mechanochemistry for Synthesis and Catalysis

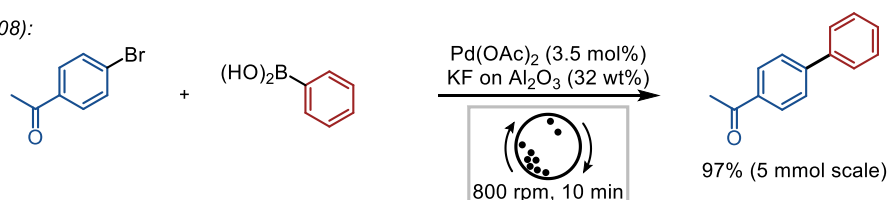
Mechanochemistry itself is not new. Nevertheless, it remained a relatively specialized topic for decades, more closely associated with materials science and inorganic solid-state chemistry than with mainstream molecular synthesis. The renewed emergence of mechanochemistry in organic chemistry began in the late twentieth century, when researchers demonstrated that numerous bond-forming reactions, e.g. aldol condensations, Knoevenagel and Michael reactions, rearrangements, and other classical organic transformations, could be achieved efficiently by grinding.¹⁹⁷⁻²⁰⁰ In the last ten years, attention shifted more towards performing homogenous catalysis under mechanochemical conditions. Researchers have shown for various well-known catalytic coupling reactions that these can be performed in a ball-mill in high yields, often with exceptionally short reaction times (Scheme 10).²⁰¹⁻²⁰⁷ For instance, Suzuki reactions achieved excellent yields within 10 min in a planetary ball mill,²⁰⁷ while more recent work explored broader functional group tolerance and the coupling of insoluble substrates.^{172, 208} The group of Borchardt established so-called direct mechanocatalysis, where the milling jar and/or balls represent the (heterogenous) catalyst. Thereby, milling equipment made from catalytically active metals, e.g. palladium, or stainless steel layered with the catalyst, is employed, enabling easy recycling and reuse (Scheme 10, B).²⁰⁹⁻²¹¹ This concept could also be transferred to twin-screw extrusion of biphenyl on

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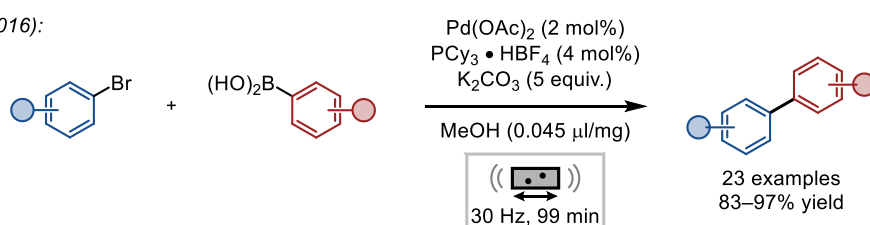
industrial scale.²¹² While several approaches for Buchwald-Hartwig-Aminations under mechanochemical conditions have been developed,^{206, 213-214} a notable report was presented by the group of Ito, demonstrating the C–N coupling of challenging aryl amines (Scheme 10, C).²¹⁵ It was shown that the same palladium catalyst could be used for sequential one-pot coupling, affording triaryl amines in operationally simple manner.

A) Suzuki-Miyaura-Coupling:

Hopf (2008):

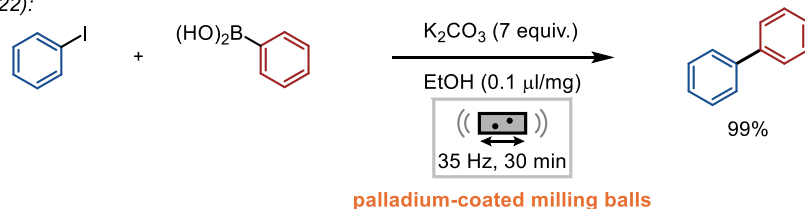


Su & Li (2016):



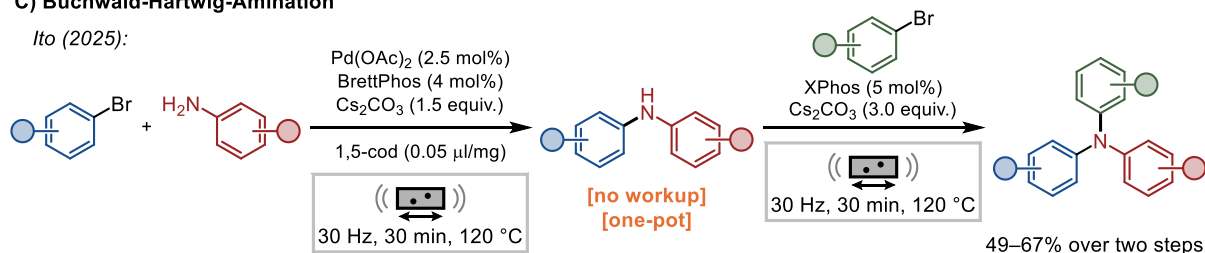
B) Direct Mechano catalysis

Borchardt (2022):



C) Buchwald-Hartwig-Amination

Ito (2025):



Scheme 10. Examples of cross-coupling reactions performed under mechanochemical conditions.^{172, 207, 209, 215}

A review of the broad range of palladium-catalyzed methodologies performed in ball-mills shows that these reactions often exhibit favorable reactivity, including shorter reaction times, high yields, and more sustainable process profiles compared to solution-phase protocols. However, translation of mechanochemistry to industrial scale, e.g. using twin-screw extruders, is only beginning to gain momentum.^{187, 216-218} Meanwhile, base-metal catalysis in the context of mechanochemistry remains comparatively underdeveloped, and its further advancement is likely to play a key role in shaping the future of the field.

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RESULTS & DISCUSSION

2. Nickel-catalyzed C–S Cross-Coupling of Sterically Hindered Substrates

2.1. Summary of Published Results

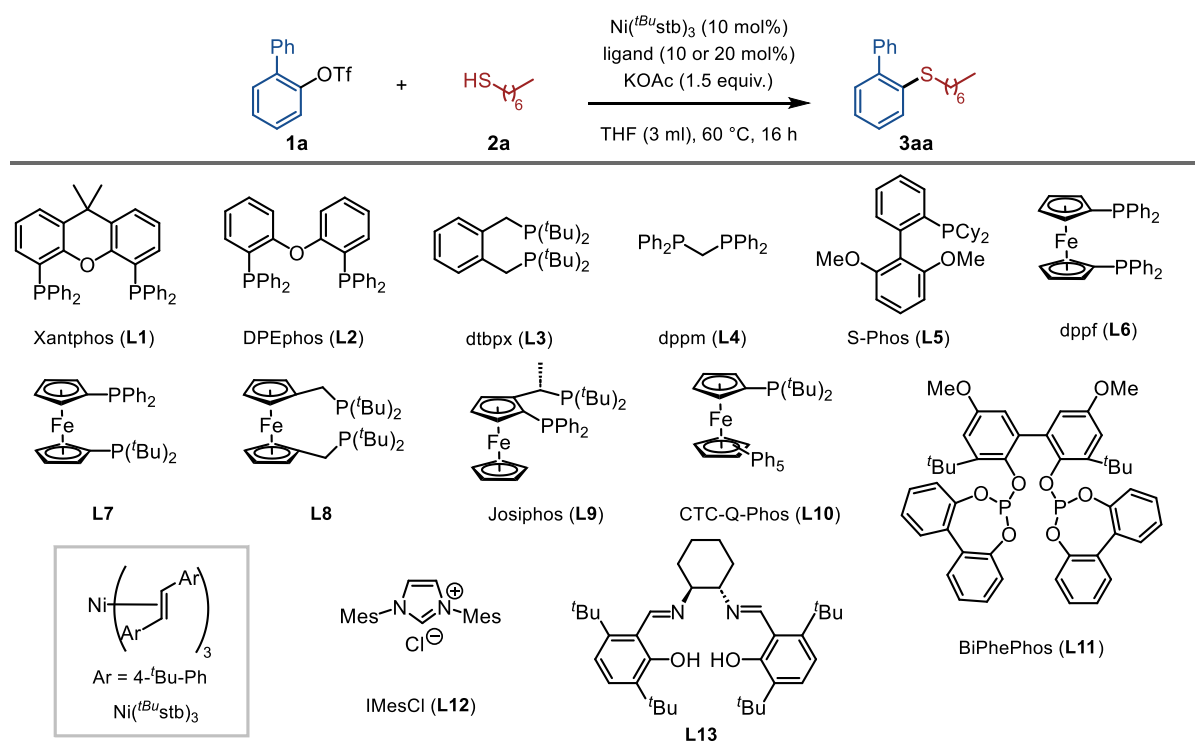
This chapter is based on the following publication:

Ivo H. Lindenmaier, Robert C. Richter and Ivana Fleischer, *Org. Chem. Front.* **2024**, *11*, 2485–2493. DOI 10.1039/D4QO00260A.

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Reaction Development and Optimization

Thioethers constitute key structural motifs in drug molecules and materials science.¹⁻² The transition-metal-catalyzed cross-coupling of aryl halides with thiols to form the corresponding thioethers recently received significant attention, mainly focusing on palladium and nickel catalysis.³⁻⁴ Early methodologies typically required harsh reaction conditions to circumvent catalyst poisoning, whereas modern approaches also enabled efficient transformations under milder conditions.⁵ The Fleischer group has contributed to this field with a nickel-catalyzed cross-coupling of aryl halides with alkyl thiols at room temperature.⁶ This system, based on a (Xantphos)Ni(*o*-tolyl)(Cl) precatalyst, exhibited high activity for *meta*- and *para*-substituted aryl halides, but showed markedly reduced reactivity for *ortho*-substituted substrates. This limitation is likely attributable to the large bite angle of the Xantphos ligand, which may hinder oxidative addition of sterically demanding substrates.⁷ To address this challenge, a ligand screening study was performed on the coupling of the model substrate 2-biphenyl trifluoromethanesulfonate (**1a**) with *n*-heptane thiol (**2a**) (Table 1). An aryl triflate was chosen as the model electrophile based on the previously demonstrated high reactivity in C–S couplings.⁸

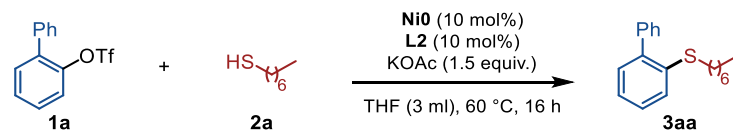
Table 1. Ligand screening for C–S cross-coupling of sterically hindered substrates.


Entry	Ligand	Conv. [%]	Yield [%]
1	Xantphos (L1)	16	4
2	DPEphos (L2)	55	45
3	dtbpx (L3)	12	n. d.
4	dppm (L4)	14	n. d.
5 ^a	S-Phos (L5)	13	n. d.
6 ^a	PPh ₃	13	n. d.
7 ^a	dppf (L6)	53	44
8	L7	21	8
9 ^a	L8	12	n. d.
10	Josiphos (L9)	14	n. d.
11	CTC-Q-Phos (L10)	12	n. d.
12	BiPhePhos (L11)	3	n. d.
13	IMesCl (L12)	13	n. d.
14	L13	17	n. d.

 Yields and conversions were determined by GC-FID using pentadecane as internal standard. ^a 20 mol% ligand.

As expected, Xantphos (**L1**) afforded only trace amounts of the desired coupling product (entry 1). However, DPEphos (**L2**) provided a promising yield of 45% under otherwise unoptimized conditions (entry 2). Other bidentate and monodentate phosphine ligands were unsuccessful as well (entries 3–11), with exception of dppf (**L6**), which showed comparable reactivity as **L2**. Other ligand classes, such as phosphite **L11**, *N*-heterocyclic carbene **L12** or salene **L13**, showed no catalytic activity (entries 12–14). Further screening also revealed that THF was the only solvent tolerated and that elevated temperatures did not improve the yield (Table 2, entries 7, 8). Ambient temperature was therefore selected for subsequent studies. Prolonged reaction times also failed to enhance product formation, suggesting that the catalyst was deactivated after 16 h (entry 9).

Table 2. Solvent and temperature screening for C–S cross-coupling of sterically hindered substrates.

			
Entry	Deviation	Conv. [%]	Yield [%]
1	none	55	45
2	NMP	52	n. d.
3	THF/NMP (2:1)	29	13
4	2-Me-THF	18	4
5	Toluene	16	3
6	DMF	58	n. d.
7	2-Me-THF, 110 °C	22	9
8	Room temperature	62	52
9	2 days reaction time	61	50
10	+ LiCl (1.0 equiv.)	17	4

Yields and conversions were determined by GC-FID using pentadecane as internal standard.

Lithium chloride, an additive frequently reported to be beneficial in related systems,⁹⁻¹⁰ was detrimental to the present reaction (entry 10). Subsequently, various nickel sources were evaluated (Table 3). While decreased catalyst loadings led to a significant drop in yield, higher loadings provided only a modest improvement (entries 2, 3). Although bench-stable nickel precatalysts are advantageous as convenient precursors to the active species, all tested compounds resulted in inferior yields in this case (entries 4–6). Nevertheless, substituting Ni(*t*Bu₃stb)₃ with Ni(cod)₂ led to near-quantitative formation of the desired product (entry 7).

Table 3. Catalyst screening for C–S cross-coupling of sterically hindered substrates.

Entry	Deviation	Conv. [%]	Yield [%]
1	none	55	45
2	5 mol% Ni0	21	8
3	15 mol% Ni0	72	69
4	Ni1 (10 mol%)	22	7
5	Ni2 (10 mol%)	14	n. d.
6	Ni3 (10 mol%)	13	n. d.
7	Ni(cod) ₂	93	95

Yields and conversions were determined by GC-FID using pentadecane as internal standard.

In preliminary screenings, other model substrates were also tested. Upon the observation that the tertiary adamantane thiol (**2b**) also afforded excellent yields under the standard conditions, reaction profile analysis was performed to determine the required reaction time and to elucidate the kinetic behavior of the system (Figure 3).

Pleasingly, it was found that the reaction with the tertiary thiol **2b** only took two hours at room temperature until full conversion and showed the expected second-order kinetic. Comparable protocols in the literature often require harsher conditions such as elevated temperatures or prolonged reaction times.¹¹ To ensure full conversion of even more challenging substrates, the standard reaction time was set to 4 h.

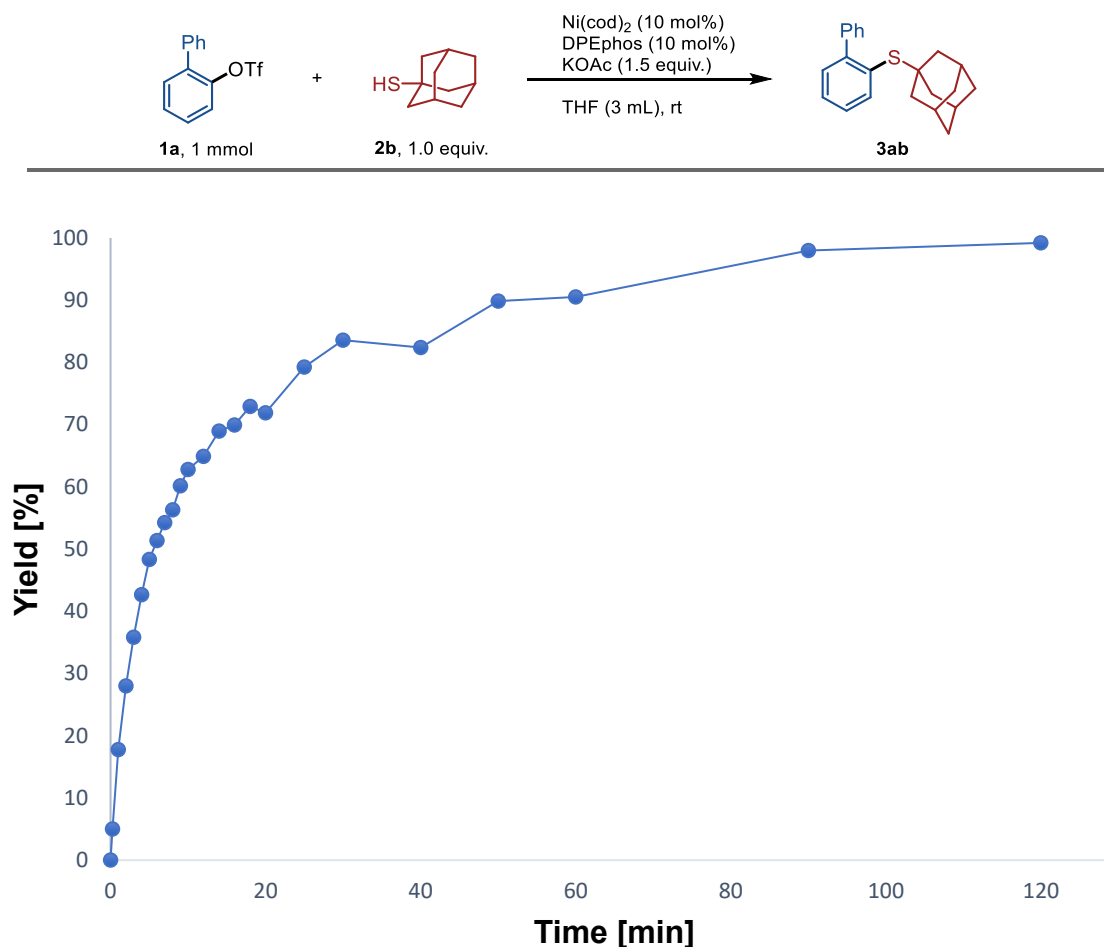


Figure 3. Reaction profile of the developed nickel-catalyzed C–S cross-coupling of **1a** with **2b**. Pentadecane was added as internal standard and samples were taken from the same reaction vessel at the desired time. Yields were determined by GC-FID.

Substrate Scope

With optimized conditions at hand, the substrate scope was investigated (Figure 4). The previously screened 2-biphenyl thioether **3ab** was isolated in excellent yield. Alkyl substituents with increasing steric demand (**3bb**, **3cb**) were well tolerated, whereas introduction of an *ortho-tert*-butyl group (**3db**) significantly reduced reactivity, affording low yield even under more forcing conditions. An allyl substituent (**3eb**) was compatible with the reaction, and the olefin functionality remained intact. In contrast, aryl triflate **1f** bearing two *ortho*-methyl substituents showed no conversion under the standard catalytic system. Further optimization identified dppbz (1,2-bis(diphenylphosphino)benzene, **L14**) as a suitable ligand for this sterically demanding substrate, although only primary thiols were effective and elevated temperature (100 °C) was required (see further screening in section 2.2). Under these modified conditions, thioether **3fc** was obtained in moderate but synthetically useful yield,

with recovery of unreacted starting material. Disubstituted thioether **3gb**, derived from 1,2-phenyl ditriflate, was synthesized in high yield without increasing catalyst loading.

Substrates bearing electron-withdrawing groups were next evaluated. The trifluoromethyl-substituted product **3hb** was formed in good yield, while the nitrile-substituted thioether **3ib** was obtained in excellent yield. Notably, biselectrophile **1j** bearing a chloro substituent selectively furnished the monosubstituted product in **3jb** good yield.

Aryl triflates containing potentially coordinating *ortho*-substituents showed little to no conversion with ligand **L1**. In contrast, **L14**, previously effective for the coupling of 2,6-dimethylphenyl triflate (**1f**), performed well in these cases. Accordingly, acyl (**3kb**) and ester (**3lb**) substituents were tolerated when using dppbz (**L14**), albeit requiring slightly elevated temperatures (60 °C). A boronic ester substituent (**1m**) was converted in high yield, providing access to **3mb** as a versatile intermediate for subsequent orthogonal cross-coupling. Likewise, a neighboring methoxy substituent enabled efficient synthesis of the acetovanillone-derived thioether **3nb** in excellent yield.

Heterocyclic substrates occasionally required more forcing conditions (longer reaction times or higher temperatures); nevertheless, thioethers containing pyridine (**3ob**), quinoline (**3pb**), thiophene (**3qb**), chromanone (**3rb**), and benzodioxole (**3sb**) motifs were obtained in high yields, also including examples when the corresponding bromides were used in place of triflates.

Moreover, successful coupling of 1-pyrene triflate (**1t**) highlights the potential of this methodology for functionalization of polyaromatic motifs relevant to functional materials. The synthesis of thioether **3ub** further illustrates access to possible sulfur-containing bioisosteres of established pharmaceuticals such as Febuxostat. Finally, thioetherification of triflates **1v** and **1w** demonstrated the applicability of the method to substrates derived from biologically active phenols or natural products.

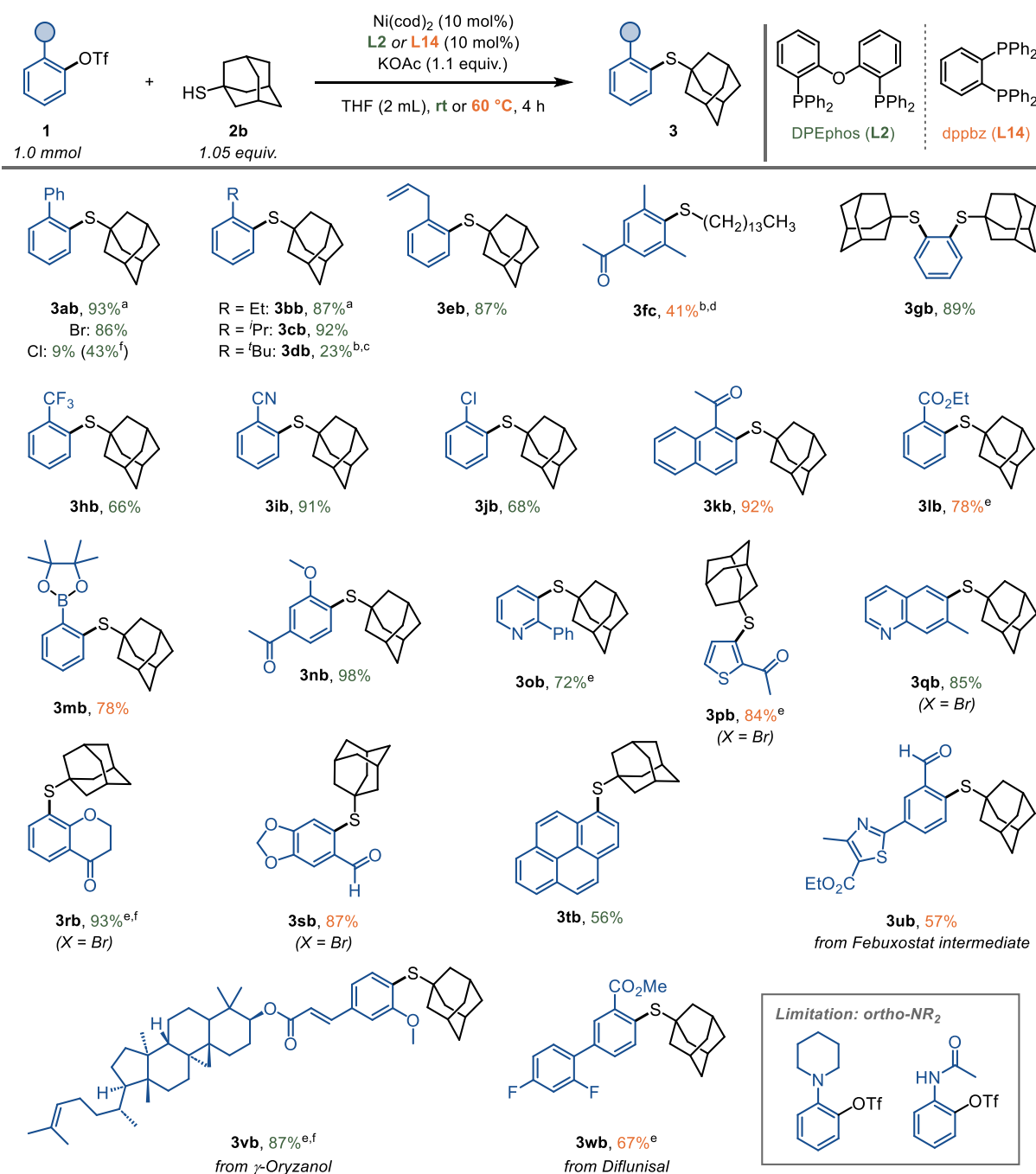


Figure 4. Substrate scope of the nickel-catalyzed C–S cross-coupling with respect to aryl (pseudo-)halides. Isolated yields. Reaction conditions:

Green color: **1** (1.0 mmol), **2b** (1.05 equiv.), $\text{Ni}(\text{cod})_2$ (10 mol%), **L2** (10 mol%), KOAc (1.1 equiv.), THF (2 mL), rt, 4 h.

Orange color: **1** (1.0 mmol), **2b** (1.05 equiv.), $\text{Ni}(\text{cod})_2$ (10 mol%), **L14** (10 mol%), KOAc (1.1 equiv.), THF (2 mL), 60 °C, 4 h.

^a 2 h. ^b 100 °C. ^c Yield estimated by GC-MS. ^d n-tetradecane thiol (**2c**) instead **2b**. ^e 6 h. ^f 60 °C.

These transformations generally required higher temperatures and longer reaction times, likely due to limited solubility of the substrates. In contrast, amine- and amide-substituted triflates showed no conversion, likely due to strong chelation to the metal center. Appropriate protecting groups may enable incorporation of nitrogen-containing substrates, although additional optimization would be required.

Subsequently, the scope of alkyl thiols was examined (Figure 5). Primary and secondary thiols initially afforded lower yields compared to the sterically demanding adamantane thiol (**2b**), likely due to increased catalyst deactivation by less hindered thiols. This effect was not observed during preliminary screening, presumably as a result of lower thiol concentrations. Optimization by dilution and slow addition of the thiol mitigated catalyst poisoning, enabling formation of primary alkyl thioether **3ac** in 78% isolated yield. Under these modified conditions, a range of primary, secondary, and tertiary alkyl thiols (**2c–e**) were successfully coupled in high to excellent yields, with a clear trend favoring more highly substituted thiols. Functional group tolerance within the thiol component was generally good: ester, ketone, and cyclic ether substituents were well accommodated (**3af**, **3ag**, and **3aj**). A cyclopropyl substituent (**3ah**) was tolerated, providing synthetically useful yield, while the azetidine-derived product **3ai** was obtained in low yield, likely due to catalyst inhibition by the carbamate functionality.

Meanwhile, aryl thiols were not compatible under the applied conditions. In contrast to the aryl triflate scope, neither use of ligand **L14** nor increased reaction temperature improved these outcomes.

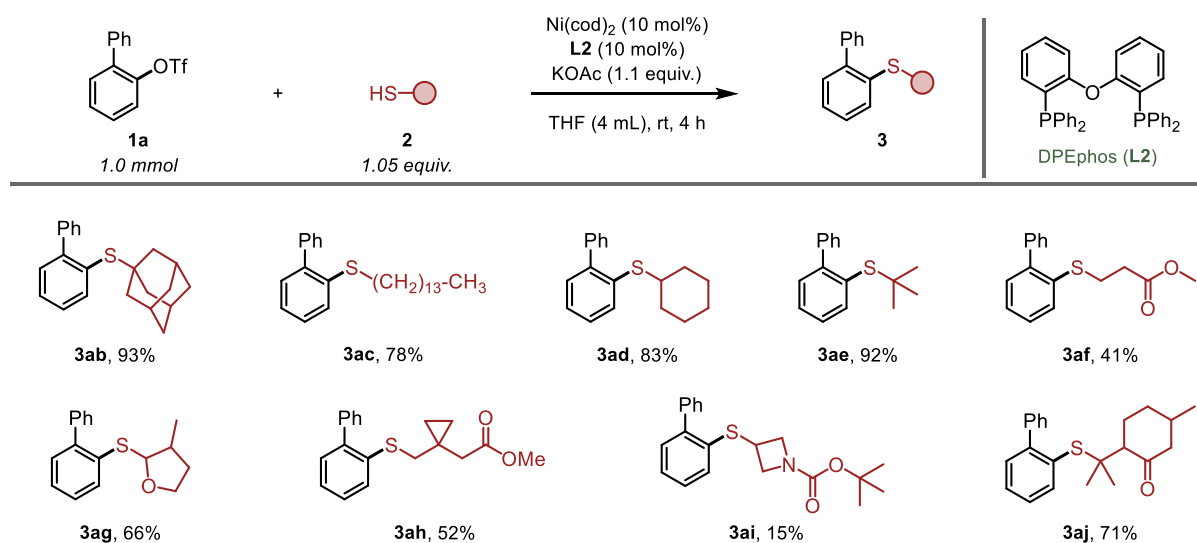
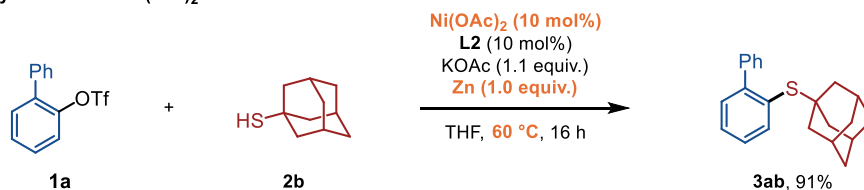


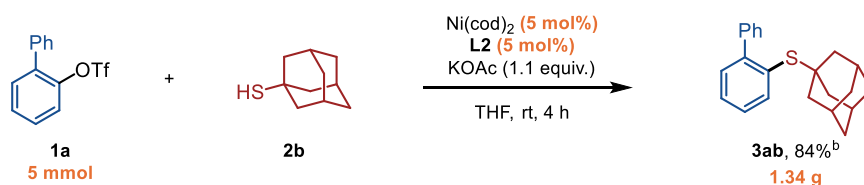
Figure 5. Substrate scope of the nickel-catalyzed C–S cross-coupling with respect to alkyl thiols. Isolated yields. Reaction conditions:

1a (1.0 mmol), **2** (1.05 equiv.), $\text{Ni}(\text{cod})_2$ (10 mol%), **L2** (10 mol%), KOAc (1.1 equiv.), THF (4 mL), rt, 4 h.

Finally, for a more convenient reaction set-up, it was demonstrated that highly air- and moisture sensitive $\text{Ni}(\text{cod})_2$ could be substituted with $\text{Ni}(\text{OAc})_2$ in the presence of Zn as reducing agent, but elevated temperatures were necessary (Scheme 11, A). Performing the reaction at gram-scale, the catalyst loading could be reduced to 5 mol% while maintaining high yields of **3ab** (Scheme 11, B).

A) Ni(II)-precatalyst instead of Ni(cod)₂

B) Upscale reaction using reduced catalyst loading

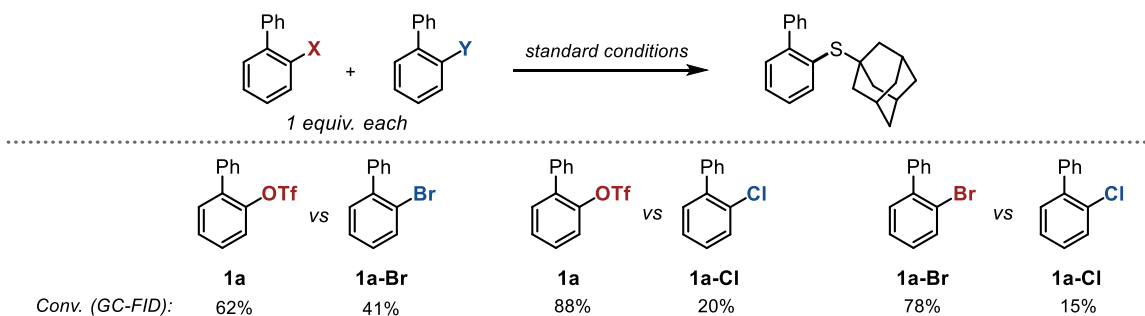
Scheme 11. Further reactivity studies, employing air-stable Ni(OAc)₂ as precatalyst and on larger scale.

Chemoselectivity and Mechanistic Studies

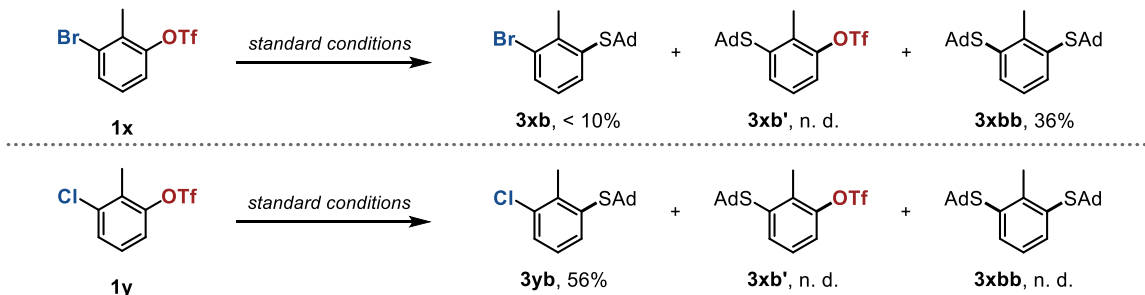
As shown in the substrate scope (Figure 4), aryl iodides, bromides and, to some extent, also chlorides were feasible coupling partners besides aryl triflates. To investigate the chemoselectivity with respect to the leaving group, competition experiments were conducted (Figure 6). Intermolecular competition experiments established the expected reactivity order of the leaving groups (OTf $\approx$ Br > Cl).¹² In intramolecular competition, the differentiation between OTf and Br was less pronounced, resulting in preferential formation of the disubstituted product **3xbb**. In contrast, chemoselective monosubstitution was achieved for OTf/Cl combinations, affording thioether **3yb** in good yield (Figure 6, B). Consistent trends were observed in the scope of 1,2-biselectrophiles (Figure 4; **3gb** and **3jb**). In summary, while the triflate group appeared more reactive than both bromide and iodide, the rate differences were not sufficient to enable effective chemoselective differentiation.

To further delineate steric and electronic effects, sterically hindered triflate **1a** was subjected to coupling in the presence of electronically less reactive 4-chlorotoluene (Figure 6, C). Notably, the higher intrinsic reactivity of the C–OTf bond effectively compensated for steric encumbrance from the *ortho*-phenyl substituent, resulting in selective transformation of **1a**, while 4-chlorotoluene remained largely unreacted.

A) Intermolecular competition of aryl (pseudo-)halides



B) Intramolecular competition of aryl (pseudo-)halides



C) Steric versus electronic discrimination

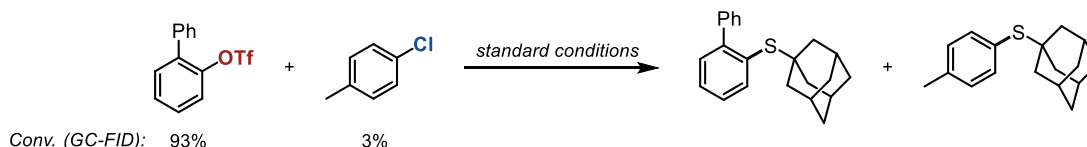


Figure 6. Chemoselectivity studies of the nickel-catalyzed C–S cross-coupling of sterically hindered substrates. Standard conditions: **1** (1.0 mmol), **2b** (1.05 equiv.), Ni(cod)₂ (10 mol%), **L2** (10 mol%), KOAc (1.1 equiv.), THF (2 ml), rt, 2 h.

Motivated by the substrate-dependent ligand requirements, efforts were directed toward a deeper mechanistic understanding, particularly in comparison to the previously reported Ni/Xantphos catalytic system. In that system, thiol coordination and deprotonation were identified as the turnover-limiting step, proceeding *via* a concerted metalation–deprotonation (CMD)-like pathway.⁶ As these findings were based on unsubstituted aryl chlorides, the impact of *ortho*-substitution on the reaction mechanism warranted further investigation. Notably, the lower bond dissociation energy of aryl triflates relative to chlorides and the increased steric demand of the present substrates are expected to exert opposing influences on reactivity. Reductive elimination is presumed to be facile in this system, driven by relief of steric strain, and was therefore not examined in detail. Instead, density functional theory (DFT) calculations were conducted by Dr. Robert C. Richter to investigate the key steps of oxidative addition (OA) and thiol coordination and deprotonation (TCD, Figure 7). Due to the inability to locate a transition state for acetate coordination to intermediate **B**, likely arising from complicating factors such as salt precipitation and solubility effects, a definitive rate-determining step could not be established. Nevertheless, detailed analysis of the OA and TCD

steps provided insight into how the reaction proceeds despite significant steric congestion at the nickel center, and it rationalized the requirement for flexible ligands.

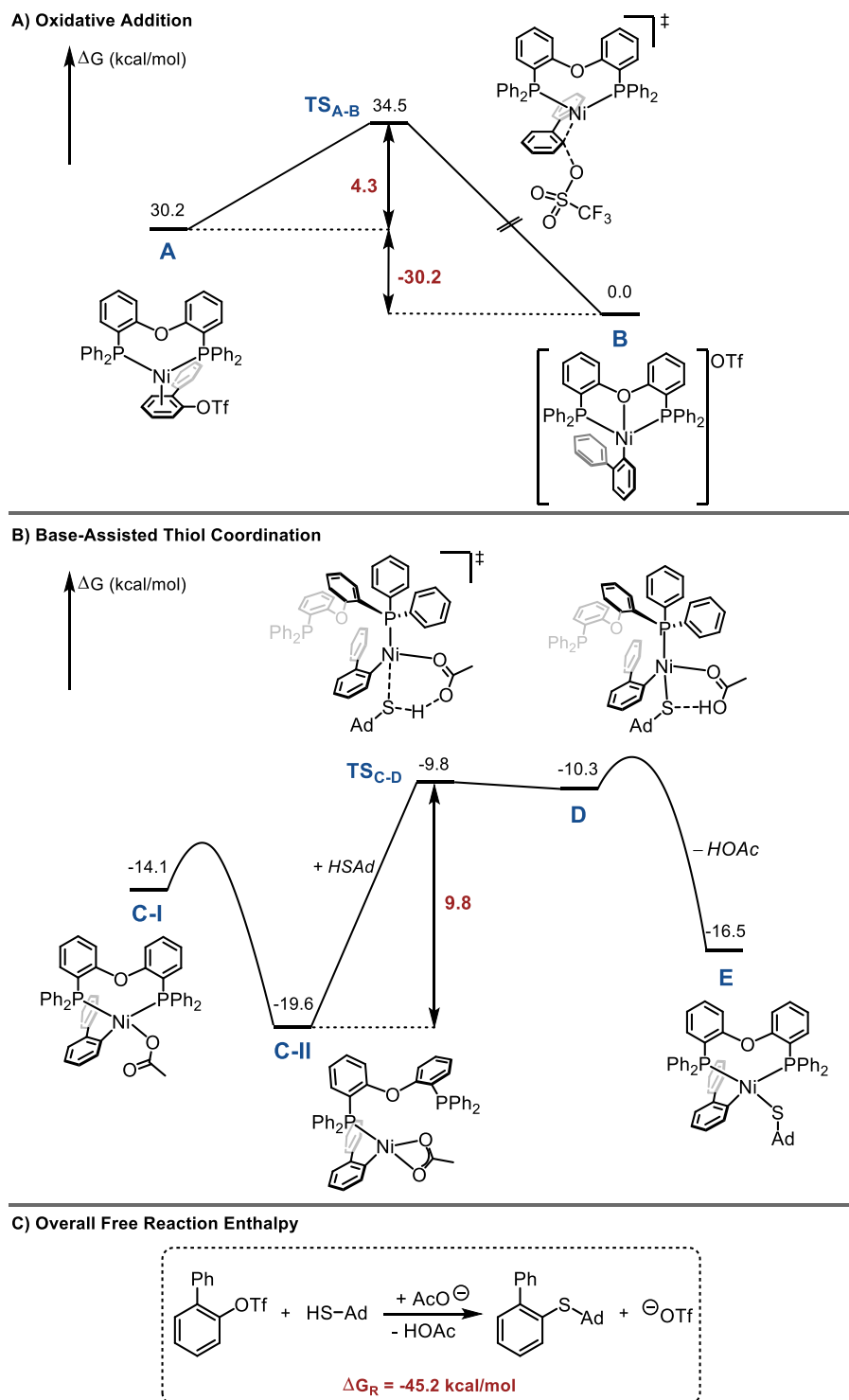


Figure 7. Free energy profiles for the oxidative addition and thiol coordination steps in the cross-coupling of **1a** with **2b**. Structures and energies were calculated at the M06-L(SMD:THF)/def2-QZVPP//B3LYP-D3BJ/def2-SVP level of theory.

Oxidative addition of Ni(0) into aryl triflates remained comparatively underexplored computationally so far, with most studies focusing on related sulfonamide or ester

systems,¹³⁻¹⁴ reporting S_N2-like mechanisms as well as three- and five-centered transition states.¹⁵⁻¹⁶ The present calculations support an S_N2-like pathway for oxidative addition (**TS_{A-B}**), while alternative pathways were associated with higher activation barriers, presumably a consequence of steric bulk. The barrier for oxidative addition is notably low ($\Delta G^\ddagger_{\text{OA}} = 4.3 \text{ kcal}\cdot\text{mol}^{-1}$) and the step is strongly exergonic, highlighting the high intrinsic reactivity of aryl triflates even in sterically congested environments. The resulting oxidative addition product is the cationic complex [(DPEphos)Ni(biphenyl)]⁺ (**B**), consistent with the experimentally determined crystal structure (*vide infra*).

Upon progressing to thiol coordination, computations indicate initial η^2 -coordination of acetate to the nickel center, which is energetically preferred over the corresponding η^1 -binding mode. This results in displacement of one phosphine coordination site, although chelating binding modes are generally seen as more favored.¹⁷ Nevertheless, intermediate **C-II** may be further stabilized by reduced steric strain. Similar η^1 -coordination modes of bidentate phosphines have been reported for sterically congested copper complexes.^{15-16, 18} Concomitant with reversion of acetate to η^1 -coordination, the newly available coordination site *trans* to the weakly bound phosphine is occupied by the thiol, followed by proton transfer to the acetate.

In the corresponding transition state (**TSC-D**), complete dissociation of the displaced phosphine arm is observed, with the inactive arm of ligand **L2** rotated away from the nickel center. No competing bidentate transition states could be located, indicating that **L2** effectively operates as a monodentate PPh₃-like ligand during TCD. Such hemilabile behavior of bidentate phosphines has previously been proposed by the Doyle group in nickel-catalyzed Suzuki–Miyaura couplings of sterically hindered substrates,¹⁹ and provided a rationale for the distinct reactivity differences between Xantphos (**L1**) and DPEphos (**L2**).

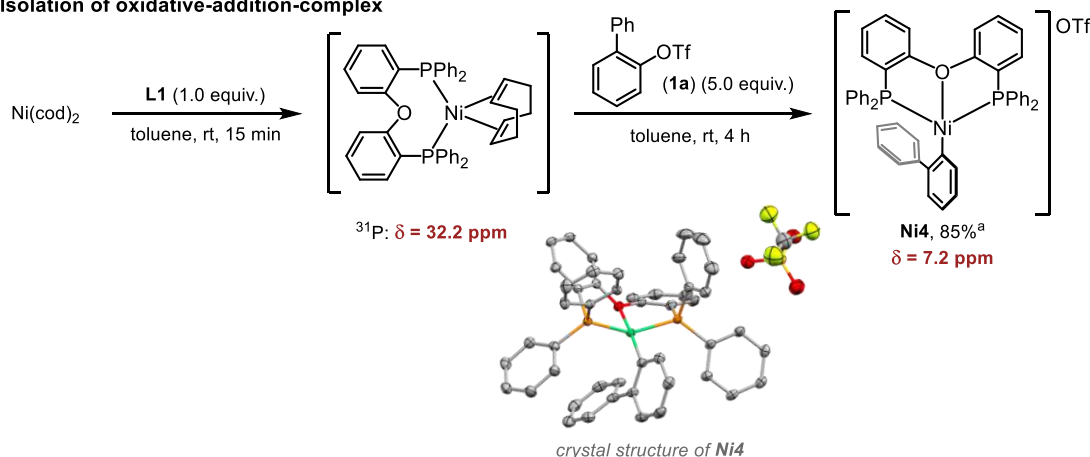
Intrinsic reaction coordinate (IRC) analysis confirms that the transition state is dominated by proton transfer from the thiol to acetate, while other bonding interactions remain largely unchanged. Energy minima were identified immediately following the transition state, in which the proton is associated with acetate but still engages in weak hydrogen bonding with the sulfur atom. The thiol coordination also exhibited a notably low barrier ($\Delta G^\ddagger_{\text{TCD}} = 9.8 \text{ kcal}\cdot\text{mol}^{-1}$). Upon completion of proton transfer (intermediate **D**), acetic acid is displaced by re-coordination of the phosphine, forming intermediate **E**, from which product formation proceeds *via* reductive elimination (not shown). Overall, these findings highlight the critical role of ligands, combining steric bulk with conformational flexibility: sufficient to stabilize reactive intermediates *via* steric shielding, yet capable of transient dissociation to

generate open coordination sites when required. The overall Gibbs free energy change of the reaction was calculated to be $-45.2 \text{ kcal}\cdot\text{mol}^{-1}$. The relatively low barriers in both steps align with the observation that room temperature is sufficient for most substrates.

To validate these computational results, the synthesis and reactivity of organometallic intermediates was investigated (Figure 8). While synthesizing any compound containing the thiol moiety remained elusive, the oxidative-addition-complex (OAC) **Ni4** was successfully isolated and characterized by NMR, HRMS and IR (Figure 8, A); additionally, the crystal structure could be determined by X-Ray diffraction of a suitable single crystal, confirming the cationic structure postulated by theoretical chemistry. Evaluating **Ni4** in both stoichiometric and catalytic coupling reactions confirmed its involvement in the catalytic cycle (

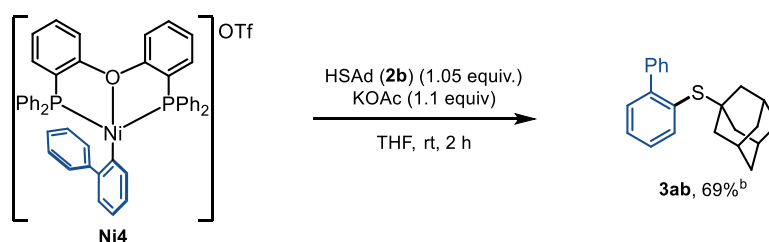
Figure 8, B).

A) Isolation of oxidative-addition-complex



B) Reactivity of Ni4

1) Stoichiometric coupling



2) **Ni4** as catalyst

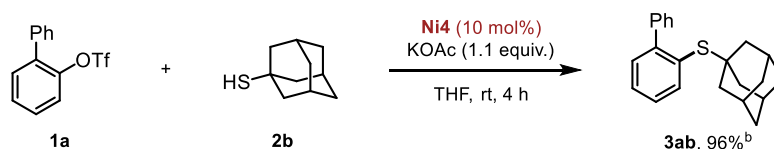


Figure 8. Isolation and reactivity of OAC **Ni4**. ^a Isolated yield. ^b GC-FID yield using pentadecane as internal standard.

Conclusion

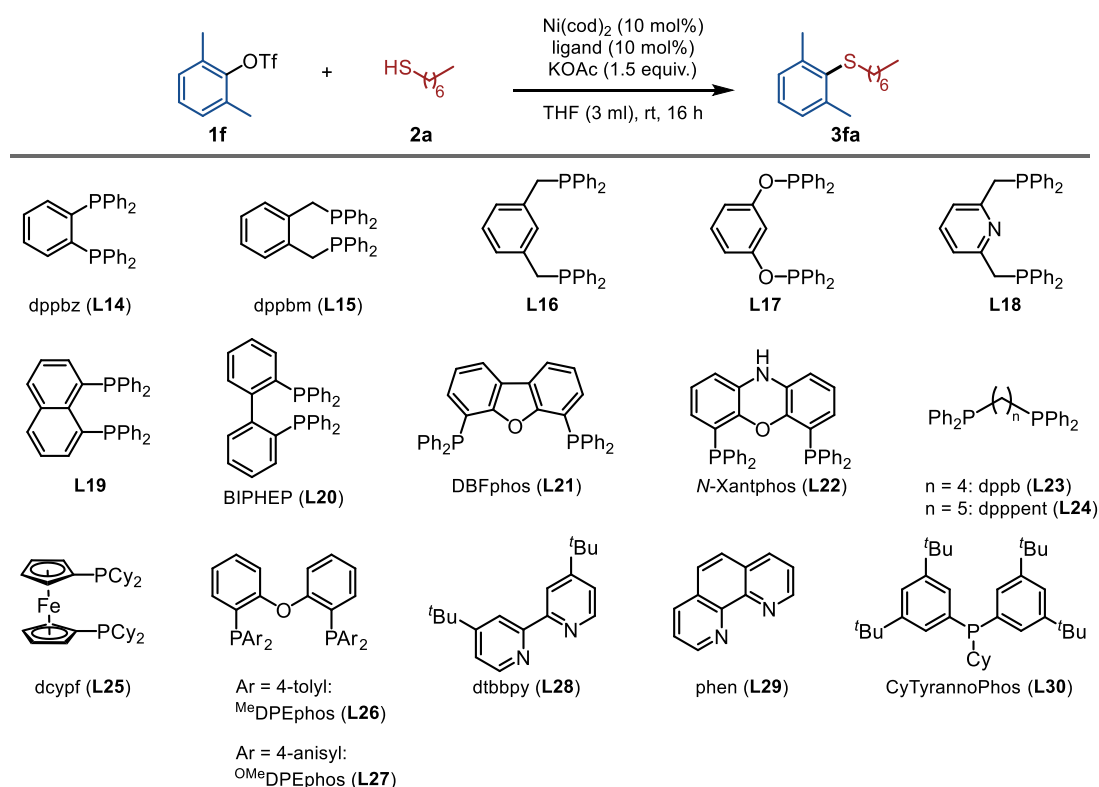
In summary, a nickel-catalyzed C–S cross-coupling protocol for *ortho*-substituted aryl triflates has been established. While aryl bromides and, to some extent, chlorides were also viable substrates, the superior reactivity of aryl triflates in combination with a flexible ligand (**L2**) enabled efficient coupling of sterically demanding substrates, including heterocycles, in high yields. Furthermore, a broad range of coordinating functional groups, such as methoxy, carbonyl, and boronic ester substituents, were well tolerated under conditions employing ligand **L14**. The synthetic applicability of the method was demonstrated through thioetherification of triflates derived from biologically relevant phenols. Mechanistic investigations, supported by both experimental and computational studies, are consistent with a Ni⁰/Ni^{II} catalytic cycle. Notably, computational analysis revealed an unusual change in the ligation mode of the bidentate phosphine, providing a rationale for the critical role of ligand flexibility in this transformation.

2.2. Summary of Unpublished Results

Optimization of 2,6-Disubstituted Aryl Triflates

As outlined in the chapter above, the coupling of 2,6-disubstituted aryl triflates was initially inefficient using established ligand **L2**. Thus, a broader ligand screening was performed to enable the coupling of this substrate class (Table 4).

Table 4. Ligand screening for C–S cross-coupling of 2,6-disubstituted aryl triflates.



Entry	Ligand	Yield [%]
1	DPEphos (L2)	n. d.
2	dppf (L6)	n. d.
3	dppbz (L14)	trace
4	L14 , 60 °C	6
5	L14 , 100 °C	30
6	dppbm (L15)	trace
7	L16	n. d.
8	L17	n. d.
9	L18	n. d.

10	L19	n. d.
11	BIPHEP (L20)	trace
12	DBFphos (L21)	n. d.
13	<i>N</i> -Xantphos (L22)	n. d.
14	dppb (L23)	n. d.
15	dpppent (L24)	n. d.
16	dcypf (L25)	n. d.
17	^{Me} DPEphos (L26)	n. d.
18	^{OMe} DPEphos (L27)	n. d.
19^a	CyTyrannophos (L28)	n. d.
20^a	PCy ₃	n. d.
21	dtbbpy (L29)	n. d.
22	phen (L30)	n. d.

Yields were determined by GC-FID using pentadecane as internal standard. ^a 20 mol% ligand.

L14 was found to be the only ligand capable of effectively catalyzing this challenging transformation, while almost all other ligands afforded no yield of the coupling product.

C–S Coupling of Axially Prochiral Substrate

With viable conditions for the transformation of *ortho*-substituted substrates at hand, attention turned to the functionalization of prochiral biaryl electrophiles, ultimately aiming at an asymmetric C–S cross-coupling. To date, such a transformation is scarce in literature and limited to nucleophilic substitution reactions^{20–22} and iodonium salt chemistry,^{23–24} despite the considerable promise of chiral thioethers for pharmaceutical applications.²⁵ Initial screening studies had indicated that most commercially available chiral phosphine ligands are ineffective for C–S cross-coupling,²⁶ consistent with the observations described above. In fact, DPEphos (**L2**) and dppf (**L6**) appeared to be the only ligands competent in the coupling of bis(triflate) **1z** with *tert*-butyl thiol (**2e**) (Table 5).

Another challenge was the selective monosubstitution of **1z**, preventing C–S coupling at the second electrophilic position. Surprisingly, monosubstitution could be achieved, although disubstitution was favored in previous chemoselectivity studies (Figure 6). Apparently, higher concentration favored the reaction (entries 1–5). A key finding was that the addition of benzonitrile strictly prevented the formation of **3zee** (entry 6). While higher temperatures did not improve the yield, even temperatures slightly below rt could be used (entries 7–12), an observation possibly helpful with regard to asymmetric induction. Additionally, employing the well-defined precatalyst (dppf)Ni(*o*-tolyl)(Cl) (**Ni5**) led to an increased yield (entry 14), potentially due to inhibitory effects of cyclooctadiene on the catalytic process.²⁷

Consequently, a chiral version of the promising ligands **L2** and **L6** is needed for fine-tuning of an asymmetric coupling. In seminal work, Jugué introduced a method for synthesizing *P*-stereogenic phosphines using ephedrine as chiral auxiliary.²⁸ This strategy implies formation of an oxazaphospholidine with the auxiliary, followed by diastereoselective ring-opening. However, the high restrictions embarked on ephedrine and related compounds complicate that route. Besides other auxiliaries that have been reported in this field,^{29–33} Zhang and co-workers published a procedure based on the auxiliary camphorquinone, leading to high levels of enantioselectivity using a similar strategy.³⁴

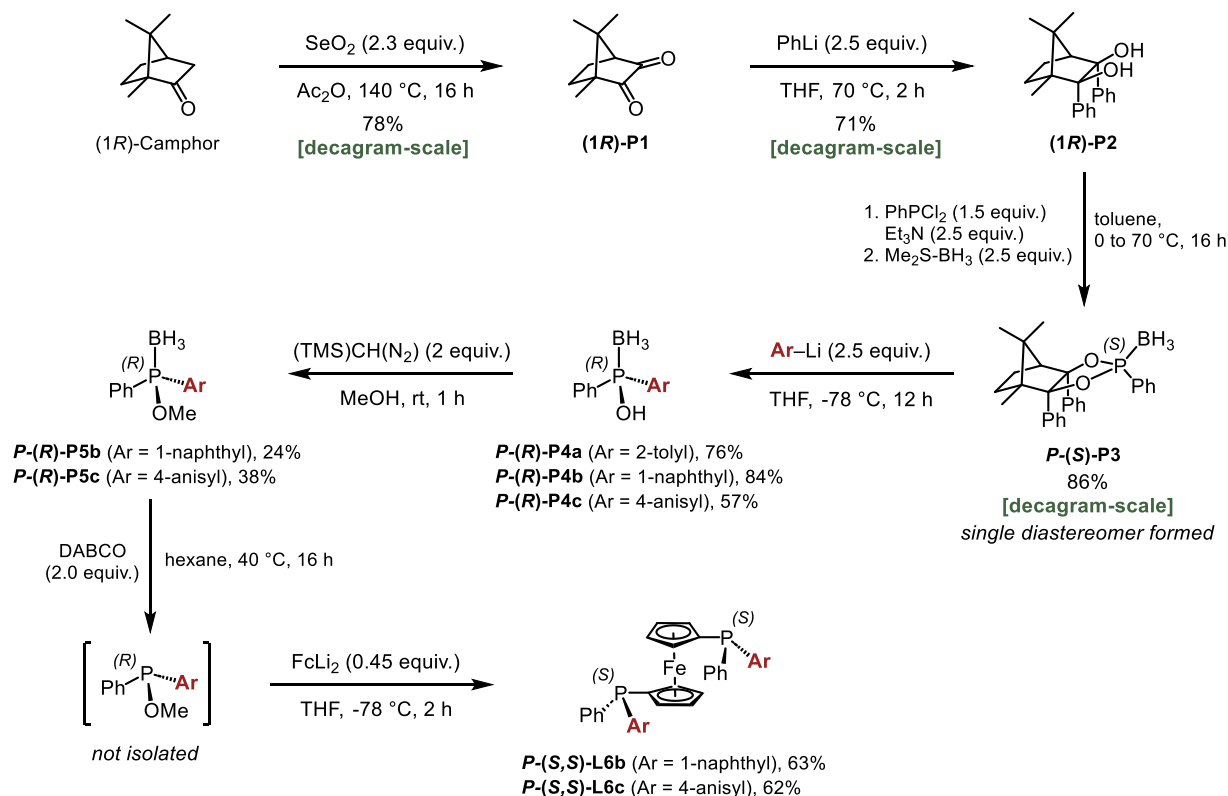
Table 5. Optimization of C–S cross-coupling of prochiral biaryl **1z**.

1z , 0.2 mmol	2e , 1.05 equiv.		3ze	3zee
Entry	Deviation	Conv. [%]	Yield 3ze [%]	Yield 3zee [%]
1	0.05 M	51	13	39
2	0.1 M	54	18	36
3	0.2 M	64	26	38
4	0.5 M	73	42	31
5	1 M	76	49	23
6	0.5 M, + 50 μ L PhCN	66	50	0
<i>Entries below this line contain PhCN (50 μL) as additive</i>				
7	5 °C	57	40	0
8	10 °C	48	31	0
9	15 °C	77	63	1
10	20 °C	72	57	0
11	25 °C	66	50	0
12	30 °C	70	57	1
13	Ni4 as catalyst	61	42	0
14	(dppf)Ni(<i>o</i> -tolyl)(Cl) (Ni5) as catalyst	84	69 (63) ^a	2

Yields and conversions were determined by GC-FID using pentadecane as internal standard. ^a Isolated yield.

Thus, a procedure for the synthesis of *P*-stereogenic ligands was established using modified literature protocols (Scheme 12). Riley-oxidation of (+)-camphor delivered camphorquinone (**P1**), followed by twofold nucleophilic attack of phenyllithium, which afforded **P2** with excellent diastereoselectivity. Both steps could be conducted on decagram-scale with high yields. Meanwhile, the addition of PhPCl₂ to **P2** at first resulted in the formation of two diastereomers in approximately 1:1 ratio, although this step was described as diastereoselective in the literature. Further optimization revealed that choosing toluene instead of THF as solvent improved selectivity, while other solvents, such as MeCN, DCM or Et₂O,

worsened selectivity or led to decomposition. Moreover, it was found that heating to 70 °C in toluene converted all *P*-(*R*)-**P3** to *P*-(*S*)-**P3**, yielding the desired product as a single diastereomer in excellent yield. With **P3** in hand, the following steps including addition of aryl lithium (**P4**), methylation (**P5**), deprotection and addition of the bidentate ligand backbone (**L6**) were achieved in good yields. The bottleneck of the synthesis was the methylation of **P4**, which proceeded only sluggishly and required overstoichiometric amounts of (TMS)CH(N₂), an expensive and highly toxic reagent.



Scheme 12. Synthetic route to chiral dppf-derived phosphine ligands. Isolated yields.

For further upscaling this route, the methylation step should be optimized. While the enantiomeric excess of isolated ligands **P6b** and **P6c** could not yet be determined by chiral HPLC due to lack of suitable methods, the purity was estimated by ³¹P NMR spectroscopy (Figure 9). Partial isomerization at the phosphine center would give rise to three stereoisomers, namely (*R,R*), (*S,S*), and (*R,S*). As the (*R,S*) isomer is a *meso*-compound, it can be distinguished from the enantiomeric pair by ³¹P NMR spectroscopy. Accordingly, observation of a single resonance indicates high enantiomeric purity. To assign the observed signals, a sample was heated for 1 d at 70 °C in CDCl₃ to promote isomerization. Analysis of the resulting spectra indicated diastereomeric and enantiomeric purities of 88% de and 94% ee for **L6b**, and 99% de and 99% ee for **L6c**.

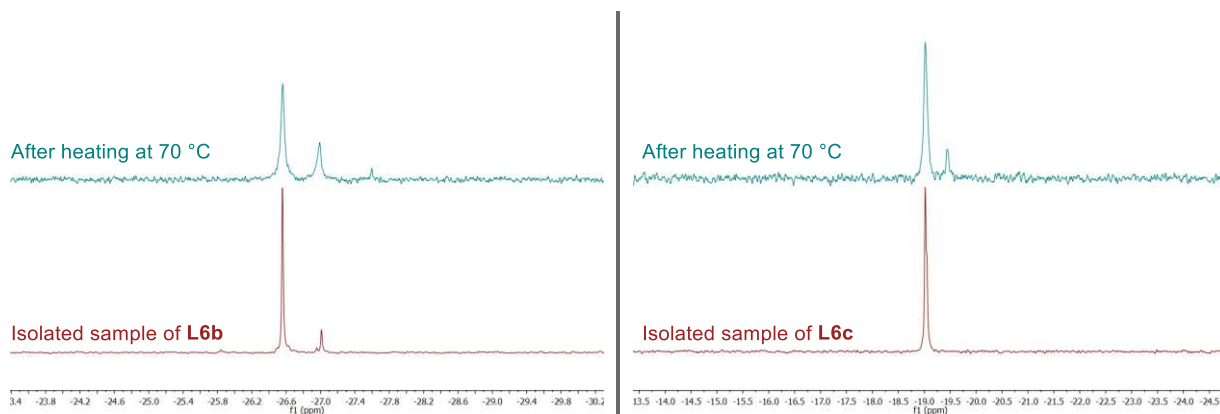


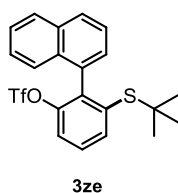
Figure 9. Determination of enantiomeric purity by ^{31}P NMR spectroscopy.

Future work should evaluate these and related ligands in the catalytic transformation. In addition, structurally analogous DPEphos-derived ligands should be synthesized and directly compared to the dppf-based systems. Varying of model substrates is also warranted, as isolation of **3ze** proved challenging due to its low polarity and difficult separation from **1z** and **3zee**.

2.3. Experimental

For general information on instrumentation, experimental details and analytical data of published results, see the Supporting Information of the published article, available free of charge at the publisher's website: DOI 10.1039/D4QO00260A.

Optimized procedure for the C–S cross-coupling of **1z**.



In a flame-dried Schlenk tube, **1z** (500 mg, 1 mmol, 1 equiv.), dry KOAc (108 mg, 1 mmol, 1.1 equiv.), and (dppf)Ni(*o*-tolyl)Cl (74.0 mg, 0.1 mmol, 10 mol%) were dissolved in dry and degassed THF (1 ml) and benzonitrile (250 μ l) followed by *tert*-butyl thiol (**2e**) (120 μ l, 1.1 mmol, 1.1 equiv.) were added. The mixture was stirred at rt for 16 h and subsequently concentrated *in vacuo*. Purification by flash column chromatography (*n*-hexane/EtOAc, gradient 100:0 to 95:5) afforded **3ze** (239 mg, 628 μ mol, 63%) as viscous colorless oil.

¹H-NMR (400 MHz, CDCl₃, δ): 7.96 – 7.88 (m, 2H), 7.83 (d, J = 7.7 Hz, 1H), 7.58 – 7.36 (m, 6H), 7.26 – 7.21 (m, 1H, *residual solvent signal under peak*), 1.13 (s, 9H).

¹³C-NMR (101 MHz, CDCl₃, δ): 148.2, 139.1, 138.3, 137.0, 133.4, 132.4, 132.0, 129.2, 129.1, 128.8, 128.4, 126.3, 125.9, 125.5, 124.7, 121.4, 118.2 (q, J = 320.4 Hz), 47.8, 31.5.

¹⁹F NMR (376 MHz, CDCl₃, δ): -74.5.

Attempted chiral resolution using HPLC:

Stationary phase: CHIRALPAK® IB N-5, 250 x 4.6 mm, 5 μ m.

Mobile phase: *n*-Pentane, isocratic 1.5 ml/min for 35 min.

Injection: 5 μ l of 1 mg/ml stock solution of **3ze** in *n*-hexane.

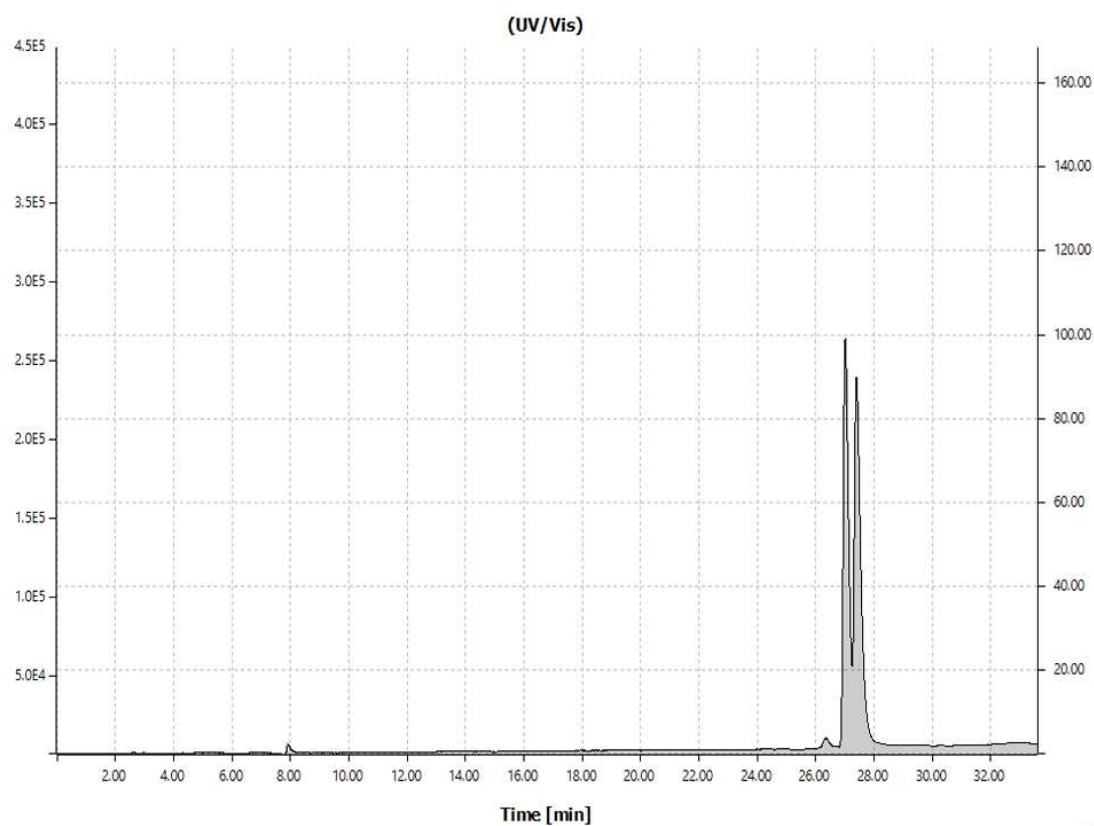


Figure 10. Attempted chiral resolution *via* HPLC of **3ze**.

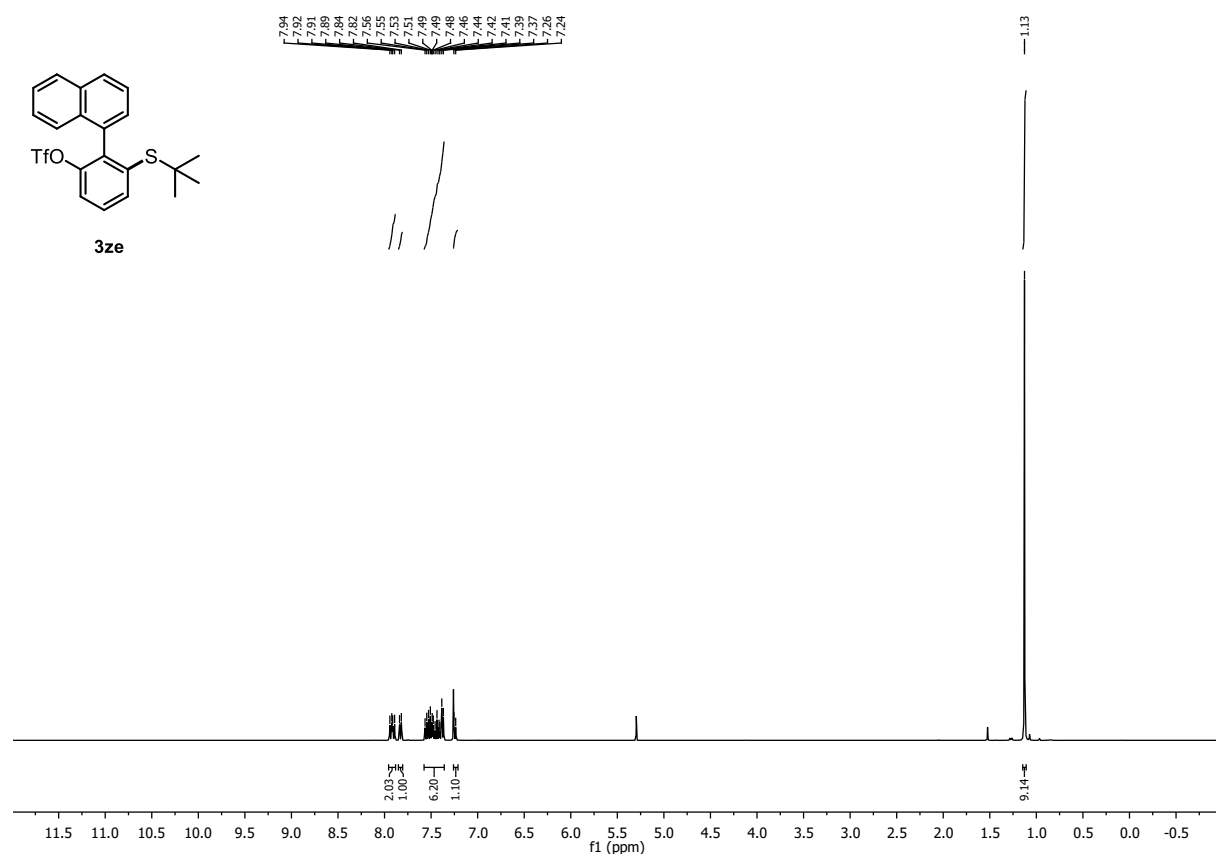


Figure 11. ¹H NMR spectrum (400 MHz, CDCl₃) of **3ze**.

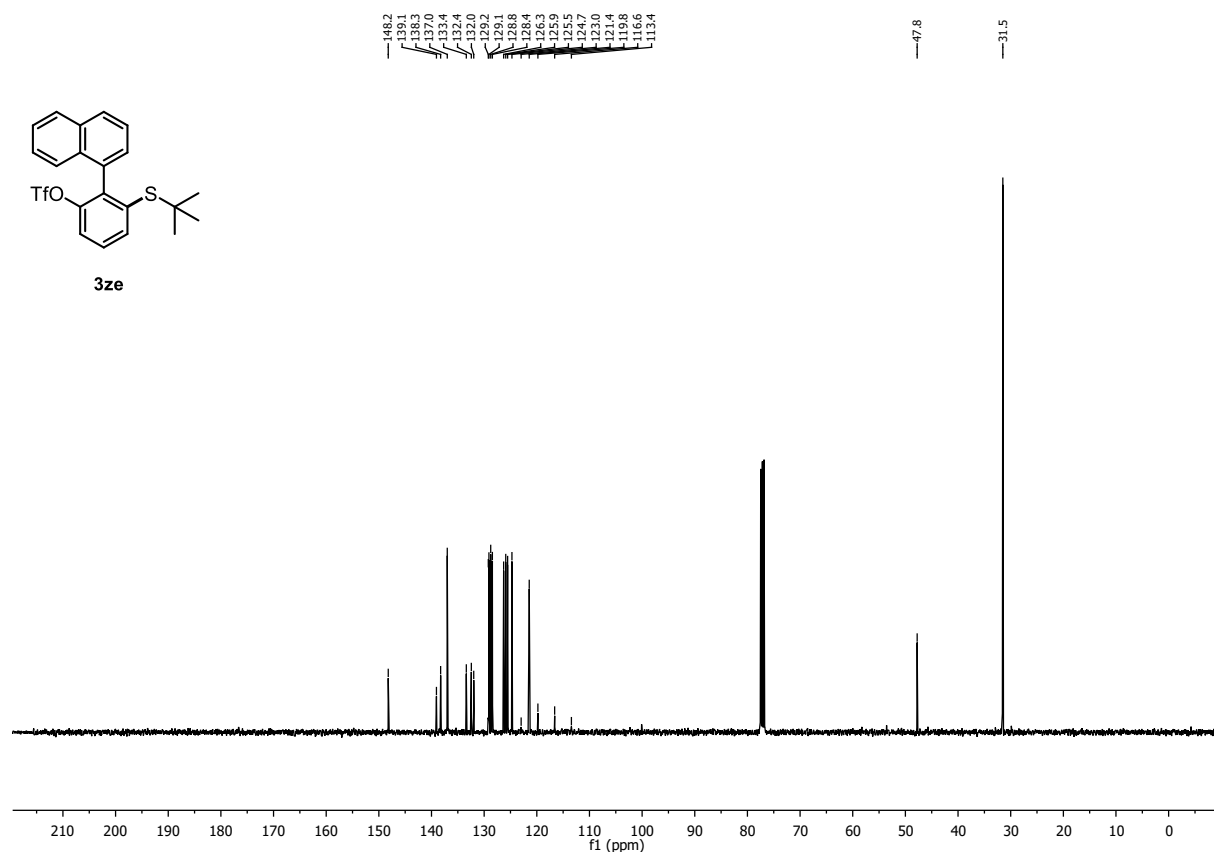


Figure 12. ¹³C NMR spectrum (101 MHz, CDCl₃) of **3ze**.

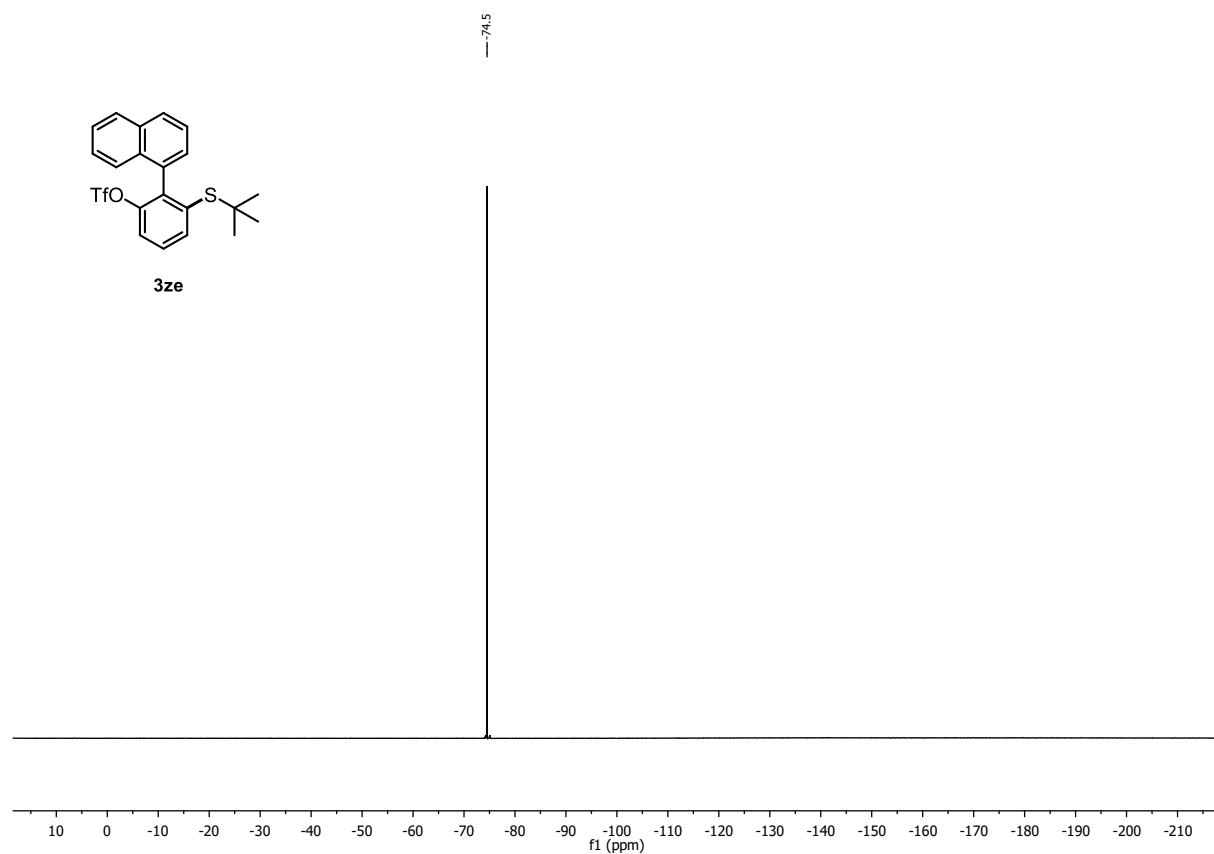
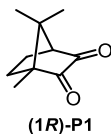


Figure 13. ¹⁹F NMR spectrum (376 MHz, CDCl₃) of **3ze**.

Camphorquinone ((1*R*)-P1).

C₁₀H₁₄O₂ (166.22 g/mol)

A literature procedure was used.³⁵

In a 250 ml round-bottom flask, (+)-campher (30.0 g, 197 mmol, 1 equiv.) and SeO₂ (50.3 g, 453 mmol, 2.3 equiv.) were suspended in Ac₂O (50 ml) and stirred at 150 °C for 16 h. The resulting mixture was filtered using a P4-frit and the residue washed with Ac₂O (2 × 10 ml). The filtrate was cooled to 0 °C and water (100 ml) was added, resulting in precipitation of a yellow solid. The mixture was filtered using a Buchner-funnel and the residue was washed with water (2 × 30 ml). The residue was dissolved in DCM (150 ml), dried over MgSO₄, filtered and the solvent was removed *in vacuo*, affording **(1*R*)-P1** (25.5 g, 153 mmol, 78%) as yellow solid.

¹H-NMR (400 MHz, CDCl₃, δ): 2.63 (d, *J* = 5.2 Hz, 1H), 2.21 – 2.11 (m, 1H), 1.96 – 1.85 (m, 1H), 1.68 – 1.59 (m, 2H), 1.10 (s, 3H), 1.06 (s, 3H), 0.93 (s, 3H).

