Rhodium-Catalyzed C−C Bond Formation via Heteroatom-Directed C−H Bond Activation

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Contents

1. Introduction

Once considered the "holy grail" of organometallic chemistry, synthetically useful reactions employing C−H bond activation have increasingly been developed and applied to natural product and drug synthesis over the past decade.[1] The ubiquity and relatively low cost of hydrocarbons makes C−H bond functionalization an attractive alternative to classical C−C bond forming reactions such as cross-coupling, which require organohalides and organometallic reagents.[2] In addition to providing an atom economical alternative to standard cross-coupling strategies, C−H bond functionalization also reduces the production of toxic byproducts, thereby contributing to the growing field of reactions with decreased environmental impact.

In the area of C−C bond forming reactions that proceed via a C−H activation mechanism, rhodium catalysts stand out for their functional group tolerance and wide range of synthetic utility. Over the course of the past decade, many Rh-catalyzed methods for heteroatom-directed C−H bond functionalization have been reported and will be the focus of this review. Material appearing in the literature prior to 2001 has been reviewed previously and will only be introduced as background when necessary.[1a−c]

The synthesis of complex molecules from relatively simple precursors has long been a goal for many organic chemists. The ability to selectively functionalize a molecule with minimal preactivation can streamline syntheses and expand the opportunities to explore the utility of complex molecules in areas ranging from the pharmaceutical industry to materials science. Indeed, the issue of selectivity is paramount in the development of all C−H bond functionalization methods. Several groups have developed elegant approaches toward achieving selectivity in molecules that possess many sterically and electronically similar C−H bonds.[3] Many of these approaches are discussed in detail in the accompanying articles in this special issue of *Chemical Reviews*. One approach that has seen widespread success involves the use of a proximal heteroatom that serves as a directing group for the selective functionalization of a specific C−H bond.

In a survey of examples of heteroatom-directed Rh catalysis, two mechanistically distinct reaction pathways are revealed. In one case, the heteroatom acts as a chelator to bind the Rh catalyst, facilitating reactivity at a proximal site (Figure 1A). In this case, the formation of a five-membered metallacycle provides a favorable driving force in inducing reactivity at the desired location. In the other case, the heteroatom initially coordinates the Rh catalyst and then acts to stabilize the formation of a metal−carbon bond at a proximal site (Figure 1B).

A true test of the utility of a synthetic method is in its application to the synthesis of natural products or complex molecules. Several groups have demonstrated the applicability of C−H bond functionalization reactions toward complex molecule synthesis.[4] Target-oriented synthesis provides a platform to test the effectiveness of a method in unique chemical and steric environments. In this respect, Rh-catalyzed methods for C−H bond functionalization stand out, with several syntheses being described in the literature that utilize C−H bond functionalization in a key step. These syntheses are highlighted following the discussion of the method they employ.

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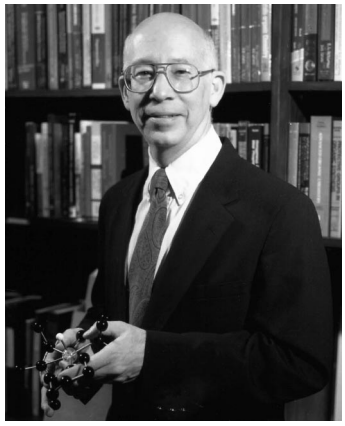


Robert Bergman received his Ph.D. at the University of Wisconsin in l966 under the direction of Jerome A. Berson. He spent l966−67 as a postdoctoral fellow in Ronald Breslow's laboratories at Columbia and afterwards joined the faculty of the California Institute of Technology. In 1977 he accepted a Professorship at the University of California, Berkeley, and a joint appointment at the Lawrence Berkeley National Laboratory; in 2002 he was appointed Gerald E. K. Branch Distinguished Professor at Berkeley. Among his previous honors are a Sloan Foundation Fellowship, a Dreyfus Foundation Teacher-Scholar Award, the American Chemical Society Award in Organometallic Chemistry, election to membership in the U.S. National Academy of Sciences and American Academy of Arts and Sciences, the U.S. Department of Energy E.O. Lawrence Award in Chemistry, and the American Chemical Society Arthur C. Cope Award. Bergman is probably best known for his discovery of the thermal cyclization of *cis*-1,5-hexadiyne-3-enes to 1,4-dehydrobenzene diradicals, a transformation that has been identified as a crucial DNA-cleaving reaction in several antibiotics that bind to nucleic acids, his discovery of the first soluble organometallic complexes that undergo intermolecular insertion of transition metals into the carbon−hydrogen bonds of alkanes, and his work on the synthesis and cycloaddition reactions of complexes with metal−heteroatom multiple bonds.

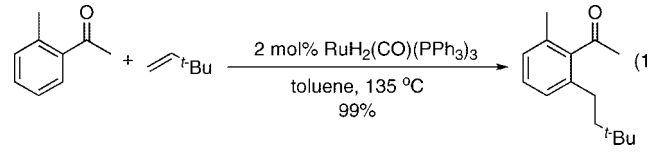
2. Chelation-Assisted Functionalization of Arenes

2.1. Intermolecular Alkylation

A key issue in the development of any C−H bond functionalization method involves the selective reactivity of a targeted C−H bond over the others present in a molecule.

Jonathan Ellman earned his B.S. degree from MIT in 1984 and his Ph.D. degree at Harvard University in 1989, working under the direction of Professor David Evans. He carried out postdoctoral research with Professor Peter Schultz at the University of California at Berkeley. In 1992 he was appointed to the faculty at the University of California at Berkeley, where he is currently Professor of Chemistry. He holds a joint appointment in the Department of Cellular and Molecular Pharmacology at the University of California at San Francisco. Among his previous honors are election as a fellow of the American Association for the Advancement of Science, a Sloan Foundation Fellowship, an American Chemical Society Cope Scholar Award, a Tetrahedron Young Investigator Award, a Society of Biomolecular Screening Achievement Award, and the Scheele Award selected by the Swedish Academy of Pharmaceutical Sciences. His laboratory is engaged in the design of chemical tools for biological studies and in the development of selective, practical, and general synthetic methods. He has collaborated with Robert Bergman since 2000 on the development of synthetic methods based upon C−H bond functionalization and the application of these methods to the expeditious syntheses of bioactive natural products and important drug candidates.

In one of the earliest reports of catalytic C−C bond formation by C−H activation, Murai demonstrated that a pendent heteroatom could function as a directing group to achieve selectivity (eq 1).[5] Although this report demonstrated an elegant approach to achieving selectivity in C−H bond functionalization, the Ru-catalyzed *ortho*-alkylation of aryl ketones proceeded exclusively with terminal, nonisomerizable olefins. Furthermore, in the absence of an *ortho*-blocking substituent, overalkylation was problematic.



(1)

The generally accepted mechanism for chelation-assisted C−H bond alkylation is outlined in Scheme 1. Initial coordination of the transition metal to the chelating heteroatom of **1** followed by facile C−H bond activation provides metallacyclic intermediate **2**. Dissociation of a phosphine ligand, followed by olefin binding and hydride insertion, gives **3**. Reductive elimination from **3** produces the product **4** and closes the catalytic cycle. The reductive elimination step has been demonstrated to be rate limiting in C−H alkylation reactions.[6,7]

Pioneering work in the field of Rh-catalyzed chelation-assisted C−H alkylation by Lim and Kang employed pyridine groups to direct functionalization.[8] More recently, the imine functionality has enjoyed widespread use and development in the realm of C−H bond functionalization by Rh (eq 2). Under optimized conditions, the Rh-catalyzed alkylation of *N*-benzyl aryl ketimines (e.g., **5**) was found to

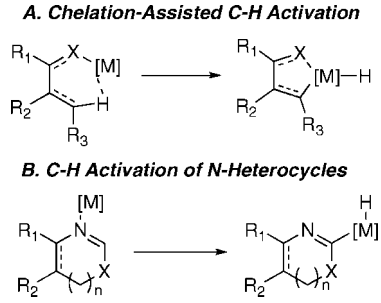
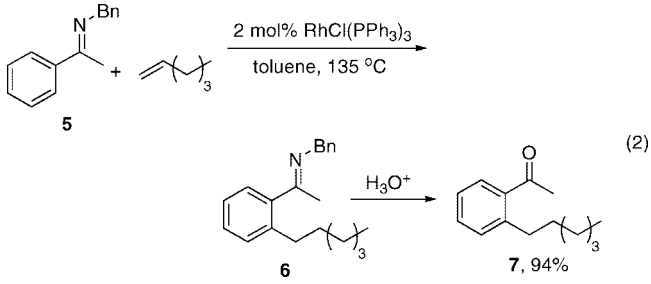


Figure 1. Modes of heteroatom-assisted C−H bond activation.

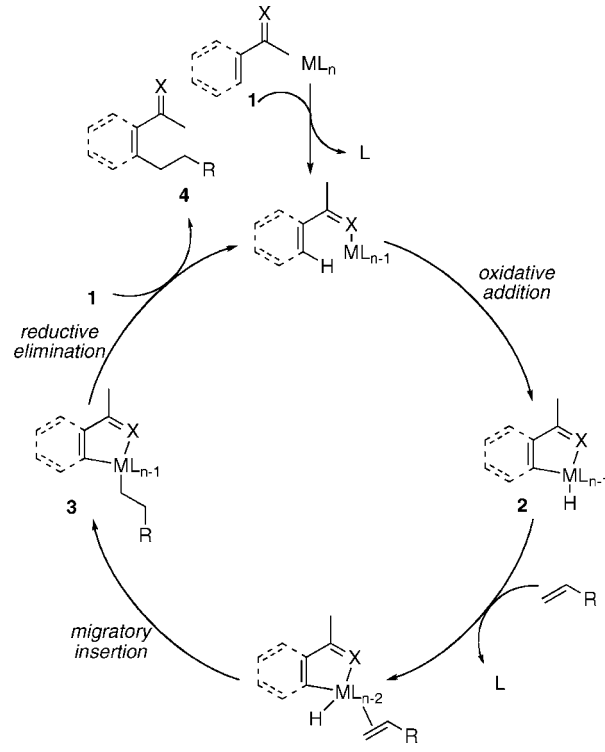
have substantially broader scope than the Ru-catalyzed alkylation of aryl ketones. Specifically, $RhCl(PPh_3)_3$ (Wilkinson's catalyst), which is relatively stable toward air and moisture, was determined to be the optimum catalyst for this transformation.[9,10] The ketimines reacted cleanly with a much broader range of alkenes than can be employed in the Ru-mediated aryl ketone alkylation, including electron-deficient alkenes, alkenes bearing allylic hydrogens, and even internal alkenes that isomerize to the terminal alkene before coupling. Furthermore, the overalkylation that plagued aryl ketone alkylation could be avoided in this case. Polymeric olefins can also serve as substrates in this transformation, and Rh-catalyzed hydroarylation has recently been applied to the chemical modification of polybutadiene.[11] Acidic hydrolysis of the product imine **6** provides the corresponding aryl ketone **7**, ultimately rendering the overall transformation analogous to Murai's reaction (eq 2).



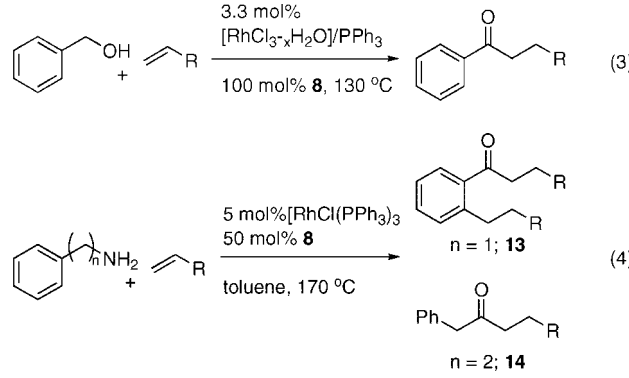
Using Wilkinson's catalyst, aldimines were reported to be competent substrates when 2-amino-3-picoline (**8**) was used as a cocatalyst (Scheme 2).[6a] However, following acidic hydrolysis, instead of isolating the *ortho*-alkylated aldehyde, an additional equivalent of olefin was consumed to generate the alkylated ketone **9**. In this example, the aldimine **10** is generated in situ and undergoes transimination with **8** to give the *N*-pyridyl imine **11**, which can coordinate the Rh catalyst through the imine or pyridyl nitrogen atoms. Coordination via the pyridyl nitrogen facilitates activation of the imine C−H bond, and hydroimination of the olefin ultimately leads to ketimine **12**. Transimination to the *N*-benzyl ketimine, followed by *ortho*-alkylation of the arene thus generates the *ortho*-alkylated ketone **9**, following acidic hydrolysis. When benzylamine was omitted from the reaction, the *ortho*-alkylation was suppressed, resulting exclusively in hydroacylation of the olefin.[12]

It was further demonstrated by Jun and co-workers that primary alcohols[9] or amines[13] could be used in hydroacylation transformations to generate the corresponding ketones. In this case, the alkene functions not only as an alkylating agent but also as a hydrogen acceptor in the oxidation of the alcohol or amine to the aldehyde (eq 3) or imine (eq 4), respectively. When alcohols were employed, hydroacylation

Scheme 1. Mechanism of Chelation-Assisted C−H Alkylation

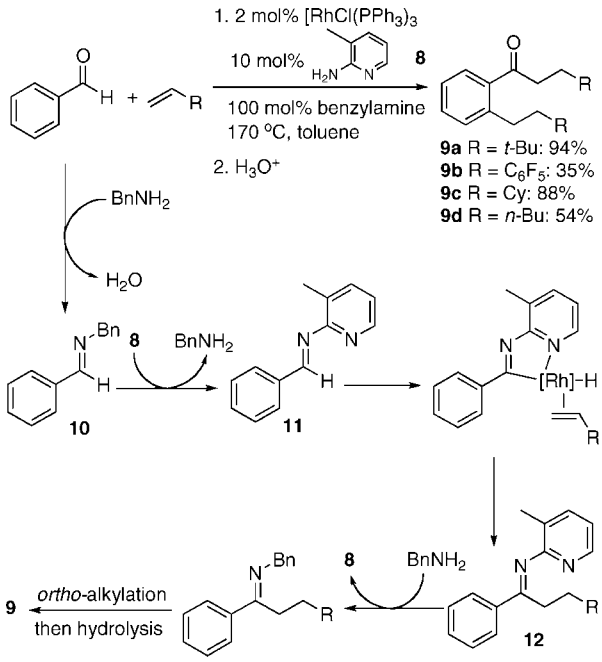


products were isolated exclusively due to the inability for the pyridyl imine to undergo *ortho*-alkylation. However, when benzylamine was used in this transformation, hydroacylation occurs with concomitant *ortho*-alkylation to produce product **13**. Following hydroacylation, the picoline substituent is exchanged for a benzyl substituent via transimination with an additional equivalent of benzylamine, which then undergoes *ortho*-alkylation. However, when phenethylamine was used, hydroacylation occurs exclusively to give **14**. In this case, *ortho*-alkylation would require the formation of a six-membered rhodacycle, which is significantly less favorable than the rhodacyclopentadiene involved in the alkylation of aryl imines.



More recently it was shown that electron-deficient, functionalized olefins alkylate aryl ketimines with markedly greater efficiency than unfunctionalized olefins. Using Wilkinson's catalyst, Jun demonstrated very good substrate scope for the *ortho*-alkylation of aryl ketimines with α,β-unsaturated esters (Table 1, entries 1−2, 6−9), amides (entry 3), sulfones (entry 4), and nitriles (entry 5).[14] Even the branched ester methyl methacrylate coupled in good yield, representing a rare example of efficient reactivity with branched olefins

Scheme 2. Hydroacylation and *ortho*-Alkylation of Aryl Aldehydes



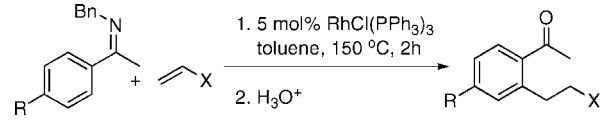
for intermolecular *ortho*-alkylation, though this substrate did require slightly higher catalyst loadings (entry 6).

In addition to the 1,1-disubstituted alkene, 1,2-disubstituted methyl crotonate was also examined (Table 1, entry 7). Instead of the expected branched product, the linear product was obtained. In order for this product to form, the olefin must isomerize out of conjugation with the ester prior to hydride insertion. It was also reported that electron-withdrawing (*p*-CF_3, entry 8) and donating (*p*-OMe, entry 9) substituents were tolerated on the aryl imine.

Mechanistically, C−H activation followed by olefin insertion into the Rh−H bond would generate intermediate **15** (Figure 2). The authors speculate that coordination of the Lewis basic functionality on the olefin to the Rh catalyst stabilizes this intermediate through the formation of a five-membered metallacycle, which serves as a driving force for the reaction. Mechanistic investigations have shown that the oxidative addition and migratory insertion steps are fast and reversible relative to reductive elimination, and this stabilizing effect would cause intermediate **15** to persist.[6,7] To investigate the involvement of the electron-withdrawing functionality on the olefin, the alkylation of **5** with *N*-methyl maleimide (**16**) was examined. This olefin is electronically similar to the acyclic olefins used in the alkylation chemistry but is incapable of forming a chelate as in **15**. As expected, the hydroarylation of *N*-methyl maleimide failed, and the only product isolated was **17**, resulting from a 1,4-addition on maleimide by **5**.

