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ALDRICHIMICA ACTA

Rhodium-Catalyzed Asymmetric Suzuki and Related Cross-Coupling Reactions
*Stephen Webster, Laura Cunningham, and Stephen P. Fletcher,** University of Oxford
Ylide-Substituted Phosphines in Palladium-Catalyzed Coupling Reactions
*Daniel Knyszek and Viktoria H. Gessner,** Ruhr-Universität Bochum

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DEAR READER:

We've been together for over a quarter century, and it is now time for me to hand over this venerable publication to the next generation of editors. During our time together, we have witnessed and experienced dramatic changes in the way scientific content and journals are produced, published, consumed, and evaluated. The majority of these changes have been for the better while a few have not. Like other scientific journals, the *Acta* has had to deal with these changes and adapt, and it is still adapting. My hope is that it will emerge at the end of this process stronger and in a better position to continue the pursuit of its important dual mission.

In its 57-year history, the *Aldrichimica Acta* has been a unique scientific publication and one of the very first open-access journals (and still is). Peerless in the chemical industry, it has consistently offered insightful, high-quality, topical scientific information as a service to the chemistry community that its publisher has served for decades. As all of us know, wide access to scientific information has always been costly and out of reach for many budget-challenged institutions and individuals, perhaps more so today than before the digital revolution.

Of course, the *Acta* had a second mission: to convey and reinforce the message that its publisher is not just a supermarket of chemical products but an enlightened high-tech company and a facilitator of access to the latest research innovations. A company that understands researchers and their needs and challenges. It maintained a dialogue with researchers through the *Acta*: researchers were not just consumers but also colleagues, partners, authors, and readers.

Reflecting on my tenure as *Acta* editor over these decades, I am honored and grateful for the opportunity that an enlightened company offered me: to be an academic in industry and to serve you the readers, authors, and customers. I'd like to believe that the *Acta* and I have made a difference. What I have enjoyed the most during this time have been my stimulating and enriching interactions with researchers throughout the world and my reading about their exciting discoveries. I cannot overstate how valuable these interactions and learning have been to my intellectual well-being. Nevertheless, I would be remiss if I didn't mention that, to publish the *Acta*, often nontrivial challenges had to be overcome: from authors and advertisers missing their deadlines, to authors in the early days submitting handwritten manuscripts and graphics, to technical and budgetary challenges, to adapting the production process to fast-paced technological changes, and on and on; but dogged perseverance paid off and helped the *Acta* survive and thrive.

As my tenure running the *Aldrichimica Acta* is coming to an end, I am looking forward to the next chapter in my life. I leave rich in the many happy memories I collected over these years and the lifelong friendships, internal and external, I had the good fortune to form during my tenure. The *Acta*'s success, and by extension mine, is owed in great measure to the hard work, support, and kindness I received over the years from legions of co-workers, readers, academics, and chemistry researchers everywhere, as well as to members of management who strongly believed in the value and mission of the *Acta* and who offered their unwavering support for it through the ups and downs of the often-turbulent world of business.

To the *Acta* readers and authors and to my colleagues I offer a heartfelt thank you and bid you all farewell. I know the *Acta* will be in good and capable hands.

Sharbil

ALDRICHIMICA ACTA
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Dear Fellow Chemists,

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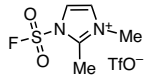

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ABOUT OUR COVER

Upward of 30 topical articles and five dedicated issues in the past ten years alone! That's how important we believe **Catalysis** is in organic synthesis. In this special issue, we are revisiting this theme by featuring insightful reviews by two European groups at the forefront of this research area. Chemical synthesis is about transformations, and catalysis is about making these transformations go faster, under milder conditions, and ideally give much improved yields. This issue of the *Aldrichimica Acta* highlights two types of transition-metal catalysis of organic reactions—rhodium and palladium homogeneous catalysis.

For our cover, we thought it best to remind our readers of the covers of earlier *Acta* issues in which catalysis was featured prominently. Our hope is that our readers would get as excited as we are about the proven worth of various existing types of catalysis as well as the promise of other types that are currently in active development. Happy reading!

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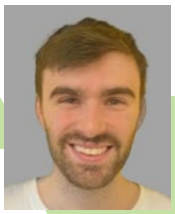
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Keywords. enantioselective; rhodium; cross-coupling; asymmetric catalysis; allylic arylation; hydroarylation; Suzuki–Miyaura; enantioconvergence; Dynamic Kinetic Asymmetric Transformation (DYKAT); boronic acids.

Abstract. We describe in this account our progress towards the development of new catalytic asymmetric cross-coupling reactions. We focus on the application of boronic acids in the synthesis of enantioenriched C(sp^2)–C(sp^3) coupled products from prochiral and racemic starting materials. Specifically, we describe the rhodium-catalyzed Suzuki–Miyaura-type arylations of allylic halides and cyclobutenes, their key mechanistic features, and their applications to complex-molecule synthesis and scale-up.

Outline

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4. Mechanistic Investigation of the Rh(I)-Catalyzed Asymmetric Suzuki–Miyaura-type Coupling
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1. Introduction

C(sp^2)–C(sp^2) cross-coupling reactions are well established. In particular, the Suzuki–Miyaura cross-coupling (SMC) has emerged as a popular synthetic tool, owing to its experimental convenience and the robustness of the arylboronic acid reagents employed.[1] Its ubiquitous application has biased the structures of drug candidate libraries towards unsaturated arene-rich scaffolds, despite low saturation and the absence of stereogenic centers reducing the chances of success in drug discovery programs.[2,3] Therefore, developing synthetic reaction systems that combine the generality and practicality of the SMC but yield enantiomerically enriched products with C(sp^3) centers has been an area of active research.[3]

Transition-metal-catalyzed asymmetric allylic addition and hydrofunctionalization of alkenes have become effective tools for enantioselectively forming C–C bonds.[4–6] However, despite sporadic reports of aryl nucleophiles being utilized in these reactions, there are not yet generally useful and selective methods for employing (hetero)aryl species as nucleophiles.[7–10]

Our group has developed several enantioselective cross-couplings between (hetero)aromatic boronic acids and a variety of coupling partners. In the rest of this article, we will review our studies on the development and applications of these asymmetric arylations (**Figure 1**).

2. Asymmetric Suzuki-type Coupling of Monocyclic Allylic Chlorides

Earlier work by our group included the in situ generation of alkylzirconium reagents from alkenes and their copper-catalyzed asymmetric conjugate addition (ACA)[11–14] as well as asymmetric allylic alkylation (AAA) with racemic allyl halides.[15] However, attempts to extend such AAA reactions to sp^2-hybridized zirconium nucleophiles (generated in situ from alkyne precursors) proved challenging, with poor enantioselectivities (~60% ee) observed.[16]

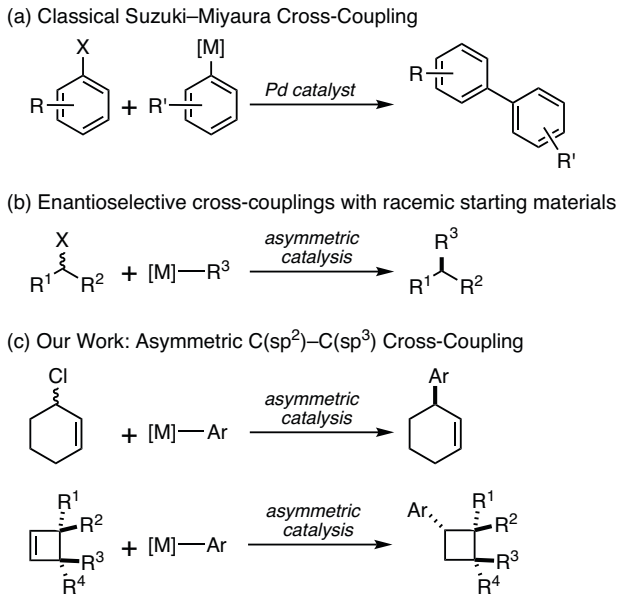
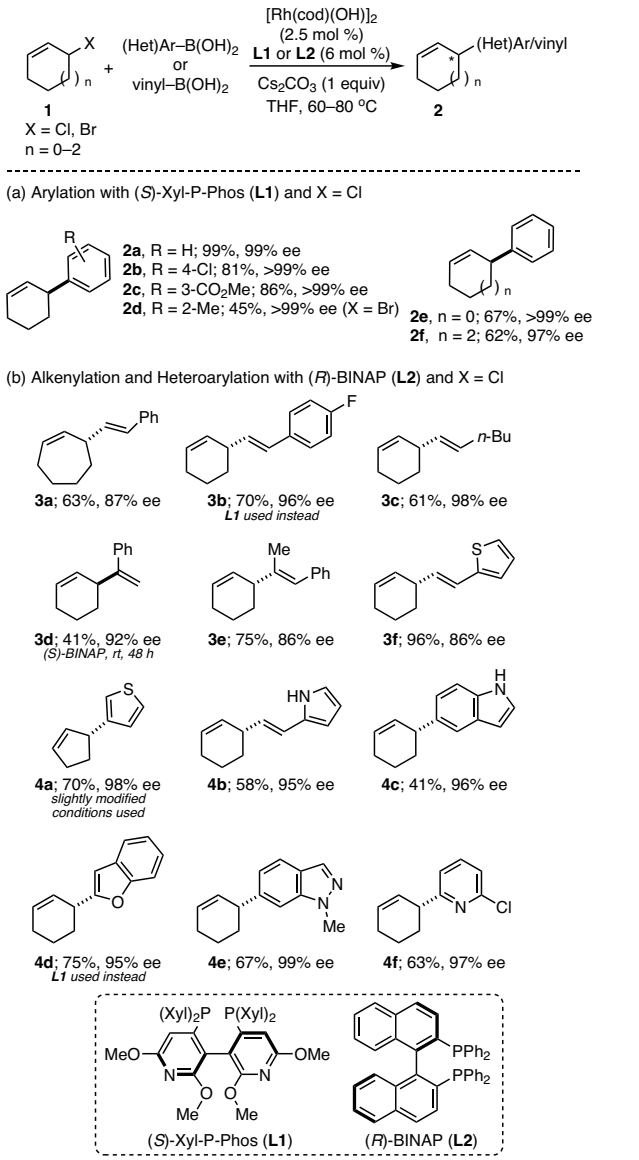


Figure 1. (a) Classical Suzuki–Miyaura cross-coupling reaction. (b) There are fewer reports of enantioselective Suzuki–Miyaura-type cross-coupling methods, where racemic starting materials are converted into enantiomerically enriched products. (c) Our work: asymmetric cross-coupling of (hetero)aromatic boron nucleophiles with racemic or prochiral electrophiles.

Inspired by the pioneering work of Hayashi and Miyaura on the rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to enones,[17] we began exploring the AAA reaction of aryl-, heteroaryl-, and vinylboronic acids with racemic allyl halides under the same reaction conditions. While these conditions did not yield good results, conditions similar to those reported by Lautens and co-workers for the desymmetrization of achiral mesocyclic allylic dicarbonates[18] gave excellent results.[19]

The method utilizes a catalyst generated in situ from $[Rh(cod)OH]_2$ and the bidentate phosphine ligand (*S*)-Xyl-P-Phos (**L1**), with Cs_2CO_3 used as base (Scheme 1).[19] This procedure gives excellent levels of enantioselectivity (generally 94 to >99% ee), is applicable to 5–7-membered rings, and tolerates a broad range of functional groups in the boronic acid cross-coupling partner. Generally good results are obtained with *racemic* allylic chlorides, but in some instances, such as ortho-substituted **2d**, better yields can be achieved using the allylic bromide.

We further developed this reaction to expand the scope of both the allyl halides and the boronic acids. Extending asymmetric addition reactions from arylboronic acids to alkenylboronic acids is not trivial owing to their different electronics, reactivity patterns, and shape. Pleasingly, several alkenyl- and styrenylboronic acids gave good results.[19,20] In most cases, BINAP was the ligand of choice; however, in some cases, better yields and/or enantioselectivities were obtained with **L1** (see **3b**). Our overall observations with these boronic acids is that individual substrates can be optimized, but alkenylboronic acids are so structurally diverse that such optimization is unlikely to lead to a general solution to adding a series of different vinylboronic acids to allyl halides. As expected, changing the stereochemistry of the ligand from (*R*) to (*S*) changed the absolute stereochemistry of the product (see **3d**).