¹³C-NMR (101 MHz, CDCl₃, δ): 204.9, 203.0, 58.8, 58.1, 42.7, 30.1, 22.4, 21.3, 17.6, 8.9.

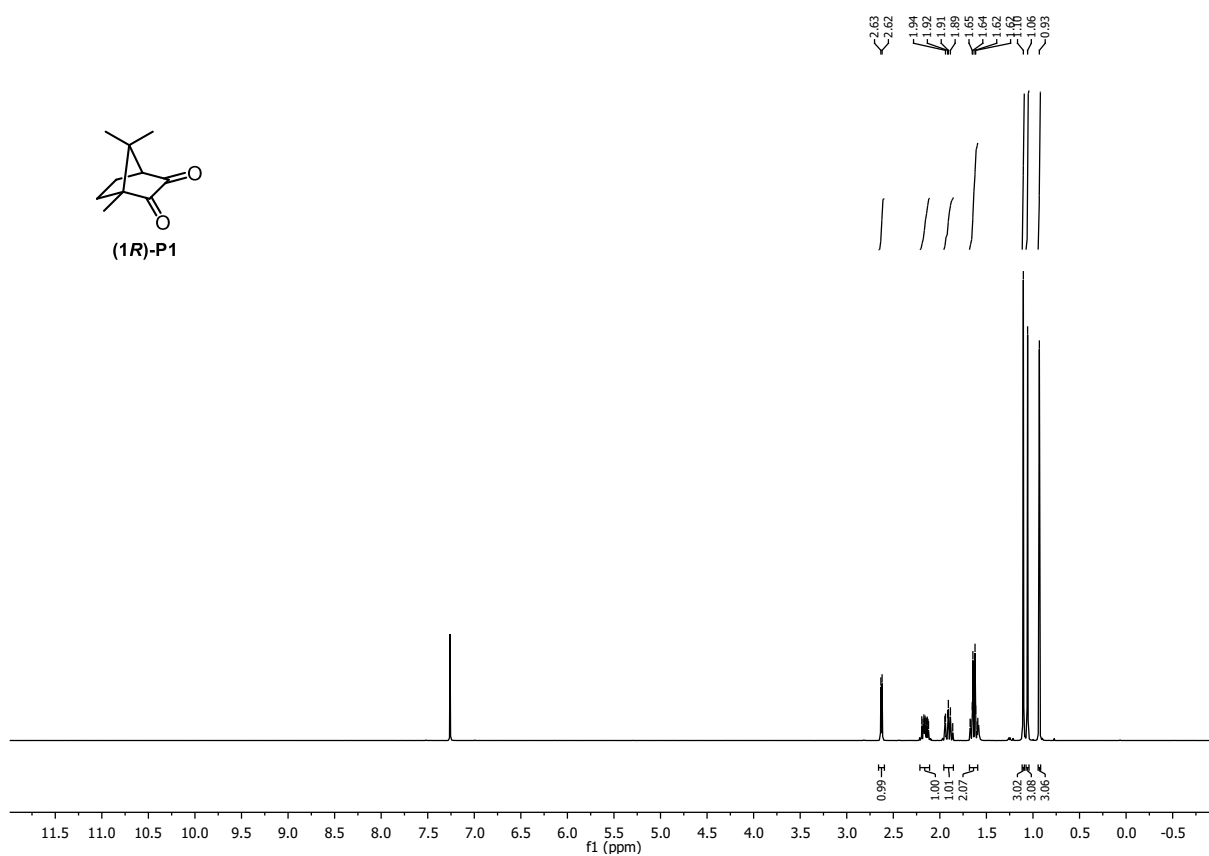


Figure 14. ^1H NMR spectrum (400 MHz, CDCl_3) of **(1R)-P1**.

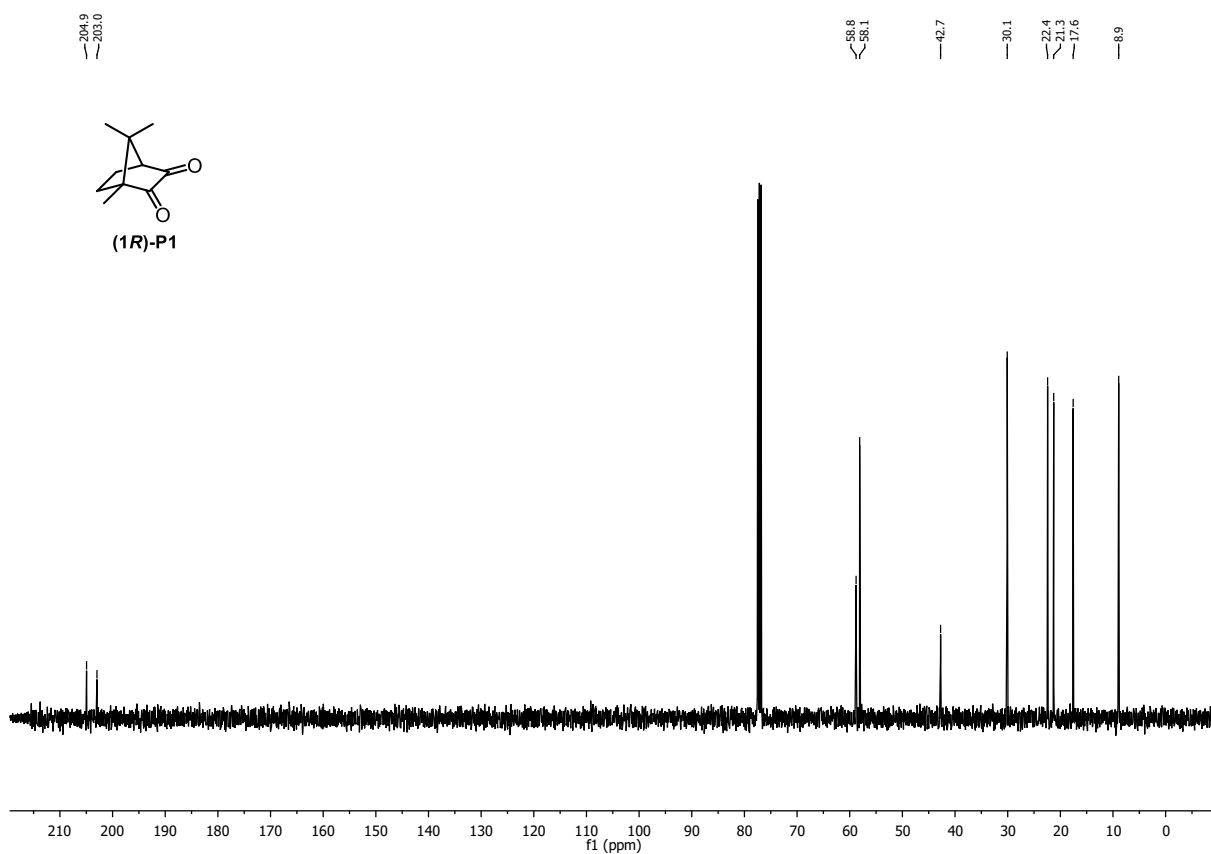
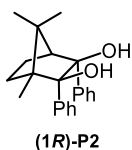


Figure 15. ^{13}C NMR spectrum (101 MHz, CDCl_3) of **(1R)-P1**.

(1R)-1,7,7-Trimethyl-2,3-diphenylbicyclo[2.2.1]heptane-2,3-diol ((1R)-P2).

C₂₂H₂₆O₂ (322.45 g/mol)

A literature procedure was used.³³

In a 500 ml Schlenk round-bottom flask, **(1R)-P1** (8.00 g, 48.1 mmol, 1 equiv.) was dissolved in THF (240 ml). Phenyllithium (1.9 M in Bu₂O (Sigma Aldrich), 63.3 ml, 120 mmol, 2.5 equiv.) was added and the solution was stirred at 70 °C for 4 h. The resulting deep purple mixture was quenched with sat. NH₄Cl solution (40 ml) and water (20 ml) and EtOAc (100 ml) were added. The layers were separated and the aqueous layer was extracted with EtOAc (2 × 40 ml). The combined organic layers were washed with brine (1 × 40 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. *n*-Hexane (100 ml) was added to the residue and the mixture was placed in a freezer at -20 °C overnight. An off-white solid precipitated, which was collected by filtration, affording **(1R)-P2** (11.1 g, 34.4 mmol, 71%).

¹H-NMR (400 MHz, CDCl₃, δ): 8.04 – 6.20 (br, 10H), 4.64 (s, 1H), 2.48 (d, *J* = 5.2 Hz, 1H), 2.43 (s, 1H), 2.05 – 1.92 (m, 1H), 1.88 – 1.76 (m, 1H), 1.50 (s, 3H), 1.27 – 1.15 (m, 2H), 1.06 (s, 3H), 0.84 (s, 3H).

¹³C-NMR (101 MHz, CDCl₃, δ): 144.0, 142.6, 129.9 (br), 127.9, 127.4, 126.0, 88.4, 86.9, 54.6, 53.1, 50.0, 30.9, 24.4, 24.0, 23.8, 10.4.

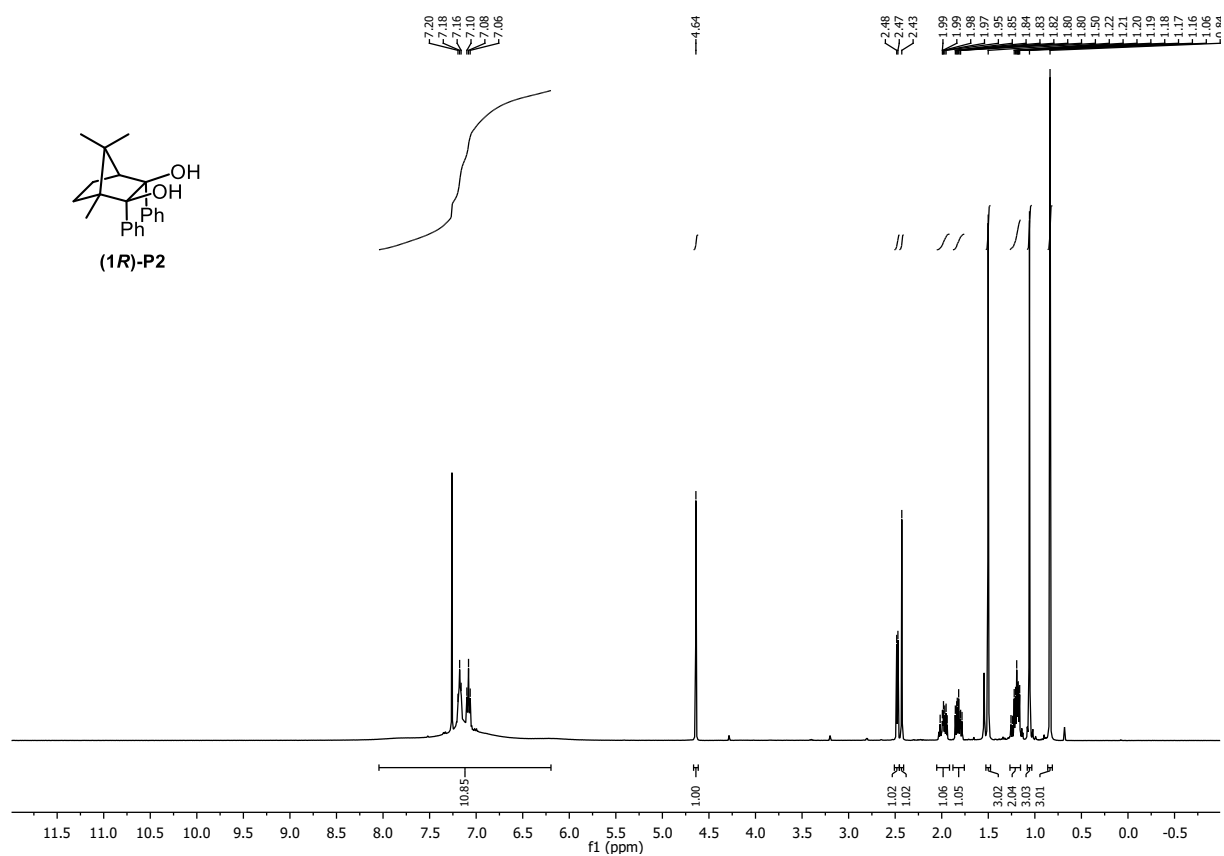


Figure 16. ¹H NMR spectrum (400 MHz, CDCl₃) of **(1R)-P2**.

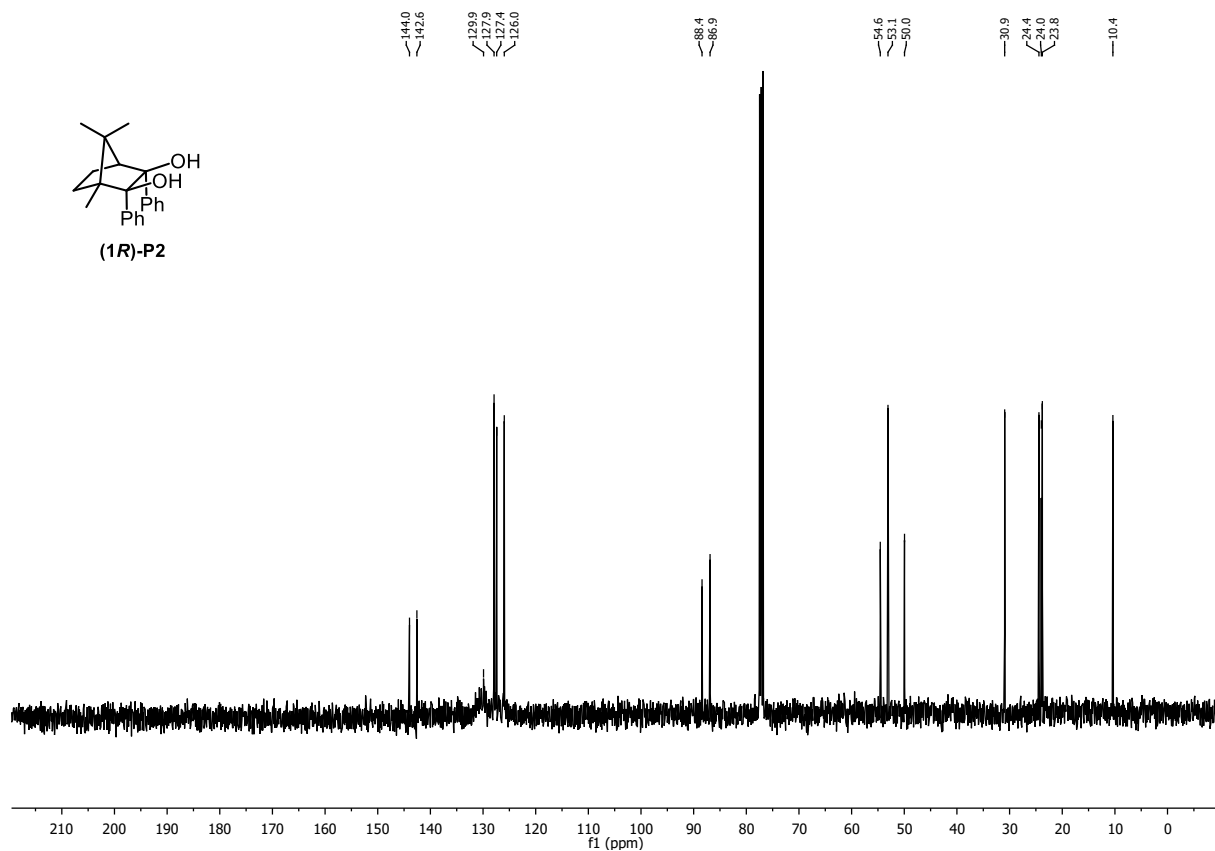
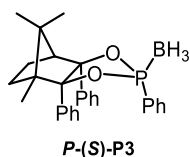


Figure 17. ¹³C NMR spectrum (101 MHz, CDCl₃) of **(1R)-P2**.

***P*-(*S*)-P3.**C₂₈H₃₂BO₂P (442.35 g/mol)A literature procedure was used.³³

In a 250 ml Schlenk round-bottom flask, **(1R)-P2** (9.50 g, 29.5 mmol, 1 equiv.) was dissolved in toluene (100 ml). Subsequently, triethylamine (analytical grade, 10.3 ml, 73.7 mmol, 2.5 equiv.) was added and the solution was cooled to 0 °C. At this temperature, PhPCl₂ (5.19 ml, 38.3 mmol, 1.3 equiv.) was added dropwise and stirred for 15 min. Then, the mixture was allowed to warm to rt and further stirred for 1.5 h, then at 70 °C for 30 min. The isomerization to one diastereomer was monitored by ³¹P NMR spectroscopy. At rt, dimethylsulfide borane (4.19 ml, 44.2 mmol, 1.5 equiv.) was added and the mixture stirred for 45 min. Finally, the reaction was quenched with sat. NH₄Cl solution (40 ml) and EtOAc (20 ml). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 40 ml). The combined organic layers were washed with brine (1 × 40 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. The pale yellow residue was crystallized from *n*-hexane/EtOAc, affording ***P*-(*S*)-P3** (11.2 g, 25.3 mmol, 86%) as an off-white solid.

¹H-NMR (300 MHz, CDCl₃, δ): 7.90 – 6.78 (m, 15H), 3.12 (d, *J* = 5.4 Hz, 1H), 2.10 – 1.96 (m, 1H), 1.71 (s, 3H), 1.50 – 1.39 (m, 1H), 1.30 – 1.19 (m, 2H), 1.14 (s, 3H), 1.00 (s, 3H).

¹¹B-NMR (128 MHz, CDCl₃, δ): -35.7.

¹³C-NMR (101 MHz, CDCl₃, δ): 136.4, 136.1, 134.9, 134.4, 131.0, 130.6, 130.1, 130.0, 129.0, 128.2, 127.8, 127.7, 127.6, 125.7, 125.3, 102.4, 102.3, 100.3, 100.2, 55.9, 55.8, 52.5, 52.44, 52.38, 47.8, 29.9, 26.0, 24.0, 22.9, 22.9, 10.0.

³¹P-NMR (121 MHz, CDCl₃, δ): 150.3 (q).

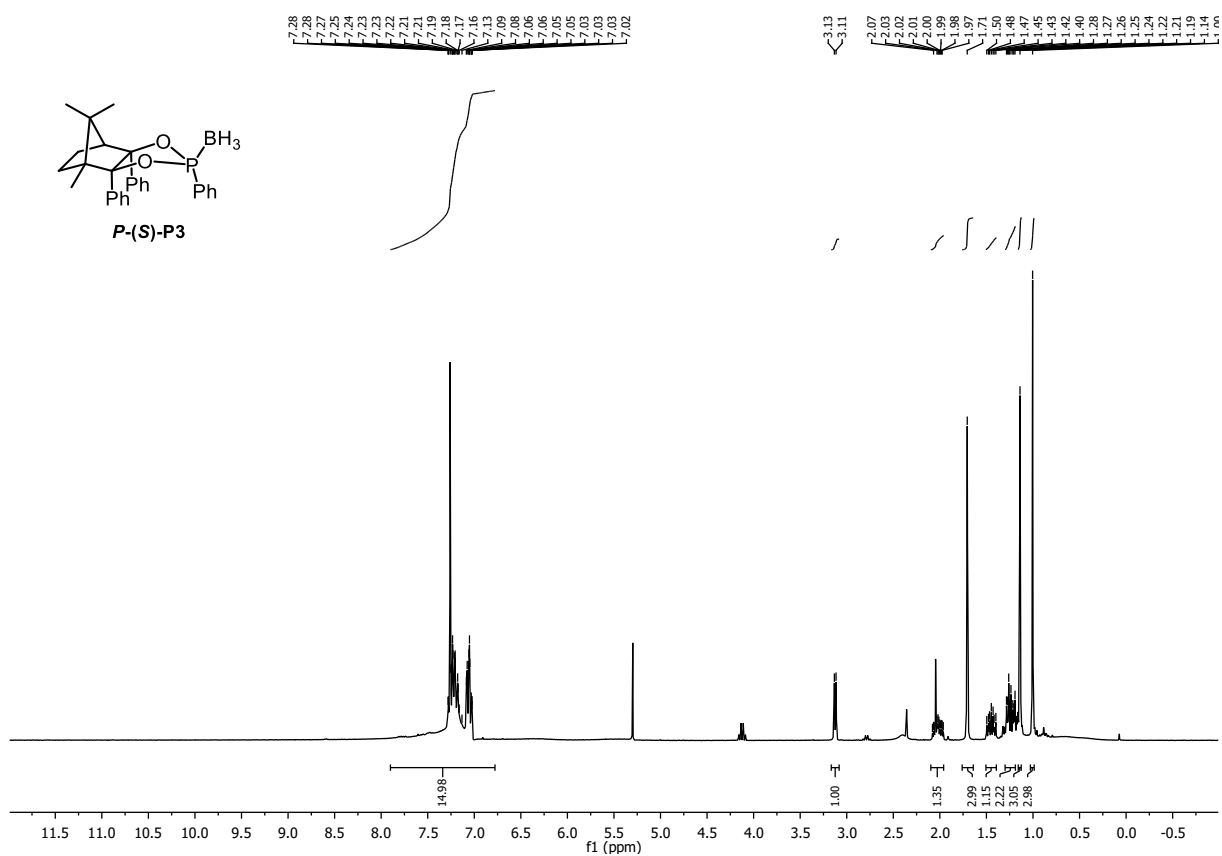


Figure 18. ^1H NMR spectrum (300 MHz, CDCl_3) of *P*-(*S*)-P3.

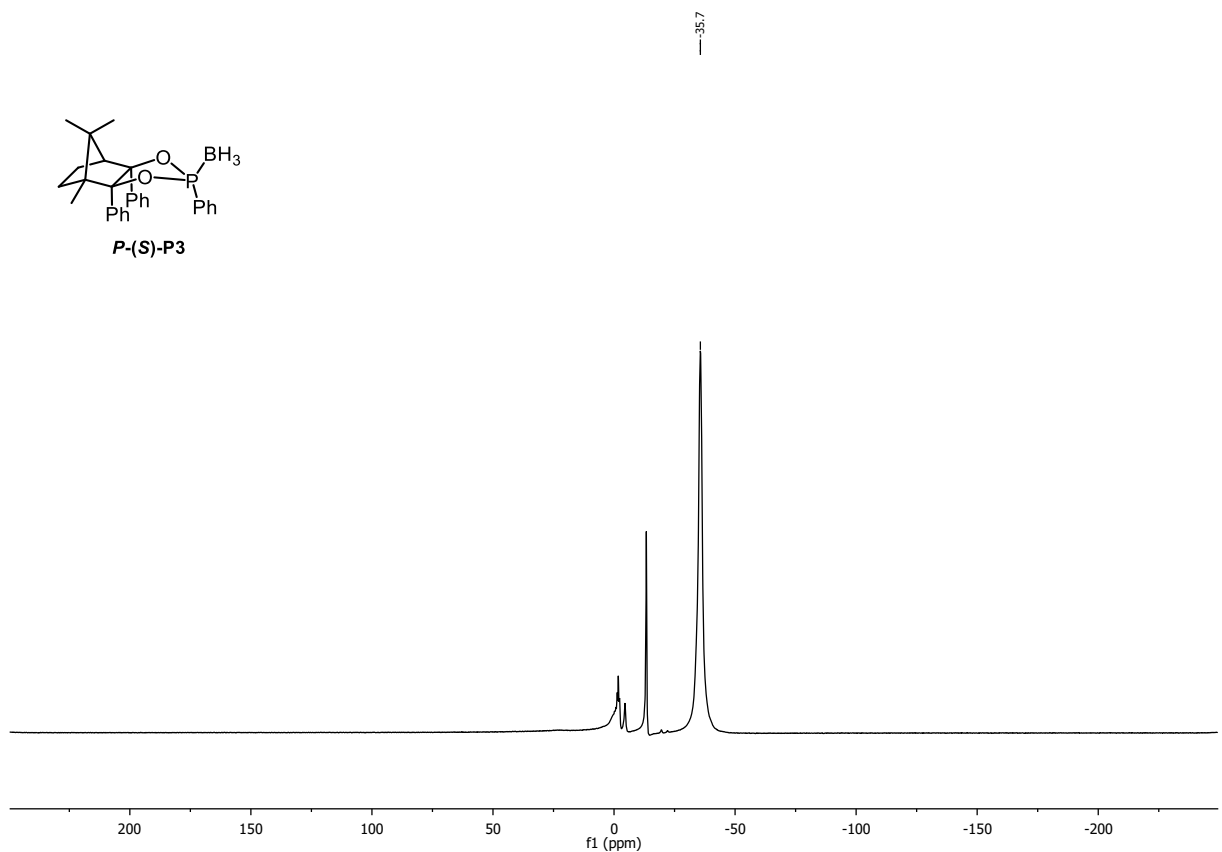


Figure 19. ^{11}B NMR spectrum (128 MHz, CDCl_3) of *P*-(*S*)-P3.

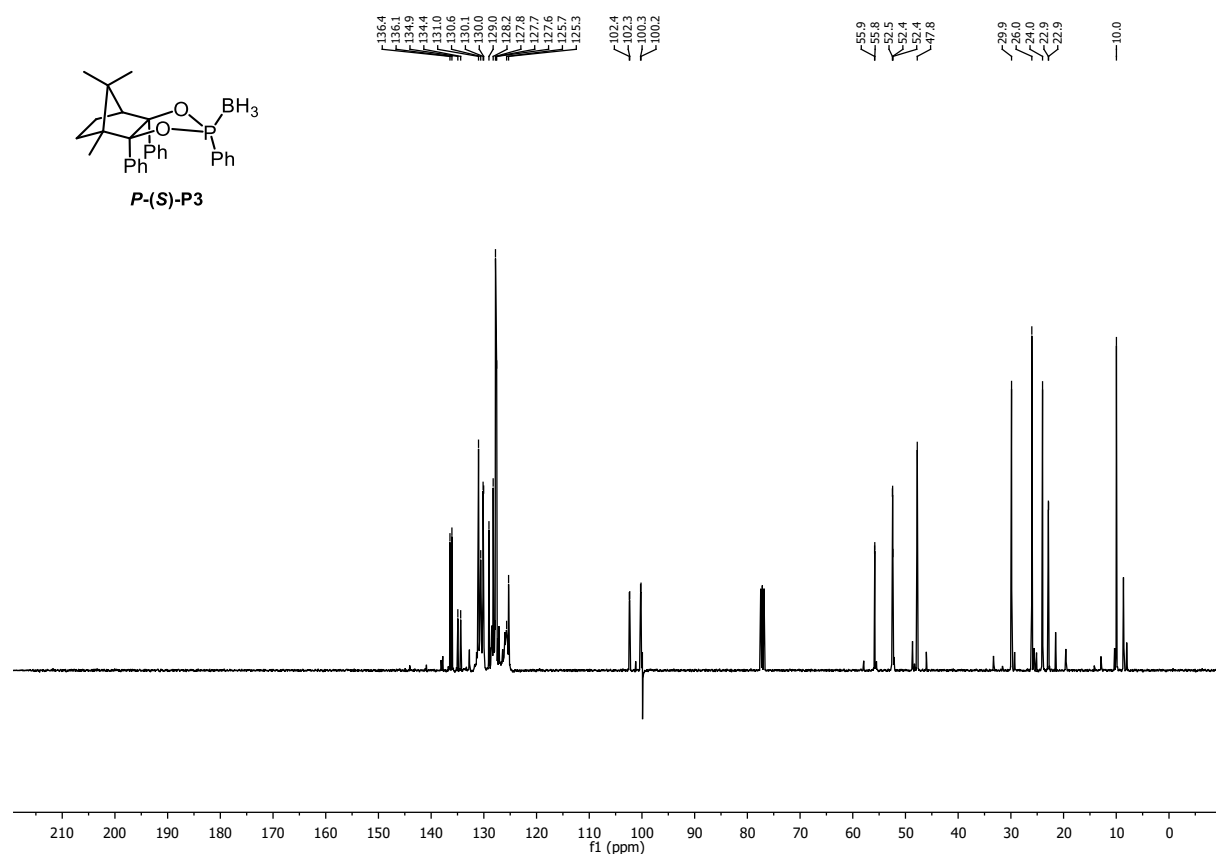


Figure 20. ^{13}C NMR spectrum (101 MHz, CDCl_3) of *P*-(*S*)-P3.

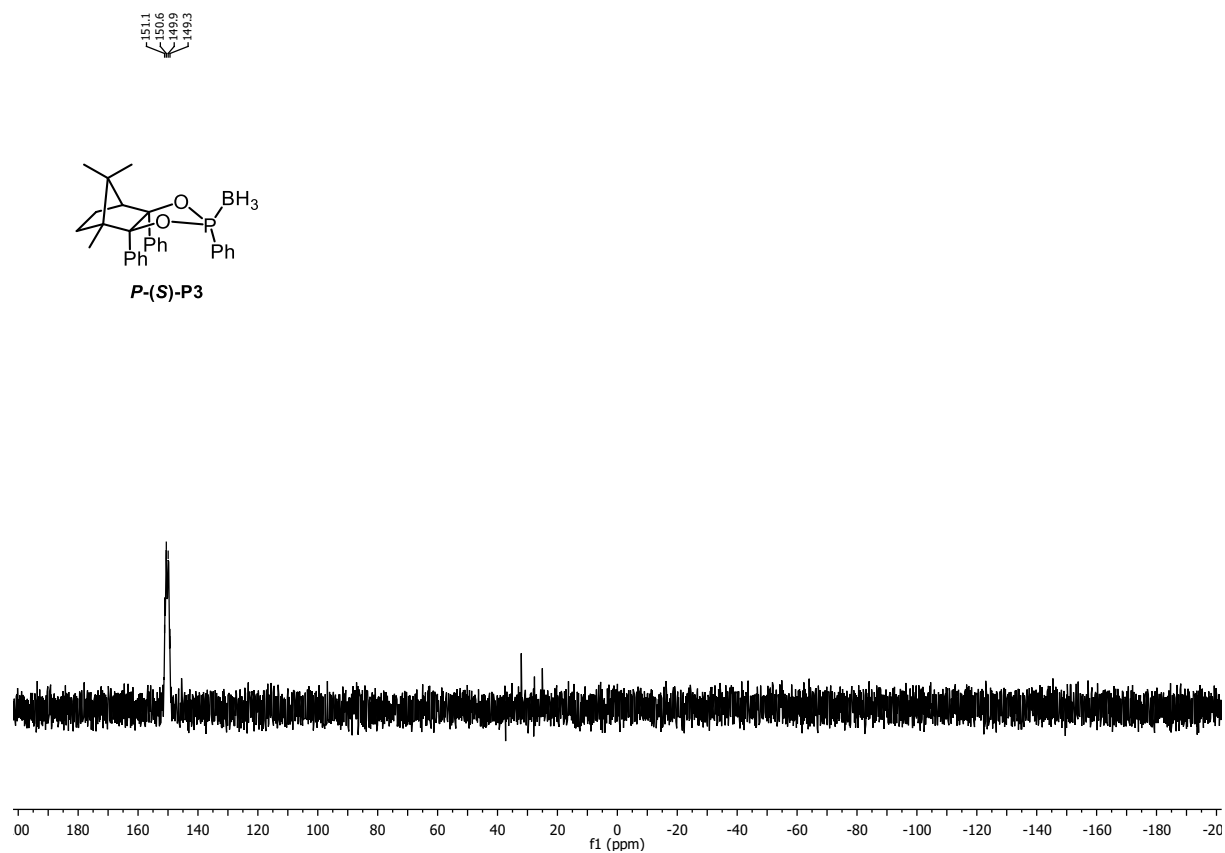


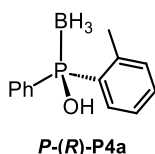
Figure 21. ^{31}P NMR spectrum (121 MHz, CDCl_3) of *P*-(*S*)-P3.

General procedure GP-P1: Synthesis of P4.

A modified literature procedure was used.³³

In a Schlenk tube, the corresponding aryl bromide (1.5 equiv.) was dissolved in THF (5 ml) and cooled to -78 °C. *n*-BuLi (2.5 M in hexane, 1.5 equiv.) was added and the mixture stirred for 1 h at -78 °C. Subsequently, a solution of **P3** (1.0 equiv.) in THF (20 ml) was added, and the reaction was stirred for 16 h at -78 °C. The reaction was quenched with sat. NH₄Cl solution (10 ml) and EtOAc (10 ml). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 10 ml). The combined organic layers were washed with brine (1 × 10 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography afforded **P4**.

Note: Poor separation usually afforded impure samples of P4, which were used for the following steps.

***P*-(*R*)-P4a.**

C₁₄H₁₉BOP (245.09 g/mol)

According to **GP-P1**, ***P*-(*R*)-P4a** was synthesized from ***P*-(*S*)-P3** (2.00 g, 4.52 mmol, 1.0 equiv.) and 2-bromotoluene (1.16 ml, 6.78 mmol, 1.5 equiv.). Purification by flash column chromatography (*n*-hexane/EtOAc, gradient 100:0 to 90:10 over 5 CV, then to 0:100 over 10 CV) afforded ***P*-(*R*)-P4a** (791 mg, 3.44 mmol, 76%) as colorless oil.

¹H-NMR (400 MHz, CDCl₃, δ): 8.03 – 7.94 (m, 1H), 7.68 – 7.62 (m, 2H), 7.49 – 7.34 (m, 5H), 7.32 – 7.27 (m, 1H), 7.19 – 7.13 (m, 1H), 2.22 (s, 3H).

¹¹B-NMR (128 MHz, CDCl₃, δ): -36.4 (d, *J* = 66.1 Hz).

¹³C-NMR (101 MHz, CDCl₃, δ): 141.7, 141.6, 133.1, 132.9, 131.5, 131.4, 131.0, 130.9, 128.6, 128.5, 125.8, 125.7, 114.4, 114.3, 14.3.

(Doublets due to C–P coupling may appear, but could not be assigned.)

³¹P-NMR (162 MHz, CDCl₃, δ): 95.8 (br).

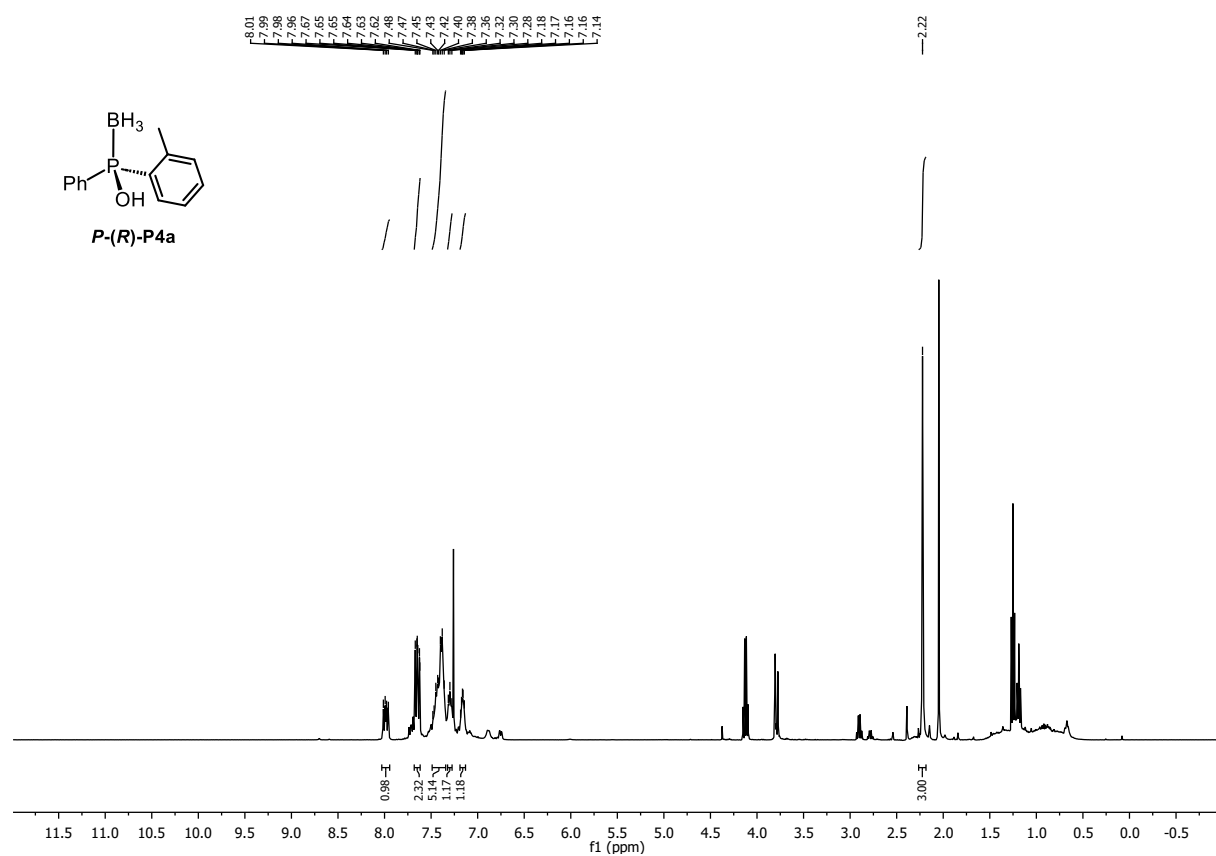


Figure 22. ^1H NMR spectrum (400 MHz, CDCl_3) of *P*-(*R*)-**P4a**.

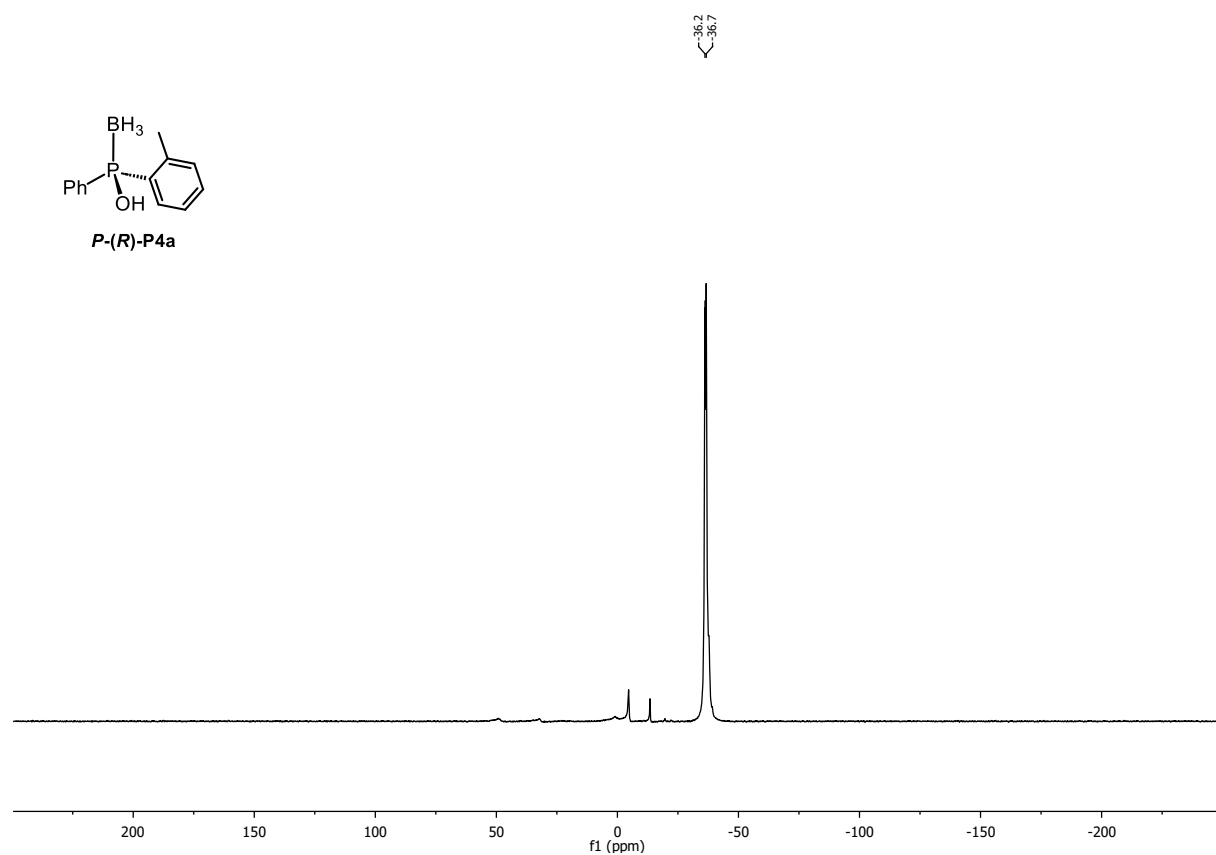


Figure 23. ^{11}B NMR spectrum (128 MHz, CDCl_3) of *P*-(*R*)-**P4a**.

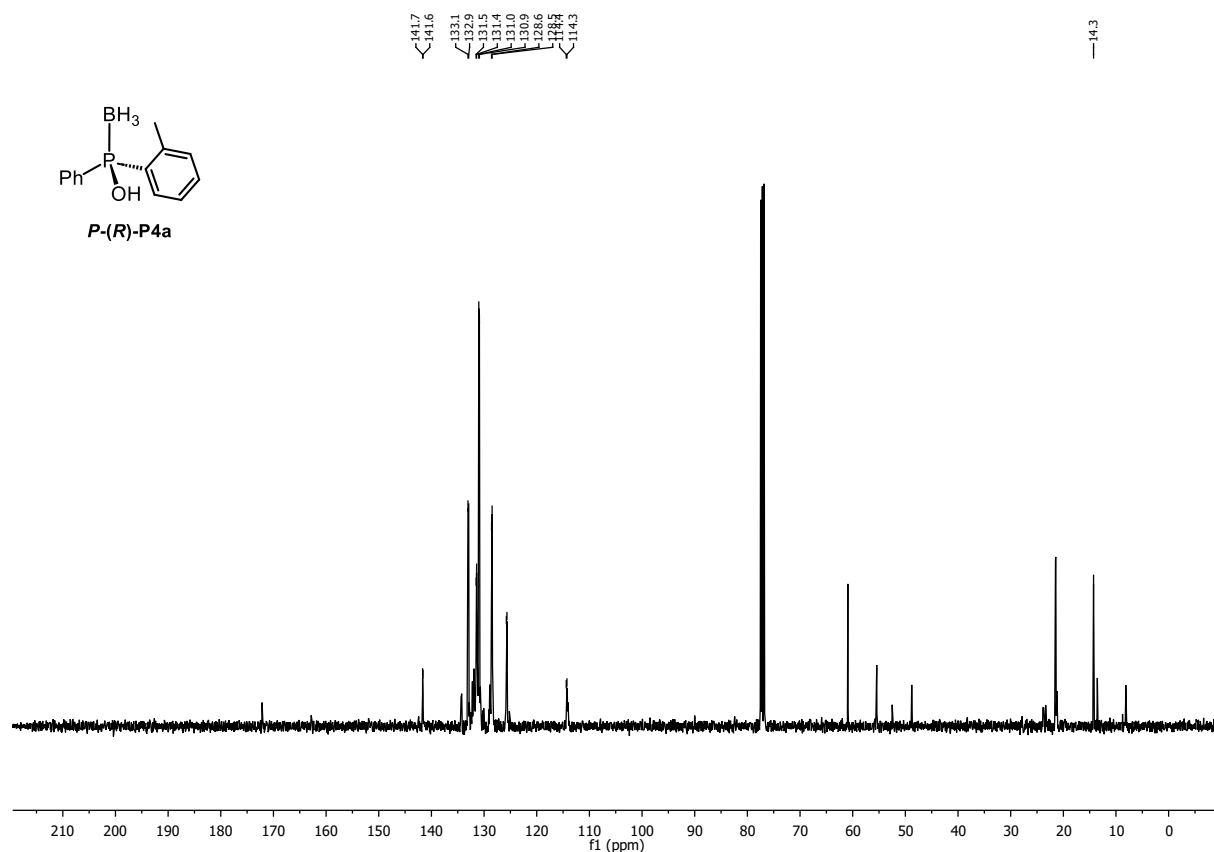


Figure 24. ¹³C NMR spectrum (101 MHz, CDCl₃) of *P*-(*R*)-P4a.

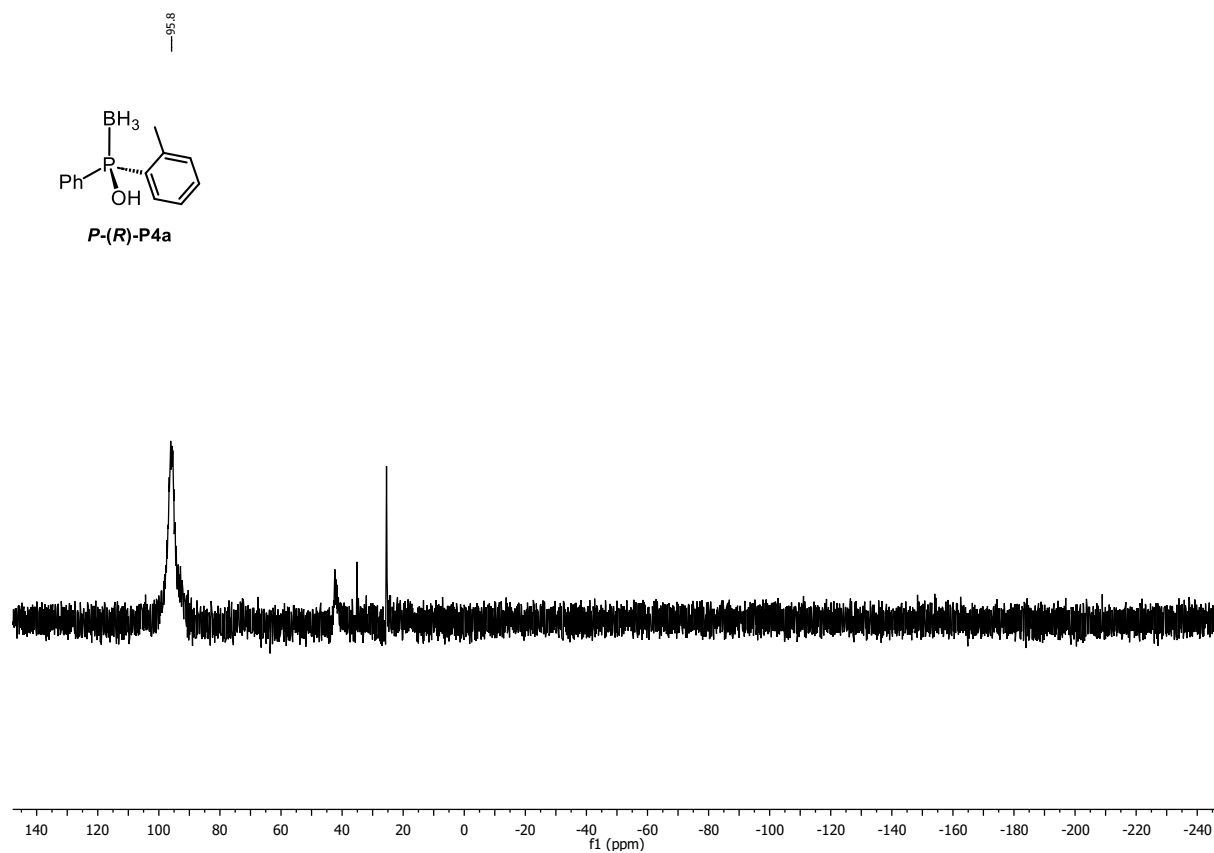
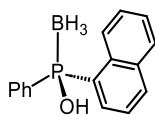


Figure 25. ³¹P NMR spectrum (162 MHz, CDCl₃) of *P*-(*R*)-P4a.

P*-(*R*)-P4b.**P*-(*R*)-P4b**

C₁₇H₁₉BOP (281.12 g/mol)

According to **GP-P1**, ***P*-(*R*)-P4b** was synthesized from ***P*-(*S*)-P3** (2.00 g, 4.52 mmol, 1.0 equiv.) and 1-bromonaphthalene (1.40 g, 6.78 mmol, 1.5 equiv.). Purification by flash column chromatography (*n*-hexane/EtOAc, gradient 100:0 to 90:10 over 5 CV, then to 0:100 over 10 CV) afforded ***P*-(*R*)-P4b** (1.01 g, 3.80 mmol, 84%) as viscous colorless oil.

¹H-NMR (400 MHz, CDCl₃, δ): 8.31 (dd, *J* = 15.1, 7.0 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.71 – 7.62 (m, 2H), 7.57 (t, *J* = 7.0 Hz, 1H), 7.49 – 7.30 (m, 6H).

³¹P-NMR (162 MHz, CDCl₃, δ): 97.1 (br).

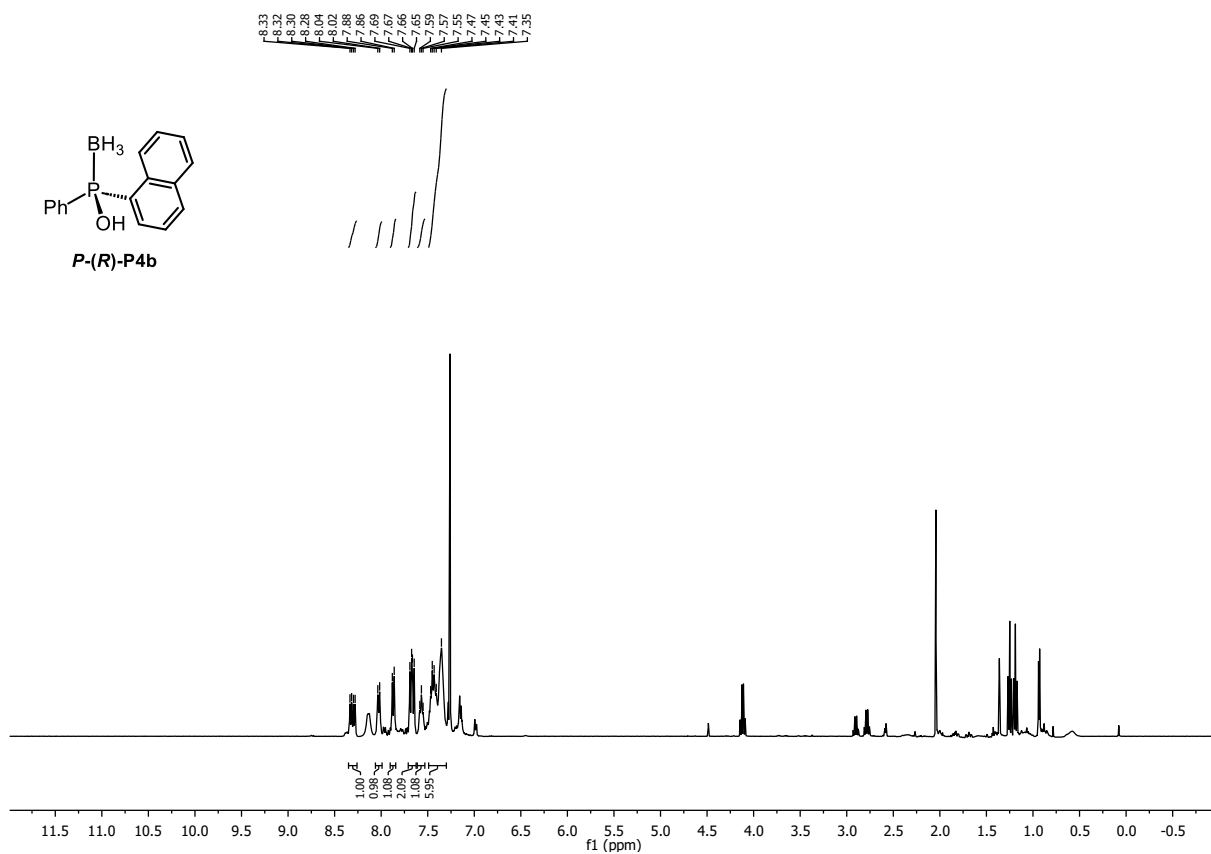


Figure 26. ^1H NMR spectrum (400 MHz, CDCl_3) of *P*-(*R*)-**P4b**.

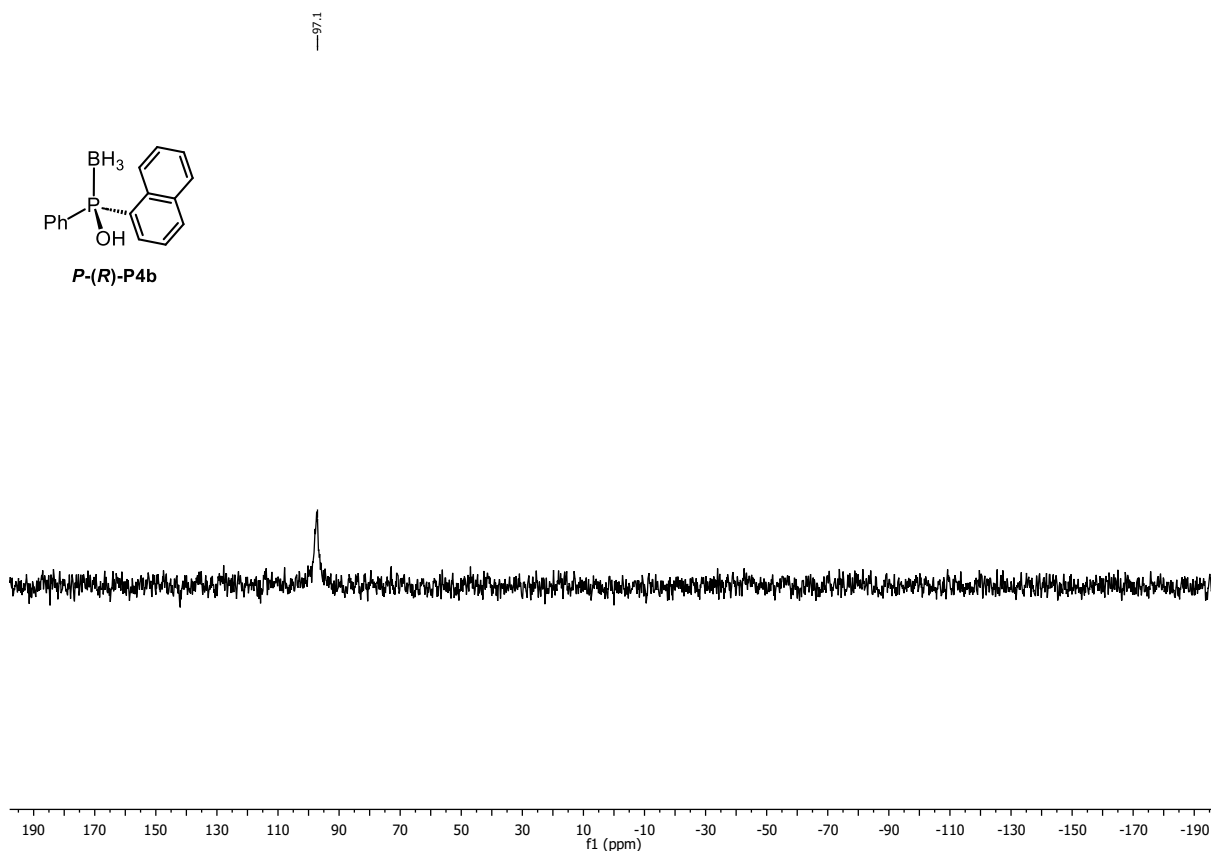
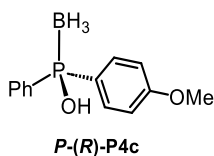


Figure 27. ^{31}P NMR spectrum (162 MHz, CDCl_3) of *P*-(*R*)-**P4b**.

P-(*R*)-**P4c**.



C₁₄H₁₉BO₂P (261.09 g/mol)

According to **GP-P1**, ***P*-(*R*)-P4c** was synthesized from ***P*-(*S*)-P3** (2.00 g, 4.52 mmol, 1.0 equiv.) and 4-bromoanisole (1.27 g, 6.78 mmol, 1.5 equiv.). Purification by flash column chromatography (*n*-hexane/EtOAc, gradient 100:0 to 90:10 over 5 CV, then to 0:100 over 10 CV) afforded ***P*-(*R*)-P4c** (637 mg, 2.59 mmol, 57%) as viscous colorless oil.

¹H-NMR (400 MHz, CDCl₃, δ): 7.76 – 7.65 (m, 4H), 7.48 – 7.36 (m, 3H), 6.91 – 6.89 (m, 2H), 3.81 (s, 3H).

¹¹B-NMR (128 MHz, CDCl₃, δ): -37.6 (d, *J* = 65.9 Hz).

¹³C-NMR (101 MHz, CDCl₃, δ): 133.1, 133.0, 131.3, 131.1, 130.9, 130.8, 128.55, 128.45, 114.2, 114.1, 55.4.

(Doublets due to C–P coupling may appear, but could not be assigned.)

³¹P-NMR (162 MHz, CDCl₃, δ): 93.0 (br).

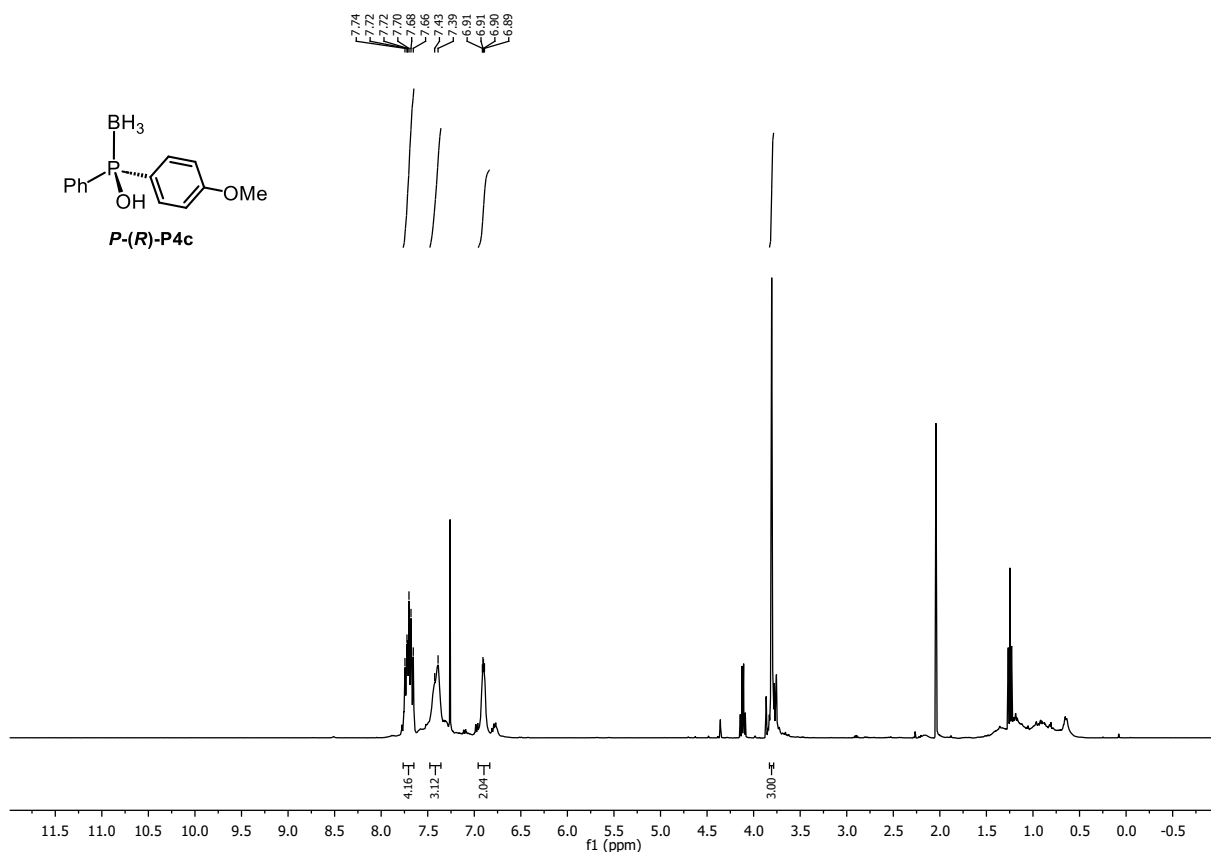


Figure 28. ¹H NMR spectrum (400 MHz, CDCl₃) of *P*-(*R*)-**P4c**.

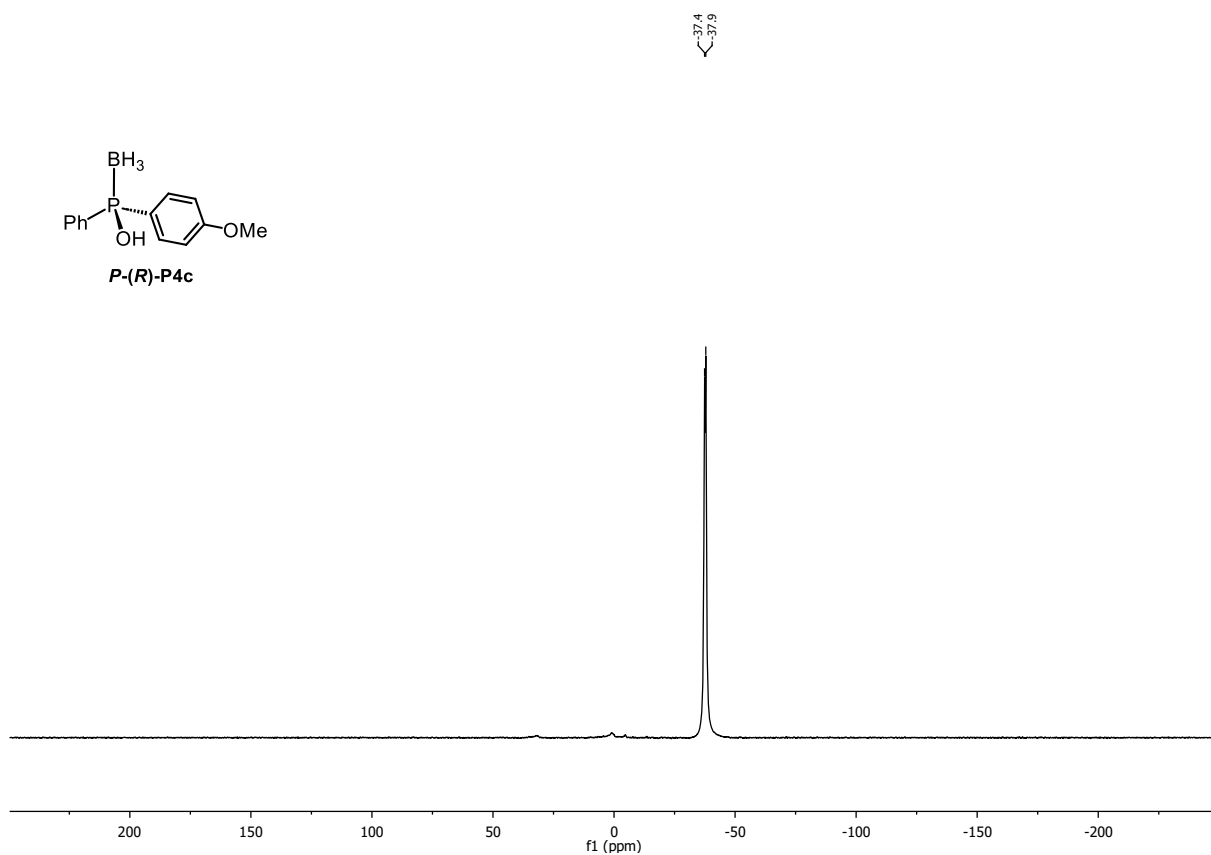


Figure 29. ¹¹B NMR spectrum (128 MHz, CDCl₃) of *P*-(*R*)-**P4c**.

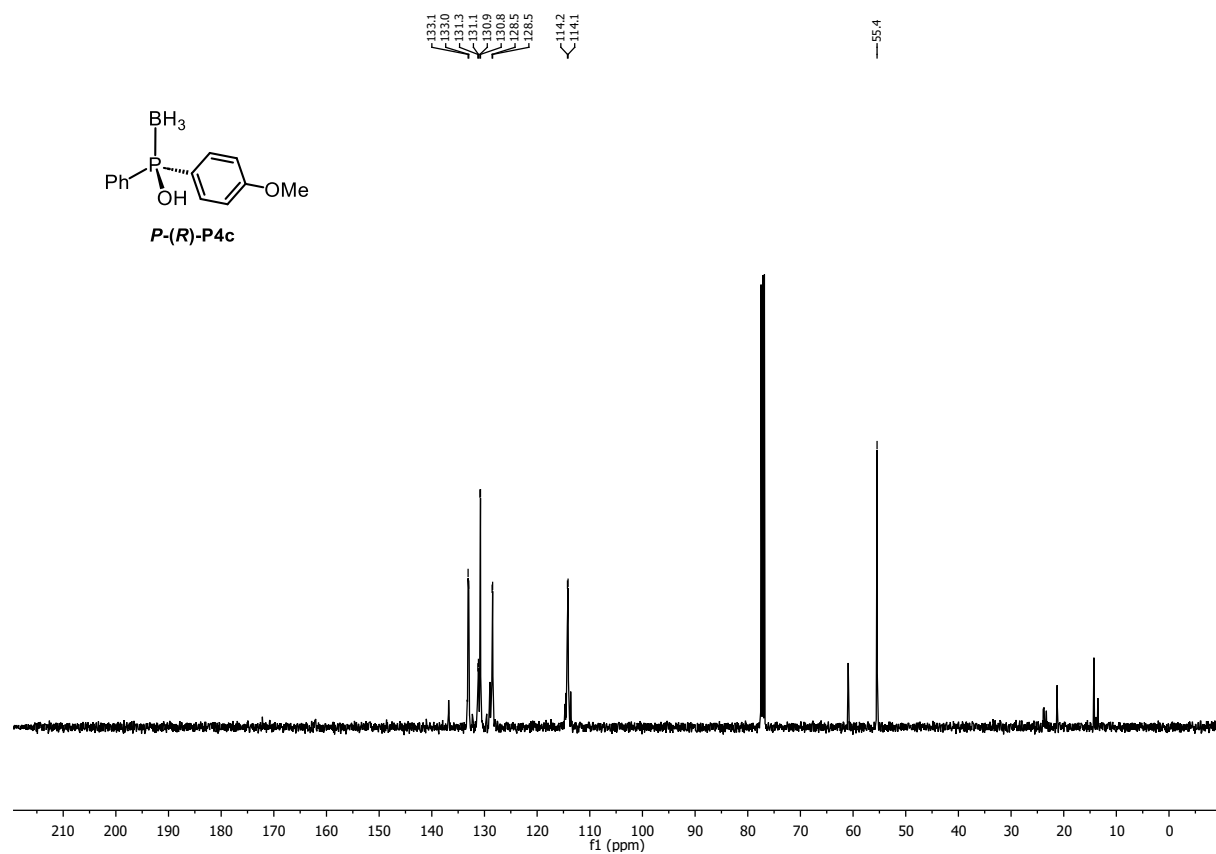


Figure 30. ^{13}C NMR spectrum (101 MHz, CDCl_3) of *P*-(*R*)-**P4c**.

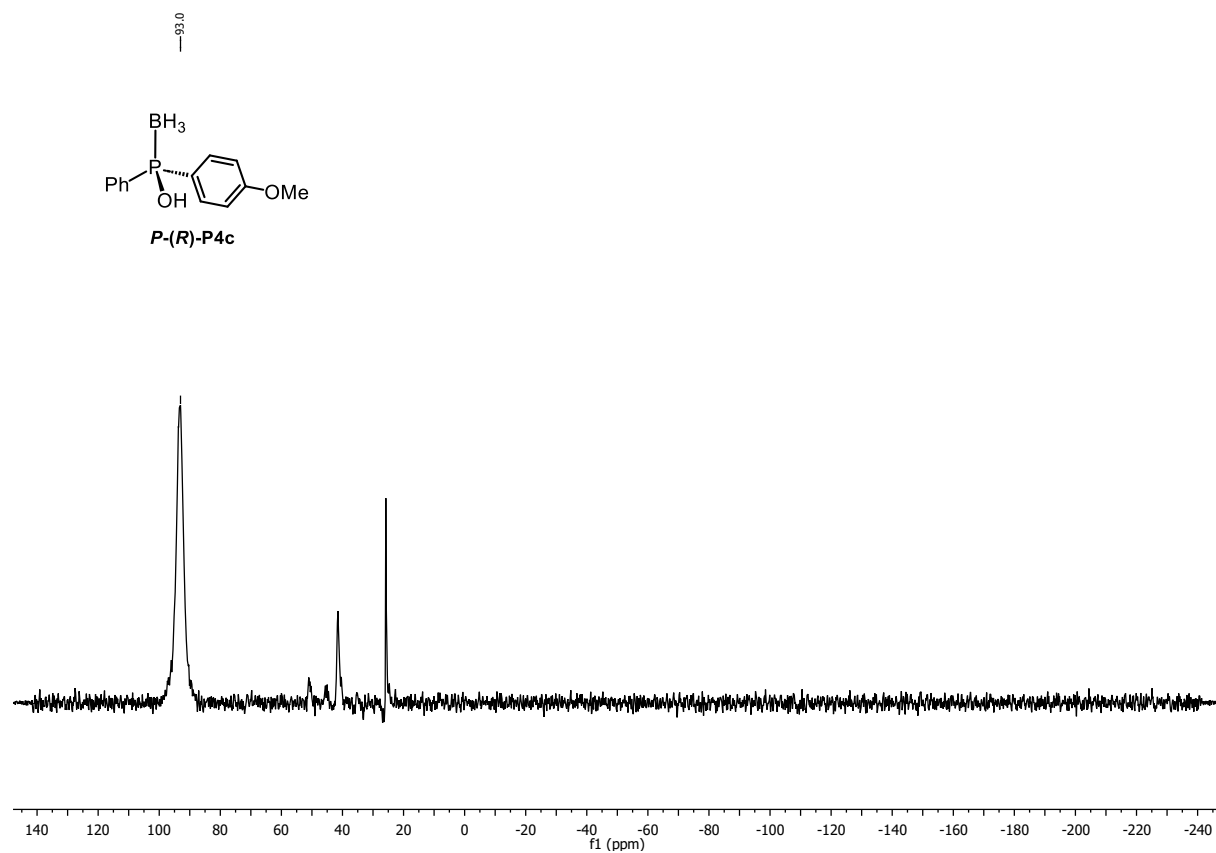
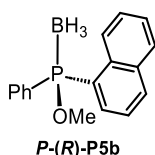


Figure 31. ^{31}P NMR spectrum (162 MHz, CDCl_3) of *P*-(*R*)-**P4c**.

General procedure GP-P2: Synthesis of P5.

A literature procedure was used.³³

To a stirred solution of **P4** (1.0 equiv.) in methanol (1 mL), (trimethylsilyl)diazomethane (0.6 M in hexane, 2.0 equiv.) was added over ten minutes at room temperature. The reaction mixture was concentrated under reduced pressure, and the crude product was purified by flash column chromatography, affording **P5**.

***P*-(*R*)-P5b.**

C₁₈H₂₁BOP (295.15 g/mol)

According to **GP-P2**, ***P*-(*R*)-P5b** was synthesized from ***P*-(*S*)-P4b** (975 mg, 3.30 mmol, 1 equiv.) and (trimethylsilyl)diazomethane (0.6 M in hexane, 11.0 ml, 6.60 mmol, 2.0 equiv.). Purification by flash column chromatography (*n*-hexane/EtOAc, gradient 100:0 to 70:30 over 10 CV) afforded ***P*-(*R*)-P5b** (250 mg, 893 μmol, 24%) as viscous colorless oil.

¹H-NMR (400 MHz, CDCl₃, δ): 8.27 (dd, *J* = 15.1, 6.7 Hz, 1H), 8.10 (m, 2H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.69 – 7.57 (m, 3H), 7.51 – 7.38 (m, 5H), 3.78 (d, *J* = 12.2 Hz, 3H).

¹¹B NMR (128 MHz, CDCl₃, δ): -38.7 (d, *J* = 70.0 Hz).

¹³C NMR (101 MHz, CDCl₃, δ): 135.4 (d, *J* = 17.2 Hz), 133.9, 133.9, 133.9, 131.75, 131.1, 131.0, 129.2, 128.8, 128.7, 127.3, 126.53, 126.49, 124.8 (d, *J* = 13.9 Hz).

³¹P-NMR (162 MHz, CDCl₃, δ): 111.0 (q, *J* = 70.0 Hz).

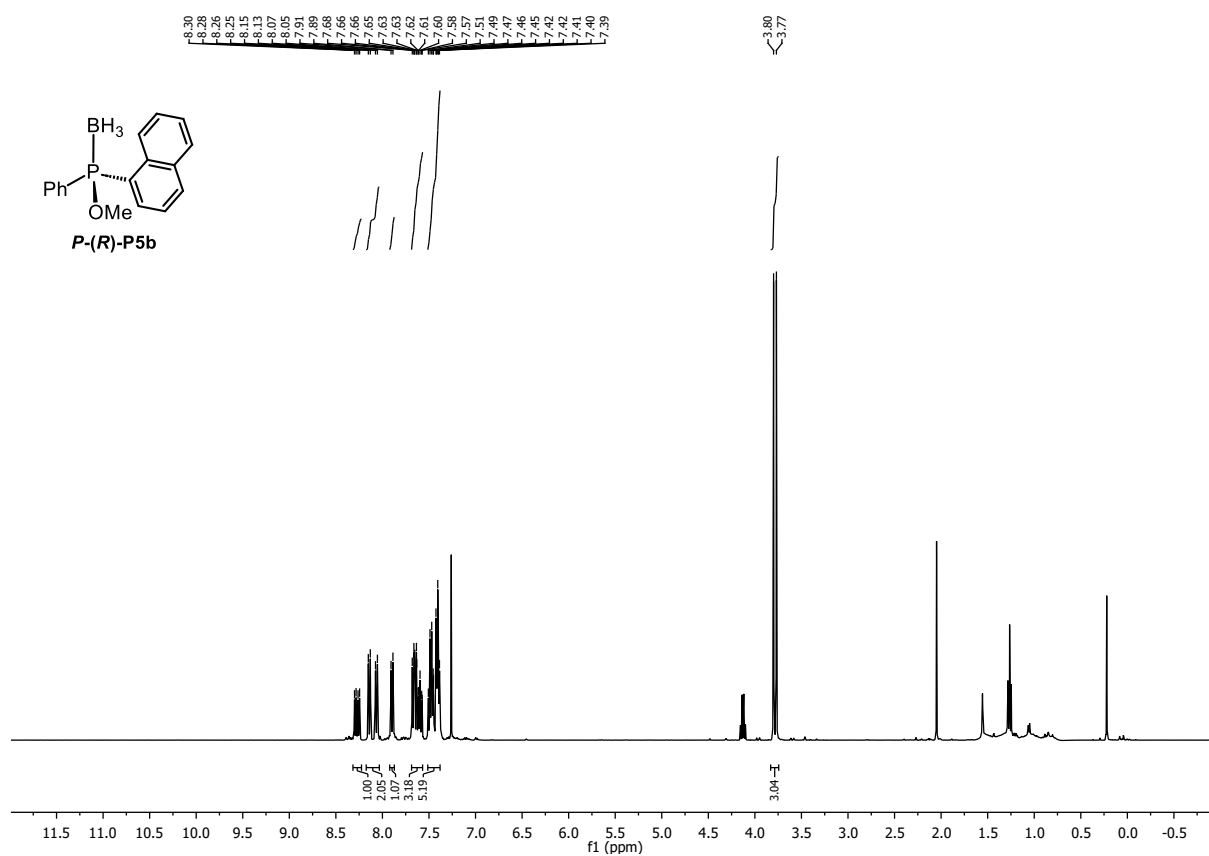


Figure 32. ^1H NMR spectrum (400 MHz, CDCl_3) of *P*-(*R*)-**P5b**.

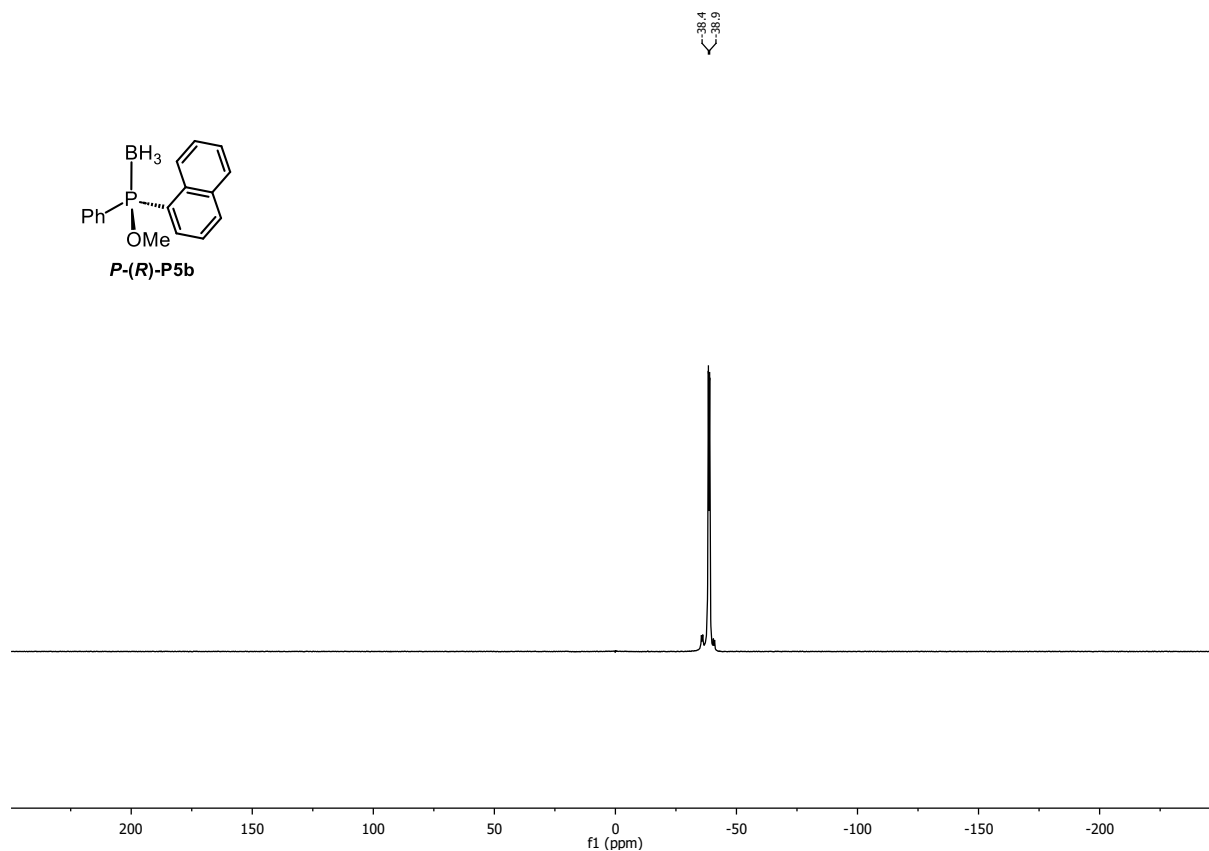


Figure 33. ^{11}B NMR spectrum (128 MHz, CDCl_3) of *P*-(*R*)-**P5b**.