Although C−H bond functionalization reactions have proven quite useful in the synthesis of complex molecules (vide infra), the high temperatures, extended reaction times, and expensive catalysts often required to achieve good conversion make these reactions troublesome for use in industry. Recent advances by Jun and co-workers have been aimed at the development of industrially applicable conditions for *ortho*-alkylation reactions. To address the issue of lengthy reaction times and high temperatures, a solvent-free microwave protocol was developed that was effective for both imine formation and *ortho*-alkylation (eq 5).[15] Imine

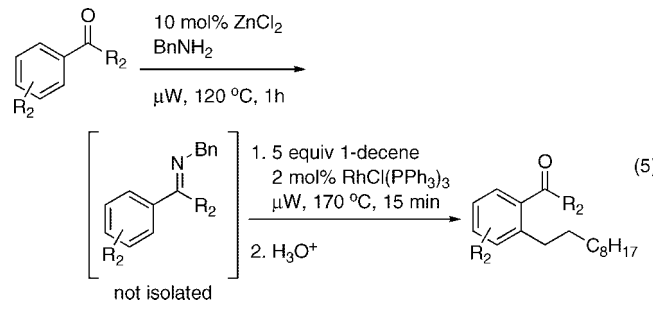
Table 1. *ortho*-Alkylation with Functionalized Olefins



Entry	R	Olefin	Product	Yield[a]
1	H	CO_2Me	CO_2Me	94%
2	H	CO_2t-Bu	CO_2t-Bu	79%
3	H	$C(O)NMe_2$	$C(O)NMe_2$	75%
4	H	SO_2Ph	SO_2Ph	43%
5	H	CN	CN	32%
6[b]	H	CO_2Me	CO_2Me	81%
7[b]	H	CO_2Me	CO_2Me	54%
8	-CF_3	CO_2Me	F_3C, CO_2Me	95%
9	-OMe	CO_2Me	MeO, CO_2Me	90%

[a] Isolated yield. [b] 10 mol % $RhCl(PPh_3)_3$ was used.

condensations with ketones are slow relative to those with aldehydes, and the addition of Lewis acids such as $ZnCl_2$ was found to improve the yield significantly. Furthermore, the imine condensation and C−H functionalization are performed in a single reaction vessel with no intermediary isolation of the imine, streamlining the synthesis of *ortho*-alkylated aryl ketones. Using pre-formed imines, the microwave protocol was further demonstrated to be very effective with functionalized alkenes such as acrylamides and acrylate esters.[16]



Jun has also reported a recyclable catalyst system for *ortho*-alkylation in which the catalyst is supported on a barbiturate (**18**) (Figure 3), which additionally serves as an H-bond acceptor.[17] The additive 2,4,6-triaminopyrimidine (**19**) serves as a H-bond donor to the barbiturate. At elevated temperatures, the H-bonding network between **18** and **19** is broken up, the solution is homogeneous, and the reaction proceeds. Upon completion of the reaction, the mixture is cooled and *n*-pentane is added, causing the **18/19** H-bonded complex to precipitate. The catalyst can then be removed

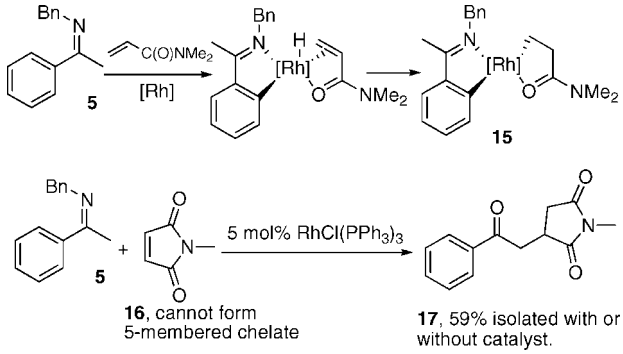
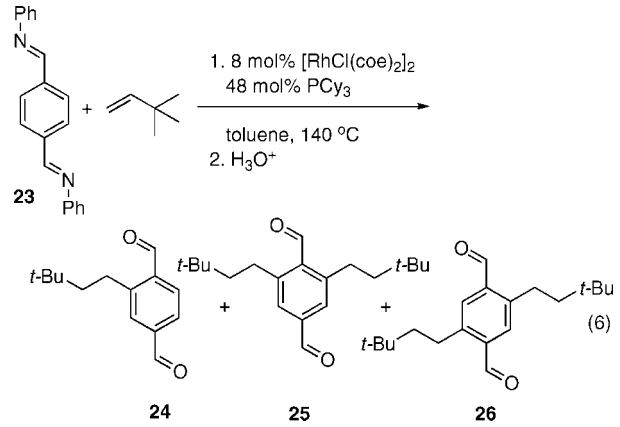


Figure 2. Mechanistic proposal involving two-point binding of the olefin.

from the imine product, excess olefin, and dioxane via filtration or centrifugation. The product mixture is hydrolyzed and the catalyst can be used again. Using this protocol, it was demonstrated that the catalyst could be recycled at least eight times with no decrease in the isolated yield of product. It was further shown that the catalyst is cleanly separated after the reaction with no remaining imine contaminating the catalyst.

In the presence of many transition metal catalysts, aldehydic substrates will readily undergo decarbonylation reactions, which typically results in low yields and catalyst decomposition when these substrates are employed.[18] The use of an imine directing group therefore has the added benefit of eliminating this decomposition pathway for the corresponding aldimines (e.g., **20**, Table 2), opening up this substrate class for use in C−H bond functionalization chemistry. For these substrates, Wilkinson's catalyst was ineffective, but a more electron-donating catalyst system employing a Rh-precatalyst and tricyclohexylphosphine (PCy_3) provided *ortho*-alkylated aryl aldehydes **21** and **22** following acidic hydrolysis (Table 2).[19] Using this more active catalyst system, overalkylation was generally observed but could be avoided by introducing a substituent at the 3-position to sterically encumber one site (entry 6) or by blocking one of the *ortho*-positions (entry 7). Electron-donating (entries 2 and 3) and -withdrawing (entries 4 and 5) substituents were tolerated on the aryl aldimine, and isomerizable olefins were effective substrates, though olefin isomerization to an internal position resulted in decreased yields.



Overalkylation can be a challenging problem to overcome in *ortho*-alkylation methods, even when substoichiometric quantities of the olefin are used, which supports the hypothesis that the second alkylation event occurs before

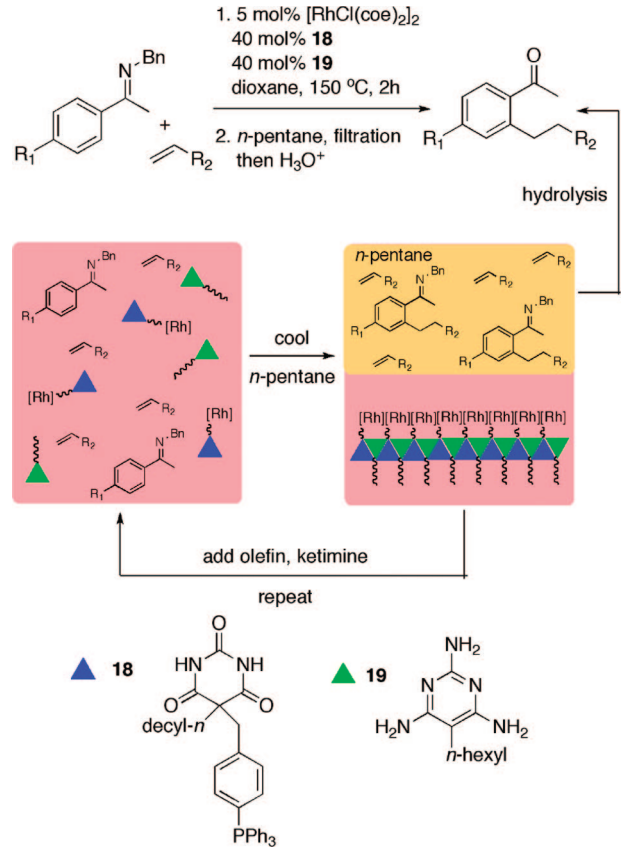
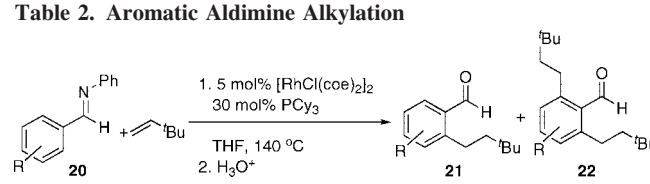


Figure 3. Recyclable catalyst system for *ortho*-alkylation.

Table 2. Aromatic Aldimine Alkylation



entry	-R	yield[a]	ratio **21**:**22**
1		93%	11:89
2	4-OMe	90%	1:99
3	4-Me	87%	5:95
4	4-Cl	88%	3:97
5	4-CF_3	90%	2:98
6	3-OMe	50%	97:3
7	2-Me	80%	100:0

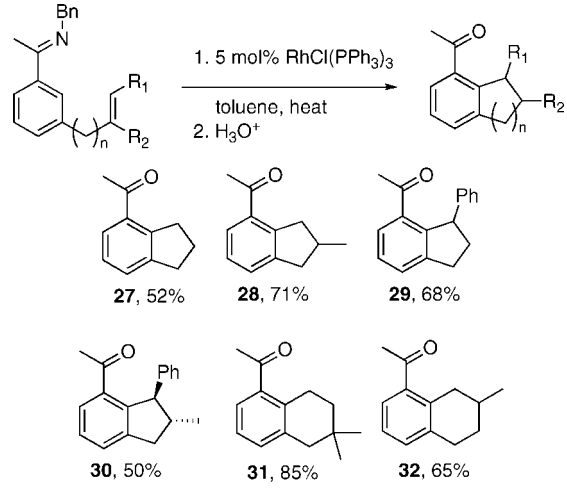
[a] Isolated yield.

the Rh catalyst dissociates from the imine. As evidence for this, Lim has carried out the alkylation of terephthaldialdimine **23**, which has up to four potential sites for alkylation (eq 6).[20] A rationale based on steric control would predict the (2,5)-dialkylated product **26** to form preferentially. However, upon analysis of the hydrolyzed product mixture from the reaction of **23** and neohexene, (2,6)-dialkylated arene **25** predominated (8:88:4, **24**:**25**:**26**). The preferential formation of **25** is evidence for the slow dissociation of the Rh catalyst from the imine, allowing a second alkylation event to occur before its departure.

2.2. Intramolecular Alkylation

While considerable advances have been made in intermolecular *ortho*-alkylation reactions, the scope, particularly with respect to the olefin, is still limited in several respects.[6a] The use of internal olefins, for example, leads to linearly

Chart 1. Intramolecular Alkylation of Aryl Ketimines

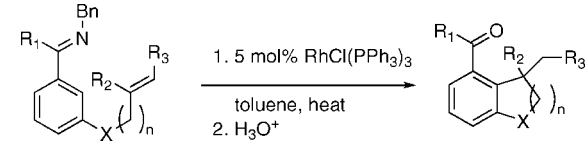


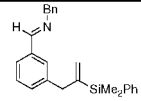
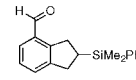
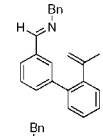
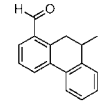
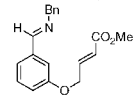
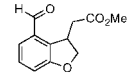
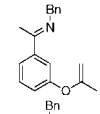
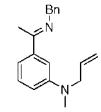
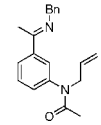
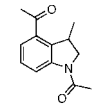
substituted products resulting from initial olefin isomerization before hydroarylation. 1,1-Disubstituted olefins are active in this transformation, but yields are substantially lower for these substrates. In addition, heteroatom-substituted olefins, such as allylic or vinyl ethers and amines, are not tolerated. It was found that many of these scope issues can be overcome in substrates in which the alkene is tethered to the *meta*-position of the aryl imine, resulting in annulated products.

Using Wilkinson's catalyst, aryl ketimines were reported to cyclize efficiently with mono- (**27**), 1,1-di- (**28**), 1,2-di- (**29**), and even trisubstituted (**30**) olefins tethered to the *meta*-position to yield indane derivatives (Chart 1).[21] Furthermore, by extending the tether length by one carbon, tetralin derivatives **31** and **32** could also be prepared. Even in examples where the olefin can isomerize to the internal position and cyclize to give an indane derivative, the tetralin derivative is formed preferentially (**32**).

The intramolecular annulation proceeded efficiently with aryl aldimines, even using Wilkinson's catalyst (Table 3, entries 1−3). In contrast, intermolecular aryl aldimine olefin hydroarylations required a more active Rh/PCy_3-based catalyst system that resulted in overalkylation.[19] Further exploration of the scope of the aryl imine annulations demonstrated that heteroatoms could be used in the tether, generating dihydrobenzofuran (entries 3 and 4) and indole (entries 5 and 6) derivatives.[21] This advancement improves upon the applicability of C−H bond functionalization to pharmaceutical and industrial targets, where heterocycles are prominent. Interestingly, when an allylic thioether tether was used in the annulation reaction, this substrate was not only unreactive but ultimately led to catalyst inactivation. The authors speculate that the high Lewis basicity of the thioether results in a strong coordination of the heteroatom to the Rh, poisoning the catalyst.

Table 3. Annulation of Aryl Imines



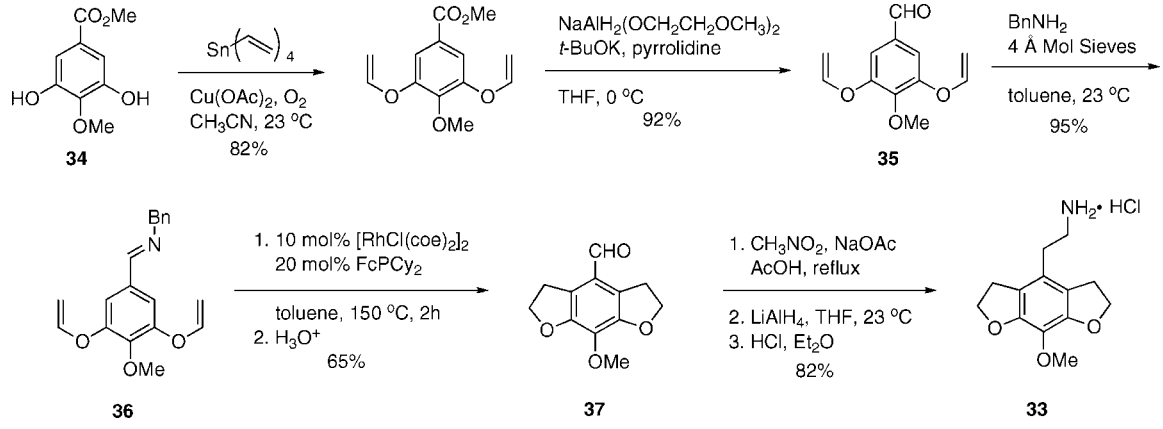
Entry	Substrate	Product	Yield[a]
1			58%
2			81%
3			50%
4			90%
5			50%
6			52%

[a] Isolated yields.

2.3. Synthesis of a Mescaline Analogue

The utility and generality of the Rh-catalyzed cyclization chemistry has been demonstrated in the synthesis of several natural products and drug candidates. In the first application of this chemistry to synthesis, imine-directed intramolecular aryl C−H bond alkylation by Rh was used in the preparation of a tricyclic mescaline analogue, **33** (Scheme 3).[22,23] Divinylation and reduction of the ester of bisphenol **34** provided aldehyde **35**, which was converted to the imine **36** for the C−H activation step. The tandem alkylation reaction of **36** proceeded in low yields using Wilkinson's catalyst.

Scheme 3. Synthesis of a Mescaline Analogue via Tandem Olefin Hydroarylation



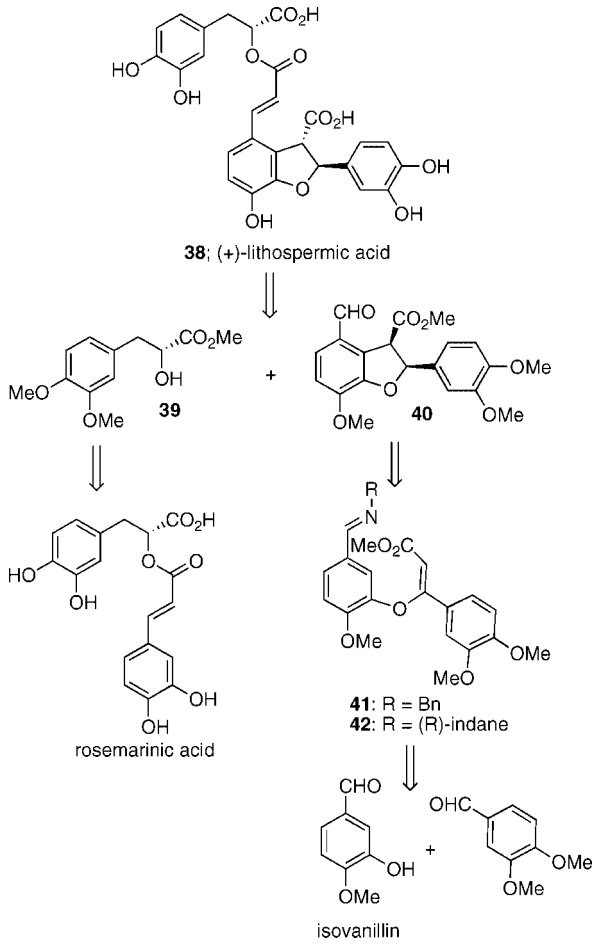


Figure 4. Retrosynthesis of **38**.

Electron-donating ligands, such as PCy_3, were much more active in this transformation, and $FcPCy_2$ was found to be the optimum ligand for the cyclization of **36** to **37**. Using 10 mol % of a rhodium precatalyst and a 1:1 ratio of rhodium/ligand, **37** was obtained in 65% yield, following hydrolysis of the imine moiety. The tricyclic aldehyde **37** was then readily converted to **33** via a Henry reaction and reduction to install the desired amino group (Scheme 3).

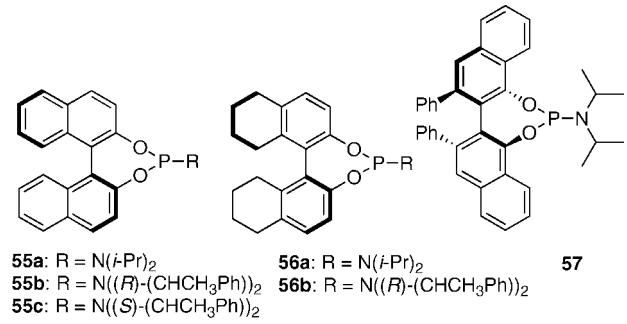


Figure 5. Phosphoramidite ligands for enantioselective olefin hydroarylation.

2.4. Synthesis of (+)-Lithospermic Acid

An intramolecular *ortho*-alkylation of an aryl aldimine was also used to generate the benzofuran core of the natural product, (+)-lithospermic acid (**38**) (Figure 4), which is a key constituent of a popular traditional herbal medicine with a variety of biological activities.[24] In a retrosynthetic analysis, **38** can be disconnected to alcohol **39**, which can be easily prepared from commercially available rosmarinic acid, and benzofuran **40** (Figure 4). It was envisioned that **40** could be accessed stereospecifically via a Rh-catalyzed intramolecular *ortho*-alkylation of **41** by *syn*-alkene insertion and reductive elimination with retention of configuration. Subsequent epimerization of the stereocenter α to the carboxylic acid would then produce the desired stereoisomer. The requisite *N*-benzyl imine **41** was prepared in four steps from methyl isovanillin and isovanillin. The initial evaluation of chiral catalysts (vide infra, section 2.6) in the cyclization of **41** did not provide satisfactory yields or enantioselectivities, and so a different approach was used.