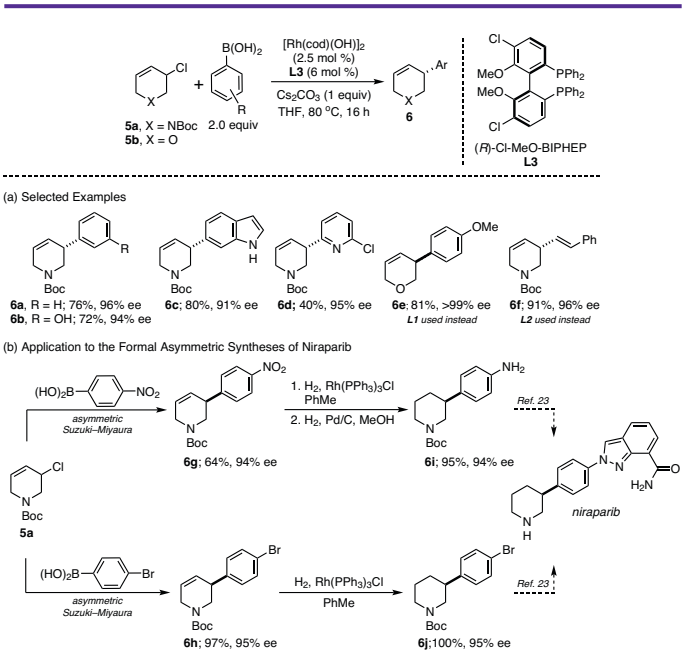


Scheme 1. Selected examples of the rhodium-catalyzed asymmetric allylic arylation, alkenylation, and heteroarylation. *(Ref. 19,20)*

Many bioactive molecules contain heterocycles, and the ability to couple heterocycles in the classical Suzuki–Miyaura reaction has undoubtedly aided its popularity in drug development. Therefore, we wanted to learn how to use heterocycles as coupling partners in rhodium-catalyzed allylic arylations, and both heterocyclic allyl halides and heterocyclic boronic acids were investigated. While we anticipated some difficulty in the

application of heteroarylboronic acids in these reactions (as they are well-known to be difficult cross-coupling partners)[21] our protocol accommodated several heteroarylboronic acids, with enantioselectivities generally >90% being observed.[20] Various heteroaromatic ring sizes (five- and six-membered and bicyclic), basic or acidic sites, and various substitution patterns were tolerated, although steric crowding next to the boronic acid often led to poor results. In addition, minor adjustments to the reaction parameters (temperature, ligand, addition of water, and stoichiometry of catalyst and reagents) for a specific combination of coupling partners gave enhanced results. While free pyridylboronic acid inhibits the catalytic cycle, we found that 2-halopyridines could be used as pyridine surrogates (see **4f**), with the halogen substituent subsequently removed or used for additional functionalization.[20]

Minor alterations of the reaction conditions were sufficient to achieve moderate-to-good results for heterocyclic tetrahydropyridine-based allyl chlorides (±)-**5a** and **5b** (**Scheme 2**, Part (a), **6a–d**).[20] Here, (*R*)-Cl-MeO-BIPHEP (**L3**) was the ligand of choice, and we were pleased to find that even two heterocyclic coupling partners could be coupled (for example, see **6c** and **6d**).

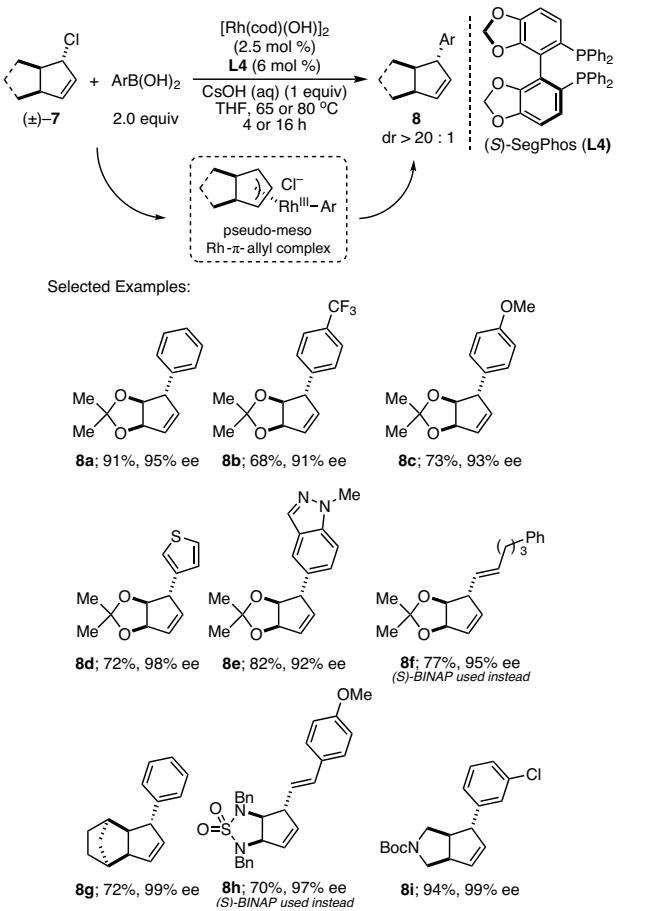


Scheme 2. Rhodium-catalyzed asymmetric allylic arylation with heterocyclic allyl chlorides. (a) Selected scope. (b) Formal asymmetric syntheses of niraparib. *(Ref. 19,20)*

Niraparib (Zujela) is a poly(ADP-ribose) polymerase (PARP) inhibitor and anticancer drug bearing a 3-arylpiperidine core.[22,23] Reported process routes follow either chiral resolution or enzymatic cyclization strategies.[24,25] Our asymmetric Suzuki–Miyaura protocol was used as the key enantio-determining step in three formal syntheses leading to niraparib, which showcases the practicality of our methodology (Scheme 2, Part (b); only two synthetic sequences depicted). We also found that pinacol esters could be employed in place of boronic acids, and, in the case of the coupling with 4-bromophenylboronic acid, better and highly reproducible results were achieved with the pinacol ester on a gram scale.[26]

3. Asymmetric Suzuki-type Coupling of Bicyclic Allylic Chlorides

Prochiral, meso starting materials can be desymmetrized to produce multiple stereogenic centers,[27–30] and we became interested in whether we could control multiple stereogenic centers in cross-coupling reactions with a *racemic* precursor. We chose fused bicyclic racemic allyl chlorides as model substrates and hypothesized that diastereoselective formation of a pseudo-meso η^3 Rh-π-allyl complex followed by enantioselective reductive elimination would set three continuous stereogenic centers in a single step (**Scheme 3**).[31]



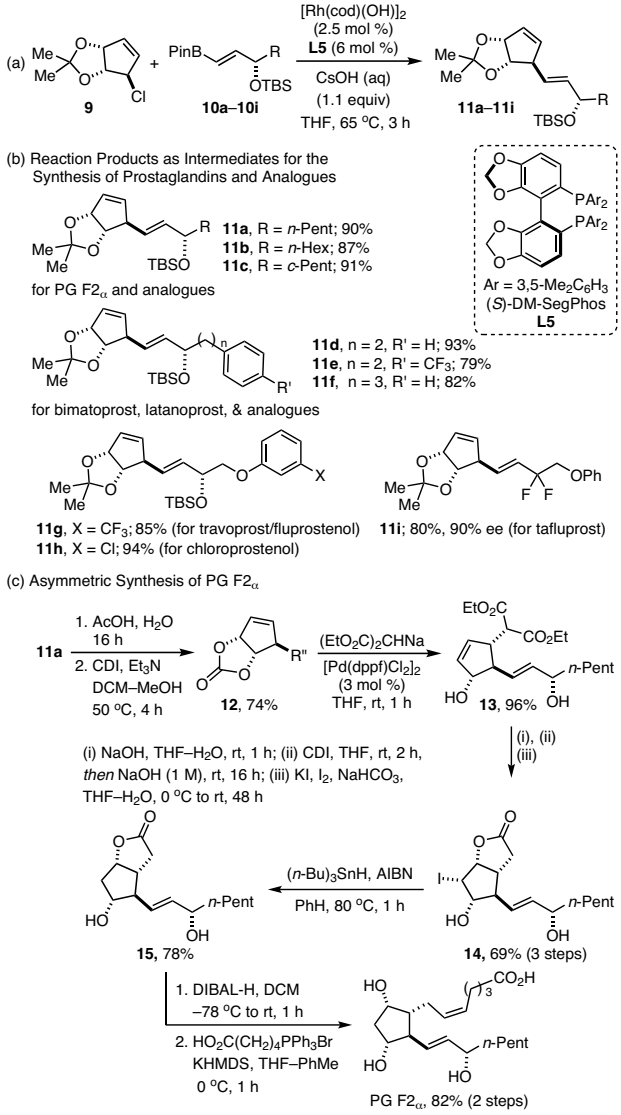
Scheme 3. Rhodium-catalyzed asymmetric allylic arylation with *racemic* bicyclic allyl chlorides. *(Ref. 31)*

Reaction optimization showed that using (*S*)-SegPhos (**L4**) as the ligand gave excellent enantiocontrol of the products.[31] The reaction is highly diastereoselective (dr > 20:1) and proceeds with overall retention of the relative stereochemistry, giving access to functionalized bicyclic cyclopentenes, which can be converted into other five-membered-ring scaffolds

with up to five contiguous stereocenters. Substrates that lack *pseudo*-symmetry gave a mixture of regioisomers, with each regioisomer highly enantioenriched. As observed before, aryl-, heteroaryl-, and alkenylboronic acids give good yields and ee's (Scheme 3, **8a–f**), with all-carbon and nitrogen-containing bicyclic allyl chlorides being suitable precursors (Scheme 3, **8g–i**). Moreover, the reaction could be easily scaled up to produce gram quantities of product.

Using the bicyclic-cross-coupling approach, we developed a strategy to synthesize a number of prostaglandin analogues.[32,33] We envisaged that a diastereo- and enantioselective Suzuki–Miyaura coupling could install the alkenyl side-chain and set the stereochemistry of the cyclopentane core (**Scheme 4**, Part (a)). Although we were aware that stereochemical issues could arise in this sequence due to competitive substrate control when using chiral boronic ester nucleophiles, in the event we found that a variety of side-chains could be added without any adverse effect on the stereochemistry.

Pleasingly, we found that the use of (*S*)-DM-SegPhos (**L5**) in the Suzuki–Miyaura coupling gave the desired cyclopentenyl product bearing three contiguous stereocenters in excellent yield and as a single diastereoisomer (Scheme 4, Part (b), **11a–i**). Compounds **11** should serve as suitable intermediates for the synthesis of PG $F2_\alpha$, bimatoprost, latanoprost, fluprostenol, cloprostenol, and tafluprost. While the relative stereochemistry about the cyclopentene core is substrate-controlled, the absolute configuration about the core is determined by which enantiomer of ligand is used, and thus offers the opportunity to access unnatural prostaglandin stereoisomers if desired. **11i** was used in the catalytic asymmetric synthesis of tafluprost, a prostaglandin drug for the treatment of intraocular pressure in open-angle glaucoma and ocular hypertension,[34,35] while **11a** was utilized in the total synthesis of PG $F2_\alpha$, an oxytocic agent used to induce labour.[36] As shown (Scheme 4, Part (c)) for the synthesis of PG $F2_\alpha$, the cyclic acetal protecting group was converted into a carbonate as a traceless activating strategy for a palladium-catalyzed diastereo- and regioselective allylic alkylation with a malonate nucleophile. The deprotection step also removed the TBS-group on the side chain (not shown), but the potentially sensitive allylic alcohol functionality revealed in this step could be carried through the rest of the synthesis without any obvious ill effects. Subsequent decarboxylation and iodolactonization gave **14**, which was converted into the target PG $F2_\alpha$ in three well-precedented synthetic steps.[33]