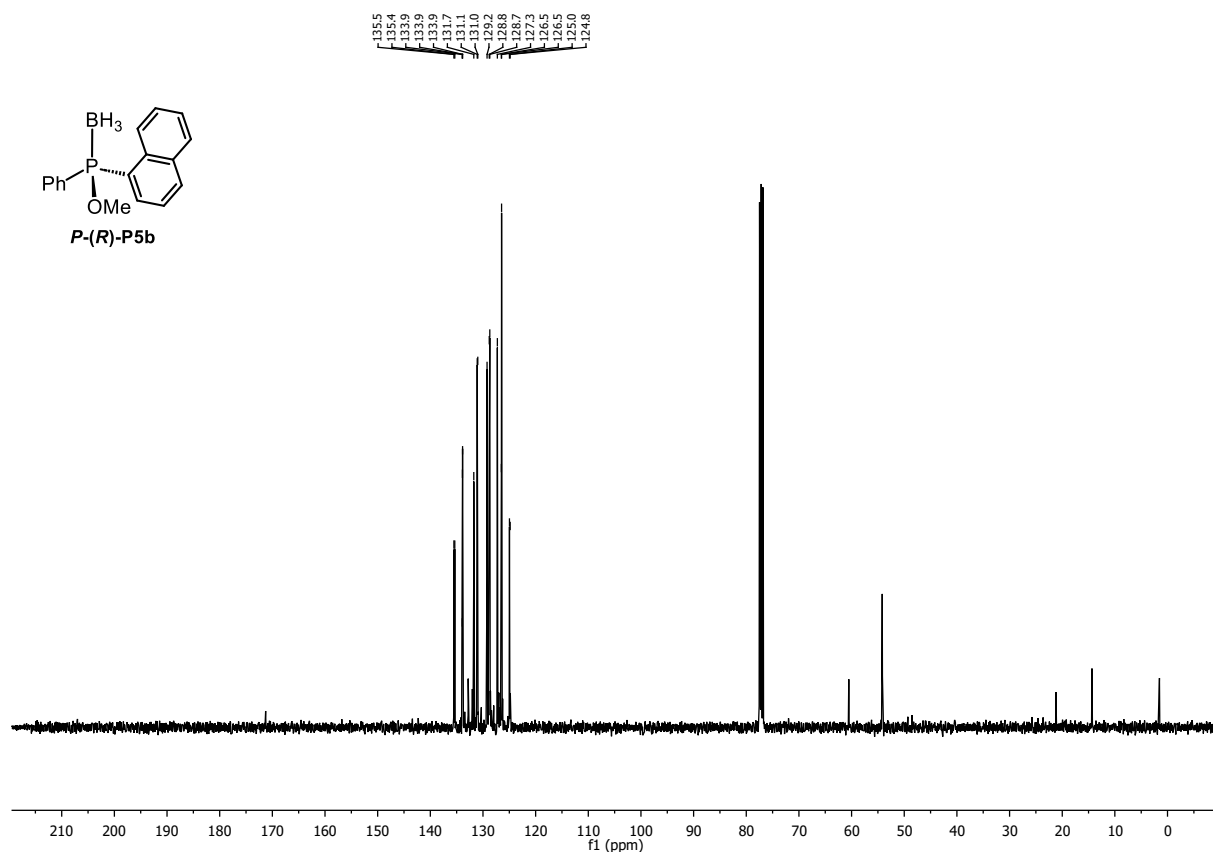


Figure 34. ¹³C NMR spectrum (400 MHz, CDCl₃) of *P*-(*R*)-**P5b**.

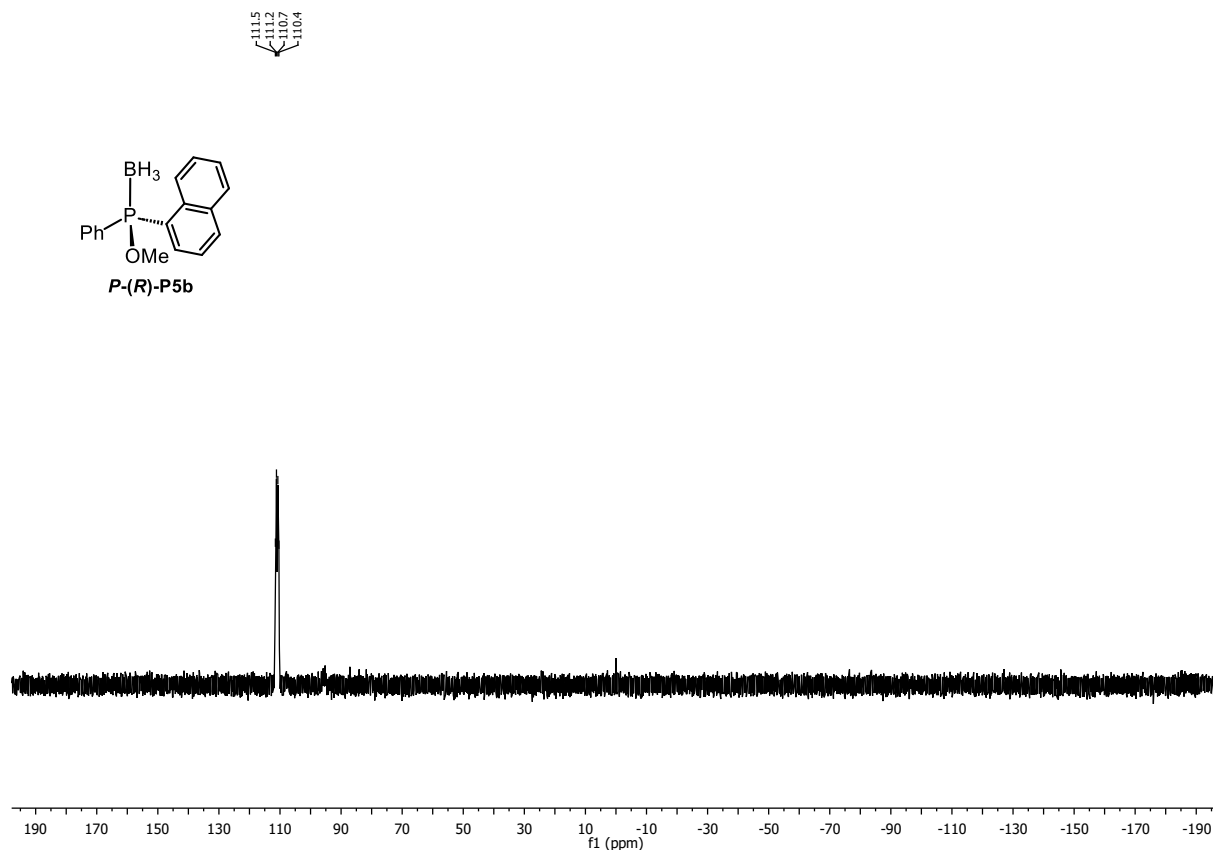
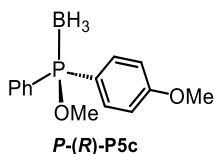


Figure 35. ³¹P NMR spectrum (400 MHz, CDCl₃) of *P*-(*R*)-**P5b**.

***P*-(*R*)-P5c.**

C₁₅H₂₁BO₂P (295.15 g/mol)

According to **GP-P2**, ***P*-(*R*)-P5c** was synthesized from ***P*-(*S*)-P4c** (613 mg, 2.49 mmol, 1.0 equiv.) and (trimethylsilyl)diazomethane (1.8 M in hexane, 11.0 ml, 6.60 mmol, 2.0 equiv.). Purification by flash column chromatography (*n*-hexane/EtOAc, gradient 100:0 to 70:30 over 10 CV) afforded ***P*-(*R*)-P5c** (248 mg, 954 μmol, 38%) as colorless oil.

¹H-NMR (400 MHz, CDCl₃, δ): 7.77 – 7.64 (m, 4H), 7.54 – 7.41 (m, 3H), 7.01 – 6.94 (m, 2H), 3.84 (s, 3H), 3.71 (d, *J* = 12.1 Hz, 3H).

¹¹B NMR (128 MHz, CDCl₃, δ): -40.7 (d, *J* = 71.3 Hz).

¹³C NMR (101 MHz, CDCl₃, δ): 162.8, 133.6 (d, *J* = 12.6 Hz), 131.8, 131.2 (d, *J* = 11.3 Hz), 128.7 (d, *J* = 10.6 Hz), 122.8, 122.2, 114.4 (d, *J* = 11.5 Hz), 55.5, 54.0.

³¹P-NMR (162 MHz, CDCl₃, δ): 106.5 (q, *J* = 71.3 Hz).

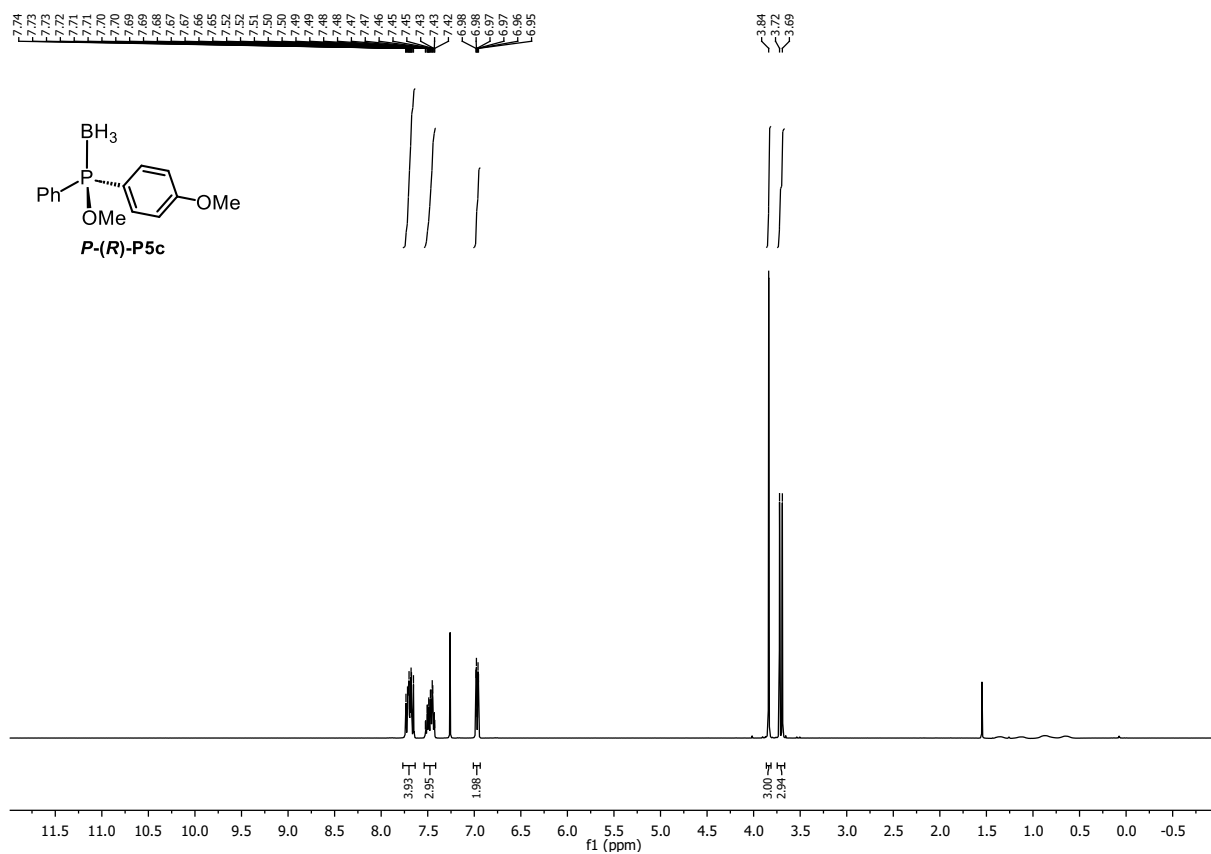


Figure 36. ¹H NMR spectrum (400 MHz, CDCl₃) of *P-(R)-P5c*.

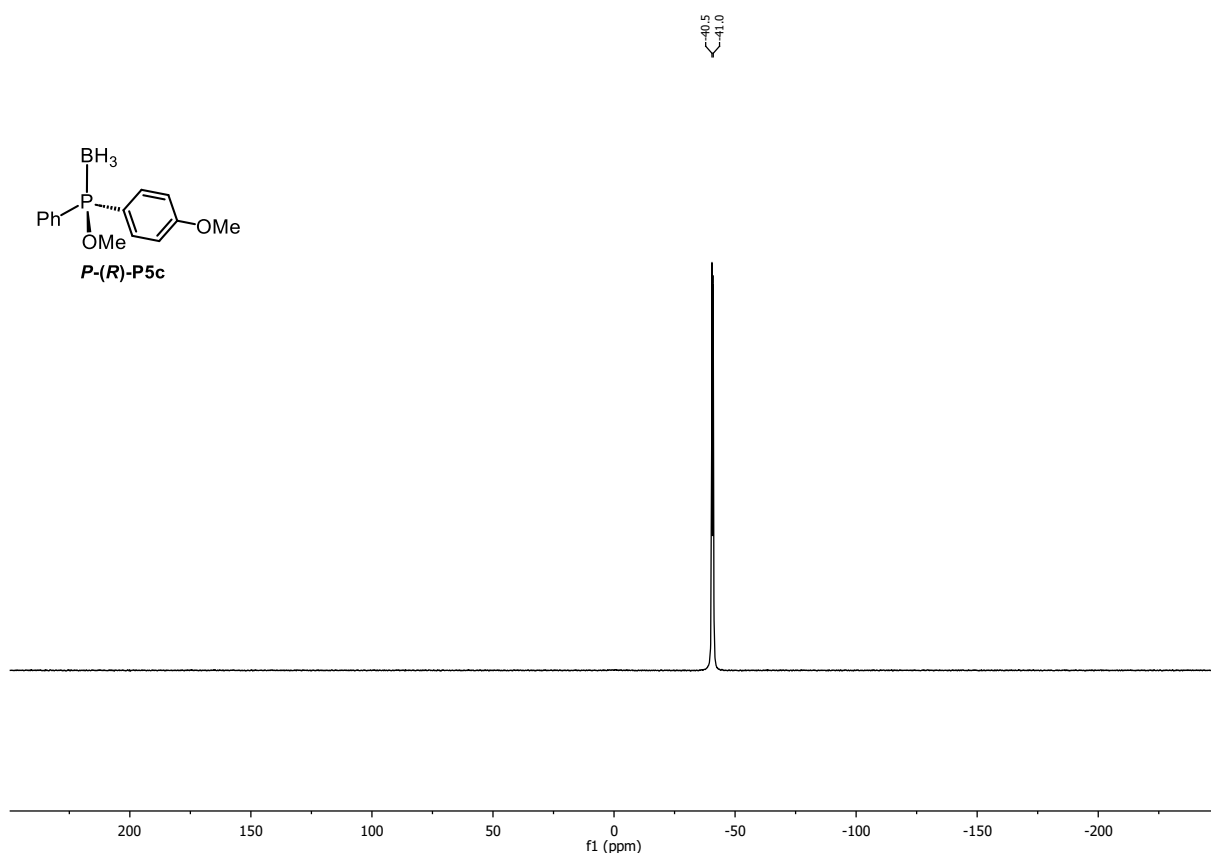


Figure 37. ¹¹B NMR spectrum (128 MHz, CDCl₃) of *P-(R)-P5c*.

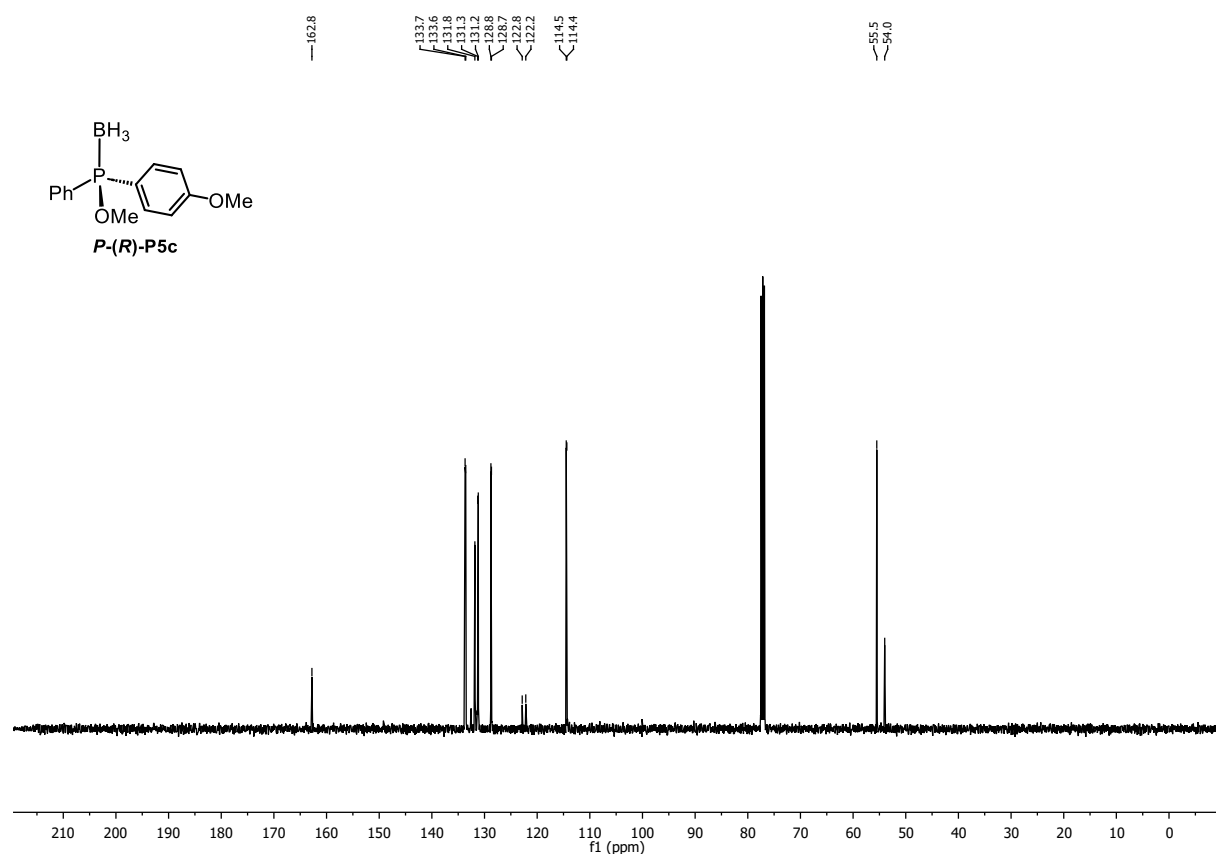


Figure 38. ¹³C NMR spectrum (101 MHz, CDCl₃) of *P*-(*R*)-**P5c**.

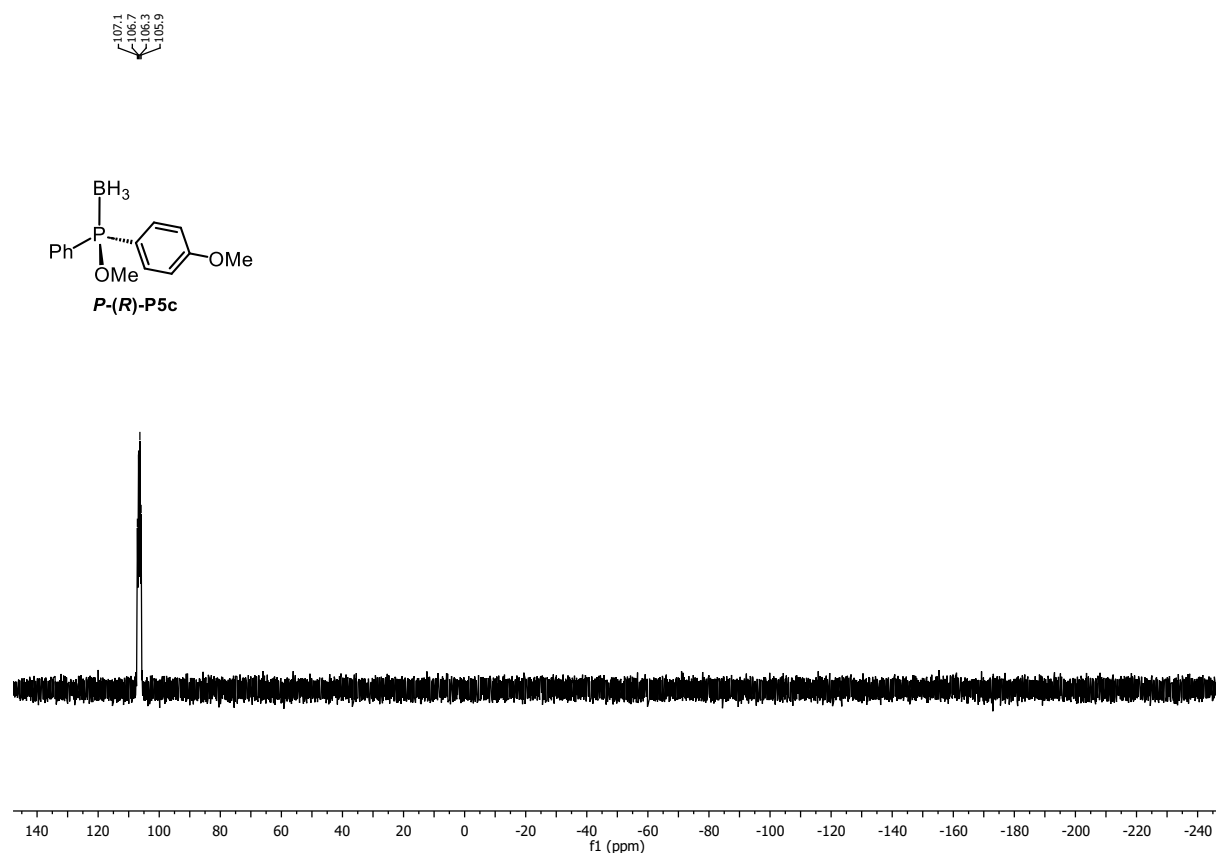
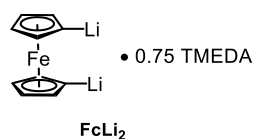


Figure 39. ³¹P NMR spectrum (162 MHz, CDCl₃) of *P*-(*R*)-**P5c**.

1,1'-Dilithioferrocene.

C_{14.5}H₂₀N_{1.5}Fe (285.08 g/mol)

A literature procedure was followed.³⁶

In a 100 ml Schlenk round-bottom flask, ferrocene (1.00 g, 5.38 mmol, 1 equiv.) and *N,N,N',N'*-tetramethylethylenediamine (2.02 ml, 13.4 mmol, 2.5 equiv.) were suspended in *n*-hexane (25 ml). Under stirring, *n*-BuLi (2.5 M in *n*-hexane, 5.38 ml, 13.4 mmol, 2.5 equiv.) was added and the mixture was stirred for 20 h. The resulting suspension was filtered under argon and the residue washed with *n*-hexane (2 × 10 ml). **FcLi₂** (1.17 g, 4.10 mmol, 76%) was isolated as orange solid containing ~75 mol% TMEDA per dilitihoferrocene.³⁷

¹H-NMR (400 MHz, THF-d₈, δ): 4.00 (s, 4H), 3.68 (s, 4H), 2.30 (s, 3H), 2.14 (s, 10H).

⁷Li NMR (156 MHz, THF-d₈, δ): 2.8.

¹³C NMR (101 MHz, THF-d₈, δ): 78.7, 69.1, 58.7, 46.0.

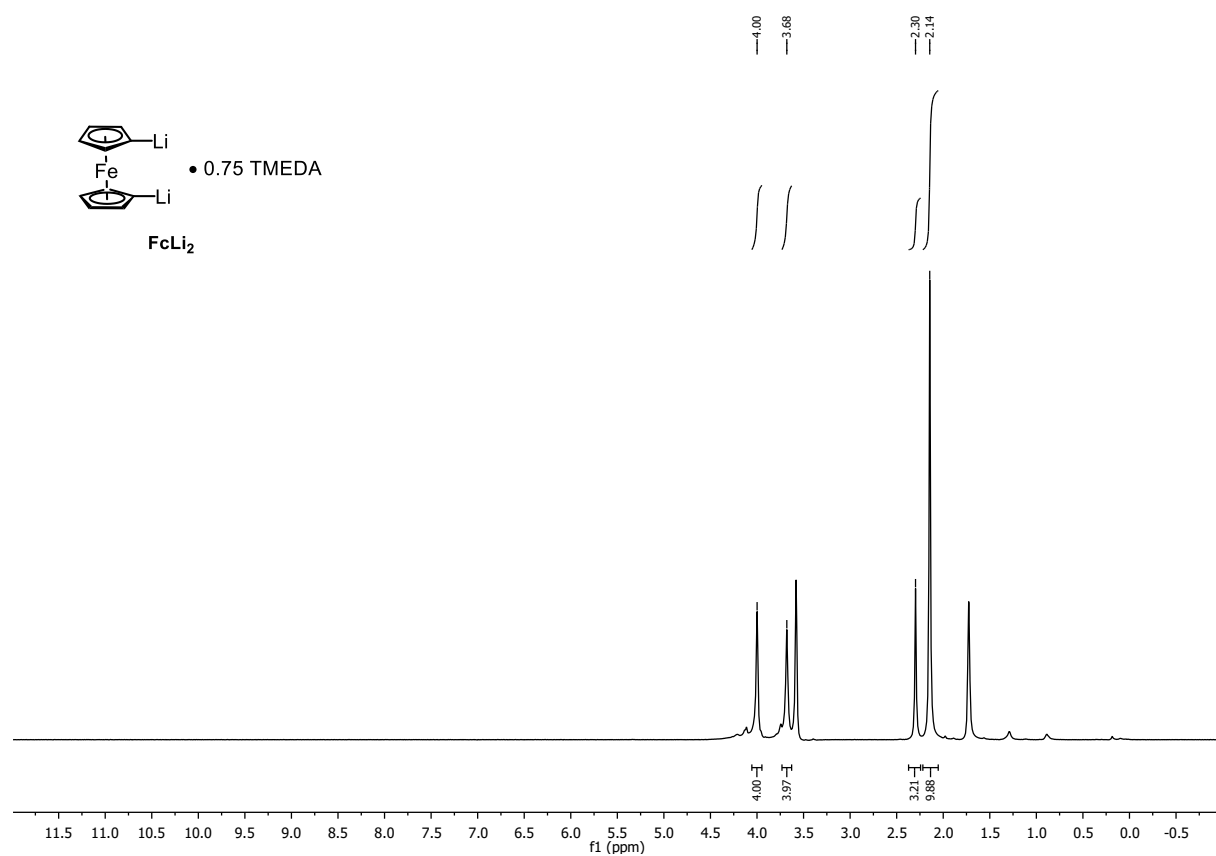


Figure 40. ^1H NMR spectrum (400 MHz, THF-d_8) of FcLi_2 .

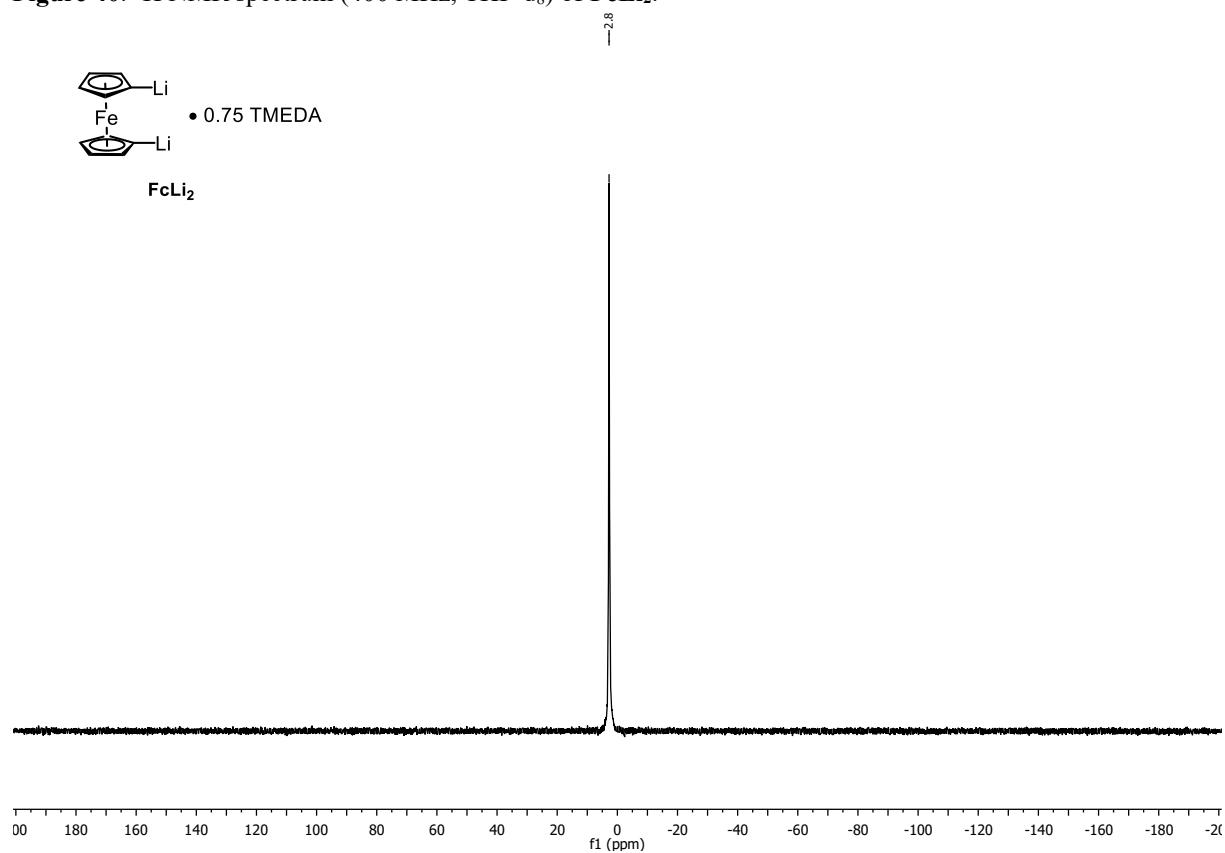


Figure 41. ^7Li NMR spectrum (156 MHz, THF-d_8) of FcLi_2 .

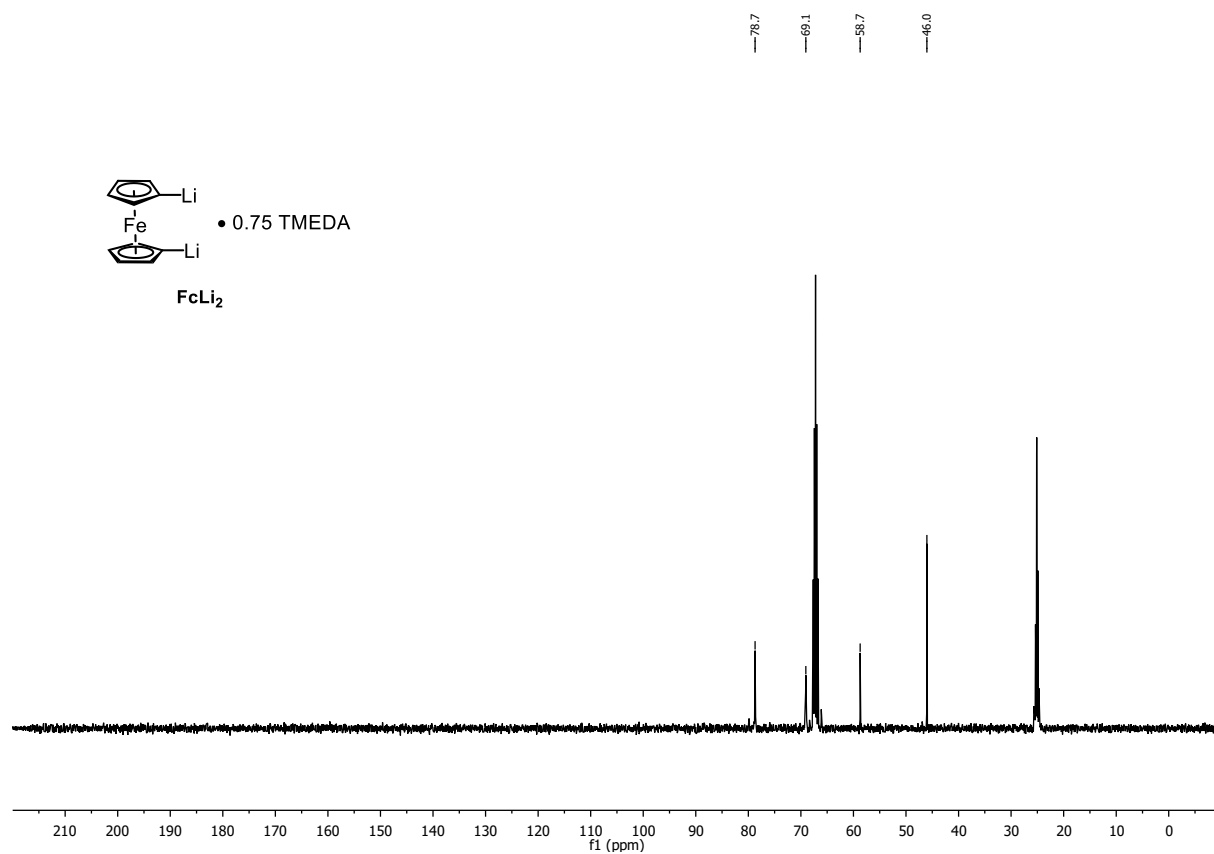
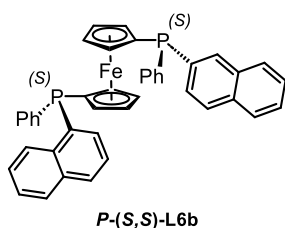


Figure 42. ^{13}C NMR spectrum (101 MHz, THF-d_8) of FcLi_2 .

General Procedure GP-P3 for the synthesis of L6.

A modified literature procedure was followed.³⁸

In a Schlenk tube, 1,4-diazabicyclo[2.2.2]octane (4.4 equiv.) was dissolved in *n*-hexane (5 ml) and **P5** (2.2 equiv.) was added. The mixture was stirred at 40 °C for 16 h. After cooling to rt, the resulting suspension was filtered under argon and the filtrate was added at -40 °C to a solution of **FcLi2** (1 equiv.) in THF (3 ml). After stirring the mixture at -40 °C for 30 min, the cooling was removed and the reaction was stirred for another 2 h, monitoring conversion *via* ³¹P NMR spectroscopy. The mixture was quenched with water (5 ml), the layers separated and the aqueous layer was extracted with EtOAc (1 × 10 ml). The combined organic layers were washed with brine (1 × 5 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification with flash column chromatography afforded **L6**.

***P*-(*S,S*)-L6b.**

C₄₂H₃₂FeP₂ (654.51 g/mol)

According to **GP-P3**, ***P*-(*S,S*)-L6b** was synthesized from ***P*-(*R*)-P5b** (250 mg, 0.892 mmol, 2.2 equiv.) and **FcLi2** (127 mg, 0.406 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane/EtOAc, gradient 100:0 to 80:20 over 10 CV) afforded ***P*-(*S,S*)-L6b** (166 mg, 254 μmol, 63%, 88% de, 94% ee by ³¹P NMR) as orange solid.

¹H-NMR (400 MHz, CDCl₃, δ): 8.35 (dd, *J* = 7.8, 4.0 Hz, 2H), 7.82 – 7.76 (m, 4H), 7.44 – 7.32 (m, 10H), 7.28 – 7.22 (m, 6H, *residual solvent peak under signal*), 7.17 – 7.11 (m, 2H), 4.40 – 4.22 (m, 6H), 3.70 (s, 2H).

³¹P-NMR (162 MHz, CDCl₃, δ): -26.6.

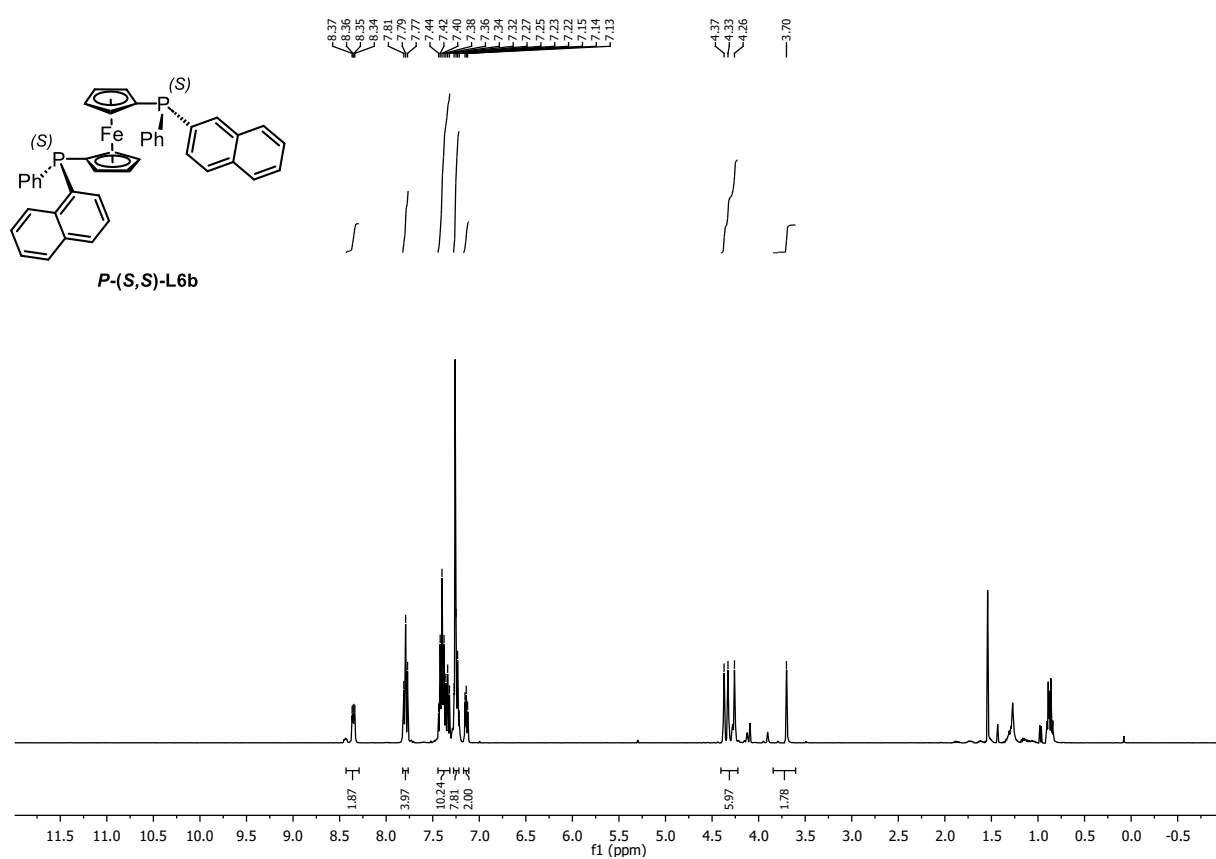


Figure 43. ^1H NMR spectrum (400 MHz, CDCl_3) of *P*-(*S,S*)-L6b.

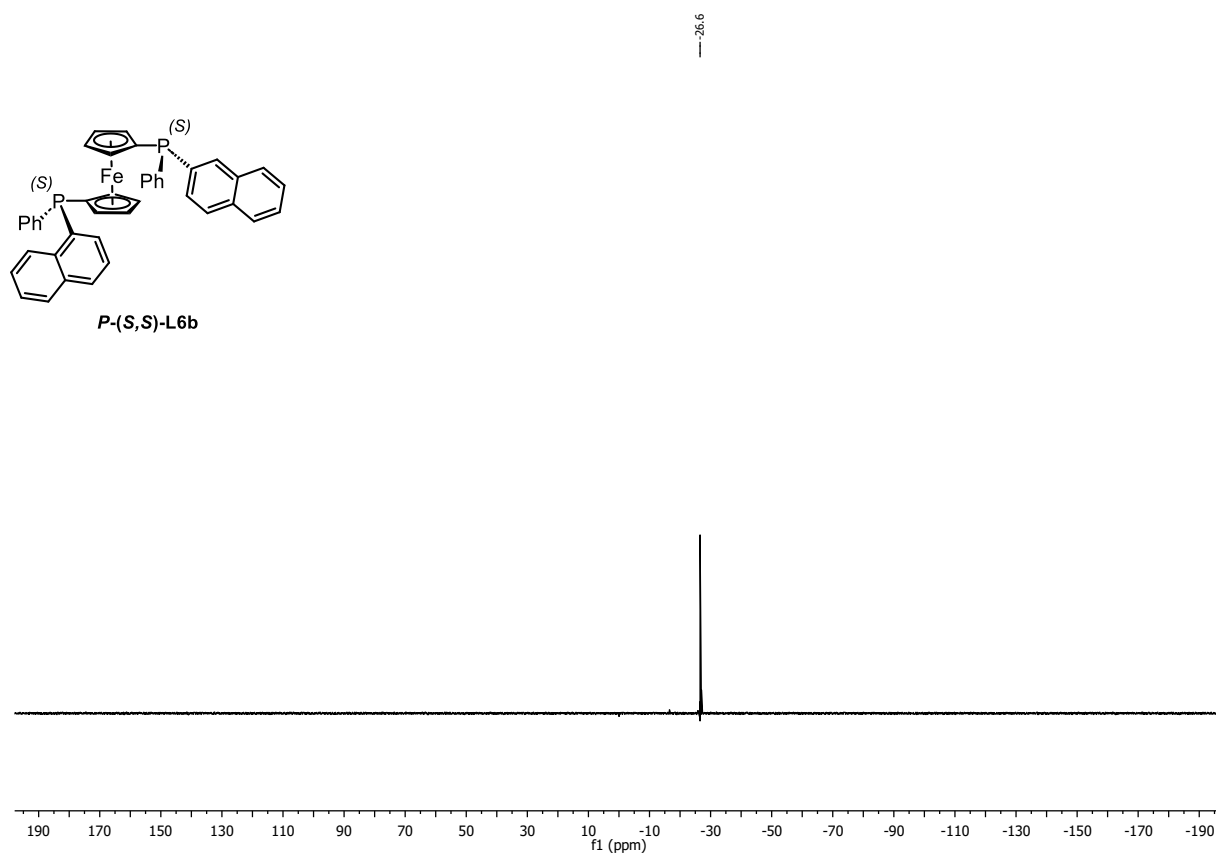
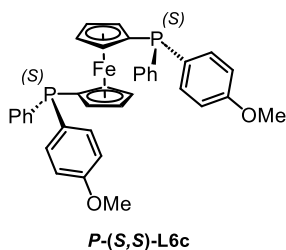


Figure 44. ^{31}P NMR spectrum (162 MHz, CDCl_3) of *P*-(*S,S*)-L6b.

***P*-(*S,S*)-L6c.**

C₃₆H₃₂FeO₂P₂ (614.44 g/mol)

According to **GP-P3**, ***P*-(*S,S*)-L6c** was synthesized from ***P*-(*R*)-P5c** (240 mg, 0.923 mmol, 2.1 equiv.) and **FeLi₂** (138 mg, 0.439 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane/EtOAc, gradient 100:0 to 70:30 over 10 CV) afforded ***P*-(*S,S*)-L6c** (168 mg, 273 μmol, 62%, 99% de and ee by ³¹P NMR) as orange solid.

¹H-NMR (400 MHz, CDCl₃, δ): 7.33 – 7.22 (m, 14H, *residual solvent peak under signal*), 6.85 (d, *J* = 8.2 Hz, 4H), 4.32 – 4.21 (m, 4H), 4.13 – 3.86 (m, 4H), 3.83 – 3.79 (m, 6H).

³¹P-NMR (162 MHz, CDCl₃, δ): -19.0.

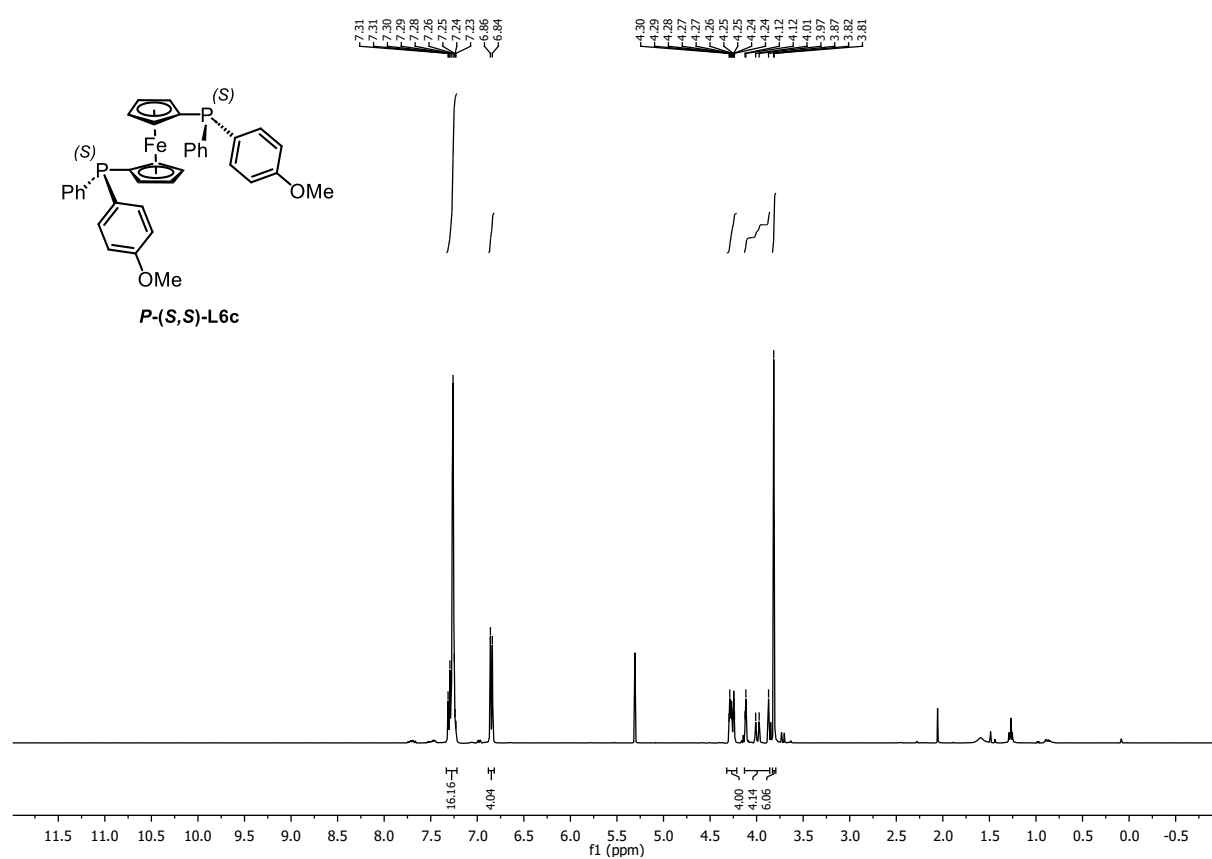


Figure 45. ^1H NMR spectrum (400 MHz, CDCl_3) of *P*-(*S,S*)-L6c.

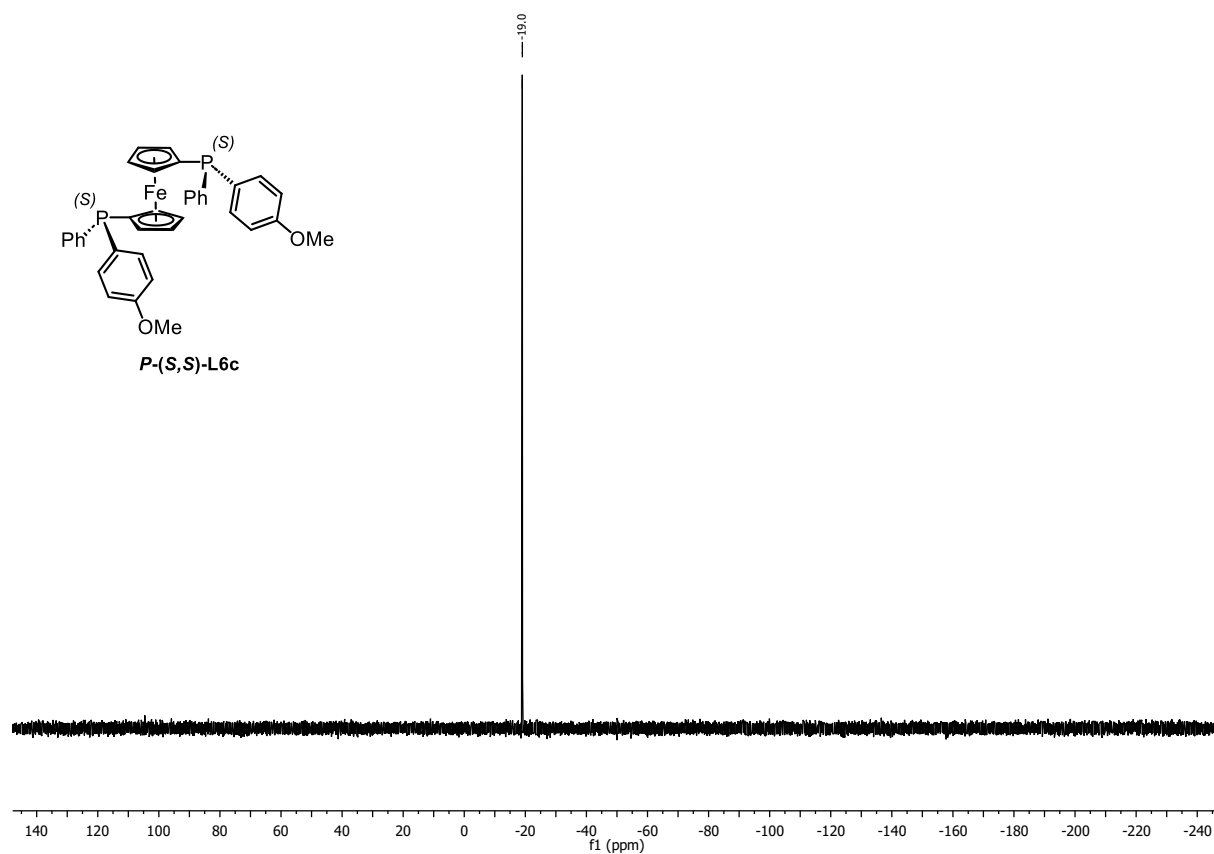


Figure 46. ^{31}P NMR spectrum (162 MHz, CDCl_3) of *P*-(*S,S*)-L6c.

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3. Influence of the Counterion on the Activation of Nickel(σ -Aryl) Precatalysts

3.1. Summary of published results

This chapter is based on the following publication:

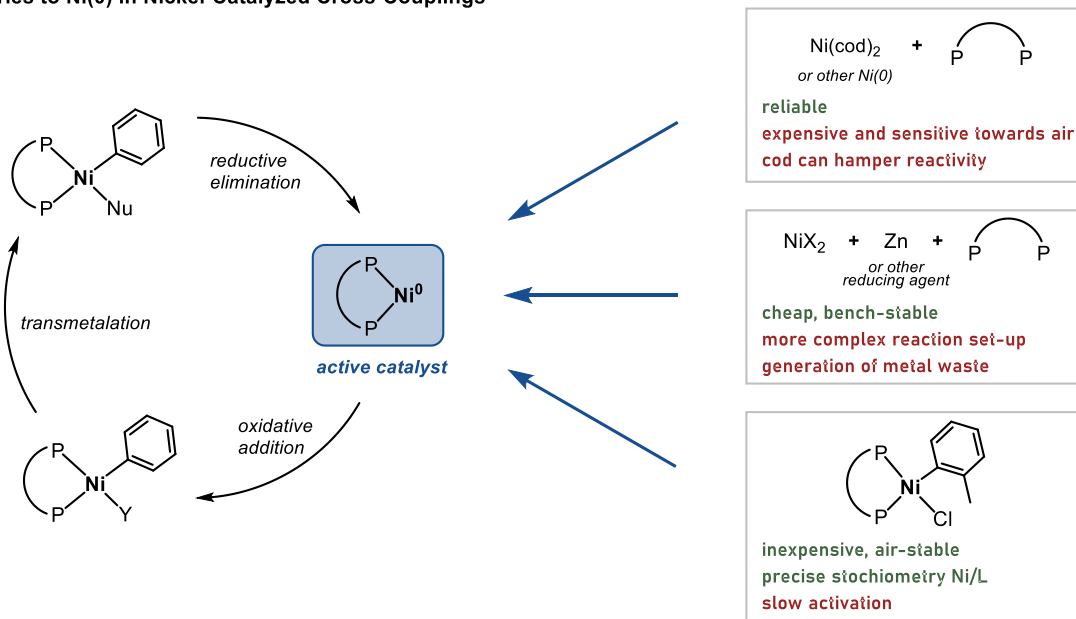
Ivo H. Lindenmaier, Anna S. Harzer, Markus Ströbele and Ivana Fleischer, *Organometallics* **2025**, 44, 4, 595–605. DOI 10.1021/acs.organomet.4c00498.

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Motivation and Synthetic Approaches for Nickel Precatalysts

Previous work had employed bench-stable nickel(σ -aryl) precatalysts for C–S cross-coupling, eliminating the need for a glovebox while enabling easier reaction set-up and ideal ligand-to-nickel ratios (Figure 47, A).¹⁻² While the overall reaction displayed high efficiency in terms of yield, analysis of the kinetic profile revealed that long initiation period of up to 15 min prolonged the total reaction time and possibly reduced effectiveness for more challenging substrates. Additionally, the reason for long initiation periods remained unclear, since the reaction rate was very high as soon as the catalyst was activated. In contrast to established precatalysts of the general formula (PR₃)₂Ni(*o*-tolyl)Cl,³ another species was isolated in a separate project as an on-cycle intermediate [(DPEphos)Ni(*o*-PhPh)]OTf (**Ni4**, see chapter 2). X-Ray diffraction revealed the cationic structure of **Ni4** and the successful employment as active catalyst led to the assumption that the triflate as counterion enabled more effective activation in comparison to the chloride. While the effect of functional groups in *ortho*-position of the σ -aryl moiety has been investigated by the Hazari and co-workers (Figure 47, B),⁴ detailed analysis of the counterion-effect on (pre)catalysts is scarce in the literature⁵ and anion effects are usually neglected even though their impact is commonly acknowledged in other fields of chemistry.⁶ Thus, identifying anion effects in precatalyst activation would not only extend the understanding of catalyst activation, but also enable optimization of the precatalyst structure resulting in more efficient catalytic systems (Figure 47, B). It is well-known that the choice of precatalyst has significant influence on the overall reaction and even small changes can lead to variation of reaction efficiency that is often hard to explain.⁷⁻⁸

A) Entries to Ni(0) in Nickel-Catalyzed Cross-Couplings



B) Activation of the Nickel Precatalyst

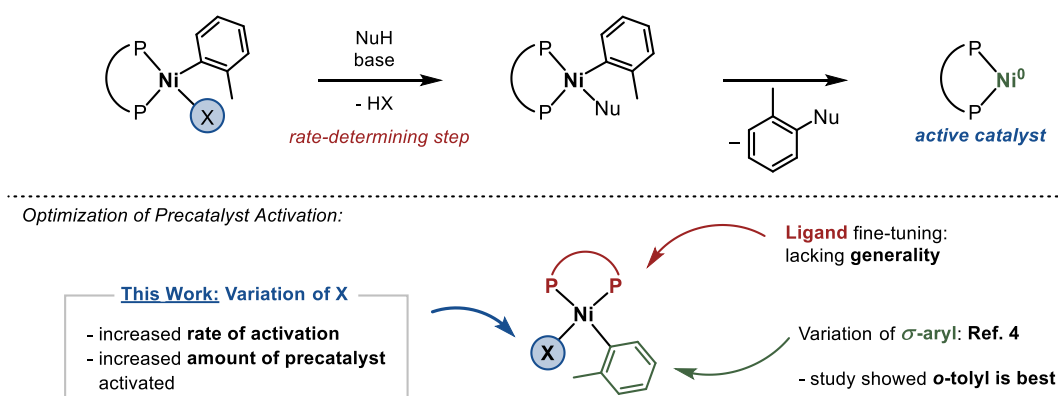
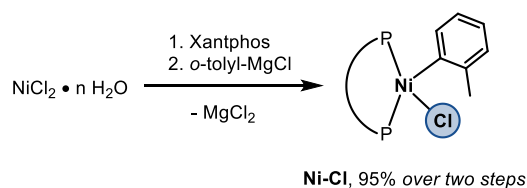


Figure 47. Applications and activation of nickel(σ -aryl) precatalysts.

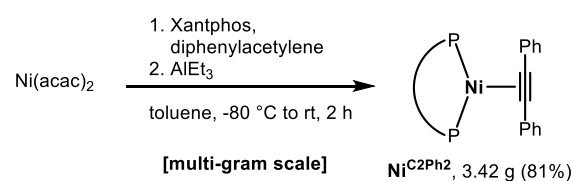
For a deeper investigation, a small library of nickel precatalysts of the general formula (Xantphos)nickel(*o*-tolyl)X ($\text{X} = \text{Cl}, \text{Br}, \text{I}, \text{OAc}, \text{OTf}, \text{BAr}_\text{F}$) was synthesized and subsequently tested in catalysis. While Jamison's established protocol enables efficient synthesis of the parent Ni-Cl complex (Scheme 13, A),³ it is not readily applicable to complexes bearing anions that are inaccessible as Ni(II) salts or incompatible with Grignard reagents, such as ester-derived or weakly coordinating counterions. Moreover, the use of inexpensive Ni(II) precursors (e.g., Ni(acac)_2) was targeted to enhance the economic viability of potential precatalysts. Beyond Jamison's method, synthetic approaches to such complexes remain limited, however two general strategies can be considered: (a) oxidative addition of aryl (pseudo)halides to Ni(0) species,⁹ and (b) salt metathesis of suitable Ni(II) complexes.¹⁰

3. Influence of the Counterion on the Activation of Nickel(σ -Aryl) Precatalysts

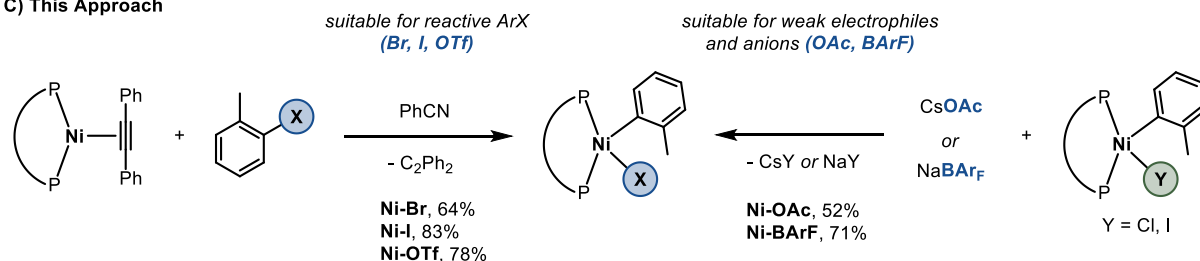
A) Jamison's Approach



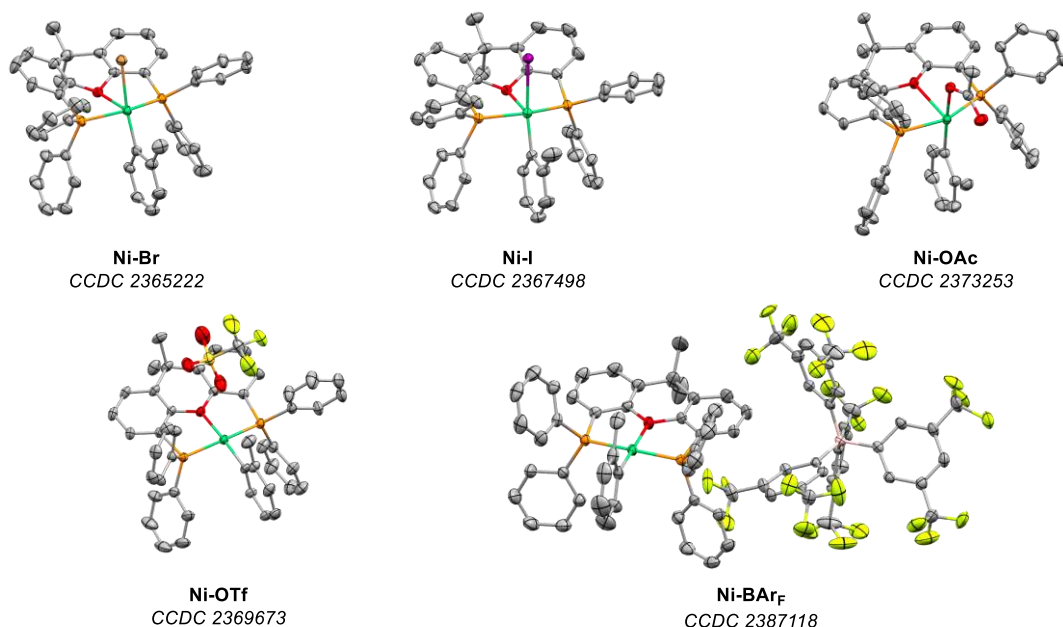
B) Synthetic Route towards (Xantphos)Ni(0)



C) This Approach



D) Crystal structures of Ni-X complexes^a



Entry	Complex	d(Ni-X) [Å]	d(Ni-O) [Å]	d(Ni-C) [Å]	α (P-Ni-P) [°]	β (C-Ni-X) [°]
1 ^b	Ni-Cl	2.2691(2)	2.5408(6)	1.898(1)	156.01(1)	169.26(4)
2	Ni-Br	2.4202(2)	2.5649(5)	1.902(1)	152.44(1)	165.00(3)
3	Ni-I	2.6026(4)	2.5705(9)	1.907(2)	152.20(2)	164.16(5)
4	Ni-OAc	1.9347(5)	2.5003(8)	1.8988(7)	153.79(1)	175.03(4)
5	Ni-OTf	2.975(1)	2.0318(7)	1.889(3)	166.45(1)	117.65(8)
6	Ni-BARf	N/A	1.9944(9)	1.885(1)	172.73(2)	N/A

Scheme 13. Synthesis and structure of (Xantphos)nickel(*o*-tolyl)X (X = Cl, Br, I, OAc, OTf, BARf) precatalysts. P-P indicate the Xantphos ligand. ^a Hydrogen atoms, as well as disordered atoms are omitted for clarity and thermal ellipsoids are shown at 50% probability level. ^b Values obtained from published data.³

Although Ni(cod)₂ is commonly employed as a Ni(0) precursor in oxidative addition chemistry,¹¹⁻¹³ it is unsuitable in combination with Xantphos, as a 1:1 mixture forms

predominantly unreactive (Xantphos)₂Ni rather than the desired (Xantphos)Ni(cod) complex.¹⁴ Consequently, alternative Ni(0) sources were explored, leading to the identification of (Xantphos)Ni(diphenylacetylene) (**Ni**^{C₂Ph₂}) as a more reactive precursor.¹⁵ Following validation of its reactivity toward *o*-tolyl iodide, a practical synthesis of this complex was developed *via in situ* reduction of Ni(acac)₂ with triethylaluminum in the presence of Xantphos and diphenylacetylene. The resulting complex, stabilized by coordination of diphenylacetylene, precipitated from toluene and was obtained in high yield (81%) on multigram scale (Scheme 13, B). An analogous procedure also enabled access to (dppf)Ni(cod), which was subsequently employed for the synthesis of ^{dppf}**Ni-OTf** (*vide infra*).

With a suitable Ni(0) precursor in hand, oxidative addition to electrophiles of the type *o*-tolyl-X furnished the corresponding (Xantphos)Ni(*o*-tolyl)X complexes (Scheme 13, C). Addition of benzonitrile was required to generate the more reactive (Xantphos)Ni(η^2 -NCPh) species *in situ*, thereby facilitating oxidative addition.¹⁶ Good to high yields were obtained for **Ni-Br** (64%), **Ni-I** (83%), and **Ni-OTf** (78%), whereas less reactive pseudohalides showed only low conversion. Alternatively, these complexes could be accessed *via* salt metathesis. For example, treatment of **Ni-I** with cesium acetate afforded **Ni-OAc** in moderate yield (52%). Introduction of weakly coordinating anion [BAr_F]⁻ was achieved by reaction of **Ni-Cl** with NaBAr_F, yielding **Ni-BAr_F** (71%; BAr_F = [B(3,5-(CF₃)₂Ph)₄]⁻). All synthesized precatalysts were characterized by single-crystal X-ray diffraction, confirming their molecular structures (Scheme 13, D). As expected, the **Ni-X** bond length increases Cl < Br < I (entries 1–3). Concomitantly, distortion from an ideal square-pyramidal geometry becomes more pronounced down the group, as reflected by decreasing α and β angles.

The crystal structure of **Ni-OAc** (entry 4) displays the shortest Ni-X bond among the isolated complexes (*d* = 1.9347(5) Å), significantly shorter than the Ni-O bond in Ni(OAc)₂(H₂O)₄ (2.0579 Å).¹⁷ Notably, the acetate ligand adopts a monodentate coordination mode, and the complex retains a geometry analogous to the halide derivatives, albeit with reduced distortion of the xanthene backbone.

In the case of **Ni-OTf** (entry 5), the triflate anion is not directly coordinated to the nickel center, resulting in a cationic complex. Nevertheless, the Ni-OTf distance (< 3 Å) indicates residual interaction in the solid state, although its relevance in solution remains unclear. The complex adopts a square-planar geometry, which is likely preserved in solution, as suggested by its diamagnetism and the pronounced upfield shift of the tolyl-CH₃ signal in the ¹H NMR

spectrum ($\delta = 1.38$ ppm) relative to **Ni-Cl** ($\delta = 3.40$ ppm). This geometry is accompanied by stronger coordination of the Xantphos oxygen donor, reflected in a shorter Ni–O bond compared to **Ni-Cl**. Furthermore, the xanthene backbone appears planar, indicative of enhanced conjugation within the ligand framework.

These structural differences are further accentuated in the **Ni-BArF** complex (entry 6), where full dissociation of the counterion leads to an even shorter Ni–O bond and almost ideal *trans* configuration of the phosphorous atoms ($172.73(2)^\circ$).

Activation and Catalytic Performance of Precatalysts

The catalytic activity of the synthesized complexes was subsequently evaluated in C–S cross-coupling. This transformation was selected as a model system due to the convenient monitoring of both catalyst activation and reaction progress by GC-FID within a practical timeframe. As a benchmark reaction, phenyl chloride (**1A-Cl**) was coupled with *tert*-1-adamantanethiol (**2b**) using KOAc as base and 5 mol% of the respective precatalyst (Figure 48). Precatalyst activation is proposed to proceed *via* ligand exchange of the counterion X with acetate, followed by thiol coordination and base-assisted deprotonation.¹ Reductive elimination then generates the active (Xantphos)Ni(0) species, which enters the catalytic cycle through oxidative addition of the electrophile, followed by the same sequence of steps.

For the **Ni-Cl** complex, an initiation phase of approximately 15 min prior to formation of significant amounts of active catalyst has previously been established. In comparison, **Ni-Br** exhibited a substantially shorter activation period of approximately 5 min, while maintaining a similar reaction rate thereafter, consistent with formation of the same active species. An even more rapid activation was observed for **Ni-OTf**, with detectable product formation occurring within 2 min. This enhanced reactivity is consistent with the cationic nature of the precatalyst, as the triflate anion is not coordinated to the nickel center, thereby facilitating ligand exchange and substrate coordination.

In contrast, the **Ni-I** complex displayed markedly reduced activity and a distinct reaction profile. Similar behavior has been reported previously for aryl iodides and has been attributed to the formation of catalytically inactive Ni(I) species. Consistent with this interpretation, addition of KI (5 mol%) to a reaction catalyzed by **Ni-Cl** significantly suppressed product formation.

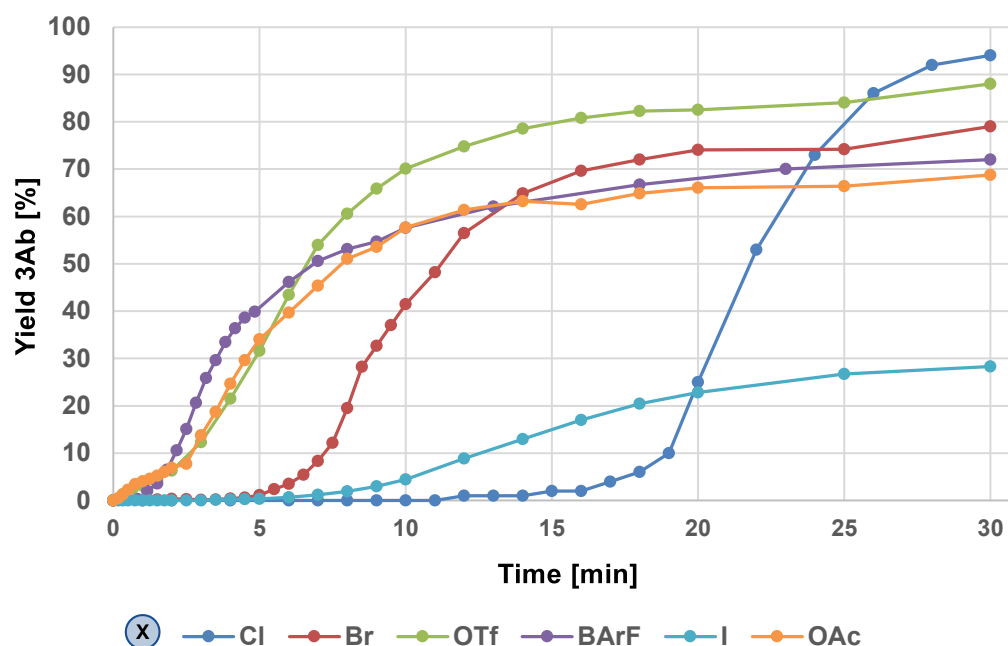
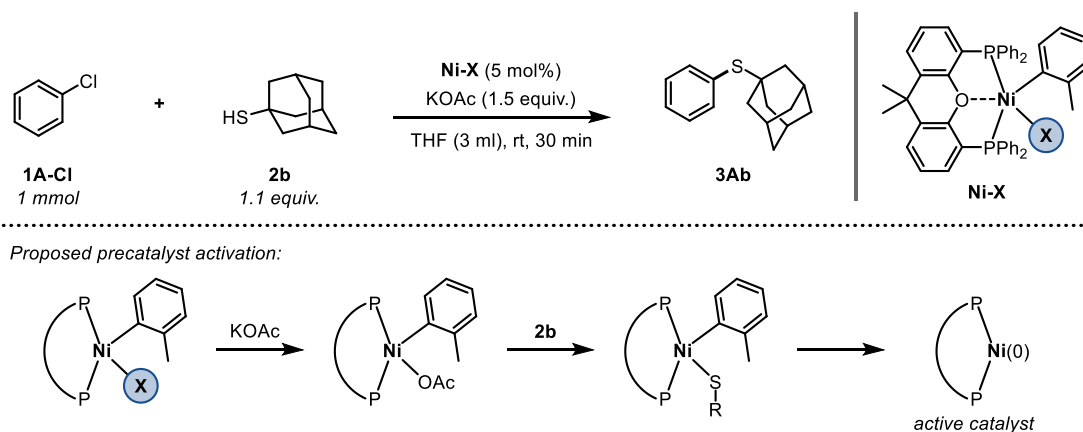


Figure 48. Reaction profiles of precatalysts **Ni-X** in C-S cross-coupling. Reaction conditions: Phenyl chloride (**1A**) (1.0 mmol, 1.0 equiv), 1-adamantanethiol (**2b**) (1.1 equiv), KOAc (1.5 equiv), **Ni-X** (5 mol %), THF (3 mL), pentadecane (100 μ L), rt, 30 min. Samples were taken from the reaction mixture with a syringe and analyzed *via* GC-FID using pentadecane as internal standard.

Motivated by the high activity of **Ni-OTf**, the weakly coordinating **BArF** anion was investigated. Although **Ni-BArF** produced trace amounts of product within 1 min, its overall reaction profile closely resembled that of **Ni-OAc**. Independent experiments demonstrated rapid and quantitative conversion of both **Ni-OTf** and **Ni-BArF** to **Ni-OAc** upon treatment with excess KOAc in THF, indicating that such ligand exchange processes are likely operative under the catalytic conditions. For **Ni-OAc** (orange trace), the highest activation efficiency was anticipated, as this species has been proposed as a key intermediate in the activation pathway. Although formation of catalytic product was observed within the first minute, the reaction rate decreased after approximately 10 min, and the final yield was among the lowest, aside from **Ni-I**.

Catalyst deactivation was initially considered as a potential cause for the reduced activity. However, *in situ* ^{31}P NMR spectroscopy indicated that the concentration of active catalyst remained essentially constant throughout the reaction, but only ~60% of the precatalyst was converted to the active species (determined using Ph_3PO as an internal standard). These observations suggest that decomposition of **Ni-OAc** before or during the activation process limits the extent of active catalyst formation, thereby reducing overall efficiency.

Consistent with this interpretation, independent ^{31}P NMR studies revealed limited stability of **Ni-OAc** in THF solution. In contrast, **Ni-OTf** and **Ni-BArF** exhibited greater solution stability, which likely contributes to their superior catalytic performance and higher overall yields.

Mechanistic Rationalization of the Initiation Period

The rate of thiol coordination was also investigated under non-catalytic conditions by exposing **Ni-Cl** to a 20-fold excess of adamantanethiol in the presence of KOAc. Contrary to expectations based on catalytic experiments (cf. Figure 48), where an activation period of approximately 15 min was observed, thioether formation (**3Bb**) occurred within less than one minute. This discrepancy between stoichiometric and catalytic conditions indicates a more complex activation process in the catalytic regime.

Under catalytic conditions, the initially generated $\text{Ni}(0)$ species can undergo oxidative addition with PhCl to form the on-cycle oxidative addition complex $(\text{Xantphos})\text{Ni}(\text{Ph})\text{Cl}$. Given that thiol coordination is rate-determining,^{1, 18} this step may outcompete further precatalyst activation. Consequently, both $(\text{Xantphos})\text{Ni}(o\text{-tolyl})\text{Cl}$ and $(\text{Xantphos})\text{Ni}(\text{Ph})\text{Cl}$ are present simultaneously and could compete for the nucleophile, likely favoring the less sterically hindered phenyl complex. Such competition would only be feasible assuming low steady-state concentration of the nucleophile, which could arise from limited solubility (KOAc) or acid-base equilibria (HS-R). As a result, consumption of the nucleophile by the catalytically active species may retard further activation of the precatalyst. In contrast, this competition is absent under stoichiometric conditions, where no oxidative addition complex is formed in the absence of PhCl .

To probe this hypothesis, a competition experiment between **Ni-X** precatalysts and a nickel on-cycle complex was conducted (Figure 49). While $(\text{Xantphos})\text{Ni}(\text{Ph})\text{Cl}$ is unstable and cannot be isolated,¹⁹ the complex $(\text{Xantphos})\text{Ni}(4\text{-CN-Ph})\text{Cl}$ ($^{4\text{-CN}}\text{Ni-Cl}$) was synthesized in 81% yield as a suitable surrogate. While not strictly identical, this complex serves as a reasonable model for comparing various **Ni-X** precatalysts, but extrapolation to the

corresponding phenyl complex remains limited. Interestingly, its crystal structure notably lacks coordination of the Xantphos oxygen donor. Treatment of $^4\text{-CNNi-Cl}$ with one equivalent of adamantanethiol in the presence of one equivalent of various Ni-X precatalysts and KOAc allowed assessment of relative reaction rates *via* product distribution **3Bb**:**3Cb**.

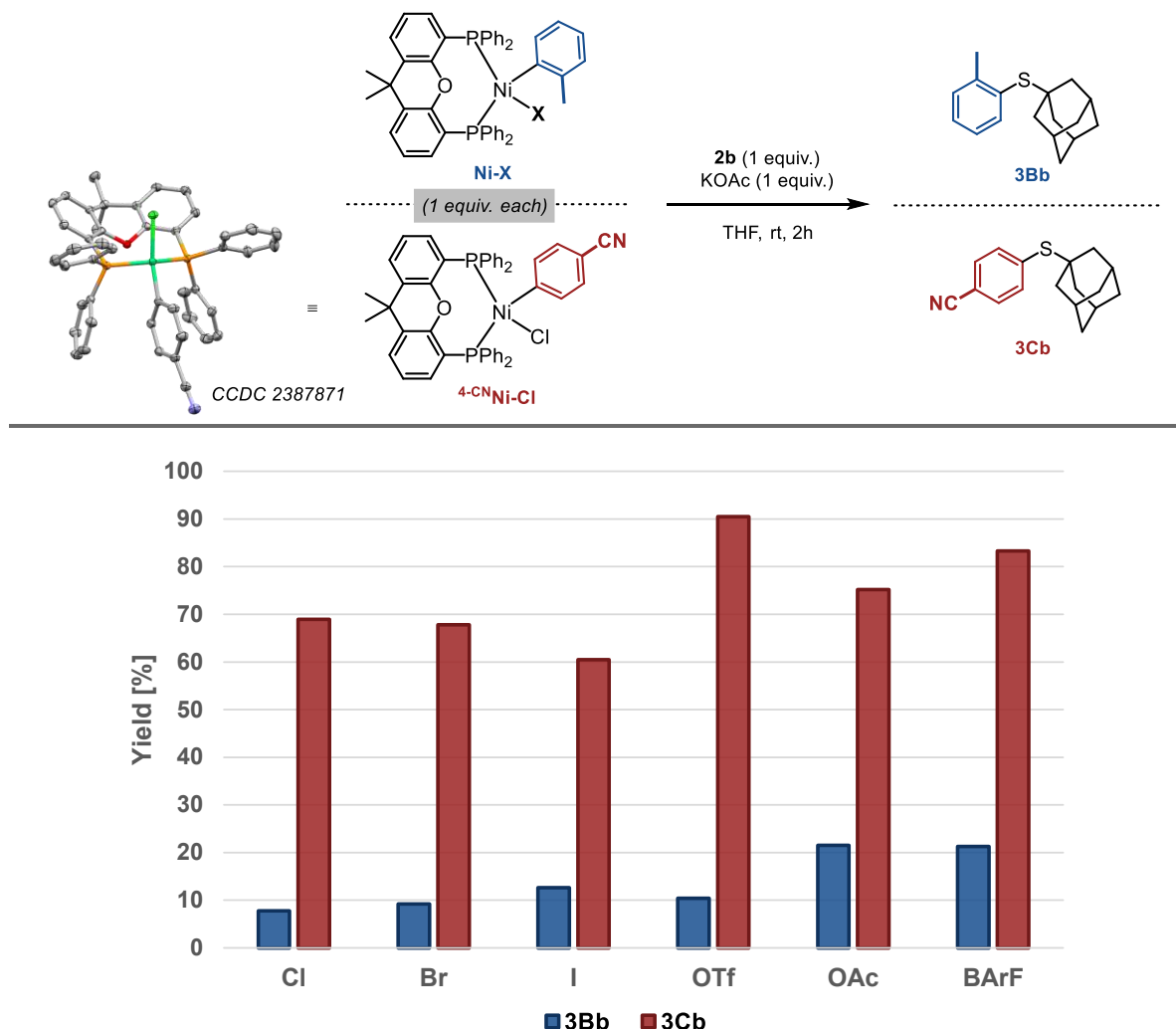


Figure 49. Competition experiments between $^4\text{-CNNi-Cl}$ and Ni-X precatalysts. Yields determined by GC-FID using pentadecane as internal standard. Reaction conditions: Ni-X (6 μmol , 1 equiv.), $^4\text{-CNNi-Cl}$ (1 equiv.), **2b** (1 equiv.), KOAc (1 equiv.), THF (2 mL), pentadecane (5 μL), rt, 2 h.