An alternative method for incorporating chirality into the cyclized product is through the use of a chiral amine auxiliary to yield a diastereoselective insertion into the prochiral olefin. Chiral nonracemic amines were condensed with aldehyde **43**, and the resultant imines were tested for their efficiency and diastereoselectivity in the Rh-catalyzed cyclization (Scheme 4). The *syn*-diastereomer **40** formed in the Rh-catalyzed cyclization reaction could be readily epimerized under basic conditions to the more thermodynamically

Scheme 4. Cyclization of 42 and Completion of the Synthesis of (+)-Lithospermic Acid

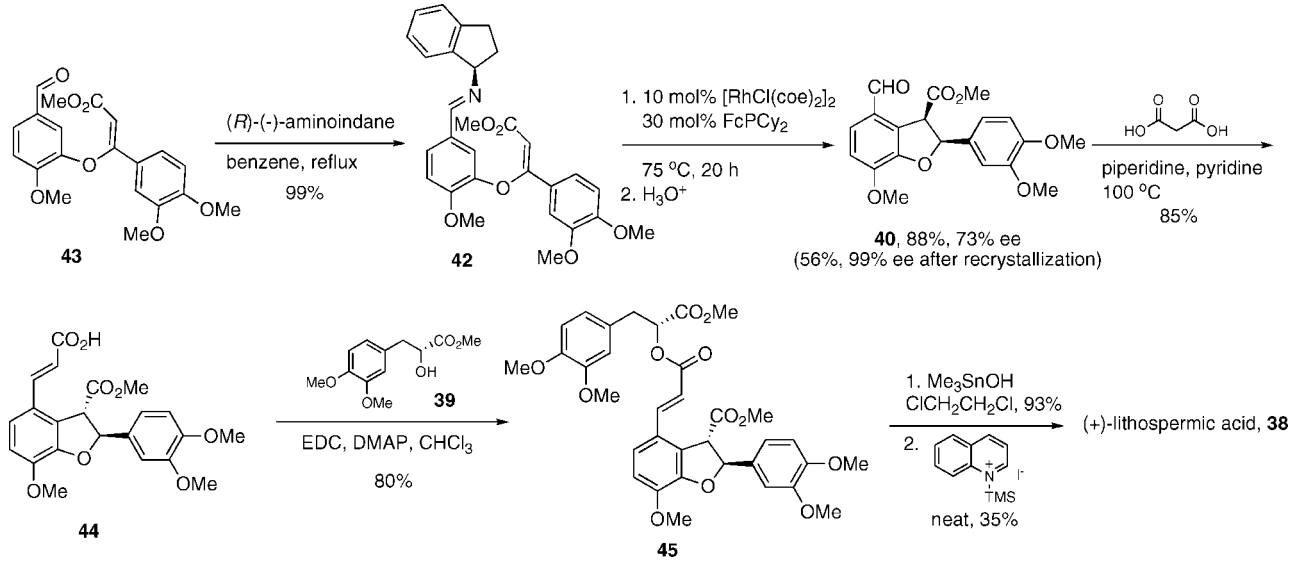
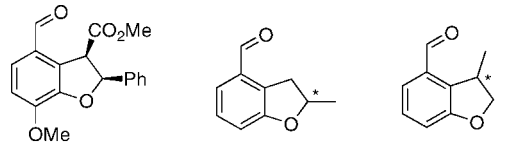


Chart 2. Asymmetric Cyclization of Chiral Imines



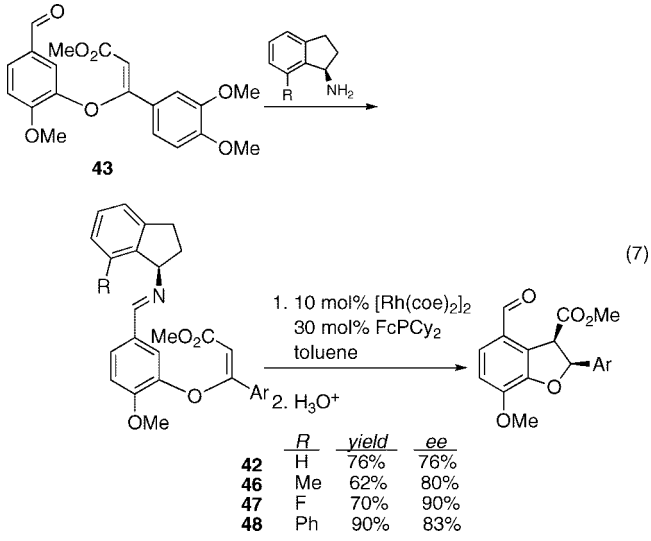
49, 81%, 70% ee **50**, 99%, 68% ee **51**, 50%, 58% ee

favorable *anti*-isomer. In the initial synthesis, the imine generated from (*R*)-aminoindane, **42**, provided the highest yield of cyclized product with good diastereoselectivity (Scheme 4).

The synthesis of **38** was completed in three steps from **40**. Knoevenagel condensation on **40**, which occurred with concomitant epimerization, provided **44** with the desired stereochemistry. Esterification of **44** with alcohol **39** was achieved using *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC) and 4-(dimethyamino)pyridine (DMAP). The global deprotection of two methyl esters and five methyl ethers on **45** proved to be very challenging, typically resulting in decomposition due to the acid and base lability of the intermediate and product. Following substantial reaction optimization, it was found that initial deprotection of the methyl esters using Me_3SnOH, with subsequent removal of the methyl ethers using precomplexed TMSI/quinoline, provided (+)-lithospermic acid, which constitutes the first, and to date only, total synthesis of this natural product.

2.5. Stereoselective Alkylation using a Chiral Auxiliary

To further increase the stereoselectivity observed in the chiral-auxiliary-directed cyclization in the synthesis of lithospermic acid, aryl aldehyde **43** was condensed with a variety of substituted aminoindane derivatives to generate imines **42** and **46**−**48**.[25] In the presence of a Rh catalyst, the imine substrates underwent diastereoselective, intramolecular *ortho*-alkylation, with the fluoro derivative **47** providing the highest enantioselectivity following hydrolysis of the chiral auxiliary (eq 7).



(7)

	R	yield	ee
42	H	76%	76%
46	Me	62%	80%
47	F	70%	90%
48	Ph	90%	83%

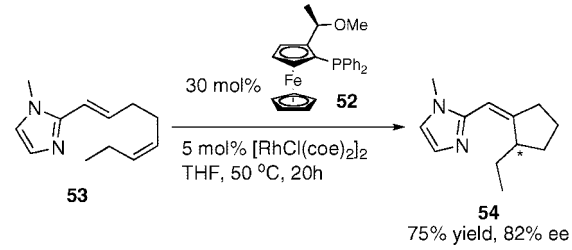
Evaluation of this chiral auxiliary-based approach with other substrates, even using the most selective fluoro-substituted indenyl imines, established that diastereoselectivity was highly dependent upon substrate structure. When the dimethoxyphenyl substituent was replaced with a phenyl ring, the enantioselectivity decreased (Chart 2, **49**). This method was also applied to substrates with 1,1- and 1,2-disubstituted vinyl ether substituents (Chart 2). The annulated product **50** was obtained in high yield for the 1,1-disubstituted olefin, albeit with diminished enantioselectivity. When a more challenging 1,2-disubstituted olefin was employed, both the yield and the enantioselectivity suffered (**51**).

2.6. Enantioselective Intramolecular Alkylation

With the widespread development of chiral ligands over the course of the past decade, the area of enantioselective transition-metal-catalyzed reactions has seen rapid growth. Despite these advances, examples of enantioselective C−H bond functionalization reactions are still rare.[26] In many examples of C−H bond alkylation, monosubstituted olefins exclusively function as coupling partners, with more highly substituted substrates giving poor conversion, hindering the development of enantioselective methods.

The first reported example of a heteroatom-directed enantioselective C−H alkylation utilized a Rh precatalyst and a ferrocenyl-based monodentate phosphine ligand **52** to achieve the intramolecular alkylation of pyridyl or imidazoyl dienes (eq 8).[27] Moderate ee's could be obtained with an imidazoyl directing group for substrate **53**, whereas the ee's were consistently low when the pyridyl directing group was employed.

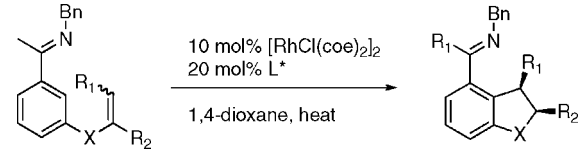
Recent reports have demonstrated that the intramolecular hydroarylation of olefins tethered to aryl imines could be achieved in a highly enantioselective and general manner.[28] An extensive ligand screen demonstrated that chelating phosphines were ineffective in this transformation, presumably inhibiting the requisite ligand dissociation step to generate a coordinatively unsaturated Rh species prior to olefin binding (Scheme 1). Similarly, the stoichiometry between the ligand and Rh precatalyst was found to be a very important parameter in achieving reaction efficiency, with a ∼1:1 ratio (L/Rh) providing the best results. Ultimately, monodentate chiral phosphoramidite ligands (Figure 5) were used with a Rh precatalyst to give high conversion and selectivites in the cyclization of 1,2- and 1,1-di-, and trisubstituted olefins (Table 4).

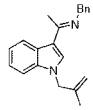
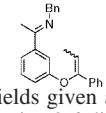
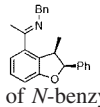


(8)

Using this method, chiral indane and benzofuran derivatives were synthesized efficiently with both aryl and alkyl substituents tolerated. *N*-Allylic indoles were also competent substrates (entry 3), though these challenging substrates required higher temperatures and gave modest ee's. It is worth noting that the trisubstituted olefins in entries 7 and 8 cyclized with very high ee's, setting two stereocenters in a single step. It was found in these transformations that the starting olefin geometry did not dictate the relative stereochemistry of the resulting benzofuran. To further investigate

Table 4. Enantioselective Annulation of Aryl Imines[a]



Entry	Substrate	Product	L*	T (°C)	% Yield	% ee
1			**55b**	50	94	95
2			**55c**	75	98	90
3			**55c**	125	99	68
4			**55c**	50	99	95
5			**56a**	75	93	87
6			**56a**	75	69	90
7			**56b**	50	80	93
8			**56b**	75	50	90

[a] Yields given are of *N*-benzylimine products as determined by ^{1}H NMR using 2,6-dimethoxytoluene as an internal standard. Enantiomeric excess was determined using chiral HPLC after hydrolysis of products with silica gel or HCl/H_2O−dioxane.

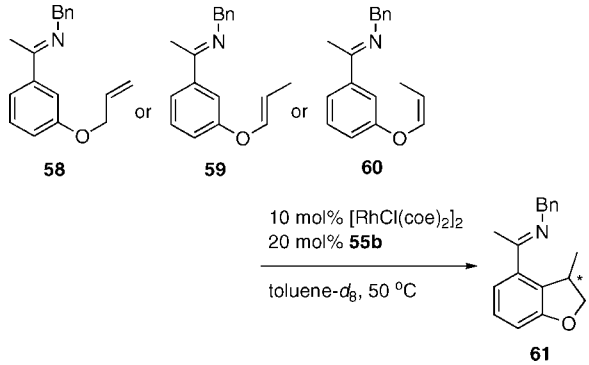


Figure 6. Cyclization of isomeric substrates **58**−**60**.

this finding, the three isomeric substrates **58**−**60** were prepared and their reactivity using ligand **55b** was examined (Figure 6). All three substrates gave benzofuran **61**, but allylic ether **58** exhibited poor reactivity, producing **61** in just 19% yield and with an overall sense of induction opposite to that observed with **59** and **60**. *Z*-Alkene **60** cyclized most efficiently, giving an 82% yield and 85% ee. *E*-Alkene **59** ultimately produced **61** with the same degree of enantioselectivity, albeit with decreased efficiency, delivering **61** in just 51% yield. In NMR analyses of reactions involving **59**

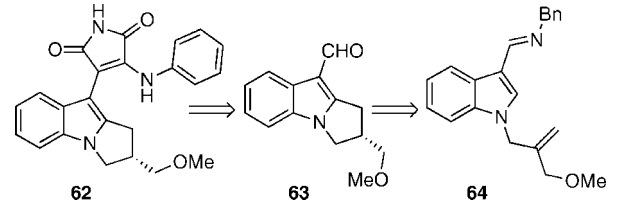
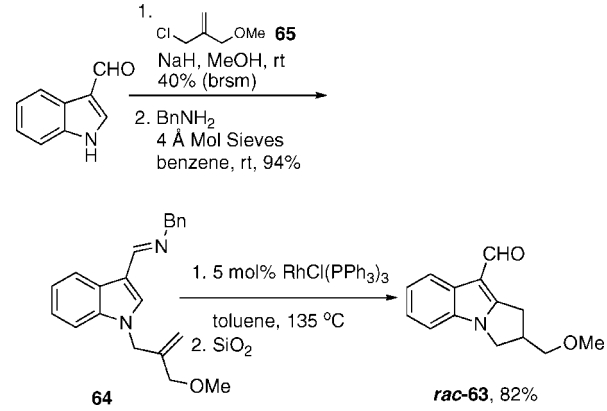


Figure 7. Retrosynthetic analysis of the key step in the synthesis of **62**.

Scheme 5. Synthesis and Racemic Cyclization of 64

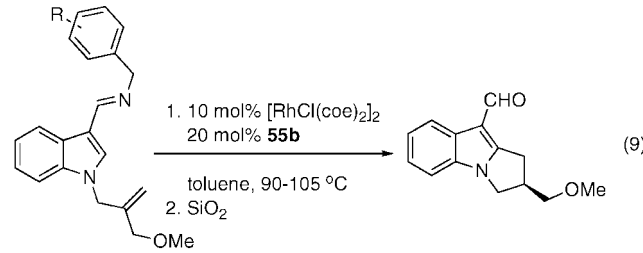


and **60**, both the *E*- and *Z*-alkenes are observed throughout the reaction, indicating rapid olefin isomerization, with cyclization occurring from the *Z*-olefin.

2.7. Synthesis of a Tricyclic Indole PKC Inhibitor

The utility of the intramolecular enantioselective olefin hydroarylation was demonstrated in its application to the synthesis of a PKC inhibitor, **62** (Figure 7).[29] In the retrosynthetic plan, the key tricyclic indole **63** was envisioned to arise from the enantioselective cyclization of *N*-allyl indole **64**.

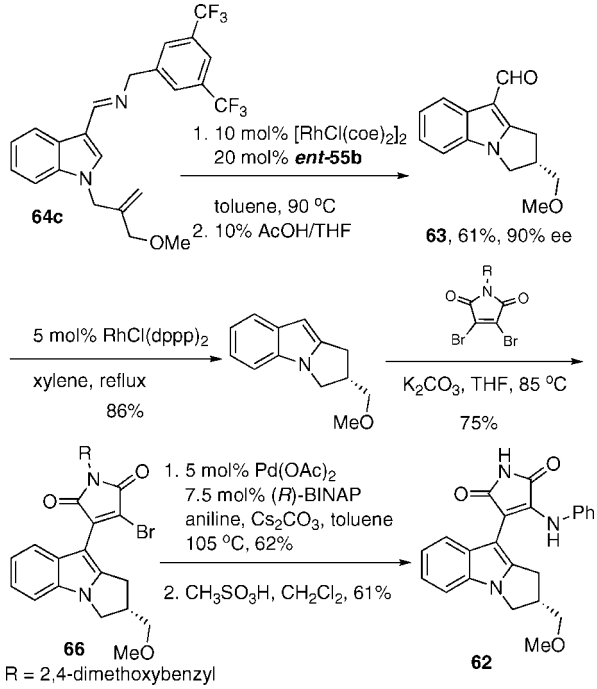
The requisite imine substrate for intramolecular cyclization (**64**) was prepared via the alkylation of indole-3-carboxaldehyde with **65**, followed by condensation with benzylamine (Scheme 5). Treatment of **64** with Wilkinson's catalyst, followed by imine hydrolysis generated racemic **63** in 82% isolated yield.



(9)

Despite the high yield obtained using Wilkinson's catalyst, employing the chiral phosphoramidite ligand **55b**, which had previously given high yields and selectivities in enantioselective cyclizations (vide supra, Table 4), resulted in very poor conversion of starting material (eq 9). A screen of chiral monodentate phosphine ligands did not provide a more active

Scheme 6. Enantioselective Cyclization and Synthesis of 62



catalyst system. Mechanistic investigations have established that reductive elimination is the rate-limiting step in the catalytic cycle for C−H bond functionalization.[6,7] Reducing the electron density on the metal center lowers the barrier for reductive elimination, improving the efficiency of the overall alkylation reaction.[6c] In this manner, substrate **64** was modified with substituents on the *N*-benzyl group. As expected, use of the more electron-rich substrate **64a** resulted in decreased reaction efficiency relative to **64**. Substrates with electron-withdrawing -CF_3 substituents on the benzyl group, however, did show improved reaction efficiency, with the 3,5-bis-trifluoromethyl-substituted substrate (**64c**) providing *ent*-**63** in 65% yield and 90% ee (eq 9).

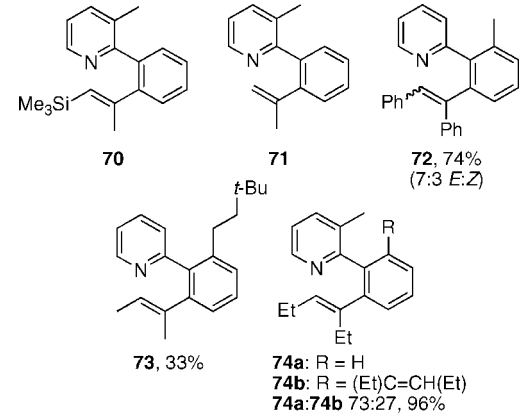
As shown in eq 9, ligand **55b** provided the enantiomer of the desired product **63**, as determined by X-ray analysis of the corresponding 4-bromo-2-nitrophenylhydrazone. The enantiomer of **55b** (*ent*-**55b**) is also commercially available and was used to produce **63** with the correct sense of induction (Scheme 6). The synthesis of **62** could then be completed in four steps from **63**. Rh-catalyzed decarbonylation, followed by a direct substitution with *N*-2,4-dimethoxybenzyl-3,4-dibromomaleimide, produced **66**. Amination of **66**, followed by deprotection of the maleimide with methanesulfonic acid, concluded the synthesis of **62**.

2.8. Directed Alkenylation

While the hydroarylation of olefins has seen broad success using Rh-catalyzed chelation-assisted methods, only a few examples of the analogous reaction with alkynes have been reported to date. The propensity for alkynes, in particular terminal alkynes, to undergo Rh-catalyzed alkyne dimer- or trimerization reactions has made their use problematic.[30] Internal alkynes, much like internal olefins, are often unreactive in C−H bond functionalization reactions. Despite this, several groups have successfully developed heteroatom-directed vinylation methods.[31]

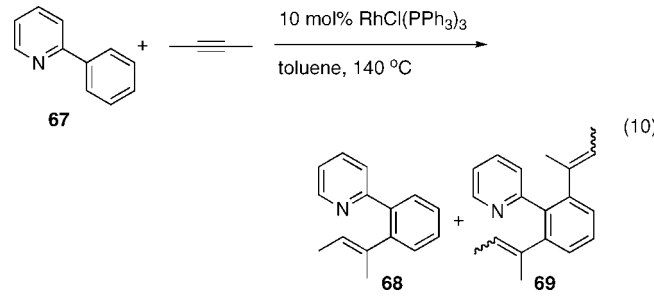
In the first example of chelation-assisted hydroarylation of an alkyne, Lim and Kang reported that 2-phenylpyridines undergo *ortho*-alkenylation using Wilkinson's catalyst (eq

Chart 3. *ortho*-Alkenylation of 2-Phenylpyridines



10).[32] Using 2 equiv of 2-butyne, **67** underwent vinylation at the *ortho*-positions to give **68** and **69** in a 19:81 ratio. Increasing the number of equivalents of the alkyne led to exclusive isolation of the dialkenylated product **69**. Although the *E*,*E* product predominates, some olefin isomerization does occur, and **69** is isolated in a 85:15 ratio of the *E*,*E* to *E*,*Z* isomers.