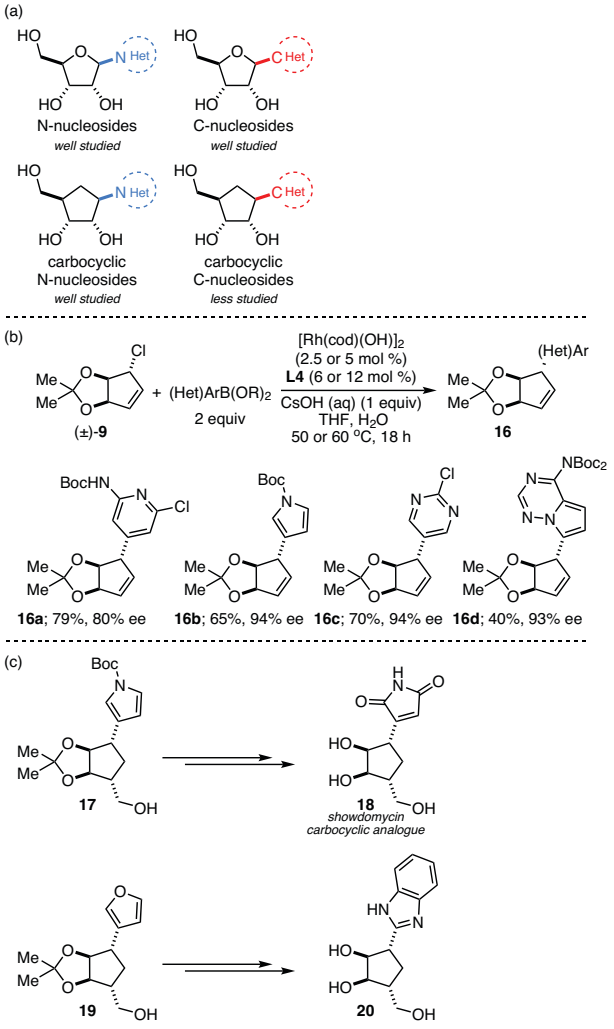


Scheme 4. (a) Model reaction. (b) Intermediates for the synthesis of prostaglandins and PG analogues. (c) Asymmetric synthesis of PG $F2_\alpha$. *(Ref. 32,33)*

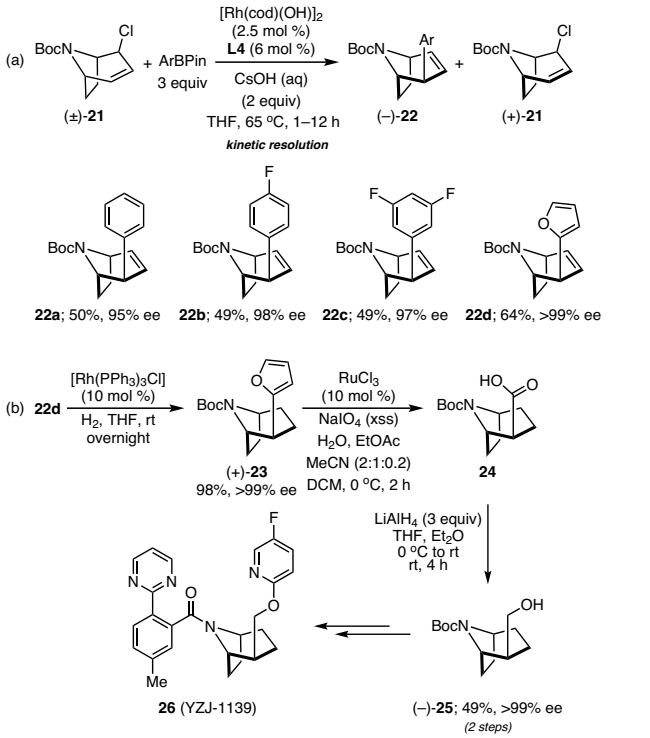
While prostaglandins are a well-established target for synthetic organic chemists, we became interested in developing a route to potentially interesting but largely unknown analogues of important biologically active molecules. A number of nucleoside analogues were of interest as possible antiviral agents during the recent SARS-Covid-2 pandemic, and we reasoned that Suzuki-type coupling of *racemic* bicycles with complex heteroarylboronic acids could provide Carbocyclic C-Nucleosides (CC-Ns; **Scheme 5**, Part (a)). Whilst N-nucleosides, C-nucleosides, and carbocyclic N-nucleosides have been extensively studied,[37-39] CC-Ns are rare, and this is at least partially due to difficulties in their synthesis.[40] For instance, the synthesis of a potential Alzheimer's disease treatment CC-N by Converso et al. is reported in 17 steps from D-(–)-ribose.[41] Informed by the preceding knowledge, we envisaged a strategy to access CC-Ns that uses an asymmetric Suzuki–Miyaura-type reaction as the key C–C bond forming step, followed by hydroborylation-homologation-oxidation. (*S*)-SegPhos (**L4**) proved to effectively enable excellent enantiocontrol in the C–C bond forming SMC, and, subsequently, a range of CC-Ns bearing simple nucleobase moieties were synthesized in moderate-to-excellent yields and good enantioselectivities (Scheme 5, Part (b)).[42] Of note is compound **16d**, synthesized from a boronic ester containing four nitrogen atoms. The SMC reactions were easily scalable to

synthesize multigrams of the products for the synthesis of CC-Ns. It is worth noting that the preparation of some complex boronic acids (and/or their corresponding esters) featuring nucleobases is highly challenging, owing to the synthetic methods producing mixtures of regioisomeric boronic acid derivatives that are difficult to separate, and some are even quite unstable.

Alternatively, CC-Ns could be accessed by coupling relatively simple boronic acids, which could later be transformed into more elaborate units. For example, a C-nucleoside analogue (**18**) of showdomycin; a natural product with antiviral, antibacterial, and antitumor properties; was synthesized by coupling of a pyrroleboronic acid (Scheme 5, Part (c)).[42] Furthermore, the coupling of a furanylboronic acid provides a synthetic handle to be transformed into a carboxylic acid, which can then be elaborated into complex heterocycles (Scheme 5, Part (c), **20**).



Scheme 5. (a). Known nucleoside types and various analogues. (b) Catalytic enantioselective approach to carbocyclic C-nucleosides (CC-Ns) through C–C bond forming SMC (selected examples). (c) Synthesis of a carbocyclic analogue of the natural product showdomycin through post-synthetic modification of pyrrole as well as modification of furan to a benzaimidazole-derived CC-N. *(Ref. 42)*



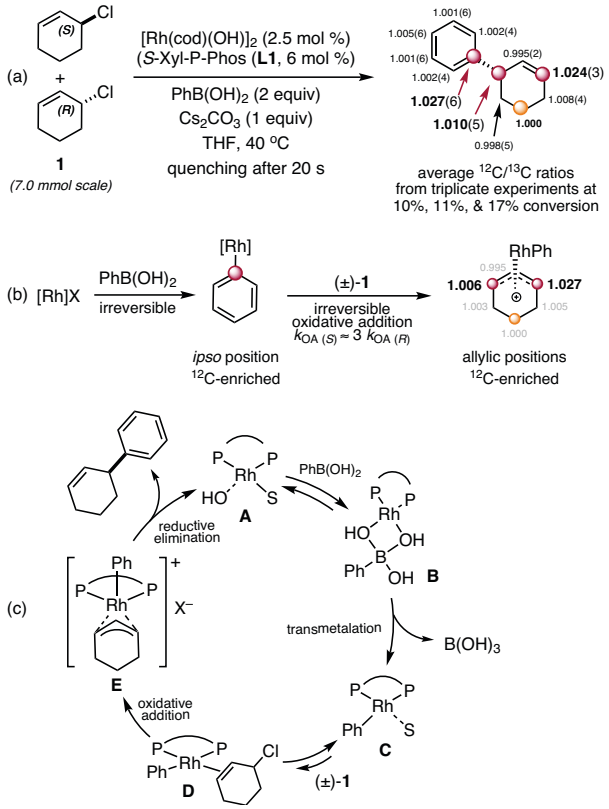
Scheme 6. (a) Rhodium-catalyzed asymmetric allylic arylation with a racemic nortropane-derived allyl chloride (selected examples). (b) Asymmetric formal synthesis of YZJ-1139. *(Ref. 45,46)*

Tropane alkaloids display a wide array of important biological and pharmaceutical activities,[43] yet strategies for preparing enantioenriched tropanes are heavily reliant on the derivatization of natural tropane alkaloids, chiral resolution, and/or synthesis from the chiral pool.[44] Aiming to provide catalytic asymmetric access to these sterically congested bicyclic N-heterocycles, experimentation led us to achieve good enantiocontrol by using (*S*)-SegPhos (**L4**), with the coupling product being isolated as a single diastereomer (typically >20:1). Intriguingly, unlike the previous Dynamic Kinetic Asymmetric Transformation (DYKAT) process, oxidative addition of (+)-**21** either does not occur or does not lead to the same intermediate as addition of its enantiomer, (–)-**21**, and coupling product formation via (+)-**21** is slow. Resolved (+)-**21** was typically isolated in >99% ee in 30–40% yield, rendering this transformation a highly selective kinetic resolution. As before, a wide variety of (hetero)arylboronic acid pinacol esters yielded the desired coupling products typically in 40–50% yields and >94% ee's as single diastereomers (**Scheme 6**, Part (a), **22a–d**).[45,46] Furthermore, the unreacted starting material could be recovered and used in subsequent stereospecific transformations. The synthetic utility of the method was demonstrated in the catalytic asymmetric formal synthesis of YZJ-1139 (**26**), an orexin receptor antagonist, which recently passed phase II clinical trials for insomnia (Scheme 6, Part (b)).[46] The previously reported syntheses of YZJ-1139 relied on preparative high-performance liquid chromatography (HPLC)

separation of the enantiomers or chiral resolution. Using our protocol, we could access enantiopure **25**, a previously reported intermediate in the synthesis of YZJ-1139, from *racemic* **21** in four steps.

4. Mechanistic Investigation of the Rh(I)-Catalyzed Asymmetric Suzuki–Miyaura-type Coupling

Asymmetric allylic additions with racemic electrophiles could occur through several distinct mechanistic pathways, and we aimed to get an in-depth understanding of these rhodium-catalyzed reactions.[47] A key experiment that led to deciphering the mechanism involved the Singleton method[48,49] using natural abundance ^{13}C kinetic isotope effects (KIE). These reactions normally involve running a reaction to high conversion and measuring the $^{12}C/^{13}C$ ratio in the recovered starting material. However, due to technical challenges associated with low-molecular-weight allyl chlorides, we chose instead to determine the $^{12}C/^{13}C$ ratio generated in the coupling product when the reaction was run to low conversion and quantifying $^{12}C/^{13}C$ ratios by quantitative ^{13}C NMR spectroscopy. Suitable results for these experiments could be achieved through running the reactions at 40 °C and quenching after 20 seconds, giving ~10% conversion (**Scheme 7**, Part (a)).[47] KIEs were observed at C-1, C-3, and C-7, (indicated by red dots in Scheme 7, Part (a)), and, when compared to calculated values from several mechanistic scenarios, they indicated a DYKAT mechanism involving irreversible anti oxidative addition of both enantiomers to a common Rh complex (Scheme 7, Part (b)). The combination of isotope labelling experiments, theoretical calculations, and competition experiments—alongside detailed kinetic investigations—allowed us to propose a mechanism that is consistent with the evidence gathered (Scheme 7, Part (c)): A monomeric active catalytic species (**A**) reacts with the arylboronic acid to form a Rh–aryl intermediate (**C**). Irreversible oxidative addition of the two enantiomers of allyl chloride gives a common pseudosymmetric η^3 complex (**E**), where one enantiomer of **1** reacts faster than the other. The subsequent reductive elimination step is enantio-determining and sets the configuration of the product, which is determined by the absolute stereochemistry of the ligand, (*S*)-Xyl-P-Phos (**L1**). It is important to note that, in the case of fused bicyclic substrates, whilst the mechanism is largely the same as for the monocyclic substrates, syn oxidative addition is observed in preference to anti oxidative addition for steric reasons. Reductive elimination remains in control of the absolute stereochemistry, but oxidative addition is the diastereo-determining step in the cycle.