In the crystal structure of $^4\text{-CNNi-Cl}$, hydrogen atoms and one molecule of co-crystallized THF are omitted for clarity and thermal ellipsoids are shown at 50% probability level. Selected bond lengths [$\text{\AA}$] and bond angles [$^\circ$]: Ni–C, 1.879(1); Ni–Cl, 2.2359(7); Ni–O, 2.6561(9); P–Ni–P, 149.94(2); C–Ni–Cl, 160.06(4)

As expected, reactivity favored the less sterically hindered complex. Across the halide series, selectivity decreased in the order $\text{Cl} > \text{Br} > \text{I}$, consistent with increasing reactivity of complexes with softer anions, although the effect remained moderate. The comparatively facile activation of Ni-I under stoichiometric conditions supports the hypothesis that iodide-derived species (e.g. KI) contribute to catalyst inhibition under catalytic conditions.

The triflate complex **Ni-OTf** exhibited reactivity comparable to **Ni-Br** in this competition experiment, despite its superior performance in catalysis. **Ni-OAc** and **Ni-BAr_F** displayed similar behavior, consistent with rapid *in situ* conversion of **Ni-BAr_F** to **Ni-OAc** upon exposure to KOAc. Both complexes showed a greater propensity for activation relative to the halide systems. The differing behavior of **Ni-OTf** and **Ni-BAr_F** under stoichiometric versus catalytic conditions may arise from differences in the rate of ligand exchange with acetate.

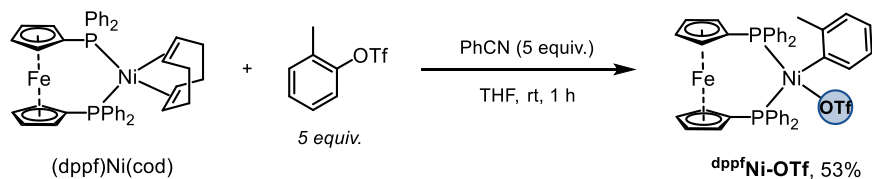
Overall, these findings are consistent with the observed induction periods in catalysis and support a mechanistic scenario in which competition between precatalyst activation and catalytic turnover governs the rate of active species formation.

Performance of a Triflate Precatalyst in other Cross-Couplings

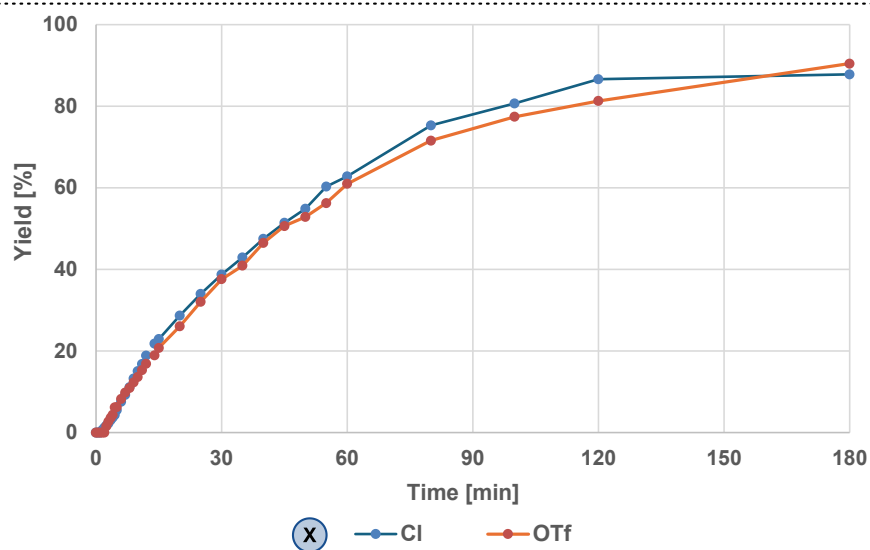
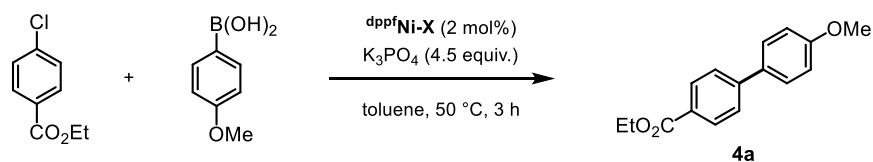
With these findings in hand, the potential transferability of the enhanced catalytic performance observed for **Ni-OTf**, characterized by a shortened activation period and high yields, was evaluated in other established cross-coupling reactions. The complex (dppf)Ni(*o*-tolyl)Cl (**^{dppf}Ni-Cl**; dppf = 1,1'-bis(diphenylphosphino)ferrocene) is known to serve as an effective precatalyst in nickel-catalyzed Suzuki–Miyaura coupling (SMC) of aryl chlorides with aryl boronic acids, as well as in nickel-catalyzed amination reactions.²⁰⁻²¹ Accordingly, the corresponding triflate analogue (dppf)Ni(*o*-tolyl)OTf (**^{dppf}Ni-OTf**) was synthesized in 53% yield and evaluated in both transformations (Figure 50).

Catalytic activity was assessed in the SMC of 4-chloroethyl benzoate with 4-methoxyphenyl boronic acid,²² as well as in the amination of 4-chlorobenzonitrile with morpholine,²¹ monitoring reaction profiles for both **^{dppf}Ni-Cl** and **^{dppf}Ni-OTf**. In the SMC, no product formation was detected within the first 2 min, and both systems exhibited comparable kinetic behavior consistent with pseudo-first-order kinetics (Figure 50, B). No improvement was observed for the triflate complex, and the nearly identical reaction profiles suggest that the counterion does not participate in the rate-determining step of catalyst activation.

A) Synthesis of dppfNi-OTf



B) Nickel-catalyzed Suzuki-Miyaura Coupling



C) Nickel-catalyzed Arylation of Morpholine

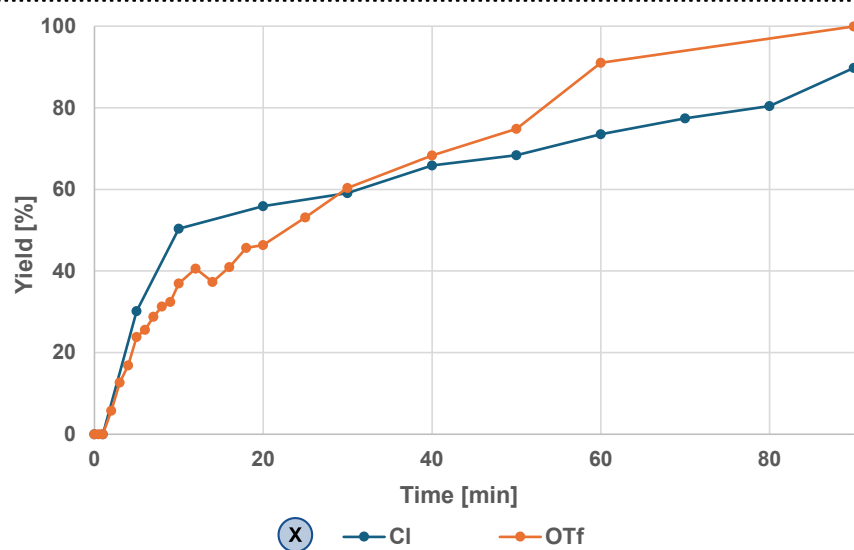
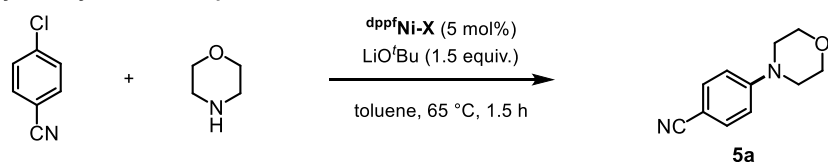


Figure 50. Synthesis of dppfNi-OTf and evaluation in SMC and amination reactions.

This observation is consistent with literature proposals in which the rate-limiting step involves formation of a nickel–oxo species derived from a μ -hydroxo-bridged dimer, which serves as the resting state.²³⁻²⁴ In such a mechanism, the nature of the counterion is not expected to influence the key activation step.

For the C–N coupling, preliminary studies revealed that arylation of morpholine with 4-chlorobenzonitrile using dppfNi-Cl proceeds efficiently at slightly reduced temperatures compared to reported conditions.²² Under these adapted conditions, both dppfNi-Cl and dppfNi-OTf displayed similar activation periods (≈ 2 min) and comparable initial rates (Figure 50, C). However, while the reaction catalyzed by dppfNi-OTf followed a typical pseudo-first-order profile, the system employing dppfNi-Cl exhibited a decrease in rate after approximately 10 min. Despite this divergence, the overall behavior of both systems remained more similar than observed in the C–S coupling.

This reduced sensitivity to the counterion may be attributed to the higher reaction temperature, which likely facilitates the sterically demanding activation step. Alternatively, the nucleophile concentration in C–C and C–N couplings is significantly higher, potentially suppressing competitive processes that were proposed to impede precatalyst activation in C–S coupling. Additionally, the presence of the oxygen donor in Xantphos-based systems may reduce the electrophilicity of the Ni(II) center, thereby disfavoring nucleophilic attack relative to dppf-based complexes, which lack an additional donor site beyond the phosphine ligands.

Conclusions

In conclusion, a series of precatalysts of the type (Xantphos)Ni(*o*-tolyl)X (X = Cl, Br, I, OTf, OAc, BAr_F) was successfully synthesized and characterized by X-ray diffraction, NMR, HRMS and elemental analysis. Their catalytic performance was systematically evaluated in C–S cross-coupling, revealing (Xantphos)Ni(*o*-tolyl)OTf (**Ni-OTf**) as the most active system, delivering high yields within 15 min at room temperature. This enhanced reactivity is attributed to the weakly coordinating nature of the triflate anion, which generates a cationic nickel center with increased propensity for nucleophile coordination, thereby facilitating rapid precatalyst activation.

Mechanistic investigations suggested that the oxidative addition complex and the precatalyst compete for the nucleophile, leading to a deceleration of the activation process under catalytic conditions.

Extension of this concept to other cross-coupling reactions was explored using (dppf)Ni(*o*-tolyl)X (X = Cl, OTf) precatalysts in Suzuki–Miyaura and Buchwald–Hartwig reactions. In these cases, no significant differences in catalytic performance were observed, indicating that the beneficial effect of the triflate counterion is less pronounced for dppf-based systems or becomes relevant primarily under conditions of low nucleophile concentration, where competition between catalytic species is significant.

Additionally, elevated reaction temperatures may mitigate activation barriers and diminish such effects. Overall, the use of more reactive precatalysts appears particularly advantageous for transformations involving weak nucleophiles at low concentrations and under mild conditions.

3.2. Summary of Unpublished Results

Rate of Oxidative Addition of Various Electrophiles to (Xantphos)Ni(0)

Based on the observation that triflate counterions accelerate the activation of (Xantphos)Ni(II) precatalysts, the influence of the leaving group on oxidative addition of aryl-X electrophiles ($X = \text{Cl}, \text{Br}, \text{I}, \text{OTf}, \text{OTs}, \text{OMs}$) was systematically investigated. A central objective was to rationalize the unusually high reactivity of aryl triflates observed in C-S cross-coupling.

For this purpose, Ni^{C2Ph2} was employed as a model Ni(0) complex and reacted with an excess of the respective electrophiles in THF- d_8 (Table 6). Reaction progress was monitored by ^{31}P NMR spectroscopy using Ph_3PO as an internal standard.

Table 6. Rates of oxidative addition of 4-CN-Ph-X electrophiles to Ni^{C2Ph2} .

Entry	X =	Temperature	k_{obs} [s^{-1}]	Standard Deviation*	k_{rel}
1	I	0 °C	9.12×10^{-4}	1.93×10^{-5}	2.12% 13
2	Br	0 °C	5.12×10^{-4}	5.55×10^{-6}	1.08% 7.4
3	OTf	0 °C	9.85×10^{-4}	3.23×10^{-5}	3.28% 14
4	Cl	0 °C	6.91×10^{-5}	1.51×10^{-6}	2.18% 1.0
5 ^a	Cl	40 °C	9.54×10^{-3}	2.79×10^{-4}	2.92% 1.0
6 ^a	OTs	40 °C	5.22×10^{-5}	6.15×10^{-7}	1.18% 5.4×10^{-3}
7 ^a	OMs	40 °C	3.06×10^{-5}	2.23×10^{-7}	0.73% 3.2×10^{-3}
8 ^a	OC(O)NMe₂	40 °C	6.31×10^{-5}	1.82×10^{-6}	2.88% 6.6×10^{-3}

Each value was determined in triplets from ^{31}P NMR spectroscopy (162 MHz, THF- d_8). Reaction conditions: Ni^{C2Ph2} (5 mg, 5.51 μmol , 1 equiv.), Ar-X (10 equiv.), Ph_3PO (5 mg), THF- d_8 (0.5 ml). ^a 20 equiv. Ar-X.

Very surprisingly, aryl triflates exhibited the highest rate constants among all substrates examined, reacting even more rapidly than the corresponding aryl iodides (entry 3), while other sulfonates displayed low reactivity even at elevated temperatures (entries 6, 7). Interestingly, the carbamate reacted faster than the tosylate (entry 8). This unexpected reactivity may be attributed to a distinct oxidative addition pathway enabled by the triflate

leaving group.²⁵ Computational studies had suggested an S_NAr-type transition state for aryl triflates,¹⁸ in contrast to classical pathways, such as three-centered transition states or radical pathways, proposed for aryl halides.²⁶ Furthermore, oxidative addition of aryl triflates to Ni(0) has been shown to be strongly exergonic, which, according to the Bell-Evans-Polanyi principle, correlates with a reduced activation barrier.²⁷⁻²⁸ In fact, these results are in stark contrast to results obtained for oxidative addition of aryl electrophiles to (dppf)Ni(cod) by Nelson and coworkers.¹⁹ In this study, aryl triflates exhibited a ca. 1000-fold lower rate relative to aryl iodides and reacted more slowly than both aryl chlorides and tosylates. These discrepancies highlight the pronounced ligand dependence of oxidative addition reactivity trends.

Future investigations should therefore focus on systematically evaluating the relative rates of oxidative addition of aryl triflates *versus* halides across a range of ligand environments, in order to identify systems in which triflate activation is significantly enhanced. Complementary Hammett studies could further elucidate the underlying mechanistic features governing these transformations.

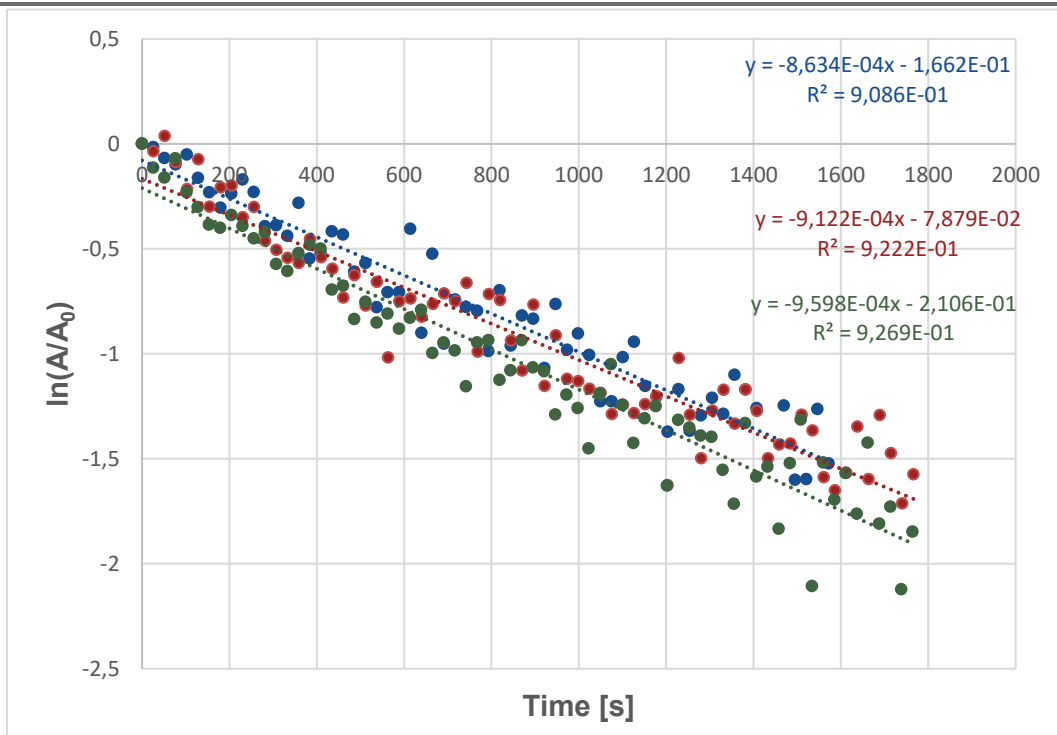
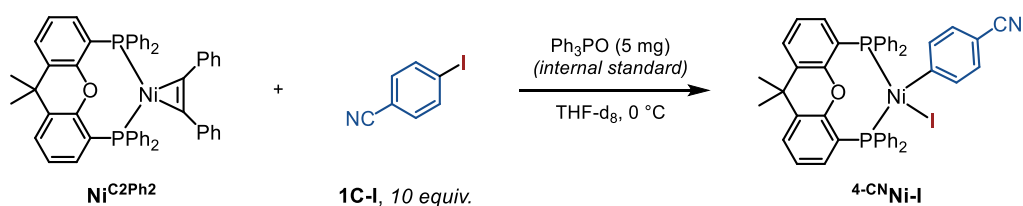
3.3. Experimental

For general information on instrumentation, experimental details and analytical data of published results, see the Supporting Information of the published article, available free of charge at the publisher's website: DOI 10.1021/acs.organomet.4c00498.

General Procedure GP-OA1: Oxidative addition of Ar–X to $\text{Ni}^{\text{C}^2\text{Ph}_2}$ (NMR analysis).

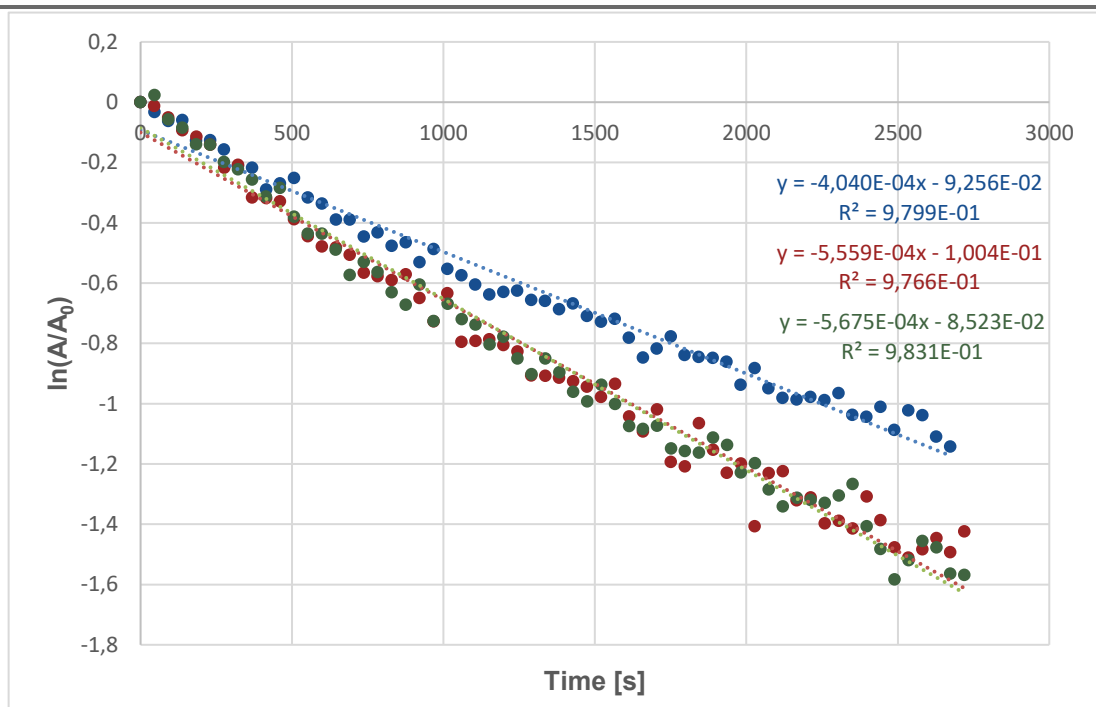
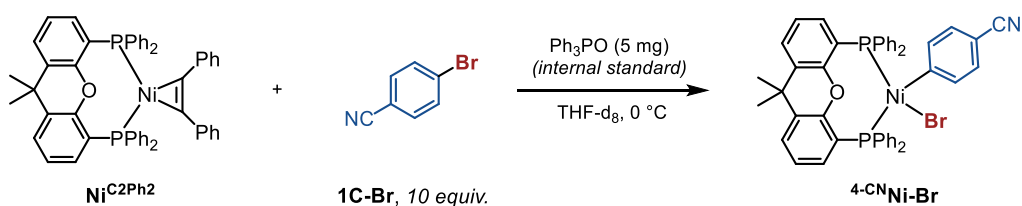
In a glovebox, $\text{Ni}^{\text{C}^2\text{Ph}_2}$ (5.0 mg, 5.51 μmol , 1 equiv.) and triphenylphosphine oxide (5 mg) were dissolved in THF- d_8 (0.5 ml) and transferred to an NMR tube (*Note: For measuring data in triplets, a stock solution containing the 3-fold amount was prepared instead*). The mixture was cooled to 77 K, subjected to the NMR spectrometer and a ^{31}P NMR reference spectrum (162 MHz) was recorded at 0 °C. Next, the aryl (pseudo-)halide (10 equiv.) was dissolved in THF- d_8 (0.1 ml) and added to the NMR tube at 77 K. While warming up, the mixture was manually shaken and subjected to the NMR spectrometer. ^{31}P NMR spectra (162 MHz) were recorded every 30 s.

Oxidative addition of 1C-I at 0 °C:



Entry	$k_{\text{obs}} [\text{s}^{-1}]$	Standard Deviation of Linear Regression	Standard Deviation of Average ^a	
1	9.12×10^{-4}	3.45×10^{-5}		
2	8.63×10^{-4}	3.32×10^{-5}	1.93×10^{-5}	2.12%
3	9.60×10^{-4}	3.27×10^{-5}		

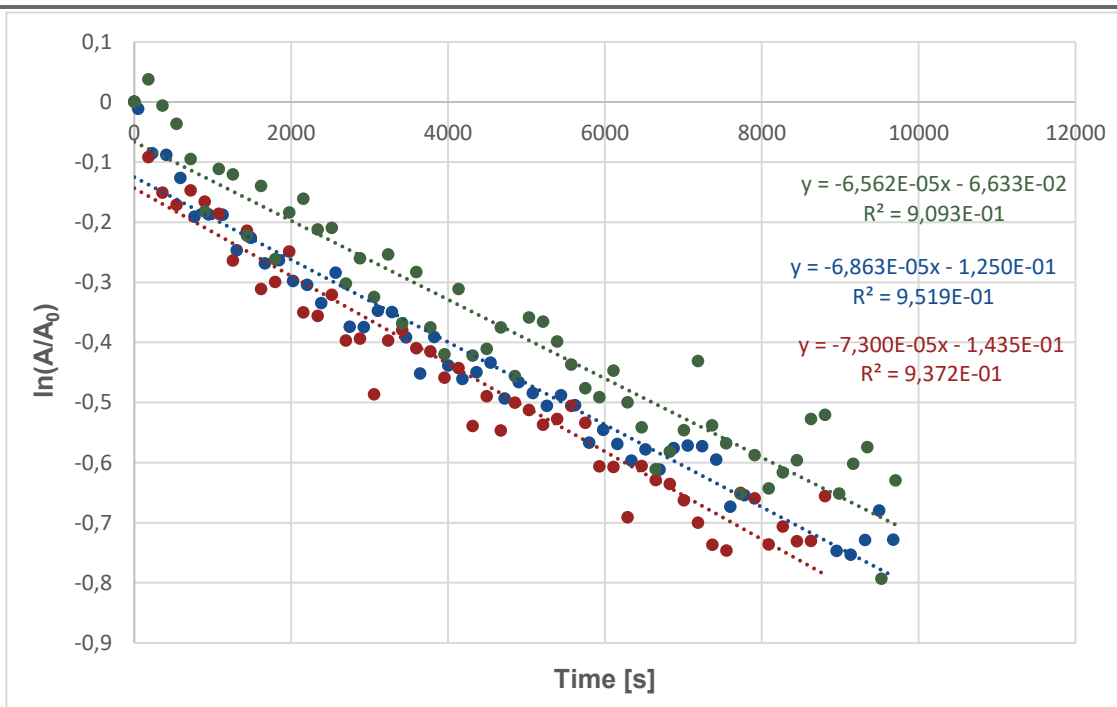
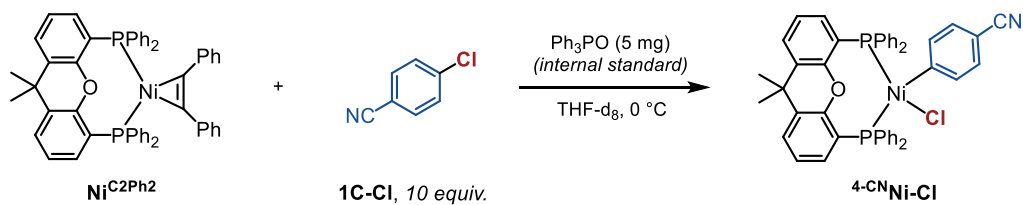
^a Standard deviation was calculated by Gaußian error propagation.

Oxidative addition of 1C-Br at 0 °C:

Entry	$k_{\text{obs}} [\text{s}^{-1}]$	Standard Deviation of Linear Regression	Standard Deviation of Average ^a	
1	5.56×10^{-4}	1.09×10^{-5}		
2	4.04×10^{-4}	7.66×10^{-6}	5.55×10^{-6}	1.08%
3	5.68×10^{-4}	1.00×10^{-5}		

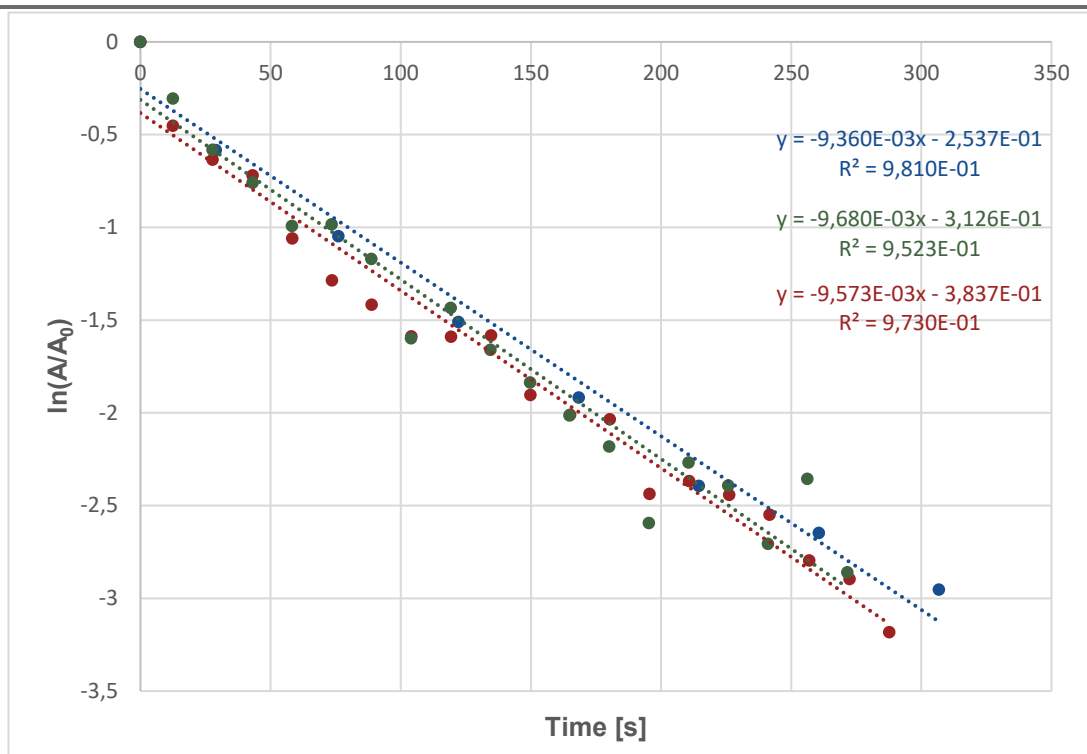
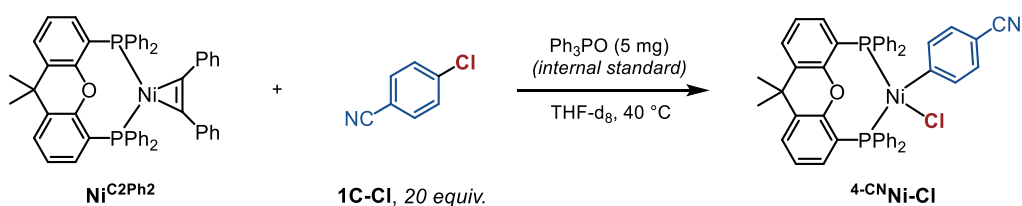
^a Standard deviation was calculated by Gaussian error propagation.

Oxidative addition of 1C-Cl at 0 °C:



Entry	k_{obs} [s ⁻¹]	Standard Deviation of Linear Regression	Standard Deviation of Average ^a	
1	7.30×10^{-5}	2.73×10^{-6}		
2	6.86×10^{-5}	2.23×10^{-6}	1.51×10^{-6}	2.18%
3	6.56×10^{-5}	2.85×10^{-6}		

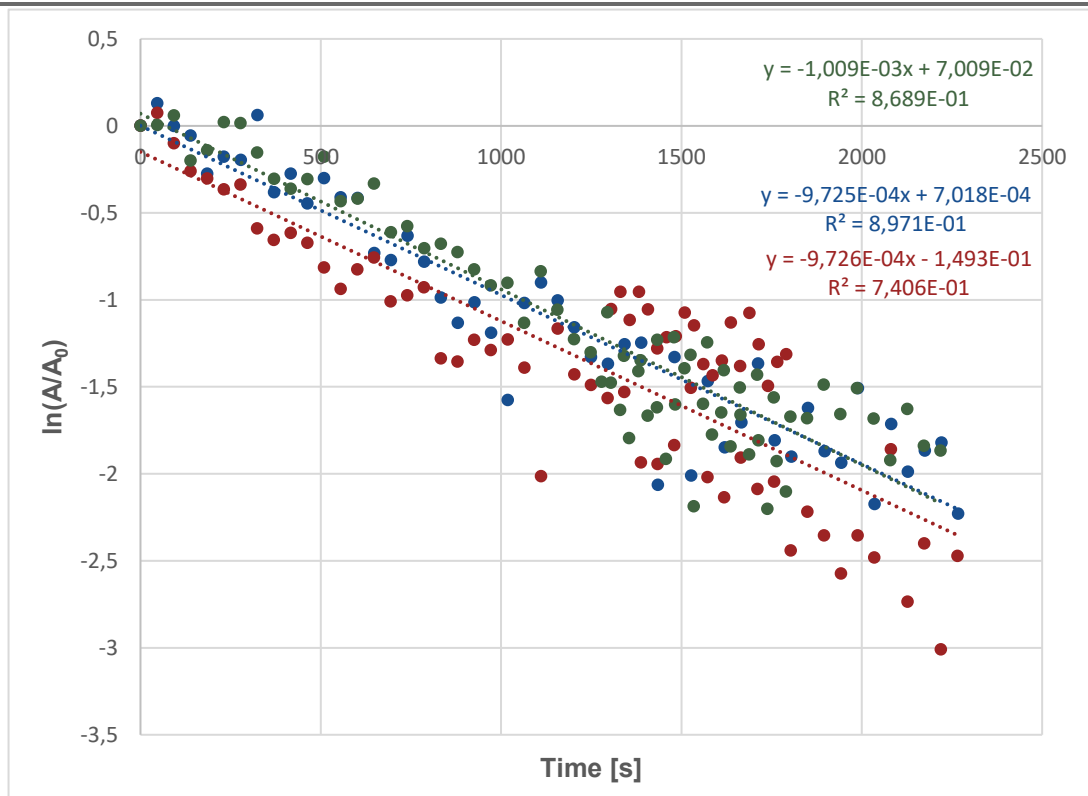
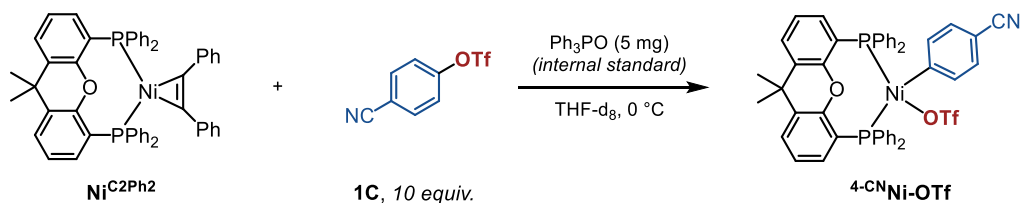
^a Standard deviation was calculated by Gaußian error propagation.

Oxidative addition of 1C-Cl at 40 °C:

Entry	k_{obs} [s^{-1}]	Standard Deviation of Linear Regression	Standard Deviation of Average ^a	
1	9.57×10^{-3}	3.76×10^{-4}		
2	9.36×10^{-3}	5.31×10^{-4}	2.79×10^{-4}	2.92%
3	9.68×10^{-3}	5.25×10^{-4}		

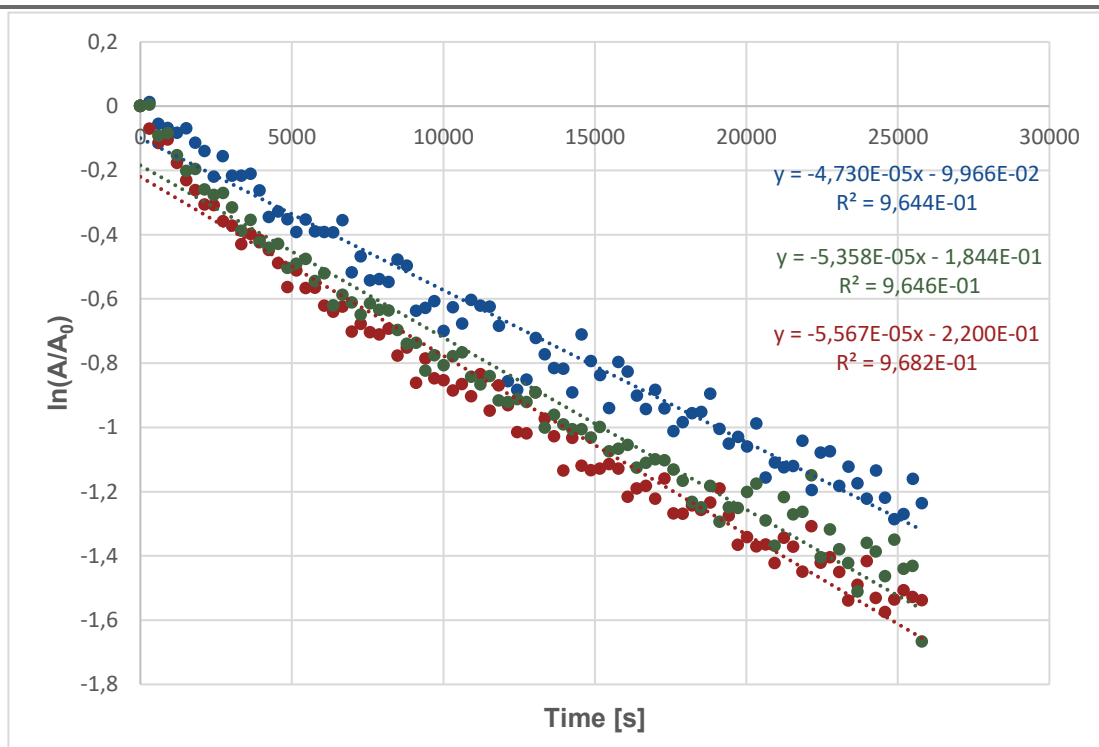
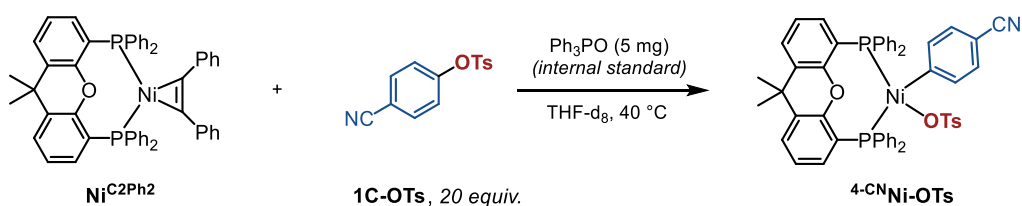
^a Standard deviation was calculated by Gaussian error propagation.

Oxidative addition of 1C at 0 °C:



Entry	$k_{\text{obs}} [\text{s}^{-1}]$	Standard Deviation of Linear Regression	Standard Deviation of Average ^a	
1	9.73×10^{-4}	4.75×10^{-5}		
2	9.73×10^{-4}	6.98×10^{-5}	3.23×10^{-5}	3.28%
3	1.01×10^{-3}	4.75×10^{-5}		

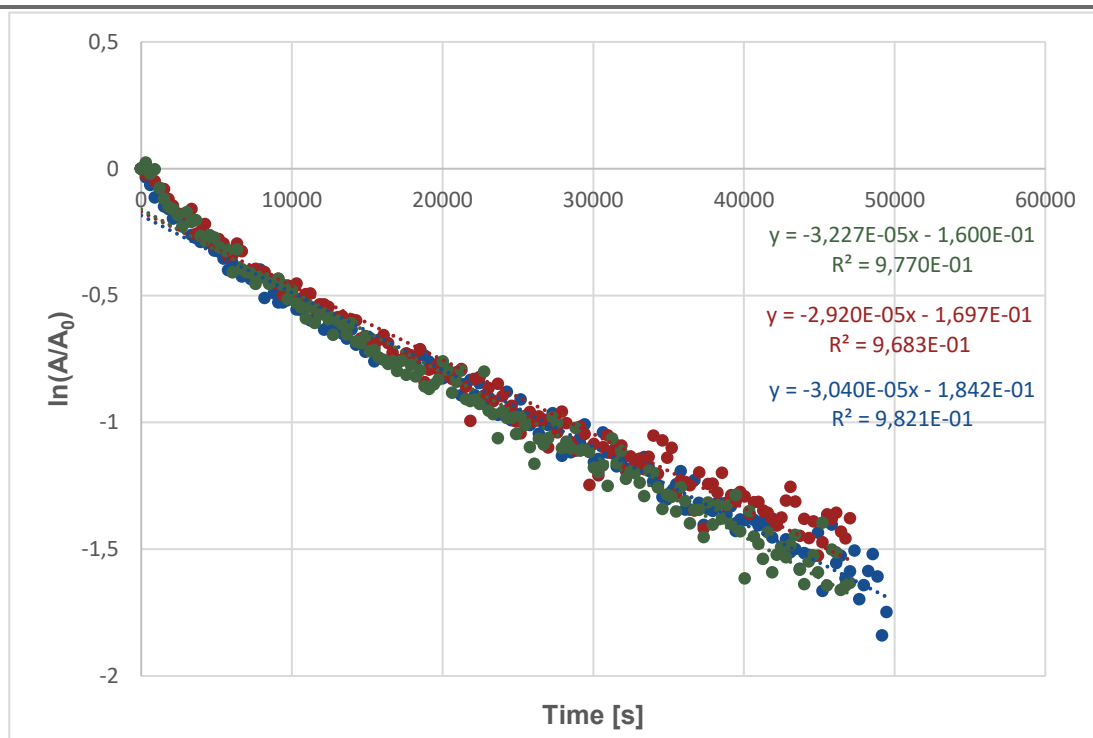
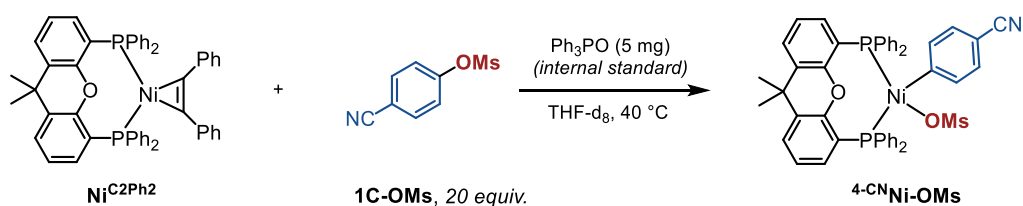
^a Standard deviation was calculated by Gaußian error propagation.

Oxidative addition of 1C-OTs at 40 °C:

Entry	k_{obs} [s ⁻¹]	Standard Deviation of Linear Regression	Standard Deviation of Average ^a	
1	5.57×10^{-5}	1.09×10^{-6}		
2	4.73×10^{-5}	9.86×10^{-7}	6.15×10^{-7}	1.18%
3	5.36×10^{-5}	1.11×10^{-6}		

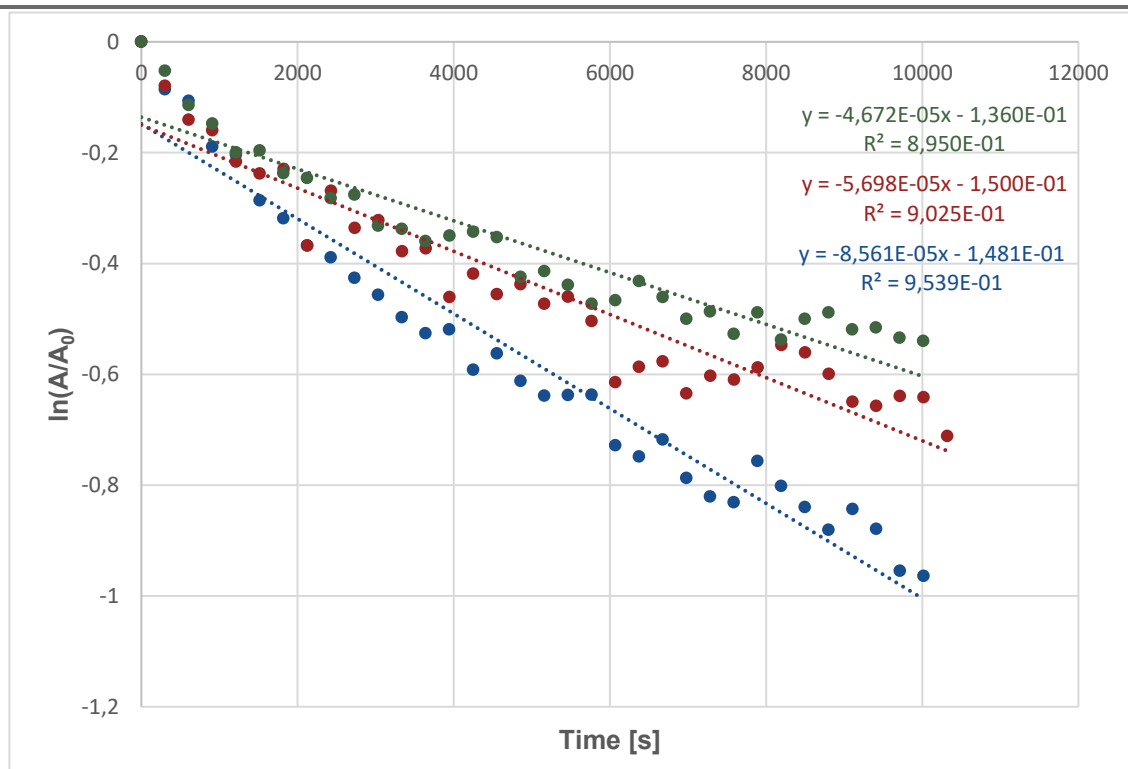
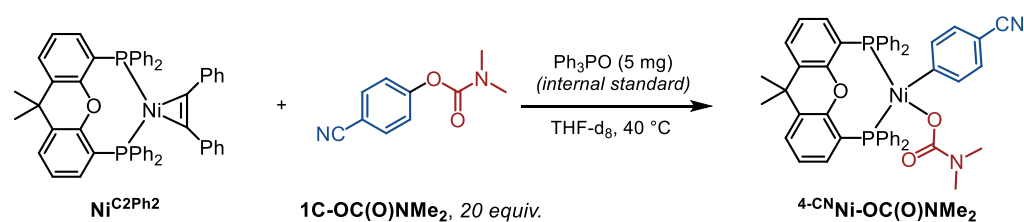
^a Standard deviation was calculated by Gaussian error propagation.

Oxidative addition of 1C-OMs at 40 °C:



Entry	k_{obs} [s ⁻¹]	Standard Deviation of Linear Regression	Standard Deviation of Average ^a	
1	2.92×10^{-5}	4.24×10^{-7}		
2	3.04×10^{-5}	3.30×10^{-7}	2.23×10^{-7}	0.73%
3	3.23×10^{-5}	3.98×10^{-7}		

^a Standard deviation was calculated by Gaußian error propagation.

Oxidative addition of 1C-OC(O)NMe₂ at 40 °C:

Entry	$k_{\text{obs}} [\text{s}^{-1}]$	Standard Deviation of Linear Regression	Standard Deviation of Average ^a	
1	5.70×10^{-5}	3.26×10^{-6}		
2	8.56×10^{-5}	3.33×10^{-6}	1.82×10^{-6}	2.88%
3	4.67×10^{-5}	2.83×10^{-6}		

^a Standard deviation was calculated by Gaußian error propagation.

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4. Nickel Catalyzed C–S Cross Coupling Enhanced by Mechanochemistry

4.1. Summary of Published Results

This chapter is based on the following publication:

Ivo H. Lindenmaier, Robert C. Richter, Marius Schier, Markus Ströbele, Ivana Fleischer, *ACS Catal.* **2025**, *15*, 21, 17871–17881. DOI 10.1021/acscatal.5c04516.

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Reaction Development and Optimization

Although numerous efficient methodologies for C–S cross-coupling have been reported, their translation to industrial applications remains limited.^{1–5} In practice, thioethers are still predominantly synthesized *via* nucleophilic substitution,^{6–9} despite the associated drawbacks of elevated temperatures, prolonged reaction times, and strongly basic conditions, which often necessitate early-stage incorporation of the thioether functionality. The limited applicability of academic cross-coupling protocols can likely be attributed to their sensitivity toward air and moisture, high catalyst loadings, and restricted scalability. Accordingly, the objective of this work was to develop a more practical C–S cross-coupling protocol that combines high efficiency and broad functional group tolerance with operational simplicity, including reaction setup under ambient conditions.

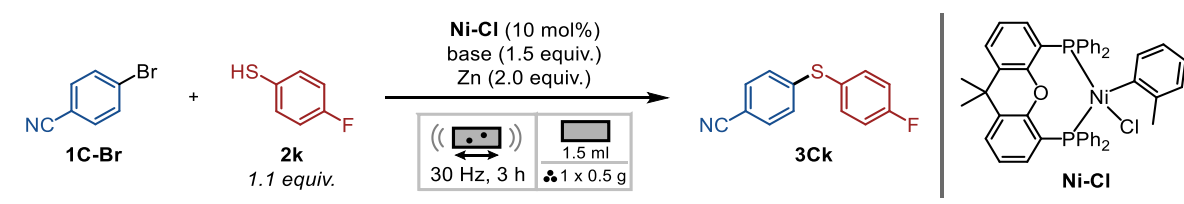
Mechanochemistry has emerged as a promising technology in chemical synthesis,^{10–12} offering the potential to conduct reactions under solvent-minimized and ambient conditions.^{13–15} Notably, several catalytic systems previously considered highly sensitive to oxygen and moisture have been shown to operate effectively under mechanochemical conditions, even when no precautions to exclude air from the system were taken.^{16–21} Despite this potential, only a limited number of mechanochemical approaches to C–S cross-coupling have been reported, often relying on expensive palladium catalysts²⁰ or exhibiting modest efficiency. For example, a nickel/bipyridine-based system developed by Guo and co-workers required high catalyst loadings (20 mol%), large excess of reagents, and afforded only

moderate to good yields.²² Based on previous experience with nickel-catalyzed C–S couplings,^{23–24} phosphine ligands have consistently demonstrated superior performance,²⁵ suggesting that the development of a more efficient mechanochemical system based on this ligand class is feasible.

Consequently, the catalytic system previously developed by the Fleischer group,^{24, 26} consisting of the precatalyst (Xantphos)Ni(*o*-tolyl)Cl in combination with the inorganic base KOAc, was applied to a C–S cross-coupling under mechanochemical conditions. A severe limitation of this system was the incompatibility with aryl thiols, which was ascribed to catalyst deactivation. It was the goal of this work to enable the coupling of both alkyl and aryl thiols, since under mechanochemical conditions, catalyst speciation may vary.

Thus, initial investigations focused on the coupling of 4-bromobenzonitrile with 4-fluorothiophenol as model substrates (Table 1). Given that reactions were conducted under ambient atmosphere, the inclusion of an external reductant (e.g., zinc) was considered necessary to suppress the literature-known aerobic oxidation of thiols to disulfides.²⁰ Under the homogeneous conditions (KOAc as base), only trace product formation was observed in the ball-mill (entry 1), indicating that direct transfer of solution-phase conditions to mechanochemistry was not feasible. Subsequent base screening revealed that certain inorganic bases such as KO^tBu and K₂CO₃ afforded high yields (entries 2 and 3), while others prevented efficient coupling (entries 5–9). Notably, organic bases, specifically Et₃N and *i*PrNEt₂, enabled quantitative product formation (entries 10, 11), whereas DBU and DABCO resulted in low yields (entries 12, 13). The superior performance of Et₃N relative to DABCO can be attributed to its liquid state, which likely facilitates efficient thiol deprotonation under milling conditions. This assumption was later supported by ¹⁹F NMR experiments, confirming complete deprotonation of 4-fluorothiophenol upon neat mixing with Et₃N. Owing to its effectiveness and ease of removal during workup, Et₃N was selected as the base for further studies.

Table 7. Base screening for mechanochemical C–S cross-coupling.

			
Entry	Base	Conv. [%]	Yield [%]
1	KOAc	7	3
2	NaO ^t Bu	13	2
3	KO ^t Bu	100	71
4	K ₂ CO ₃	97	89
5	K ₃ PO ₄	10	9
6	NaNH ₂	3	4
7	KOH	83	24
8	NaOBz	0	n.d.
9	KOPiv	9	n.d.
10	NEt ₃	100	99
11	DIPEA (ⁱ Pr ₂ NEt)	100	97
12	DBU	30	19
13	DABCO	8	n.d.

Yields and conversions were determined by GC-FID using pentadecane as internal standard.

Optimization of catalyst loading and precatalyst demonstrated that loadings as low as 1 mol% still afforded high yields (Table 8, entries 1–4). However, reduced catalyst loadings also led to increased formation of protodehalogenated byproducts (entry 5). Therefore, 2.5 mol% catalyst loading was chosen to ensure robustness of the system when applied to more challenging substrates. Interestingly, (dppf)Ni(*o*-tolyl)Cl (**Ni5**) was also compatible with the catalytic system (entry 6), and Ni(acac)₂ in combination with Xantphos proved to be a viable low-cost alternative to the precatalyst (Xantphos)Ni(*o*-tolyl)Cl (entry 7), although the latter was preferred due to its defined stoichiometry and operational simplicity. Control experiments confirmed that both nickel and zinc are essential for productive catalysis (entries 8 and 9). Interestingly, omission of the nickel catalyst still resulted in 52% conversion of the aryl bromide, raising questions about the role of zinc. Although mechanochemical formation of

4. Nickel Catalyzed C–S Cross Coupling Enhanced by Mechanochemistry

organozinc species from alkyl bromides is known, quenching experiments with D₂O or iodine provided no evidence for analogous intermediates derived from aryl bromides. Optimization of reagent stoichiometry revealed that 1.05 equivalents of thiol, 1.1 equivalents of base, and 0.5 equivalents of zinc were sufficient for product formation in excellent yield.

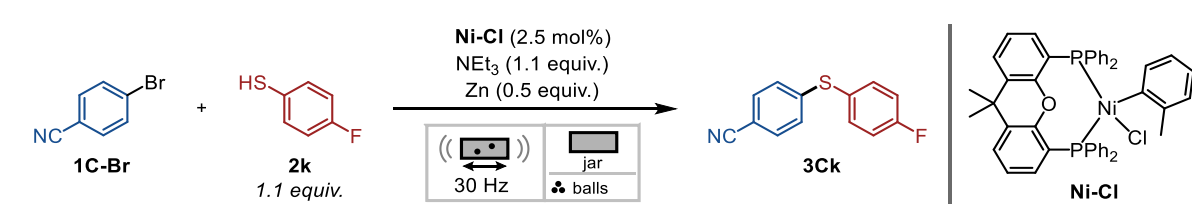
Table 8. Catalyst screening for mechanochemical C–S cross-coupling.

Entry	Deviation	Conv. [%]	Yield [%]
1	–	100	99
2	5 mol% Ni	100	99
3	2.5 mol% Ni	100	90
4	1 mol% Ni	100	87
5	1C–I , 0.1 mol% Ni	86	55
6	(dppf)Ni(<i>o</i> -tolyl)Cl (2.5 mol%)	100	97
7	Ni(acac) ₂ /Xantphos	100	91
8	No Ni	52	n.d.
9	No Zn	4	n.d.

Yields and conversions were determined by GC-FID using pentadecane as internal standard.

Mechanochemical parameters were also systematically optimized (Table 9). Reaction efficiency was found to depend strongly on the milling setup, with optimal conditions identified as a 10 mL stainless-steel jar equipped with 2 × 3 g stainless-steel balls for a 1 mmol scale reaction. These parameters governed both energy input and internal temperature, which increased to approximately 30–35 °C during milling.

Table 9. Screening of mechanochemical parameters for C–S cross-coupling.

			
Entry	Deviation	Conv. [%]	Yield [%]
1	2 × 0.5 g balls, 1 h	1	n. d.
2	4 × 0.5 g balls, 2.5 h	100	90
3	1 × 3 g ball, 2 h	97	90 (76)
4	2 × 3 g ball, 1 h, 1 mol% Ni	100	93 (82)

Yields and conversions were determined by GC-FID using pentadecane as internal standard. Isolated yield in parentheses.

While full conversion was typically achieved after 1 h, a milling time of 1.5 h was adopted to ensure general applicability across substrates. Finally, the addition of nitrile additives as promotor for oxidative addition was examined,²⁷ as more electron-rich substrates initially gave low conversions. Benzonitrile (100 μ L) proved optimal, significantly enhancing conversion.

Substrate Scope

With optimized conditions established, the electrophile substrate scope was examined (Figure 51). The model substrate 4-bromobenzonitrile (**1C-Br**) afforded the desired product in excellent isolated yield (90%). The corresponding iodide and chloride were also viable substrates, although efficient conversion of aryl chlorides was largely limited to electronically activated systems (*vide infra*). Electron-neutral aryl bromides provided good to excellent yields (**3Ek**, **3Fk**), whereas sterically hindered substrates exhibited diminished reactivity (**3Dk**), indicating that oxidative addition may be rate-limiting. Halogen substituents, including fluoro (**3Hk**), chloro (**3Ik**), and bromo (**3Jk**), were well tolerated; however, increased formation of disubstituted products was observed down the halogen series. Electron-deficient aryl bromides bearing trifluoromethyl (**3Kk**), sulfone (**3Lk**), ester (**3Mk**), and boronic ester (**3Nk**) substituents furnished the corresponding thioethers in good to excellent yields.

4. Nickel Catalyzed C–S Cross Coupling Enhanced by Mechanochemistry

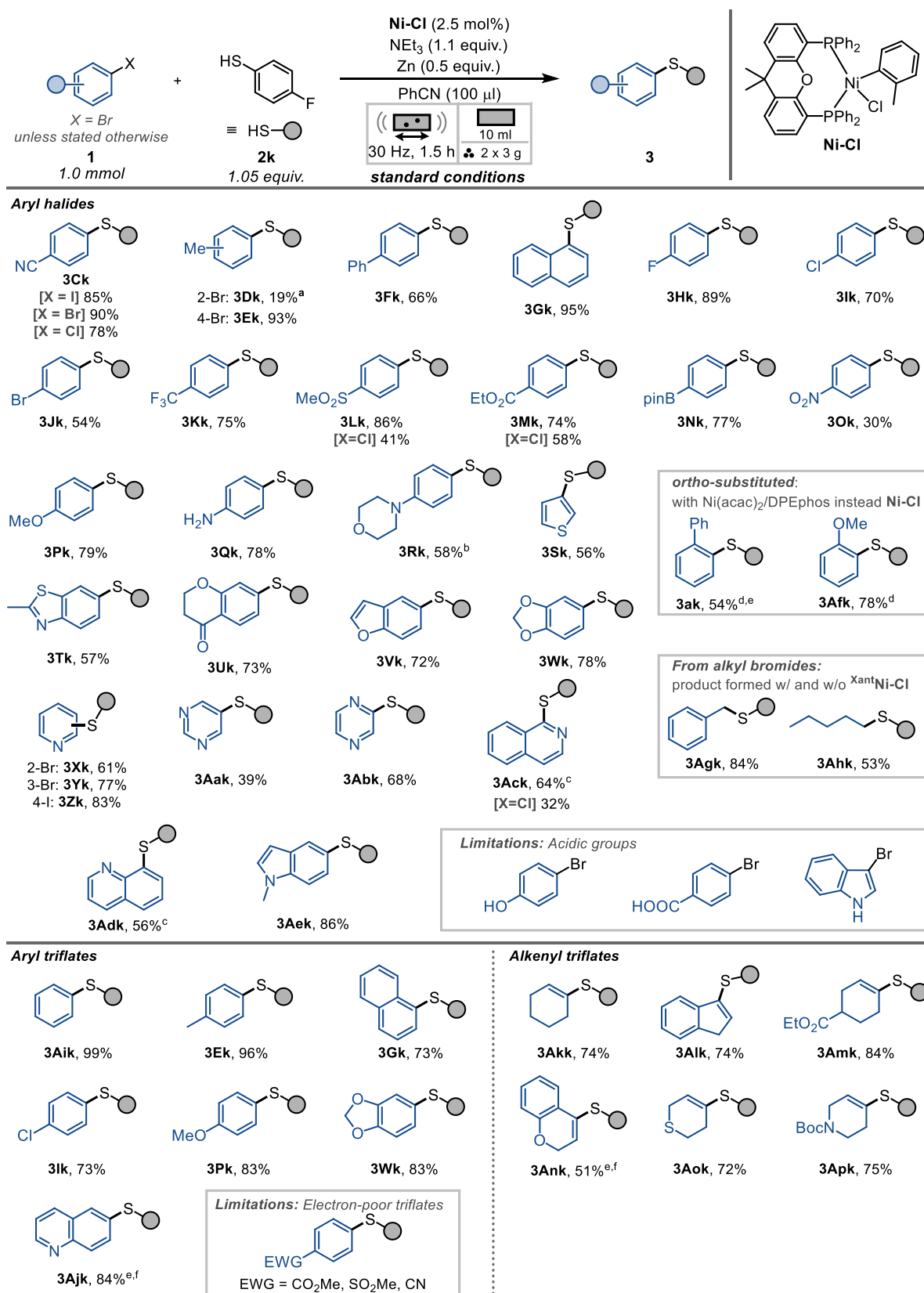


Figure S1. Substrate scope of the mechanochemical C–S cross-coupling with respect to aryl (pseudo-)halides. Isolated Yields. Reaction conditions: **1** (1.0 mmol), **2k** (1.05 equiv.), **Ni-Cl** (2.5 mol%), NEt_3 (1.1 equiv.), Zn (0.5 equiv.), PhCN (100 μl) in a SS jar (10 ml) with SS balls (2 x 3 g) at 30 Hz for 1.5 h. ^a ¹H NMR yield. ^b 2 equiv. Zn . ^c 3 h. ^d $\text{Ni}(\text{acac})_2/\text{Xantphos}$ (2.5 mol%) instead of **Ni-Cl**, 2 equiv. Zn . ^e 5 mol% Ni .

Even substrates containing strongly deactivating nitro groups (**3Ok**) were converted, albeit in moderate yield. Electron-donating substituents, such as methoxy (**3Pk**) and amino groups (**3Qk**, **3Rk**), were likewise well tolerated, affording high yields. The scope was further extended to heterocyclic substrates. 3-Bromothiophene afforded the product in moderate yield (**3Sk**). Benzo-fused heterocycles, including benzothiazole (**3Tk**), chromanone (**3Uk**), benzofurane (**3Vk**), and benzodioxole (**3Wk**), delivered good to high yields. Nitrogen-containing heteroarenes were also compatible: All regioisomers of bromopyridine underwent coupling (**3Xk–3Zk**), with the 4-position showing optimal reactivity. Pyrimidine **1Aa–Br** gave moderate yield, while pyrazine (**3Abk**) and (iso)quinolines bearing nitrogen proximal to the reactive site provided good yields (**3Ack**, **3Adk**). Meanwhile, protected indole **3Aek** was isolated in excellent yield.

For sterically demanding substrates, the more flexible ligand DPEphos in combination with Ni(acac)₂ enabled efficient coupling (**3ak**, **3Afk**), as found in chapter 2. Benzyl (**3Agk**) and alkyl bromides (**3Ahk**) also furnished the corresponding thioethers; however, control experiments indicated that these transformations proceeded *via* uncatalyzed nucleophilic substitution. A key limitation of the catalytic system is the incompatibility with substrates containing acidic protons, such as alcohols, carboxylic acids, as well as unprotected heterocyclic NH groups. Motivated by the high reactivity observed for 4-chlorobenzonitrile (**3Ck**), the scope of aryl chlorides was further explored. In general, only electron-deficient chloroarenes (**3Lk**, **3Mk**, **3Ack**) afforded satisfactory yields, whereas electron-neutral and -rich substrates exhibited low conversions. This observation suggests that oxidative addition is more challenging under mechanochemical conditions compared to solution-phase systems.²⁴

Sulfonate esters were also evaluated as electrophiles. Aryl triflates, readily accessible from phenols, proved to be highly effective substrates, delivering full conversion and excellent isolated yields (**3Aik**, **3Ek**, **3Gk**). In contrast, less reactive sulfonates such as mesylates and tosylates showed poor reactivity. The functional group tolerance of triflates closely paralleled that of aryl bromides, enabling incorporation of chloro (**3Ik**), ether (**3Pk**, **3Wk**), and heteroaromatic (**3Ajk**) substituents. Notably, *para*-substituted electron-withdrawing groups were not tolerated, suggesting a mechanistic divergence from halide substrates. This observation is consistent with an S_N2-type oxidative addition pathway proposed for aryl triflates,²⁸ involving positive charge buildup in the transition state that may be destabilized by electron-withdrawing substituents. Additionally, alkenyl triflates proved to be viable

substrates (**3Akk**, **3Alk**), tolerating ester (**3Amk**), ether (**3Ank**), and heterocyclic substituents (**3Aok**, **3Apk**).

Encouraged by the broad functional group tolerance, high yields and efficiency, the applicability of this method to more challenging substrates was investigated (Figure 52). Consequently, poorly soluble aryl bromides with relevance to materials science were subjected to the standard reaction conditions, affording high yields of the corresponding thioethers (**3Aqk–3Atk**). Furthermore, late-stage functionalization of pharmaceutically relevant molecules was achieved, including derivatives of fenofibrate (**3Auk**), cholestan-3-one (**3Avk**), estrone (**3Awk**), and 8-bromocaffeine (**3Axk**), all of which furnished the corresponding thioethers in good to excellent yields.

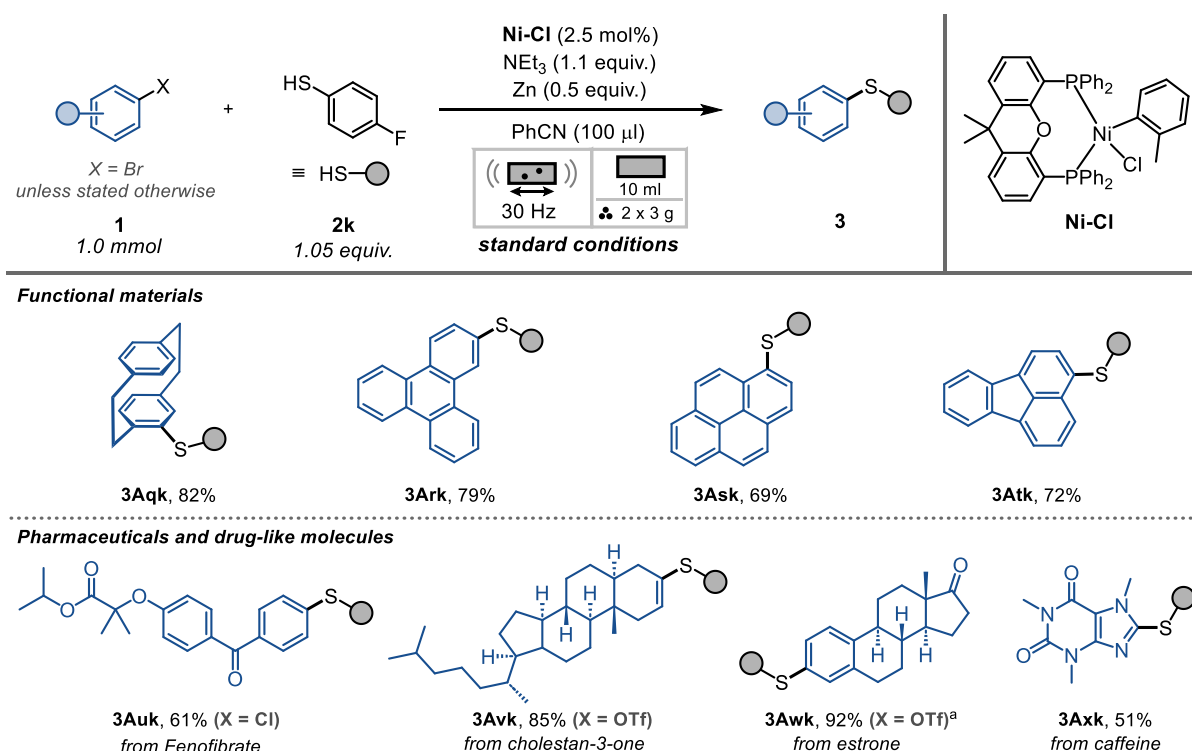


Figure 52. Substrate scope of challenging aryl (pseudo-)halides. Isolated Yields. Reaction conditions: **1** (1.0 mmol), **2k** (1.05 equiv.), **Ni-Cl** (2.5 mol%), NEt₃ (1.1 equiv.), Zn (0.5 equiv.), PhCN (100 μ l) in a SS jar (10 ml) with SS balls (2 $\times$ 3 g) at 30 Hz for 1.5 h. ^a 5 mol% Ni, 2 equiv. Zn.

Subsequently, the scope of thiols was examined (Figure 53). Initial studies with varying aryl thiols revealed low conversions under standard conditions. However, increasing the zinc loading to 2 equivalents enabled efficient coupling in most cases. Under these conditions, electron-neutral thiophenols (**3Cl–3Cn**) afforded high yields. Sterically demanding thiols, such as mesityl and 2,4,6-triisopropylbenzenethiol, were well tolerated (**3Co**, **3Cp**), indicating that steric effects are less inhibiting on the nucleophile compared to the electrophile. A chloro-substituted thiophenol afforded moderate yield (**3Cr**), with formation of symmetrical

thioethers observed as a side reaction. Both electron-rich (**3Cs–3Cu**) and electron-deficient (**3Cv**) thiophenols were compatible. While pyridine-2-thiol was unreactive, likely due to chelation or reduced nucleophilicity, pyridine-4-thiol afforded moderate yield (**3Cw**). Additionally, 2-mercaptothiophene was efficiently coupled (**3Cx**). Notably, 4-mercaptophenol proved to be a competent substrate, affording high yield (**3Cy**), despite the general incompatibility of phenolic functionalities on the electrophile. This behavior is attributed to initial thiol deprotonation, which increases the pK_a of the phenol moiety.

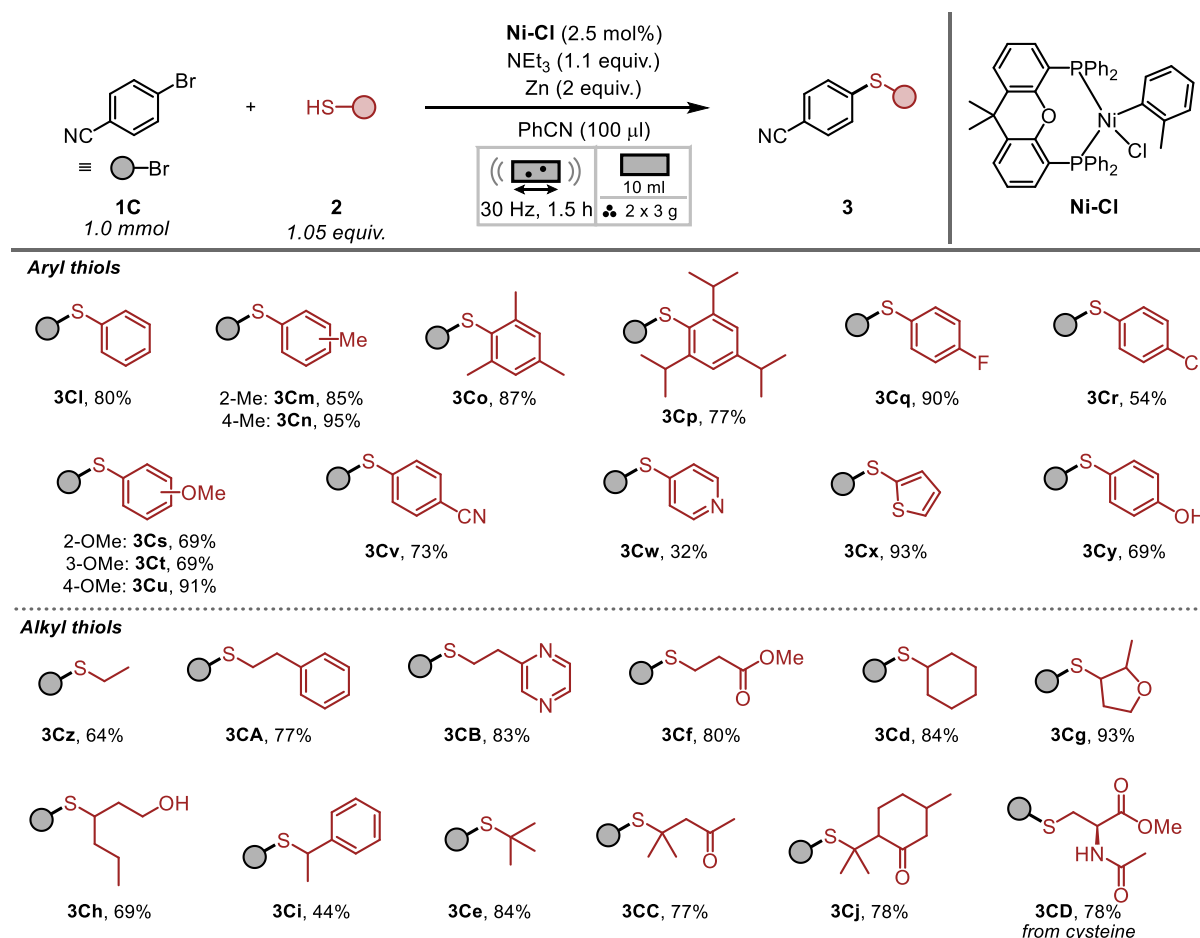


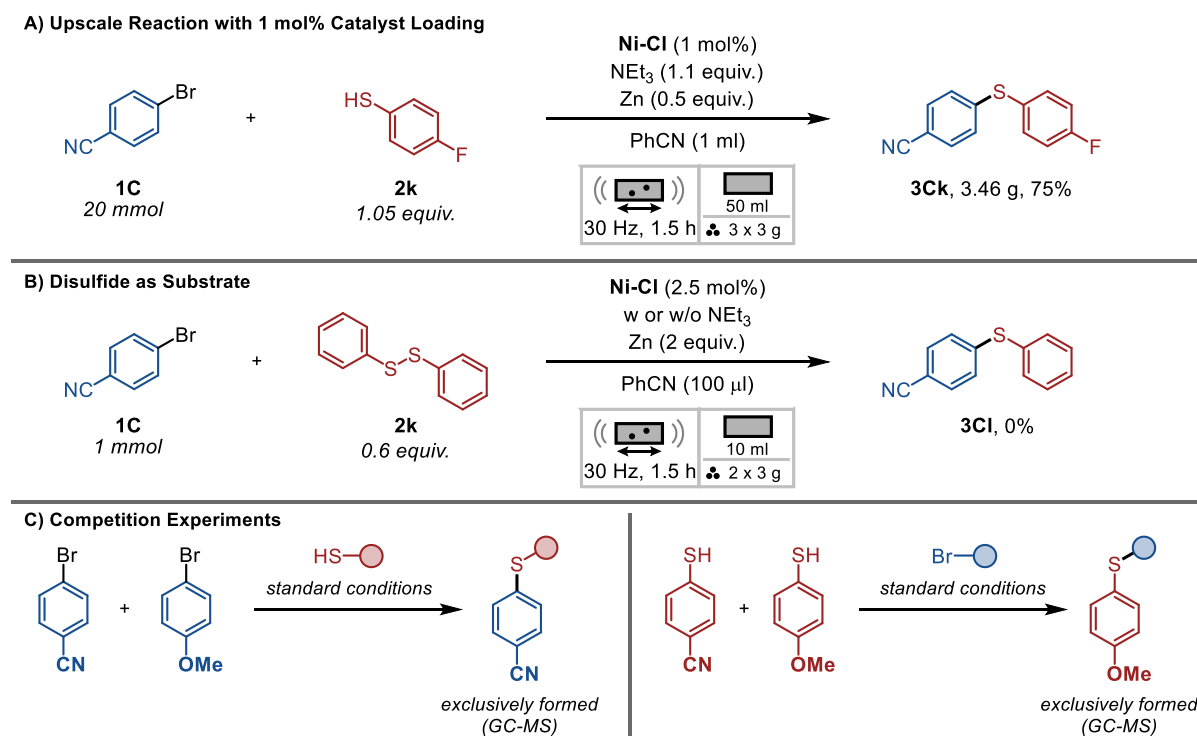
Figure 53. Substrate scope of the mechanochemical C–S cross-coupling with respect to thiols. Isolated Yields. Reaction conditions: **1C** (1.0 mmol), **2** (1.05 equiv.), **Ni-Cl** (2.5 mol%), NEt_3 (1.1 equiv.), Zn (2 equiv.), PhCN (100 μl) in a SS jar (10 ml) with SS balls (2 $\times$ 3 g) at 30 Hz for 1.5 h.

Extension to alkyl thiols revealed similar trends: increased zinc loading was required to achieve full conversion. Under these conditions, primary (**3Cz**, **3CA**), secondary (**3Cd**), and tertiary thiols (**3Cg**) were all competent coupling partners, affording the corresponding aryl alkyl thioethers in high yields. A range of functional groups on the thiol component was well tolerated, including esters (**3Cf**), ketones (**3CC**, **3Cj**), and heterocyclic motifs (**3CB**, **3Cg**). Notably, thiols bearing alcohol functionalities underwent selective *S*-arylation in good yield (**3Ch**). While benzyl mercaptan showed only minimal reactivity, the corresponding

secondary benzylic thiol furnished improved yields (**3Ci**). Importantly, a protected cysteine derivative was efficiently converted to the *S*-arylated product (**3CD**), highlighting the potential of this methodology for the functionalization of amino acid derivatives.

Overall, the developed protocol exhibited broad substrate scope and consistently high yields, underscoring its robustness. In contrast to many reported systems that preferentially accommodate either aryl or alkyl thiols,^{24, 29–30} this method demonstrated comparable efficiency for both substrate classes. Relative to existing procedures, the reaction proceeded more rapidly, delivered improved yields, and operated under comparatively mild conditions. Although the mechanochemical protocol requires (super)stoichiometric amounts of zinc, resulting in reduced atom economy, it offers significant practical advantages. The operational simplicity enables straightforward reaction setup without specialized training, minimizing systematic errors and reducing preparation time. Furthermore, tolerance toward ambient atmosphere obviates the need for inert-gas techniques, vacuum equipment, or glovebox infrastructure. A current limitation, however, is the requirement for a ball mill, which is not yet standard equipment in many laboratories.

Showcasing the scalability of the protocol, product **3Ck** was isolated in high yield (75%, 3.46 g) on a 20 mmol scale, with a reduced catalyst loading of only 1 mol% (Scheme 14, A).



Scheme 14. Further reactivity studies.

Although disulfides have been proposed as intermediates in related transformations or employed directly as thiol surrogates,²² they proved unsuitable under the present conditions (Scheme 14, B). Furthermore, intermolecular competition experiments revealed a preference for electron-deficient electrophiles and electron-rich nucleophiles (Scheme 14, C), consistent with established reactivity trends in transition-metal-catalyzed cross-coupling reactions.