The scope in alkyne was limited primarily to internal, symmetrical alkynes. Terminal alkynes generated primarily polymeric materials, and unsymmetric alkynes, such as 2-hexyne, led to regioisomeric mixtures. However, unsymmetric alkynes with a single bulky substituent, such as 1-(trimethylsilyl)-1-propyne, showed high regioselectivity and favored the monoalkenylated product. Reaction of 3-methyl-2-phenylpyridine with this alkyne led to a 42:58 mixture of **70** and **71**, the latter of which was produced by protiodesilylation of **70** (Chart 3). In addition to 2-butyne, 3-hexyne, 4-octyne, and diphenylacetylene were all competent substrates, though subsequent olefin isomerization of the alkenylated product was often observed with hexyne and octyne to give regioisomeric mixtures of products. Substrates with one *ortho*-position blocked underwent clean monoalkenylation (**72** and **73**, Chart 3), although bulky substituents resulted in decreased yield. In order for the cyclometalated intermediate to form, the pyridine and phenyl ring must become coplanar. Because of this, in the analogous 2-phenylpyridine alkylation chemistry,[8] the presence of a substituent at the 3-position on the pyridine ring sterically prevented a second alkylation step from occurring. Interestingly, this steric interaction does not play as strong a role for the alkenylation chemistry, presumably because of the decreased size of the vinyl substituent, and mixtures of mono- and dialkenylated products are obtained for substrates such as **74**.



(10)

Recently, the scope of the alkenylation of 2-phenylheterocycles using a Rh/PPh_3 catalyst was expanded to include imidazole (**75**) and benzimidazole (**76**) directing groups when

Chart 4. *N*-Directed Alkenylation with Triisopropylsilylacetylene

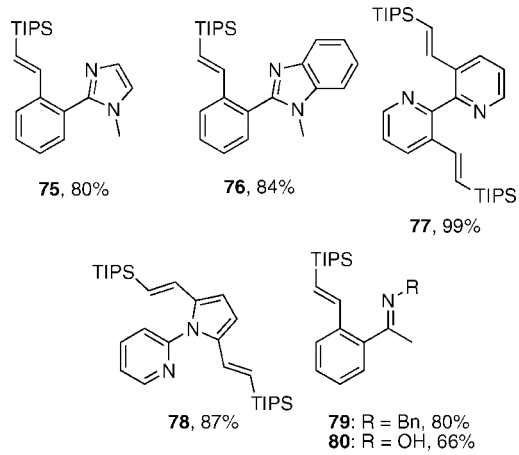
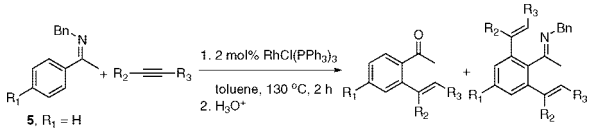


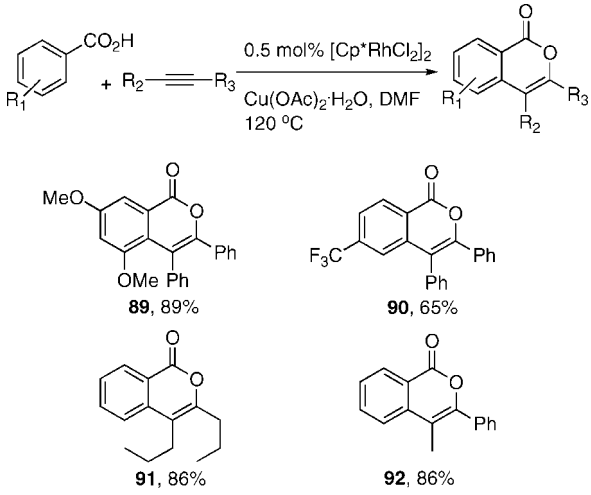
Table 5. *ortho*-Vinylation of Ketimines



Entry	R_1	Alkyne	Ratio[a] (mono:di)	Yield[b]
1	H (**5**)		100:0	88
2	H (**5**)		100:0	85
3	H (**5**)	Ph—≡—Ph	100:0	93
4	H (**5**)		86:14	96
5[c]	-CF_3		82:18	81
6[c]	-OMe		76:24	41

[a] Determined by GC. [b] Isolated yield. [c] Reaction solution was heated at 100 °C for 30 min.

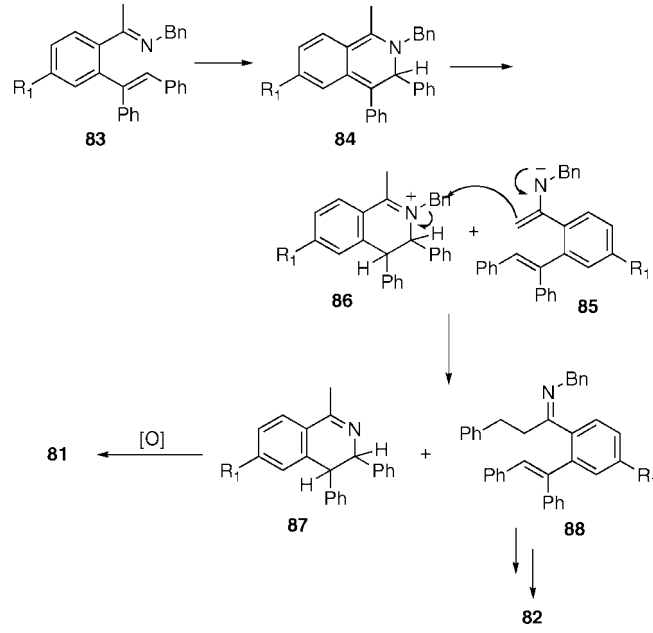
Chart 5. Oxidative Coupling of Benzoic Acids to Alkynes



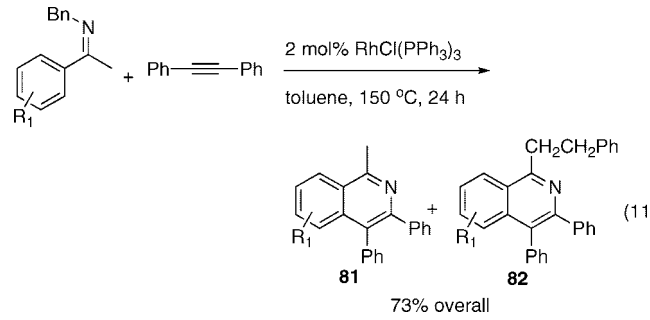
triisopropylacetylene is used as the coupling partner (Chart 4).[33] Pyridine (**77**) and pyrrole (**78**) were also cleanly alkenylated using a pyridyl directing group. In addition to heterocyclic directing groups, the ketimine (**79**) and ketoxime (**80**) derivatives of acetophenone reacted with triisopropylacetylene to give monoalkenylated products.

Jun has also demonstrated that aryl ketimines will undergo *ortho*-alkenylation with terminal alkynes and diphenylacetylene using Wilkinson's catalyst.[34] Using near-stoichiometric

Scheme 7. Mechanism of the Formation of 81 and 82



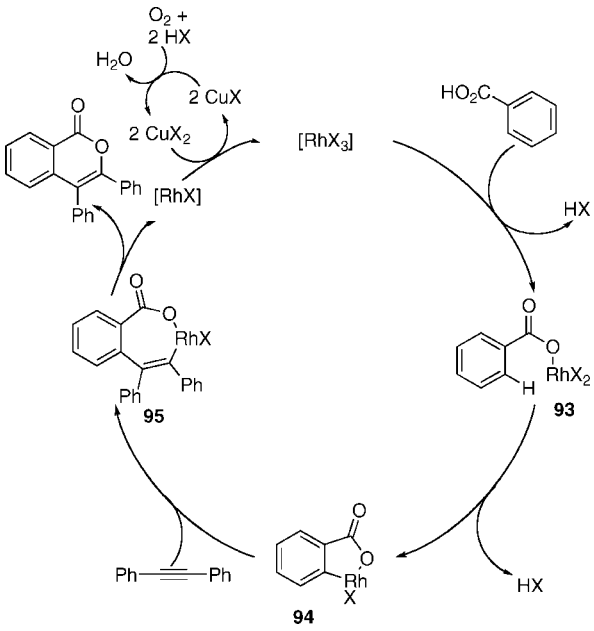
quantities of imine **5** and alkyne, **5** reacted with linear alkyl acetylenes and diphenylacetylene to give good yields of monoalkenylated products (Table 5, entries 1−3). The sterically bulky alkyne *tert*-butylacetylene gave a mixture of mono- and dialkenylated products (entry 4). Electron-deficient aryl imines were determined to be more active than electron-rich imines in this transformation (compare entries 5 and 6). For these functionalized imines and *tert*-butylacetylene, overalkylation could be reduced by decreasing the temperature and reaction time (entries 5−6) but could not be completely avoided.



(11)

It was also reported by Jun that increased temperatures and prolonged reaction times ultimately provided isoquinoline products **81** and **82** in nearly equimolar quantities (eq 11). Isoquinoline **82** was generated via the migration of the *N*-benzyl group, presumably through an enamine intermediate. A mechanistic rationale is given in Scheme 7. The *ortho*-alkenylated imine **83** can undergo electrocyclization to give the 1,2-dihydroisoquinoline **84**, with concomitant loss of aromaticity. Iminium **86** is subsequently generated from **84** by proton transfer from another molecule of **83**. Enamine **85**, produced upon proton transfer from **83**, then displaces the benzyl group on iminium **86** to produce 2,3-dihydroisoquinoline **87**, which can undergo further oxidation to **81**, and **88**, which can then cyclize by the same mechanism. Jun further demonstrated that aryl ketones and benzylamine could be used directly in this transformation with in situ formation of the imine, bypassing the need for initial imine isolation.

Scheme 8. Plausible Mechanism for Rh-Catalyzed Isocoumarin Synthesis



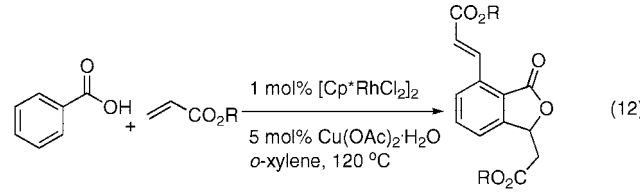
Carboxylate groups can also function as directing groups in oxidative couplings of benzoic acids and alkynes using a Rh−Cu co-catalytic system, where the Cu serves to oxidize the Rh catalyst to render the transformation catalytic.[35] When run under air, the reaction also becomes catalytic in Cu. This approach was used to synthesize a series of isocoumarin derivatives from benzoic acids and internal alkynes using the Rh(III) catalyst $[Cp^*RhCl_2]_2$ (Cp^* = pentamethylcyclopentadienyl) (Chart 5). Both electron-rich (**89**) and electron-deficient (**90**) benzoic acids were competent substrates, and both alkyl (**91**) and aryl alkynes could be used. The unsymmetric alkyne, 1-phenylpropyne, provided predominantly a single regioisomer **92**.

The mechanism of this transformation is considerably different from that of Murai-type reactions (Scheme 8). In this case, a Rh(III) species is the active catalyst, and following anionic ligand exchange to generate a Rh−benzoate complex, the activation of the *ortho*-C−H bond occurs to generate the rhodacycle **94**.[36] Carbometalation of the alkyne followed by reductive elimination provides the isocoumarin product. The resulting Rh(I) species must then undergo oxidation by copper to regenerate the active Rh(III) catalyst.

Naphthalene derivatives, in which 2 equiv of the alkyne were incorporated, were found to be a minor byproduct in these reactions. These derivatives could form via decarboxylation of intermediate **95**, followed by a second insertion step. Interestingly, use of the analogous iridium catalyst $[Cp^*IrCl_2]_2$ with Ag_2CO_3 as the oxidant led exclusively to these naphthalene derivatives instead of the isocoumarin products.

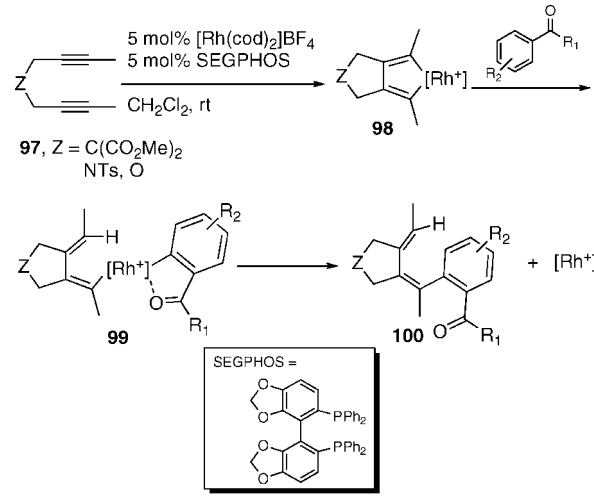
When acrylates were employed in this transformation, alkenylation rather than alkylation was also observed (eq 12). The authors postulate that the mechanism of this transformation is similar to that given in Scheme 8, with β-hydride elimination of the Rh-alkyl species occurring to generate the vinyl derivatives. In this case, substitution at both *ortho*-positions was observed with subsequent intramolecular conjugate addition of the carboxylate onto the acrylate ester to generate phthalide derivatives **96a** and **b**.

Aryl ketones have been reported to undergo alkenylation reactions with diynes or enynes in a tandem process utilizing



96a: R = *n*-Bu, 66%
96b: R = Et, 76%

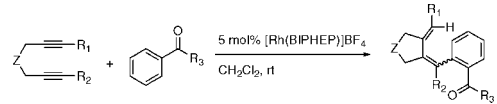
Scheme 9. Tandem Cycloisomerization/C−H Activation



a cationic Rh catalyst. In the first report of this transformation, Tanaka and co-workers demonstrated the use of $[Rh(cod)_2]BF_4$ and SEGPHOS to facilitate the reaction between 1,6-diynes and aryl ketones (Scheme 9).[37] Mechanistically, the authors proposed initial [2 + 2] cycloisomerization of the diyne **97** to generate rhodacyclopentadiene **98**. *ortho*-Rhodation of the aryl ketone via C−H activation or electrophilic aromatic substitution would furnish **99**, which could then reductively eliminate to form **100**. The authors reported that monoalkynes failed to react with aryl ketones using this catalyst system, which supports a mechanism involving cycloisomerization prior to C−H bond activation. When 3,5-disubstituted aryl ketones were employed, the resulting products displayed axial chirality; however, only modest ee's were obtained using SEGPHOS.

Soon after this report, Shibata and co-workers reported the use of $[Rh(BIPHEP)]BF_4$ to facilitate a related reaction between diynes or enynes and aryl or α,β-unsaturated ketones.[38] The reaction between diynes and aryl ketones proceeded in good yields, but in some cases, a mixture of isomers was obtained (Table 6, entries 2 and 3). When an unsymmetrical diyne was used, a single regioisomer of

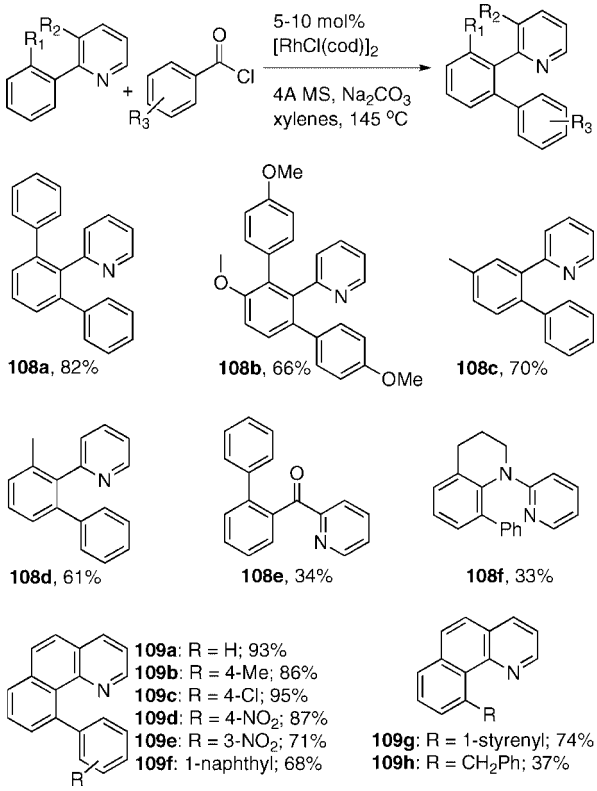
Table 6. Cyclization of Diynes and Aryl Ketones



entry	Z	R_1	R_2	R_3	yield	*E*/*Z*
1	NTs	Me	Me	Me	55%	>20:1
2	NTs	Ph	Ph	Ph	73%	1:2
3	NTs	Me	Ph	Ph	86%	1:1
4[a]	NTs	Me	Ph	Ph	63%	>20:1
5	$C(CO_2Bn)_2$	Me	Me	Ph	78%	1:>20[b]

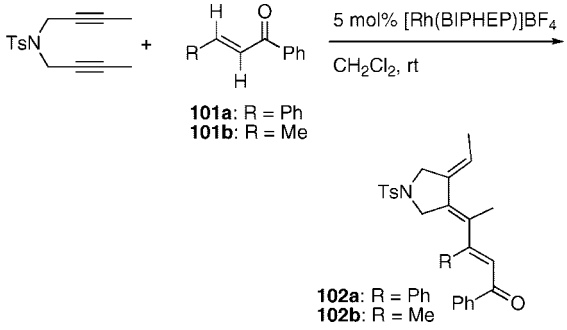
[a] *rac*-BINAP was used as a ligand. [b] Due to nomenclature rules. The major geometry is the same as that for entries 1, 3, and 4.

Chart 6. Pyridyl-Directed Arylation Using Acid Chlorides



product was obtained, albeit with poor *E*/*Z* selectivity (entry 3). Interestingly, when BINAP was used in place of BIPHEP for this particular product, complete selectivity for the *E* isomer was seen (entry 4).

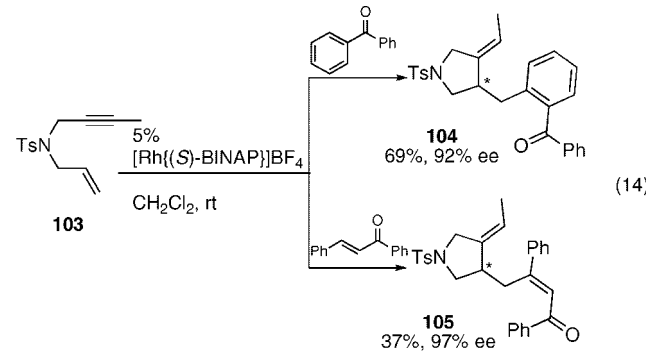
When *trans*-chalcone **101a** was used as a carbonyl compound, vinylic C−H activation occurred preferentially over aryl C−H activation to give **102a** exclusively and as a single isomer (eq 13). The (*Z*,*Z*) geometry of the α,*β* and *γ*,*δ* alkenes results from complete isomerization of these olefins. This isomerization was also seen with enone **101b** to produce **102b** exclusively.