Scheme 7. (a) Natural abundance ^{13}C kinetic isotope effect (KIE) experimental results (standard errors in parenthesis). (b) Combination of elementary KIEs. A ratio of 3.3:1 for the oxidative addition of the (*S*) over the (*R*) enantiomer of the starting 3-chlorocyclohexene gives the observed level of ^{12}C enrichment. (c) Simplified proposed catalytic cycle. *(Ref. 47)*

5. Asymmetric Arylation with Activated Alkenes

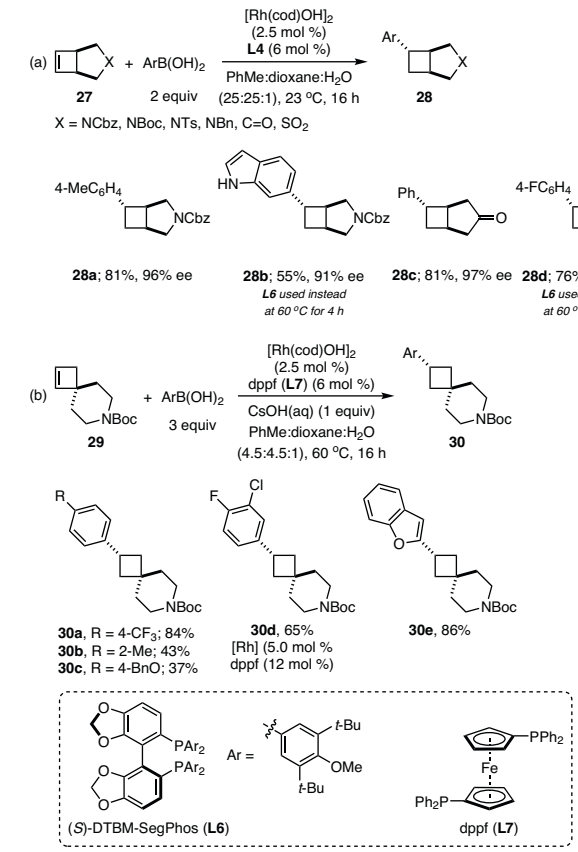
Having developed a series of deracemizing cross-coupling reactions with allyl halides, we pondered whether we could expand cross-coupling-type arylation reactions to activated alkene electrophiles. While the functionalization of activated alkenes is well described, particularly in the case of those activated through ring strain, the use of aryl-based nucleophiles in these transformations is remarkably underrepresented.[50–55] We envisaged that an asymmetric cross-coupling between cyclobutenes and arylboronic acids, initiated by a Rh-catalyzed carbometallation, would form chiral cyclobutanes. Asymmetric carbometallation was previously unknown for unactivated cyclobutenes, due to its comparatively low olefinic strain (1.9 kcal mol^{-1}), limiting synthetic methods to complex chiral cyclobutanes.[56–58]

Initial experimentation revealed that coupling bicyclic cyclobutenes with arylboronic acids using rhodium catalysis is indeed possible under mild, base-free conditions. Reaction optimization showed that (*S*)-SegPhos (**L4**) or (*S*)-DTBM-SegPhos (**L6**) (depending on the bicyclic backbone) gives excellent enantiocontrol, enabling access to a range of arylated cyclobutanes in good yields and enantioselectivity (**Scheme 8**, Part (a), **28a–d**).[59] A variety of boronic acids are tolerated, including aryl and heteroaryl nucleophiles, with electron-donating substituents promoting higher yields, and ortho substitution unsurprisingly resulting in modest yields. Modifications to the bicyclic backbone, including changes to the nitrogen protecting group, or substituting the pyrrolidine nitrogen with a carbon or sulfur atom (**Scheme 8**, Part (a), **28c**) are well tolerated.

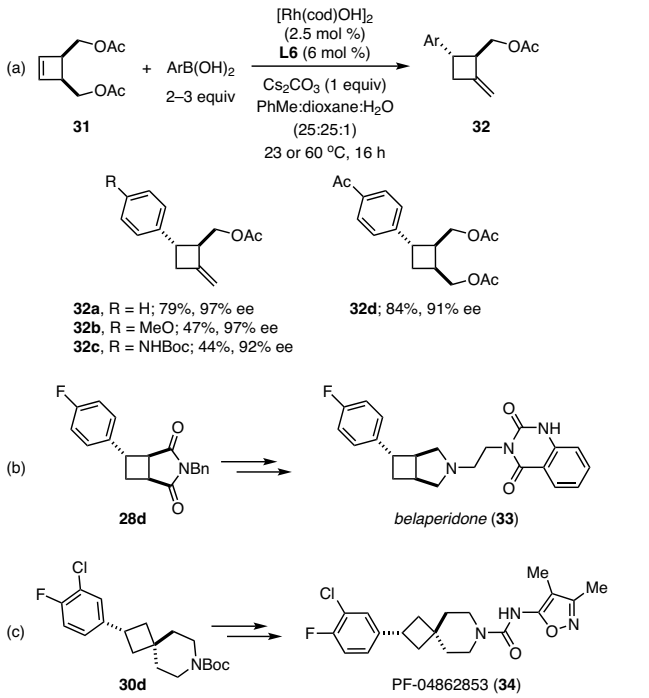
Small changes to the reaction conditions were sufficient to achieve arylation of non-symmetrical spirocyclic cyclobutenes (Scheme 8, Part (b)), giving the achiral products with complete regioselectivity. In this case, an achiral Rh/dppf catalyst in combination with CsOH at 60 °C was used to produce a range of arylated and heteroarylated products (Scheme 8, Part (b), **30a-e**).

When employing cyclobutenes bearing pendant leaving groups (**Scheme 9**, Part (a), **31**), elimination of one leaving group generated a cyclobutene product bearing two stereogenic centers and an exocyclic alkene (Scheme 9, Part (a), **32**). These products could be accessed in excellent enantioselectivity from a range of electron-rich boronic acid starting materials. Intriguingly, the use of electron-deficient boronic acids gave rise to rhodoarylation products (Scheme 9, **32d**) instead of the elimination products, suggesting boronic acid controlled mechanistic divergence after carbometallation.

The method was applied in the enantioselective formal synthesis of belaperidone (**33**) from **28d**[60–63] and the formal synthesis of the fatty acid amide hydrolase inhibitor drug candidate PF-04862853 from **30d** (Scheme 9, Parts (b) and (c)).[64] The cross-coupling can easily be scaled up to gram quantities, and we were able to decrease the catalyst loading from 2.5 to 0.5 mol % of dimeric $[Rh(cod)OH]_2$.

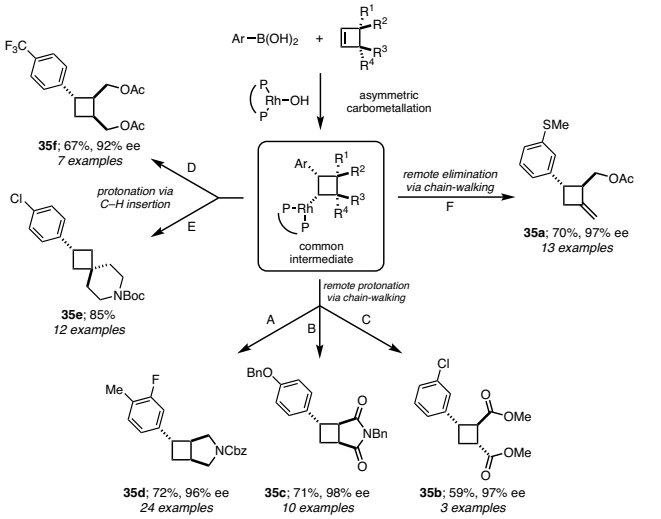


Scheme 8. (a) Hydroarylation of cyclobutene derivatives (selected examples). (b) Hydroarylation of spirocyclic cyclobutenes (selected examples). *(Ref. 59)*



Scheme 9. (a) Divergent arylation of cyclobutenes bearing remote leaving groups (selected examples). (b) Formal syntheses of belaperidone and PF-04862853. *(Ref. 59)*

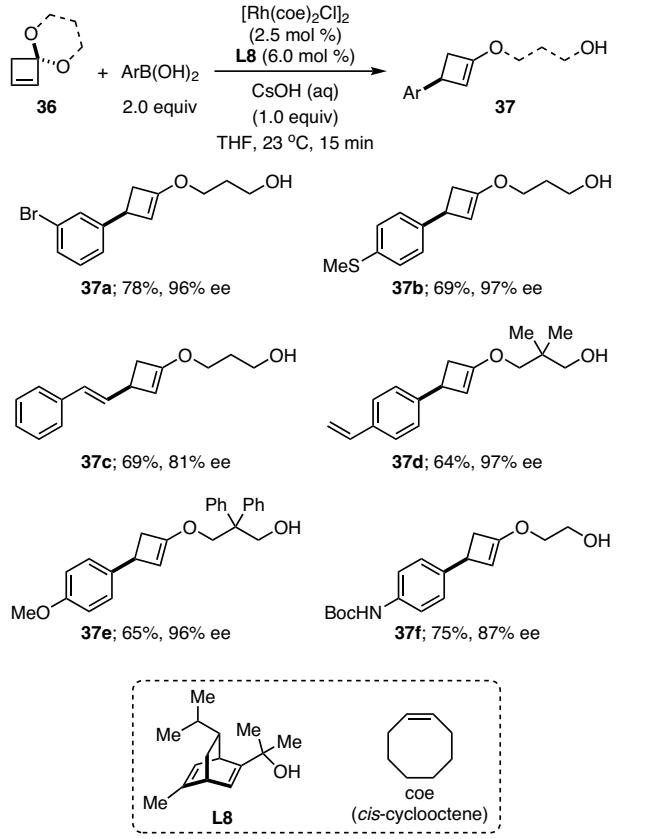
While these Rh-catalyzed cross-couplings give a range of divergent products, depending on which cyclobutenes are used as starting materials, we found that deuterium labelling experiments helped understand the pathways observed. All the reactions share a common cyclobutyl-rhodium complex as the catalytic intermediate, which is formed in an enantioselective carbometallation step (**Scheme 10**).[59]



Scheme 10. Asymmetric carbometallation to a common cyclobutyl–rhodium intermediate that affords different arylated products. *(Ref. 59)*

Depending on the cyclobutene, this common intermediate can undergo either chain-walking or C—H insertion. Protonation or elimination can then serve as a terminating mechanism, enabling the divergent reactivity observed with the various cyclobutene substrates. *Meso*-bicyclic and monocyclic β,γ-unsaturated carbonyl cyclobutenes undergo terminating protonation remote to the addition site via chain-walking (Scheme 10; Steps A, B, and C). An alternative protonation pathway via C—H insertion enables reductive Heck reactions to monocyclic cyclobutenes (Scheme 10; Step D), with high regioselectivity obtained for achiral products from non-symmetrical cyclobutenes (Scheme 10; Step E). When cyclobutenes bearing pendant leaving groups are employed, the cyclobutyl–rhodium intermediate undergoes chain-walking and subsequent β-oxygen elimination to give the exocyclic alkene product (Scheme 10; Step F). However, when using electron-deficient boronic acids, an alternative C—H insertion process takes place (which is faster for electron-deficient boronic acids) followed by protonation to give the hydroarylation product instead of the elimination product (Scheme 10; Step D).

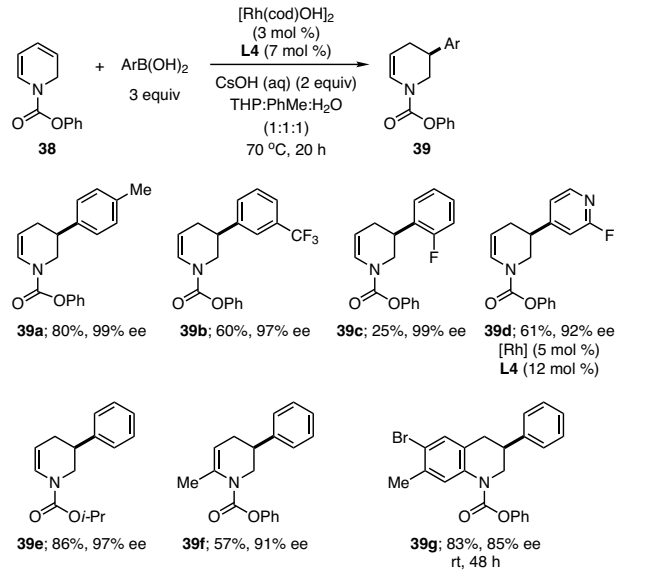
It occurred to us that a rhodium chain-walking/elimination pathway may allow us to access products of the same type that would arise from asymmetric 1,4-addition to cyclobutenone, which is itself quite unstable.[65] Furthermore, in a conjugate addition to cyclobutenone, an achiral product would be obtained upon protonation of the resulting α-enolate. We found that carbometallation of the double bond of **36** (**Scheme 11**), followed by β-oxo elimination, results in the formation of an enol ether with retention of the chiral information.[66] In contrast to the methods presented above, diene ligands gave the best results—with **L8** providing good yields and enantioinduction in room temperature reactions—over 15 minutes. A range of arylboronic acids can be used, typically achieving 65–93% yields and enantioselectivities typically in the range of 91% to 98% ee. Alkenylboronic acids can also undergo the reaction in good yields, but with more modest ee's (79–81% ee). Changes to the acetal were also well tolerated, with dimethyl and diphenyl substitutions on the acetal ring having no impact on yield or enantioselectivity (Scheme 11, **37d, 37e**). The reaction could be easily scaled up to synthesize gram quantities of the products.