Sustainability Assessment

Mechanochemistry is often declared as more environmentally friendly compared to solution-phase bulk synthesis.^{31–32} To judge the present system with respect to green metrics, a sustainability assessment of the reaction with model substrates **1C** and **2k** was performed (Figure 54).³³

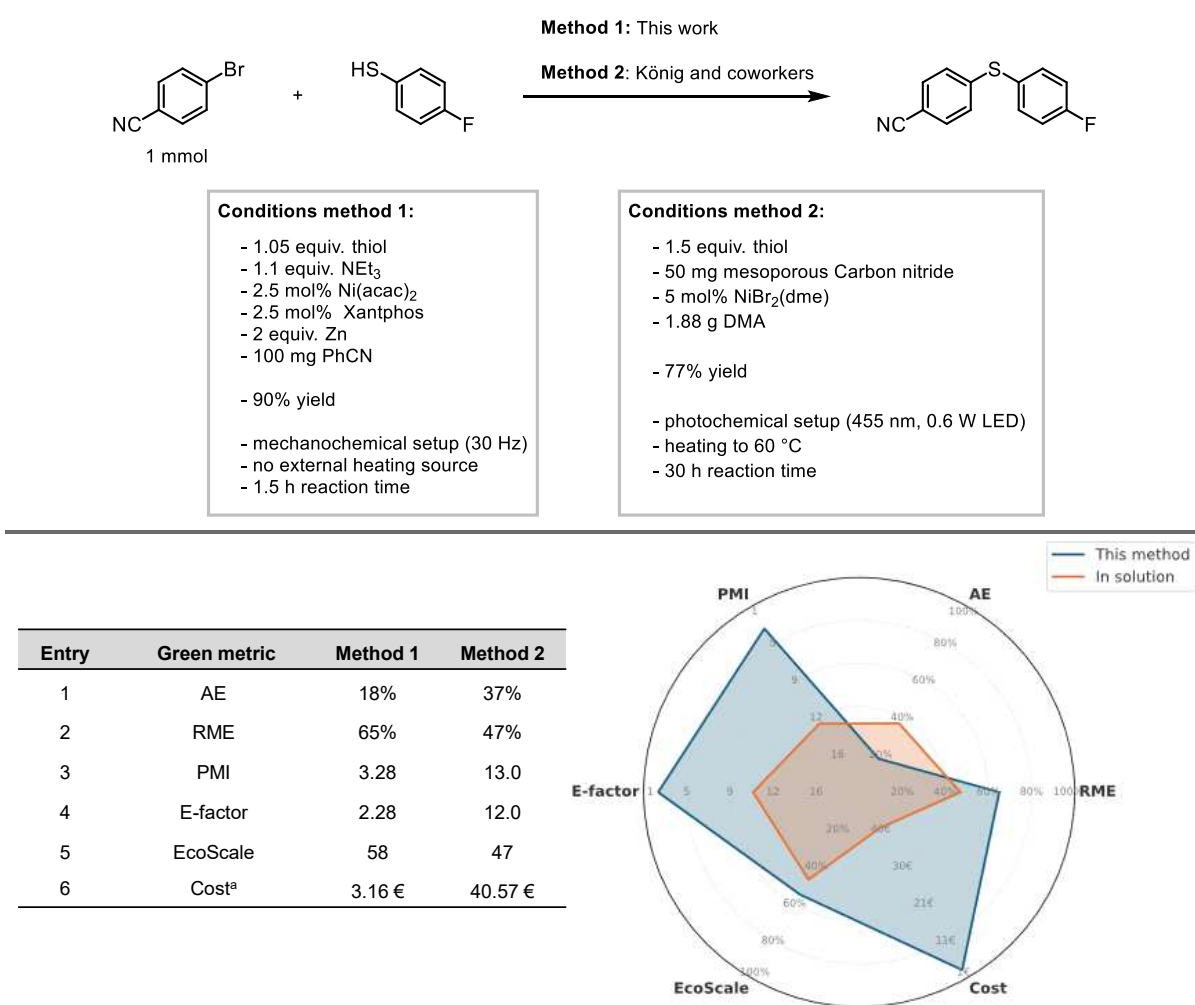


Figure 54. Evaluation of green metrics for the developed system and a photochemical C–S coupling published by König and coworkers.³⁴ AE = Atom Efficiency, RME = Reaction Mass Efficiency, PMI = Process Mass Intensity. ^a Cost of reagents and electricity for 10 mmol product.

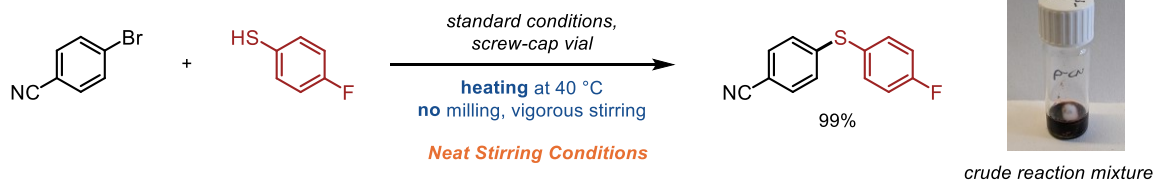
For comparison, a literature report recently published by König and coworkers³⁴ in *Green Chemistry* was also studied and compared. While the mechanochemical method suffered from

low Atom Efficiency (AE), it performed better in Reaction Mass Efficiency (RME) and Process Mass Intensity (PMI) that take all reagents, including solvents, into account. While the Ecoscale was comparable for both methods, the photochemical method suffered from lower E-factor and over 10-fold higher cost per 10 mmol of product.

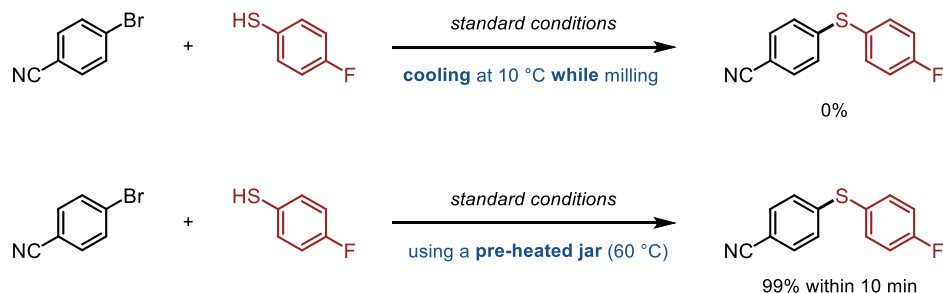
Role of Mechanical Activation

Early in the optimization studies, it was observed that the reaction did not strictly require high-energy ball milling. Comparable yields were obtained by conducting the transformation in a sealed vial under vigorous stirring at slightly elevated temperature (40 °C), as it was observed that the internal jar temperature increased to ca 35 °C during a milled reaction.

A) Reaction without Milling



B) Temperature Dependency



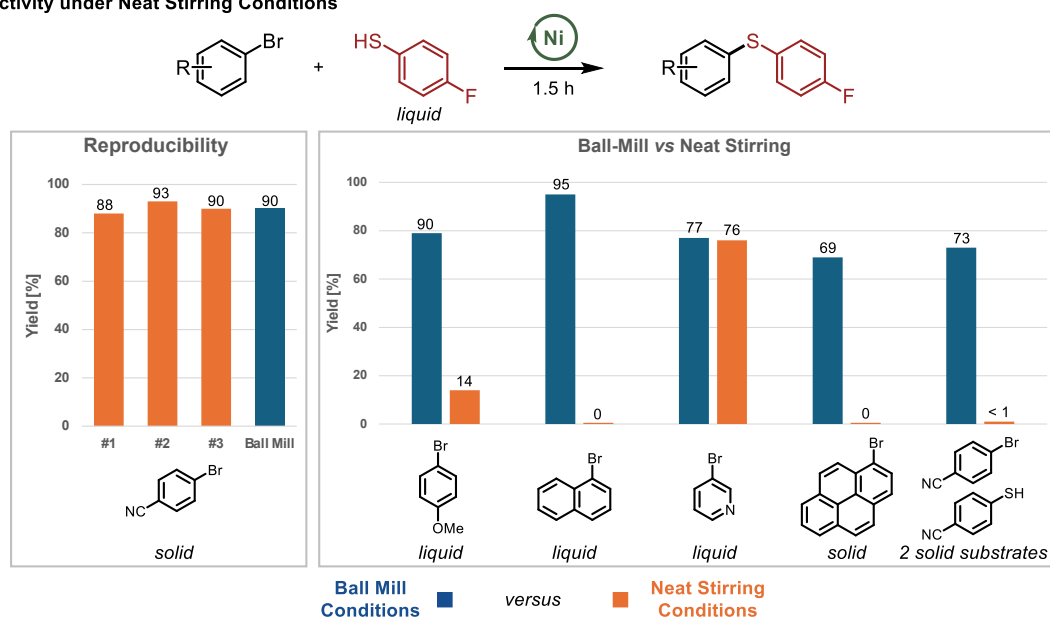
Scheme 15. Reaction without milling and temperature dependency of mechanochemical coupling. GC-FID yields.

In contrast, cooling the mechanochemical reaction to approximately 10 °C during milling, achieved by a stream of cooled nitrogen, resulted in complete suppression of product formation. Moreover, using a pre-heated milling jar (60 °C) greatly enhanced the reaction speed and full conversion was achieved in only 10 min. These findings suggest that thermal effects, rather than mechanical force alone, play a decisive role in promoting the reaction. As the high complexity of mechanochemical activation remains insufficiently understood and is controversially discussed in the mechanochemical community,^{11-12, 35-38} more experiments were conducted to investigate the role of mechanical activation in the present reaction.

Motivated by the observation that simple stirring afforded high yields, possibly rendering the ball-mill redundant, this alternative protocol was examined in greater detail (Figure 55). Reproducibility under neat stirring conditions was confirmed through repeated experiments,

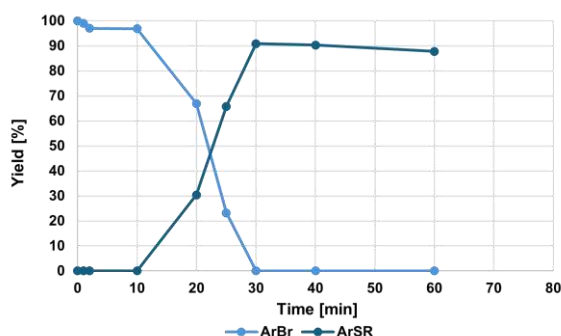
which consistently delivered excellent yields. However, evaluation of a representative substrate scope revealed notable limitations. While electron-deficient substrates afforded similar yields under both conditions, electron-neutral and electron-rich substrates, as well as poorly soluble compounds, exhibited significantly diminished reactivity under stirring. These findings suggest that ball milling not only ensures efficient mixing but may also facilitate challenging steps such as oxidative addition through mechanical activation.^{11, 36}

A) Reactivity under Neat Stirring Conditions



B) Reaction Profiles

1. In the Ball-Mill



2. Under Neat Stirring Conditions

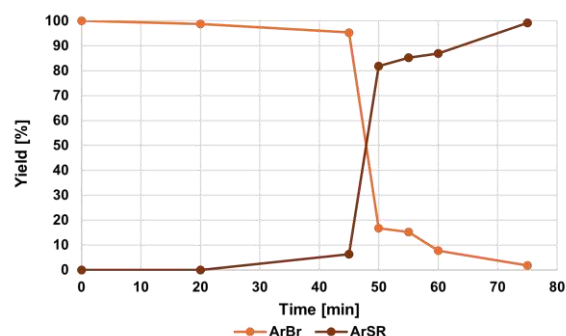


Figure 55. Evaluation of substrate scope and reaction profiles of mechanochemical versus stirring conditions. GC-FID yields. Reaction profiles were obtained from independent data sets measured as doublets.

Mechanochemical reaction conditions: Aryl halide (1.0 mmol), thiol (1.05 equiv.), Et₃N (1.1 equiv.), Ni-Cl (2.5 mol%), Zn (0.5 equiv.), PhCN (100 µl). SS jar (10 ml), SS milling balls (2 × 3 g), 30 Hz, 1.5 h.

Neat stirring conditions: Aryl halide (1.0 mmol), thiol (1.05 equiv.), Et₃N (1.1 equiv.), Ni-Cl (2.5 mol%), Zn (0.5 equiv.), PhCN (100 µl). In a screw-cap vial (3 ml) equipped with a magnetic stirring bar, 40 °C, 1.5 h.

To further compare both methodologies, reaction profiles were analyzed (Figure 55, B). Due to the closed nature of the milling vessel, time-resolved data were obtained from parallel reactions quenched at defined intervals and analyzed by GC-FID. Under mechanochemical

conditions, an induction period of approximately 10 min was observed, followed by a rapid increase in reaction rate, reaching full conversion within an additional 20 min. Prolonged milling led to slight product decomposition. In contrast, the stirred reaction exhibited a significantly longer induction period of approximately 40 min, although the subsequent catalytic turnover proceeded rapidly, reaching completion within minutes. The origin of these induction periods is likely associated with activation of the zinc surface, which is expected to occur more efficiently under mechanochemical conditions.³⁹⁻⁴⁰ Alternatively, precatalyst activation could contribute to this behavior, as proposed in related systems.⁴¹ However, the use of a preformed oxidative addition complex, (Xantphos)Ni(4-CN-Ph)Cl, as catalyst resulted in a similar induction period, indicating that precatalyst activation is not the dominant factor governing the observed kinetics.

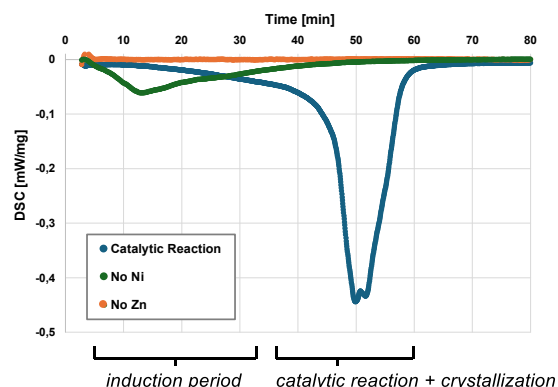
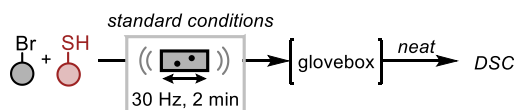
Mechanistic Studies

To gain further insight into the origin of the induction period, reaction profiles were additionally investigated by differential scanning calorimetry (DSC) and NMR spectroscopy by Dr. Robert C. Richter (Figure 56). For these studies, a new workflow for *in situ* analysis of the reaction was developed. Initially, all reagents were milled for 2 min to ensure formation of a homogeneous reaction mixture while remaining below the onset of catalytic turnover. Subsequently, the milling jars were opened inside a glovebox under inert atmosphere, and the resulting liquid reaction mixture was transferred to an appropriate vessel for further investigation. DSC measurements conducted at 300 K revealed an initial induction period, in agreement with GC-FID data. Notably, this phase was accompanied by a slowly increasing exothermic signal, indicating that additional processes preceded productive coupling. This observation would be consistent with catalyst activation occurring prior to turnover and/or acid-base chemistry. Shortly after the strongly exothermic coupling, a second thermal event observed in the DSC trace is attributed to crystallization of the product. Control experiments showed that no exothermic signal was detected in the absence of zinc, whereas exothermic behavior persisted without the nickel catalyst, suggesting that side reactions involving zinc contribute to the initial heat release. Indeed, independent experiments demonstrated that mixtures of zinc, thiol, and Et₃N evolve hydrogen gas, providing a plausible origin for the observed exothermicity. The altered shape of the DSC trace in the presence of nickel indicates that this side reaction is less relevant under catalytic conditions. Consistent with previous observations, the ¹⁹F NMR spectra showed no product formation occurred during the initial

induction period; however, rapid product formation followed, coinciding with disappearance of the thiol signal (Figure 56, B).

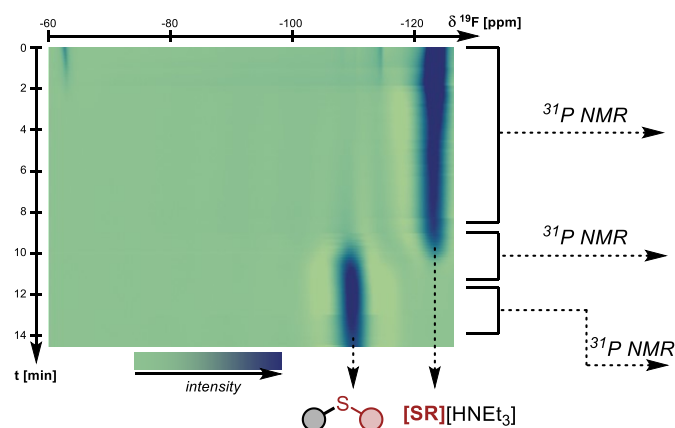
A) DSC analysis (300 K)

General workflow:



B) Neat ^{19}F and ^{31}P NMR spectroscopy

1. Heat map by ^{19}F NMR spectroscopy (303 K)



2. In situ neat ^{31}P NMR spectroscopy

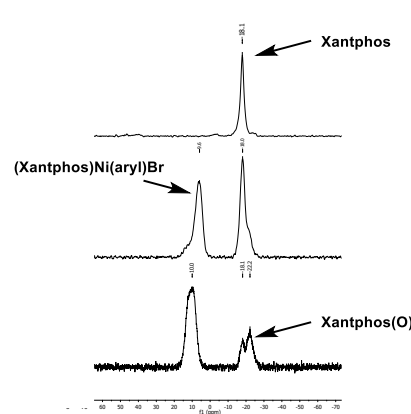


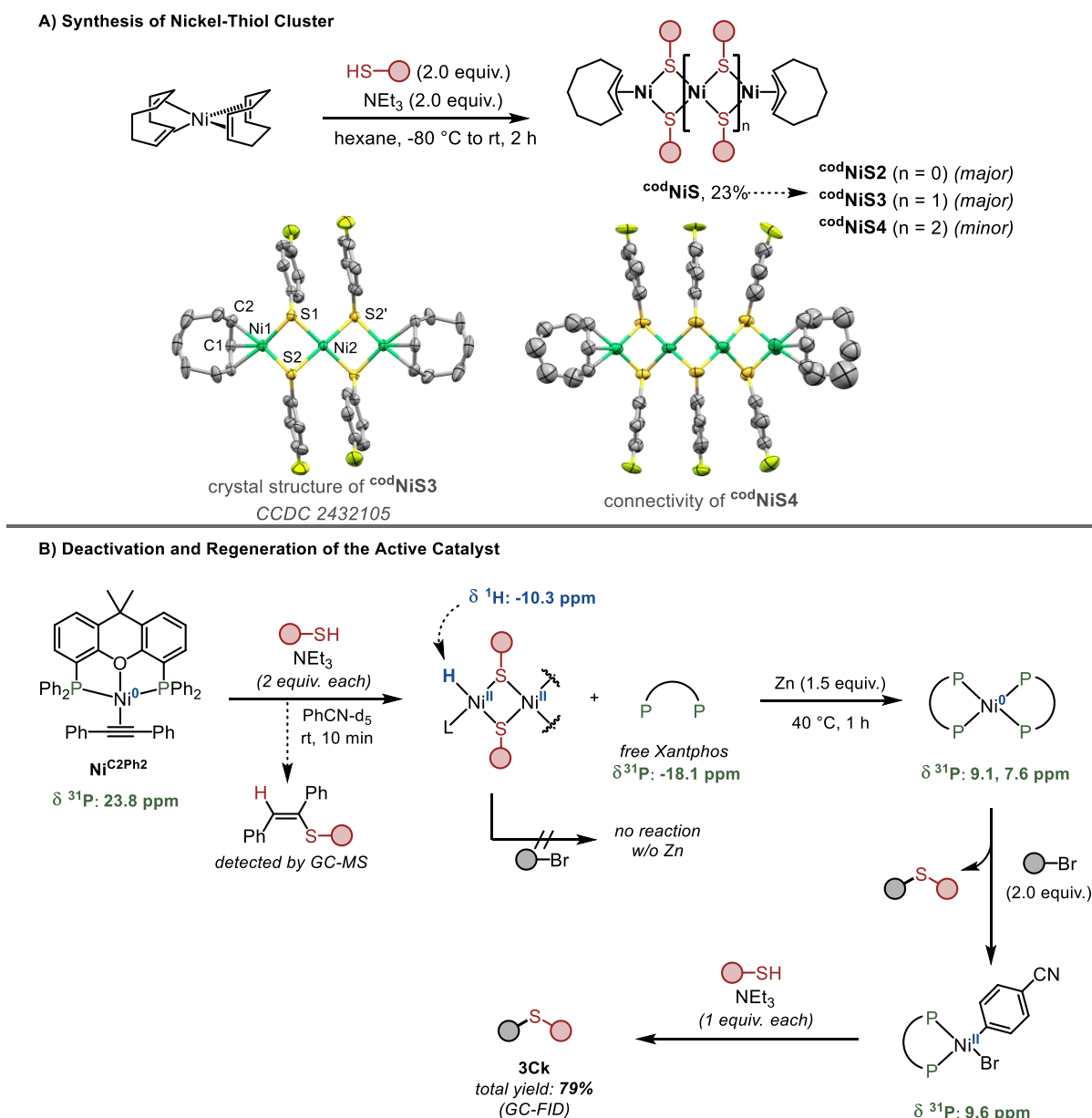
Figure 56. Mechanistic studies by DSC, ^{19}F and ^{31}P NMR spectroscopy.

Simultaneous acquisition of ^{19}F and ^{31}P NMR spectra provided further mechanistic insight. During the induction period, only signals corresponding to free Xantphos were detected in the ^{31}P NMR spectrum, indicating that the ligand was fully dissociated from nickel. This behavior was reproduced in control experiments, where treatment of **Ni-Cl** or (Xantphos)Ni(diphenylacetylene) (**NiC^{2Ph2}**) with thiol and base resulted in complete formation of free Xantphos. These findings suggest that the thiol displaces the phosphine ligand from Ni(0), forming a catalytically inactive nickel–thiolate species that is silent in ^{31}P NMR. However, during the product formation period, a new phosphorus signal at 9–10 ppm emerged, which is consistent with the oxidative addition complex (Xantphos)Ni(4-CN-Ph)Br, as independently confirmed by mixing Ni(cod)₂ with Xantphos and **1C-Br**. After completion of the reaction, significant signal broadening occurred due to product crystallization, limiting further analysis.

Collectively, these results indicate that the nickel catalyst initially forms an inactive, phosphine-free species, which is subsequently reactivated during the induction period to generate the catalytically competent species responsible for cross-coupling. It is well established that thiols can generate catalytically inactive species with many transition metals,⁴² a phenomenon commonly referred to as catalyst poisoning. However, such species are rarely characterized in detail. In a seminal study, Hartwig and co-workers identified off-cycle intermediates in palladium-catalyzed C–S cross-coupling, including $\text{LPd}(\text{SR})(\text{H})$ and anionic $[\text{LPd}(\text{SR})_2]^-$ complexes as likely resting states.⁴³ Polynuclear $[\text{Pd}(\text{SR})_2]_n$ clusters have also been observed upon treatment of $\text{Pd}(\text{II})$ salts with thiols.⁴⁴ In the context of nickel catalysis, a recent study by Ananikov and co-workers proposed the formation of metal–thiolate clusters and oxidative addition complexes in ligand-free systems conducted in ionic liquids.⁴⁵ However, these findings do not directly translate to the present system, as the phosphine ligand is essential for catalytic turnover — omission of the ligand completely suppressed reactivity.

To address the limited understanding of off-cycle species in nickel-catalyzed C–S cross-coupling, catalyst deactivation and regeneration were investigated in more detail (Scheme 16). NMR titration experiments indicated that approximately two equivalents of thiol are sufficient to convert $(\text{Xantphos})\text{Ni}(\text{C}_2\text{Ph}_2)$ into a species that is silent in ^{31}P NMR spectroscopy. Despite extensive efforts, this inactive species could not be isolated or fully characterized, likely due to its dependence on benzonitrile for formation, which simultaneously inhibited crystallization. To circumvent this limitation, benzonitrile was replaced with a π -coordinating alkene ligand, rendering $\text{Ni}(\text{cod})_2$ as ideal precursor. Treatment with two equivalents of thiol **2k** afforded a dark red mixture, from which a solid $^{\text{cod}}\text{NiS}$ could be isolated and partially characterized. NMR analysis revealed a mixture of at least two major species containing both thiolate and cyclooctadiene-derived fragments. Single-crystal X-ray diffraction identified one component as a trinuclear nickel thiolate cluster $^{\text{cod}}\text{NiS3}$ featuring a central square-planar nickel atom coordinated by four μ_2 -bridging thiolate ligands, with additional nickel centers capped by allylic cyclooctenyl moieties. The solution-state structure appeared to reflect the solid state, supported by 2D NMR spectroscopy, including ROESY correlations between thiolate and allylic protons. Further fractional crystallization suggested the presence of a second, likely dimeric species with a 1:1 ratio of thiolate to cyclooctenyl ligands ($^{\text{cod}}\text{NiS2}$), although this species could not be characterized by XRD. The allylic fragments can be interpreted as indirect proof for a nickel hydride species, as they arise from insertion of cyclooctadiene into a Ni-H bond, followed by chain-walking. This implied that $\text{Ni}(0)$

underwent oxidative addition with thiols to generate hydride–thiolate species of the type LNi(H)(SR) , analogous to reactivity reported for palladium systems.⁴³ The reactivity of such nickel–thiolate clusters was further explored (Scheme 16, B).



Scheme 16. Synthesis and reactivity of nickel–thiolate clusters. Stoichiometric coupling was performed in an NMR tube in PhCN-d_5 (0.5 ml).

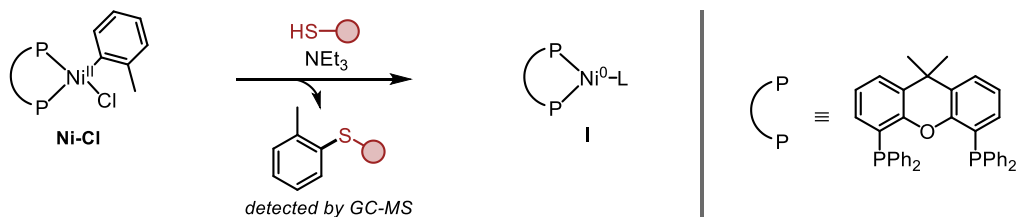
Consistent with the hypothesis discussed above, treatment of $(\text{Xantphos})\text{Ni}(\text{C}_2\text{Ph}_2)$ with excess thiol and base led to the observation of a broad hydride signal at $\delta \approx -10.3$ ppm in the ^1H NMR spectrum. This mixture did not exhibit catalytic activity unless zinc was added. Upon addition of zinc, new phosphorus-containing species were detected, including signals consistent with $(\text{Xantphos})_2\text{Ni}(0)$ and possibly $(\text{Xantphos})\text{Ni}(\text{PhCN})$.⁴⁶ Subsequent addition of aryl bromide **1C-Br** resulted in formation of the oxidative addition complex

(Xantphos)Ni(aryl)(Br), whose ^{31}P NMR signal matched that observed under catalytic conditions (Figure 56). This complex is therefore proposed to represent the resting state of the catalytic cycle. Addition of thiol then led to efficient formation of the cross-coupled product **3Ck**.

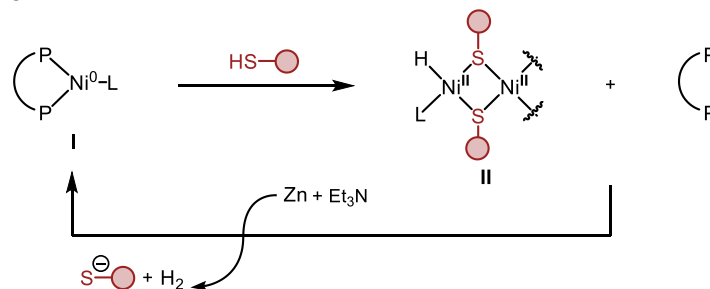
These findings indicate that zinc does not primarily serve to suppress aerobic thiol oxidation but rather plays a crucial role in reactivating off-cycle nickel–thiolate species through reductive processes, thereby regenerating catalytically active Ni(0) species. The absence of detectable EPR-active intermediates in the reaction mixture further supports a closed-shell mechanism without involvement of persistent radical species.

These investigations enabled the formulation of a mechanistic proposal for the mechanochemical C–S cross-coupling (Scheme 17). Upon mixing all components, the precatalyst **Ni–Cl** undergoes activation *via* ligand exchange with the thiolate, followed by reductive elimination of 2-tolyl sulfide, a process discussed above (chapter 3) and confirmed in this case by GC–MS analysis (Scheme 17, A). This step generates a phosphine-ligated Ni(0) species **I**. Subsequently, **I** reacts with excess thiol, leading to oxidation of the nickel center and formation of a catalytically inactive nickel hydride species (**II**) (Scheme 17, B). It is unlikely that **II** corresponds to a single, well-defined structure; rather, it is best described as a dynamic mixture of nickel hydride–thiolate clusters of varying nuclearity. In contrast to analogous palladium systems,⁴³ the phosphine ligand does not remain coordinated in these species, and no evidence for anionic nickelate complexes was obtained. Intermediate **II** is then reduced by zinc, regenerating the active Ni(0) species **I** and releasing hydrogen gas as a byproduct. Notably, this regeneration step is highly temperature-sensitive: it proceeds only sluggishly at 25 °C but becomes efficient at slightly elevated temperatures (≈ 35 °C). The interplay between deactivation and regeneration likely constitutes a pre-equilibrium that persists until a sufficient fraction of protons has been reduced, a process that may account for the initial exothermic signal observed in DSC experiments. Once formed, **I** enters the productive catalytic cycle (Scheme 17, C), comprising oxidative addition of the electrophile, thiolate coordination, and reductive elimination to furnish the thioether product. Benzonitrile likely facilitates this process by forming a more reactive monoligated species (Xantphos)Ni(PhCN) (**I-A**), thereby avoiding the formation of less reactive bis-ligated (Xantphos)₂Ni (**I-B**).⁴⁶

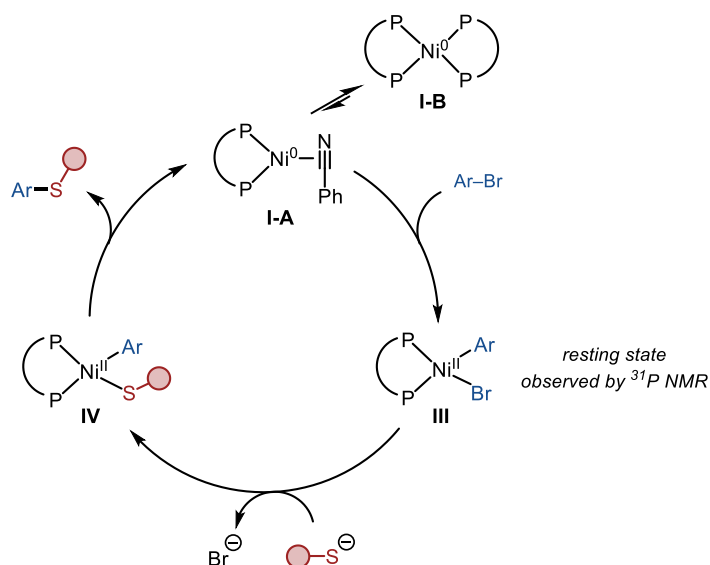
A) Initial Activation of the Precatalyst



B) Deactivation and Regeneration



C) Proposed Catalytic Cycle

**Scheme 17.** Proposed catalyst deactivation, regeneration and catalytic cycle.

In situ ³¹P NMR studies indicated that the oxidative addition complex (III) serves as the resting state under the examined conditions, although this may vary depending on substrate electronics and the facility of oxidative addition. Finally, differences in acidity and nucleophilicity between aryl and alkyl thiols suggest that mechanistic details may not be directly transferable across substrate classes.

Conclusion

In summary, an operationally simple mechanochemical protocol was established for the thioetherification of aryl bromides and activated aryl chlorides under ambient atmosphere. In addition, aryl and alkenyl triflates proved to be competent electrophiles, enabling access to thioethers from phenol- and ketone-derived substrates. Both aryl and alkyl thiols furnished the corresponding products in consistently high yields, and the method exhibited broad functional group tolerance. The method is not only characterized by high efficiency, but beneficial green metrics compared to recent methodologies as revealed by sustainability assessment. Mechanistic studies indicated that mechanical input enhances reaction efficiency, whereas catalytic turnover itself is predominantly thermally driven. This is underscored by the observation that electron-deficient aryl bromides can also be converted under simple stirring conditions without the need for ball-milling. Further investigations revealed that, under mechanochemical conditions, the catalyst initially reacts with the thiol to form catalytically inactive nickel–thiolate clusters. A model system for these off-cycle species could be isolated using cyclooctadiene as a stabilizing ligand and structurally characterized, including X-ray diffraction. Reduction of these clusters with zinc in the presence of the phosphine ligand regenerates the active Ni(0) species, which subsequently operates through a conventional Ni(0)/Ni(II) catalytic cycle. This mechanistic proposal is supported by a combination of control experiments and stoichiometric studies.

4.2. Experimental

For general information on instrumentation, experimental details and analytical data of starting materials, nickel complexes and coupling products, see the Supporting Information of the published article, available free of charge at the publisher's website: DOI 10.1021/acscatal.5c04516.

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5. Mechanochemical Nickel-Catalyzed XEC of Thioesters with Alkyl Bromides

5.1. Summary of Published Results

This chapter is based on the following publication:

Ivo H. Lindenmaier,[†] Robert C. Richter,[†] Liesa Renz, Mattis T. Vochezer, Marius Schier, Pascal Faßnacht, Markus Ströbele and Ivana Fleischer, *Chem. Comm.* **2026**, 62, 5284–5288. DOI: 10.1039/D6CC00297H.

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Reaction Development and Optimization

Ketones constitute a fundamental class of compounds and are ubiquitous in both natural products and synthetic chemistry due to their versatility as intermediates for further functionalization.¹ Although numerous classical textbook methods,^{2–7} as well as metal-catalyzed^{8–11} methods for ketone synthesis have been established, cross-electrophile coupling (XEC) of an acyl source with an appropriate electrophile has emerged as an attractive alternative, as it avoids the use of sensitive and often hazardous organometallic reagents.¹² Early contributions by Mukaiyama,¹³ Weix¹⁴ and Gong¹⁵ demonstrated the feasibility of such transformations; however, these protocols often suffered from long reaction times and reproducibility issues associated with the use of metallic reductants.^{12, 16–22} Mechanochemistry offers a promising strategy to address these limitations by enhancing mass transfer and promoting efficient surface activation of metallic reductants,^{23–27} frequently resulting in shorter reaction times and improved robustness.^{28–32} To date, only a single mechanochemical approach toward cross-electrophile ketone synthesis has been reported by the Browne group, employing twisted amides³³ as acyl sources in coupling reactions with alkyl bromides.²⁵ While this study demonstrated the general feasibility of the concept, mechanistic insight remained limited, and the structural tunability of twisted amides is inherently restricted. In contrast, thioesters represent versatile acyl electrophiles whose reactivity can be readily

modulated through variation of the sulfur substituent.³⁴⁻³⁶ Motivated by these advantages, the use of thioesters in mechanochemical XEC for ketone synthesis was investigated (Table 1). Initial studies focused on the coupling of *S*-phenyl benzothioate (**6a**) with hydrocinnamyl bromide (**7a**), affording the desired ketone **8aa**. Under typical XEC conditions employing a phenanthroline ligand, zinc as reductant, and *N,N'*-dimethylpropylene urea (DMPU) as solvent, the product was obtained in a promising 44% yield (entry 1). Ligand screening identified dtbbpy as the optimal ligand (entry 3), whereas related bipyridine derivatives with varying electronic properties afforded diminished yields (entries 1–5).

Table 10. Ligand screening for mechanochemical XEC of thioesters with alkyl bromides.

Entry	Ligand	Conv. 6a [%]	Yield [%]
1	phen (L14)	55	44
2	bpy (L15)	86	24
3	dtbbpy (L16)	98	54
4	L17	25	20
5	L18	98	24
6	terpy (L19)	52	19
7	PyBOX (L20)	86	4
8	PPh ₃	33	1
9	dppf (L6)	34	1

Yields and conversions were determined by GC-FID using pentadecane as internal standard.

Alternative nitrogen-based ligands, such as terpyridine, as well as bisoxazoline derivatives, proved less effective (entries 6, 7), and phosphine ligands did not promote product formation (entries 8, 9).

Next, reducing agents were examined (Table 10). Substituting zinc with other metals such as manganese or magnesium resulted in inferior yields (entries 1–3). Interestingly, productive coupling was also possible using organic reductant **OR1**,³⁷ although no product formation was observed using dihydropyrazine **OR2** (entries 4, 5).

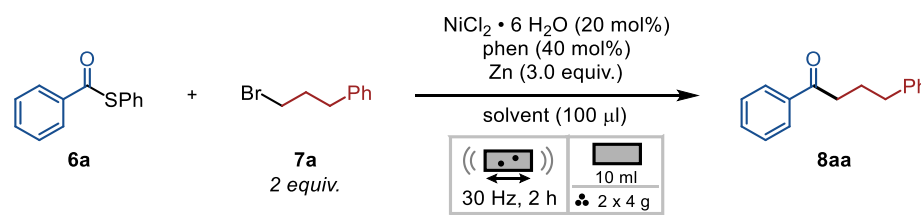
Table 11. Reductant screening for mechanochemical XEC of thioesters with alkyl bromides.

Entry	Reductant	Conv. 6a [%]	Yield [%]
1	Zn	98	51
2	Mn	63	21
3	Mg	100	2
4	OR1	39	27
5	OR2	43	0

Yields and conversions were determined by GC-FID using pentadecane as internal standard.

The choice of liquid additive proved critical (Table 11), a common phenomenon in liquid-assisted grinding (LAG).³⁸ Less polar or solvent-free conditions led to significantly reduced yields (entries 1, 7, 8), whereas polar additives facilitated the transformation. Among these, DMA, commonly employed in solution-phase XEC, gave encouraging results (entry 3). Surprisingly, pyridine emerged as the optimal LAG additive (entry 9), enabling the formation of the desired ketone in excellent yield. This Lewis base may diminish the inhibitory effect of ZnX_2 , which is a byproduct of the reaction.^{39–40} Indeed, the addition of one equivalent of ZnBr_2 under standard conditions resulted in a dramatic decrease in yield to 6%, highlighting its inhibitory role. Additional support for the role of pyridine in this reaction was obtained from a complex that crystallized after aqueous work-up from the reaction mixture and was analyzed by X-Ray diffraction, revealing complexation of Zn^{2+} ions by pyridine (Figure 53).

Table 12. Solvent screening for mechanochemical XEC of thioesters with alkyl bromides.

			
Entry	Solvent	Conv. 6a [%]	Yield [%]
1	None	23	8
2	DMPU	55	44
3	DMA	98	51
4	DMF	67	32
5	MeOH	62	31
6	MeCN	61	22
7	THF	41	15
8	toluene	29	11
9	pyridine	100	87

Yields and conversions were determined by GC-FID using pentadecane as internal standard.

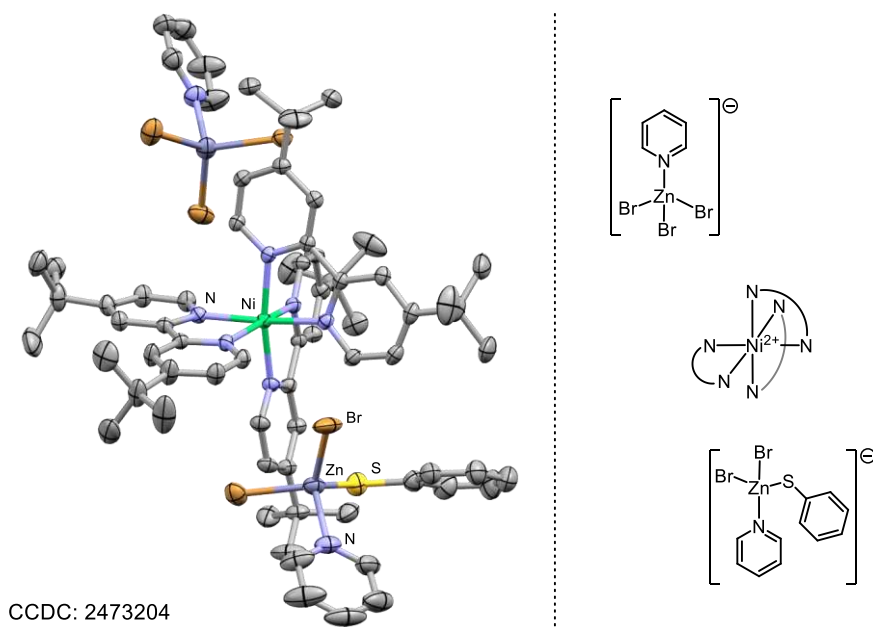


Figure 57. ORTEP representation of $[\text{Ni}(\text{dtbbpy})_3][\text{Zn}(\text{PyH})\text{Br}_3][\text{Zn}(\text{PyH})(\text{SPh})\text{Br}_2]$ (CCDC: 2473204) crystallized from crude reaction mixture after aqueous workup. Hydrogen atoms are omitted for clarity, and the thermal ellipsoids are drawn at 50% probability level.

Further additive screenings identified sodium chloride as effective and low-cost additive,⁴¹⁻⁴² and combination with pyridine allowed reduction of the Ni/L loading to 10/20 mol% as well as zinc loading to 2 equiv. Moreover, reaction time screening revealed that 1 h reaction time was sufficient for full conversion. Under these optimized conditions, ketone **8aa** was isolated in 85% yield, and the protocol could be readily scaled to gram quantities, affording 4 g of product without loss in efficiency.

Substrate Scope

Subsequently, the substrate scope was investigated (Figure 51). Beyond simple benzoic thioester (**8aa**), sterically more demanding thioesters were also competent substrates, affording the desired ketones in good yields (**8ba**, **8ca**). A broad range of substituents on the aromatic ring was tolerated, including both electron-withdrawing and -donating groups. Functional groups such as halides (**8da**, **8ea**), a trifluoromethyl group (**8fa**), esters (**8ga**), and methoxy substituents (**8ha**) were well accommodated, generally providing good yields. In contrast, more electron-rich systems such as benzodioxole resulted in diminished efficiency (**8ia**). Notably, substrates bearing electron-withdrawing groups tended to form increased amounts of decarbonylated side products. Aliphatic thioesters also proved viable, furnishing dialkyl ketones in excellent yields (**8ja**, **8la**). However, homobenzylic thioesters exhibited a propensity for decarbonylation and homocoupling, leading to elevated levels of byproducts (**8ka**). Substrates containing unsaturated alkyl chains were well tolerated (**8ma**). Furthermore, thioesters incorporating secondary aliphatic cyclic motifs on the acyl fragment afforded the corresponding ketones in good to high yields (**8na**, **8qa**), and heterocyclic substrates were similarly compatible (**8oa**, **8pa**). Even sterically congested tertiary thioesters underwent coupling, albeit with reduced efficiency (**8ra**).

The scope of the alkyl bromide component was subsequently examined. Primary alkyl bromides provided the desired products in good yields (**8ja**, **8jb**). The protocol exhibited broad functional group tolerance, including alkyl and aryl chlorides (**8jc**, **8jd**), trifluoromethyl substituents (**8jf**), and aryl bromides (**8je**), the latter offering a useful handle for downstream functionalization. Ketones bearing protected alcohols (silyl or methyl ethers; **8jg**, **8jh**) as well as ester functionalities (**8ai**, **8ji**) were obtained in moderate to good yields. Secondary alkyl bromides were also suitable coupling partners despite their increased steric demand, affording products in good to high yields (**8jj–8jl**).

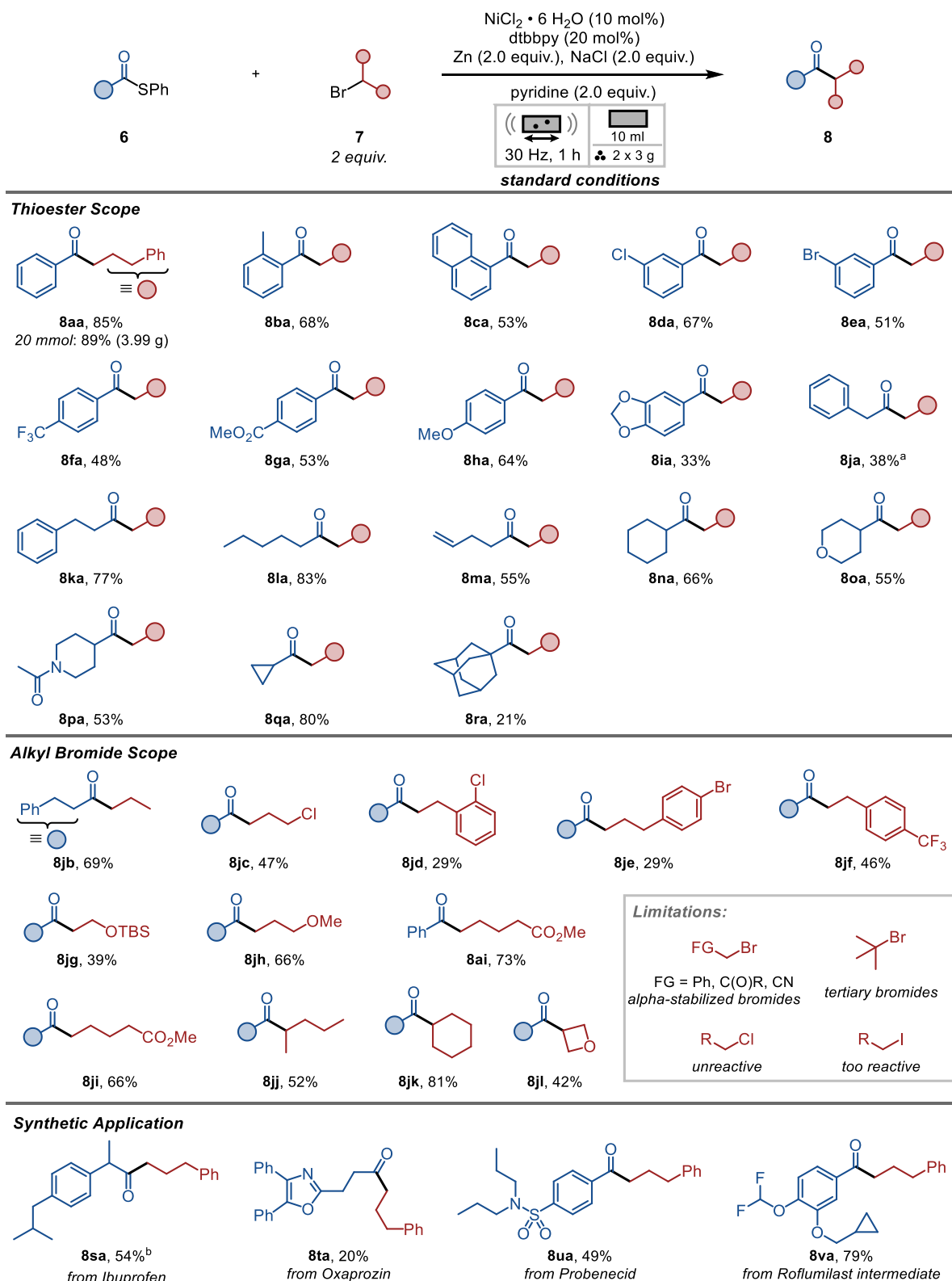


Figure 58. Substrate scope of the mechanochemical XEC of thioesters with alkyl bromides. Isolated Yields. Reaction conditions: **6** (1.0 mmol), **7** (2.0 equiv.), $\text{Ni}(\text{H}_2\text{O})_6\text{Cl}_2$ (10 mol%), dtbbpy (20 mol%), Zn (2.0 equiv.), NaCl (2.0 equiv.), pyridine (2.0 equiv.) in a SS jar (10 ml) with SS balls (2×4 g) at 30 Hz for 1 h. ^a ¹H NMR yield from an isolated sample. ^b 2 h.

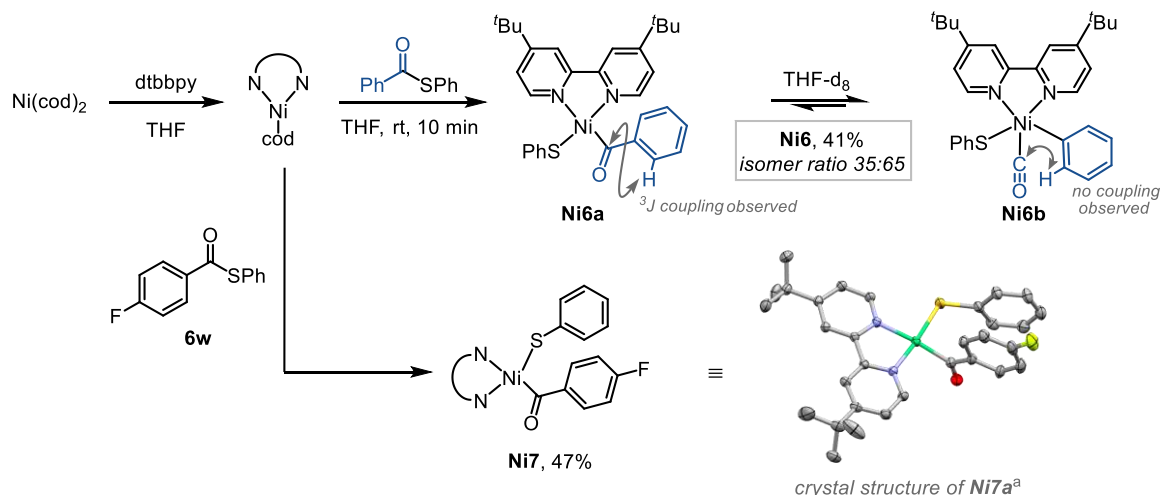
Limitations were observed for tertiary alkyl bromides, which showed low conversions, and for activated bromides, as well as alkyl iodides, which predominantly underwent homocoupling.

Finally, the synthetic utility of the method was demonstrated by employing thioesters derived from pharmaceutically relevant compounds, including Ibuprofen, Oxaprozin, and Probenecid, as well as an intermediate in the synthesis of Roflumilast. These substrates furnished the corresponding ketones in moderate to good yields (**8sa–8va**).

Mechanistic Studies

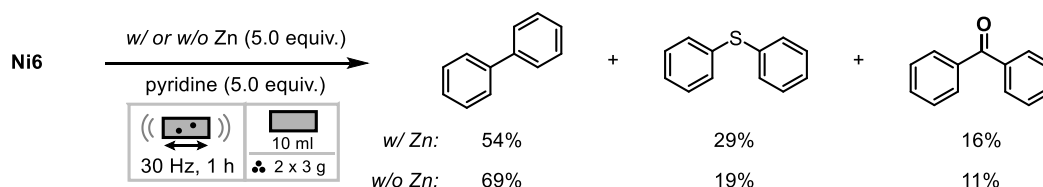
Next, we turned our attention to the reaction mechanism (Scheme 17), as both a Negishi-type pathway and a radical-chain mechanism appeared plausible.^{12, 24-25, 43} Particular emphasis was placed on the activation of thioesters, for which clear mechanistic evidence regarding oxidative addition to nickel remains scarce. Consequently, we attempted the synthesis of a defined oxidative addition complex by treating thioester **6a** with a dtbbpy-ligated nickel(0) species, affording complex **Ni6** (Scheme 17, A). Interestingly, **Ni6** was obtained as a mixture of the acyl complex **Ni6a** and its CO-deinserted isomer **Ni6b**, with the latter predominating (ca. 35:65). This assignment was based on ¹H–¹³C HMBC NMR spectroscopy, which revealed the presence or absence of a three-bond coupling between the carbonyl carbon and an *ortho*-proton of the aryl ring. Variation of the addition temperature (80 °C to rt) as well as the measurement temperature (40 °C to rt) had little impact on this ratio, suggesting the presence of a rapid equilibrium between both species in solution. While crystallization of **Ni6** remained unsuccessful, a 4-fluoro-substituted analogue (**Ni7a**) could be structurally characterized by X-ray diffraction. The solid-state structure confirmed a square-planar nickel(II) center bearing an intact acyl ligand, although this acyl form likewise represented the minor species in solution. The observed structure and diamagnetic behavior are consistent with literature on nickel-acyl complexes.⁴⁴ Given that the isomer distribution observed in THF solution may not directly reflect mechanochemical conditions, a control experiment was conducted (Scheme 17, B). Subjecting **Ni6** to ball-milling resulted in the formation of several scrambling products, with decarbonylated species predominating. This observation suggested that either **Ni6b** is the dominant species under these conditions or that it reacts more rapidly. In contrast, when **Ni6** was subjected to stoichiometric coupling with alkyl bromide **7a**, the ketone product **8aa** was formed as the major product, accompanied by only minor amounts of the decarbonylated byproduct **9**.

A) Isolation and Characterization of Oxidative Addition Complexes

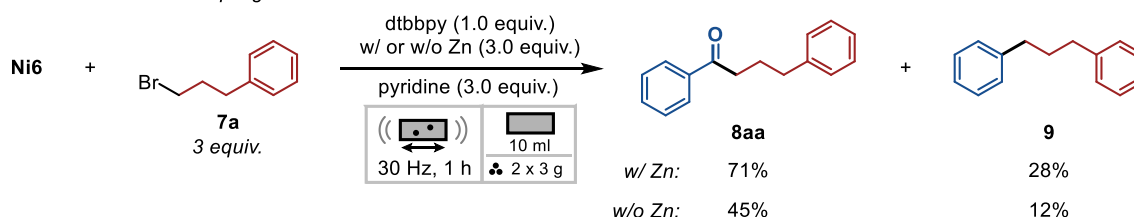


B) Reactivity of **Ni6**

1. Under mechanochemical conditions^b



2. In stoichiometric coupling^c

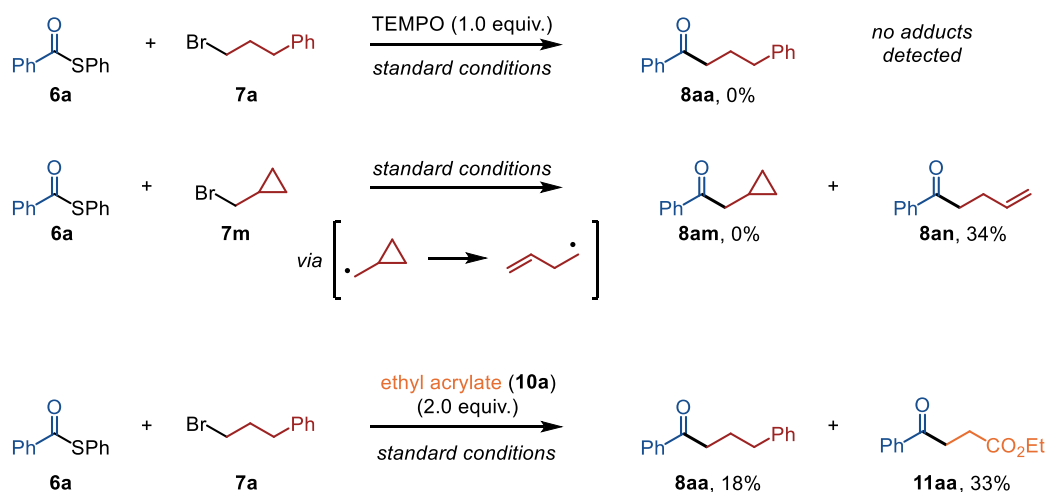


Scheme 18. Isolation and reactivity studies of oxidative addition complex **Ni6**. ^a Selected bond lengths and angles for **Ni7a** ([Å] or [°]): Ni–C 1.859(1), C–O 1.220(1), N–Ni–C 94.66(4), S–Ni–C 90.21(3). ^b Yields estimated by GC-MS. ^c Yields determined by GC-FID using pentadecane as internal standard.

These results indicate that **Ni6a** reacts more rapidly with alkyl bromides than **Ni6b** and is likely regenerated from **Ni6b** under the reaction conditions, consistent with a Curtin-Hammett-type scenario. A plausible explanation is that **Ni6b** must first undergo CO extrusion prior to productive radical capture. Notably, catalytic reactions employing more electron-deficient aryl thioesters led to increased formation of decarbonylated products, suggesting that CO extrusion becomes more competitive in such cases.

We next focused on the coupling step. Compelling evidence for a radical-chain mechanism was obtained from inhibition experiments, as the addition of the radical scavenger TEMPO suppressed product formation (Scheme 18). Furthermore, the use of a radical reporter **7m** led to the formation of the corresponding ring-opened product (**8an**), consistent with the involvement of radical intermediates. The activation of alkyl bromides *via* single-electron

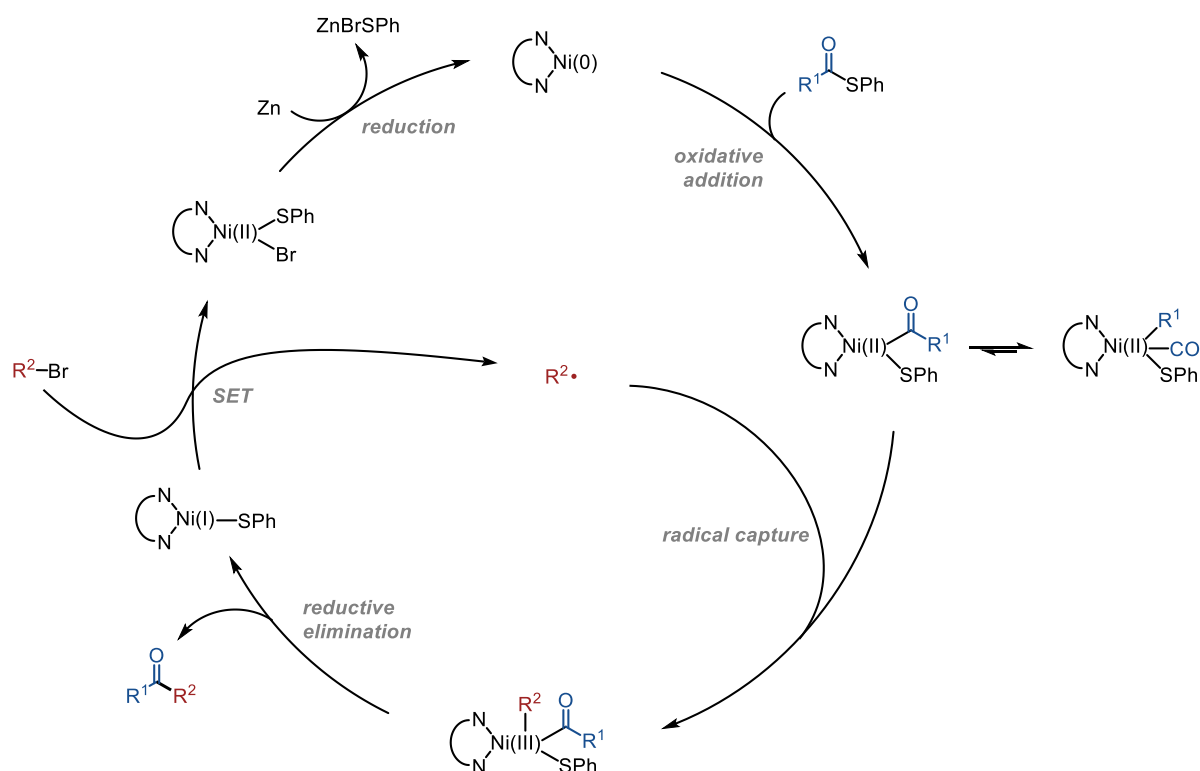
transfer (SET) from nickel is well preceded in the literature.¹² Although Browne and co-workers reported the formation of organozinc intermediates under related conditions,^{24-25, 43} the absence of product **8am** in our system argues against a Negishi-type pathway.



Scheme 19. Addition of radical scavengers and reporters to mechanochemical XEC of thioesters with alkyl bromides. Isolated yields.

This conclusion is further supported by the observation that organic reductants could replace zinc, albeit with reduced efficiency. In addition, the introduction of a Michael acceptor into the reaction mixture resulted in formation of the formal Giese-adduct **12aa**, indicating the intermediacy of an acyl radical,⁴⁵ although a competing nickel-mediated migratory insertion pathway cannot be definitively excluded and is subject to further investigation (chapter 6).

On the basis of these findings, we propose a radical-chain mechanism consistent with recent reports (Scheme 19).^{14, 17, 25, 46} The catalytic cycle likely begins with oxidative addition of the thioester to nickel, forming the corresponding oxidative addition complex. Subsequent capture of an alkyl radical, presumably generated via SET from a Ni(I) species,⁴⁷ followed by reductive elimination affords the ketone product. The resulting Ni(II) species is then reduced by zinc to regenerate the active catalyst, thereby closing the catalytic cycle.



Scheme 20. Proposed catalytic cycle of the mechanochemical XEC of thioesters with alkyl bromides.

Conclusion

In summary, an efficient method for the cross-electrophile coupling of aliphatic and aromatic thioesters with alkyl bromides was developed. The protocol exhibits broad substrate scope, including biologically relevant molecules, and benefits from the operational simplicity of mechanochemical conditions, obviating the need for inert-atmosphere techniques such as Schlenk lines or gloveboxes. Compared to existing mechanochemical approaches to ketone synthesis, this method provided comparable yields with significantly reduced reaction times. Moreover, the preliminary mechanistic studies presented herein contribute to a deeper understanding of the reactivity of acyl electrophiles under mechanochemical conditions.

5.2. Experimental

For general information on instrumentation, experimental details and analytical data of published results, see the Supporting Information of the published article, available free of charge at the publisher's website: DOI: 10.1039/D6CC00297H.

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6. Mechanochemical Nickel-Catalyzed Hydroacylation of Activated Alkenes

6.1. Summary of Published Results

This chapter is based on the following publication:

Ivo H. Lindenmaier, Fabian Bölzle and Ivana Fleischer, *Chem. Sci.* **2026**. DOI 10.1039/d6sc04272d.

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Reaction Development and Optimization

1,4-Dicarbonyl compounds are important synthetic intermediates for the preparation of heterocycles and cyclopentenones.¹⁻⁴ Their synthesis remains challenging because the direct coupling of acyl electrophiles with electron-deficient alkenes is disfavored by intrinsic polarity mismatch, requiring polarity inversion (umpolung) of either the alkene or the acyl component. Established acyl umpolung strategies are effective but often require prefunctionalized substrates, multiple synthetic steps, and strong bases,⁵⁻⁶ although organocatalytic variants offer milder alternatives.⁷⁻⁹

Rhodium-catalyzed hydroacylation of alkenes has been extensively developed and provides efficient access to carbonyl-containing products.¹⁰⁻¹² However, the high cost and limited sustainability of rhodium reduce its practical attractiveness. More recently, photoredox methods have enabled *in situ* generation of acyl radicals from aldehydes,¹³ α -keto acids,¹⁴⁻¹⁵ and selected carboxylic acid derivatives.¹⁶⁻¹⁷ These radicals undergo Giese-type addition to activated alkenes, furnishing linear 1,4-dicarbonyl products after termination.¹⁸ Despite their synthetic utility, such methods commonly suffer from limited substrate scope, extended reaction times, and scale-up challenges. Nickel-catalyzed intermolecular hydroacylation has also been reported, but existing methods rely on silane-derived nickel hydride species and predominantly yield branched 1,3-dicarbonyl products,¹⁹⁻²⁰ or are limited to specific substrates such as dienes or styrenes.²¹⁻²³ To date, nickel-catalyzed hydroacylation of acrylates without photochemical activation remains underexplored.

In the course of investigating thioesters as acyl donors in nickel-catalyzed mechanochemical cross-electrophile coupling with alkyl halides, a competing formation of acylated Michael adducts was observed in the presence of ethyl acrylate (see chapter 5). This reactivity, which leverages the inherent polarity of both coupling partners under reductive conditions, prompted further study. Initial conditions were adopted from the preliminary hit, leading to systematic optimization of ligands for more efficient coupling (Table 13). Among bipyridine-type ligands, electron-poor ligands performed best, revealing **L21** (10 mol%) to be optimal (entries 1–9). Neither terpyridine, bisoxazoline derivatives, nor phosphines afforded the coupling product in satisfactory yields (entries 10–15).

Next, solvents that were used for liquid-assisted grinding were screened (Table 12).²⁴ While polar coordinating solvents such as DMA and DMF provided encouraging results (entries 1, 2), other polar and unpolar solvents furnished trace yield (entries 3–11). Interestingly, alcohols and even water did not fully suppress product formation, but also gave inferior yields (entries 4, 8). Although DMF appeared as the best solvent, an additional hydrogen source further increased the yield. Indeed, using a mixture of DMF and H₂O resulted in 82% GC-FID yield for the best ratio of 5:1 (entries 13–18).

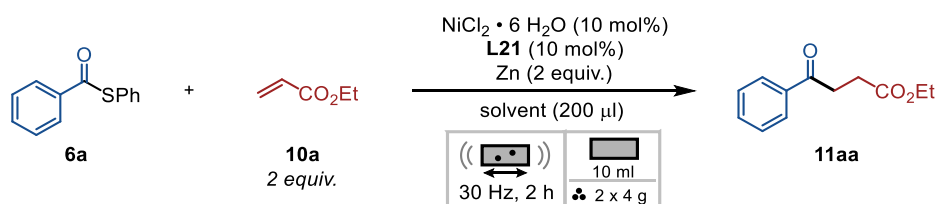
Table 13. Ligand screening for mechanochemical hydroacylation of acrylates.

Entry	Ligand	Conv. 6a [%]	Yield [%]
1	dtbbpy (L16)	39	18
2	phen (L14)	2	1
3	bpy (L15)	9	4
4	4,4'-OMebpy (L17)	6	3
5	5,5'-CF ₃ bpy (L18)	93	49
6	4,4'-CF ₃ bpy (L21)	89	52
7	4,4'-CO ₂ Me bpy (L22)	76	43
8	5,5'-CO ₂ Et bpy (L23)	62	24
9	2,2'-bipyrimidine (L24)	7	5
10	terpy (L19)	15	7
11	PyOX (L26)	48	22
12	PPh ₃	14	5
13	dppf (L6)	11	0
14	L21 (10 mol%)	85	57

Yields and conversions were determined by GC-FID using pentadecane as internal standard.

6. Mechanochemical Nickel-Catalyzed Hydroacylation of Activated Alkenes

Table 14. Solvent screening for mechanochemical hydroacylation of acrylates.



Entry	Solvent	Conv. 6a [%]	Yield [%]
1	DMA	89	52
2	DMF	94	59
3	MeCN	35	7
4	H ₂ O	35	17
5	toluene	18	6
6	DCM	31	3
7	acetone	18	3
8	MeOH	24	4
9	hexane	14	6
10	EtOAc	14	3
11	THF	14	3
12	—	24	9
13	DMF/H ₂ O (1:1)	94	67
14	DMF/H ₂ O (3:1)	98	77
15	DMF/H ₂ O (5:1)	100	82
16	DMF/H ₂ O (6:1)	100	77
17	DMF/H ₂ O (5:1, 100 μL)	100	78
18	DMF/H ₂ O (5:1, 400 μL)	100	83

Yields and conversions were determined by GC-FID using pentadecane as internal standard.

Next, nickel sources were examined (Table 15). The system appeared relatively independent from the nickel source used, but no product was obtained when omitting catalyst. Thus, $\text{NiCl}_2(\text{H}_2\text{O})_6$ was chosen as the most cost-effective source.

Table 15. Catalyst screening for mechanochemical hydroacylation of acrylates.

Entry	Nickel source	Conv. 6a [%]	Yield [%]
1	NiCl ₂ (H ₂ O) ₆	100	82
2	NiCl ₂ (dme)	100	83
3	NiBr ₂ (dme)	100	81
4	Ni(acac) ₂	99	73
5	Ni(OAc) ₂ (H ₂ O) ₄	96	65
6	—	8	n. d.

Yields and conversions were determined by GC-FID using pentadecane as internal standard.

Substrate Scope

After identifying optimal conditions, the substrate scope was examined (Figure 59). A range of aryl thioesters served as viable acyl donors, although the electronic properties of the aroyl group strongly influenced reactivity. Electron-neutral substrates furnished the desired products in high yields (**11aa**, **11xa**, **11ya**), whereas electron-withdrawing substituents led to reduced yields (**11da–11fa**). Substrates bearing strongly electron-withdrawing groups (e.g. esters, nitriles) were unreactive. In contrast, electron-rich aryl thioesters generally provided high yields (**11ha**, **11ia**). A heteroaromatic substrate delivered the coupling product in moderate yield (**11za**), likely due to its electron-deficient nature.

Primary alkyl thioesters afforded high yields (**11la**, **11ma**), while secondary analogues required extended reaction times but remained effective (**11qa–11pa**). Formation of the tertiary ketone **11ra** occurred in low yield, highlighting the effect of steric hindrance. Thioesters derived from pharmaceutically relevant and naturally occurring carboxylic acids were readily prepared and successfully applied, providing the corresponding 1,4-dicarbonyl products in good yields (**11ua**, **11va**, **11Aa**).

The scope of activated alkenes was more sensitive to steric effects. Various acrylates afforded high yields (**11ab–11af**), whereas substitution at either the α - or β -position

6. Mechanochemical Nickel-Catalyzed Hydroacylation of Activated Alkenes

completely suppressed product formation. Other electron-withdrawing activating groups, including ketones (**11ag**), amides (**11ah**), and nitriles (**11ai**), were also tolerated.

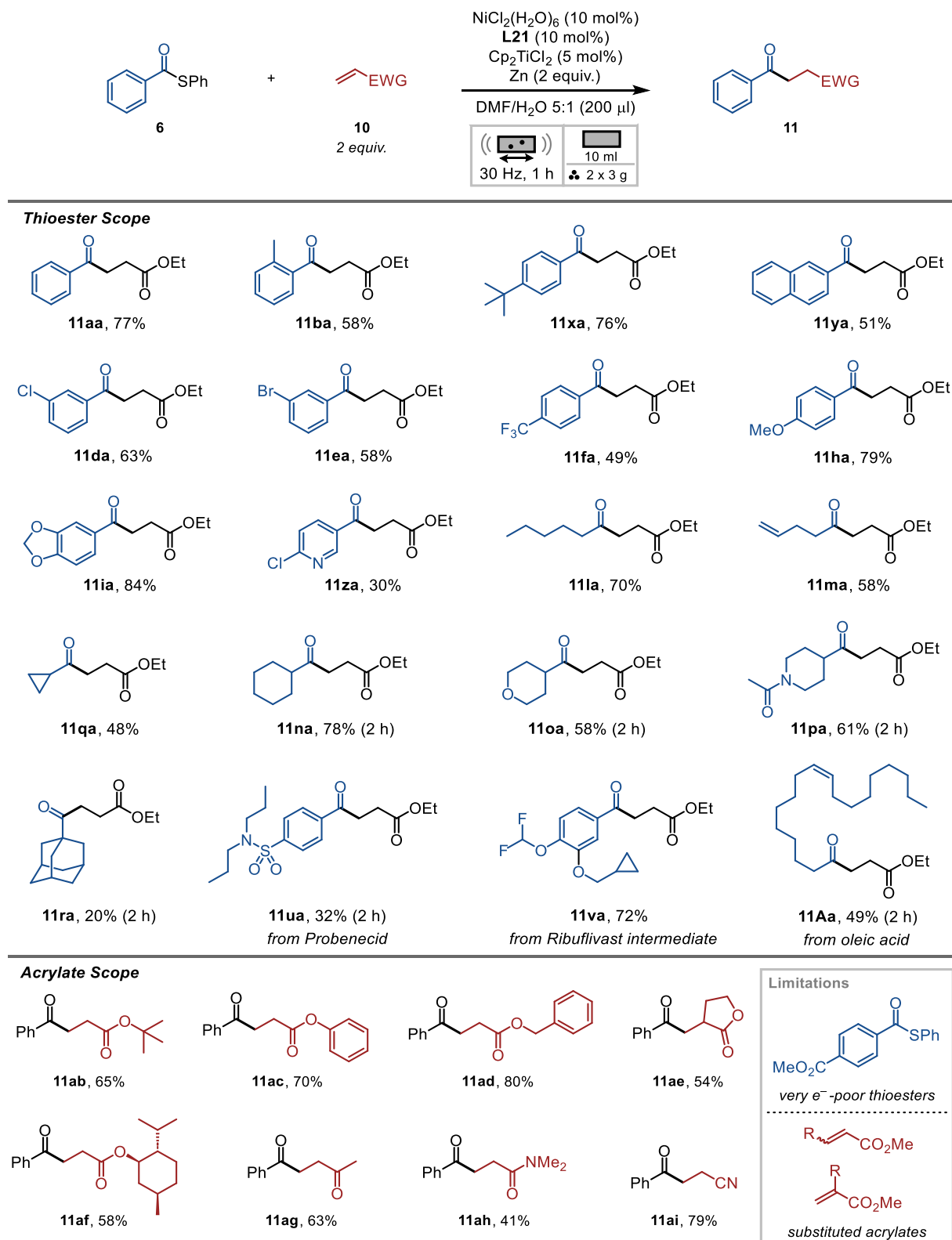


Figure S9. Substrate scope of the nickel-catalyzed hydroacylation of acrylates with thioesters.

Deuteroacylation Studies

To enable product deuterium labeling, water was replaced with deuterium oxide (D_2O), a readily available and economical deuterium source. A slight increase in solvent volume (400 μ l instead of 200 μ l) and increasing the water ratio was required to maximize deuterium incorporation to 99% D. Moreover, a water-free nickel precursor was employed, affording selective deuteration at the C3 position with excellent deuterium incorporation. With these modified conditions in hand, the generality of this method was studied (Figure 60). Overall, coupling products were received in yields comparable to the standard procedure (**11aa-D**, **11ea-D**, **11la-D**, **11ai-D**), while deuterium incorporation was consistently high and selective. The synthesis of **11aj-D** demonstrated that a more complex acrylate, derived from estrone, was suitable for deuteroacylation and furnished the product in good yield. Notably, the use of deuterated acrylates afforded **11ak-D₅** and **11ak-D₄**, which contain CD_2 groups, representing valuable intermediates for the synthesis of deuterated heterocycles.¹⁻² In addition, the synthetic value of 3-deuterated 1,4-ketoesters was demonstrated by derivatization of **11aa-D**, furnishing deuterated alcohol **12** and heterocycle **13**.

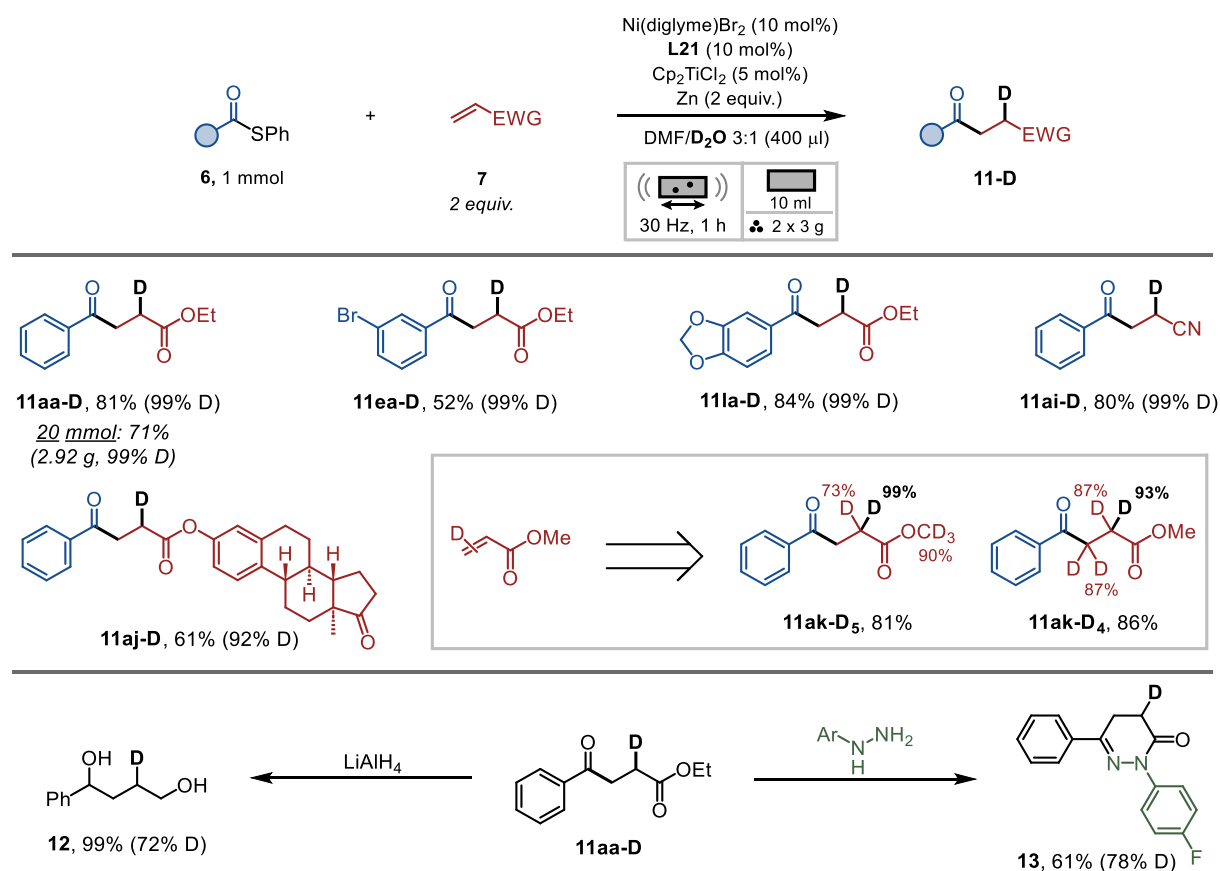


Figure 60. Substrate scope of the nickel-catalyzed deuteroacylation of acrylates with thioesters and derivatization.

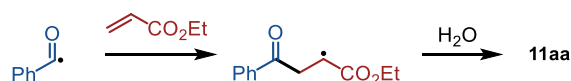
Mechanistic Investigations

Initially, it was unclear whether the reaction proceeds *via* a Giese-type addition of an acyl radical, which can be generated from thioesters by 1-e⁻-reduction,²⁵⁻²⁶ or if a migratory insertion would occur on the nickel center (Scheme 21, A). A mechanism involving nickel hydride intermediates, as proposed in related systems, appeared unlikely because such pathways typically furnish branched rather than linear products.¹⁹⁻²⁰

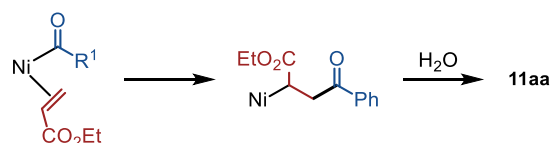
To probe the hydrogen-transfer event, a primary kinetic isotope effect (KIE) was measured (Scheme 21, B). Because accurate rate determination under mechanochemical conditions is challenging, low-conversion competition experiments were conducted instead. Competition between H₂O and D₂O gave a primary KIE of $k_H/k_D = 3.1$. As hydrogen atom abstraction by organic radicals from protic sources generally exhibits higher KIE values,²⁷ this result is inconsistent with a simple radical hydrogen atom transfer step and instead supports a more complex termination process. Secondary KIE experiments provided additional mechanistic insight. Competition between α,β -deuterated methyl acrylate and the protonated analogue gave an inverse secondary KIE of $k_H/k_D = 0.8$, while use of only α -deuterated acrylate afforded a value of 0.9. These observations are consistent with simultaneous rehybridization of both alkene carbons from sp² to sp³ in the product-determining step. Such behavior strongly supports migratory insertion of the alkene into a Ni–acyl bond, whereas a radical addition pathway would initially involve rehybridization only at the β -carbon, therefore an sKIE ~ 1 would be expected for the α -deuterated acrylate. Additional experiments using radical inhibitors further disfavored a radical mechanism (Scheme 21, C). The presence of TEMPO, BHT, or galvinoxyl lowered the reaction yield but did not completely inhibit product formation, indicating that free-radical processes are unlikely to be the dominant pathway.