(13)

Interestingly, unlike Tanaka and co-workers, the authors report that benzophenone reacted with the monoalkyne diphenylacetylene in refluxing dichloroethane to produce the vinylated benzophenone in 70% yield. Deuterium incorporation studies also demonstrated complete transfer of the arene C−H bond to the diyne. Shibata and co-workers therefore proposed that C−H bond activation of the aryl or α,*β*-unsaturated ketone preceded two tandem insertion events (first hydrometalation of an alkyne and then carbometalation of the remaining alkyne), followed by reductive elimination. Given that minor ligand changes are the primary difference between the two systems, it is likely that the same mechanism is operating in each case. Further studies are necessary to determine which mechanism predominates in this transformation.

When enynes (e.g., **103**) were employed in place of the diynes, chiral products were obtained with high ee's in moderate to high yields with aryl (**104**) or α,*β*-unsaturated ketones (**105**) using (*S*)-BINAP as a ligand (eq 14). In contrast to the reaction of 1,6-diynes with enones (eq 13), isomerization of the product alkene was not observed in reactions between 1,6-enynes and enones. In a recent report from Tanaka and co-workers, (*R*)-H_8-BINAP was additionally reported to provide moderate to good yields and high enantioselectivities for the *ortho*-functionalization of aryl ketones with 1,6-enynes.[39] Tanaka also noted that although electron-donating substituents (e.g., 3-OMe) were tolerated on the aryl ketone moiety, the presence of electron-withdrawing substituents (e.g., 3-CF_3) resulted in the complete attenuation of reactivity under these conditions.

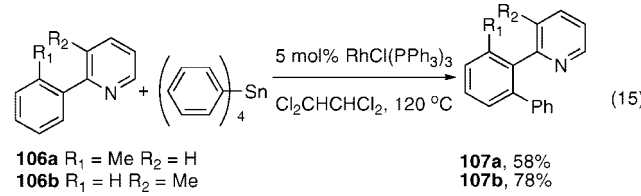


(14)

2.9. Directed Arylation

The ability to selectively arylate an arene or alkene via cross coupling methods has revolutionized the areas of medicinal and materials chemistry. Some of the drawbacks to the industrial-scale use of this transformation are the relatively limited availability and high cost of prefunctionalized reagents and the generation of a stoichiometric metal-halide byproduct. The development of C−H arylation reactions is therefore the subject of active investigation. While the Rh-catalyzed arylation of heterocycles has been well developed (vide infra), few methods for chelation-assisted arylation using Rh catalysis have been reported.[40]

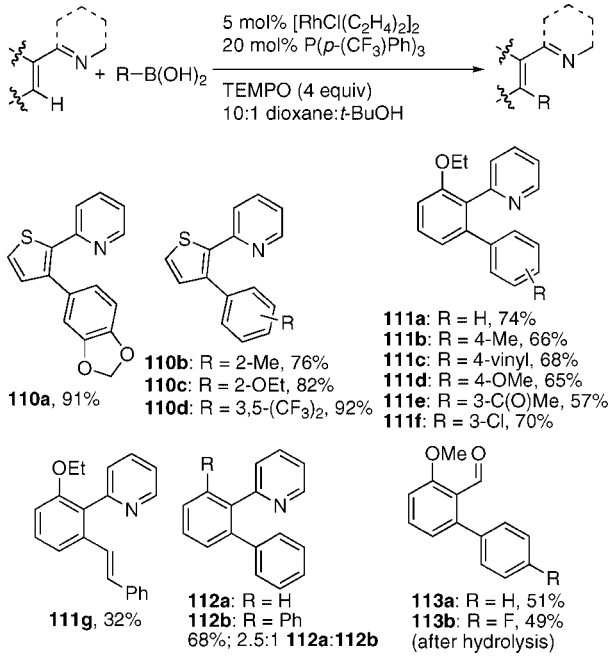
The earliest example of chelation-assisted arylation involved the arylation of 2-arylpyridines with tetraphenylstannane using Wilkinson's catalyst (eq 15).[41] Overarylation could be avoided by blocking one of the *ortho*-positions on the aryl substituent or by introducing a substituent at the 3-position of the pyridine ring. In the absence of these blocking groups, however, mixtures of mono- and dialkylated products were obtained.



(15)

More recently, pyridyl-directed arylation exhibited good scope and efficiency when aryl acid chlorides were used as the arylating agent (Chart 6).[42] In the absence of a blocking substituent, overarylation could not be prevented and good yields of diarylated products were obtained (**108a**,**b**). For

Chart 7. Oxidative Arylation of 2-Arylpyridines



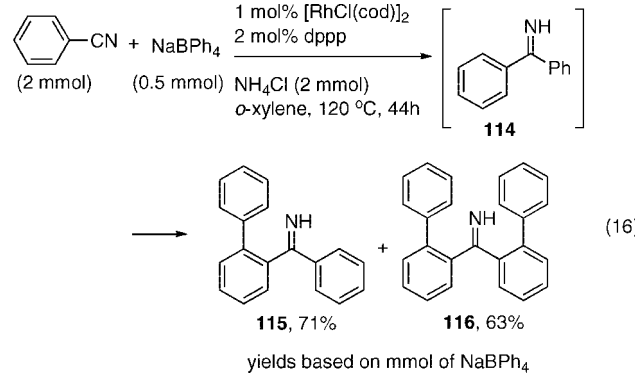
products **108e** and **108f**, a six-membered rhodacycle is generated upon C−H activation. The formation of this metallacycle is less favorable than that for the five-membered variant, and these products are generated with markedly lower efficiency.

The scope in acid chloride was fully explored using benzo[*h*]quinoline. In addition to functionalized phenyl substituents (**109a**−**f**), alkenyl (**109g**), and benzyl (**109 h**) substituents were transferred (Chart 6). The proposed mechanism involves initial oxidative addition into the acyl chloride, followed by decarbonylation to give a Rh(III)-aryl species. In the presence of a base, this can then undergo chelation-assisted C−H activation and reductive elimination to give the arylated product.

A pyridyl-directed oxidative coupling of arylboronic acids with arenes has also been recently reported.[43] Reaction optimization demonstrated that the electron-deficient phosphine ligand $[(p\text{-}(CF_3)C_6H_4)]_3P$ produced a Rh catalyst with the best reaction efficiency. Using this catalyst system and TEMPO as the oxidant, good yields could be obtained for the arylation of 2-arylpyridines, including a thiophenyl derivative (**110**), using a variety of arylboronic acids with differing steric and electronic properties (Chart 7). An alkenylboronic acid also coupled, but with poor reaction efficiency (**111g**). Finally, an aldimine moiety was demonstrated to serve as a directing group for the oxidative arylation of an aryl aldehyde (**113a**,**b**).

Based on the necessity of added oxidant and on the observed ligand effects, the C−H bond activation step is speculated to proceed via electrophilic aromatic substitution of a Rh(III) intermediate, as opposed to oxidative addition from a Rh(I) species.

Aryl imines were also demonstrated to undergo *ortho*-arylation using sodium tetraphenylborate as the arylating agent. In their studies on the coupling of aryl halides with arylboron species, Miura and co-workers noted that arylnitriles underwent 1,2-addition with the arylboronate to generate an imine (**114**), followed by *ortho*-arylation to generate mono- (**115**) and diarylated (**116**) products (eq 16).[44] When the preformed imine of benzophenone, **114**, was used, the yield of **115** and **116** nearly doubled, and more than one phenyl group was transferred from the tetraphenylborate. However, mixtures of mono- and diarylated products were still obtained. In this report, no oxidant was added and the imine **114** served as a hydrogen acceptor, generating diphenylaminomethane as a byproduct.



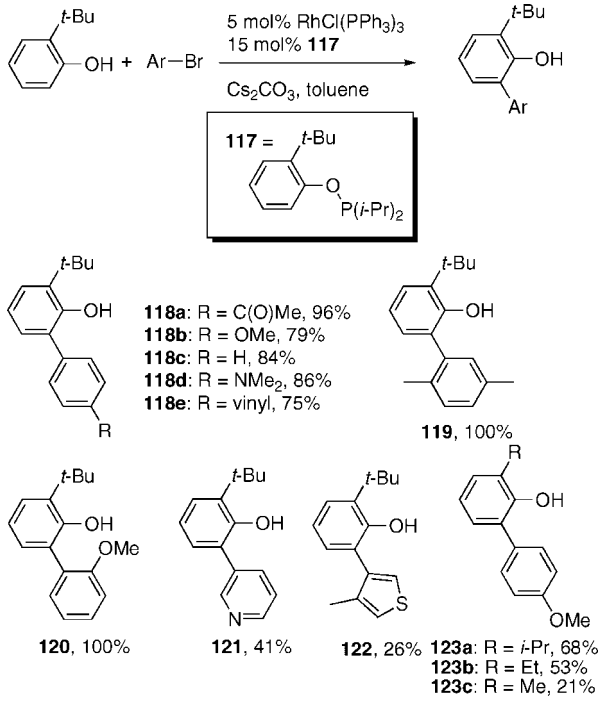
To suppress the undesired consumption of the imine substrate, Miura and co-workers have recently reported the use of α-chloroacetate as a hydrogen acceptor in the arylation of aryl imines with sodium tetraarylborates.[45] Using this additive, the *ortho*-arylation of phenyl pyridines, imidazoles, benzimidazoles, pyrazoles, and oxazolines with sodium tetraphenylborate proceeded in good to high yields, though arylation of both *ortho*-positions occurred in some cases.

Phenols have also been shown to undergo *ortho*-arylation via a unique mechanism for chelation-assisted C−H bond functionalization. For these transformations, phosphinites, phosphites, or phosphorus triamides are used both as ligands and as chelating agents for cyclometalation of the phenol. Phenols do not typically favor *ortho*-metalation, as this would form a highly strained four-membered metallacycle. When the phenol is incorporated into a phosphinite as an aryloxy substituent, however, a favorable five-membered metallacycle can form.[46]

Bedford demonstrated the *ortho*-arylation of phenols with aryl bromides using Wilkinson's catalyst and a cocatalytic quantity of phosphinite **117** (Chart 8).[47] A wide range of aryl halides with electron-withdrawing (**118a**) or electron-donating (**118b**,**d**) substituents reacted with 2-*tert*-butylphenol to give the *ortho*-arylated products. Substituents were also tolerated in the *ortho*- and *meta*-positions on the aryl bromide (**119** and **120**). Heterocyclic aryl bromides also reacted; however, decreased yields and byproducts resulting from overarylation were obtained (**121** and **122**). Phenols with less bulky *ortho*-substituents also participated in this chemistry, albeit with a corresponding decrease in yield with increasingly smaller substituents (**123a**−**c**). Phosphinite **117** was used catalytically in the syntheses of **123a**−**c**, which leads to a mixture of products that must be separated. This could be avoided only if the starting phenol and the aryloxy substituent on the phosphinite additive were equivalent.

The exact mechanism of this process is unknown. Oxidative addition of the aryl bromide, followed by cyclometalation of the phosphinite with loss of HX from a Rh(III) center, is one possibility. It is also possible that cyclometalation precedes oxidative addition of the aryl halide. In any event, reductive elimination followed by ligand exchange would close the catalytic cycle. A competition experiment between *p*-tolyl bromide and *p*-dimethylaminophenyl bromide produced products in equimolar quantities. Because no differ-

Chart 8. Phenol Arylation



ence was seen in the reactivity of these electronically dissimilar substrates, the authors maintain that oxidative addition of the aryl halide is not involved in the rate-determining step. In addition, the strong dependence on a bulky *ortho*-substituent to achieve good reaction efficiency supports rate-determining cyclometalation.

Improvements in reactivity were demonstrated by using catalytic quantities of hexamethylphosphorous triamide (HMPT, $P(NMe_2)_3$) in place of the phosphinite additive. This improvement was reported independently by Bedford[47] and Oi and Inoue.[48] The use of HMPT over phosphinite ligands enabled the coupling of sterically challenging aryl bromides and reduced the requirement for a substituent at the 2-position of the phenol, although diarylated products were obtained for substrates lacking adequate steric blocking. Furthermore, HMPT is commercially available and, unlike the phosphinites, will not produce product mixtures resulting from the reactivity of the aryloxy substituent.

2.10. Directed Carbonylation

Although examples of C−C bond formation via chelation-assisted C−H bond activation using alkenes, alkynes, and functionalized arenes are now prevalent in the literature, C−C bond formation via carbonylation has been slower to develop. Reported examples of chelation-assisted C−H bond carbonylations frequently employ Ru catalysts, which have proven efficient in this transformation.[49] Early examples using Rh catalysts involved the dehydrogenation of saturated *N*-heterocycles, followed by CO/olefin coupling.[50] More recently, nitrogen-containing directing groups have been employed to direct the *ortho*-carbonylation of arenes. In the earliest report utilizing this approach, Chatani and co-workers demonstrated the reaction of *N*-arylpyrazoles with CO and ethylene using $Rh_4(CO)_{12}$ as the catalyst (Chart 9).[51] The transformation was tolerant of electron-donating substituents on the arylpyrazole ring (**124a**−**d**), in addition to heteroarenes (**125** and **126**) and 1- and 2-naphthalene (**127** and **128**), although in some cases dialkylation was observed as the

Chart 9. Carbonylation of *N*-Arylpyrazoles

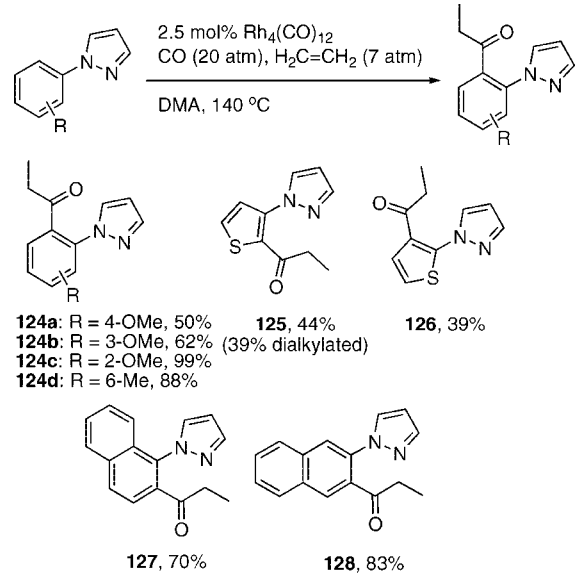
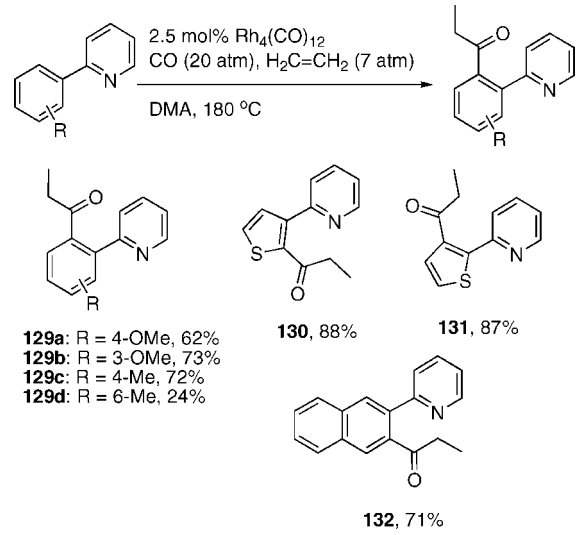


Chart 10. Carbonylation of 2-Arylpyridines

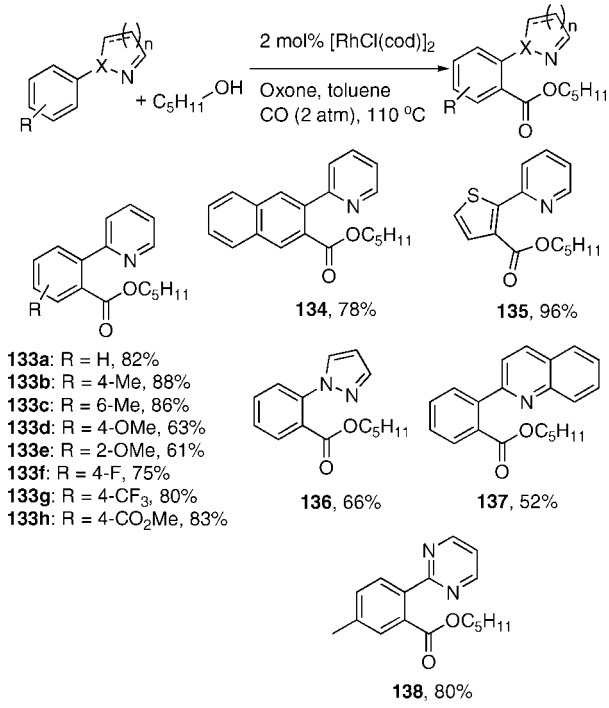


major product in the absence of a blocking substituent. Substrates incorporating an electron-withdrawing substituent such as CF_3 or carbonyl functionalities gave poor yields, and the starting heterocycle was recovered.

Heterocycle-directed carbonylative couplings with CO and ethylene using $Rh_4(CO)_{12}$ have also been applied to 2-arylpyridine derivatives, though increased temperatures were required to achieve high conversions.[52] As was observed for the *N*-arylpyrazole substrates, electron-withdrawing substituents were well tolerated, whereas electron-withdrawing substituents resulted in substantially lower yields (Chart 10). Heterocyclic arenes and naphthalene could also be employed.

Until recently, C−H carbonylations employing Rh or Ru exploited reductive couplings with alkenes. A recent report from Liang and Zhang demonstrated the feasibility of an oxidative carbonylative coupling with CO and alcohols to generate esters.[53] In this case, the $[RhCl(cod)]_2$ precatalyst was used in the presence of CO, *n*-pentanol, and a terminal oxidant, Oxone, to generate *ortho*-esterified 2-arylpyridine derivatives in good yields (Chart 11). A broad range of substituents were tolerated on the 2-arylpyridine, with both electron-rich (**133b**−**e**) and electron-poor (**133f**−**h**) arenes performing well. Fluorinated arenes were also tolerated

Chart 11. Oxidative Carbonylation of Arenes



(**133f**), as were thiophene and naphthalene derivatives. In addition, the heterocycle could be varied to include *N*-phenylpyrazole (**136**), 2-phenylquinoline (**137**), and 2-phenylpyrimidine (**138**) derivatives. Although *n*-pentanol performed consistently well under these conditions, the use of branched alcohols resulted in substantially reduced yields.