Scheme 11. Asymmetric arylation of cyclobutenone ketals (selected examples). *(Ref. 66)*

Dihydropyridines are conjugated dienes that can be synthesized in a single step from pyridines. Having demonstrated that catalytic asymmetric carbometallation is possible with cyclobutenes despite their low olefinic strain, we next considered dihydropyridines as a starting point for the facile construction of enantioenriched tetrahydropyridines and, after further reduction, 3-substituted piperidines.

Reaction optimization showed again that (*S*)-SegPhos (**L4**) and CsOH give good yields and high enantioselectivities (**Scheme 12**);[67] however, critical to observing good yields in this reaction is the use of biphasic solvent mixture, in most cases THP/PhMe/H_2O.



Scheme 12. Rh-catalyzed hydroarylation of dihydropyridines leading to tetrahydropyridines (selected examples). *(Ref. 67)*

Most of the phenylboronic acids we examined furnished products with ee's ≥ 96% and yields of 50–80%, but ortho-substituted boronic acids do not perform well in these reactions. Alkenylboronic acids gave good yields and excellent

enantioselectivity. 2-Halo pyridylboronic acids can also be used in the reaction, where we believe the halogen reduces the Lewis basicity of the pyridine nitrogen (e.g., **39d**). Changes to the dihydropyridine itself were well tolerated, with various carbamate groups such as in **39e** having no detrimental effect on either enantioselectivity or yield. Dihydroquinolines also undergo the cross-coupling, although lower temperatures need to be used to minimize an observed reduction in enantioselectivity (**39g**). The reaction can be scaled up to afford gram-scale quantities of the products, with no impact on yield or enantioselectivity.

6. Summary and Outlook

In the field of asymmetric catalysis, developing reaction systems that can exploit the generality and practical simplicity of the Suzuki–Miyaura cross-coupling but yield enantiomerically enriched three-dimensional products with sp^3 centers has been a longstanding challenge. We have developed a number of asymmetric Rh-catalyzed cross-couplings of sp^2-hybridized boronic acid derivatives with allylic (pseudo)halides and mildly activated olefins. We have also demonstrated the applicability of these new methodologies on scales that are relevant to "real-world" process settings by scaling up an asymmetric cross-coupling reaction to give over 100 g of product.[68] In that work, a racemic bicyclic substrate was coupled with furan-2-boronic acid pinacol ester using standard equipment available in an academic laboratory. The simplicity and typical efficiency of the reactions described above—both in terms of practical efficiency and atom economy—make these reactions an important step forward in developing useful asymmetric sp^3–sp^2 coupling reactions. There are, however, many major challenges that remain in developing such reactions before they can be widely used in a variety of transformations, in particular, the challenge of developing regio- and enantioselective reactions of acyclic and non-symmetrical acyclic racemic allyl halides. Developing and applying such methods that do not involve simple pseudo-symmetrical substrates offer many exciting opportunities in the future.

7. References

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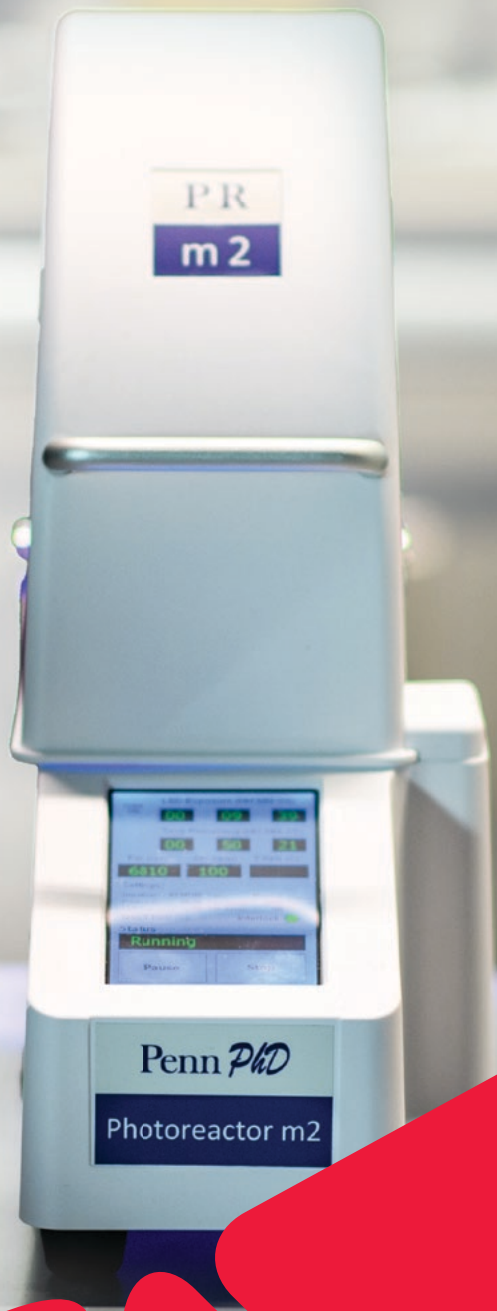

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Ylide-Substituted Phosphines in Palladium-Catalyzed Coupling Reactions


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Abstract. Palladium-catalyzed coupling reactions have become an indispensable tool for the formation of complex organic molecules. Many advances have benefited from the development of new, sophisticated ligands, particularly electron-rich organophosphines. This review provides an overview of the development of these phosphines for application in palladium-catalyzed cross-couplings. It focuses on recently reported ligands with donor capacities beyond tri(*tert*-butyl)phosphine, in particular the highly electron-rich, ylide-substituted phosphines developed in our group.

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1. Introduction

Palladium-catalyzed coupling reactions have developed into one of the most important methodologies for the construction of carbon–carbon and carbon–heteroatom bonds. Owing to the reliability of many coupling protocols, their broad substrate scope, mildness, and efficiency, this methodology has become indispensable for the formation of complex molecules such as pharmaceuticals, agrochemicals, and organic materials. Accordingly, the pioneering work done in this area by Richard F. Heck, Akira Suzuki, and Ei-ichi Negishi was recognized with the awarding of the Nobel Prize to those three in 2010.[1] Since then, the field has seen continuous advances many of which have been connected with the development of new, more effective catalysts. Although many transition metals have been shown to promote coupling reactions, palladium remains in general the most effective and hence most applied metal in this type of chemistry.

Organophosphines are the dominant class of ligands in this area. The tuning of their electronic and steric properties to accelerate the rate-limiting step within the catalytic cycle has enabled many advances. Early work has focused on the use of simple arylphosphines, with PPh_3 remaining one of the most applied phosphine ligands for the coupling of aryl iodides and bromides owing to its cost-effectiveness. Further

improvements were achieved by the use of diphosphines; followed by electron-rich, bulky alkylphosphines, which currently dominate advanced applications such as the coupling of aryl chlorides and triflates.[2] The search for strongly electron-donating monophosphines started with the use of tri(*tert*-butyl)phosphine, P(*t*-Bu)$_3$, introduced by Fu in 1998.[3] Since then, various types of alkylphosphines have been reported and are nowadays commercially available. In this review, we focus on phosphines exceeding the donor strength of P(*t*-Bu)$_3$, concentrating on our previously reported ylide-functionalized phosphines, which we discuss in the context of the ongoing development of electron-rich ligands and their impact on coupling chemistry.

2. Ligand Properties and the Catalytic Cycle

2.1. The Catalytic Cycle of Palladium-Catalyzed Coupling Reactions

The development of new, more effective catalysts relies on understanding the underlying mechanism of a given reaction. In general, coupling reactions are thought to proceed through a catalytic cycle involving oxidative addition, transmetalation, and reductive elimination (**Figure 1**).[4] It is noteworthy that the effectiveness of the formation of the active catalyst may also decisively affect the efficiency of a reaction protocol. Bulky alkylphosphines usually form monoligated palladium complexes LPd as active species. To effectively produce these species, various well-defined precatalysts have been designed and repeatedly shown to improve reaction outcomes.[5]

Depending on the specific transformation, the substrates employed, and the reaction conditions, each step of the cycle may be rate-limiting. Vast kinetic studies of the impact of catalyst properties on the reaction rate have revealed fundamental structure–activity relationships. These relationships demonstrated that opposing ligand properties favor different steps within the catalytic cycle, which cannot be moderated by a single ligand structure. For example, electron-rich ligands in general facilitate the oxidative addition step but slow down the reductive elimination step. It is worth noting that anionic pathways have been also proposed.[6]

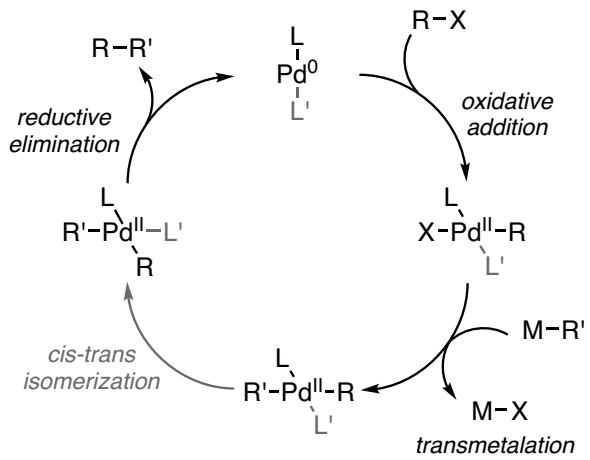


Figure 1. Generally accepted catalytic cycle of palladium-catalyzed coupling reactions. L usually refers to a monophosphine or N-heterocyclic carbene (NHC). L′ may be identical to L, a weakly bound solvent molecule, or other ligand present in the reaction mixture. *(Ref. 4)*

2.2. Ligand Electronic Properties

To compare the electronic properties of different phosphine ligands, a reliable scale for their quantification is required. A first general measure of the ligand donor strength was introduced by Tolman.[7] The so-called "Tolman electronic parameter" (TEP) was determined by measuring the symmetric CO stretching frequency of LNi(CO)$_3$ complexes, and remains the most often used parameter for donor-strength quantification to date. Tolman employed tri(*tert*-butyl)phosphine, the most strongly donating phosphine known at that time, as a reference to define the contribution of each substituent at phosphorus to the overall donor strength. The *t*-Bu group was assigned a value of $\chi = 0$, with less donating groups having values greater than one. Due to the limited electron-donating ability of alkyl groups, P(*t*-Bu)$_3$ remained the most donating phosphine for a long time. It is thus not surprising that this ligand too became an important player in the advancement of palladium-catalyzed cross-couplings.[3]

Besides TEP, many other electronic parameters have been developed over the past decades, with few of them finding popularity comparable to that of TEP itself.[8] Noteworthy are other carbonyl complexes, such as [LRh(acac)CO] or [LIr(CO)$_2$Cl], that were introduced as substitutes to the toxic nickel tetracarbonyl. The values obtained here were correlated with the nickel scale, thus providing a large set of data for phosphines as well as other donor ligands. Besides other spectroscopic, crystallographic, and electrochemical parameters, computationally derived descriptors have become popular in recent years due to their facile determination and possible use for property predictions.[9] This is important for catalyst design based on linear free energy relationships established through machine learning and statistical models rooted in experimental data.

2.3. Ligand Steric Properties

Besides its electronic properties, the steric profile of a ligand plays a likewise important role in catalyst design. In general, bulky phosphines are particularly effective, since the increased steric demand facilitates the formation of monoligated palladium species, which are often assumed to be the active species in cross-coupling catalysis. As in the case of the electronic properties, various descriptors have been developed to quantify the ligand spatial requirements, allowing comparison of different catalyst structures. Some of the often-employed steric descriptors are the Tolman cone angle,[4] the percent buried volume,[10] or the Sterimol parameters.[11] However, not only the plain steric demand has been reported to be a decisive factor, secondary metal–ligand interactions have also been shown to increase catalyst stability and influence the selectivity of reactions. Prominent examples

are the Buchwald-type biarylphosphines, in which the lower aryl group can engage in additional arene–metal interactions. Furthermore, conformational flexibility decisively influences the true steric demand of a ligand and can be beneficial in accommodating substrates with different steric profiles at the metal center, thus making ligand design a delicate task.[12]

3. The Development of Electron-Rich Phosphine Ligands

3.1. Trialkylphosphines beyond P(*t*-Bu)$_3$

The historic benchmark for electron-rich phosphines is tri(*tert*-butyl)phosphine (**Figure 2**, Part (a)). It served as a versatile ligand in various palladium-catalyzed coupling reactions, including the Suzuki–Miyaura, Heck, and Sonogashira reactions, as well as the Buchwald–Hartwig aminations.[13] The preparation of the even more electron-donating tris(1-adamantyl) phosphine (PAd$_3$) proved to be challenging, since traditional approaches involving Grignard reagents were unsuitable. Therefore, initially, unsymmetrical diadamantylphosphines came into play,[14] with Beller's PAd$_2$(*n*-Bu) (commercially known as cataCXium® A) becoming the most popular and applied derivative.[15] In 2016, Carrow finally succeeded in the synthesis of PAd$_3$ via an electrophilic approach and thus could confirm the increased donor capacity of the adamantyl group compared to the *tert*-butyl one.[16] Based on a TEP value of 2052.1 cm^{-1} for PAd$_3$, a substituent increment of χ_{Ad} = −1.3 cm^{-1} was calculated.