A) Mechanistic Scenarios

1) Radical coupling



2) Migratory Insertion

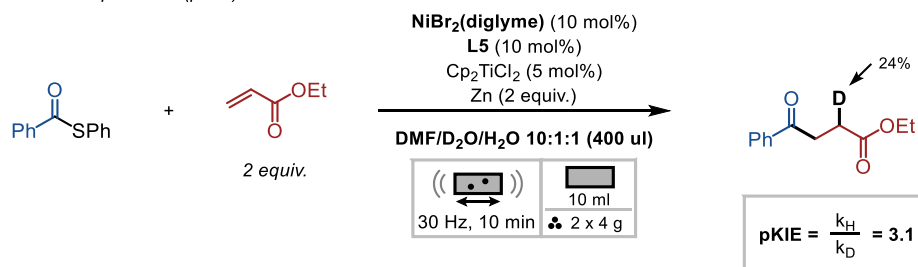


- ✗ pKIE **contradicted** H-atom abstraction
- ✗ sKIE **contradicted** stepwise rehybridization
- ✗ radical scavengers showed **no inhibition** of the reaction

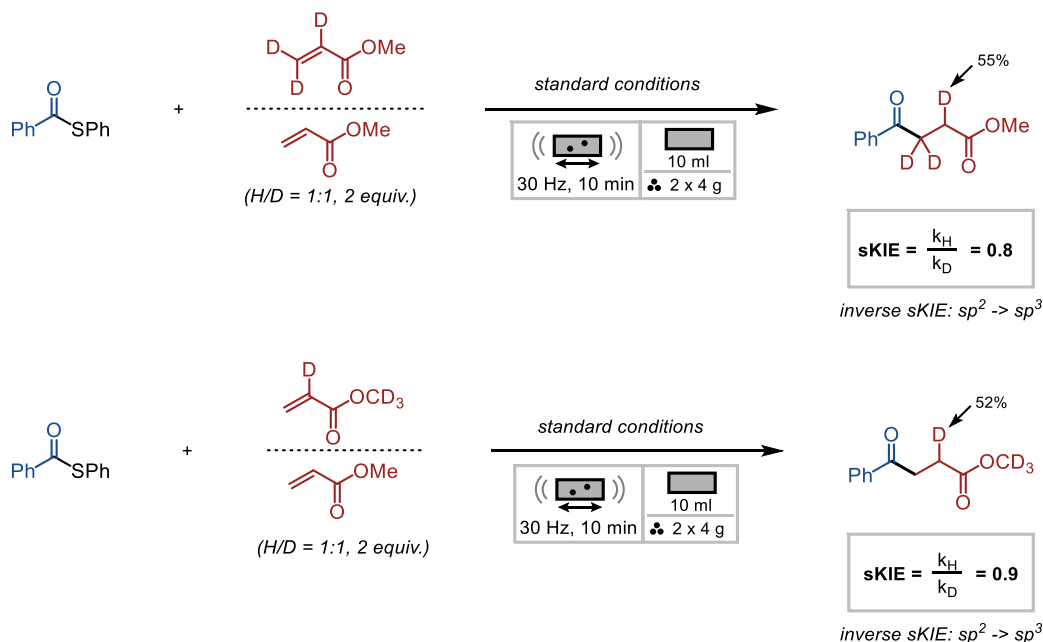
✓ sKIE indicated rehybridization of both carbons in one step

B) Kinetic Isotope Effect Studies^a

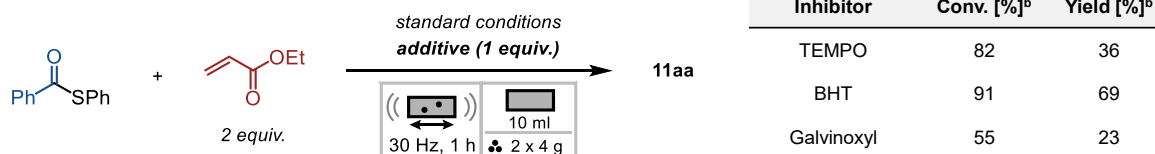
1) Primary Kinetic Isotope Effect (pKIE)



2) Secondary Kinetic Isotope Effect (sKIE)



C) Radical Scavengers



Scheme 21. Mechanistic studies regarding the protonation step. ^a KIEs were determined from product ratios (¹H NMR) after isolation. ^b Yields determined by GC-FID using pentadecane an internal standard.

Next, the oxidative addition step was investigated. While the oxidative addition of thioesters to transition metals is well-known,²⁸ the mechanism remains experimentally underexplored. Thus, this step was then investigated by Hammett analysis (Figure 61, A). Low-conversion

competition experiments with *para*-substituted benzoyl thioesters gave a reaction constant of $\rho = +1.02$. This positive value suggests buildup of negative charge at the carbonyl fragment in the product-determining step. Although analogous studies on acyl electrophiles are scarce, the modest magnitude of ρ is most consistent with a concerted oxidative addition process. By comparison, concerted oxidative addition of aryl halides to Ni(0) commonly produces larger ρ values of approximately 2.²⁹⁻³⁰

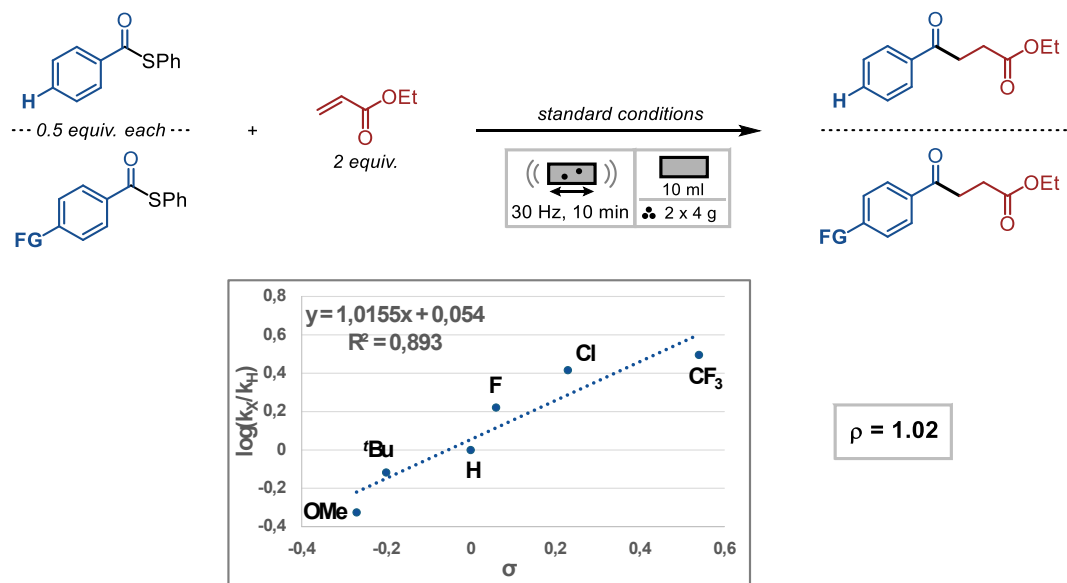
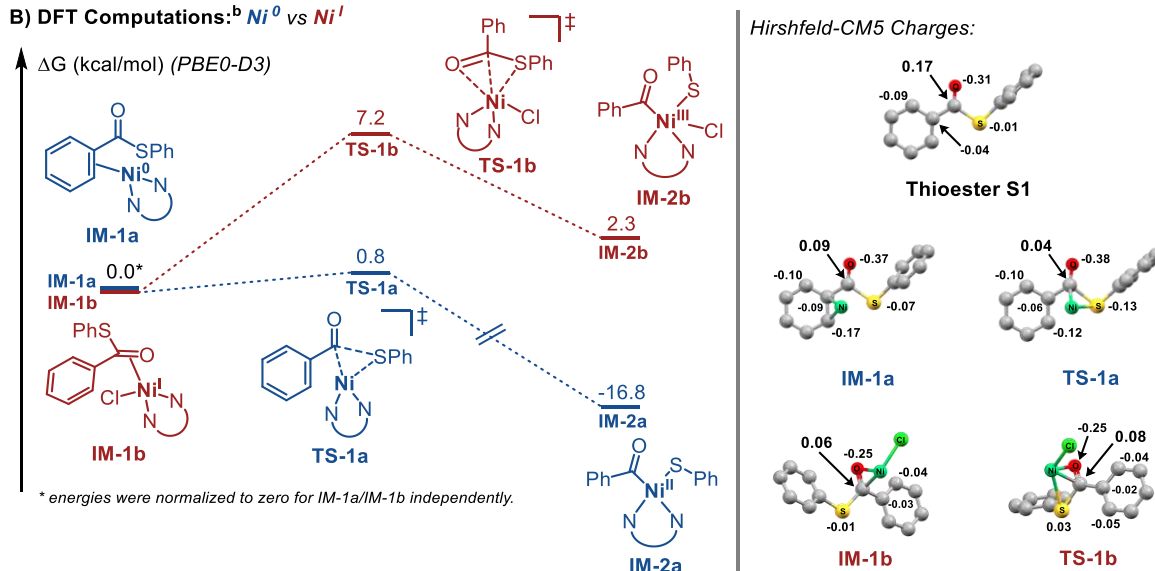
A) Hammett Analysis^aB) DFT Computations:^b Ni^0 vs Ni^I 

Figure 61. Mechanistic investigations regarding the oxidative addition of thioester to nickel. ^a Ratio of products determined by ¹H NMR from an isolated sample. ^b PBE0-D3(BJ)/def2-TZVP(Ni), def2-SVP (other atoms), SMD(DMF) level of theory. Each reaction pathway was normalized independently by setting its respective starting structure to $\Delta G = 0$. Consequently, the absolute energies of the two pathways cannot be compared directly.

Previous computational work by Yu and co-workers also showed that electron-withdrawing substituents lower the barrier for concerted oxidative addition of thioesters to Pd(0),³¹ which is in agreement with the trend observed in this study.

To further elucidate the nickel-catalyzed C–S bond activation step, the oxidative addition of *S*-phenyl benzothioate to (**L21**)Ni(0) was investigated with density functional theory (DFT) calculations performed by Fabian Bölzle (Figure 61, B). At the PBE0-D3(BJ)/def2-TZVP(Ni), def2-SVP (other atoms), SMD(DMF) level of theory, concerted oxidative addition of the C–S bond starting from Ni(0) proceeded with a close to barrierless energy of activation of 0.8 kcal/mol. In comparison, starting from a Ni(I) complex, a higher barrier of 7.2 kcal/mol was observed, but in contrast this process appeared slightly endergonic. These results are in line with previous reports describing oxidative addition of *S*-alkyl thioesters to related Ni(0) complexes.³² Analysis of Hirshfeld-CM5 atomic charges³³⁻³⁴ at the carbonyl carbon of the thioester **6a**, **IM-1** and **TS-1** revealed depletion of positive charge during the reaction for both pathways, which is consistent with the experimentally observed Hammett correlation.

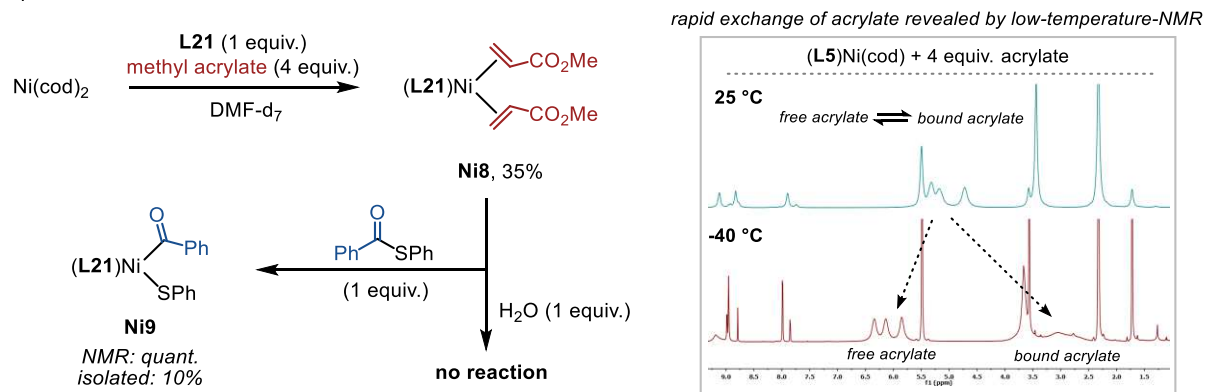
Additional mechanistic evidence was obtained from NMR investigations of organometallic intermediates (Figure 62, A). Treatment of Ni(cod)₂ and **L21** with methyl acrylate in DMF-*d*₇ produced broadened, upfield-shifted alkene resonances, consistent with coordination of the alkene to a Ni(0) center. Notably, the position of these signals depended on the amount of acrylate added, suggesting a dynamic binding equilibrium in solution. This behavior was confirmed by low-temperature NMR spectroscopy: reaction of (**L21**)Ni(cod) with four equivalents of acrylate at –40 °C resolved separate signals for free and coordinated alkene, indicating that the exchange process becomes slow on the NMR timescale at this temperature. On preparative scale, a Ni(0)–acrylate complex (**Ni8**) was isolated. Solution-phase NMR analysis indicated the presence of multiple species, most likely interconverting isomers. Importantly, **Ni8** remained unchanged in the presence of water for 24 h at room temperature, showing that direct reaction of the coordinated Ni(0) complex with water is not favored.

Upon addition of one equivalent of thioester to **Ni8**, the oxidative addition complex **Ni9** was formed, accompanied by release of coordinated acrylate as evidenced by restoration of the free alkene chemical shift. Unexpectedly, **Ni9** did not undergo further reaction with acrylate, regardless of whether water and/or zinc were present. This lack of reactivity prompted a broader set of stoichiometric coupling experiments using different nickel precursors (Figure 62, B). When Ni(0) sources such as Ni(cod)₂ or **Ni8** were combined stoichiometrically with thioester and acrylate, no coupling product was detected, even in the presence of zinc.

6. Mechanochemical Nickel-Catalyzed Hydroacylation of Activated Alkenes

These results suggest that Ni(0) species are unlikely to constitute the productive catalytic manifold, consistent with the inertness of oxidative addition complex **Ni9**. Similarly, $\text{NiCl}_2(\text{H}_2\text{O})_6$, although effective under catalytic conditions, failed to effectively promote stoichiometric coupling.

A) NMR Studies



B) Stoichiometric Coupling

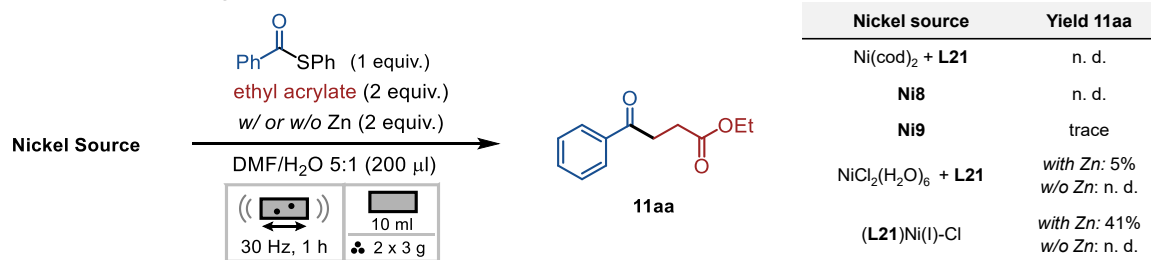
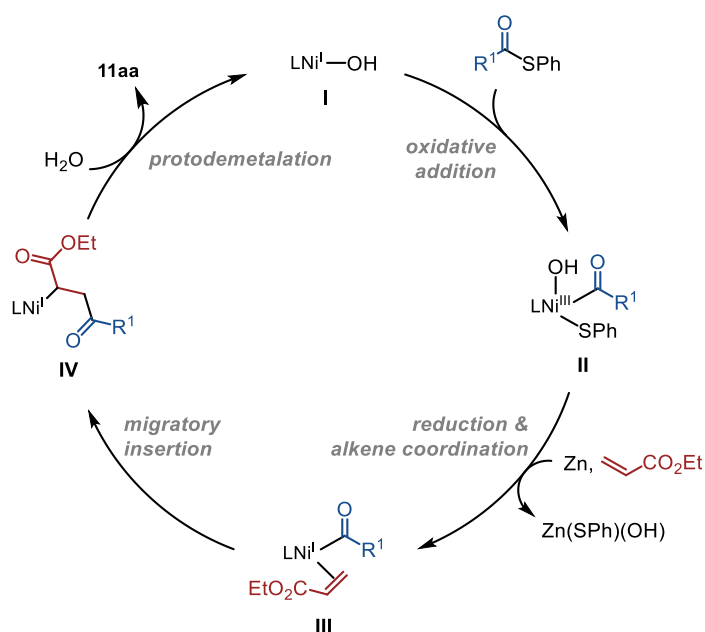


Figure 62. NMR studies of organometallic species and stoichiometric coupling experiments.

In contrast, the independently prepared Ni(I) complex **(L21)NiCl (Ni10)** furnished the desired product in moderate yield, implicating Ni(I) as a catalytically competent oxidation state. This proposal aligns with computational studies by Wu and co-workers,³² who showed that oxidative addition of thioesters to phenanthroline-ligated Ni(I) species proceeds with an activation barrier comparable to that of the analogous Ni(0) complex. Consistent with this hypothesis, addition of one equivalent of thioester **11aa** to **Ni10** in THF-d_8 led to disappearance of the paramagnetic ^1H NMR signals of **Ni10**, indicating rapid consumption of the Ni(I) precursor.

Although zinc is commonly proposed to regenerate the active catalyst by reducing off-cycle nickel species after product release in cross-electrophile coupling processes,³⁵ its necessity even under stoichiometric conditions indicates that reduction must occur before C–C bond formation. This observation contradicts a catalytic sequence in which high-valent Ni(III) species are involved in the productive coupling step.

Based on these findings, the following catalytic cycle is proposed (Scheme 22): Initial reduction of the precatalyst $\text{NiCl}_2(\text{H}_2\text{O})_6$ by zinc generates the active Ni(I) species **I**. Oxidative addition of the thioester to Ni(I) then furnishes a high-valent Ni(III) acyl intermediate **II**. Subsequent reduction by zinc, followed by alkene coordination, affords intermediate **III**. Migratory insertion of the activated alkene into the Ni–acyl bond then produces alkyl–nickel intermediate **IV**. Since alkene coordination to the isolated Ni(II) oxidative addition complex **Ni9** was not detected, this species appeared unproductive and likely lies outside the main turnover pathway. Finally, protodemetalation of intermediate **IV** releases the hydroacylation product and regenerates the active Ni(I) catalyst **I**.



Scheme 22. Proposed catalytic cycle for the nickel-catalyzed hydroacylation of acrylates with thioesters.

The observed regioselectivity towards the linear product is attributed to substrate-directed insertion, in which coordination of the acrylate carbonyl group controls alkene orientation during migratory insertion, in agreement with previous reports.²⁰

Conclusion

A mechanochemical method for the hydroacylation and deuterioacylation of activated alkenes using thioesters as acyl donors has been developed. The protocol operates under ambient conditions, proceeds within short reaction times, and employs water or deuterium oxide as convenient hydrogen or deuterium sources, respectively. The synthetic utility of the method was demonstrated through the preparation of various (3-deutero-)1,4-ketoesters,

including gram-scale examples with excellent yield and highly selective deuterium incorporation. These products provide versatile building blocks for the synthesis of deuterium-labeled heterocycles. Mechanistic studies support an ionic Ni(I)/Ni(III) catalytic manifold and disfavor pathways involving free radical intermediates.

6.2. Experimental

For general information on instrumentation, experimental details and analytical data of published results, see the Supporting Information of the published article, available free of charge at the publisher's website: DOI 10.1039/d6sc04272d.

6.3. References

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APPENDIX

7. Appendix (Publications)

Publication A1: Nickel-catalyzed C–S Cross-Coupling of Sterically Hindered Substrates. *Org. Chem. Front.* **2024**, *11*, 2485–2493. Reprinted with permission from Royal Society of Chemistry. Copyright 2024 Royal Society of Chemistry.

Publication A2: Influence of the Counterion on the Activation of Nickel(σ -Aryl) Precatalysts. *Organometallics* **2025**, *44*, 4, 595–605. Reprinted with permission from American Chemical Society. Copyright 2025 American Chemical Society.

Publication A3: Nickel-Catalyzed C–S Cross-Coupling Enhanced by Mechanochemistry. *ACS Catal.* **2025**, *15*, 21, 17871–17881. Reprinted with permission from American Chemical Society. Copyright 2025 American Chemical Society.

Publication A4: Nickel-catalyzed cross-electrophile-coupling of thioesters with alkyl bromides to form ketones under mechanochemical conditions. *Chem. Comm.* **2026**, *62*, 5284–5288. Reprinted with permission from Royal Society of Chemistry. Copyright 2026 Royal Society of Chemistry.

Publication A5: Nickel-Catalyzed Hydro- and Deuteroacylation of Acrylates using Water as Hydrogen Source. *Chem. Sci.* **2026**, DOI 10.1039/d6sc04272d. Reprinted with permission from Royal Society of Chemistry. Copyright 2026 Royal Society of Chemistry.

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Nickel catalyzed C–S cross coupling of sterically hindered substrates enabled by flexible bidentate phosphines†

Ivo H. Lindenmaier, Robert C. Richter and Ivana Fleischer *

Due to the smaller size of nickel compared to palladium, the C–S cross-coupling of sterically challenging aryl electrophiles with alkyl thiols under nickel catalysis remained elusive. Herein, we report the nickel-catalyzed cross-coupling of alkyl thiols with aryl triflates bearing functional groups in *ortho*-position relative to the leaving group using Ni(cod)₂/DPEphos (**L1**) or dppbz (**L2**) as the catalytic system. For substrates featuring non-coordinating *ortho*-substituents, the reaction operates under mild conditions using **L1**, while for electrophiles bearing coordinating groups, the ligand **L2** and elevated temperatures are required. The synthetic utility could be demonstrated on numerous examples, including biologically relevant compounds, and on larger scale. Instead of Ni(cod)₂, more cost-efficient Ni(OAc)₂ can also be employed in the presence of zinc as reductant. Furthermore, insights into the reaction mechanism were obtained by competition experiments, isolation of organometallic intermediates and computations.

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Introduction

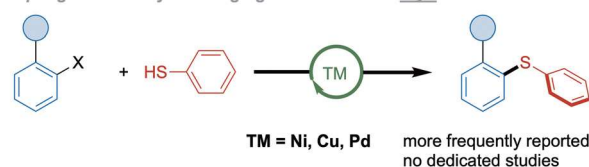
Thioethers are represented in a large range of natural compounds,¹ pharmaceuticals,² agrochemicals³ as well as in functional materials.⁴ Additionally, compounds containing sulfur in higher oxidation state can be conveniently accessed from the corresponding thioethers.⁵ Therefore, the efficient and selective construction of the C–S bond has been thoroughly investigated leading to the development of the transition-metal catalyzed Migita reaction as the most prominent procedure.⁶ Until today, a wide variety of synthetic methods under catalysis of Fe, Ni, Cu and Pd has been established, covering even less activated electrophiles such as aryl chlorides or carbamates while operating under mild conditions.⁷

Despite numerous contributions towards the coupling of *electronically* deactivated electrophiles, the usage of *sterically* demanding aryl (pseudo)halides has been much less studied. Compared to other cross-couplings such as the Suzuki–Miyaura-coupling, for which *ortho*-substituted substrates have been frequently reported,⁸ in C–S couplings, the low reactivity of the electrophile is more problematic due to the high binding affinity of thiol(ate)s,⁹ possibly leading to off-cycle species before catalytic turnover can occur. In addition, if

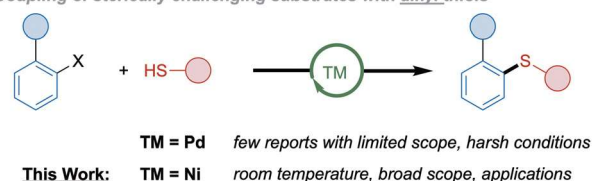
neighboring groups contain heteroatoms, catalysis can be hampered by coordination to the catalyst. Whereas aryl thiols seem to be less problematic and have been more frequently reported (Scheme 1A),¹⁰ only few protocols operating under palladium catalysis can tolerate sterically demanding electrophiles in couplings with more nucleophilic alkyl thiols.

Such systems have been independently published by the groups of Nolan,¹¹ Buchwald¹² and Hartwig,¹³ but all of these protocols still required harsh conditions that are typical for many C–S couplings (Scheme 1B). The only example for Pd-catalyzed coupling of bulky aryl halides with alkyl thiols under mild conditions was presented by Organ.¹⁴ However, these

A. Coupling of sterically challenging substrates with aryl thiols



B. Coupling of sterically challenging substrates with alkyl thiols



Scheme 1 Literature overview for the C–S coupling of sterically hindered electrophiles and our objective.

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† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d4qo00260a>



Research Article

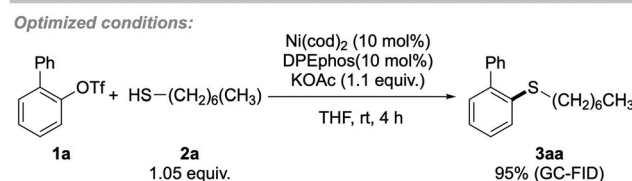
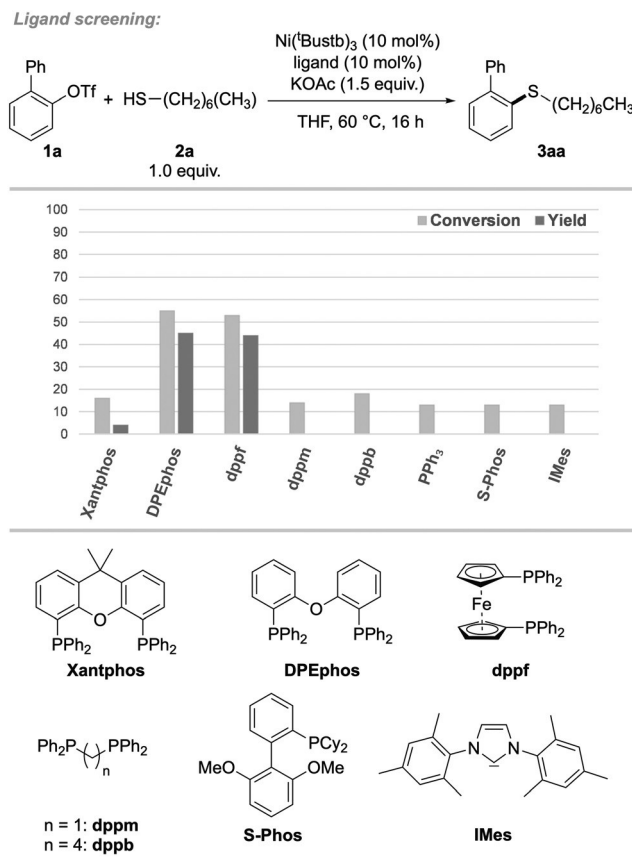
reports do not primarily focus on sterically challenging substrates, which is why the scope of *ortho*-substituted halides is limited to few examples.

Meanwhile, no general efficient procedures exist under nickel catalysis, with the only recently published exceptions requiring photoredox conditions.¹⁵ This may owe to the smaller radius of nickel compared to palladium, resulting in higher steric strain around the metal center. Recently, our group reported the coupling of aryl chlorides and triflates with sterically demanding alkyl thiols at room temperature using a nickel precatalyst containing Xantphos ligand (4,5-bis-(diphenylphosphino)-9,9-dimethylxanthene).¹⁶ Aryl triflates not only showed superior reactivity, but can also be accessed from the corresponding phenols, a widely available and naturally abundant substance class. Nevertheless, substituents in *ortho*-position were not tolerated even at higher temperatures with *ortho*-methyl as the only exception. Consequently, we envisioned the development of a nickel-catalyzed procedure that would allow for the synthesis of sterically hindered aryl alkyl thioethers (Scheme 1B).

Results and discussion

In the beginning of our investigations, 2-biphenyl trifluoromethanesulfonate (2-PhPhOTf, **1a**) was chosen as the model substrate in the coupling with *n*-heptane thiol (**2a**). In previous projects we found the inorganic base KOAc explicitly suitable for mild C–S couplings and decided to take advantage of this reactivity again. The earlier used precatalyst (Xantphos)Ni(*o*-tolyl)Cl, as well as a catalytic system consisting of Ni(cod)₂ and Xantphos proved ineffective, thus a ligand screening was performed (Scheme 2). It revealed, that bidentate triaryl phosphines with wide bite-angles were necessary for this reaction. Other ligand classes such as N-heterocyclic carbenes, bidentate alkyl-, monodentate aryl and alkyl phosphines or bidentate N-ligands were generally ineffective (for detailed screening information, see ESI, Table S1†). Of all ligands tested, DPEphos (bis[(2-diphenylphosphino)phenyl] ether, **L1**), as well as ferrocene derivative dppf (1,1'-bis(diphenylphosphino)ferrocene) showed the highest reactivity, while other ligands led to no conversion to the product. For further investigations, DPEphos was chosen for its higher economic efficiency compared to dppf. Since bulky substrates would imply steric strain on the metal center, we hypothesized that the ligand needed to be flexible in the backbone, which was represented by the large difference in reactivity between more rigid Xantphos and more flexible DPEphos.¹⁷

Having identified a suitable catalytic system, other reaction parameters were investigated. Conveniently, lowering the reaction temperature to room temperature did not result in reduced yields. Surprisingly, the Ni(0)-precatalyst Ni(cod)₂ performed much better than Ni(0)-stilbene. This can be explained by the challenging oxidative addition that may be more hindered by the coordination of stilbene compared to cod, or the higher molar ratio of stilbene. To our delight, even tertiary ada-

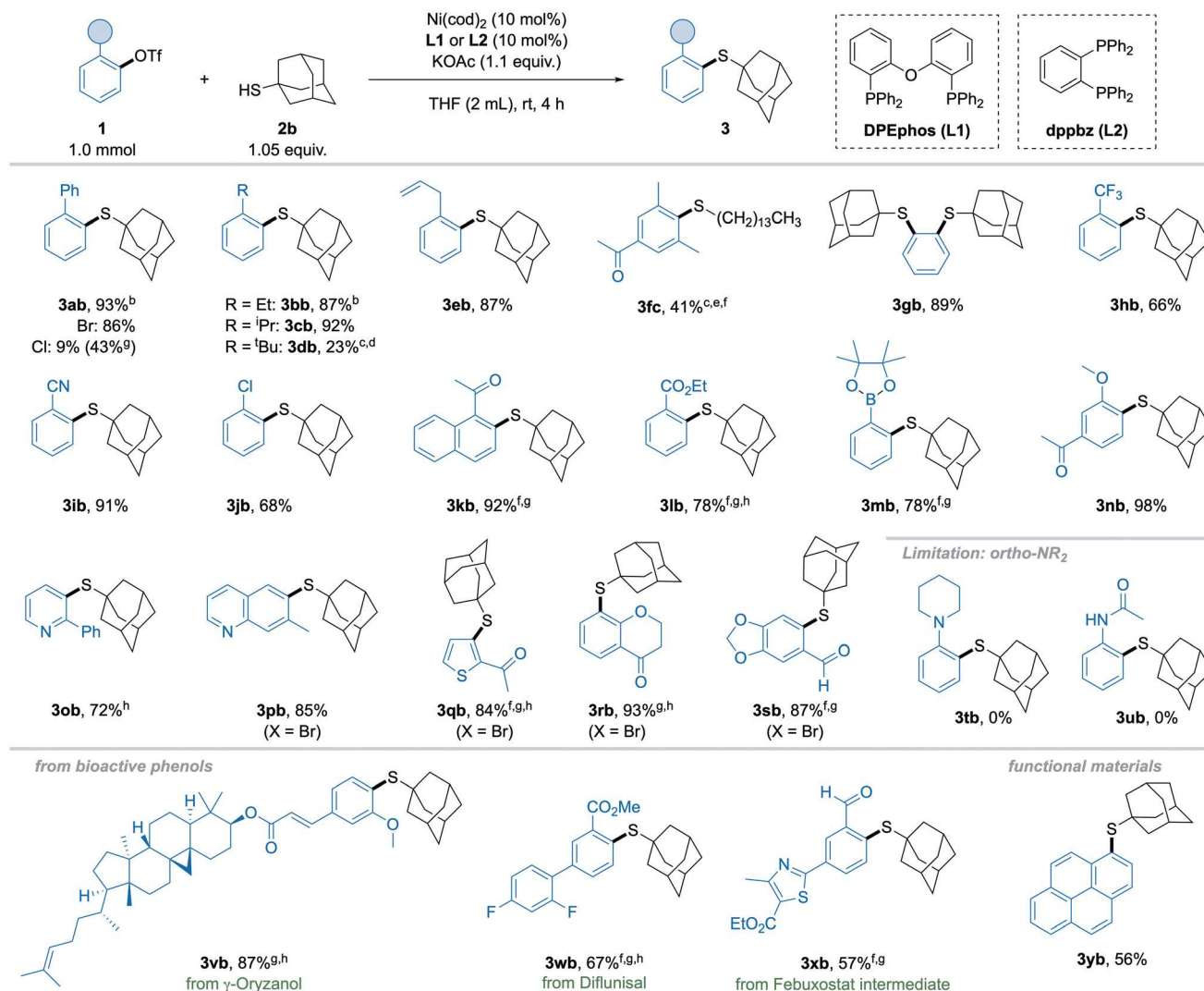


Scheme 2 Optimization of reaction parameters. 2-Biphenyl triflate (**1a**) (0.1 mmol), heptane thiol (**2a**) (1.0 equiv.), KOAc (1.5 equiv.), Ni(4-*t*-Bu-stilbene)₃ (10 mol%), ligand (10 mol%), THF (2 mL), 60 °C, 16 h. For monodentate ligands, 20 mol% were used. Yield and conversion were determined by GC–FID using pentadecane as internal standard.

mantane thiol (**2b**) gave excellent yield at room temperature with a short reaction time of two hours (for kinetic investigation see ESI, Fig. S1†) and therefore this bulky thiol was chosen as model substrate for further studies. Remarkably, conversions were close to yields and unreacted aryl triflate could be recovered. This was generally the case for most substrates presented in both aryl triflate and alkyl thiol scope (*vide infra*). For ligands that gave no product, the conversion was usually ~10%, indicating that oxidative addition had occurred, but further catalytic steps were not supported.

With these optimized conditions in hand, the substrate scope with respect to electrophiles was explored (Scheme 3). The isolation of previously screened 2-biphenyl thioether **3ab** was successful in excellent yield. Simple alkyl substituents with increasing steric demand showed high yields of **3bb** and **3cb**, while an *ortho-tert*-butyl group in **3db** proved more chal-





Scheme 3 Substrate scope with respect to aryl triflates. Standard conditions: **1** (1 mmol), **2b** (1.05 equiv.), KOAc (1.1 equiv.), **L1** (10 mol%), Ni(cod)_2 (10 mol%), THF (2 mL), rt, 4 h. Isolated yields. ^a 2 h. ^b 100 °C, 16 h. ^c GC-MS. ^d Tetradecane thiol (1.05 equiv.) instead of **2b**. ^e **L2** (10 mol%) instead of **L1**. ^f 60 °C. ^g 6 h.

lenging, giving poor yield even under harsher conditions. An allyl substituent of **3eb** was tolerated in excellent yield, leaving the double bond intact. Despite these promising results, aryl triflate **1f** bearing two *ortho*-methyl groups gave no yield with the catalytic system discussed above. Thus, we further optimized towards the coupling of this highly challenging substrate and found ligand dppbz (1,2-bis(diphenylphosphino) benzene, **L2**) competent for this transformation, albeit only primary thiols could be used, and higher temperature was necessary. Using these modified conditions, thioether **3fc** was formed in modest, but still synthetically useful yield, especially since the starting material can be recovered. The synthesis of disubstituted thioether **3gb** derived from 1,2-phenyl ditriflate was possible in high yield without raising the catalyst loading. Next, electron-withdrawing functional groups were investigated. The trifluoromethyl-substituted thioether **3hb** was obtained in good yield, while nitrile **3ib** gave excellent yield. Remarkably, biselectrophile **3jb** with a chloro-substituent gave

the desired monosubstituted product in good yield. When we moved towards substrates bearing functional groups with potentially coordinating ability in *ortho*-position, **L1** gave little to no product. To our surprise, **L2**, which was previously used for the coupling of 2,6-dimethylphenyl triflate (**1f**), performed well with these substrates. Accordingly, acyl **3kb** as well as ester **3lb** groups were feasible when using dppbz (**L2**), although slightly elevated temperatures were necessary. Strikingly, boronic ester substituted triflate **1m** was converted in high yield, possibly enabling subsequent functionalization of **3mb** by orthogonal cross-coupling protocols. Conveniently, a neighboring methoxy group, which is commonly present in numerous bioactive phenols,¹⁸ gave the acetovanillone-derived thioether **3nb** in excellent yield. Although heterocycles occasionally needed slightly more forcing conditions (longer reaction times or higher temperatures), thioethers with pyridine (**3ob**), quinoline (**3pb**), thiophene (**3qb**), chromanone (**3rb**) and benzodioxol (**3sb**) functionalities were furnished in

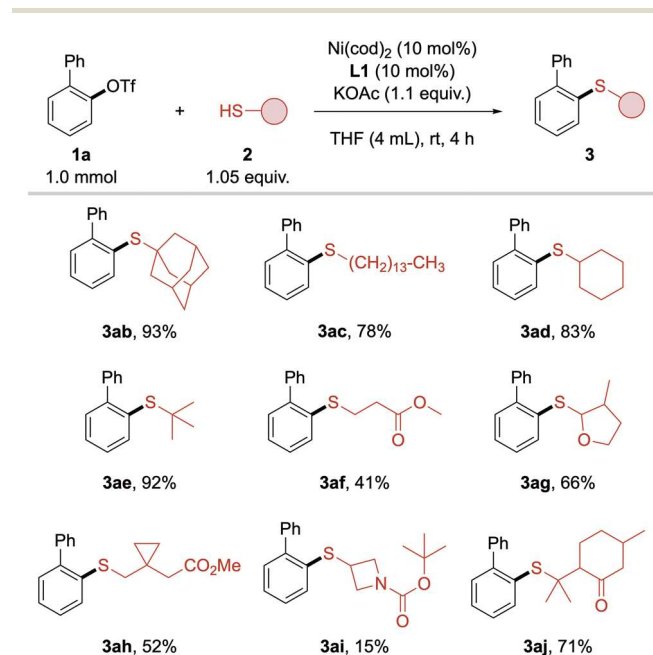


high yields even when using the corresponding bromide instead of triflate. Notably, amine- and amide-substituted triflates showed no conversion to the products in this reaction (**3tb** and **3ub**), probably due to strong chelating effects. However, suitable protecting groups could render nitrogen-containing groups feasible, but would require additional optimization. Finally, the thioetherification of triflates **1v–1x** demonstrated the possibility to employ substrates derived from biologically active phenols or natural products, though higher temperatures and longer reaction times were generally required, which can be explained by the low solubility of such compounds. Synthesis of thioether **3xb** also highlights the possibility to obtain sulfur bioisosteres of well-known drug molecules, such as Febuxostat. In addition, 1-pyrene triflate **1y** was subjected to the reaction, showcasing the possibility for functionalization of motifs relevant for functional materials.

Subsequently, the scope of alkyl thiols was investigated (Scheme 4). Surprisingly, primary and secondary thiols initially gave diminished yields compared to sterically more demanding adamantane thiol (**2b**), which can be ascribed to the stronger poisoning effect of sterically less hindered thiols. This effect was not present in preliminary screening experiments, probably due to lower concentration of thiol in the reaction mixture. Fortunately, lowering the thiol concentration by adding more solvent combined with slower addition of thiol resulted in the formation of primary alkyl thioether **3ac** in 78% isolated yield. Using this slightly modified procedure, simple primary, secondary and tertiary alkyl thiols **2c–e** were coupled in high to excellent yields, clearly favoring higher substituted thiols. In the thiol moiety, functional groups such as ester, ketone and cyclic ether were tolerated, although yields of

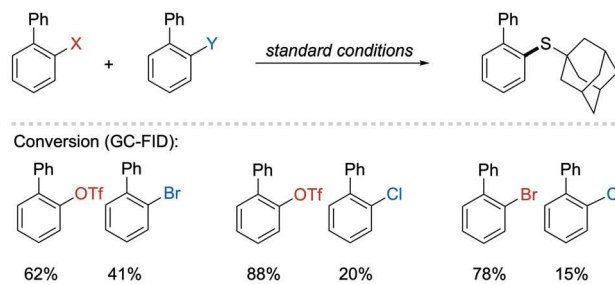
3af, **3ag** and **3aj** were lower when the functionality was in close proximity to the thiol group. Contrary to the aryl triflate scope, yields with these thiols could neither be improved by employing **L2** nor by higher temperatures. The cyclopropyl group in **3ah** was compatible with the method but showed modest yield. Azetidine **3ai** only gave poor yield, which could be explained by poisoning by the carbamate. Aryl thiols were not compatible with this method.

Aiming for a better understanding of the reactivity in this system, competition experiments were performed.¹⁹ Accordingly, the expected reactivity order between halogens $\text{OTf} \approx \text{Br} > \text{Cl}$ was revealed by intermolecular competition (Scheme 5A). In an intra-

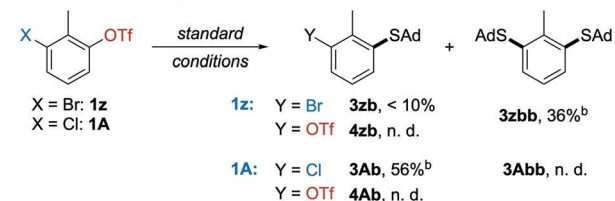


Scheme 4 Substrate scope with respect to alkyl thiols. Standard conditions: **1a** (1 mmol), **2** (1.05 equiv.), KOAc (1.1 equiv.), **L1** (10 mol%), $\text{Ni}(\text{cod})_2$ (10 mol%), THF (4 mL), rt, 4 h. Isolated yields.

A. Intermolecular competition of aryl (pseudo-)halides



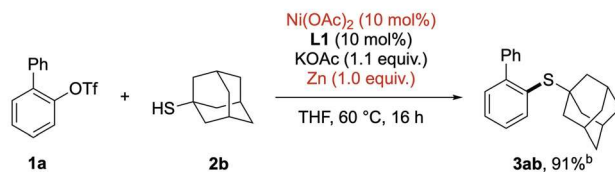
B. Intramolecular competition



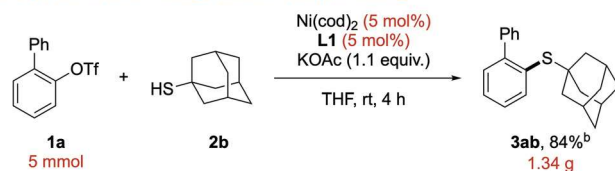
C. Steric vs electronic discrimination



D. Ni(II)-precatalyst instead of Ni(cod)₂



E. Upscale reaction using reduced catalyst loading



Scheme 5 Further exploration of reactivity in the C–S cross-coupling of (pseudo)halides with alkyl thiols. Standard conditions: aryl (pseudo-) halides (each 0.2 mmol), **2b** (1.05 equiv.), KOAc (1.1 equiv.), **L1** (10 mol%), $\text{Ni}(\text{cod})_2$ (10 mol%), THF (2 mL), rt, 4 h. Yields and conversions were determined by quantitative GC-FID unless stated otherwise. ^a Isolated yield.



molecular competition, chemoselectivity between OTf and Br was even less expressed, and the disubstitution product **3zbb** was favored. Yet, chemoselective monosubstitution was possible between OTf/Cl yielding thioether **3Ab** in good yield (Scheme 5B).

Further results of intramolecular competition were previously observed in the investigation of scope for 1,2-biselectrophiles (Scheme 3, **3gb** and **3jb**). Next, sterically hindered triflate **1a** was subjected to coupling in the presence of the electronically less reactive 4-chloro toluene to compare the influence of both factors (Scheme 5C). Interestingly, the higher reactivity of C–OTf bond can overcome the steric hinderance caused by an *ortho*-phenyl group, leaving 4-chloro toluene almost unreacted. Furthermore, the air-sensitive Ni(cod)₂ could be replaced by Ni(OAc)₂ under reductive conditions (Scheme 5D), greatly improving the cost-efficiency of this reaction as well as enabling storage of all reagents under bench-top-conditions. However, longer reaction times and heating were required for the activation of the precatalyst. Upscaling of the model reaction to 5 mmol proceeded without issues and delivered 1.34 g of thioether **3ab** (Scheme 5E).

Intrigued by the substrate-depending demand for different ligands, we thrived to get a better understanding of the mechanistic steps, especially compared to our previously developed Ni/Xantphos catalytic system.^{16a,b} In these studies, the coordination and deprotonation of the thiol was identified to be the likely slowest step, operating in a concerted-metalation-deprotonation (CMD)-like fashion.²⁰ Since this was only computed for unsubstituted aryl chlorides, we questioned how the

mechanism would differ when introducing *ortho*-substituents. The lower BDE of aryl triflates compared to chlorides and the high steric demand of the herein presented substrates should exhibit opposite effects on the reactivity.

Reductive elimination, though, would be presumably facile in this system as the relief of steric strain acts as the driving force and was therefore not further investigated. Hence, DFT computations were performed to study the steps of oxidative addition (OA) and thiol coordination and deprotonation (TCD, Fig. 1).²¹ The computed barriers were $\Delta G_{\text{OA}}^{\ddagger} = 4.3 \text{ kcal mol}^{-1}$ and $\Delta G_{\text{TCD}}^{\ddagger} = 9.8 \text{ kcal mol}^{-1}$, indicating that oxidative addition occurs more easily, showcasing the high reactivity of triflates even in a constrained environment. In contrast, the coordination of the bulky thiol required a higher activation barrier. Since we were unable to determine the transition state for the acetate coordination to **B** due to more complex effects such as salt precipitation and solubility, no rate-determining state could be identified. However, the mechanism of the OA and TCD were studied more detailed to elucidate the proceeding of the reaction despite the high steric strain around the nickel center aiming to rationalize the need for flexible ligands. Generally, oxidative addition of Ni(0) into aryl triflates is computationally poorly investigated with most reports focusing on sulfonamides or esters.²² The reported mechanisms differ between S_N2-like, 3- or 5-centered transition states.²³ Our computations indicated an S_N2-like mechanism for the oxidative addition (TS_{A-B}), while competing pathways showed higher energy barriers. Presumably, the steric pressure would render

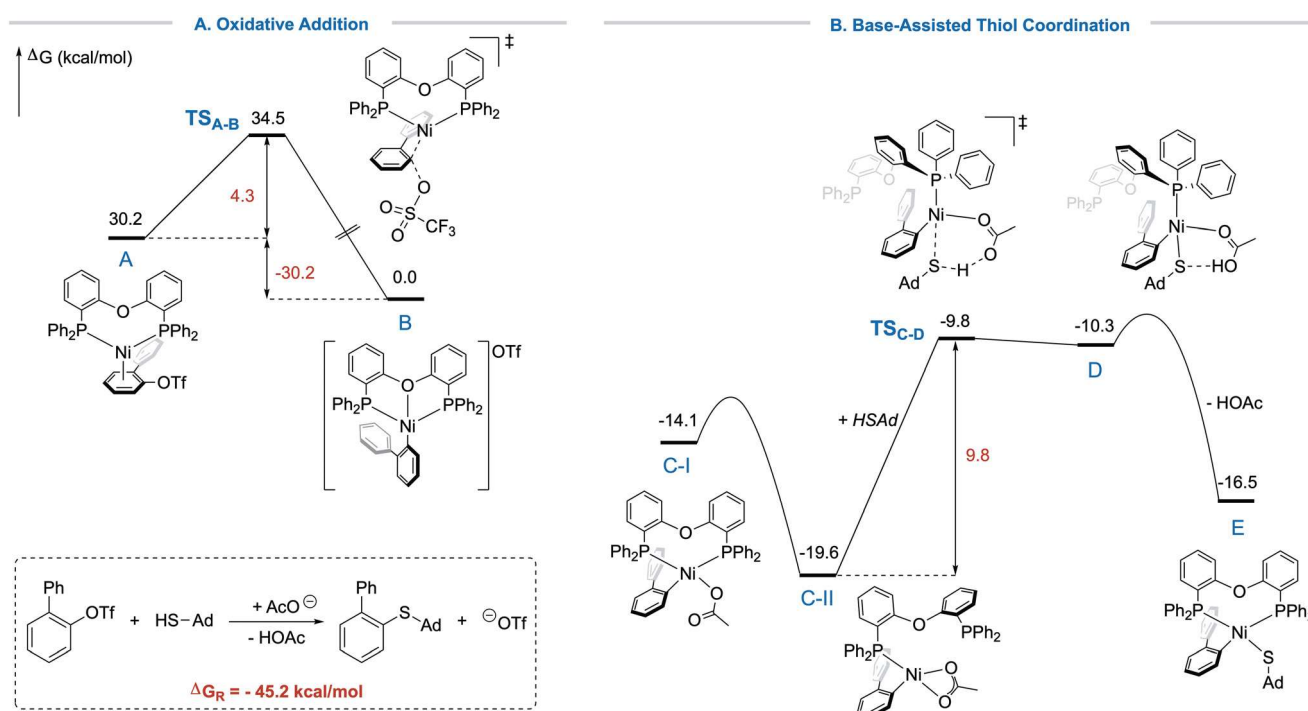


Fig. 1 Free energy profile for the oxidative addition and thiol coordination in the cross-coupling of 2-PhPhOTf with HSAd. Structures and energies were calculated at the M06-L(SMD : THF)/def2-QZVPP//B3LYP-D3BJ/def2-SVP level of theory.

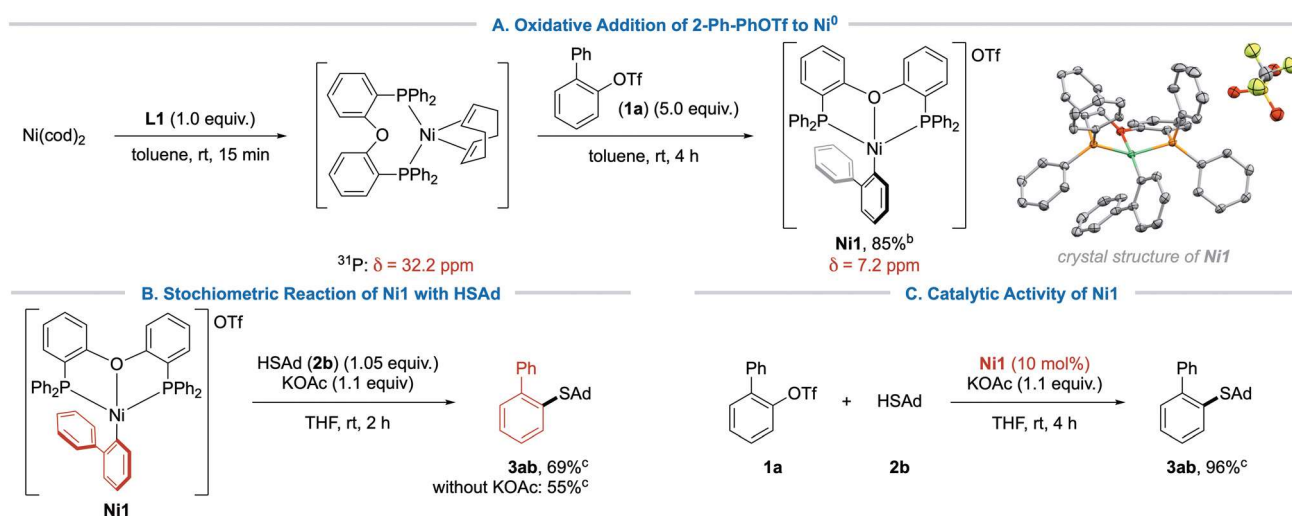


the S_N2 -mechanism more favorable in this case. The barrier of the oxidative addition, however, is remarkably low, and the process is strongly exergonic, showcasing the high reactivity of aryl triflates. Nevertheless, we found the initial precoordination of the π -system (**A**) fairly unfavored, but possible due to the great excess of **1a** at the beginning of the reaction (see SI). The product of the oxidative addition is the $[(DPEphos)Ni(biphenyl)]^+$ -cation (**B**), which is in accordance with the obtained crystal structure (*vide infra*).

Notably, when we moved towards the thiol coordination, computations pointed out a displacement of one of the phosphines from nickel by initial η^2 -coordination of the acetate, which is energetically more favorable than the corresponding η^1 -structure, demonstrating a major difference to previous results.^{16a} However, structure **C-II** could be energetically favored due to reduced steric strain. A similar η^1 -coordination of DPEphos was previously demonstrated on sterically demanding Cu-complexes.²⁴ Simultaneously to the acetate switching back to η^1 -coordination, the free coordination site *trans* to the loosely bound phosphine is occupied by the thiol, followed by proton transfer to acetate. In the transition state, a complete dissociation of the previously displaced phosphine is observed with the now inactive arm of **L1** rotated away from nickel (**TS_{C-D}**). Competing bidentate transition-states could not be located. Essentially, **L1** appears to act as monodentate PPh_3 -like ligand during the step of thiol coordination and deprotonation. This feature of bidentate phosphine ligands was previously proposed from the group of Doyle for the nickel-catalyzed Suzuki–Miyaura coupling of sterically hindered substrates.²⁵ This proposed mechanism could explain the large difference in reactivity between the otherwise similar Xantphos and DPEphos (**L1**). Analysis of the intrinsic reaction coordinate (IRC) revealed that the reactive mode of the transition state corresponds to a H^+ -transfer from thiol to acetate

while all other bonds remained almost unchanged. We additionally found energy minima shortly after the transition state, where the proton is bound to the acetate, but still exhibits weak H-bond interactions to the sulfur atom. As soon as the H^+ -transfer from thiol to acetate is complete (**D**), acetic acid is displaced by the phosphine, leading to structure **E**, from which product formation will eventually occur *via* reductive elimination (not shown). This interplay demonstrates the need for a specific ligand that is both bulky and flexible to protect sensitive intermediates by steric repulsion, but allows for the generation of additional coordination sites, when necessary. The Gibbs Energy of the overall reaction was computed to amount to $-45.2 \text{ kcal mol}^{-1}$.

Encouraged from these findings, we sought to obtain additional indices for the mechanism, *e.g.* isolating the product of oxidative addition to $Ni(0)$. It is a known issue that addition of bidentate phosphine ligands to $Ni(cod)_2$ can lead to mixtures of $Ni(cod)_2$, $(P^iP)Ni(cod)$ and $(P^iP)_2Ni$. $(P^iP)_2Ni$ is considered a catalytic sink, which will not engage in oxidative addition.²⁶ In accordance with previous reports,²⁶ we only observed NMR-signals for $(DPEphos)Ni(cod)$ upon mixing a 1 : 1 ratio of DPEphos and $Ni(cod)_2$. However, when adding 1 equiv. of 2-PhPhOTf (**1a**), no reaction was observed after 1 hour. We speculated that the aryl triflate would initially bind with its π -surface, meaning that it must displace *cod* in an equilibrium, which could be shifted by using an excess of aryl triflate. Accordingly, complex **Ni1** was isolated as a fine orange powder (Scheme 6A), and characterized by NMR, HR-MS and X-Ray analysis. The obtained connectivity of **Ni1** showed a distorted square-planar complex that crystallized as a cation due to the moderate coordination ability of the triflate counterion.²⁷ Consequently, the reactivity of complex **Ni1** was further investigated. Thus, the reaction of **Ni1** with 1.05 equiv. adamantane thiol (**2b**) in the presence of KOAc yielded coupling



Scheme 6 Isolation and reactivity of oxidative addition product **Ni1**. The ORTEP of **Ni1** was obtained by X-Ray diffraction of suitable crystals. Thermal ellipsoids are shown at 50% probability and hydrogen atoms are omitted for clarity. ^a Isolated yield. ^b Yield determined by quantitative GC-FID using pentadecane as internal standard.



product **3ab** in 69% yield (Scheme 6B). In absence of base, the reaction gave slightly lower yield, which can be explained by reduced efficiency of the thiol coordination and deprotonation. Furthermore, **Ni1** could be efficiently employed as an active catalyst in the standard reaction (Scheme 6C), indicating that **Ni1** was indeed an intermediate of the catalytic cycle. We thus propose that the reaction proceeds *via* the typical $\text{Ni}^0/\text{Ni}^{\text{II}}$ -cycle that has been previously proposed in our earlier work.^{16a} Although our calculations indicated a flexible η^1/η^2 -ligation state of DPEphos during base-assisted thiol coordination, we were unable to obtain experimental data to support this hypothesis.

Conclusions

In summary, we developed the first nickel-catalyzed C–S cross coupling for aryl triflates bearing substituents in *ortho*-position. Although aryl bromides and, to some extent, chlorides were feasible substrates as well, the combination of the superior reactivity of aryl triflates with a flexible ligand (**L1**) allowed for the coupling of sterically hindered substrates, including heterocycles, in high yields. Additionally, a wide range of functional groups with coordinating abilities, such as the methoxy group, carbonyls and boronic ester, was tolerated when using another ligand (**L2**). Moreover, the synthetic utility could be demonstrated by the thioetherification of triflates derived from biologically relevant phenols. Experimental and computational mechanistic studies supported a $\text{Ni}^0/\text{Ni}^{\text{II}}$ catalytic cycle. Furthermore, computations indicated an unusual switch in the ligation state of the bidentate phosphine, rationalizing the need for a flexible ligand.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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Influence of the Counterion on the Activation of Nickel(σ -Aryl) Precatalysts

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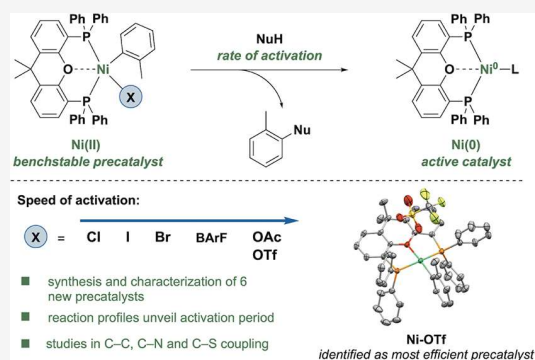
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ABSTRACT: Complexes of the type $L_nNi(\sigma\text{-aryl})Cl$ are known to be competitive precatalysts for various transformations, avoiding the use of expensive and sensitive $Ni(0)$ -precursors, such as $Ni(cod)_2$. The *in situ* activation requires a transmetalation step with a nucleophile, yielding the active $Ni(0)$ catalyst after reductive elimination. Steric hindrance is usually implemented in the σ -aryl group (e.g., *o*-tolyl or 1-naphthyl) to enhance kinetic stability. Simultaneously, this steric hindrance can render the activation process slow, thus increasing the reaction time and possibly reducing the amount of active catalyst. To circumvent this issue, we envisaged substitution of the anionic chloride ligand of the precatalyst with more labile ligands that would facilitate transmetalation. In this work, a series of $(Xantphos)Ni(o\text{-tolyl})X$ complexes was successfully synthesized, and the effect of the counterion X on the reaction profile was investigated using C–S cross-coupling as the model reaction. $(Xantphos)Ni(o\text{-tolyl})OTf$ was identified as the most efficient precatalyst, probably due to the weak coordinating ability of the triflate anion that facilitated the activation step. Finally, this concept was also studied in Suzuki–Miyaura coupling and Buchwald–Hartwig amination reactions using $(dppf)Ni(o\text{-tolyl})X$ precatalysts.



INTRODUCTION

Nickel catalysis has emerged as an expedient tool for C–X bond formation,¹ enabling transformations and electrophiles that are unfeasible with other metal catalysts, such as palladium.² However, a big drawback of nickel is the low availability of nickel(0) precursors, which are expensive and often highly sensitive toward air and moisture, which limits larger scale applications. Although there has been success to stabilize nickel(0) by electron-accepting ligands and steric hindrance, rendering certain $Ni(0)$ complexes stable even at ambient conditions,³ these complexes sometimes perform poorly as catalysts due to the stabilizing ligands that can be detrimental to catalysis by blocking free coordination sites.⁴ While $Ni(0)$ can be synthesized *in situ* by electroreduction,⁵ active nickel catalysts can also be generated from nickel(II) salts, using external reductants such as zinc, manganese or metalorganic compounds,⁶ but this comes with the disadvantage of a more complex reaction setup and the additional generation of metal waste (Scheme 1A). To overcome these problems, suitable air-stable nickel(II) complexes, first reported by Chatt and Shaw in 1960,⁷ have been recognized to give active nickel(0) catalysts after *in situ* activation.⁸ Advantageously, these precatalysts do not need external reductants but can be activated by the nucleophile of a cross-coupling reaction, greatly simplifying reaction development.⁹ In their seminal work, Jamison et al. developed an efficient route toward a wide range of bench-stable $(R_3P)_2Ni(o\text{-tolyl})Cl$ and $-Br$ complexes in high yields starting from

inexpensive $NiX_2(H_2O)_n$.^{8d} Another advantage is that the ideal ratio of ligand to nickel is ensured by the well-defined molecular structure, also leading to less components that have to be handled during the reaction setup. Such complexes proved effective for catalysis in numerous reactions, including C–C,^{8d,9,10} C–N,¹¹ C–O,¹² C–S¹³ and C–Se¹⁴ bond formations. One key feature of this established structure is the apparent necessity for sterical bulk on the σ -aryl-group, kinetically stabilizing the complex against decomposition.⁷ On the other hand, the same steric shielding of nickel slows down the activation step, which requires transmetalation with a nucleophile. Depending on the structure, the precatalyst can be unstable in solution, leading to reduced amounts of catalytically active species (Scheme 1B, green line). On the other hand, excessive stabilization of the precatalyst can lead to a slow activation step, preventing generation of an active catalyst (Scheme 1B, blue line). Finding the right balance between stabilization and reactivity is key for obtaining a short initiation period and a high amount of active catalyst (Scheme 1B, orange line). Despite the great success of these type of

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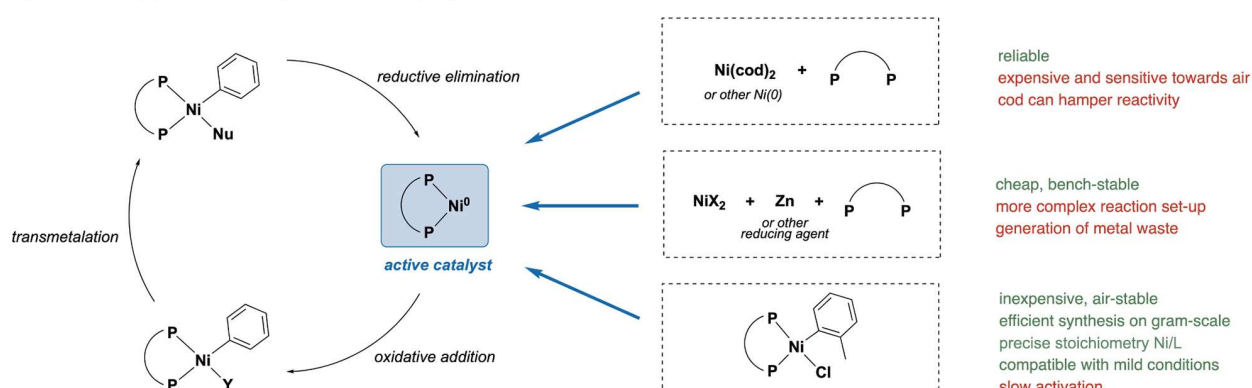
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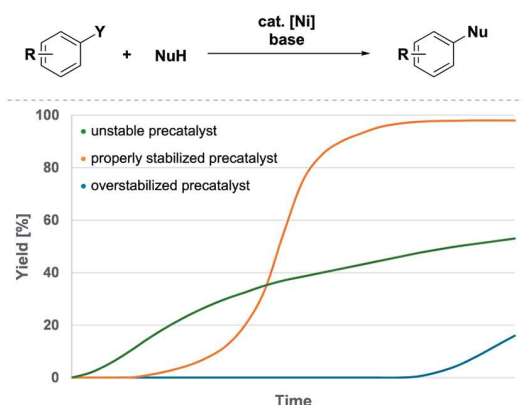


Scheme 1. Overview of Common Methods for the Generation of Active Nickel Catalysts, Features of Ni(II)-Precatalysts, and the Aim of This Work

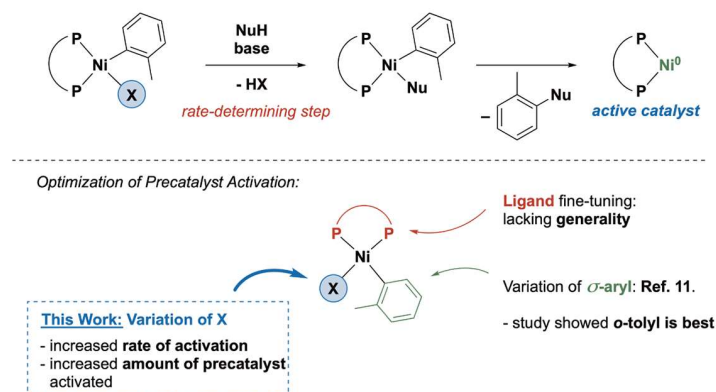
A) Entries to Ni(0) in Nickel-Catalyzed Cross-Couplings



B) Typical Reaction Profiles using Nickel Precatalysts



C) Activation of the Nickel Precatalyst



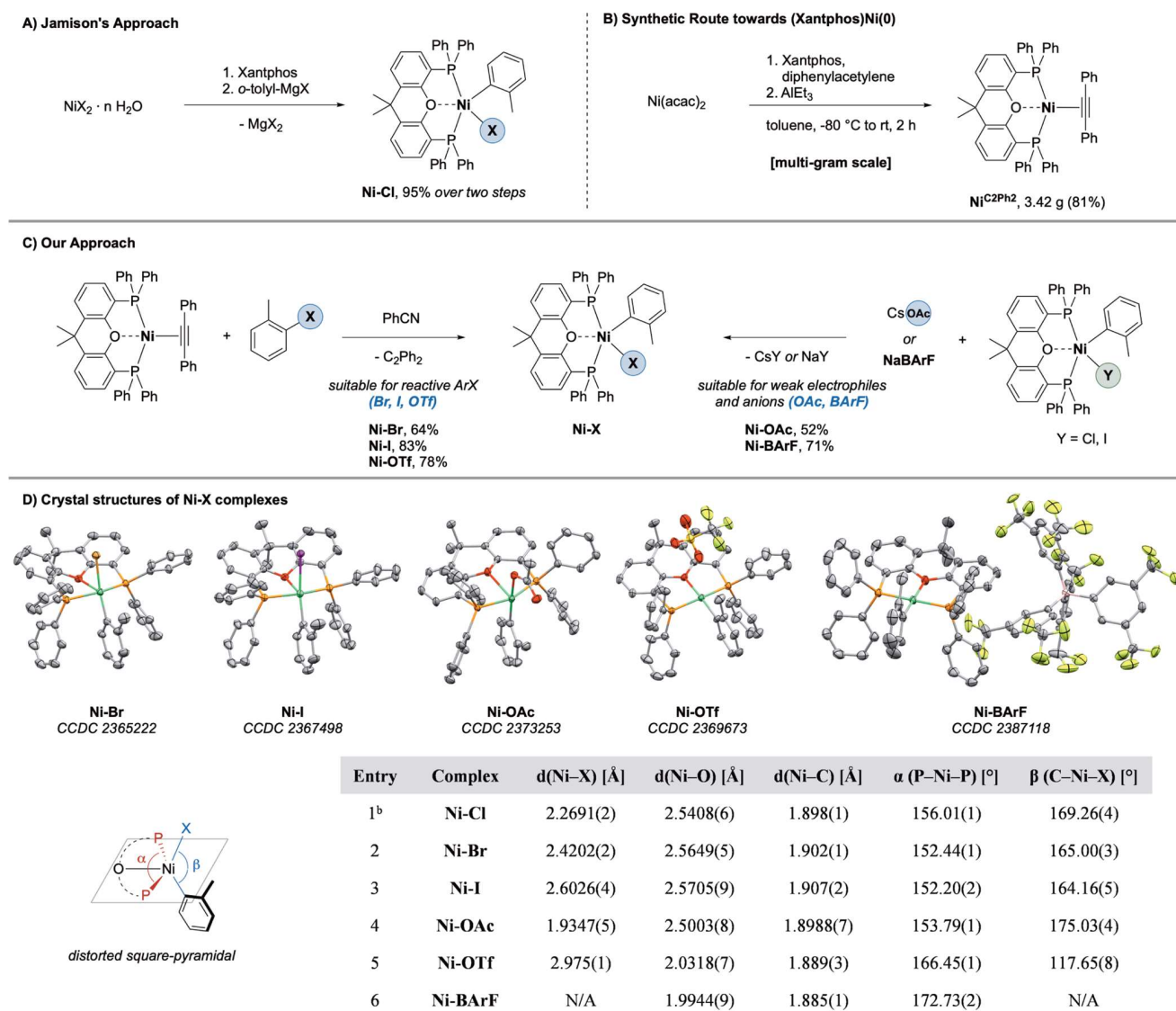
complexes, only low effort has been invested into further advancements in this field, e.g., optimization of the precatalyst structure toward a more efficient activation step.¹⁵ In fact, systematic approaches are yet limited to one report by Hazari and coworkers, who studied the influence of modifications on the σ -aryl-group on activation and catalysis (Scheme 1C).¹⁶ Still, their work revealed the already known *ortho*-tolyl as the best substituent for most reactions. One earlier study focused on naphthyl-derivatives as the aryl substituent combined with several (pseudo)halides as the counterion,^{10b} but the more empirical approach of assessing precatalyst performance with overall yields at varying conditions complicated the interpretation of their data and prevented the identification of the most efficient precatalyst. Therefore, we envisaged that finetuning of the precatalyst structure could facilitate the activation process, ultimately leading to a faster reaction.¹⁷ While the reactivity of a complex can always be tuned by subtle modifications of the respective ligands, this approach requires reoptimization for every catalytic system and thus lacks generality. In our search for more efficient precatalysts, we noticed that the effect of the anionic ligand on nickel is poorly understood, and—with few exceptions¹⁸—neglected in the literature. Herein, we demonstrate that the anion influences the activation and by choosing a more reactive precatalyst, reaction times can be shortened by up to 50%. Moreover, it is well-known that active Ni(0) can comproportionate with Ni(II)-species,¹⁹ leading to Ni(I)-species that, depending on the catalytic system, may lack discernible catalytic activity.^{19,20}

The amount of active catalyst generated from the precatalyst could therefore also depend on the respective counterion. Based on our previous work, in which (Xantphos)Ni(*o*-tolyl)Cl that was used as a precatalyst for C–S coupling, showed activation times of up to 20 min,^{13b} we decided to use this catalytic system to study the performance of various precatalysts bearing different anions.

RESULTS AND DISCUSSION

Precatalyst Synthesis. We began our investigations by synthesizing (Xantphos)Ni(*o*-tolyl)X (Ni–X) precatalysts. Although Jamison's well-known synthetic procedure proved highly efficient for the parent complex Ni–Cl (Scheme 2A),^{8d} the development of another synthetic route was necessary for obtaining complexes with anions that are unavailable as the nickel(II) salt and/or are incompatible with Grignard reagents, e.g., counterions such as esters or weak coordinating species. Additionally, one of our goals was to start the synthesis from inexpensive Ni(II) salts, such as Ni(acac)₂ to render a possible precatalyst economically feasible. In the literature, no well-explored routes toward such complexes other than Jamison's method exist, but we envisaged two approaches, that have been used in the past for the preparation of similar complexes:

- Oxidative addition of an aryl (pseudo)halide to a Ni(0)-complex.²¹
- Salt metathesis of a suitable Ni(II)-complex with a respective metal salt.²²

Scheme 2. Synthesis and ORTEPs of Nickel Precatalysts Studied in This Work^a

^aSelected bond lengths and angles are given below. ^bHydrogen atoms, as well as disordered atoms are omitted for clarity and thermal ellipsoids are shown at 50% probability level. ^cValues obtained from published data.^{8d}

In many related published examples, Ni(cod)₂ is a frequently used starting material for the synthetic route of oxidative addition.^{15,23} Unfortunately, Ni(cod)₂ is an unsuitable starting material when dealing with Xantphos, since it is known that upon mixing a 1:1 ratio of Ni(cod)₂ and Xantphos, a mixture of (Xantphos)₂Ni and Ni(cod)₂ is formed instead of (Xantphos)Ni(cod).²⁴ (Xantphos)₂Ni is considered unreactive and it does not engage easily in oxidative addition reactions.²⁴ Consequently, we searched the literature for better suited Ni(0) precursors and found that (Xantphos)Ni(diphenylacetylene) (Ni^{C2Ph2}) displayed better reactivity.²⁵ Having confirmed that this complex could react with *o*-tolyl iodide, a low-cost synthesis of Ni^{C2Ph2} was developed. For this purpose, the nickel(0) complex was generated by reduction of Ni(acac)₂ with triethylaluminum in the presence of Xantphos and diphenylacetylene in a one-step procedure. The vacant site is occupied by diphenylacetylene, and the product precipitated from toluene. Conveniently, this synthesis could be conducted on multigram scale giving high yield (81%) (Scheme 2B).

Notably, a similar procedure was successful for preparing (dppf)Ni(cod), which was used for the synthesis of ^{dppf}Ni-OTf (*vide infra*). With a suitable starting material in hand, we exposed it to various electrophiles of the general structure *o*-tolyl–X to synthesize the corresponding (Xantphos)Ni(*o*-tolyl)X complexes (Scheme 2C). The addition of PhCN as a promoter was necessary to generate the more reactive complex (Xantphos)Ni(η²-NCPh) *in situ*, facilitating oxidative addition.^{20b,c} Moderate to good yields were obtained for Ni–Br (64%), Ni–I (83%) and Ni–OTf (78%), while less reactive aryl pseudohalides gave only low conversions. We found that these complexes are more easily synthesized by salt metathesis of Ni–I with the corresponding cesium (pseudo)halide salt, giving access to Ni–OAc in moderate yield (52%). Likewise, a weak coordinating anion (WCA) was introduced by reacting Ni–Cl with NaBARF, yielding Ni–BARF (71%, BARF = [B(3,5-(CF₃)₂Ph)₄][–]). Single-crystals of all precatalysts were obtained and analyzed by X-ray diffraction, and the corresponding structures are given below (Scheme 2D).

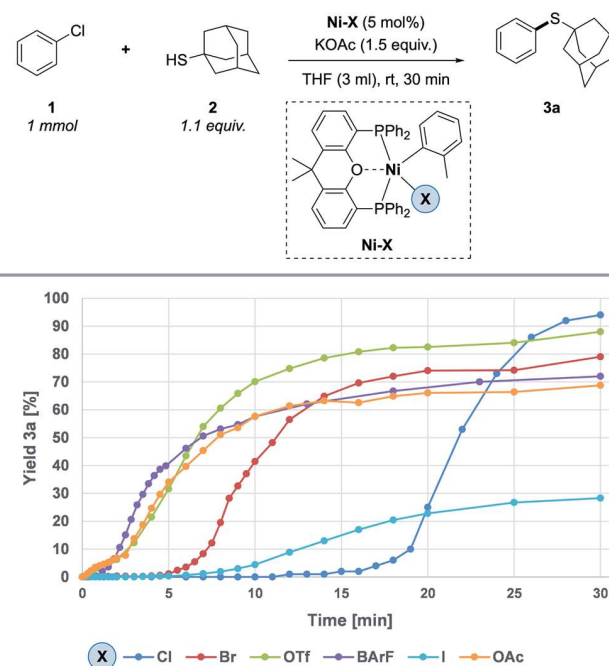
As expected, the distance between nickel and the corresponding halide ligands Cl, Br and I increases down the group (Entries 1–3). Interestingly, the distortion of the square pyramidal geometry also increases down the group, as displayed by decreasing angles α and β .

The crystal structure of **Ni-OAc** (Entry 4) exhibits the shortest Ni–X bond of all complexes obtained ($d = 1.9347(5)$ Å), which is shorter than the Ni–O bond in $\text{Ni}(\text{OAc})_2(\text{H}_2\text{O})_4$ (2.0579 Å).²⁶ It is noteworthy that the acetate in **Ni-OAc** acted as a monodentate ligand, and the complex showed the same geometry as the corresponding halide complexes, although the xanthene backbone is less distorted. For the triflate complex **Ni-OTf**, the crystal structure shows no coordination of the triflate anion to nickel, rendering the complex cationic. Still, the Ni–OTf distance of less than 3 Å suggests that some interaction remains in the solid state (Entry 5), albeit the interaction in solution is still unclear. Moreover, a square-planar geometry is adopted, which is likely retained in solution, as indicated by the ^1H NMR of the tolyl- CH_3 protons ($\delta = 1.38$ ppm), that displayed a strong upfield shift compared to the respective signal in **Ni-Cl** ($\delta = 3.40$ ppm). Apparently, this geometry requires the oxygen atom of the Xantphos ligand to bind significantly more tightly to nickel, as reflected by the shorter bond length compared to **Ni-Cl** (Entry 1 and 5). Additionally, the xanthene backbone is planar in this structure, suggesting an increased conjugation of the aromatic system. The differences between the halide and triflate complexes are even more exaggerated in the structure of **Ni-BArF** (Entry 6). The full dissociation of the counterion leads to an even shorter Ni–O bond and the phosphorus atoms are coordinated almost ideally *trans* ($172.73(2)^\circ$).

Performance of Precatalysts in Catalysis. Next, the activity of the obtained complexes was evaluated in C–S cross-coupling. This model reaction was chosen, because the activation period, as well as the reaction progress can be conveniently monitored via GC-FID in a reasonable time frame. As a benchmark, phenyl chloride was reacted with tertiary 1-adamantanethiol using KOAc as a base and 5 mol % of the respective precatalyst (Scheme 3). The proposed activation step of the precatalyst includes ligand exchange of the counterion X with acetate followed by base-assisted thiol coordination and deprotonation.^{13b,c} Reductive elimination yields the active catalyst (Xantphos)Ni(0) that subsequently engages in the catalytic reaction by oxidative addition of the electrophile followed by the same steps described above.