3. Chelation-Assisted Functionalization of Olefins

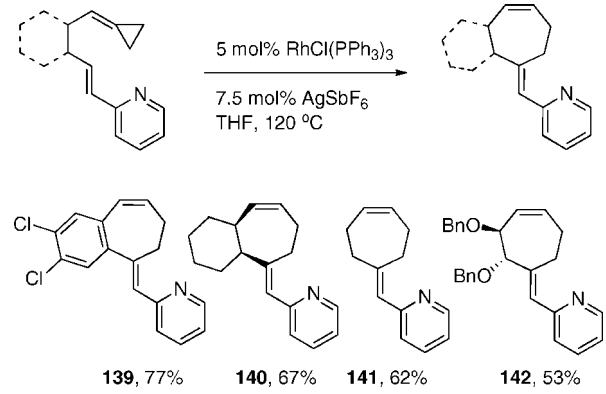
In comparison to the C−H bond functionalization reactions that have been developed with arenes, the reactivity of olefins remains underexplored. This is perhaps because the leading chelating moieties for Rh catalysis, namely the imine and carbonyl functionalities, serve to activate pendent olefins toward other reactions such as conjugate addition and polymerization. These side reactions are not at play for aryl systems. Additionally, the issue of olefin isomerization in acyclic substrates presents further challenges to the development of these methods. Despite these challenges, several methods have emerged for olefin functionalization using chelation assistance.[54]

3.1. Alkylation Reactions

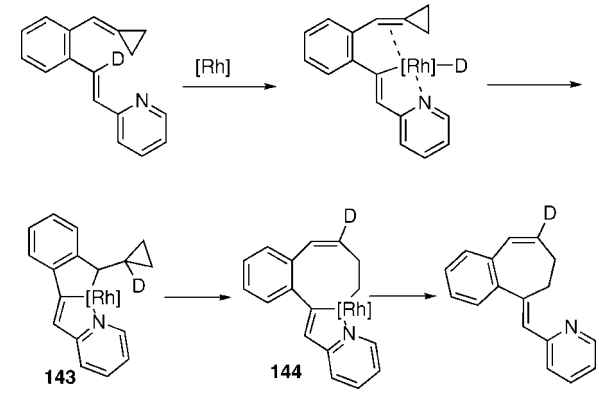
Early examples of Rh-catalyzed hydrovinylation of alkenes avoided the reactivity of α,β-unsaturated carbonyl derivatives by utilizing heterocyclic directing groups such as pyridine, imidazole, and oxazoline to afford inter-[55] and intramolecular[27] alkylation. While olefin isomerization could often be avoided in intramolecular transformations by careful selection of the reaction parameters, this side reaction was difficult to avoid in intermolecular reactions where acyclic products were generally formed.

More recently, Fürstner has developed a tandem pyridyl-directed olefin C−H bond activation and cycloisomerization of a tethered alkylidenecyclopropane using a cationic Rh catalyst generated from $RhCl(PPh_3)_3$ and $AgSbF_6$ (Chart 12).[56] The reaction proceeded in moderate yields when a rigid tether consisting of an aryl or cyclohexyl ring (**139** and **140**,

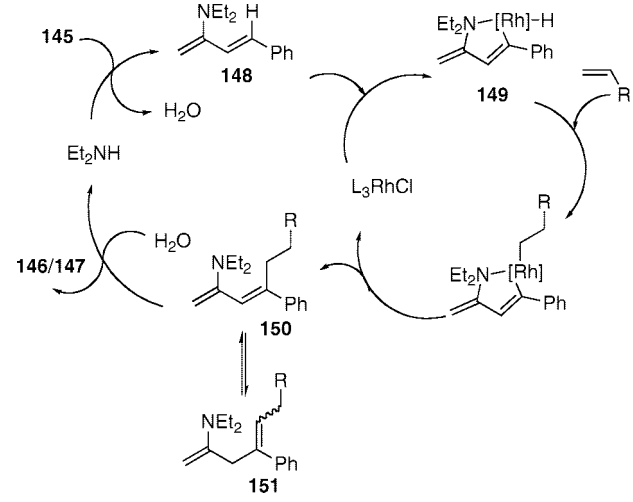
Chart 12. Tandem C−H Activation/Cycloisomerization



Scheme 10. Mechanism for C−H Activation/ Cycloisomerization Tandem



Scheme 11. Mechanism for the β-Alkylation of 145

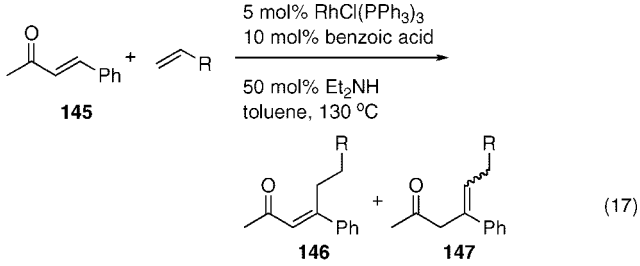


respectively) is present or when flexible linkers are used (**141** and **142**). The structures of the resulting products were verified by X-ray crystallography.

Mechanistically, initial C−H bond activation followed by hydrometalation of the alkylidenecyclopropane generates intermediate **143** (Scheme 10). Subsequent cycloisomerization furnishes **144**, which undergoes reductive elimination to give the product. This mechanism is supported by deuterium labeling studies, which demonstrate complete transfer of a vinylic deuterium to the site of the newly formed double bond as shown in Scheme 10.

Jun was the first to report on the Rh-catalyzed alkylation of an α,β-unsaturated carbonyl derivative.[57,58] In the presence of a dialkylamine, Wilkinson's catalyst facilitates the alky-

lation of enone **145** with a variety of alkyl- and silyl-monosubstituted olefins to produce a mixture of substituted ketones **146** and **147** (eq 17). The formation of **147** is of particular note, as the olefin has undergone isomerization out of conjugation with the ketone. It is surprising that this is the major component of the product mixture. A substoichiometric quantity of benzoic acid was determined to be a required additive for this transformation to proceed, presumably facilitating the initial condensation of the amine with the ketone.



(17)

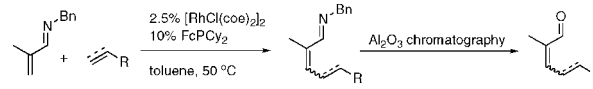
146/147a: R = *n*-Bu; 71%, 35:65 (**146**:**147**)
146/147b: R = Cy; 77%, 23:77
146/147c: R = H; 99%, 24:76
146/147d: R = *t*-Bu; 57%, 15:85
146/147e: R = $SiMe_3$; 99%, 5:95

A plausible mechanism for this transformation is given in Scheme 11. Initial condensation of **145** with diethylamine, followed by tautomerization, gives enamine **148**. Coordination of the Rh catalyst to the amine, followed by oxidative addition of the β C−H bond, produces rhodacycle **149**. Hydrometalation of the olefin, followed by reductive elimination, yields enamine **150**, which can then undergo further Rh-catalyzed isomerization to **151**. Enamine hydrolysis then provides products **146** and **147**. The authors independently prepared the piperidyl enamine of **146c** and found that, upon subjecting this product to the catalytic reaction conditions, a mixture of **146c** and **147c** was obtained. Subjecting the piperidyl enamine of **146c** to the hydrolysis conditions gave back pure **146c** with no isomerization, supporting the hypothesis that the deconjugation to **147c** involves a Rh complex.

Significant advances in catalyst design enabled the application of this transformation to α,β-unsaturated *N*-benzyl aldimines with substantially broadened scope and generality.[59] Although substantial *E*/*Z* isomerization of the product imine was observed using Wilkinson's catalyst, electron-donating ligands such as PCy_3 and (dicyclohexylphosphinyl)ferrocene ($FcPCy_2$) produced a much more efficient catalyst, allowing the temperature to be decreased and minimizing olefin isomerization. Using $[RhCl(coe)_2]_2$ as a Rh precatalyst and $FcPCy_2$, the scope of this transformation included monosubstituted olefins possessing alkyl (Table 7, entries 1 and 2), aryl (entry 3), ester (entries 4 and 5), and chloro substituents (entry 6). In addition, the terminal alkyne *tert*-butylacetylene underwent hydrovinylation to give the dienal product (entry 7). Under standard hydrolysis conditions, complete isomerization to the *E* isomer was seen (entries 2 and 5). However, concomitant hydrolysis and chromatography on activity III neutral alumina afforded the trisubstituted *Z* enal products with good stereoselectivity (entries 1, 3−4, 6−7).

This method can also be successfully applied to β-substituted aldimines to generate β,β-disubstituted carbonyl compounds stereoselectively. These structures are very difficult to prepare stereoselectively by standard methods

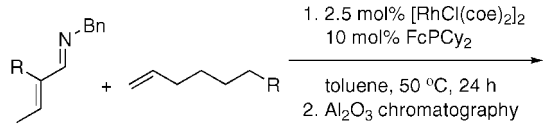
Table 7. Alkylation of α,β-Unsaturated Aldimines

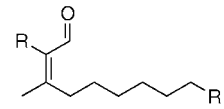


Entry	Alkene(yne)	Time (h)	Imine (*Z*:*E*)	Yield (*Z*:*E*)[a]
1		12	>95:5	91% (10:1)
2[b]		12	>95:5	77% (5:>95)
3	C_6H_5	24	10:1	74% (5:1)
4	OMe, O	4	>95:5	78% (5:1)
5[b]	OMe, O	4	>95:5	73% (5:>95)
6	Cl	8	>95:5	80% (10:1)
7		4	>95:5	86% (20:1)

[a] Isolated yields. [b] Crude imine was stirred at a concentration of 0.1 M in a 5:5:2 solution of THF/acetic acid/H_2O for 16 h prior to isolation.

such as the Wittig, Horner−Wadsworth−Emmons, and olefin cross-metathesis. Aldimines **152** and **153** underwent stereoselective alkylation with 1-hexene to give the tri- and tetrasubstituted enal products in good yield and isomer ratio (eq 18).





(18)

R = H, 86%, 10:1 (*Z*:*E*)
R = Me, 66%, 10:1 (*Z*:*E*)

3.2. Synthesis of (−)-Incarvillateine

The potential utility of β-alkylation of α,β-unsaturated imines, in particular for the stereoselective synthesis of highly substituted α,β-unsaturated enals, was clearly demonstrated in the context of an intramolecular alkylation in the total synthesis of the potent analgesic (−)-incarvillateine (**154**) (Figure 8).[60] Taking advantage of the *C*2 symmetry of **154**, an obvious retrosynthetic disconnection at the ester linkages gives cyclobutane **155**, which can be synthesized in two steps from ferulic acid, and piperidine **156**,[61] which could be accessed very efficiently by employing an intramolecular β C−H bond alkylation of substrate **158**. As illustrated in Figure 8, intramolecular alkylation of **158** via Rh-catalyzed C−H activation followed by *syn*-alkene insertion and reductive elimination would exclusively provide the desired exocyclic double bond geometry and the requisite *anti* relationship of the methyl and ester functionalities.

The requisite imine substrate **158** was prepared in four steps from commercially available **159** (Scheme 12). An asymmetric allylation of **159**, followed by protection of the hydroxyl group, provided **160** in high enantioselectivity. Olefin metathesis gave aldehyde **161**, which was converted to **158** via condensation with methylamine.

The C−H bond functionalization of **158** was of particular interest because it represented the first example of diastereocontrol in intramolecular alkylation arising from a stereocenter on the tether. Ligand screening revealed that

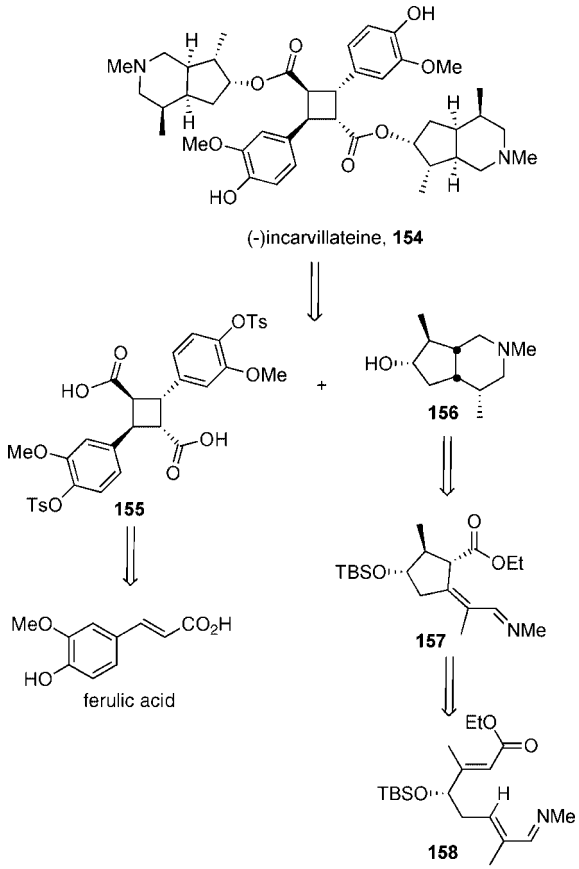


Figure 8. Retrosynthesis of (−)-Incarvillateine **154**.

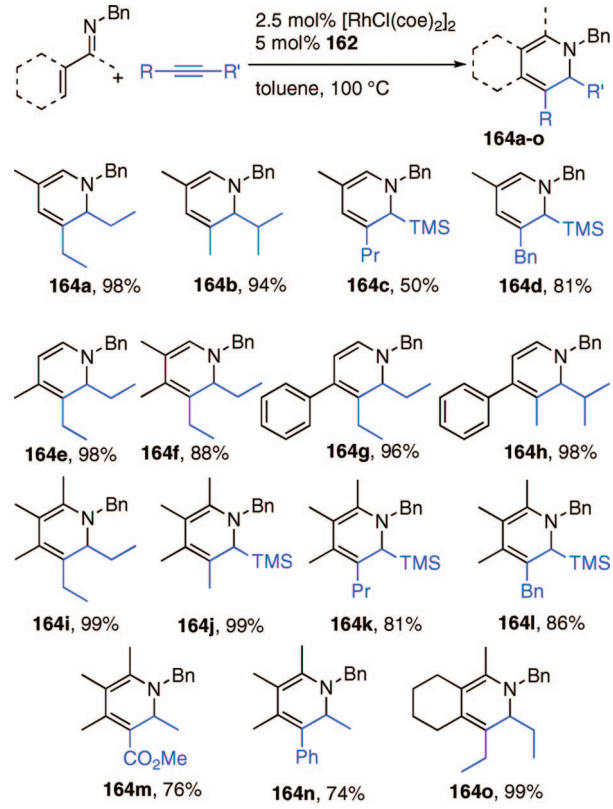
electron-donating phosphine ligands were best suited for the desired transformation, and use of the *p*-(*N*,*N*-dimethylaminophenyl)diethylphosphine ((DMAPh)PEt_2, **162**) ligand shown in Scheme 12 provided quantitative conversion to **157** with 5:1 diastereoselectivity.

Compound **157** was found to undergo facile tautomerization to the dienamine conjugated to the ester, racemizing the α-stereocenter. However, direct reduction of the crude imine product, followed by lactamization, provided lactam **163** as a single stereoisomer in 51% overall yield from acyclic precursor **158**. Facial selective hydrogenation of **163**, followed by reduction of the lactam to the piperidine and deprotection of the hydroxyl group, provided **156**, which was required for coupling to **155**. The Mitsunobu coupling of **155** and **156** proceeded in good yield with inversion at the hydroxyl stereocenter. Deprotection of the tosylate protecting groups using sodium/anthracene furnished (−)-incarvillateine **154** in only 11 steps and 15.4% overall yield.

3.3. Alkenylation Reactions

As discussed previously, upon reaction of an *N*-benzyl imine with *tert*-butylacetylene, the *β*-alkenylation product could be isolated (Table 7, entry 7).[59] In contrast, reactions with internal alkynes or less bulky alkynes generated alkenylated products that underwent electrocyclization under the reaction conditions to yield 1,2-dihydropyridine (DHP) products (eq 19). This reactivity had been previously observed by Jun and co-workers with aryl imine substrates, though more forcing conditions were required to disrupt the aromaticity of the aryl imine (vide supra).[34] Odom also reported a single example of a one-pot hydroamination/C−H alkenylation sequence that generated a 1,2-DHP from the *N*-phenyl imine of 1-acetylcyclohexene.[62]

Chart 13. Dihydropyridine Synthesis from Imines and Alkynes[a]



[a] Yields determined by NMR integration relative to 2,6-dimethoxytoluene as an internal standard

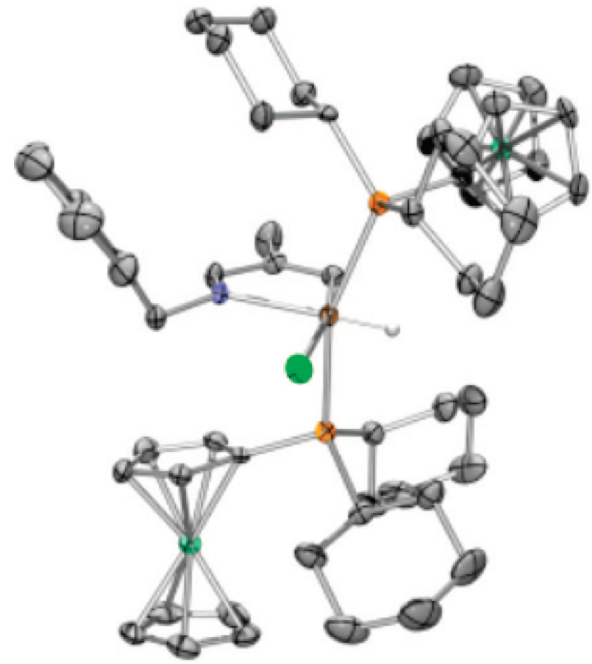
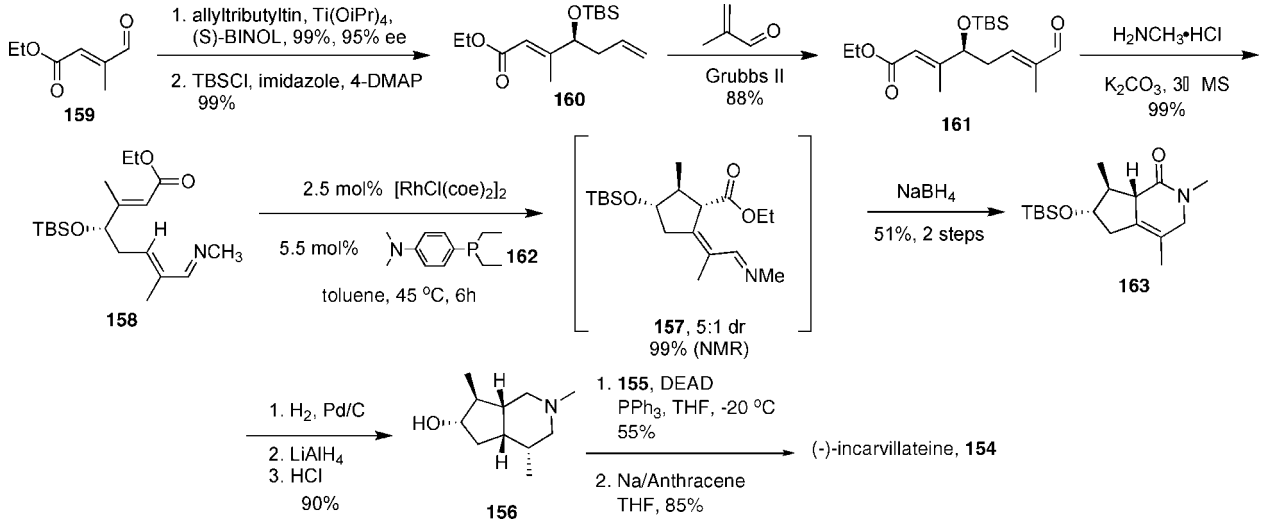


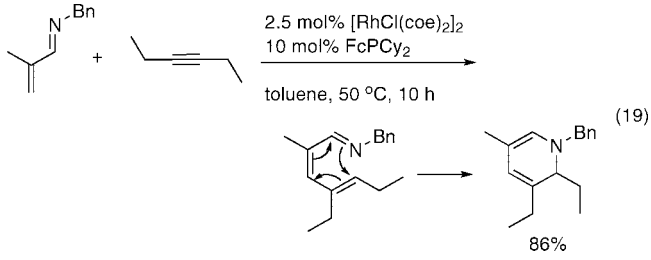
Figure 9. X-ray crystal structure (ORTEP diagram) of **165** with thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms distant from the metal center have been omitted for clarity.