That tertiary alkyl substituents do not per se lead to high donor strengths was demonstrated very recently by Perry and Schley.[17] Introduction of bicyclo[1.1.1]pentyl groups as in PBcp$_3$ led to a TEP value of only 2061.0 cm^{-1} as a consequence of the high ring strain and the increased s-character in the P—C bonds.

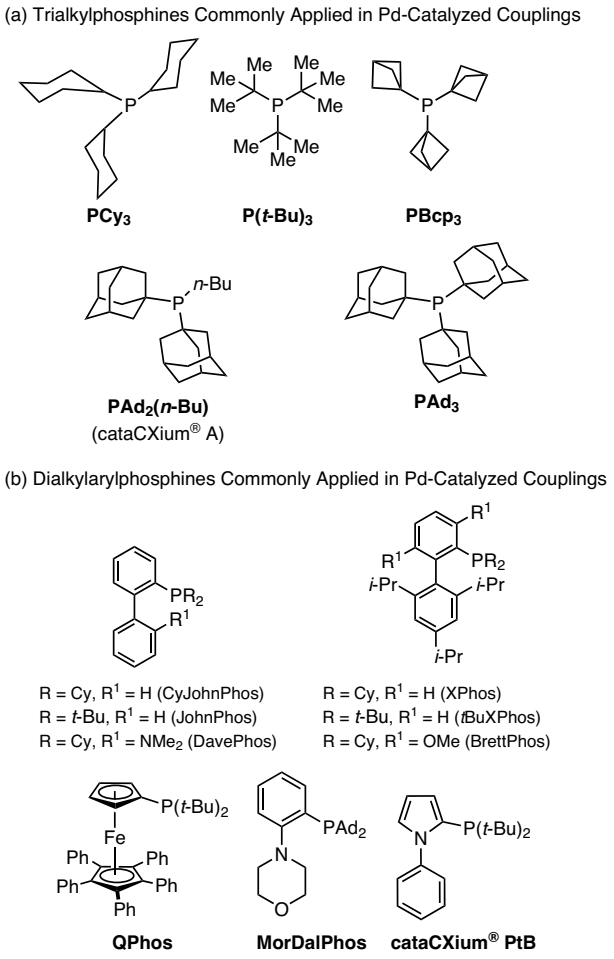


Figure 2. Selected examples of (a) trialkylphosphines and (b) dialkylarylphosphines commonly employed in palladium-catalyzed cross-couplings. PBcp$_3$ = Tris(bicyclo[1.1.1]pentyl)phosphine.

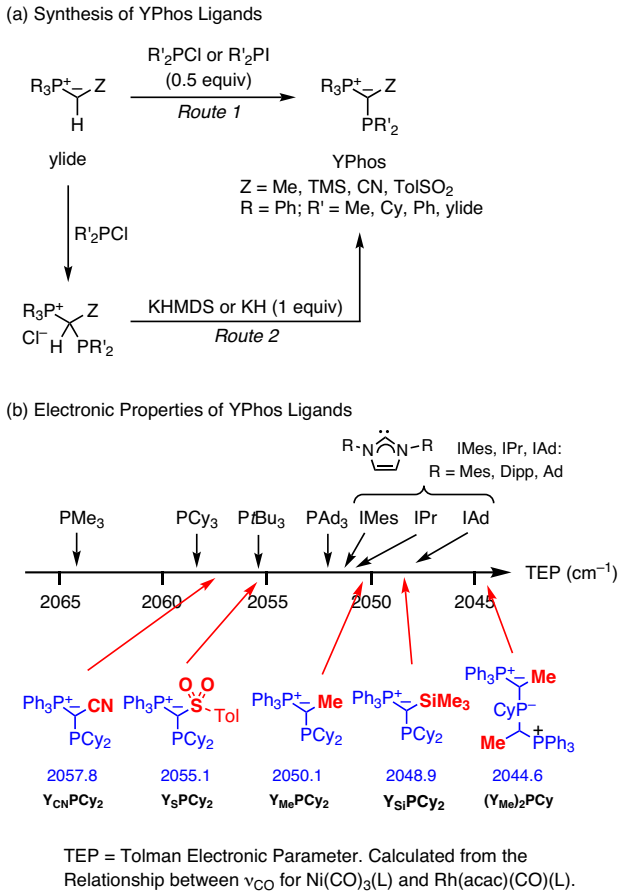
3.2. Biarylphosphines

Due to limitations in increasing the donor ability of trialkylphosphine ligands, dialkylarylphosphines emerged as alternative ligand structures (Figure 2, Part (b)). In this group of ligands, the aryl substituent was utilized to introduce steric bulk and to fine-tune the electronic properties. Within this group, the most notable subgroup is the dialkyl*biaryl*phosphines pioneered by Buchwald. Over the years, a wide range of ligands with various substitution patterns at the biaryl moiety have been prepared and applied in various palladium-catalyzed processes, often setting new standards in terms of activity and selectivity.[18] This was not only attributed to the electronic properties of these ligands, but also to their spatial properties, in particular the propensity of the biaryl moiety to shield one side of the metal center and to stabilize the low-coordinate metal species (LPd) through additional secondary interactions with the lower aryl group (or donor groups attached).[19] The concept of stabilizing reactive intermediates within a catalytic cycle through similar structural motifs has been explored by various research groups. Other prominent subgroups of dialkylarylphosphines are the DalPhos ligand systems introduced by Stradiotto and co-workers, Hartwig's QPhos ligand, and Beller's cataCXium® PtB.[20]

3.3. Ylide-Functionalized Phosphines

Owing to the limited donor strength of alkyl groups, other molecular design strategies are required to further increase the donor capacity of phosphines.[21] Given our previous work on the use of ylides as donor substituents to stabilize electron-deficient main group compounds,[22] we used this strategy for the preparation of a new family of highly electron-rich phosphines. These ylide-functionalized phosphines (YPhos) are easily accessible on a multigram scale via a high-yielding and highly modular protocol utilizing inexpensive starting materials (**Scheme 1**, Part (a)).[23] Variation of the phosphine and phosphonium moiety as well as the backbone substituent Z allow tuning of the ligand steric and electronic properties. Due to the formal negative charge next to the phosphine group, YPhos ligands are in general highly electron-rich. This was confirmed by determination of the Tolman electronic parameters, showing that YPhos ligands cover a range of donor strengths, including donor capacities usually only reached with N-heterocyclic carbenes (Scheme 1, Part (b)). The ylide groups

covered substituent increments similar to that of tert-butyl (χ = 0) up to a highly negative value of χ_{ylide} =–7.4.[23]



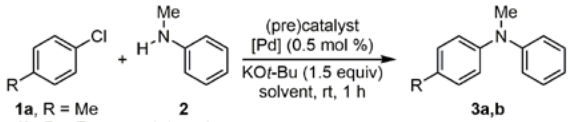
Scheme 1. (a) General synthesis of ylide-functionalized phosphines, and (b) quantification of their donor properties measured by the Tolman electronic parameter (TEP). *(Ref. 23)*

Despite their high donor capacity, the initially prepared YPhos ligands with a PPh_3 phosphonium group were only efficient in gold catalysis,[24] while being incompatible with palladium-catalyzed coupling conditions due to a facile P—C_{Ph} bond cleavage. This initial limitation was circumvented by introduction of a PCy_3 group, which, due to the increased P—C(sp^3) bond strength, was stable under palladium catalysis conditions. Therefore, only these PCy_3-substituted YPhos ligands will be discussed in the following sections.

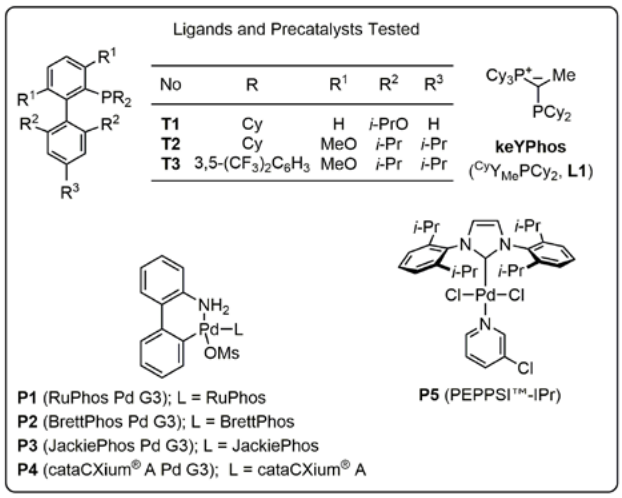
4. YPhos in Palladium-Catalyzed C–N Coupling Reactions

4.1. Initial Coupling Experiments

Given the high donor strength of the YPhos ligands, our group, in collaboration with Gooßen's group, applied them early on in Buchwald–Hartwig aminations, a widely used cross-coupling reaction in industry owing to the importance of aryl- and alkylamines in agrochemicals, natural products, and pharmaceuticals.[25] We also expected to observe a high activity in the coupling of aryl chlorides under mild reaction conditions. Indeed, the first PCy_3-substituted ligand, which we later named keYPhos (**L1**), in combination with Pd_2dba_3 as palladium source, showed high catalytic performance at low catalyst loadings of 0.5 mol % at room temperature and in very short reaction times (**eq 1**).[26] A broad substrate scope was realized for a multitude of aryl halides and aryl- as well as alkylamines. No other state-of-the-art catalyst–ligand combination (**T1–T3, P1–P5**) performed as well in the coupling leading to diarylamine **3** under these reaction conditions.



R	(Pre)catalyst	Solvent	Yield
Me	**L1**•Pd_2dba_3	THF	95%
Me	**L1**•Pd_2dba_3	dioxane	99%
F	**L1**•Pd_2dba_3	THF	83%
F	**P1–P5**	THF	<1%
F	**T1–T3**•Pd_2dba_3	THF	<1%

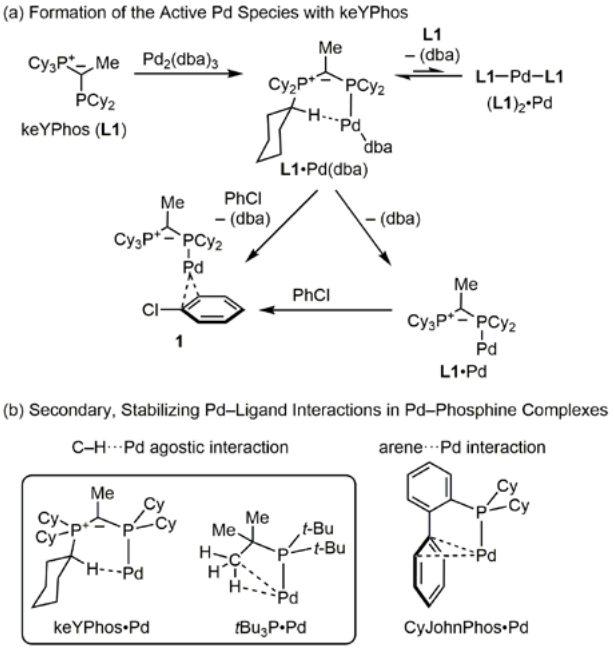


eq 1 *(Ref. 26)*

4.2. Mechanistic Considerations

To understand the efficiency of the keYPhos–palladium catalyst, and to further develop this ligand class for broader applications, we performed mechanistic studies in comparison to P(*t*-Bu)$_3$ and CyJohnPhos (see Figure 2). We focused initially on elucidating the nature of the catalytically active palladium species.[27] KeYPhos quickly formed the monophosphine complex, LPd(dba) when treated with Pd_2dba_3 (**Scheme 2**, Part (a)). This complex features an additional stabilizing C—H···Pd agostic interaction due to a cyclohexyl C—H bond in the phosphonium group pointing towards the metal center (Scheme 2, Part (b)). This agostic interaction is energetically more favorable than in P(*t*-Bu)$_3$, in which the *tert*-butyl groups and hence the C—H bonds point away from the

metal center.[28] This efficient formation and enhanced stability of the LPd species is important for a fast reaction initiation and for minimizing catalyst degradation. The observed lower catalytic activity of P(*t*-Bu)$_3$ and CyJohnPhos under the reaction conditions was mostly attributed to the hampered formation of the catalytically active species, LPd, from these ligands and Pd_2dba_3.