For the chloride complex, it was already demonstrated that it takes about 15 min before significant amounts of active catalyst are generated and the overall reaction begins.^{13b} The reaction profile of **Ni-Br** (red line) shows that the activation period is with ca. 5 min much shorter than with **Ni-Cl** (blue line). In turn, the reaction rate remained approximately the same, as the active catalyst is the same in both reactions. An even further enhanced activation process was observed for **Ni-OTf** (green line). In this reaction, detectable amounts of thioether **3a** were produced after the first 2 min. This could be explained by the structure of the precatalyst, which features no coordination of the triflate anion to nickel (Scheme 2D), rendering the metal cationic, possibly leading to a facilitated acetate or thiol coordination. The potential of triflate-ligated nickel precatalysts has already been recognized by the group of Buchwald in the past, although they were unable to isolate the corresponding σ -aryl complex and instead relied on η^3 -allyl.²⁷ The iodide complex **Ni-I** (turquoise line) gave a sluggish

Scheme 3. Comparison of Ni-X Precatalysts in C–S Cross-Coupling by Analysis of the Reaction Profile^a



^aReaction conditions: Phenyl chloride (**1**) (1.0 mmol, 1.0 equiv), 1-adamantanethiol (**2**) (1.1 equiv), KOAc (1.5 equiv), Ni-X (5 mol %), THF (3 mL), pentadecane (100 μL), rt, 30 min. Samples were taken from the reaction mixture with a syringe and analyzed via GC-FID using pentadecane as internal standard.

reaction rate that had little in common with the other reaction profiles. A similar behavior was already observed in earlier work when aryl iodides have been employed as substrates, which could be traced back to the formation of detrimental Ni(I)-species,²⁸ that were proposed to be catalytically inactive.^{13b} Indeed, addition of 5 mol % of KI to a reaction catalyzed by **Ni-Cl** reduced the product yield to 6% (see ESI section 5). The promising results of **Ni-OTf** led to the use of the even weaker coordinating anion tetrakis[3,5-bis-(trifluoromethyl)phenyl]borate (BArF). While **Ni-BArF** gave traces of catalytic product after only 1 min, the reaction profile displayed a strong similarity to the curve of **Ni-OAc**. In a separate experiment, it was shown that both **Ni-OTf** and **Ni-BArF** were converted to **Ni-OAc** quantitatively within 5 min upon exposure to 5 equiv of KOAc in THF, suggesting that this exchange also occurred under catalytic reaction conditions (see Scheme S21). When it comes to the curve of **Ni-OAc** (orange line), we expected the highest efficiency in activation, as **Ni-OAc** was proposed to be an intermediate of the activation process.^{13b,29} Although **Ni-OAc** delivered detectable amounts of catalytic product within the first minute of the reaction, the reaction rate decreased after ca. 10 min and the overall yield at the end of the reaction was the lowest with exception of **Ni-I**. We hypothesized that catalyst deactivation could be a reason for the reduced reaction rate. However, *in situ* ^{31}P NMR spectroscopy revealed that the concentration of active catalyst remained approximately constant during the reaction, while the amount of catalyst activated was determined to ca. 60% using Ph_3PO as internal standard (Scheme S20). Thus, decomposition of **Ni-OAc** during the activation process is most likely responsible for the decrease in

active catalyst formation and low overall yield. The instability of Ni-OAc in THF-solution was also observed independently by ^{31}P NMR spectroscopy. Meanwhile, Ni-OTf and Ni-BArF displayed higher stability in solution which could be responsible for the higher overall yields observed.

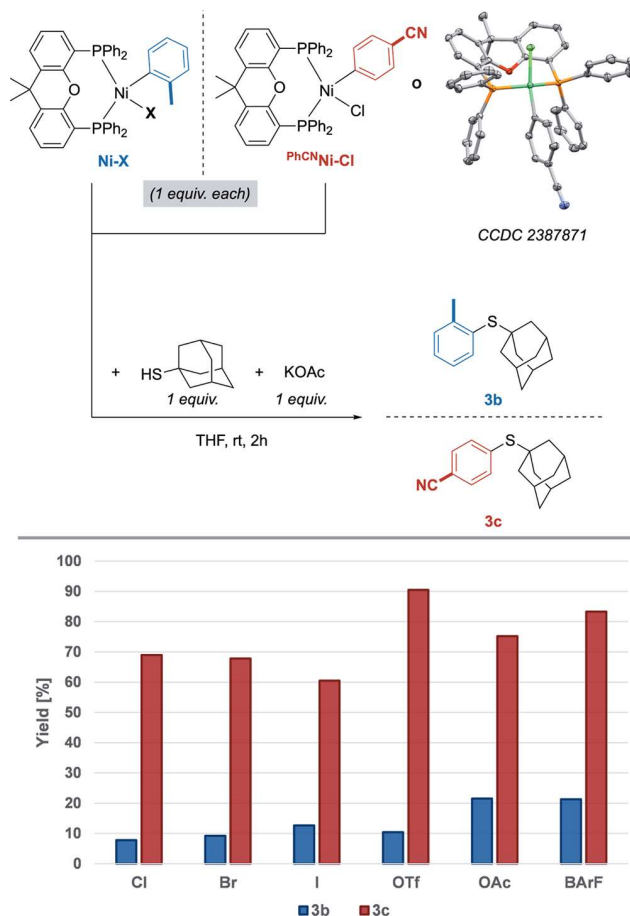
Mechanistic Rationalization of the Initiation Period.

In another experiment, the rate of thiol coordination was investigated under noncatalytic conditions. Hence, Ni-Cl was exposed to a 20-fold excess of adamantanethiol in the presence of KOAc. Contrary to our expectation that the activation process would take around 15 min as previously seen in catalysis (Scheme 3), the formation of thioether **3b** was observed within less than one minute (Scheme S22). This discrepancy in reactivity under stoichiometric versus catalytic conditions indicated that a more complex process could take place under catalytic conditions. We envisioned that in a catalytic reaction, the initially formed Ni(0) can engage in oxidative addition with PhCl, yielding the on-cycle nickel oxidative-addition-complex (OAC) (Xantphos)Ni(Ph)Cl. Since the thiol coordination is rate-determining,^{13b} this process occurs faster than further activation of precatalyst. At this point, the two species (Xantphos)Ni(*o*-tolyl)Cl and (Xantphos)Ni(phenyl)Cl coexist and could undergo competition for the nucleophile, proposedly favoring the phenyl complex as a result of steric hindrance. In this scenario, the full activation of Ni-Cl may be hindered by the active catalyst consuming the nucleophile, slowing down the propagation of precatalyst activation. A competition would be feasible because the corresponding nucleophile, either the acetate or the thiolate, should be present only in low concentrations as a result of low solubility or acid–base equilibrium, respectively. In contrast, this competition cannot exist in the stoichiometric reaction, because the absence of PhCl prevents the formation of the on-cycle oxidative addition complex.

Therefore, we decided to further study the activation by designing a competition experiment between Ni-X and a nickel OAC. While the intermediate (Xantphos)Ni(phenyl)Cl is known to be unstable and cannot be isolated,^{7,9} we succeeded in the isolation of (Xantphos)Ni(4-CN-Ph)Cl ($^{\text{PhCN}}\text{Ni-Cl}$) as a surrogate for the phenyl complex in 81% yield. Interestingly, the corresponding crystal structure shows no coordination of the oxygen to nickel (Scheme 4). Although $^{\text{PhCN}}\text{Ni-Cl}$ cannot be directly compared to (Xantphos)Ni(Ph)(Cl), it can serve as a model compound in this competition to compare various Ni-X complexes. $^{\text{PhCN}}\text{Ni-Cl}$ was treated with one equivalent of adamantanethiol in the presence of one equivalent of various Ni-X precatalysts and the base KOAc. Analysis of the product mixtures provided insight into the relative reaction rates.

In general, the reaction was, as expected, more selective toward the sterically less hindered complex. Down the halide group, this selectivity decreased $\text{Cl} > \text{Br} > \text{I}$, indicating that softer anions increased the reactivity of these precatalysts. However, this effect was not very expressed, still favoring **3c**. The fact that Ni-I underwent activation more easily than Ni-Br in the stoichiometric reaction underlines the probability of formed KI as a source for catalyst inhibition. The triflate complex Ni-OTf, which performed best in the catalytic reaction, gave a similar ratio as Ni-Br, although their catalytic reaction profiles differed. Again, the acetate and BArF complexes behaved similarly, which can be attributed to the reaction of Ni-BArF with potassium acetate (*vide supra*). Still, both complexes furnished more of the precatalyst activation product **3b** compared to the halide complexes. Although the

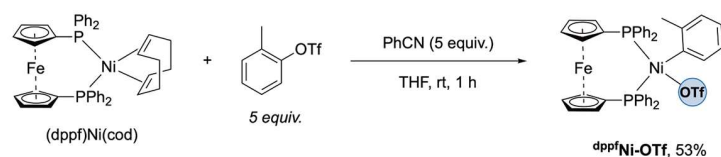
Scheme 4. Stoichiometric Competition Experiment Between the Oxidative-Addition Complex $^{\text{PhCN}}\text{Ni-Cl}$ and Various Ni-X Precatalysts^a



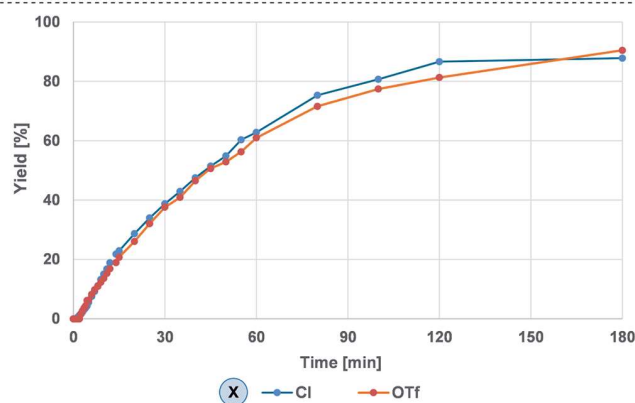
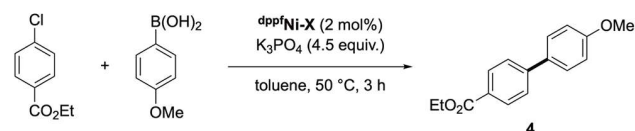
^aReaction conditions: Ni-X (6 μmol), $^{\text{PhCN}}\text{Ni-Cl}$ (1 equiv), 1-adamantanethiol (1 equiv), KOAc (1 equiv), THF (2 mL), pentadecane (5 μL), rt, 2 h. Yields given were obtained via GC-FID using pentadecane as internal standard. In the crystal structure of $^{\text{PhCN}}\text{Ni-Cl}$, hydrogen atoms and one molecule of cocrystallized THF are omitted for clarity and thermal ellipsoids are shown at 50% probability level. Selected bond lengths [$\text{\AA}$] and bond angles [$^\circ$]: Ni-C, 1.879(1); Ni-Cl, 2.2359(7); Ni-O, 2.6561(9); P-Ni-P, 149.94(2); C-Ni-Cl, 160.06(4).

reason, why Ni-OTf gave different results than Ni-BArF in the stoichiometric, but behaved similarly in the catalytic reaction, remains unclear, we propose that the rate-difference of the exchange with KOAc could be responsible. In conclusion, these results are in line with the observed initiation periods in the catalytic reaction. This supports the existence of a competition in the catalytic reaction as an explanation for the slower activation of precatalyst in catalytic versus stoichiometric reactions.

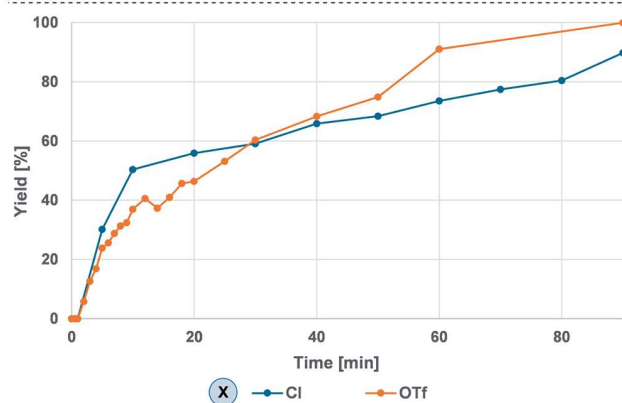
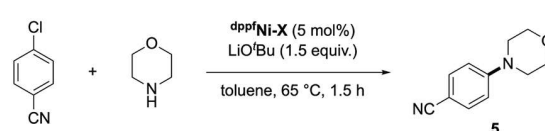
Application to Other Cross-Coupling Reactions. With these results in hand, we explored if the improvement in catalytic activity using the precatalyst Ni-OTf, which gave a short activation period while maintaining high yield, could also be applied to other well-known cross-coupling reactions. It has been already discovered in the past, that the complex (dppf)Ni(*o*-tolyl)Cl ($^{\text{dppf}}\text{Ni-Cl}$, dppf = 1,1'-bis-(diphenylphosphino)ferrocene) can be used as a precatalyst for the nickel-catalyzed Suzuki-Miyaura coupling (SMC) of

Scheme 5. Comparison of dppfNi-X ($\text{X} = \text{Cl}$, OTf) Precatalysts in C–C and C–N Cross-Coupling Reactions^aA) Synthesis of dppfNi-OTf 

B) Nickel-catalyzed Suzuki–Miyaura Coupling



C) Nickel-catalyzed Arylation of Morpholine



^aReaction Conditions: A) ethyl 4-chlorobenzoate (1.0 mmol), 4-methoxyphenyl boronic acid (2.5 equiv), K_3PO_4 (4.5 equiv), dppfNi-X (2 mol %), toluene (4 mL), pentadecane (100 μL), 50 $^\circ\text{C}$, 3 h. B) 4-chlorobenzonitrile (1.0 mmol), morpholine (1.5 equiv), LiO^tBu (1.5 equiv), dppfNi-X (5 mol %), toluene (3 mL), naphthalene (100 mg), 65 $^\circ\text{C}$, 1.5 h. All yields were calculated via GC-FID using pentadecane/naphthalene as internal standard.

aryl chlorides with aryl boronic acids,^{10a} as well as for the nickel-catalyzed amination of aryl chlorides.^{11b} Consequently, we were able to synthesize $(\text{dppf})\text{Ni}(o\text{-tolyl})\text{OTf}$ (dppfNi-OTf) in 53% yield (Scheme 5A) and employed this complex as a precatalyst in the SMC of 4-chloro ethylbenzoate with 4-methoxyphenyl boronic acid, and in the amination of 4-chloro benzonitrile with morpholine. After confirming that this complex was catalytically active, we monitored each reaction profile for both dppfNi-Cl and dppfNi-OTf (Scheme 5B). In the SMC, no product formation was observed in the first 2 min, and the reaction profile resembled that of a typical (pseudo)-first order kinetic. No improved performance could be noticed using the triflate complex and the reaction profiles appeared nearly identical. This indicates that the chloride or triflate, respectively, are not involved in the rate-determining step of the activation process. In the literature, the rate-determining step in the nickel-catalyzed SMC is often proposed as the formation of a so-called nickel-oxo species that forms from a μ -hydroxo-bridged dimer³⁰ that may act as the resting state.³¹ Our results are in line with this mechanistic proposal, since the counterion does not play a role in the formation of a nickel-oxo species from its respective dimer.

Regarding the C–N coupling reaction, we found in preliminary screenings that the arylation of morpholine with 4-chloro benzonitrile using dppfNi-Cl as the catalyst, was successful at slightly lower temperature than reported in the literature.^{11b,32} Accordingly, we subjected each dppfNi-Cl and dppfNi-OTf to these adapted reaction conditions and

monitored the overall reaction progress (Scheme 5C). Both reaction profiles exhibited the same activation period (around 2 min) and a similar initial rate. However, when using dppfNi-OTf , the profile resembled a typical (pseudo)first order reaction, while the reaction utilizing dppfNi-Cl slowed down after ca. 10 min. Still, both reactions were quite similar, contrary to the results obtained for the C–S coupling reaction. We hypothesized, that the higher temperature could be a factor in overcoming the sterically hindered activation step. Alternatively, the competition for the nucleophile that is proposedly responsible for a slow precatalyst activation in C–S coupling, may not be present in either of the C–C or C–N couplings, respectively, as the concentration of the nucleophile is high. Another reason for the slower activation of (Xantphos) nickel catalysts could be the oxygen donor atom that may lower the electrophilicity of Ni(II), rendering the nucleophile attack more difficult compared to the dppf ligand, which lacks a third donor moiety beside the phosphine.

CONCLUSIONS

In conclusion, we successfully synthesized a series of precatalysts of the type $(\text{Xantphos})\text{Ni}(o\text{-tolyl})\text{X}$ ($\text{X} = \text{Cl}$, Br , I , OTf , OAc , BARF) and elucidated their crystal structure using X-ray spectroscopy. Moreover, the catalytic activity of these complexes was probed and compared in a C–S cross-coupling reaction. We observed the best reactivity for $(\text{Xantphos})\text{Ni}(o\text{-tolyl})\text{OTf}$, which gave high yields of the coupling product within 15 min at room-temperature. This could be attributed

to the low coordinating ability of the triflate anion, which rendered the cationic nickel center prone to nucleophile coordination, resulting in a fast and efficient precatalyst activation. Further experiments indicated that the oxidative addition complex and the precatalyst engaged in a competition for the nucleophile, which slowed down the activation process. Finally, this concept was transferred to other coupling reactions, comparing the catalysts (dppf)Ni(*o*-tolyl)X (X = Cl, OTf) in Suzuki-Miyaura cross-coupling and Buchwald-Hartwig amination. No difference between these precatalysts could be observed in both coupling reactions, suggesting that the higher reactivity of the triflate complex is either less expressed with the dppf-ligand, or, that this only plays a significant role when low nucleophile concentrations are present that lead to a competition between the oxidative addition complex and the precatalyst. A higher reaction temperature could also facilitate the activation process. Therefore, using a more reactive precatalyst could be especially useful for reactions including weak nucleophiles that are present in low concentrations and at low reaction temperatures.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under an argon atmosphere using standard Schlenk techniques or an argon atmosphere Glovebox (GS MEGA E-Line, Glovebox Systemtechnik) and predried glassware, unless noted otherwise. Solvents used were dried using a solvent-purification-system (MB-SPSS, MBraun) and stored over 3 Å molsieves. Chemicals were purchased from abcr, Acros, Alfa Aesar, BLDChem, Carbolution Chemicals, Carl Roth, Fluorochem, Sigma-Aldrich or TCI. 1-Adamantanethiol was purchased from Sigma-Aldrich or BLDpharm (both 95% purity, used as received), stored and handled in a glovebox at room temperature. KOAc was dried under vacuum for 1 h at 130 °C and stored under argon. Other reagents were used as received. (Xantphos)Ni(*o*-tolyl)Cl (Ni–Cl),^{13b} (dppf)Ni(*o*-tolyl)Cl (^{dppf}Ni–Cl)^{8d} and *o*-tolyl trifluoromethanesulfonate^{13c} were prepared according to literature procedures.

Caution: Triethylaluminum is a highly pyrophoric compound and should only be handled under inert atmosphere using appropriate safety equipment.

Analytical Techniques. NMR spectra were recorded using Bruker Avance III HD 400 or Bruker Avance III HDX 700 at room temperature in commercially available deuterated solvents.^{13C}, ^{19F} and ^{31P} NMR experiments were performed in proton-decoupled mode. Chemical shifts (δ) are reported in ppm relative to the residual NMR solvent signals (THF: ^{1H} 3.58 ppm and ^{13C} 67.21 ppm; acetone: ^{1H} 2.05 ppm and ^{13C} 206.26 ppm).³³ Hetero-NMR chemical shifts are given relative to external standards^{19F}: CFCl₃; ^{31P}: H₃PO₄ (85%). The coupling constants (*J* values) are given in Hz and spin multiplicity with the usual designations for splitting patterns (*s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet, *br s* = broad singlet). *Note:* In ^{13C} NMR spectra of (Xantphos)nickel complexes, some signals appear as triplets due to virtual C–P coupling. Ni–X (X = Cl, Br, I) exist as two isomers.^{8d} HR-MS (ESI, APCI, EI) measurements were carried out by the mass spectrometry department of the Institute of Organic Chemistry, University of Tübingen. Measurements were carried out using maXis 4G from Bruker (ESI, APCI) or by a MAT95 from Finnigan (EI). The molecular ions are given in *m/z* units. GC-FID (flame ionization detection) analysis was carried out on an Agilent 7820A system using dry hydrogen as carrier gas. An Agilent 19091J–431 column (30 m × 320 μ m × 0.25 μ m) was used. Program 50–280M15: heating from 50 to 280 °C within 15 min. Conversion and yield were determined via calibration against the internal standard pentadecane or naphthalene. X-ray data were collected on a XtaLAB Synergy, Dualflex, HyPix diffractometer (Cu K α (λ = 1.54184 Å)) at 149.99 K. The structures were solved with the

ShelXT 2018/2 solution program³⁴ using dual methods and by using Olex2 1.5 as the graphical interface.³⁵ The model was refined with olex2.refine 1.5³⁶ using full matrix least-squares minimization on *F*². Elemental analyses were performed on an Elementar Vario MICRO cube.

Reaction Monitoring of C–S Cross-Coupling. A 10 mL inert, flame-dried and septum-caped Schlenk-tube equipped with a stirring bar was charged with KOAc (147 mg, 1.50 mmol, 1.5 equiv), 1-adamantanethiol (**2**) (186 mg, 1.1 mmol, 1.1 equiv) and the respective nickel catalyst Ni–X (5 mol %). After addition of chlorobenzene (**1**) (112 mg, 1.0 mmol, 1.0 equiv) and internal standard pentadecane (100 μ L), the mixture was dissolved in dry THF (3 mL) under stirring, which marked the start of the reaction. Samples (ca. 20 μ L) were taken from this mixture via syringe, quenched with brine and diluted with EtOAc. The organic phase was filtered (glass pipet filled with cotton, Celite, Al₂O₃ and MgSO₄) and analyzed via quantitative GC-FID.

Reaction Monitoring of Suzuki–Miyaura Coupling. A 10 mL inert and septum-caped Schlenk-tube was charged with potassium carbonate (322 mg, 4.50 mmol, 4.5 equiv). The solid was dried under vacuum using a heat-gun for 10 min. After cooling to room-temperature, 4-methoxyphenylboronic acid (380 mg, 2.5 mmol, 2.5 equiv) and the respective nickel catalyst ^{dppf}Ni–X (2 mol %) were added. After addition of ethyl 4-chloro benzoate (184 mg, 1.0 mmol, 1.0 equiv) and internal standard pentadecane (100 μ L), the mixture was dissolved in dry toluene (4 mL) under stirring and the tube was placed in a preheated aluminum block at 50 °C, which marked the start of the reaction. Samples (ca. 20 μ L) were taken from this mixture via syringe, quenched with brine and diluted with EtOAc. The organic phase was filtered (glass pipet filled with cotton, Celite, Al₂O₃ and MgSO₄) and analyzed via quantitative GC-FID.

Reaction Monitoring of Buchwald–Hartwig Amination. A 10 mL inert, flame-dried and septum-caped Schlenk-tube was charged with dry lithium *tert*-butoxide (120 mg, 1.50 mmol, 1.5 equiv), 4-chloro benzonitrile (138 mg, 1.0 mmol, 1.0 equiv), internal standard naphthalene (100 mg) and the respective nickel catalyst ^{dppf}Ni–X (5 mol %). After addition of morpholine (131 mg, 1.5 mmol, 1.5 equiv) and internal standard pentadecane (100 μ L), the mixture was dissolved in dry toluene (3 mL) under stirring and the tube was placed in a preheated aluminum block at 65 °C, which marked the start of the reaction. Samples (ca. 20 μ L) were taken from this mixture via syringe, quenched with brine and diluted with EtOAc. The organic phase was filtered (glass pipet filled with cotton, Celite, Al₂O₃ and MgSO₄) and analyzed via quantitative GC-FID.

Competition Experiment of Ni–X Versus ^{PhCN}Ni–Cl. *Note:* Except KOAc, all reagents were taken from freshly prepared stock solutions (THF). In a glovebox, a 5 mL vial was charged with the corresponding nickel complex Ni–X (6 μ mol, 1 equiv), ^{PhCN}Ni–Cl (4.7 mg, 6 μ mol, 1 equiv), KOAc (0.6 mg, 6 μ mol, 1 equiv) and THF (1.5 mL). While stirring, a solution containing 1-adamantanethiol (1.0 mg, 6 μ mol, 1 equiv) and internal standard pentadecane (5 μ L) in THF (0.5 mL) was added in one portion. After stirring for 2 h, the mixture was quenched with brine. The organic phase was filtered (glass pipet filled with cotton, Celite, Al₂O₃ and MgSO₄) and analyzed via quantitative GC-FID.

Synthesis of (Xantphos)nickel Complexes. (Xantphos)Ni-(diphenylacetylene)(toluene) (Ni^{C2Ph2}). In a 250 mL Schlenk round-bottom flask, Ni(acac)₂ (1.20 g, 4.67 mmol, 1.0 equiv) was dried in an oil-bath at 120 °C under vacuum for 30 min. After cooling to rt, (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane) (2.70 g, 4.67 mmol, 1.0 equiv), diphenylacetylene (1.67 g, 9.34 mmol, 2 equiv) and dry toluene (20 mL) were added. The mixture was cooled to –80 °C and AlEt₃ (1.3 mL in heptane, 7.55 mmol, 2.1 equiv) was added over the course of 5 min under stirring, which led to a color change to dark brown. The reaction was further stirred at this temperature for 1 h, after which the cooling bath was removed. While warming up, the reaction slowly turned yellow. After warming to rt, the mixture was stirred for another hour. The yellow suspension was transferred to an inert frit (P3) and filtered. The yellow filter cake was washed with toluene (3 × 10 mL) and hexane

(3 × 10 mL). The residue was dried under high vacuum to give the toluene adduct $\text{Ni}^{\text{C}^{2\text{Ph}_2}}$ (toluene) (3.42 g, 3.77 mmol, 81%) as an air-sensitive yellow solid. Conforms to reported analytical data.²⁵ ^1H NMR (400 MHz, $\text{THF}-d_8$, δ): 7.52–7.46 (m, 2H), 7.38–7.29 (m, 8H), 7.21–7.05 (m, 8H), 7.03–6.96 (m, 10H), 6.71–6.59 (m, 10H), 6.45–6.37 (m, 2H), 2.30 (s, 3H), 1.63 (s, 6H). ^{13}C NMR (176 MHz, $\text{THF}-d_8$, δ): 157.9, 138.2, 137.3 (t, J = 6.1 Hz), 136.0, 134.5 (t, J = 6.6 Hz), 133.1, 133.0, 131.6, 131.3, 129.5, 129.1, 128.7, 128.3, 128.2, 127.6, 127.4, 125.8, 124.3, 123.8, 37.3, 26.9, 21.3. ^{31}P NMR (162 MHz, $\text{THF}-d_8$, δ): 23.0.

(Xantphos)Ni(o-Tolyl)Br (Ni-Br). In a 100 mL Schlenk round-bottom flask, $\text{Ni}(\text{acac})_2$ (300 mg, 1.17 mmol, 1.0 equiv) was dried with a heat-gun for 10 min under vacuum. Then, Xantphos (676 mg, 1.17 mmol, 1.0 equiv) and dry toluene (10 mL) were added. The mixture was cooled to -80°C and AlEt_3 (1.3 M in heptane, 1.89 mL, 2.45 mmol, 2.1 equiv) was added dropwise under stirring. The reaction was further stirred at this temperature for 1 h, after which *o*-tolyl bromide (999 mg, 5.84 mmol, 5.0 equiv) was added. The cooling bath was removed, and the reaction was allowed to warm to room temperature and stirred for 2 h. The orange precipitate was filtered on a frit (P3), washed with toluene (3 mL) and hexane (4 × 5 mL). The filter cake was dried under high vacuum to give Ni-Br (601 mg, 0.743 mmol, 64%) as a yellow solid. ^1H NMR (700 MHz, $\text{THF}-d_8$, δ): 8.54–8.32 (m, 4H), 7.75–7.64 (m, 2H), 7.51–7.32 (m, 6H), 7.22–7.11 (m, 4H), 7.04–6.92 (m, 2H), 6.85–6.68 (m, 4H), 6.39–6.20 (m, 5H), 6.08–5.97 (m, 1H), 5.33–5.15 (m, 2H), 3.47 (s, 3H), 2.00 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (176 MHz, $\text{THF}-d_8$, δ): 156.6 (t, J = 5.8 Hz), 151.1 (t, J = 32.5 Hz), 141.5, 140.4 (t, J = 4.8 Hz), 138.3 (t, J = 6.4 Hz), 135.4, 135.3, 135.1, 133.2, 131.6 (t, J = 19.6 Hz), 131.3, 131.0, 128.5, 127.7, 127.4, 125.2, 124.9, 124.6, 123.9 (t, J = 20.0 Hz), 120.6, 36.8, 33.4, 23.5. ^{31}P NMR (162 MHz, $\text{THF}-d_8$, δ): 8.8 (major isomer), 3.4 (minor isomer). HR-MS (ESI): m/z calc. for $[\text{M}-\text{Br}]^+$ 727.18241, found 727.18263. Elemental analysis: calc. C: 68.35, H: 4.86; found: C: 67.74, H: 5.21.

(Xantphos)Ni(o-tolyl)i (Ni-I). In a 100 mL Schlenk round-bottom flask, $\text{Ni}^{\text{C}^{2\text{Ph}_2}}$ (toluene) (1.00 g, 1.1 mmol, 1 equiv) was dissolved in dry THF (40 mL). Under stirring, PhCN (568 mg, 5.5 mmol, 5 equiv) and *o*-tolyl iodide (1.20 g, 5.5 mmol, 5 equiv) were added via syringe. The orange homogeneous solution was stirred for 3.5 h until crude ^{31}P NMR spectroscopy indicated full consumption of the starting material. The mixture was concentrated to 10 mL and *n*-hexane (40 mL) was added. The suspension was cooled to 0°C and filtered using a filter cannula. The red filter cake was washed with *n*-hexane (3 × 10 mL) under argon and dried under high vacuum for 24 h. Ni-I (783 mg, 915 μmol , 83%) was received as a red powder. ^1H NMR (700 MHz, acetone- d_6 , δ): 7.99–7.92 (m, 4H), 7.84–7.81 (m, 2H), 7.55–7.50 (m, 2H), 7.43–7.37 (m, 6H), 7.32–7.28 (m, 2H), 7.25–7.20 (m, 2H), 7.08–7.03 (m, 4H), 6.94–6.86 (m, 4H), 6.29 (d, J = 7.1 Hz, 1H), 6.22 (dd, J = 7.1, 6.8 Hz, 1H), 5.90 (d, J = 7.4 Hz, 1H), 5.68 (dd, J = 7.4, 6.8 Hz, 1H), 2.80 (s, 3H), 1.94 (s, 3H), 1.79 (s, 3H). ^{13}C NMR (176 MHz, acetone- d_6 , δ): 156.1 (t, J = 6.3 Hz), 149.2 (t, J = 30.8 Hz), 142.8, 139.2 (m), 137.8 (t, J = 5.8 Hz), 135.1, 134.4 (t, J = 4.8 Hz), 134.1 (t, J = 24.3 Hz), 131.8, 131.2, 130.1, 129.04, 129.02, 128.99, 128.7 (t, J = 4.6 Hz), 127.4, 125.7, 124.8, 124.6 (t, J = 19.6 Hz), 121.9, 36.7, 32.5, 27.0, 23.9. ^{31}P NMR (162 MHz, toluene- d_8 , δ): 12.5 (major isomer), 7.2 (minor isomer). HR-MS (ESI): m/z calc. for $[\text{M}-\text{I}]^+$ 727.18241, found 727.18280. Elemental analysis: calc. C: 64.59, H: 4.60; found: C: 67.64, H: 4.47.

(Xantphos)Ni(o-tolyl)OTf (Ni-OTf). In a 100 mL Schlenk round-bottom flask, $\text{Ni}^{\text{C}^{2\text{Ph}_2}}$ (toluene) (200 mg, 220 μmol , 1 equiv) was dissolved in dry THF (20 mL). Under stirring, PhCN (114 mg, 1.1 mmol, 5 equiv) and *o*-tolyl trifluoromethanesulfonate (264 mg, 1.1 mmol, 5 equiv) were added via syringe. The orange homogeneous solution was stirred for 6 h until crude ^{31}P NMR spectroscopy indicated full consumption of the starting material. All volatiles were removed *in vacuo* and *n*-hexane (20 mL) was added, followed by sonication for 5 min. The suspension was cooled to 0°C and filtered using a filter cannula. The red filter cake was washed with *n*-hexane (3 × 5 mL) under argon and dried under high vacuum. Ni-OTf (151 mg, 172 μmol , 78%) was received as a yellow powder. ^1H NMR (700

MHz, $\text{THF}-d_8$, δ): 7.92–7.87 (m, 6H), 7.47–7.46 (m, 4H), 7.44–7.40 (m, 2H), 7.39–7.36 (m, 2H), 7.33–7.30 (m, 2H), 7.20–7.17 (m, 4H), 6.88–6.82 (m, 6H), 6.51–6.48 (m, 1H), 6.37–6.30 (m, 2H), 6.27–6.24 (m, 1H), 1.75 (s, 3H), 1.71 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (176 MHz, $\text{THF}-d_8$, δ): 154.5 (t, J = 9.3 Hz), 142.9, 136.5, 134.7 (t, J = 6.2 Hz), 134.4, 133.6 (t, J = 6.0 Hz), 133.3, 132.7, 132.6, 132.3, 131.7, 130.0 (t, J = 5.0 Hz), 129.8, 129.6, 129.3 (t, J = 4.4 Hz), 127.7, 126.6 (t, J = 27.2 Hz), 124.2, 123.8, 119.5 (q, J = 319.9 Hz), 119.1 (t, J = 17.4 Hz), 35.2, 34.1, 32.7, 24.0. ^{19}F NMR (376 MHz, $\text{THF}-d_8$, δ): –78.8. ^{31}P NMR (162 MHz, $\text{THF}-d_8$, δ): 9.8. HR-MS (ESI): m/z calc. for $[\text{M}-\text{OTf}]^+$ 727.18241, found 727.18234. Elemental analysis: calc. C: 64.33, H: 4.48, S: 3.65; found: C: 64.59, H: 4.68, S: 2.94.

(Xantphos)Ni(o-tolyl)OAc (Ni-OAc). Note: The synthesis can be conducted in a 2-step procedure with isolation of Ni-I or in one-pot procedure, which gave higher overall yield. One-pot procedure: In a 100 mL Schlenk round-bottom flask, $\text{Ni}^{\text{C}^{2\text{Ph}_2}}$ (500 mg, 551 μmol , 1 equiv) was dissolved in dry THF (20 mL). Under stirring, PhCN (284 mg, 2.75 mmol, 5 equiv) and *o*-tolyl iodide (601 mg, 2.75 mmol, 5 equiv) were added via syringe. The orange homogeneous solution was stirred for 2 h and CsOAc (317 mg, 1.65 mmol, 3 equiv) was added as solid. The mixture was further stirred at rt for 2 h until crude ^{31}P NMR spectroscopy indicated full consumption of the starting material and of *in situ* formed Ni-I. All volatiles were removed *in vacuo* and the residue was extracted with toluene under argon (3 × 10 mL). The filtrate was concentrated to 10 mL and *n*-hexane (20 mL) was added, which led to precipitation of an orange solid. The mixture was filtered using a filter cannula and the orange filter cake was washed with *n*-hexane (3 × 10 mL) under argon and dried under high vacuum. Ni-OAc (208 mg, 264 μmol , 48%) was received as a red powder. ^1H NMR (700 MHz, $\text{THF}-d_8$, δ): 7.77–7.71 (m, 2H), 7.54–7.43 (m, 4H), 7.20–7.10 (m, 8H), 6.98–6.92 (m, 2H), 6.91–6.86 (m, 2H), 6.78–6.70 (m, 4H), 6.56–6.46 (m, 4H), 6.12–6.06 (m, 1H), 5.88–5.84 (m, 1H), 5.83–5.72 (m, 2H), 2.95 (s, 3H), 1.95 (s, 3H), 1.61 (s, 6H, under solvent peak). ^{13}C NMR (176 MHz, $\text{THF}-d_8$, δ): 176.2, 156.2, 147.1, 137.4, 134.7, 134.3, 134.2, 133.3, 129.5, 128.9, 128.7, 128.7, 128.2, 127.6, 125.0, 122.3, 120.4 (t, J = 19.1 Hz), 36.8, 33.1, 32.4, 26.0, 24.6. ^{31}P NMR (162 MHz, $\text{THF}-d_8$, δ): 3.1. HR-MS (ESI): m/z calc. for $[\text{M}-\text{OAc}]^+$ 727.18241, found 727.18258. Elemental analysis: calc. C: 73.21, H: 5.38 found: C: 73.07, H: 5.51.

(Xantphos)Ni(o-tolyl)BarF (Ni-BarF). In a 100 mL Schlenk round-bottom flask, Ni-Cl (200 mg, 262 μmol , 1 equiv) and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (255 mg, 288 μmol , 1.1 equiv) were suspended in toluene (20 mL) and stirred for 1 h. The mixture was concentrated to 10 mL and filtered using a filter cannula. The residue was extracted with toluene (2 × 3 mL) and the filtrate was concentrated to 2 mL. *N*-hexane (20 mL) was added, and the mixture was subjected to sonication for 5 min, which led to the precipitation of a yellow solid. The suspension was filtered with a filter cannula and the residue was washed with *n*-hexane (2 × 5 mL) and dried under high vacuum. Ni-BarF (295 mg, 185 μmol , 71%) was received as a yellow solid. ^1H NMR (700 MHz, $\text{THF}-d_8$, δ): 7.92–7.86 (m, 6H), 7.67 (br s, 8H), 7.55–7.51 (m, 4H), 7.50–7.44 (m, 8H), 7.42 (dd, J = 7.5, 7.4 Hz, 2H), 7.36 (dd, J = 7.7, 7.7 Hz, 2H), 7.20 (dd, J = 7.5, 7.7 Hz, 4H), 6.79–6.73 (m, 5H), 6.56 (dd, J = 7.3, 7.2 Hz, 1H), 6.38 (dd, J = 7.5, 7.5 Hz, 1H), 6.29 (d, J = 7.3 Hz, 1H), 1.73–1.68 (m, 6H), 1.39 (s, 3H). ^{13}C NMR (176 MHz, $\text{THF}-d_8$, δ): 161.8 (q, $J_{\text{B-C}}$ = 50.0 Hz), 153.6 (t, J = 9.9 Hz), 141.4, 136.5 (t, J = 26.6 Hz), 135.5 (t, J = 3.3 Hz), 134.6, 134.1, 133.8 (t, J = 6.6 Hz), 132.8, 132.5 (t, J = 5.5 Hz), 132.2, 131.8, 131.5, 129.5 (t, J = 5.7 Hz), 129.3 (m), 129.1 (m), 128.9 (m), 128.8 (t, J = 5.1 Hz), 128.0 (t, J = 27.1 Hz), 127.3 (m), 125.0 (t, J = 27.5 Hz), 124.5 (q, $J_{\text{C-F}}$ = 272.5 Hz), 123.8, 123.6, 118.5 (t, J = 17.2 Hz), 117.2 (m), 34.4, 33.7, 31.5, 23.2. ^{19}F NMR (376 MHz, $\text{THF}-d_8$, δ): –63.4. ^{31}P NMR (162 MHz, $\text{THF}-d_8$, δ): 9.8. HR-MS (ESI): m/z calc. for $[\text{M}-\text{BarF}]^+$ 727.18241, found 727.18320. Elemental analysis: calc. C: 58.86, H: 3.23; found: C: 59.40, H: 3.45.

(Xantphos)Ni(4-CN-phenyl)Cl ($^{\text{PhCN}}$ Ni-Cl). In a 100 mL Schlenk round-bottom flask, $\text{Ni}^{\text{C}^{2\text{Ph}_2}}$ (toluene) (500 mg, 551 μmol , 1 equiv) and 4-chloro benzonitrile (1.52 g, 11.0 mmol, 20 equiv) were

suspended in dry THF (20 mL). The orange homogeneous solution was stirred for 3 h until crude ^{31}P NMR spectroscopy indicated full consumption of the starting material. The mixture was concentrated to 5 mL and *n*-hexane (20 mL) was added, which led to the precipitation of a red solid. The suspension was filtered using a filter cannula. The red filter cake was washed with *n*-hexane (3 $\times$ 10 mL) under argon and dried under high vacuum. $^{\text{PhCN}}\text{Ni}-\text{Cl}$ (347 mg, 448 μmol , 81%) was received as a red powder. ^1H NMR (400 MHz, THF- d_8 , δ): 8.37–8.27 (m, 4H), 7.79–7.71 (m, 4H), 7.58–7.39 (m, 8H), 7.21–7.17 (m, 4H), 7.09 (s, 2H), 6.92–6.84 (m, 4H), 6.49–6.35 (m, 4H), 2.01 (s, 3H), 1.76 (s, 3H, *under solvent peak*). ^{13}C NMR (176 MHz, THF- d_8 , δ): 167.8 (t, $J = 33.0$ Hz), 156.7, 137.8, 135.7, 134.6, 134.0 (t, $J = 24.4$ Hz), 133.3, 131.8, 130.5, 129.3, 129.0, 128.7, 128.2, 128.1, 127.1, 125.1, 122.7 (t, $J = 20.3$ Hz), 120.3, 104.2, 37.0, 33.7, 32.5. ^{31}P NMR (162 MHz, toluene- d_8 , δ): 7.6. HR-MS (ESI): m/z calc. for $[\text{M}-\text{Cl}]^+$ 738.16201, found 738.16195. Elemental analysis: calc. C: 71.30, H: 4.68, N: 1.81; C: 69.79, H: 4.61, N: 1.85.

Synthesis of (dppf)Nickel Complexes. (*dppf*)Ni(*cod*). In a 250 mL Schlenk round-bottom flask, Ni(acac) $_2$ (2.00 g, 7.78 mmol, 1.0 equiv) was dried in an oil-bath at 120 $^\circ\text{C}$ under vacuum for 30 min. After cooling to rt, 1,1'-bis(diphenylphosphino)ferrocene (4.32 g, 7.78 mmol, 1.0 equiv), 1,5-cyclooctadiene (1.77 g, 16.4 mmol, 2.0 equiv) and dry toluene (20 mL) were added. The mixture was cooled to -80 $^\circ\text{C}$ and AlEt $_3$ (1.3 M in heptane, 12.6 mL, 16.4 mmol, 2.1 equiv) was added over the course of 5 min under stirring, which led to a color change to dark brown. The reaction was further stirred at this temperature for 1 h, after which the cooling bath was removed. After warming to rt, static vacuum was applied to the flask. This was achieved by closing the valve at the Schlenk flask, applying vacuum to the hose, closing the vacuum valve and opening to the reaction flask. This procedure was repeated 5 times over the course of 1 h. The static vacuum resulted in the evolution of gas and an orange solid precipitated. The mixture was filtered, and the orange filter cake was washed with toluene (3 $\times$ 5 mL) and hexane (2 $\times$ 10 mL). The residue was dried under high vacuum to give the toluene adduct (dppf)Ni(*cod*)(toluene) (4.50 g, 5.56 mmol, 71%) as an air-sensitive orange solid. Conforms to reported analytical data.^{20c} ^1H NMR (400 MHz, THF- d_8 , δ): 7.61–7.55 (m, 8H), 7.39–7.33 (m, 12H), 7.22–7.04 (m, 5H), 4.30–4.22 (m, 4H), 4.05 (s, 8H), 2.30 (s, 3H), 1.60–1.47 (m, 8H). ^{13}C NMR (176 MHz, THF- d_8 , δ): 139.8, 139.5, 134.2 (m), 129.5 (toluene), 128.75 (toluene), 128.71 (toluene), 128.0 (m), 125.8 (toluene), 85.2 (m), 75.3 (m), 71.7, 30.1, 21.3 (toluene). Note: Observed higher order signals due to magnetically inequivalent phosphorus atoms. ^{31}P NMR (162 MHz, THF- d_8 , δ): 34.3.

(*dppf*)Ni(*o*-tolyl)OTf (*dppf* Ni-OTf). In a 100 mL Schlenk round-bottom flask, (dppf)Ni(*cod*)(toluene) (456 mg, 541 μmol , 1 equiv) was dissolved in dry THF (5 mL). Under stirring, PhCN (279 mg, 2.71 mmol, 5 equiv) and *o*-tolyl trifluoromethanesulfonate (650 mg, 2.71 mmol, 5 equiv) were added via syringe. The mixture was stirred for 1 h and *n*-hexane (20 mL) was added. The suspension was cooled to 0 $^\circ\text{C}$ and filtered using a filter cannula. The residue was washed with *n*-hexane (4 $\times$ 5 mL) under argon and dried under high vacuum. *dppf* Ni-OTf (247 mg, 289 μmol , 53%) was received as a dark yellow solid. ^1H NMR (400 MHz, CD $_3$ CN, δ): 8.09–7.87 (m, 5H), 7.54 (m, 4H), 7.44–7.16 (m, 8H), 6.94 (m, 2H), 6.78–6.51 (m, 4H), 6.33 (m, 1H), 5.33 (m, 1H), 4.83 (m, 1H), 4.55–4.41 (m, 2H), 4.36–4.26 (m, 2H), 3.65 (m, 2H), 2.50 (s, 3H). ^{19}F NMR (376 MHz, CD $_3$ CN, δ): –79.3. ^{31}P NMR (162 MHz, CD $_3$ CN, δ): 29.7 (d, $J = 27.3$ Hz), 16.6 (d, $J = 27.3$ Hz). HR-MS (ESI): m/z calc. for $[\text{M}-\text{OTf}]^+$ 703.09120, found 703.09079. Elemental analysis: calc. C: 59.12, H: 4.13, S: 3.76; found: C: 58.89, H: 4.78, S: 2.83.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.organomet.4c00498>.

General procedures, synthetic details, analytical data, and NMR spectra (PDF)

Accession Codes

Deposition Numbers 2365222, 2367498, 2369673, 2373253, 2387118, and 2387871 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Nickel-Catalyzed C–S Cross-Coupling Enhanced by Mechanochemistry

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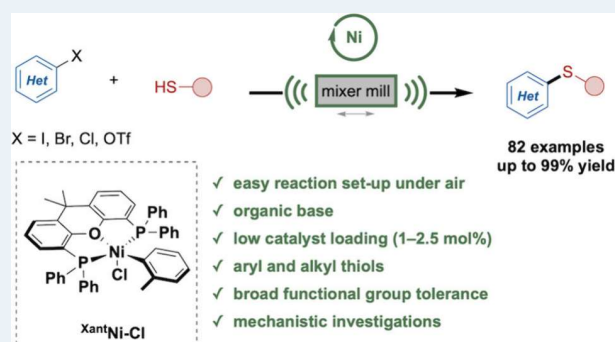
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ABSTRACT: We report a nickel-catalyzed cross-coupling between aryl (pseudo)halides and thiols under mechanochemical conditions. The reaction tolerated both alkyl and aryl thiols and required a lower catalyst loading than the same catalyst under homogeneous conditions (2.5 vs 5 mol %). Moreover, the reaction can be set up under air, greatly simplifying and shortening the reaction setup. Notably, trialkyl amines proved most efficient as a base under mechanochemical conditions. This class of bases has been rarely used in C–S cross-couplings before. The applicability of this system was demonstrated on numerous examples, including compounds relevant to materials science and pharmaceuticals. While mechanistic studies revealed that the reaction is mainly driven by thermal energy produced by the mixer mill, mechanical force appeared to accelerate the reaction, enabling otherwise unfeasible substrates. Using neat NMR and DSC techniques, it could be shown that the catalyst is initially deactivated by excess thiol, forming a mixture of nickel(hydrido)(thiolate) species. Upon reduction by zinc, the active catalyst is formed, able to engage in a Ni(0)/Ni(II) catalytic cycle.

KEYWORDS: mechanochemistry, nickel catalysis, cross-coupling, thioether, nickel-thiolate cluster



INTRODUCTION

Mechanochemistry is currently emerging in synthetic organic chemistry as a more sustainable alternative to traditional homogeneous synthesis.^{1–3} Not only are mechanochemical approaches usually solvent-minimized and therefore considered more eco-friendly,⁴ but they also often offer new reactivities or selectivities.⁵ While palladium catalysis has been frequently exploited for the development of new synthetic protocols,^{6–10} the use of third-row transition metals is still underexplored in mechanochemistry.² For instance, nickel catalysis is, with the exception of reductive couplings, less developed, despite the unique reactivity of nickel that can surpass the scope of other metals.¹¹ Therefore, the combination of nickel with mechanochemistry could enable new possibilities in synthetic chemistry.

One example is the transition-metal-catalyzed C–S cross-coupling, also referred to as the Migita reaction.^{12,13} Typical obstacles related to the use of thiols, such as catalyst deactivation and the requirement of strong bases, have been overcome by decades of development, featuring efficient catalysts mostly based on copper,¹⁴ palladium,¹⁵ and nickel (Scheme 1A).^{16,17} Especially mild conditions were found using photochemistry.^{18–20} However, these systems usually require certain, often toxic, solvents for the stabilization of catalytically active species, high temperatures to overcome catalyst deactivation, and an inert atmosphere. Meanwhile, mechanochemistry promises a

more convenient reaction setup that eliminates these limitations, but there are only a limited number of examples for C–S coupling (Scheme 1B). Recently, the group of Browne published an efficient and simple solution for the palladium-catalyzed cross-coupling of aryl halides with thiols and disulfides.²¹ Protocols utilizing zinc and copper catalysts have also been reported.^{22,23} However, nickel-catalyzed approaches are limited to the work of Guo and co-workers, who relied on a bipyridine-supported nickel catalyst.²⁴ Even so, this approach required 20 mol % of nickel and large excess of both substrate and additives.

Based on our previous experience in nickel-catalyzed C–S couplings,^{17,25} we expected that a phosphine-ligated nickel catalyst would increase the efficiency of the mechanochemical coupling. An important limitation of our earlier approaches was the impeded use of aryl thiols, most likely due to catalyst inhibition, and we questioned whether this could be overcome under mechanochemical conditions (Scheme 1C). Furthermore, a goal was to eliminate air-sensitivity and the strict

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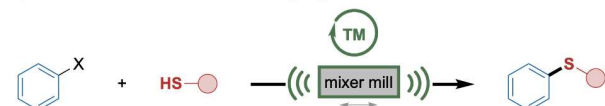
Scheme 1. Overview of Traditional and Mechanochemical Approaches in C–S Coupling Reactions

A) Homogeneous nickel-catalyzed C–S cross coupling



- usually inert atmosphere is required
- high Ni loadings
- high temperatures and reaction times
- toxic solvents

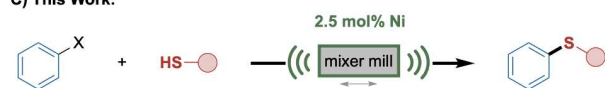
B) Mechanochemical C–S cross coupling



Literature reports: 1) Browne and coworkers: 1 mol% Pd, sand as additive

2) Guo and coworkers: Ni-catalyzed coupling with disulfides, 20 mol% Ni and many additives required

C) This Work:



X = I, Br, Cl, OTf R = ° aryl or alkyl

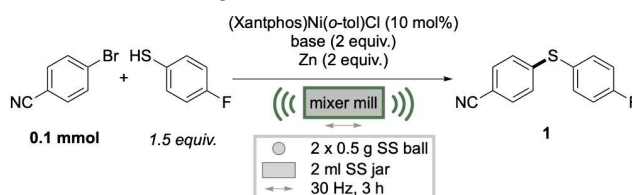


requirement of THF as a solvent to facilitate applications in industrial processes.

RESULTS AND DISCUSSION

We began the investigations by applying our previously developed catalytic system¹⁷ to mechanochemistry using 4-bromobenzonitrile and 4-fluorothiophenol as model substrates. Since the reaction was set up under air, we assumed that the addition of an external reductant, such as zinc, was necessary to prevent the literature-known aerobic oxidation of thiols to disulfides.²¹ Initial screening using the established KOAc as a base¹⁷ showed only trace product formation (Table 1, Entry 1), indicating that the conditions developed for homogeneous catalysis could not be directly transferred to mechanochemistry. In turn, screening of bases unveiled that several inorganic bases, such as KO^tBu and K₂CO₃, gave high yields of the sulfenylated product (Entries 2 and 3). Surprisingly, organic bases Et₃N and ^tPrNEt₂ led to quantitative yield (Entries 4 and 5), while DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and DABCO (1,4-diazabicyclo(2.2.2)octane) resulted in poor yields (Entries 6 and 7). While DBU might represent a mismatch in terms of basicity, one reason why Et₃N performed very differently compared to the structurally related DABCO could be the liquid state of Et₃N probably facilitating deprotonation of the thiol. Indeed, ¹⁹F NMR studies confirmed complete deprotonation of 4-fluorothiophenol upon neat mixing with Et₃N. We decided to choose Et₃N as the base due to its solubility in organic solvents, which facilitated the workup after milling. Next, the catalyst loading and stoichiometry of thiol, base, and zinc were optimized. Pleasingly, catalyst loadings as low as 1 mol % were sufficient for obtaining high yields (Entry 9). Using less catalyst

Table 1. Optimization of Nickel-Catalyzed Mechanochemical C–S Cross-Coupling^a



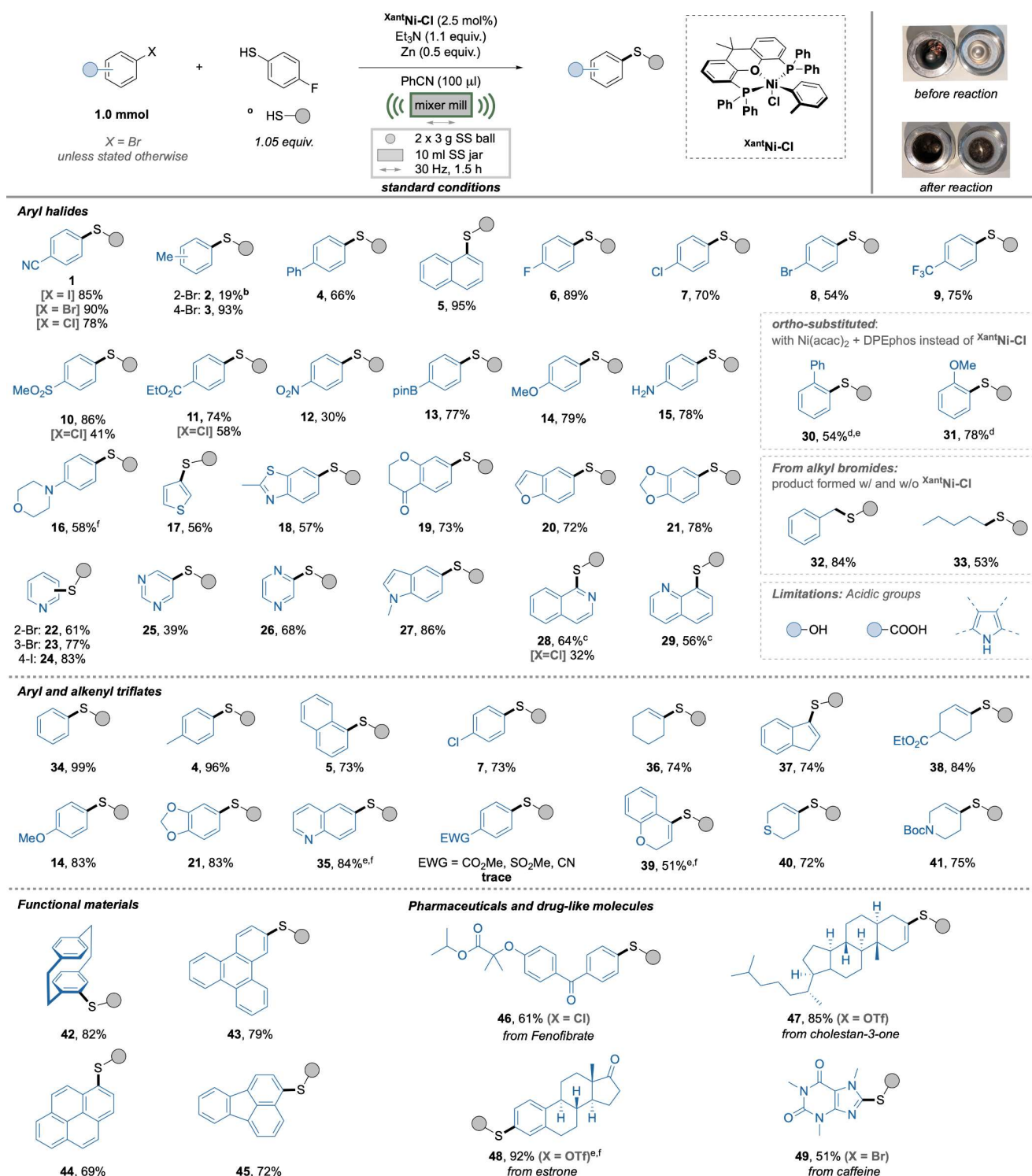
Entry	Deviation	Conv. [%]	Yield [%]
1	KOAc	7	3
2	KO ^t Bu	quant.	71
3	K ₂ CO ₃	97	89
4	Et ₃ N	quant.	99
5	^t PrNEt ₂	quant.	97
6	DBU	30	19
7	DABCO	8	n. d.
Entries below this line contain Et ₃ N as a base			
8	2.5 mol% Ni	100	95
9	1 mol% Ni	100	87
10	1 mol% Ni, 1.05 equiv. thiol, 1.1 equiv. base, 0.5 equiv. Zn	quant.	93
11	Xantphos + Ni(acac) ₂ instead of XantNi-Cl	quant.	91
12	no Zn	4	n. d.
13	no Ni	52	n. d.

^aAll reagents were filled in a stainless-steel jar (2 mL) with two SS balls (4 mm, 0.5 g) under air and subjected to ball-milling (30 Hz) for 3 h. Yields and conversion were determined by GC-FID using pentadecane as an internal standard.

resulted in full conversion but gave lower yields, and the protodehalogenated arene was detected as the major side-product by GC-MS. Nevertheless, we chose 2.5 mol % for the continuing investigations to ensure the robustness of the system. Subsequent experiments revealed that 1.05 equiv of thiol, 1.1 equiv of base, and 0.5 equiv of zinc were sufficient to afford high yields (Entry 10). To our delight, Ni(acac)₂ with Xantphos could also be used as a low-cost alternative to the precatalyst XantNi-Cl (Entry 11). Nevertheless, this precatalyst offers a simpler reaction setup and optimal ligand to nickel ratio, which is why it was used for further investigations.

No product yield was detected when omitting either zinc or nickel (Entries 12 and 13). Interestingly, omitting the nickel catalyst resulted in 52% conversion of the aryl bromide, questioning the role of zinc in this reaction. While organozinc species are known to be formed under mechanochemical conditions from alkyl bromides,²⁶ quenching experiments provided no evidence toward the formation of organozinc species from the aryl bromide (see Supporting Information (SI) section 4.3).

Additionally, the mechanochemical parameters were screened. The reaction strongly depends on the size of the mixing jar and balls, and the optimal conditions for 1 mmol of substrate was determined to be a 10 mL stainless-steel (SS) jar in combination with two SS balls with a diameter of 10 mm and a weight of 3 g (see the SI for detailed screening information). These parameters influence the energy input and also the jar temperature, which rises to ca. 30–35 °C during the reaction due to kinetic energy. Although full conversion was achieved

Scheme 2. Substrate Scope with Respect to Aryl Halides^a

^aStandard conditions: aryl bromide (1 mmol, 1 equiv), thiol (1.05 mmol, 1.05 equiv), NEt₃ (1.1 mmol, 1.1 equiv), zinc (0.5 mmol, 0.5 equiv), XantNi-Cl (2.5 mol %), PhCN (100 μL) in a 10 mL SS jar containing 2 × 3 g SS balls, 30 Hz, 1.5 h. Isolated yields. ^bDue to separation issues, yield was determined from the crude sample by ¹H NMR spectroscopy. ^c3 h. ^dNi(acac)₂ (2.5 mol %) and DPEphos (2.5 mol %) instead of XantNi-Cl, zinc (2 equiv). ^e5 mol % of Ni. ^f2 equiv of zinc.

after 1 h, the standard milling time was set to 1.5 h to increase the robustness of the method with other substrates. After these conditions were optimized for the model substrates, it was found that nitriles as a promoter can facilitate the oxidative addition,

similar to previous findings in homogeneous catalysis.²⁷ The optimal amount of benzonitrile was 100 μL, giving high conversion of the electron-rich aryl bromide.

With these optimized conditions in hand, the substrate scope, with respect to aryl halides, was explored (Scheme 2). The previously used model substrate 4-bromobenzonitrile gave an excellent isolated yield (90%), and further experiments proved that 4-iodo- and 4-chlorobenzonitrile were also viable substrates (1), although we found that only activated aryl chlorides gave good yields (*vide infra*). Electron-neutral bromoarenes furnished good to excellent yields (3, 4, and 5), but it appeared that sterically hindered electrophiles possess inferior reactivity (2), again indicating that oxidative addition is the limiting step in this reaction. Fluoro (6), chloro (7) and even bromo substituents (8) were tolerated, but increasing amounts of disubstituted product formed when going down the group. Next, electron-poor aryl bromides were investigated. Trifluoromethyl-substituted compounds (9), sulfones (10), esters (11), and boronic esters (13) provided good to excellent yields, and even the electrophile containing the rather rarely tolerated nitro group (12) was coupled in modest yield. Electron-donating substituents such as methoxy (14) and amino groups (15) resulted in high yields.

Subsequently, we turned our attention toward heterocyclic substrates. A morpholine substituent was well tolerated (16), and 3-bromothiophene afforded the product (17) in moderate yield. Meanwhile, benzo-annulated heterocycles such as benzothiazole (18), chromanone (19), benzofurane (20), and benzodioxole (21) led to good yields. Nitrogen-containing heteroarenes were also well tolerated. All positions in pyridine were viable for cross-coupling (22–24), performing best at the 4-position. While pyridazine (25) provided only moderate yield, protected indole (28) resulted in very high yield. (Iso)-quinolines with the nitrogen in proximity to the reactive site proved more challenging but still gave the products in synthetically useful yields (28 and 29). Based on our previous experience with nickel-catalyzed C–S couplings,²⁸ we found that the more flexible ligand DPEphos ([oxydi(2,1-phenylene)]bis(diphenylphosphane)) in combination with Ni(acac)₂ could be used for the coupling of sterically challenging substrates in good yields (30 and 31). Interestingly, benzyl (32) and alkyl (33) bromides could also be coupled, but a control experiment without the catalyst clearly revealed that this reaction is an uncatalyzed nucleophilic substitution. Important limitations of the catalytic system include all substrates that contain acidic protons, such as alcohols, acids, and unprotected heterocyclic NH groups such as those present in indole or imidazole (see the SI for a list of unsuccessful substrates).

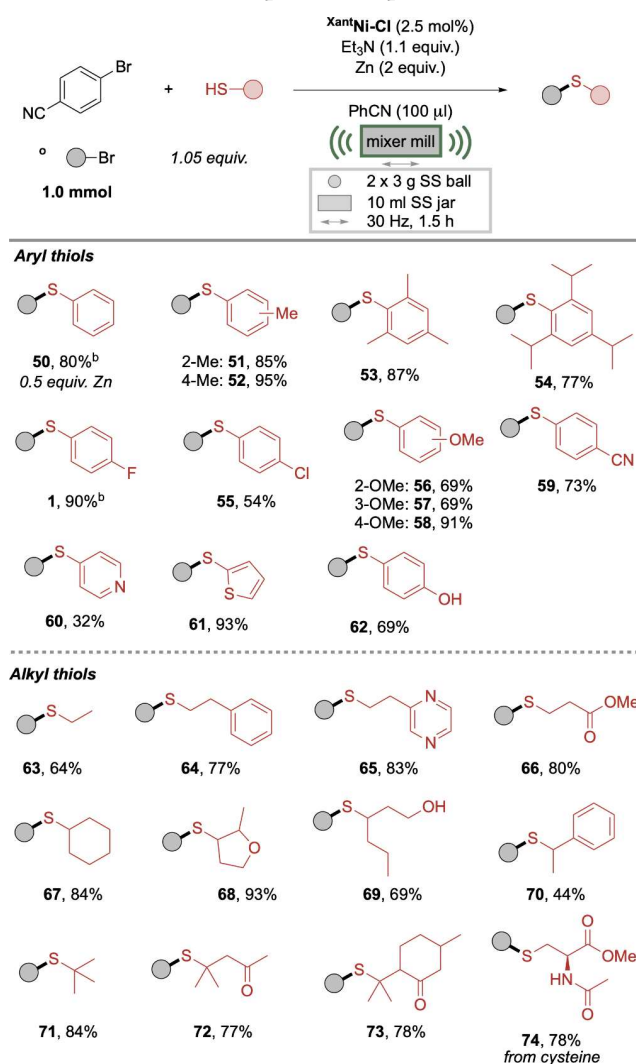
Encouraged by the initial finding that 4-chlorobenzonitrile gave a high yield (1), we also explored the scope of aryl chlorides. Unfortunately, only electron-poor aryl chlorides (1, 10, 11, and 28) gave reasonable yields, while electron-neutral or electron-rich chloroarenes suffered from low conversions. Thus, we concluded that the oxidative addition is more difficult under mechanochemical conditions compared to homogeneous conditions, where the same catalyst could be used for the thioetherification of a broad range of chloroarenes,¹⁷ which displayed a strong influence of solvents on catalytic intermediates and reactivity. Furthermore, we turned our attention to sulfonate esters as substrates. These electrophiles can be easily synthesized in a one-step procedure from abundant and low-cost phenols and ketones and have been demonstrated to be viable coupling partners in C–S cross-couplings.²⁵ Conveniently, phenyl triflate as well as other electron-neutral aryl triflates gave full conversion under standard conditions, and the corresponding thioethers could be isolated in excellent yields

(34, 4, and 5). Meanwhile, less reactive sulfonates such as phenyl mesylate or tosylate gave low conversions. A selected scope confirmed that triflates exhibited similar functional group tolerance as bromides, effectively yielding thioethers containing chloro (7) and ether substituents (14 and 21) as well as a quinoline (35). Surprisingly, electron-withdrawing substituents in the *para*-position were not tolerated, indicating that triflates could react mechanistically differently compared to halides. In the literature, the oxidative addition of aryl triflates to Ni(0) has been proposed to occur via an S_N2-like mechanism,^{28,29} generating a positive charge in the transition state that could be destabilized by electron-withdrawing substituents. Alkenyl triflates were also feasible in this reaction (36 and 37), tolerating esters (38), ethers (39), and heterocyclic substituents (40 and 41).

To demonstrate the applicability of the developed system, substrates containing motifs that are used in materials science and pharmaceutical research were subjected to the reaction. Especially extended π -systems that are relatively insoluble in common organic solvents pose a challenge to homogeneous catalysis that can be overcome with mechanochemical methods.^{2,6} Hence, brominated hydrocarbons such as paracyclophane (42), triphenylene (43), pyrene (44), and fluoranthene (45) gave high yields of the coupling product. To demonstrate the application of this system to late-stage functionalization, pharmaceutically relevant molecules were subjected to the standard conditions. Thioethers derived from fenofibrate, an antilipemic (46), steroid-like structures cholestan-3-one (47) and estrone (48), as well as 8-bromocaffeine (49) were obtained efficiently, underlining the possibility to use various, also complex electrophiles.

Subsequently, the scope of thiols was investigated (Scheme 3). First, various aryl thiols were tested. To our surprise, most thiols gave low conversions under standard conditions, but further screening quickly uncovered that more zinc was necessary, although it remained unclear why some thiols seemed to require higher amounts of zinc. Still, it could be shown that 2 equiv of zinc was sufficient for high conversions of most thiols tested, but it should be noted that this amount can be reoptimized for each thiol. With this slightly adapted procedure, electron-neutral phenyl and tolyl thiols could be efficiently coupled (50–52).

As previously demonstrated for alkyl thiols,¹⁷ the reaction is less susceptible to steric hindrance on the thiol moiety compared to the electrophile counterpart. In fact, sterically highly encumbered mesityl thiol as well as 2,4,6-triisopropylbenzenethiol gave high yields of the corresponding thioethers (53 and 54). A chloro substituent led to modest yields (55), as scrambling of the product to symmetrical thioethers was observed as a side-reaction, while disubstitution was not observed. Both electron-donating (56–58) and electron-poor thiophenols (59) were feasible. While pyridine-2-thiol gave no conversion, probably due to strong deactivation of the sulfur or chelating effects, 4-pyridinethiol could be coupled in modest yield (60). Furthermore, 2-mercaptothiophene could be efficiently arylated (61). Unexpectedly, 4-mercaptophenol was a feasible substrate, furnishing the thioether in a high yield (62), although phenol groups were not tolerated in the electrophile moiety. The first deprotonation of the thiol probably increases the pK_a of the phenol group significantly. In continuation, alkyl thiols were explored. Analogously to most aryl thiols, aliphatic coupling partners required 2 equiv of zinc to give full conversion. Consequently, simple primary (63 and 64), secondary (67), and

Scheme 3. Substrate Scope with Respect to Thiols^a

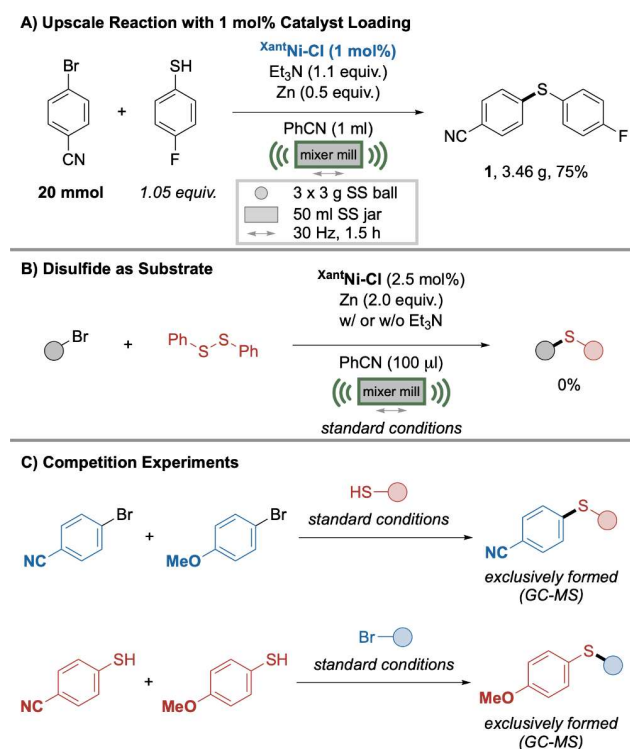
^aStandard conditions: aryl bromide (1 mmol, 1 equiv), thiol (1.05 mmol, 1.05 equiv), NEt_3 (1.1 mmol, 1.1 equiv), zinc (2 mmol, 2 equiv), $\text{Xant}^{\text{Ni}}\text{-Cl}$ (2.5 mol %), PhCN (100 μL) in a 10 mL SS jar containing 2 x 3 g SS balls, 30 Hz, 1.5 h. Isolated yields. ^bzinc (0.5 equiv)

tertiary thiols (71) were subjected to the reaction and delivered the aryl alkyl thioether in high yields. Thiols containing functional groups such as esters (66), ketones (72 and 73), and heterocyclic moieties (65 and 68) were well tolerated. Again, a thiol containing an alcohol group was arylated at the sulfur in a good yield (69). Notably, benzyl mercaptan gave only trace amounts of the product, but the yield increased when a secondary benzylic thiol was used (70). To our delight, a protected cysteine gave the *S*-arylated product in high yield (74), demonstrating the applicability of the reaction toward the functionalization of amino acids.

Overall, the developed method features a broad scope and high yields, representing the robustness of this system. While literature reports sometimes show a preference toward either aryl^{30,31} or alkyl thiols,¹⁷ this system tolerates both substrate classes equally. Compared to many published procedures, the reaction is faster, more efficient in terms of yield, and operates under milder conditions.^{32,33} Whereas this mechanochemical

protocol exhibits reduced atom-economy due to the (super)-stoichiometric amounts of zinc required, it features an extremely simple reaction setup that can also be performed by untrained personnel (e.g., undergraduate students). This also reduces the possibility of systematic errors in the reaction setup and saves time. Moreover, tolerance toward ambient atmosphere eliminates the need for vacuum pumps, Schlenk equipment, and an inert-gas supply. Nevertheless, the requirement of a ball-mill, which is not (yet) standard equipment in most chemical laboratories, is a disadvantage of the developed method. In addition, the Green Metrics are better or at least comparable to those of recent literature (see the SI for the sustainability assessment and comparison to a photochemical method).

Additionally, we demonstrated that the reaction also performed well at a larger scale (20 mmol), giving **1** in high yield (75%, 3.46 g) at only a 1 mol % catalyst loading (Scheme 4A). In the literature, disulfides have been postulated as

Scheme 4. Further Reactivity Studies^a

^aStandard conditions: 10 mL SS jar containing 2 x 3 g SS balls, 30 Hz, 1.5 h. As a standard electrophile, 4-bromobenzonitrile was used. As a standard nucleophile, 4-fluorothiophenol was used.

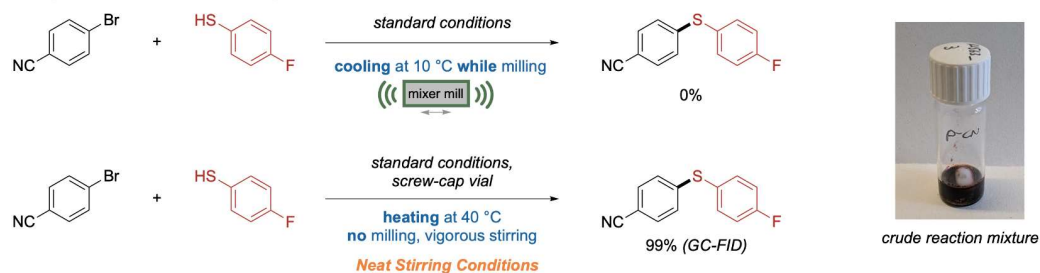
intermediates of similar reactions²¹ or have been directly used as thiol surrogates.²⁴ However, in our system, disulfides were not a feasible starting material (Scheme 4B).