The development of new ligands for C−H bond functionalization was required to achieve sufficient scope for this transformation.[7] In addition, the ratio of ligand/Rh was also found to be an important parameter in improving the

Scheme 12. Synthesis of 154

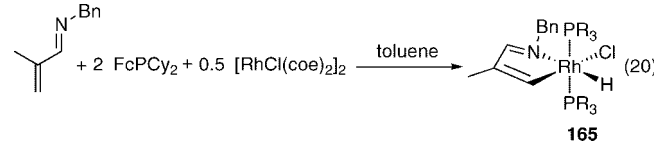


efficiency of the method. Catalyst optimization ultimately revealed that use of the (DMAPh)PEt_2 ligand **162** in a 1:1 ratio of L/Rh provided the highest yields of DHP products. Under these conditions, β-unsubstituted aldimines reacted cleanly with internal alkynes having alkyl (**164a**,**b**), silyl (**164c**,**d**), or benzyl (**164d**) substituents (Chart 13). Unsymmetrical alkynes typically reacted to give a single regioisomer, provided one of the substituents was α-branched. In nearly every case, the more sterically bulky substituent is oriented proximal to the DHP nitrogen, with smaller substituents in the distal position. This supports a mechanism that includes hydrometalation of the alkyne as opposed to carbometalation (Scheme 1). Aldimines with alkyl (**164e**,**f**) or aryl (**164g**,**h**) substituents at the β-position also reacted to produce highly substituted DHP products in good yields. In addition to the aldimines, ketimines were very efficient substrates in this chemistry (**164i**−**o**). The ketimines also exhibited clean conversion to DHP products with ester (**164m**) and aryl (**164n**) substituted alkynes.



Mechanistic investigations were carried out on this system. In a stoichiometric reaction between the *N*-benzyl imine of methacrolein, a Rh precatalyst, and $FcPCy_2$, a new complex, **165**, formed immediately upon combination of the reagents at room temperature (eq 20). X-ray quality crystals of **165** could be isolated by vapor diffusion, providing the structure shown in Figure 9. The geometry of **165** is distorted octahedral, and the Rh−H bond length is 1.36(4) Å. When isolated **165** is redissolved in toluene-d_8 or THF-d_8, a 2:1 equilibrium mixture of **165**:free imine is obtained. This result indicates that C−H bond activation is facile and reversible under the reaction conditions, which is in agreement with deuterium labeling studies independently performed by Brookhart and Murai.[6]

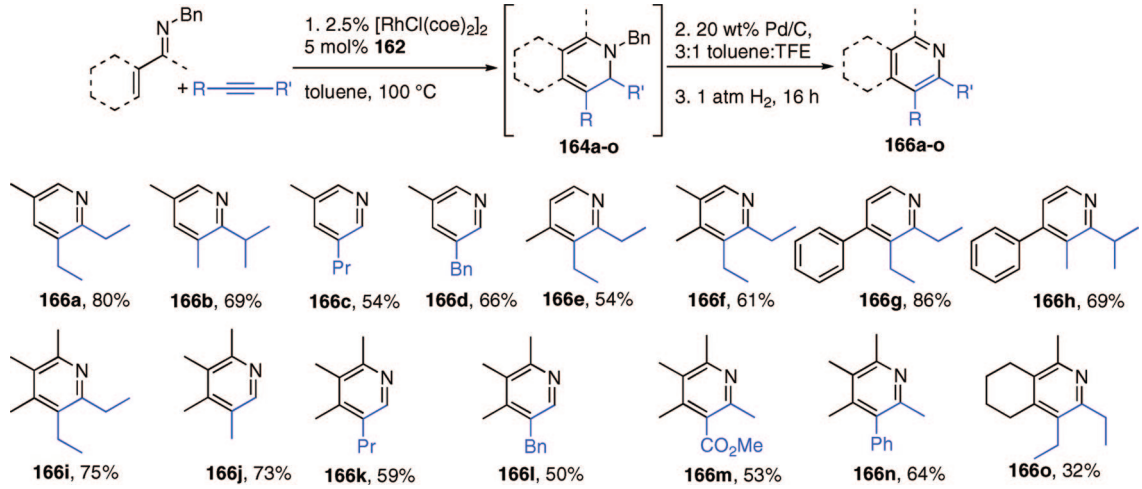
It was further found that reducing the reaction temperature in the catalytic synthesis of **164a** sufficiently slowed the electrocyclization step such that the azatriene intermediate could be observed to grow in and then decay when the reaction was monitored by NMR. In addition to providing evidence against a [4 + 2] cycloaddition-based mechanism, the observation of this intermediate enabled further kinetic analysis. Computational simulations were performed on this system in order to elucidate further mechanistic information based on the method of numerical integration using the Copasi program.[63] These simulations also corroborated earlier mechanistic studies, implicating rate limiting reductive elimination with facile oxidative addition and migratory insertion steps (Scheme 1).



Dihydropyridines have proven to be versatile intermediates for the synthesis of piperidines and pyridines, which are prevalent in natural products, drugs, and materials. Further application of the alkenylation/electrocyclization DHP synthesis to the preparation of pyridines would be particularly useful from a pharmaceutical and materials science standpoint because few methods are available for the selective synthesis of highly substituted pyridine derivatives.[64] To achieve this, an oxidation protocol was developed that enabled a one-pot synthesis of pyridines from imines and alkynes (Chart 14). Following DHP synthesis, the crude solution was subjected to catalytic oxidation using Pd/C and air, which generates the *N*-benzylpyridinium salt. Subsequent hydrogenolysis of the benzyl group under an atmosphere of H_2 provided the pyridine derivatives in modest to high yields for the three-step, one-pot protocol. During reaction optimization, it was found that careful control of the temperature was needed to avoid α-dealkylation of the pyridine. In derivatives that displayed a silyl group α to the nitrogen, however, desilylation could not be avoided and this group was cleaved (**166c**,**d**,**j**−**l**). In this case, the silyl group can be used as a convenient blocking group, forcing bulkier substituents distal to the pyridine nitrogen.

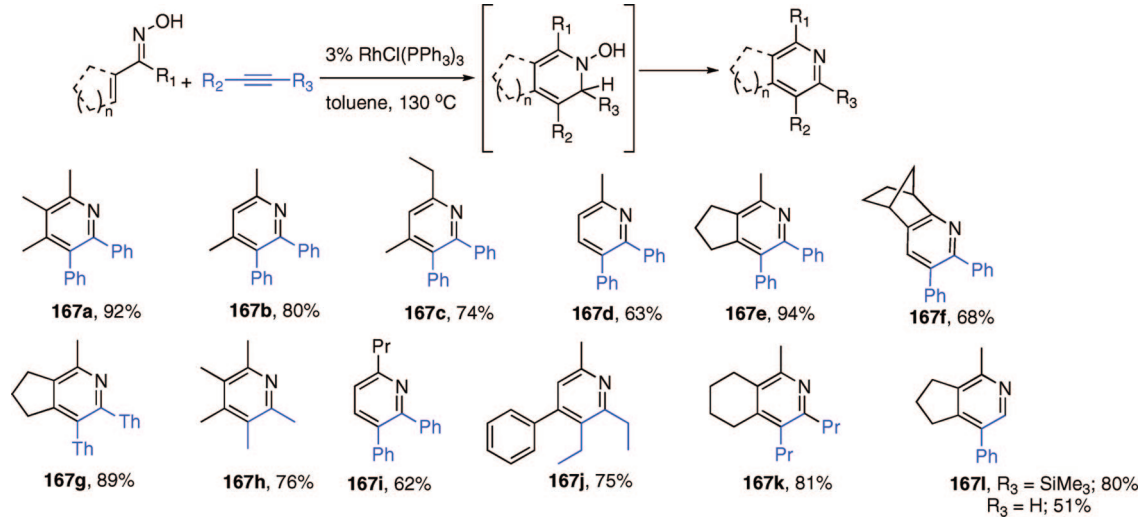
A related synthesis of pyridines from ketoxime derivatives and alkynes using Wilkinson's catalyst has also been reported (Chart 15), though this transformation was not demonstrated

Chart 14. One-Pot Synthesis of Pyridines from Imines and Alkynes[a]



[a] Yields given are isolated yields based on starting imine.

Chart 15. Pyridine Synthesis from Ketoximes and Alkynes



to proceed with aldoxime substrates.[65] In this example, elimination of water from the DHP intermediate generates the pyridine directly, rendering the oxidation step required with *N*-benzyl imines unnecessary. The scope in ketoxime for this transformation was quite good, with cyclic and acyclic ketoximes with alkyl and aryl substituents performing well (Chart 15). In addition to di(2-thiophenyl) acetylene, symmetrically substituted alkyl alkynes (**167h**,**j**,**k**) and di(2-thienyl)acetylene (**167g**) also coupled in good yield. Unsymmetrically substituted phenylacetylenes reacted to give a single regioisomer of product when a sterically bulky trimethylsilyl or a sterically small hydrogen substituent was present (**167l**). However, 1-phenyl-1-propyne and 1-phenyl-1-butyne both gave regioisomeric mixtures. It is interesting to note that the trimethylsilyl substituent is also lost in this transformation to give desilylated pyridine **167l**, despite the fact that no formal oxidation is performed. With the *N*-benzyl imines, the silyl group is maintained in the Rh-catalyzed transformation and lost only upon oxidation (vida supra, Chart 14).

When the alkenylation reaction conditions were applied to the oxime of acetophenone, the alkenylated product could be isolated prior to electrocyclization. Electrocyclization requires breaking aromaticity in aryl substrates and is therefore less facile than that for α,β-unsaturated substrates. Exposure of the alkenylated product to increased reaction temperatures induced cyclization and dehydration, and the isoquinoline was obtained in high yield. This is evidence in favor of a mechanism that involves C−H alkenylation, rather than a hetero -Diels−Alder mechanism.[66]

The alkenylation of α,β-unsaturated imines was applied to an intramolecular transformation for substrates that have alkynes tethered via the imine nitrogen (e.g., **168**, Scheme 13).[67] Depending on the direction of the migratory insertion step, two different products are expected, **169** or **170**. Subjecting substrate **168** to a variety of Rh-based catalysts produced the highly strained bicyclic enamine **170** exclusively.

Enamine **170** possesses several unique structural characteristics, namely a bridgehead enamine that lacks the proper geometry for conjugation and a bridgehead double bond in a nine-membered ring. As evidence for the distinctive reactivity of the unconjugated enamine, **170** underwent methylation with dimethyl sulfate to provide the *N*-methylated product **171**, as opposed to the *C*-alkylated product that is normally obtained from enamine alkylation. X-ray quality crystals of **171** were obtained, validating the highly strained structure of this bicycle (Figure 10).

Substituent effects and the dependence on tether length were investigated, and the results are summarized in Table 8. Substrate **172**, possessing a tether with one fewer

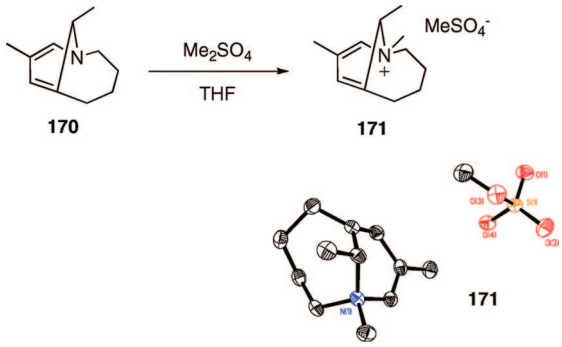
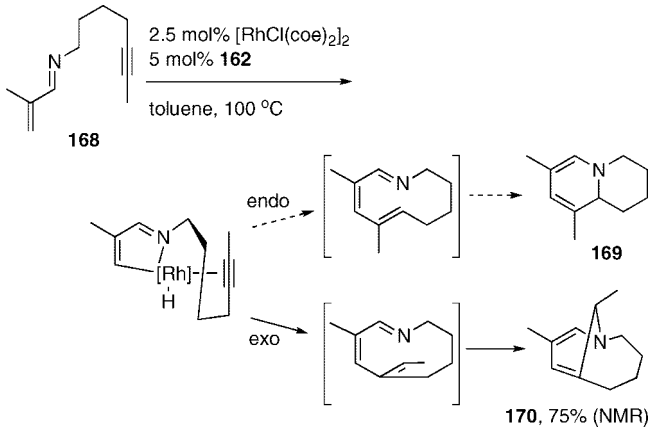


Figure 10. Methylation of **170**. ORTEP diagram of **171** with thermal ellipsoids drawn at the 50% probability level.

Scheme 13. Possible Reaction Pathways for 168



methylene, underwent alkenylation, but the resulting triene decomposed without cyclizing, presumably due to the strain required to form a smaller ring with a bridgehead double bond. Substrate **173**, with a methyl group α to the nitrogen on the tether chain, underwent alkenylation and slow electrocyclization to give a single diastereomer of product, **174**. Substrates with *β*-substituents on the α,*β*-unsaturation (**175** and **177**) produced products with exocyclic double bonds. Isomerization likely occurs under the reaction conditions in order to relieve ring strain.

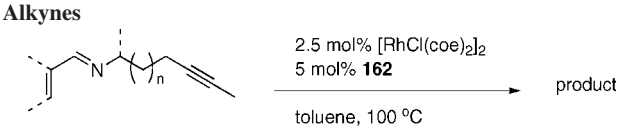
4. Alkylation of N-Heterocycles

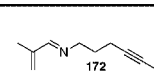
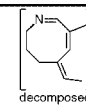
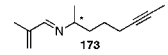
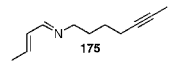
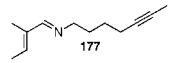
An alternative paradigm for achieving selectivity in C−H bond functionalization reactions is to exploit the electronic stabilizing effect of a pendent heteroatom on the M−C bond (Figure 1B). This approach has been utilized in the Rh-catalyzed alkylation and arylation of *N*-heterocycles. The rapid synthesis of a variety of substituted *N*-heterocycles is of practical importance to the pharmaceutical and material science industries, which rely on the structural fine-tuning of these compounds to achieve a desired function.[68] The selective and mild functionalization of C−H bonds represents an appealing approach towards generating a wide variety of substituted heterocyclic analogues.

4.1. Intramolecular Alkylation of Azoles

The first example of azole alkylation by C−H activation was reported by Bergman, Ellman, and co-workers in their intramolecular annulation of imidazole and benzimidazole derivatives (eq 21).[69,70] Extensive screening of transition-metal catalysts for the cyclization of **179** led to the finding that Wilkinson's catalyst was an effective catalyst for the

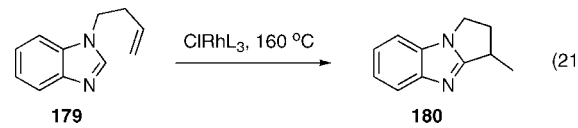
Table 8. C−H Bond Functionalization of Imines with Tethered Alkynes



Substrate	Time	Product	Yield[a]
	3 h	 decomposed	-
	9 days	 174	63%
	4 h	 176	50%
	48 h	 178	20%

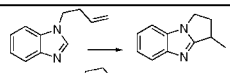
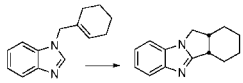
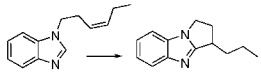
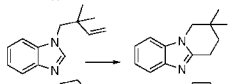
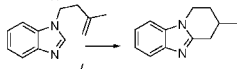
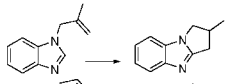
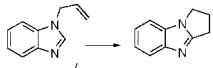
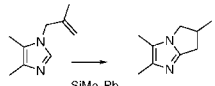
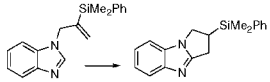
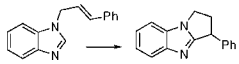
[a] Isolated yields.

conversion of **179** to **180**. When the reaction was monitored using ^{1}H NMR, isomerization of the double bond of **179** to the internal position was observed prior to C−C bond formation, resulting in the exclusive production of the five-membered ring. Using the Rh-precatalyst $[RhCl(coe)_2]_2$, phosphine ligands with varying steric and electronic properties were surveyed to reveal that electron-rich secondary alkyl phosphines such as PCy_3 provided a much more efficient catalyst system, producing **180** in 86% yield in 3.5 h. Using these conditions, dimethylimidazole and benzimidazoles with a variety of *N*-tethered olefins underwent annulation in good yield (Table 9, column 3, method **A**). To achieve high conversion, disubstituted olefins generally required higher catalyst loadings (entries 3 and 5) and the trisubstituted olefin in entry 2 additionally required increased reaction temperature and prolonged reaction time. In most cases, the five-membered adduct was generated; however, in substrates where the olefin cannot isomerize (entry 4) or when formation of the five-membered ring would require the formation of a quaternary center (entry 5), the six-membered ring was preferred.

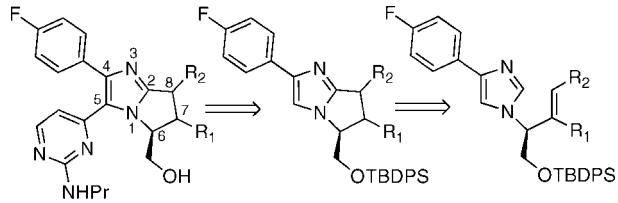


It was later found that the reaction was considerably more efficient in the presence of a Lewis or Brønsted acid additive such as lutidinium chloride or $MgBr_2$, providing an increase in both the reaction rate and the conversion. The convenient use of air-stable $[HPCy_3]Cl$ as a source of both the Brønsted acid and ligand enabled a simplified protocol for the annulation of azoles under microwave conditions that did not require extensive solvent purification or the rigorous exclusion of air (Table 9, column 4, method **B**).[71] Under these reaction conditions, the substrate scope was expanded to include styrenyl derivatives and sterically bulky silyl substituted alkenes (entries 9 and 10).