Scheme 2. (a) Formation of Pd(0) complexes with keYPhos. (b) Secondary, stabilizing metal–ligand interactions in selected phosphine–palladium complexes. *(Ref. 27)*

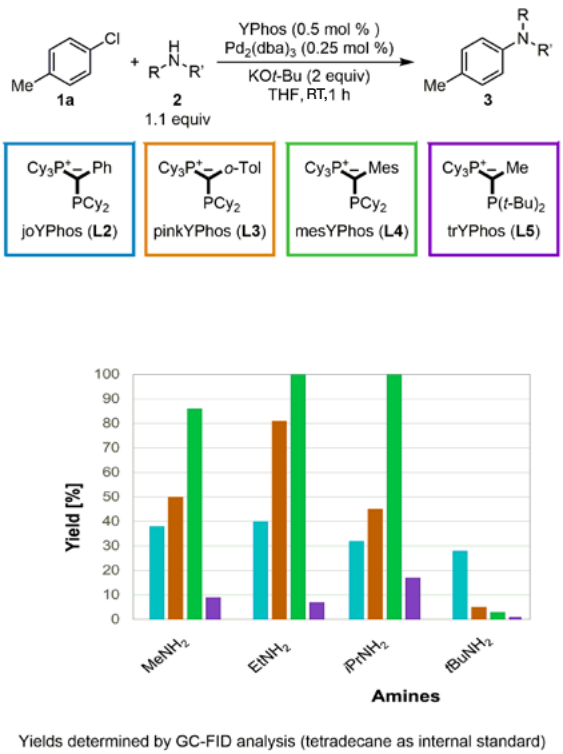
Interestingly, despite its steric bulk, keYPhos still forms the bisligated palladium species, (**L1**)$_2$Pd, which is not catalytically active and hence would be detrimental to catalysis. Yet, the formation of this L_2Pd species is slow and thus not, or only minimally, occurring under the catalysis conditions. This was confirmed by a crystal structure analysis of the (**L1**)$_2$Pd complex, which features longer Pd—P bonds compared to those of reported L_2Pd species formed from such ligands as P(*t*-Bu)$_3$. The longer Pd—P bonds indicate that the two ligands just fit onto the metal center. This is possible because of the flexibility of the P—C—P linkage, which, through partial widening, compensates for the steric bulk of the keYPhos ligand.

Besides facile formation of the catalytically active species, **L1**•Pd, computational studies revealed low activation barriers for all steps within the catalytic cycle for the cross-coupling of phenyl chloride with piperidine in the presence of keYPhos–Pd(dba), reflecting the fast reaction rate observed experimentally. This was ascribed to the high donor strength of the YPhos ligand facilitating the oxidative addition step and to the steric bulk of keYPhos together with the flexibility of the P—C—P angle. This flexibility was found to be important throughout the catalytic cycle since it allows facile coordination of the amine to the oxidative addition complex as well as a smooth reductive elimination of the arylamine. Kinetic studies revealed the oxidative addition step to still be rate-limiting, suggesting that further enhancement of the ligand donor strength should allow for an even faster catalysis.

4.3. Selective Monoarylation of Primary Amines

While the first catalytic studies with the keYPhos–Pd catalyst showed good results for the coupling of secondary alkylamines with aryl chlorides; primary and small, unbranched alkylamines did not undergo the coupling as well. This was due to selectivity issues with respect to mono- and diarylation as well as a possible β-hydride elimination and competing imine formation. Very bulky ligands are in general required to solve these selectivity issues. Yet, this usually comes at a price, as known literature protocols either require harsh reaction conditions, exhibit a limited functional group tolerance, or necessitate the use of highly sophisticated, expensive ligands.

To probe whether a simple backbone modification in the YPhos ligands could improve the selectivity and activity reached thus far with keYPhos, other YPhos ligands incorporating aryl-substituted ylides were prepared: joYPhos (**L2**), with a phenyl group, and pinkYPhos (**L3**) and mesYPhos (**L4**), with a sterically more demanding ortho-tolyl and mesityl backbone, respectively (**eq 2**).[29,30] joYPhos showed generally higher



eq 2 *(Ref. 29,30)*

activities than keYPhos with secondary amines. In combination with the *tert*-butylindenyl palladium chloride precursor, this ligand enabled unprecedented reaction rates of more than 10,000 h^{-1} for the room temperature coupling of aryl chlorides. In contrast, pinkYPhos and even more so mesYPhos proved to be beneficial for the coupling of small primary alkylamines. Even methyl- and ethylamine were successfully monoarylated. The steric limit of these two ligands was *tert*-butylamine and secondary amines.

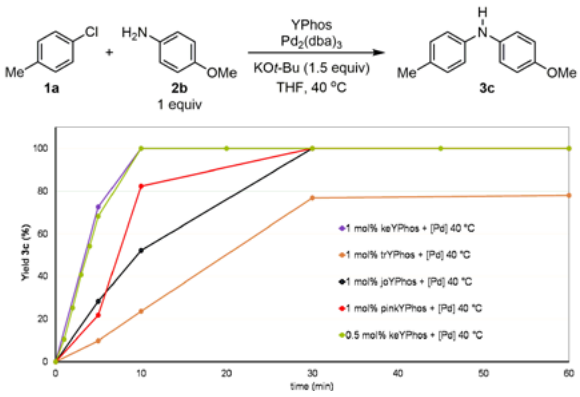
It is important to note that the steric demand measured by the buried volume of all ligands used in this study varied only by 4%, showing that the steric bulk towards the metal center is not the decisive factor for the observed selectivity differences, but rather the rigidity of the ligands. The larger mesityl group in mesYPhos (**L4**) prevents the catalyst from opening a cavity for larger substrates by increasing its P—C—P angle. This results in a reduced flexibility of the ligand structure and hence in a less active, but more selective catalyst for small amines. This was further showcased in the substrate scope of the study.

The modification of the steric bulk of the ligand by varying the phosphine moiety from PCy_2 in keYPhos to $P(t\text{-Bu})_2$ in trYPhos (**L5**) did not lead to the same effect as the modification in the backbone. Although trYPhos is considerably more sterically demanding, its enhanced donor strength and reactivity resulted in a lower stability of the active catalyst in solution, proving that backbone modification is more effective for catalyst fine-tuning.

4.4. Formation of Triarylamines

Di- and triarylamines are important compounds that are used in electronic devices such as organic photovoltaics (OPVs), organic field-effect transistors (OFETs), and organic light-emitting diodes (OLEDs).[31] In particular, triarylamines with alkyl groups in the ortho position are desirable due to improved properties, such as higher thermal stability or longer device lifetime. However, the synthesis of these sterically demanding substrates usually requires harsher reaction conditions. In line with observed structure–reactivity relationships, keYPhos, the most flexible ligand, gave the best results for the synthesis of sterically demanding diarylamines even with 0.5 mol % catalyst loading (**eq 3**). For triarylamines, slightly elevated temperatures of 50 or 60 °C were required.[32]

The formation of di- vs triarylamines from primary amines can simply be controlled by the number of equivalents of aryl halide utilized, and even mixed triarylamines can be synthesized by sequential addition of different aryl halides. Using keYPhos, it was possible to synthesize a naphthyl analogue of a commercial OLED material from Sony® in 50% yield (**eq 4**).[32,33] Known protocols utilizing $P(t\text{-Bu})_3$ for these substrates only gave 30–40% yields under harsher reaction conditions.



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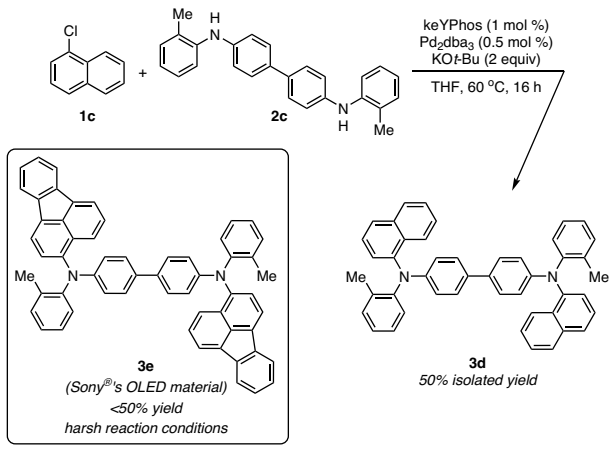
eq 3 *(Ref. 32)*



eq 4 *(Ref. 32,33)*

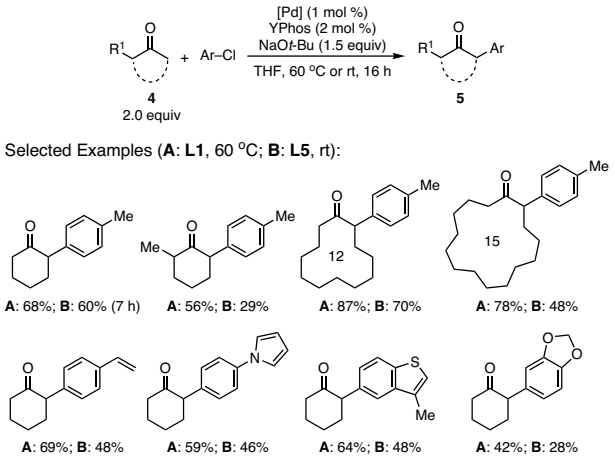
5. YPhos in Palladium-Catalyzed C–C Coupling Reactions

5.1. α-Arylation of Ketones

Following the successful use of the YPhos ligands in amination reactions, we, together with Gooßen's group, expanded their application to C—C coupling reactions, focusing on the use of the more challenging, but more abundant and generally less expensive, aryl chlorides. While the α-arylation of ketones is already well established for aryl bromides and iodides, aryl chlorides have been less well explored,[34,35] especially with small, unbranched alkyl ketones, due to the occurrence of competing multiple arylations. The higher temperatures often needed for state-of-the-art catalysts, including complexes with $P(t\text{-Bu})_3$ or CataCXium® A, usually result in mixtures of arylated products.[36]

To our delight, the increased donor capacity of YPhos ligands allowed the coupling of aryl chlorides at lower temperatures and hence with higher selectivities.[37] In the arylation of cyclohexanone with 4-chlorotoluene (**1a**) at 60 °C with 1 mol % catalyst and $Pd(cod)Cl_2$ as palladium source, keYPhos outperformed the state-of-the-art ligands and proved to be robust for numerous substrates (**eq 5**). The $P(t\text{-Bu})_2$ YPhos analogue, trYPhos (**L5**), exhibited an even higher catalytic activity and set new records at room temperature. This suggests that a further improvement can be achieved by

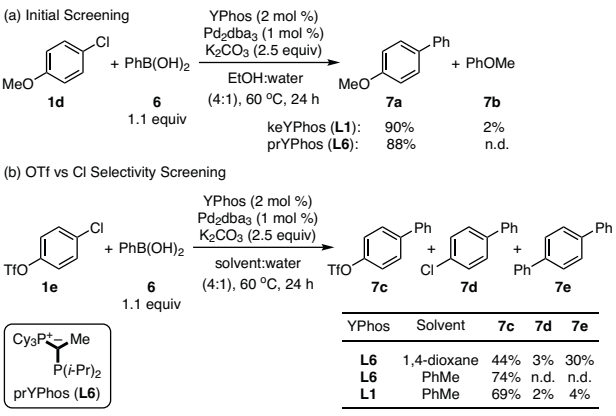
combining the robustness of keYPhos (**L1**) with the increased catalytic activity of trYPhos (**L5**).