Finally, an intermolecular competition experiment showed that electron-deficient electrophiles and electron-rich nucleophiles are the preferred coupling partners (Scheme 4C). This resembles the expected reactivity for typical cross-coupling mechanisms.^{17,34}

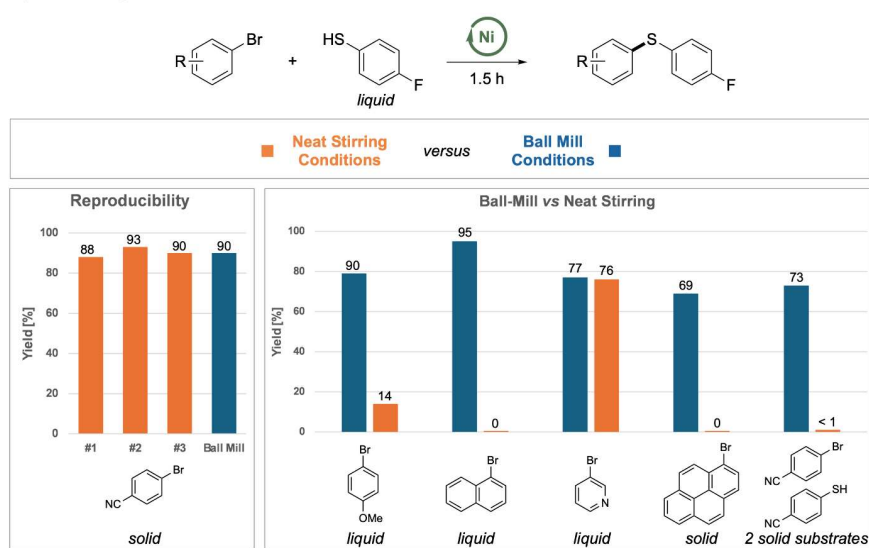
Mechanistic Investigations. Next, we turned our attention toward the reaction mechanism. In the past, a classical Ni(0)/Ni(II) catalytic cycle was proposed for the same precatalyst in THF solution.¹⁷ Since the mechanochemical reaction is solvent-minimized with benzonitrile, requires an external reducing

Scheme 5. Investigation of the Role of Mechanical Force in the Reaction^a

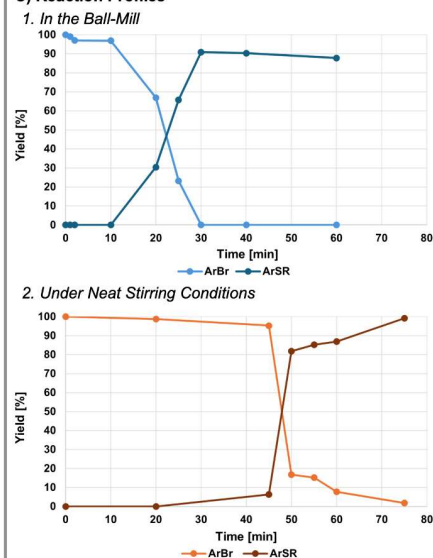
A) Temperature Dependency and Reaction without Milling



B) Neat Stirring Conditions



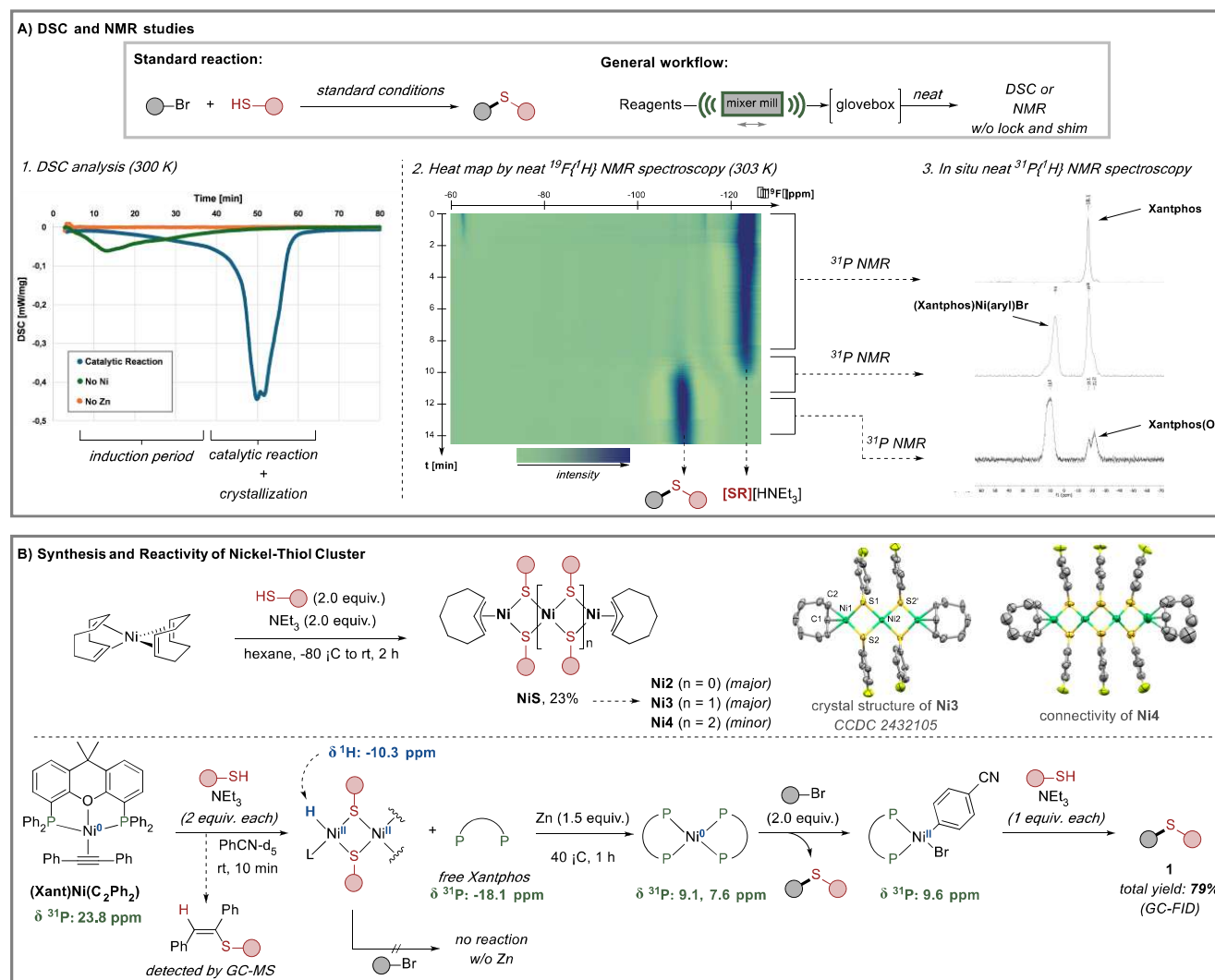
C) Reaction Profiles



^aDepicted are isolated yields, if not stated otherwise. Yields for reaction profile analysis were collected in duplicate from independent reaction mixtures by GC-FID using pentadecane as an internal standard.

agent, and features fewer limitations, we wondered if the mechanism would be altered. Moreover, the role of mechanical force was unclear.^{35–38} To elucidate the role of mechanical force vs a thermally driven mechanism, the influence of temperature was studied (Scheme 5A). Temperature measurements showed that the temperature of the jar increased to ca. 30–35 °C during the reaction. Interestingly, heating a filled milling jar in a 60 °C oven before subjecting it to the mixer mill greatly decreased the necessary reaction time to reach full conversion to only 10 min. Meanwhile, cooling the jar with a cold stream of nitrogen while milling inhibited the reaction (Scheme 5A). These experiments underlined that catalytic turnover strongly depends on the temperature. With these results in hand, we reasonably questioned whether milling was required at all or if it was just acting as a heating device. Indeed, a control experiment conducted in a heated (40 °C) screw-cap vial instead of a milling jar under vigorous stirring gave an excellent yield of the coupling product. This demonstrated that mechanical force by a mixer mill was not required for product formation in this case. Interestingly, the reaction mixture appeared as a deep red liquid in most cases (see more photographs in the SI), which could indicate that the solid reactants are soluble in the liquid reagents or that the formation of eutectic mixtures decreased the melting point to room temperature.³⁸ Intrigued by the finding that simple stirring under air led to excellent yields, we investigated this methodology in more detail (Scheme 5B). First, the reproducibility of the coupling under neat stirring conditions

was confirmed by repeated experiments that reliably produced yields comparable to those of the reaction conducted in the ball-mill. However, when testing a narrow but diverse substrate scope under stirring conditions, most products gave inferior yields compared with the reactions conducted in the ball-mill. Notably, only electron-poor substrates gave the coupling products in comparable yields to those obtained in the mechanochemical protocol, while electron-neutral and electron-rich substrates as well as more insoluble substrates gave poor yields. This led us to the assumption that not only does milling ensure better and more reliable mixing of the reactants, but mechanical force can also directly play a role in cases where oxidative addition is more challenging.^{35,36} Subsequently, the reaction profiles of both methodologies were investigated. Since it is not possible to draw samples from the closed milling jar, several independent reactions were stopped at a certain time, followed by GC-FID analysis of the reaction mixture (Scheme 5C). In the first 10 min of the reaction, no product was formed, but the rate greatly increased after this initiation period, and full conversion was achieved within 20 min from this point, while further milling slightly led to the decomposition of the coupling product. Meanwhile, for the stirred reaction, the initiation period appeared at about 40 min twice as long, while the catalytic reaction proceeded within 5 min. One explanation for the observed induction periods could be the activation of the zinc surface, which would proceed more efficiently in the ball-mill.^{26,39} Alternatively, this could originate from the activation of

Scheme 6. Mechanistic Studies^a

^aIn the connectivity of Ni₄ and the crystal structure of Ni₃, hydrogen atoms and disordered molecules were omitted for clarity. Selected bond lengths [Å] and bond angles [deg] of Ni₃: Ni1–Ni2, 3.034; Ni1–C1, 1.960; Ni1–C2, 2.034; Ni1–S1, 2.192; Ni1–S2, 2.189; Ni2–S1, 2.214; Ni2–S2, 2.241; S1–Ni1–S2, 85.5; S1–Ni2–S2, 83.8; S1–Ni2–S2', 96.2.

the precatalyst, as observed in previous reports.⁴⁰ In contrast, using the oxidative addition complex (OAC) (Xantphos)Ni(4-CN-Ph)Cl as a catalyst resulted in the same induction period, indicating that the precatalyst activation was not responsible (SI section 4.6).

To obtain more information about this process, reaction profiles were also studied by differential scanning calorimetry (DSC) and NMR spectroscopy (Scheme 6A). Exploiting the observation that milling was not strictly necessary for catalytic turnover, we developed a workflow to investigate this reaction outside of the ball-mill: First, the reaction mixture was milled for a short time (usually 2 min), resulting in the formation of a dark red liquid, which was transferred to an appropriate vessel (NMR tube or DSC crucible) in a glovebox. The reaction rate differed along various reaction vessels, which could be a result of different temperatures and different distributions of heat, but the general reaction profile remained similar. Following this protocol, DSC measurements were performed at 300 K with the aim of potentially revealing processes that could not be followed by NMR spectroscopy. Analogously to the reaction

profile obtained by GC-FID, an initiation period was observed. However, during this time, an exothermic process was observed due to unknown reactions that occurred before the coupling process. This could indicate catalyst activation before the catalytic process occurred. In the DSC curve, a second minimum can be observed that most likely represents the crystallization enthalpy of the product. To exclude the possibility that the observed heat during the initiation period was produced by background reactions, control experiments were conducted. When zinc was omitted, no formation of heat was observed (Scheme 6A, orange line), while exothermic reactivity was observed when the nickel catalyst was omitted but not zinc (green line). In a separate experiment, we observed that mixtures of zinc with thiol and Et₃N produced hydrogen gas, which could resemble the observed exothermic reaction. Meanwhile, the shape of this curve indicated that this side-reaction did not occur equally when the nickel catalyst was present.

For the acquisition of ¹⁹F NMR spectra, the sample was measured without locking or shimming at 303 K, which allowed

the direct observation of the reaction without the necessity of deuterated solvents. Although this approach resulted in a broadening of signals, sufficient separation of all signals was achieved, and a heat map of the reaction could be created. As observed previously, no coupling occurred for several minutes, but after this induction period, the product peak appeared quickly, while the thiol signal disappeared. Intrigued by these initial results, we pursued monitoring of the reaction with ^{19}F NMR spectroscopy while acquiring ^{31}P NMR spectra at the same time. Surprisingly, during the initiation period, no phosphorus signal other than that of the unbound Xantphos ligand was detected. A similar observation was previously made by Buchwald and co-workers in a Pd-catalyzed C–S cross-coupling.⁴¹ Control experiments confirmed that the addition of 3 equiv of thiol and base to $^{\text{Xant}}\text{Ni-Cl}$ led to the same result: the signal of $^{\text{Xant}}\text{Ni-Cl}$ fully disappeared, and free Xantphos formed. This was reproduced directly using the nickel(0) complex (Xantphos)nickel(diphenylacetylene) ($(^{\text{Xant}}\text{Ni}(\text{C}_2\text{Ph}_2))$), indicating that the thiol displaced the Xantphos ligand from a Ni(0) complex and formed a species containing nickel and thiol(ate). During the phase of product formation, a second peak appeared in the phosphorus spectrum. This second peak, located at 9–10 ppm, most likely belongs to the oxidative addition complex (Xantphos)Ni(4-CN-Ph)Br, as this signal could be reproduced independently in solution by mixing 4-bromobenzonitrile and $(^{\text{Xant}}\text{Ni}(\text{C}_2\text{Ph}_2))$. After full conversion was reached, the spectra suffered from increased broadening due to crystallization of the coupling product in the NMR tube, preventing interpretation of the obtained data. Nonetheless we concluded that the inhibited nickel catalyst, which is silent in ^{31}P NMR, is reactivated during the initiation period, after which the reaction can occur.

It is well-known that thiols can form catalytically inactive species with many metals (so-called catalyst poisoning).³³ However, they are rarely characterized in the literature. In a seminal work, Hartwig and co-workers investigated off-cycle species in the palladium-catalyzed C–S coupling, identifying $\text{LPd}(\text{SR})(\text{H})$ and $[\text{LPd}(\text{SR})_2]^-$ complexes as resting states.⁴² $[\text{Pd}(\text{SR})_2]_n$ clusters were also obtained from mixtures of Pd(II) salts with thiols.⁴³ Regarding nickel catalysis, a recent study from Ananikov and co-workers proposed various catalytic species for the ligand-free C–S coupling in ionic liquids, including metal(thiolate) clusters and oxidative addition complexes.⁴⁴ However, this does not seem to apply to our catalytic system because the phosphine ligand appeared pivotal for catalysis, as no reaction occurred when omitting the ligand (SI section 3.2). To contribute to this gap in the literature on off-cycle species in nickel-catalyzed C–S couplings, we decided to investigate the catalyst deactivation and regeneration in more detail. First, the approximate stoichiometry of the reaction of nickel with thiolate was determined by NMR-titration experiments (see SI section 4.5 for details). Apparently, 2 equiv of thiol was sufficient to convert $(^{\text{Xant}}\text{Ni}(\text{C}_2\text{Ph}_2))$ to a ^{31}P NMR-silent species. Despite our continuous efforts, we were unable to isolate and characterize this catalytically inactive species, especially as the presence of benzonitrile seemed to be required for its formation but also prevented crystallization. Consequently, to obtain more information about the structure of this deactivated catalyst, we decided to substitute benzonitrile by another π -coordinating ligand, such as an alkene. Therefore, $\text{Ni}(\text{cod})_2$ was considered as a suitable starting material. Upon mixing it with 2 equiv of thiol, a dark red mixture formed. Using hexane as the solvent, a dark red solid $^{\text{cod}}\text{NiS}$ could be isolated by crystallization and

characterized (Scheme 6B). NMR analysis showed that a mixture consisting of mainly two compounds formed, bearing thiol- and cod-related moieties. It should be noted that the yield of $^{\text{cod}}\text{NiS}$ was low, suggesting that other species may also be present in the rather complex crude reaction mixture, and evidence for other minor species was found both in the ^1H and ^{19}F NMR spectra. We succeeded in obtaining a single crystal from the $^{\text{cod}}\text{NiS}$ mixture, and X-ray diffraction (XRD) showed that it is the nickel-thiolate cluster **Ni3** formed with two allylic cyclooctenylate units as capping ligands, a motif that is in line with the ^1H NMR spectrum. In this structure, a central nickel atom is coordinated by four thiolate ligands in square-planar geometry. All thiolates coordinate in a μ^2 -fashion, bridging to outer nickel atoms, that bear allylic cyclooctenylate ligands. While the Ni–S bonds of the central nickel are in the typical range of μ -bridging thiophenolates with 2.214 and 2.241 Å,⁴⁵ the Ni–S bonds of the outer nickel are shorter with 2.192 and 2.189 Å, indicating tighter binding. Importantly, the solid-state structure could be confirmed by 2D-NMR spectroscopy in toluene- d_8 solution, featuring a nuclear Overhauser effect (NOE) between the thiol and the allylic protons in the ROESY spectrum (SI section 5.1). Furthermore, we separated the other major species of $^{\text{cod}}\text{NiS}$ by fractional crystallization. While only NMR analysis was possible, it suggested that this complex also contains a (cyclooctenylate)Ni(SR) unit, but the ratio of these ligands was determined to be 1:1 by ^1H NMR integration. Most likely, this is a dimeric species **Ni2**. Thus, all of the major signals in the NMR spectra of $^{\text{cod}}\text{NiS}$ could be assigned to either **Ni2** or **Ni3**. The allylic ligands are most likely a product of the formal insertion of cod into a Ni–H bond, followed by chain-walking of nickel.⁴⁶ This implies that $\text{LNi}(0)$ reacts with the thiol in an oxidative addition-like fashion, yielding $\text{LNi}(\text{H})(\text{SR})$, a reactivity that was previously reported for palladium.⁴²

Indeed, upon mixing $(^{\text{Xant}}\text{Ni}(\text{C}_2\text{Ph}_2))$ with excess thiol and Et_3N in $\text{PhCN-}d_5$, a broad hydride signal could be detected at $\delta(^1\text{H}) = -10.3$ ppm in the ^1H NMR spectrum, along with two smaller signals in the hydride region (see SI section 4.5). In an attempt to crystallize **Ni2**, a single crystal of **Ni4** was obtained, but the size of the crystal allowed us to obtain only the connectivity rather than the full crystal structure. Since the structure of **Ni4** could not be assigned to major signals in the NMR spectra, we believe that it represents a minor species in the $^{\text{cod}}\text{NiS}$ mixture. Furthermore, $^{\text{cod}}\text{NiS}$ was shown to be a competent catalyst in the developed mechanochemical C–S cross-coupling (with an additional ligand added). For a better understanding of the activation as well as the catalytic processes, stoichiometric experiments were performed and monitored by ^{31}P NMR spectroscopy (Scheme 6B). $(^{\text{Xant}}\text{Ni}(\text{C}_2\text{Ph}_2))$ was used as a model compound for the active catalyst that forms in the reaction of the precatalyst $^{\text{Xant}}\text{Ni-Cl}$ with 1 equiv of thiol in the presence of the base.¹⁷ Reacting $(^{\text{Xant}}\text{Ni}(\text{C}_2\text{Ph}_2))$ with 2 equiv of thiol under basic conditions in benzonitrile- d_5 resulted in the formation of a dark red mixture that showed only one resonance in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum, corresponding to the free Xantphos ligand. Importantly, this mixture was not active in catalysis without the addition of zinc. The product of the hydrothiolation of diphenylacetylene was detected as a side-product by GC-MS, explaining why 2 equiv of thiol was necessary. On the other hand, upon the addition of zinc, a new signal was observed in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum, which unambiguously corresponds to the complex multiplet of the

AA'XX' spin-system of $(\text{Xantphos})_2\text{Ni}(\text{O})$.⁴⁷ Another signal that could correspond to the $(\text{Xantphos})\text{Ni}(\text{PhCN}-d_3)$ complex was also observed.^{48,49} Then, 4-bromobenzonitrile was added, and oxidative addition occurred, giving rise to a new signal with the same chemical shift of $\delta(^{31}\text{P}) = 9.6$ ppm as observed in the neat NMR spectra of the catalytic reaction (Scheme 6A3,B). Thus, we propose that the OAC $(\text{Xantphos})\text{Ni}(\text{aryl})(\text{Br})$ is the resting state of the reaction. Upon adding 4-fluorothiophenol, the cross-coupled product formed in high yield (79%, determined by GC-FID). Contrary to our initial assumption that zinc was necessary to reverse the literature-known aerobic oxidation of thiols under mechanochemical conditions,²¹ these results imply that the role of zinc is to reduce the off-cycle species $[\text{LNi}(\text{H})(\text{SR})]_n$ and form the active catalyst. This is also in line with the observation that zinc is necessary for product formation when performing the reaction under an inert atmosphere (see SI section 3.2). Finally, we were unable to detect EPR-active intermediates from crude reaction mixtures, providing no evidence for open-shell intermediates (see SI section 4.6).

These investigations allowed us to propose a mechanism for the developed mechanochemical C–S coupling (Scheme 7). Upon mixing all reactants, the precatalyst XantNi-Cl undergoes the literature-known activation by ligand exchange with the thiolate, followed by the reductive elimination of 2-tolyl sulfide,¹⁷ which could be observed by GC-MS in catalytic reactions (Scheme 7A). The formed phosphine-ligated $\text{Ni}(\text{O})$

intermediate **I** reacts with the excess thiol, resulting in the oxidation of nickel and the formation of the catalytically inactive nickel hydride species **II** (Scheme 7B). It should be stressed that **II** does not necessarily resemble the structure of the model complex codNiS , as the absence of cod may vary the outcome. However, based on the observed reactivity, we propose that it resembles a “cocktail” of nickel-hydride-thiolate clusters of varying sizes. In contrast to palladium-catalyzed coupling, the phosphine ligand is not bound to any of these species. Also, no evidence for charged nickelates, as observed for palladium,⁴² was found. This intermediate **II** is reduced by zinc to form complex **I** and hydrogen as a side-product. It is noteworthy that the formation of the active catalyst **I** from **II** seems to be highly sensitive to temperature, barely occurring at 25 °C but taking place already at 30 °C. This deactivation and regeneration cycle may consist of several turnovers until a sufficient number of protons is reduced. We speculate that this process was previously observed by the initial generation of heat in the DSC measurements (Scheme 6A).

Next, **I** engages in a classical catalytic cycle, involving the oxidative addition of the electrophile, thiolate coordination, and reductive elimination of the substrate (Scheme 7C). The role of benzonitrile is most likely to form the complex $(\text{Xantphos})\text{-nickel}(\text{PhCN})$ (**I-A**) to overcome the sluggish reactivity of $(\text{Xantphos})_2\text{Ni}$ (**I-B**).⁴⁸ According to *in situ* ^{31}P NMR spectroscopy (Scheme 6A), the OAC **III** seems to be the resting state of the catalytic reaction, although this may change depending on the substrate and the ease of oxidative addition. It should also be noted that alkyl thiols differ in reactivity due to altered acidity and nucleophilicity, questioning whether these results can directly be applied to the coupling of aliphatic thiols.

CONCLUSION

In summary, an operationally simple mechanochemical protocol for the thioetherification of aryl bromides and activated chlorides under air was developed. Moreover, aryl and alkenyl triflates were also viable substrates, giving access to thioethers from phenols and ketones. Both aryl and alkyl thiols were demonstrated to provide high yields of the coupled product. A broad range of functional groups was tolerated in the transformation. Mechanistic studies showed that the reaction is accelerated by mechanical force, although catalytic turnover seems driven by thermal energy, enabling the coupling of electron-poor aryl bromides under neat stirring conditions without a ball-mill. Further investigations revealed that under mechanochemical conditions, the catalyst initially reacts with the thiol, forming a catalytically inactive nickel-thiolate cluster. Using cod as a stabilizing ligand, a model compound for this species could be isolated and characterized, including X-ray diffraction. Reduction of these species with zinc in the presence of the ligand regenerates the active phosphine-ligated catalyst, which engages in a classical $\text{Ni}(\text{O})/\text{Ni}(\text{II})$ catalytic cycle. Not only is this proposal in line with numerous control experiments, but it could also be demonstrated in a stoichiometric fashion.

ASSOCIATED CONTENT

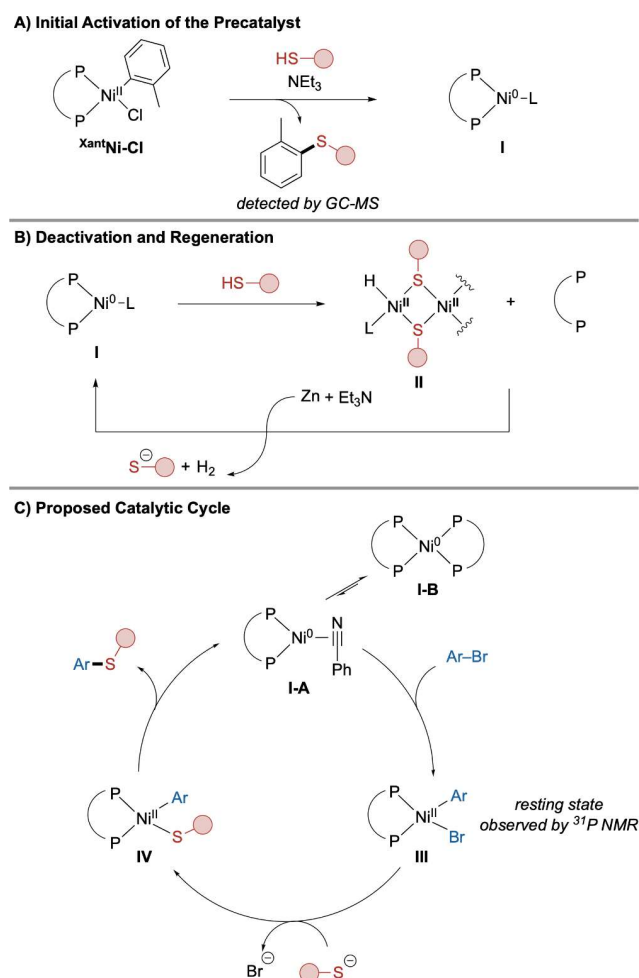
Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscatal.5c04516>.

Crystallographic data for Ni3 (CIF)

Crystallographic data for Ni4 (CIF)

Scheme 7. Proposed Mechanism



Chemicals and general techniques, analytical techniques, general procedures, detailed screening information, competition experiments and mechanistic studies, analytical data and NMR spectra, unsuccessful substrates, crystallographic data, and GC-FID calibration data (PDF)

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Notes

The authors declare no competing financial interest.

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Nickel-catalyzed cross-electrophile-coupling of thioesters with alkyl bromides to form ketones under mechanochemical conditions

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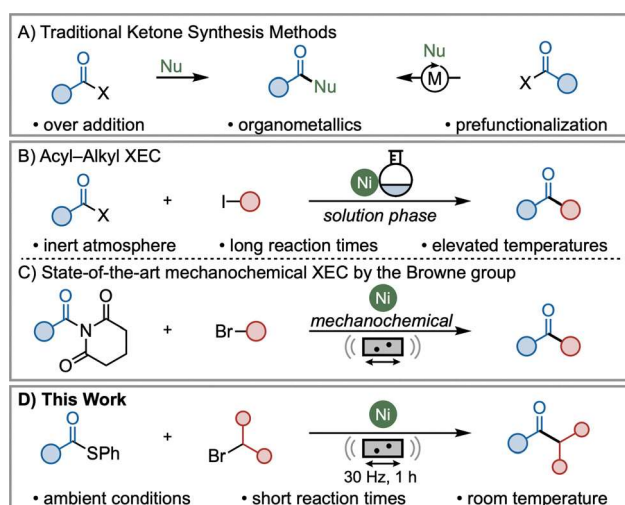
A solvent-minimized nickel-catalyzed synthesis of ketones, enabled by mechanochemistry, using thioesters as an acyl source is demonstrated. Mechanistic studies suggest a radical-chain-type mechanism.

Ketones represent a fundamental compound class in organic chemistry, ubiquitous in pharmaceuticals and natural products.¹ Classical syntheses typically rely on nucleophilic 1,2-additions to carboxylic acid derivatives. However, due to the electrophilicity of the resulting ketone, undesired over-addition can occur, necessitating pre-functionalization or metal catalysis (Scheme 1A).^{2–5} These approaches also depend on nucleophilic reagents, often organometallic species, which limit the functional group tolerance and are frequently toxic, air-sensitive and less readily available than electrophiles.⁶ Another approach towards ketones is the Wacker-type oxidation of alkenes.^{7–10}

In addition, cross-electrophile couplings (XECs) have emerged as a powerful alternative, enabling the union of two electrophiles under reductive conditions.⁶ Due to the abundance of electrophiles and high functional group tolerance, this strategy offers a broad scope. The first ketone synthesis *via* nickel-catalyzed XEC was reported by Mukaiyama in 1981.¹¹ Subsequent developments, independently pioneered by the Weix and Gong groups, expanded the scope of acyl-alkyl XECs through the use of bidentate nitrogen ligands and acyl chlorides.^{12,13} Since then, various XEC variants have been developed offering a diverse toolkit towards the synthesis of ketones (Scheme 1B).^{14–19} Nonetheless, XECs still face challenges including extended reaction times, elevated temperatures, and reproducibility issues associated with heterogeneous metal reductants.^{6,20} Mechanochemistry offers a promising solution by enabling rapid, solvent-minimized reactions under

ambient conditions.²¹ Vigorous mixing conditions improve the reactivity of solid reductants, enhancing the reaction efficiency and reproducibility.^{21–26}

Moreover, mechanochemical methods align with green chemistry principles, offering a more sustainable alternative to conventional solution-phase synthesis.^{27–30} Despite progress in mechanochemical XECs,^{21,31–33} application to ketone synthesis remains underexplored, with to the best of our knowledge only a single report by Browne and co-workers describing the coupling of twisted amides with alkyl bromides (Scheme 1C).³¹ In this work, *N*-acyl glutarimides were used as the only acyl source. While they have several advantages,³⁴ fine-tuning the reactivity is rather difficult. Our ongoing studies on thioesters demonstrated that they are attractive electrophiles in coupling reactions as they are readily accessible, bench-stable and their reactivity is tunable by the modulation of the *S*-substituent.^{35–37} While thioesters represent established electrophiles in solution-phase chemistry,^{2,38,39}



Scheme 1 Brief overview of traditional ketone syntheses alongside solution phase and mechanochemical XEC alternatives.

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Communication

they have never been applied to mechanochemistry. Motivated by this potential, we envisioned a mechanochemical XEC of thioesters with alkyl halides to access ketones under ambient conditions (Scheme 1D).

Preliminary experiments revealed that *S*-ethyl thioesters remained unreactive, while *S*-phenyl thioesters furnished the desired ketone. Ligand screening identified bidentate nitrogen ligands, particularly 1,10-phenanthroline (phen) and 4,4'-di-*tert*-butyl-2,2'-dipyridine (dtbbpy), as most effective (Table 1, entries 1 and 2), while other ligand classes resulted in diminished reactivity (see the SI, Section S3). Subsequently, liquid-assisted grinding (LAG) media were explored. Polar amide solvents such as DMA, commonly used in XECs, proved effective, while protic MeOH presented an interesting alternative (entry 3). Even water could serve as an LAG medium, leading to substantial but not complete loss of yield. This highlights moisture tolerance, which is consistent with ambient conditions and utilization of non-dried LAG agents (see the SI, Section S3).

Additive screening revealed that both pyridine and triphenylphosphine oxide (TPPO) enhanced the reaction efficiency, whereas ZnBr₂ had a detrimental effect (entries 4–6). These results suggest that Lewis-basic pyridine and TPPO may reduce the inhibitory effect of *in situ* generated Zn(II), an interpretation supported by a previous report by Weix,⁴⁰ and the observed solid-state structure of a [(pyridine)ZnBr₃][−] complex obtained from the crude reaction mixture *via* single-crystal X-ray diffraction (see the SI, Section S4). Alternative reductants such as manganese and tetrakis(dimethylamino)ethylene (TDAE) were both tolerated but provided lower yields compared to zinc

(entries 7 and 8). The use of other nickel salts decreased the efficiency (see the SI, Section S3). A key discovery was that pyridine could act as both an additive and LAG agent, eliminating the need for DMA. This change increased the yield, reduced the catalyst loading (10 mol%), and shortened the reaction time to 1 h (entry 10). Finally, adding NaCl, potentially acting as a grinding auxiliary or enabling more complex interactions,^{31,41} further improved the outcome, defining the optimized conditions for subsequent studies. Control experiments confirmed the necessity of both NiCl₂·6H₂O and the ligand (entry 11).

With the optimized conditions at hand, the substrate scope was investigated (Scheme 2). Aside from simple benzoic thioester (**3aa**), sterically hindered thioesters could be coupled in good yields (**3ba**, **3ca**). An upscaled reaction gave **3aa** in 89% yield (3.99 g). Both electron-withdrawing and -donating groups were accommodated, including aryl halides (**3da**, **3ea**), a trifluoromethyl group (**3fa**), an ester (**3ga**), or a methoxy substituent (**3ha**) in good yields. Meanwhile, more electron-rich benzodioxol decreased the yield (**3ia**). It should be noted that electron-withdrawing substituents led to increased amounts of the decarbonylated coupling product. To our delight, aliphatic thioesters could also be used, efficiently yielding dialkylketones in excellent yields (**3ja**, **3la**). However, homobenzylic thioesters suffered from decarbonylation and homocoupling, producing higher amounts of side-products (**3ka**). Unsaturated alkyl chains were also viable (**3ma**). Gratifyingly, ketones with secondary aliphatic cycles on the acyl moiety could be obtained in good to high yields (**3na**, **3qa**), and heterocyclic substrates were well tolerated (**3oa**, **3pa**). Notably, even the coupling of a sterically encumbered tertiary thioester was successful, albeit in a reduced yield (**3ra**). Next, the alkyl bromide scope was studied. Primary alkyl bromides afforded products in good yields (**3ja**, **3jb**). The reaction was compatible with alkyl and aryl chlorides (**3jc**, **3jd**), a trifluoromethyl group (**3jf**) and even aryl bromides (**3je**), representing a handle for further functionalization. Ketones containing silyl- or methyl-protected alcohols (**3jg**, **3jh**) as well as esters (**3ai**, **3ji**) could be produced in moderate to good yields. Secondary alkyl bromides were also feasible despite their higher steric demand, delivering ketones in good to high yields (**3jj**–**3jl**). Notable limitations included the use of tertiary (low conversions) and benzylic bromides (homocoupling). Finally, thioesters derived from pharmaceutically active compounds Ibuprofen, Oxaprozin or Probenecid as well as an intermediate in the Roflumilast synthesis could be coupled in moderate to good yields (**3sa**–**3va**).

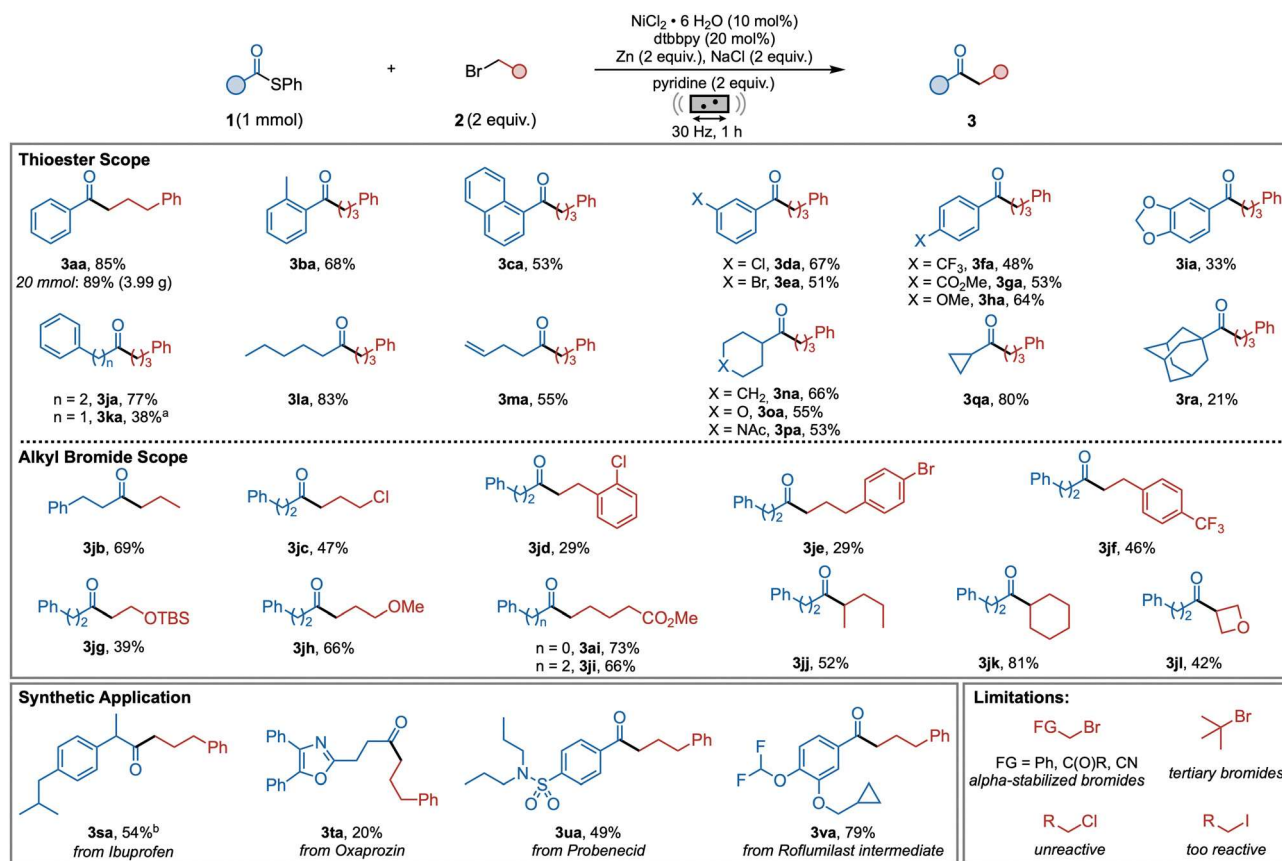
Next, we turned our attention to the reaction mechanism (Scheme 3), as both a Negishi-type as well as a radical-chain mechanism seemed possible.^{21,42} We were especially interested in the activation of thioesters, as there is no clear mechanistic evidence on their oxidative addition (OA) to nickel. Consequently, we sought to synthesize the OA complex by adding thioester **1a** to a dtbbpy-preligated nickel(0) complex, affording **Ni1** (Scheme 3A). Interestingly, a mixture of the acyl complex **Ni1a** and its CO-deinserted isomer **Ni1b** was obtained with the latter as the major product (*ca.* 35:65). This was revealed by ¹H¹³C-HMBC NMR spectroscopy, showing the presence or

Table 1 Optimization of the nickel-catalyzed mechanochemical acyl-alkyl XEC

Entry	Variation	Yield ^a (%)
1	None	51
2 ^b	Phen as ligand	44
3	MeOH as LAG	47
4	+ Pyridine (1 equiv.)	64
5	+ TPPO (1 equiv.)	60
6	+ ZnBr ₂ (1 equiv.)	6
7	Mn instead of Zn	21
8	TDAE instead of Zn	27
9 ^c	Pyridine as LAG and 10 mol% catalyst loading	78
10 ^c	+ NaCl (2 equiv.)	>99
11 ^c	No Ni/no ligand	2/0

Reaction conditions: performed in a stainless steel (SS) milling jar (10 ml) with 2 × 4 g SS milling balls for 2 h at 30 Hz. ^a GC-FID yields. ^b *N,N*-Dimethylpropyleneurea (DMPU) instead of DMA. ^c NiCl₂·6H₂O (10 mol%), dtbbpy (20 mol%), Zn (2 equiv.), pyridine (2 equiv.) mixer mill (30 Hz, 1h).





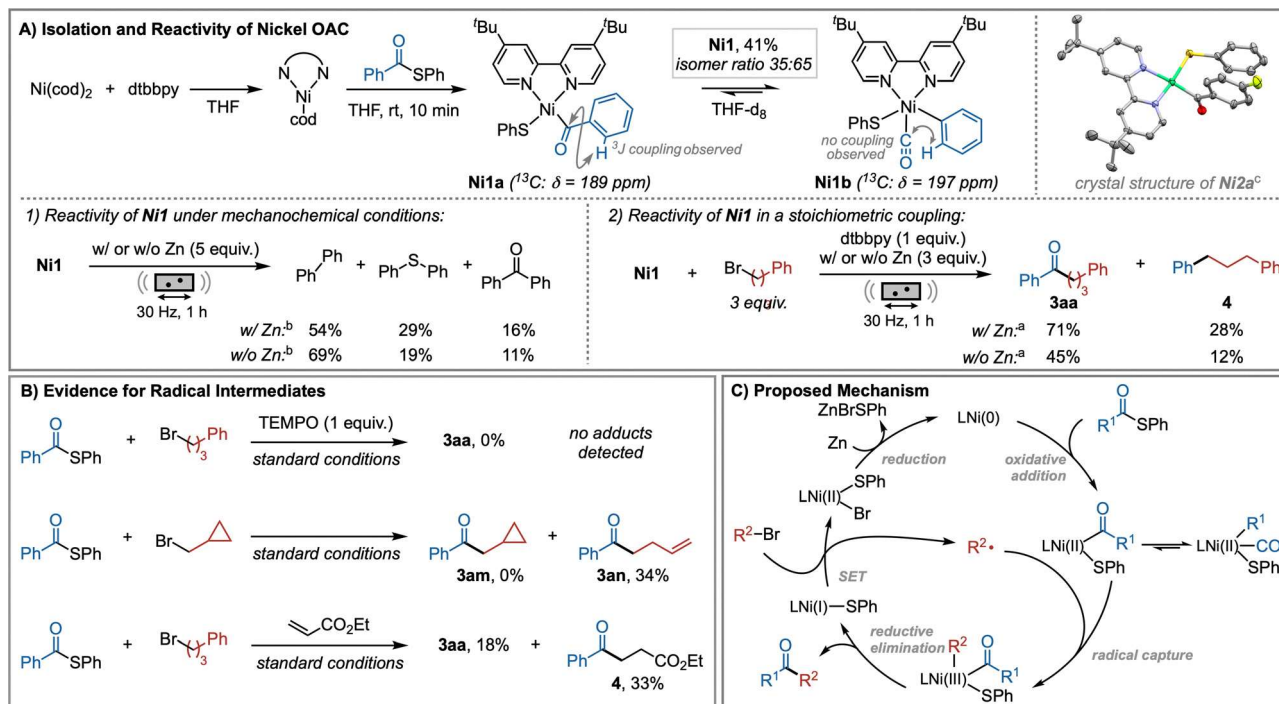
Scheme 2 Substrate scope for the nickel catalyzed mechanochemical XEC of S-phenyl thioesters with alkyl bromides. Reaction conditions: **1a** (1 mmol), **2a** (2 equiv.), NiCl₂·6 H₂O (20 mol%), dtbbpy (40 mol%), Zn (2 equiv.), NaCl (2 equiv.), pyridine (2 equiv.) in a stainless steel (SS) milling jar (10 ml) with 2 × 4 g SS milling balls for 1 h at 30 Hz. Isolated yields. ^a Yield calculated by ¹H NMR from an isolated sample (inseparable mixture of products). ^b 2 h.

absence of ³J coupling of the carbonyl carbon with a proton in the *ortho*-position of the aromatic ring. Varying the addition temperature (−80 °C to rt) or measurement conditions (−40 °C to rt) did not significantly influence this ratio, suggesting that a fast equilibrium between these two species is present in solution. While attempts to crystallize **Ni1** remained unsuccessful, a 4-fluoro-substituted derivative **Ni2a** could be characterized by XRD, displaying a square-planar coordination of nickel(II) with an intact acyl moiety, although the acyl form was also the minor form in solution for this derivative. The solid-state structure is in line with the literature and the observed diamagnetism.⁴³

Because the isomer ratio **Ni1a/Ni1b** in THF solution may not be directly transferable to mechanochemical conditions, we performed a control experiment: Upon subjecting **Ni1** to the ball mill, several scrambling products were obtained. Interestingly, the major products resembled decarbonylated species, indicating that under these conditions, **Ni1b** was also the major species or reacted faster. However, upon subjecting **Ni1** to a stoichiometric coupling with alkyl bromide **2a**, mainly the ketone product **3aa** was obtained, along with a minor amount of decarbonylated product **4**. This suggests that **Ni1a** reacts faster with **2a** than **Ni1b** and is (re-)generated from **Ni1b** during the reaction in a Curtin-Hammett-like scenario. A reason could

be that **Ni1b** requires extrusion of CO before radical capture is possible. Notably, for more electron-poor aryl thioesters, considerable amounts of the decarbonylated product were observed in catalytic reactions, suggesting that this reaction may be competitive in cases where extrusion of CO is more favorable. Evidence for a radical-chain mechanism was obtained by suppression of the coupling reaction when adding a radical inhibitor (TEMPO) and the formation of the ring-opened coupling product (**3an**) upon using a radical reporter (Scheme 3B). The radical activation of alkyl bromides by SET from nickel is consistent with numerous literature reports.⁶ While Browne and co-workers also reported the formation of organozinc species under similar conditions,^{24,31} the absence of **3am** contradicts a Negishi-type mechanism, which is also supported by the finding that organic reductants can be used (Table 1, entry 8). Moreover, adding a Michael-acceptor to the standard reaction resulted in the formation of the formal Giese-adduct **4**, pointing towards the formation of an acyl radical,^{35,44} although a competitive migratory insertion mediated by nickel cannot be excluded. Thus, we propose a radical-chain mechanism, consistent with recent literature,^{31,45} involving oxidative addition of the thioester to afford the respective oxidative-addition complex (Scheme 3C). Capture of the alkyl radical, likely produced by SET from a Ni(I) species,⁴⁶ followed by





Scheme 3 Mechanistic studies. Isolated yields unless stated otherwise. ^a Yields determined by GC-FID using pentadecane as the internal standard. ^b Yields estimated by GC-MS. ^c Selected bond lengths and angles for **Ni2a** (Å) or (°): Ni–C 1.859(1), C–O 1.220(1), N–Ni–C 94.66(4), S–Ni–C 90.21(3).

reductive elimination yields the coupling product, while the catalytic cycle is closed by reduction of the resulting Ni(II) complex with zinc. The detailed mechanism of oxidative addition may be a subject of future investigations.

In conclusion, an efficient procedure for XEC of aliphatic and aromatic thioesters with alkyl bromides was developed. Applicability was demonstrated on numerous examples, including biologically relevant compounds. The mechanochemical set-up enables rapid, simple reactions without the need for Schlenk-techniques or a Glovebox. Compared to recent mechanochemical methods for the synthesis of ketones, our work featured comparable yields at shorter reaction times. Moreover, preliminary mechanistic studies advance the current understanding on mechanochemical transformation of acyl electrophiles.

Conflicts of interest

There are no conflicts to declare.

Data availability

All data supporting this article have been included as part of the supplementary information (SI). Supplementary information: general procedures, further condition screening and compound characterization. See DOI: <https://doi.org/10.1039/d6cc00297h>.

CCDC 2491069 (**Ni2a**) contains the supplementary crystallographic data for this paper.⁴⁷

Acknowledgements

We thank the analytics department of the University of Tübingen for their excellent work. The financial support from the University of Tübingen, FCI (scholarship I. H. L.) and Studienstiftung des Deutschen Volkes (scholarship R. C. R.) is gratefully acknowledged.

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Nickel-catalyzed hydro- and deuterioacylation of acrylates using water as the hydrogen source

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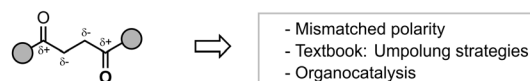
Acylation of activated alkenes provides useful and quick access to synthetically useful 1,4-difunctionalized compounds. In this work, an operationally simple mechanochemical protocol for the hydroacylation of acrylates and related activated alkenes is reported using thioesters as acyl donors and water as the hydrogen source. This approach selectively furnished linear coupling products, complementing previous nickel-catalyzed methodologies that predominantly yielded branched 1,3-adducts. Substitution of water with D₂O enables straightforward synthesis of deuterium-labeled products with high levels of selective isotopic incorporation. Detailed mechanistic investigations, including primary and secondary KIE studies, Hammett analysis, DFT computations and NMR spectroscopy, support a pathway involving migratory insertion at the nickel center, while providing no evidence for the involvement of radical intermediates.

Introduction

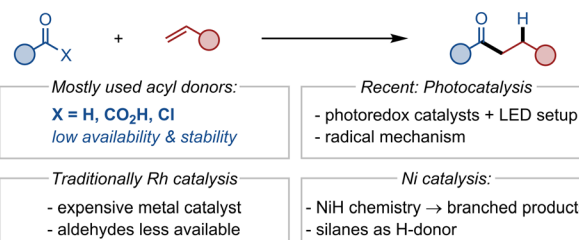
1,4-Dicarbonyl compounds are valuable intermediates for the synthesis of heterocycles and cyclopentenones,^{1–3} but their preparation is inherently challenging due to polarity mismatch, necessitating umpolung of either the alkene (*e.g.*, *via* homoenolate equivalents)^{4,5} or the acyl component (Scheme 1A). Traditional protocols for acyl umpolung are well known,^{6,7} but additional synthetic steps and strong bases are often needed, although organocatalysis offers an interesting alternative.^{8–10} Extensive efforts have been devoted to rhodium-catalyzed hydroacylation of alkenes using aldehydes (Scheme 1B),^{11–13} resulting in highly efficient protocols. However, the high cost of rhodium limits the practicality of these methods. More recently, attention shifted to the photochemical generation of acyl radicals that undergo Giese-type addition to activated alkenes, providing the linear 1,4-dicarbonyl coupling product after radical quenching.¹⁴ Such acyl radicals are typically generated *in situ* from aldehydes, α -ketoacids or, more rarely, carboxylic acid derivatives.^{15–19} Generally, these reactions provide an elegant approach towards 1,4-dicarbonyl compounds, but suffer from limited substrate availability, long reaction times and poor scalability. In addition, the nickel-catalyzed intermolecular hydroacylation of alkenes has been reported,^{20,21} including an enantioselective version.²² These examples rely on the use of silanes to forge a nickel-hydride catalyst, resulting in the branched 1,3-dicarbonyl coupling product. To the best of our knowledge, no nickel-catalyzed hydroacylation of acrylates has been reported that proceeds without photochemical activation,

although related transformations have been described for 1,3-dienes, styrenes, and alkynes.^{23–25} In our continuous efforts to utilize thioesters as acyl donors,^{26–29} we noticed a side reaction that occurred in the mechanochemical cross-electrophile coupling (XEC) of thioesters with alkyl halides under nickel

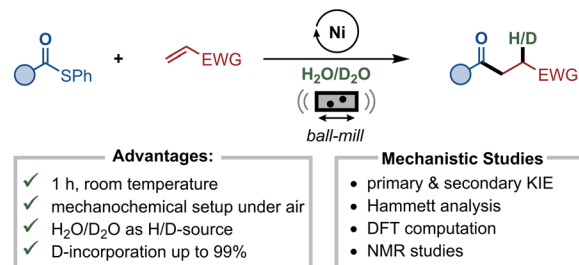
A) Synthesis of 1,4-dicarbonyl compounds



B) Hydroacylation of Alkenes



C) This Work: Ni-catalyzed Hydroacylation using H₂O



Scheme 1 Overview of various methods for the hydroacylation of alkenes.

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catalysis: In the presence of ethyl acrylate, the acylated Michael-adduct was formed next to the desired coupling product.²⁹ Intrigued by this rather unusual reactivity that exploited the natural polarity of both coupling partners under reductive conditions, we decided to study this reaction in more detail. The previously established mechanochemical conditions represented an ideal starting point for our investigations, as they enable reaction setup at ambient conditions, without the need for inert atmosphere techniques. Instead, all reagents can be subsequently weighed into the milling jar and subjected to the ball-mill. Moreover, mechanochemistry can enhance reaction kinetics,³⁰ selectivity³¹ and is usually seen as more sustainable compared to solution-based methods.³²

Development & scope

Initial screenings utilizing a similar catalytic system as in XEC delivered the linear addition product in 18% GC yield (Table 1). Ligand screening revealed superior performance of electron-deficient bipyridines (entries 1–7), identifying 4,4'-bis(trifluoromethyl)-2,2'-bipyridine (**L5**) as the best ligand. **L5** is commercially available but can also be synthesized in a one-step reaction on decagram scale (see SI Section 5.2). In contrast, alternative ligand classes, including phosphines and bis(oxazoline) derivatives, proved less effective (see SI). At this point we speculated that the added hydrogen atom would originate from the nickel precatalyst $\text{NiCl}_2(\text{H}_2\text{O})_6$. Thus, the substoichiometric amount of coordinated water might require an external source to achieve higher yields. Systematic solvent screening with **L1** (entries 8–12) revealed that polar amide solvents, but also water afforded the highest yields of the coupling product, while other solvents resulted in diminished reactivity. Fine tuning of the solvent with **L5** revealed a 5 : 1 mixture of DMF/ H_2O as the optimal medium (entry 14). It should be noted that solvents could be used straight from the bottle (HPLC grade) without the need for extensive deoxygenation or drying procedures. Upon performing the reaction under anhydrous conditions, no productive coupling was observed, and the starting materials were recovered. Control experiments confirmed the necessity of both nickel and ligand for productive reactivity, while the system showed low dependence on the specific nickel source, so we continued with $\text{NiCl}_2(\text{H}_2\text{O})_6$ as the most cost-effective precatalyst. In contrast, the influence of the mechanochemical setup is less transparent: replacing ball milling with magnetic stirring still afforded the coupling product, albeit in lower yield and at a substantially reduced reaction rate (see SI). Increasing the solvent volume to achieve solution-phase conditions further diminished the reaction efficiency. We propose that ball milling facilitates activation of the zinc metal,^{33,34} while also promoting efficient mixing under highly concentrated conditions.³⁵

Furthermore, addition of catalytic amounts of Cp_2TiCl_2 , likely acting as a Lewis-acid,^{28,36} did not greatly vary the yield of **1**, but was advantageous for functionalized, especially electron-poor thioesters and was therefore employed for subsequent investigation of the substrate scope (see SI for more detailed screening results). Other acyl sources, including aroyl halides,

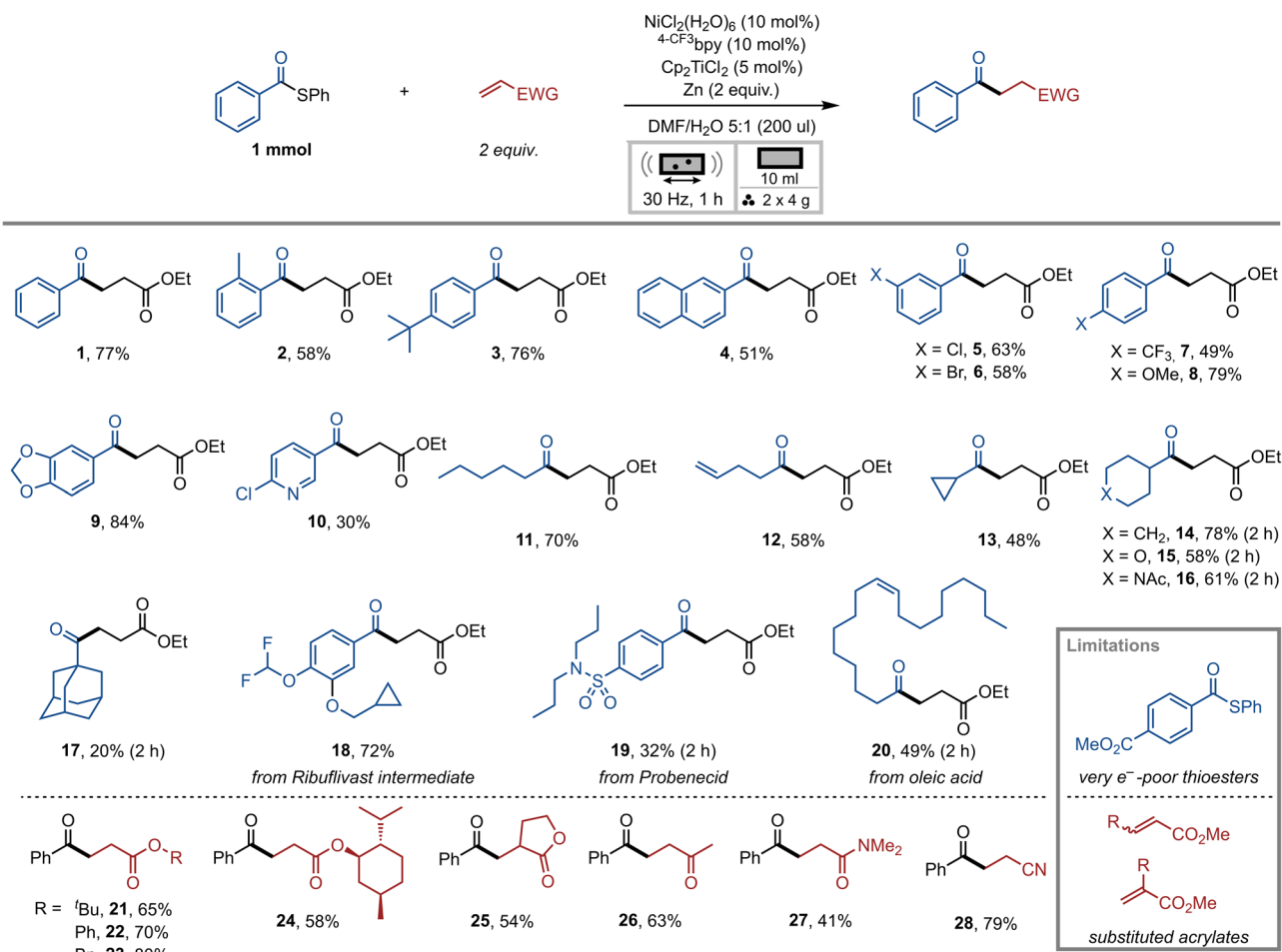
Table 1 Optimization screening^a

Entry	Deviation	Conv. [%]	Yield [%]
1	None	39	18
2	L2	9	4
3	L3	2	1
4	L4	6	3
5	L5	88	58
6	L6	93	49
7	L7	76	43
8	DMF	28	15
9	H_2O	30	16
10	MeOH	19	4
11	DCM	27	3
12	THF	8	3
Lines below contain L5 (10 mol%) as ligand			
13	DMF	94	59
14	DMF/H_2O (5 : 1)	100	82 (77)^b

^a Conversion and yields were determined by GC-FID using pentadecane as internal standard. Reaction conditions: thioester (1 mmol, 1 equiv.), ethyl acrylate (2 mmol, 2 equiv.), $\text{Ni}(\text{H}_2\text{O})_6\text{Cl}_2$ (10 mol%), ligand (20 mol%), Zn (2 equiv.), solvent (200 µl), SS milling jar (10 ml), SS milling balls (2 × 4 g), milling at 30 Hz for 1 h. ^b Isolated yield.

anhydrides, and twisted amides, were also evaluated under the developed reaction conditions (see SI). However, these substrates afforded inferior yields, highlighting the optimal reactivity of thioesters in this transformation. An advantage of thioesters compared to commonly employed aldehydes is the easy access from widely available carboxylic acids, their increased stability under benchtop conditions and tunability through the *S*-substituent.

With optimized conditions at hand, we isolated **1** in 77% yield and turned our attention towards the generality and limitations of this system (Scheme 2). Various aryl thioesters posed feasible acyl sources, but a strong influence of the electronic properties of the aroyl moiety was observed. Electron-neutral substrates delivered the product in high yields (**2–4**), whereas more electron-withdrawing substituents led to



Scheme 2 Scope of the nickel-catalyzed hydroacylation of activated alkenes. Isolated yields. Reaction conditions: thioester (1 mmol, 1 equiv.), acrylate (2 mmol, 2 equiv.), $\text{Ni}(\text{H}_2\text{O})_6\text{Cl}_2$ (10 mol%), L5 (10 mol%), Cp_2TiCl_2 (5 mol%), Zn (2 equiv.), premixed DMF/ H_2O (5 : 1, 200 μl), SS milling jar (10 ml), SS milling balls (2 $\times$ 4 g), milling at 30 Hz for 1 h.

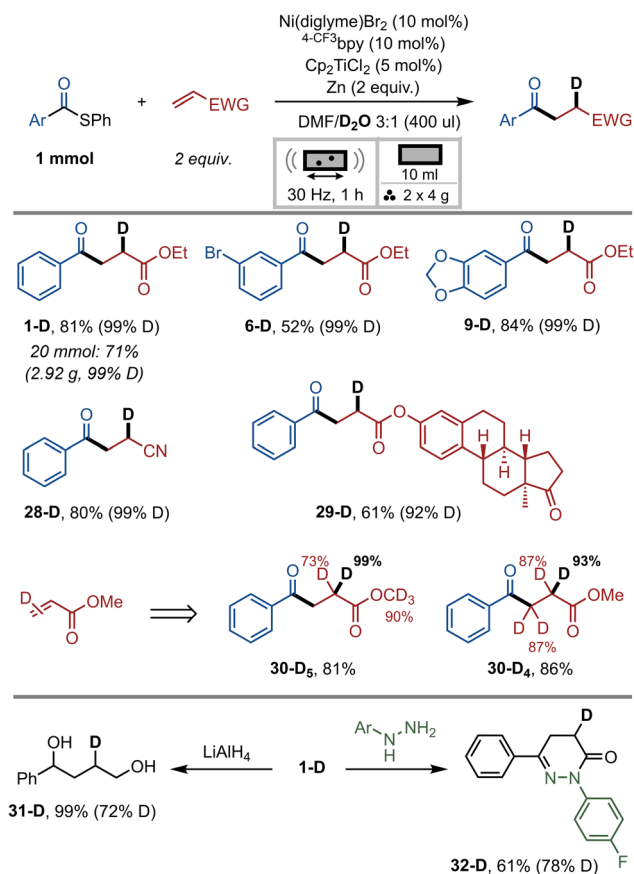
diminished yields (5–7). Substituents exhibiting $-M$ -effects (*e.g.*, esters, nitriles) suppressed reactivity entirely. On the other hand, electron-rich substrates generally gave high yields (8, 9). A heteroaromatic substrate afforded the coupling product in moderate yield (10), consistent with the electron-deficient nature of the pyridine moiety. Meanwhile, alkyl thioesters were also compatible, enabling access to aliphatic 1,4-ketoesters. Primary alkyl thioesters afforded the coupling product in high yields (11, 12), while secondary thioesters were feasible but required longer reaction times (13–16). Formation of a tertiary ketone 17 proceeded in low yield, showcasing the impact of steric hindrance. Thioesters derived from pharmaceutically relevant and natural compounds were synthesized from the corresponding carboxylic acids and used as substrates in the developed system, affording the corresponding 1,4-dicarbonyl compounds in good yields (18–20).

In contrast, the scope of activated alkenes proved more sensitive towards steric hindrance: While a range of acrylates afforded high yields (21–24), substitution at the α - or β -position prevented product formation. In addition, alternative activating groups, including ketones (25), amides (26), and nitriles (27)

were also compatible. In all examples, linear coupling products were obtained exclusively. Non-activated alkene derivatives, such as styrenes, were unreactive, regardless of the electronic properties on the aromatic moiety (see SI for examples). One possible reason could be that the steric constraint of the aromatic ring prevents effective coupling, as the reaction appeared to be highly sensitive to steric hindrance. Alternatively, polarization of the alkene or a coordinating functionality to stabilize a putative nickel-alkyl complex could be necessary (*vide infra*), as it was previously observed for the nickel-mediated migratory insertion of an acrylate into a $\text{Ni-C}(\text{sp}^2)$ -bond.³⁷

Deuteroacylation studies

Given that water appeared to be the hydrogen source in this reaction, we questioned if deuterium oxide, one of the widest commercially available sources for deuterium, would offer a straightforward strategy for selective deuteroacylation (Scheme 3). Indeed, after minor reoptimization of the nickel source and solvent, the deuterated 1,4-ketoester **1-D** was



Scheme 3 Scope of deuterated 1,4-ketoesters and derivatization of products. Isolated yields. Deuterium content was determined by ^1H NMR. Reaction conditions: thioester (1 mmol, 1 equiv.), acrylate (2 mmol, 2 equiv.), Ni(diglyme)Br_2 (10 mol%), **L5** (10 mol%), Cp_2TiCl_2 (5 mol%), Zn (2 equiv.), premixed $\text{DMF/D}_2\text{O}$ (3 : 1, 400 μl), SS milling jar (10 ml), SS milling balls (2 x 4 g), milling at 30 Hz for 1 h.

received in 80% isolated yield with excellent and selective deuterium incorporation (99% D), as confirmed by HR-MS and ^1H NMR spectroscopy. To the best of our knowledge, this constitutes the only thermal method for the synthesis of 3-deutero-1,4-dicarbonyl compounds. Comparable photochemical protocols suffer from lower deuterium incorporation and challenging scale-up.^{18,38} The studied scope demonstrated the generality of this approach, providing deuteroacylated products (**1-D**, **6-D**, **9-D**, **28-D**) in yields comparable to the standard protocol and consistently high levels of deuterium incorporation. Notably, aryl bromide functionalities remained intact under the reaction conditions (**6-D**), providing a convenient handle for subsequent cross-coupling transformations, enabling synthesis of larger structures containing the C3-deuterated 1,4-ketoester motif. The formation of **29-D** further demonstrated that more complex acrylates, such as estrone-derived acrylate, were suitable for deuteroacylation and furnished the product in good yield.

Use of deuterated acrylates afforded coupling products containing CD_2 -groups (**30-D₄**, **30-D₅**), which represent valuable intermediates for the synthesis of deuterium-labelled pyrroles

and furans. The degree of deuteration on non-participating positions reflected the starting material, indicating that no H/D exchange or enolization occurred during the reaction.

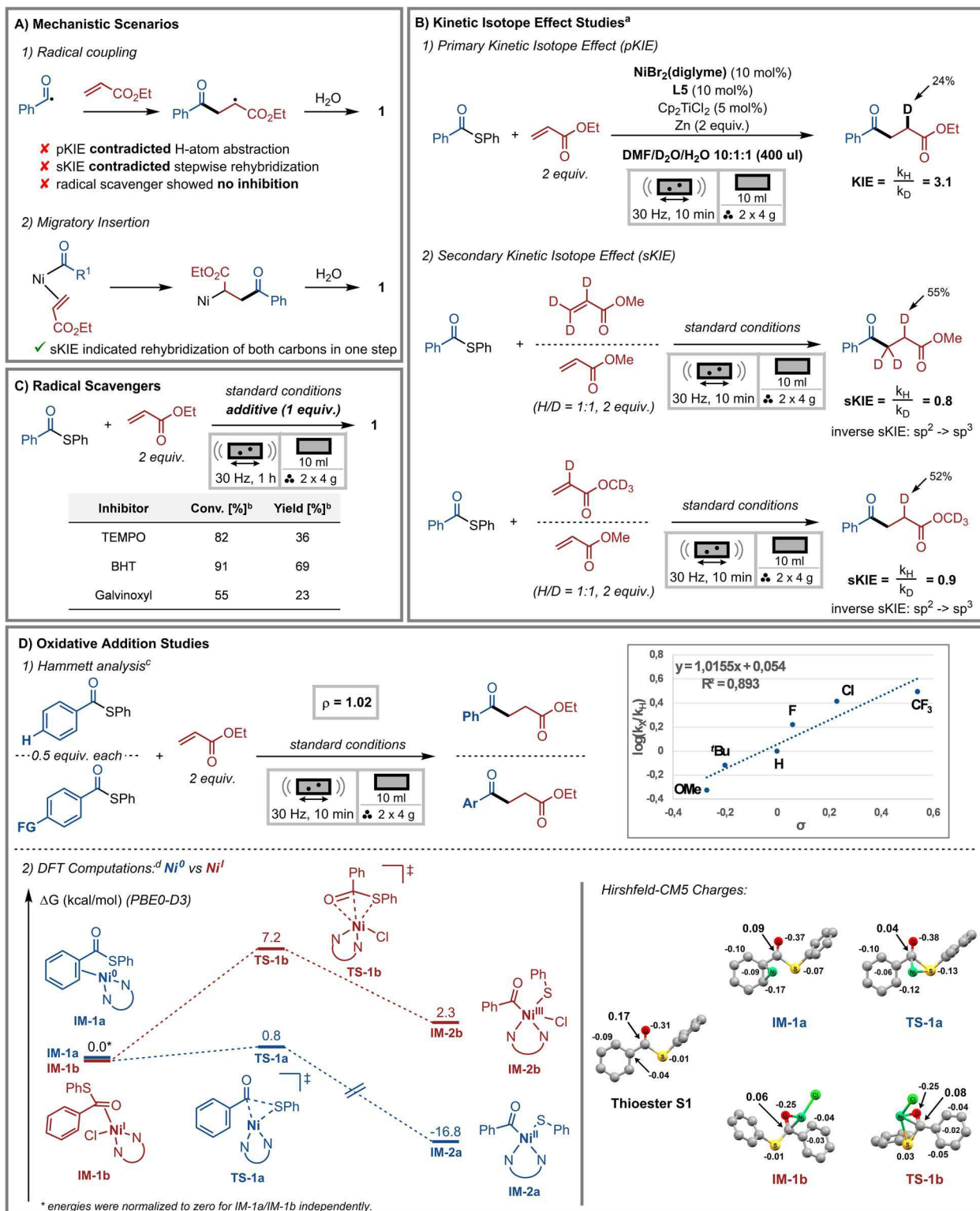
Further derivatization of deuterated 1,4-ketoester **1-D** demonstrated the utility of this methodology for the preparation of labelled compounds (**31-D**, **32-D**), although partial H/D-exchange was observed under basic conditions.

Mechanistic investigations

Next, we decided to investigate the reaction mechanism. Specifically, it remained unclear if a radical mechanism involving a Giese-type addition of an acyl radical to the alkene, or an ionic mechanism mediated by nickel was operative (Scheme 4A). A mechanism involving nickel hydride intermediates, as proposed in related systems, seemed unlikely as they typically afford branched rather than linear products.³⁹ Initially, a primary kinetic isotope effect (KIE) was studied, to provide information about the possible coupling mechanism (Scheme 4B). Due to the limitations of mechanochemical setups for precise rate measurements, competition experiments at low conversion were utilized. From competition between $\text{H}_2\text{O/D}_2\text{O}$ a primary KIE = $k_{\text{H}}/k_{\text{D}}$ = 3.1 was determined. Given that hydrogen atom abstraction by organic radicals from protic sources typically exhibits KIE values ≥ 6 ,⁴⁰ these results argue against a radical pathway. Instead, the observed KIE suggests a more complex quenching step, although the precise mechanism remains unresolved. To obtain more definitive mechanistic insight into the coupling step, we conducted secondary KIE (sKIE) studies. Such experiments are particularly informative in reactions involving changes in carbon hybridization, such as at alkene carbons.⁴¹ In the present case, sKIE analysis can differentiate between the two proposed mechanisms by probing carbon rehybridization: In a radical mechanism, initial rehybridization would be expected to occur only at the β -carbon, as the unpaired electron resides in a p-orbital at the α -position.

Competition between methyl acrylate and its α,β -deuterated analogue resulted in an inverse secondary KIE of $k_{\text{H}}/k_{\text{D}}$ = 0.8, consistent with a rehybridization of the carbon centers from sp^2 to sp^3 in the product-determining step.⁴¹ A complementary experiment, employing an α -deuterated acrylate gave an sKIE of 0.9. Together, these findings indicate that both carbon atoms of the alkene are rehybridized in the same product-determining step. This is conclusive with a migratory insertion of the alkene into a Ni-acyl bond, but inconsistent with a radical mechanism, where only the β -carbon is rehybridized initially.

Additional evidence against radical intermediates was obtained from inhibition experiments (Scheme 4C). The presence of radical scavengers such as (2,2,6,6-tetramethylpiperidin-1-yl) oxyl (TEMPO), butylhydroxytoluene (BHT), or galvinoxyl reduced the yield but did not fully suppress product formation, further supporting a non-radical pathway, albeit the competitive radical acceptor ability of acrylate may question the reliability of these experiments.⁴² Our empirical observations on substrate scope and limitations are also consistent with a migratory insertion mechanism, which should proceed faster with electronically polarized alkenes, where the electrophilic β -



Scheme 4 Mechanistic studies of coupling steps. ^aKIE was determined from product ratios (¹H NMR) after isolation. ^bYields determined by GC-FID using pentadecane as an internal standard. ^cRatio of products determined by ¹H NMR from an isolated sample. ^dCalculations were performed at the PBE0-D3(BJ)/def2-TZVP(Ni), def2-SVP (other atoms), SMD(DMF) level of theory. Each reaction pathway was normalized independently by setting its respective starting structure to $\Delta G = 0$. Consequently, the absolute energies of the two pathways cannot be compared directly.

carbon is susceptible to nucleophilic attack. In a mechanistic simplification, the Ni-acyl intermediate can be considered as a "Ni⁺-C(O)R" equivalent, and the acyl fragment would undergo

nucleophilic addition to the β -carbon,⁴³ thereby accounting for the observed perfect regioselectivity. In contrast, a radical pathway would be expected to also enable productive coupling

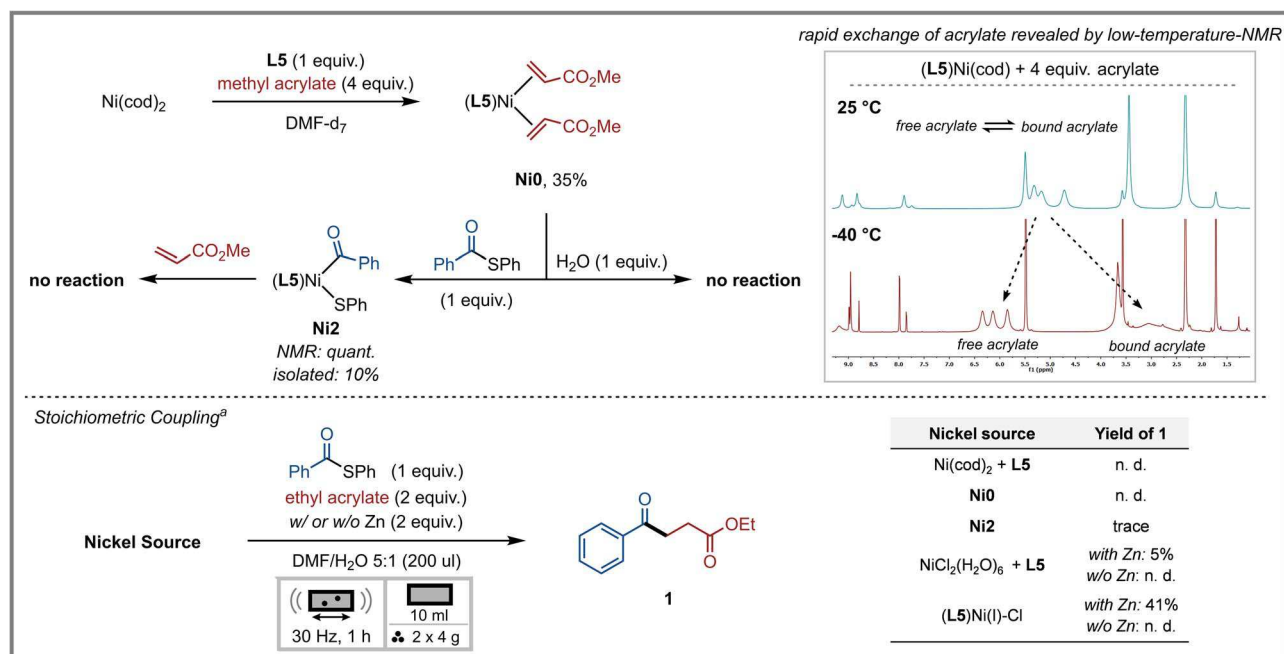
with styrene substrates, as known from related photochemical methods.^{18,44,45} Moreover, we decided to study the oxidative addition in more detail (Scheme 4D). Once again utilizing low-conversion competition experiments, a Hammett study was performed using *p*-substituted benzoate thioesters. It gave rise to a ρ -value of 1.02, indicating the accumulation of a negative charge in the product-determining step at the carbonyl moiety. Although comparable studies for acyl electrophiles are scarce, we see this relatively small positive value in best agreement with a concerted oxidative addition, considering that the oxidative addition of aryl halides to Ni(0) gives rise to ρ -values around ~ 2 .^{46,47} Yu and co-workers reported in a computational study that in the oxidative addition of thioesters to palladium(0), the C–S-bond activation barrier is lowered by electron-withdrawing substituents,⁴⁸ which is in line with our results.

To gain more insight in the nickel-catalyzed C–S-bond activation step, the oxidative addition of *S*-phenyl benzothioate to (L5)Ni(0) was studied by density functional theory (DFT, Scheme 4D). The concerted oxidative addition of the C–S bond appeared to be nearly barrierless (0.8 kcal mol^{−1}) at the PBE0-D3(BJ)/def2-TZVP(Ni), def2-SVP (other atoms), SMD(DMF) level of theory, consistent with reported oxidative addition of *S*-alkyl thioesters to a comparable nickel(0) complex.⁴⁹ Comparison of atomic charges at the carbonyl atom in the thioester, intermediate **IM-1** and the transition-state **TS-1** revealed depletion of positive charge (*i.e.* accumulation of negative charge), which is in agreement with the experimental Hammett results. As we found later evidence for a Ni(I)/Ni(III) catalytic cycle (*vide infra*), the oxidative addition of a thioester to the corresponding (L5)Ni(I)–Cl complex was equally studied. Comparable to previous studies,⁴⁹ our computational analysis revealed a competitively low barrier of oxidative addition (7.2 kcal mol^{−1}). Meanwhile,

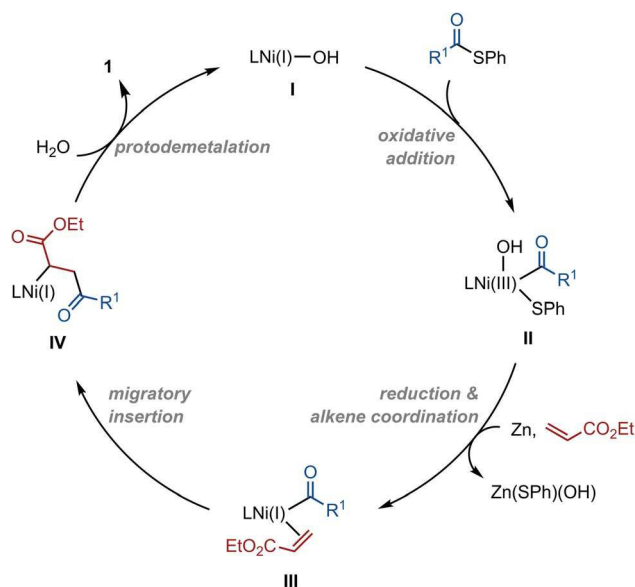
depletion of positive charge was only observed for substrate coordination but was surprisingly absent for the oxidative addition. As expected, the lower stability of Ni(III) compared to Ni(II) render the oxidative addition to Ni(I) slightly endergonic. These results make both mechanisms possible, and the viability of oxidative addition to either Ni(0) or Ni(I) was also validated in stoichiometric experiments (see below).

Further mechanistic insight was obtained from NMR studies of organometallic intermediates (Scheme 5). Mixing Ni(cod)₂ and L5 with methyl acrylate in DMF-d₇ led to upfield-shifted and broadened alkene signals, indicative of coordination to nickel(0). Interestingly, the chemical shift of the alkene protons was dependent on the amount of acrylate added, showcasing that a dynamic equilibrium could be present. Indeed, low-temperature NMR of the reaction of (L5)Ni(cod) with 4 equiv. acrylate revealed that this equilibrium could be frozen at −40 °C, showing distinct signals for coordinated and unbound acrylate. On preparative scale, a Ni(0)-acrylate complex (**Ni0**) was isolated, although solution-phase NMR indicated the presence of multiple species, likely isomers. Notably, **Ni0** showed no reactivity toward water over 24 h at room temperature.

On the other hand, adding 1 equiv. of thioester to **Ni0** resulted in the formation of the oxidative addition complex **Ni2**, releasing the acrylate, as observed from the alkene proton chemical shift. To our surprise, no reaction of **Ni2** with the acrylate occurred, neither in the presence nor in the absence of water and/or zinc, indicating that this complex represented an off-cycle species and is not an intermediate of the catalytic cycle. In following stoichiometric coupling experiments, various nickel sources were subjected to stoichiometric amounts of thioester and acrylate, either in the presence or absence of zinc. Surprisingly, no reaction occurred starting from nickel(0)



Scheme 5 Synthesis and reactivity of potential nickel intermediates. ^aGC-FID yields using pentadecane as internal standard.



Scheme 6 Proposed mechanism.

sources, such as $\text{Ni}(\text{cod})_2$ or **Ni0**, indicating that this oxidation state may not be part of the catalytic cycle, conclusive with the lack of reactivity of oxidative addition complex **Ni2**. Another unexpected result was the inability of $\text{NiCl}_2(\text{H}_2\text{O})_6$ to promote the coupling in stoichiometric manner, even though it performed well when used in catalytic amounts. In contrast, independently synthesized nickel(i) complex (L5)**Ni**(Cl) (**Ni1**) furnished the coupling product in moderate yield, indicating that productive coupling relied on a Ni(i) complex. In agreement with our computational findings, addition of 1 equiv. of thioester to **Ni1** in THF-d_8 at room temperature led to the disappearance of its signals in the paramagnetic ^1H NMR spectrum (see SI). Opposing to common proposals in XEC where zinc serves to close the catalytic cycle by reducing inactive species after product release,⁵⁰ the observation that zinc is required even under stoichiometric conditions implied that a reduction step occurs prior to product formation. Thus, we propose the following catalytic cycle (Scheme 6): initial reduction of the precatalyst $\text{NiCl}_2(\text{H}_2\text{O})_6$ yields nickel(i) complex **I**.

Oxidative addition of the thioester to Ni(i) affords high-valent Ni(III) intermediate **II**. Subsequent reduction by zinc and alkene coordination leads to intermediate **III**, which transforms to **IV** after migratory insertion of the alkene into the Ni-acyl bond. According to our experimental data, the alkene does not coordinate to a Ni(II) oxidative addition complex (**Ni2**), which therefore represents a catalytically inactive species. Protodemetalation of Ni-alkyl intermediate **IV** yields the coupling product and regenerates the active catalyst **I**. The regioselectivity of the insertion is controlled by the coordination of the acrylate carbonyl moiety, as proposed in the literature.²¹

Conclusions

A mechanochemical procedure for the hydro- and deuteroacylation of activated alkenes using thioesters as acyl source is

reported. Key features are the tolerance towards ambient conditions, short reaction times and the general use of water or deuterium oxide as H- or D-source, respectively. The applicability was demonstrated on the synthesis of a range of 3-deutero-1,4-ketoesters, which could also be obtained in gram scale with excellent and selective deuterium incorporation, offering a broad entry for synthesis of deuterated heterocycles. Mechanistic investigations suggested an ionic Ni(I)/(III) mechanism without the involvement of radicals.

Author contributions

I. H. L. conceived the project with help from I. F., conducted the experimental work and data analysis, and wrote the SI. F. carried out computational analysis. I. F. provided funding and supervised the project. The manuscript was written through contributions of all authors.

Conflicts of interest

There are no conflicts to declare.

Data availability

All data supporting this article have been included as part of the supplementary information (SI). Supplementary information: general procedures, further conditions screening and compound characterization. See DOI: <https://doi.org/10.1039/d6sc04272d>.

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