eq 5 *(Ref. 37)*

5.2. Coupling of Boron and Silicon Nucleophiles

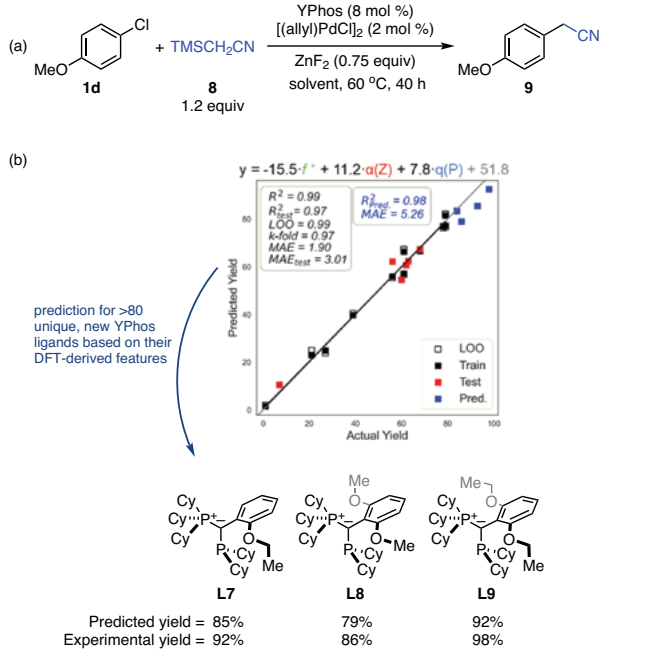
Given the high activity of our YPhos–Pd catalysts in reactions with rate-limiting oxidative addition, we challenged their application in coupling reactions of weaker boron and silicon nucleophiles, where transmetalation may become the slowest step in the catalytic cycle. In the case of the Suzuki–Miyaura cross-coupling—one of the most applied cross-coupling reactions due to its high functional group tolerance and the easy handling of arylboron nucleophiles—the YPhos ligands showed high chemoselectivities for C—Cl bonds and high reactivity at low temperatures.[38] In the coupling of electron-rich aryl chlorides with arylboronic acids, keYPhos, in combination with Pd_2dba_3, performed well, but furnished small amounts of byproducts such as the dehalogenated arene. This led us to prepare the slightly less electron-rich P(*i*-Pr)$_2$ analogue, prYPhos (**L6**), which features a higher TEP of 2053.6 cm^{-1} compared to 2050.1 cm^{-1} for keYPhos (**Scheme 3**). Indeed, this decreased donor strength reduced the overall activity of the catalyst, but at the same time facilitated the transmetalation and reductive elimination steps, leading to enhanced selectivities for biaryl formation. Mechanistic studies indicated that transmetalation is the slowest step within the catalytic cycle, confirming the enhanced performance of the less electron-rich prYPhos (**L6**) ligand.



Scheme 3. The Suzuki–Miyaura cross-coupling performed with YPhos–Pd catalysts to form functionalized biaryls. (a) Initial screening reaction. (b) Selectivity screening of the electrophile leaving group. *(Ref. 38)*

It is important to note that prYPhos enabled the chemoselective coupling of aryl chlorides over triflates, which contrasts with the usually observed selectivity in Pd-catalyzed cross-coupling reactions.[39] This selectivity has been explained by Houk and Schoenebeck based on computational studies, which indicated that monoligated palladium complexes undergo preferential C—Cl bond activation, while bicoordinate species such as Pd(PCy$_3$)$_2$ favor C—OTf insertion.[2b] Yet, also the solvent was later shown to impact the chemoselectivity of coupling reactions.[40]

Besides boron nucleophiles, the YPhos ligands allowed the coupling of silicon nucleophiles to form α-aryl nitriles **9**, which are important motifs in the pharmaceutical industry.[41] In contrast to the usual routes to α-aryl nitriles **9**, the Hiyama coupling has a high functional-group tolerance starting from bench-stable precursors, making it attractive for late-stage functionalization.[42] Moreover, Wu and Hartwig reported a successful protocol for the coupling of α-silyl nitrile **8**; however, the procedure was limited to aryl bromides.[43] Initial benchmarking showed higher conversions for the coupling of anisyl chloride with α-silyl nitriles when using YPhos ligands in comparison to other popular ligands in palladium-catalyzed



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eq 6 *(Ref. 44)*

coupling reactions.[44] Since the first attempts to improve the yield of the reaction by ligand optimization based on chemical intuition only led to a maximum of 80% conversion, we decided to use a machine-learning approach to predict an optimal ligand structure. Since the first experiments with the YPhos catalysts indicated a superior performance of ligands with an aryl substituent in the ylide backbone (**eq 6**),[44] we developed a statistical model, which allowed us to correlate ligand properties with the reaction yield. Multivariate linear regression revealed not only the electron donating, but also the acceptor properties and the steric shielding, of the ylidic carbon atom as important ligand features, suggesting again that transmetalation may be rate-limiting.

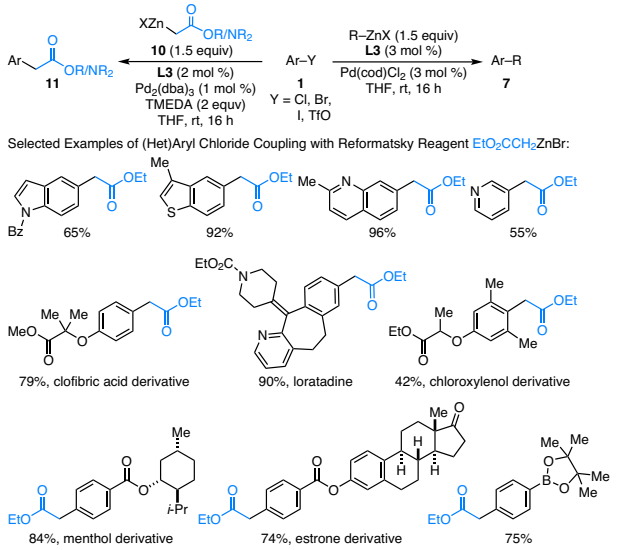
The computational model was highly predictive and pointed to several structures with improved yields compared to the test and training sets. The synthesis and reactions of some of these ligands confirmed their superior performance, with a bis(ethoxy)phenyl-substituted YPhos, **L9**, giving full conversion and an overall increase of yield for the full substrate scope from 48%, with the best performing ligand of the training set, to an average of 88% yield. This outcome impressively demonstrates the potential of inverse catalyst design and the advantage of the modular YPhos structure for optimizing catalytic protocols.

5.3. Coupling of Strong Nucleophiles

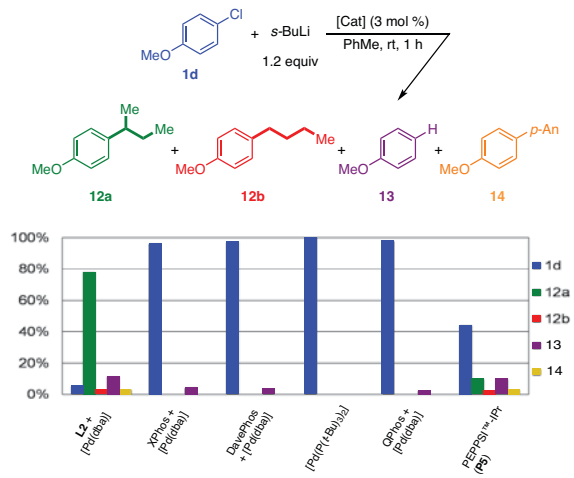
Given the fast oxidative addition of aryl chlorides by YPhos palladium catalysts, it seemed obvious that these catalysts should perform particularly well in coupling reactions with strong nucleophiles and should facilitate the development of experimental protocols under milder reaction conditions. This was demonstrated for the Negishi coupling of Reformatsky reagents **10** to yield α-aryl esters and amides **11** (**Scheme 4**).[45] As anticipated, the YPhos ligands outperformed other state-of-the-art systems, with the *o*-tolyl-substituted pinkYPhos (**L3**) being the best ligand for this application. Using TMEDA as additive to break up the dimeric structure of the zinc enolate, high yields were obtained at room temperature. The efficiency of this protocol was demonstrated for a large variety of aryl and heteroaryl chlorides, including natural products and drug-like molecules. Many substituents and functional groups are tolerated including fluoro, ester, trifluoromethyl, and trimethylsilyl groups as well as nitriles, mesylates, and even pinacol boronates. Simple aryl and alkyl zinc reagents were also successfully coupled. As in the case of the Suzuki–Miyaura cross-coupling, the oxidative addition of aryl halides was favored over that of aryl triflates. Nonetheless, also triflates could be coupled, thus allowing the consecutive functionalization of substrates with different leaving groups.

While organozinc reagents are generally considered milder and thus more tolerant of functional groups than the analogous Grignard or organolithium compounds, the direct cross-coupling of the s-block metal reagents is still attractive. This is because these reagents can often be prepared by direct metalation of the C—H compounds or are precursors to silicon or boron reagents, whose formation and thus the additional salt waste generated could be avoided by direct use of the lithium or magnesium compounds. However, the coupling of organolithium compounds represents a synthetic challenge since the lithium reagent itself can undergo lithium–halogen exchange or other side reactions such as with the solvent prior to the coupling process.

Pioneering work on the coupling of organolithium compounds was reported by Murahashi[46] and further advanced by Feringa in 2013, resulting in the first broadly applicable cross-coupling protocol for aryl- and alkyllithium reagents.[47,48] However, few examples of the coupling of aryl chlorides and the more reactive alkyllithium reagents were reported. This limitation could be overcome using the joYPhos (**L2**) ligand. When testing the cross-coupling of branched organolithiums like sec-butyllithium with aryl chlorides, high yields of the desired branched product **12a** were achieved (**eq 7**).[49] Other ligands previously applied in the coupling of aryl bromides could not undergo oxidative addition of the aryl chloride fast enough under the reaction conditions and hence did not result in any conversion. Moreover, Organ's PEPPSI™ precatalyst **P5** gave mixtures of products with very low yields of the desired product.[50] In contrast, joYPhos (**L2**) easily enabled oxidative addition of aryl chlorides at room temperature, and the subsequent cross-coupling was accomplished with minimal amounts of byproduct. The reaction worked most efficiently with aryl chlorides, while the heavier aryl halides resulted in the formation of more byproducts, presumably because of faster lithium–halide exchange. Nonetheless, aryl bromides could still be coupled in high yields. At low temperatures, the bromide could even be selectively converted in the presence of a chloride.



Scheme 4. Negishi cross-coupling of (hetero)aryl chlorides with Reformatsky (**10**) and aryl/aryl zinc reagents using the pinkYPhos (**L3**) ligand. *(Ref. 45)*



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eq 7 *(Ref. 49)*

In general, only little isomerization of branched to linear alkyl groups (e.g, **12b**) was observed (<8%) due to fast reductive elimination. However, with *t*-BuLi, complete isomerization to the *i*-butyl product occurred, suggesting preferred β-hydride elimination. Mechanistic investigations by means of DFT calculations revealed that isomerization depends on the strength of the different agostic interactions between the metal and the ligand (see Scheme 2 above) or the alkyl groups. If the latter—as in the case of the *t*-Bu group—is favored, isomerization takes place. Nonetheless, the developed protocol proved to be applicable to a range of alkyl- and aryllithium compounds and allowed the high-yield coupling of aryl chlorides incorporating alkyl, fluoro, ether, thioether, and tertiary amino groups. Furthermore, we also successfully applied the same catalyst in the Kumada cross-coupling, allowing for an enhanced tolerance of functional groups such as nitriles and esters. Overall, the YPhos ligand has enabled the so far most efficient sp^2-sp^3 cross-coupling reaction of aryl chlorides with organolithiums. This has been achieved because of the superior activity of the catalyst in the oxidative addition step, which makes the utilization of aryl chlorides feasible at room temperature and therefore enables very high selectivities.

6. Conclusions

Although ylide-substituted phosphines (YPhos) only found applications in homogeneous catalysis for the first time in 2018, this class of ligands has already demonstrated its impressive capabilities in homogeneous catalysis, particularly in palladium-catalyzed coupling reactions. Their increased donor capacity compared to traditional trialkylphosphines enables their palladium complexes to easily activate the otherwise less reactive aryl chlorides, making these substrates accessible for new applications at milder reaction conditions. The modular structure of YPhos ligands, in combination with their straightforward preparation, allows the fine-tuning of their properties and hence their easy optimization for different applications. This flexibility of the YPhos ligands is important for future catalyst design, in particular computationally derived structure predictions based on structure–activity relationships.

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