Table 9. Substrate Scope for Azole Annulation

Entry	Reaction	Yield A[a]	Yield B[d]
1		79%	76%
2		75%[b,c]	-
3		59%[b]	84%
4		89%	-
5		71%[b]	78%
6		82%	97%
7		70%[b]	50%[e]
8		71%	-
9		-	74%
10		-	62%

[a] Conditions for method **A**: 2.5% $[RhCl(coe)_2]_2$, 7.5% PCy_3, 160 °C, 20 h in THF. [b] Method **A** using 5% $[RhCl(coe)_2]_2$ and 15% PCy_3. [c] Method **A** at 180 °C for 3 days. [d] Conditions for method **B**: 2.5% $[RhCl(coe)_2]_2$, 7.5% $[HPCy_3]Cl$, 225−250 °C (microwave), 6−12 min in 1,2-dichlorobenzene/acetone. [e] Method **B** using 5% $[RhCl(coe)_2]_2$ and 15% $[HPCy_3]Cl$.



181a: $R_1 = R_2 = H$
181b: $R_1 = Me$, $R_2 = H$
181c: $R_1 = H$, $R_2 = Me$

182a-c **183a-c**

Figure 11. Retrosynthesis of JNK3 inhibitors **181a−c**.

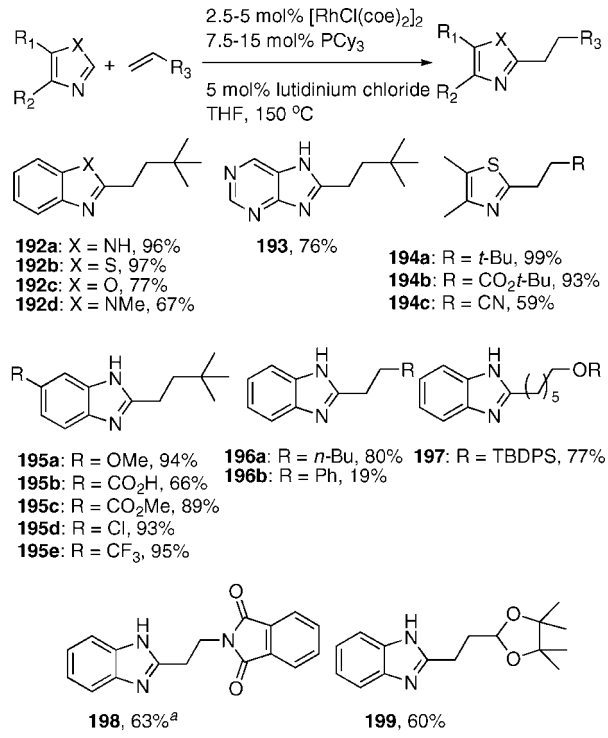
4.2. Synthesis of c-Jun *N*-Terminal Kinase Inhibitors

Intramolecular azole alkylation was also employed in the efficient syntheses of several bicyclic bisarylimidazole c-jun N-terminal kinase 3 (JNK3) inhibitors (**181a−c**, Figure 11).[72] By utilizing C−H alkylation chemistry to generate the bicyclic imidazole core, substituents could be easily introduced at the C7 and C8 positions by incorporating tethered olefins with varying substitution patterns (**183a−c**, Figure 11). Substitution at these positions would be difficult to access by the previously reported route to this class of inhibitors.[73] The cyclization of substrates **183a−c** also provided a platform on which to test the diastereoselectivity of heteroatom-directed alkylations.

For all substrates, the stereocenter at C6 was established using the *tert*-butanesulfinamide chiral amine reagent. The synthesis of **181a** began with the addition of vinylmagnesium bromide to sulfinyl imine **184** (Scheme 14). Acidic cleavage of the sulfinyl and silyl groups then provided homoallylic amine **185** in enantiopure form. Condensation of **185** with glyoxylic acid, followed by a van Leusen cyclization of the resulting imine with 4-fluorophenyl tosylmethyl isonitrile (**186**) efficiently generated the arylimidazole core of **187**. Silyl protection of the hydroxyl group then produced the requisite cyclization precursor **183a**. The steric hindrance introduced by the bulky silyl substituent at C6 impeded the Rh-catalyzed alkylation, and forcing conditions were used. Ultimately, **182a** was produced in 50% yield and 92% ee using a Rh/PCy_3 catalyst system with $MgBr_2$ as an additive at 180 °C. Detectable side products in the reaction included olefin isomers and reduction products. The presence of these species suggested that the minor degradation in enantiopurity was a result of racemization by olefin isomerization during the reaction. Bromination of the C5 position of **182a** followed by Stille coupling of the required pyrimidine moiety produced **188a**. The thioether of **188a** could then be converted to the necessary amine functionality by oxidation of the thioether to the sulfone followed by displacement with propylamine. Finally, cleavage of the silyl protecting group provided **181a** in 13% yield for the overall sequence.

Cyclization substrates **183b** and **189** were also prepared and examined in order to evaluate the diastereocontrol of the Rh-catalyzed alkylation and to showcase the flexibility of this synthetic approach toward the bicyclic bisarylimidazole core (Scheme 15). For substrate **189**, cyclization was expected to proceed to give the five-membered ring, as was observed in previous studies (vide supra, Table 9). The requisite amines **190** and **191** were prepared by addition of isopropenyl- or allylmagnesium bromide, respectively, to sulfinyl imine **184** (Scheme 15). Condensation with glyoxylic acid and cyclization with **186** followed by protection of the hydroxyl moiety then provided cyclization substrates **183b** and **189**. Substrate **183b** underwent intramolecular alkylation to give **182b** in 61% yield as a 3:1 mixture of diastereomers.

Chart 16. Substrate Scope for Intermolecular Azole Alkylation[a]



192a: X = NH, 96%
192b: X = S, 97%
192c: X = O, 77%
192d: X = NMe, 67%

193, 76%

194a: R = *t*-Bu, 99%
194b: R = CO_2*t*-Bu, 93%
194c: R = CN, 59%

195a: R = OMe, 94%
195b: R = CO_2H, 66%
195c: R = CO_2Me, 89%
195d: R = Cl, 93%
195e: R = CF_3, 95%

196a: R = *n*-Bu, 80%
196b: R = Ph, 19%

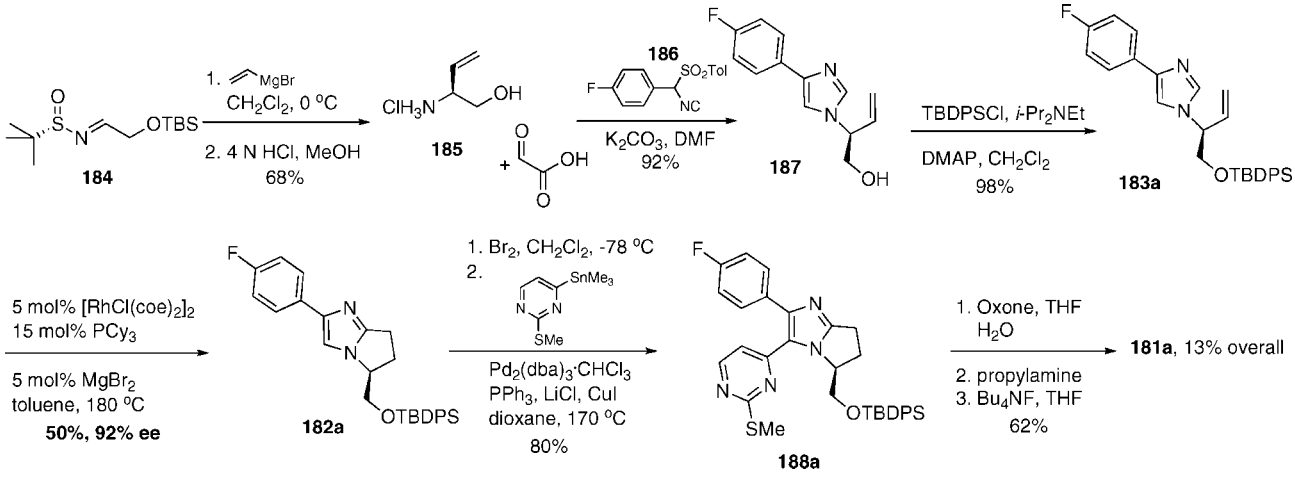
197: R = TBDPS, 77%

198, 63%[a]

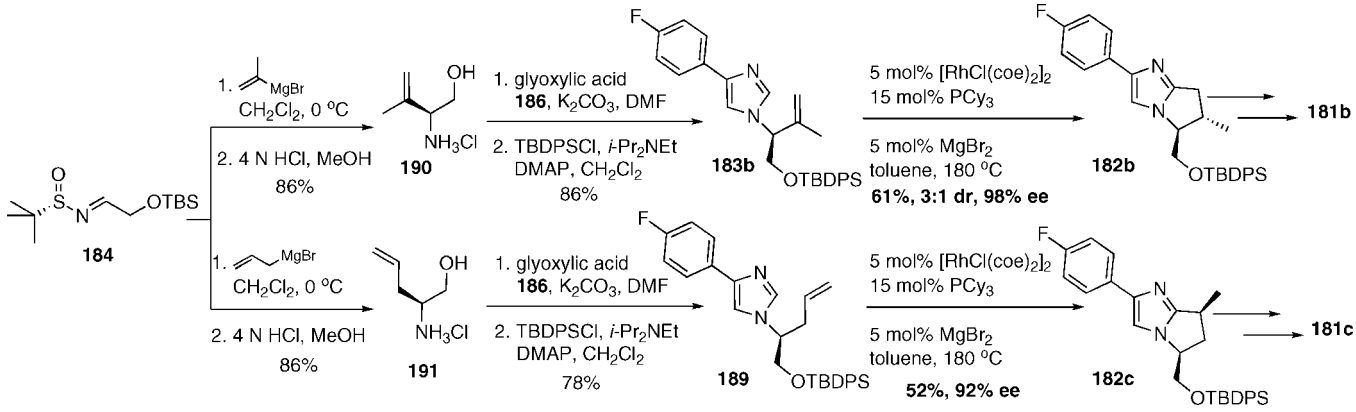
199, 60%

[a] $[HPCy_3]Cl$ was used in place of PCy_3 and lutidinium chloride.

Scheme 14. Synthesis of 181a



Scheme 15. Synthesis of 181b and c



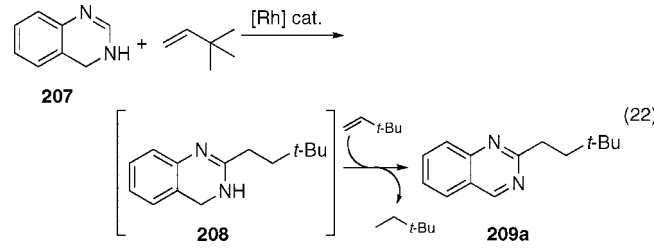
As was observed for substrate **183a**, olefin isomerization was a significant side reaction in this transformation. The diastereomeric mixture was further manipulated as in Scheme 14, with separation of the two isomers being achieved for the sulfone intermediate. Ultimately, **181b** was obtained enantio- and diastereomerically pure in 15% overall yield from the commercially available silyloxyacetaldehyde starting material. As expected, substrate **189** cyclized with preceding olefin isomerization to produce **182c** in a 86:14 mixture of diastereomers. The desired product **182c** could be isolated as a single diastereomer in 52% yield and 92% ee. Cyclization product **182c** was subsequently converted to **181c** according to Scheme 14 in 18% yield for the overall sequence.

In addition to **181a**−**c**, the enantiomers of **181b** and **c** were also prepared. All five compounds displayed comparable inhibitory activity against JNK3 (1.63−8.10 nM IC_{50} values), with *ent*-**181b** providing a 3- to 4-fold increase in potency relative to the parent inhibitor **181a**.

4.3. Intermolecular Alkylation of Azoles

Catalyst optimization for the intramolecular alkylations ultimately rendered the reaction conditions applicable to an intermolecular synthesis of 2-alkyl azoles.[74] Using either lutidinium chloride or $[HPCy_3]Cl$ as a Brønsted acid source, this transformation showed broad substrate scope for terminal, monosubstituted olefins, both in terms of the heterocycle and the functionality on the olefin (Chart 16). With respect to the heterocycle, benzimidazole, benzthiazole, benzoxazole, purine, thiazole, and functionalized benzimidazoles all reacted cleanly with neohexene (**192**−**195**). In addition to neohexene, isomerizable olefins also coupled cleanly (**196a** and **197**), as did olefins with siloxy, dioxolane, phthalamide, phenyl, ester, and nitrile functionality (**194b**, **194c**, **196b**, **197**−**199**).

The use of nonaromatic heterocycles in Rh-catalyzed C−H alkylation was also demonstrated to proceed cleanly in the presence of a protic acid additive. The reaction between 4,4-dimethyloxazoline and monosubstituted and 1,1- and 1,2-disubstituted olefins gave alkylated products in good yields (Chart 17).[75] In particular, the oxazoline framework functions as a synthon for esters and carboxylic acids, and so this alkylation can be considered a one-carbon elongation of alkenes. As was observed in the alkylation of azoles, broad functional group tolerance was observed. Good yields were obtained with ester, phenyl, siloxy, dioxolane, and carbamate substituents present on the olefin.



Dihydroquinazolines are versatile synthetic intermediates that can be readily converted to the corresponding quinazolines, quinazolinones, or tetrahydroquinazolines. Using the

Chart 17. Substrate Scope in 4,4-Dimethyloxazoline Alkylation

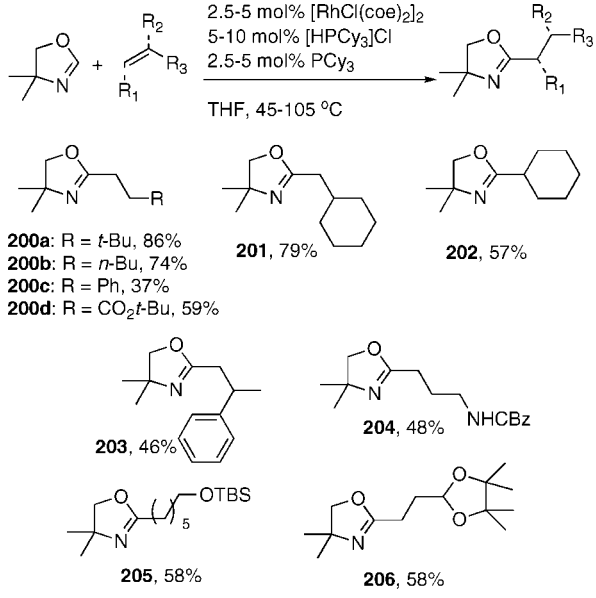
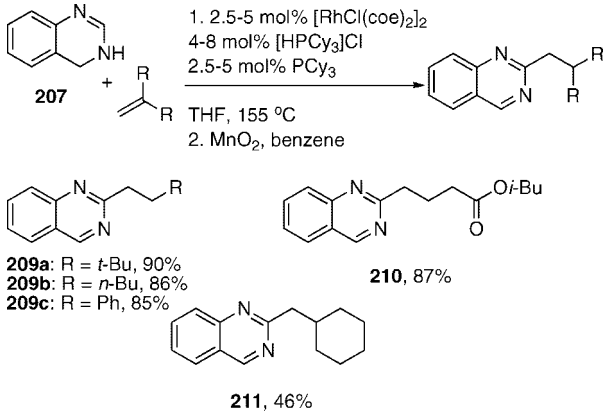


Chart 18. Dihydroquinazoline Alkylation



same reaction conditions that proved successful for oxazoline alkylation, 3,4-dihydroquinazoline (**207**) underwent facile intermolecular alkylation to give the fully aromatic quinazoline product **209a**.[76] Despite the propensity for 3,4-dihydroquinazolines to undergo dehydrogenative aromatization in the presence of transition metal catalysts, careful monitoring of the reaction between **207** and neohexene by ^{1}H NMR led to the discovery that the Rh-catalyzed alkylation of the nonaromatic heterocycle precedes aromatization (eq 22). The aromatic parent quinazoline was found to be inert to the reaction conditions.

As was observed for oxazoline alkylation, both mono- (**209a−c**, **210**) and disubstituted (**211**) olefins could be employed (Chart 18). The intramolecular alkylation of dihydroquinazolines with pendent olefin functionality was also explored and proceeded efficiently for di- and trisubstituted olefins. To simplify the workup and isolation, the crude dihydroquinazoline products were oxidized using MnO_2 to the corresponding quinazolines prior to being isolated.

4.4. Synthesis of Vasicoline

The intramolecular alkylation of dihydroquinazolines was applied to the total synthesis of vasicoline (**212**) (Scheme 16).[76] Initial investigations centered on the cyclization of

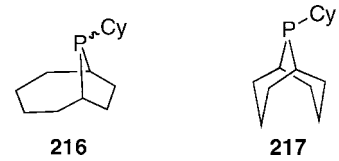
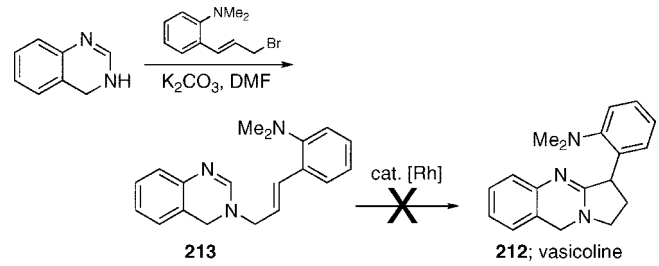
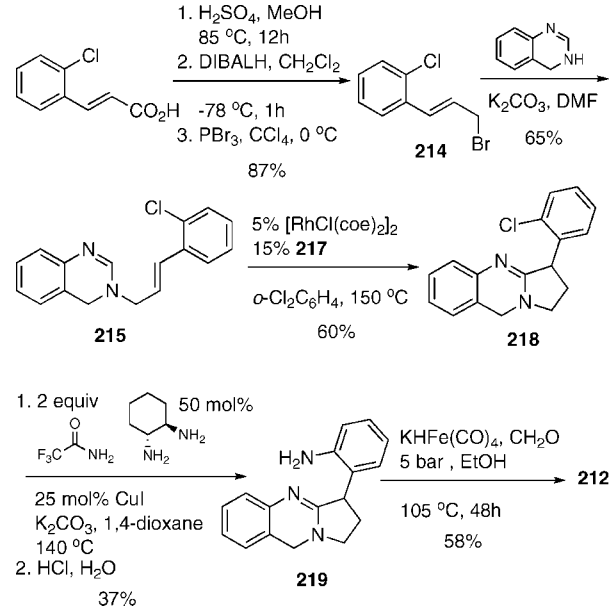


Figure 12. Cy-Phob ligands.

Scheme 16. Attempted Synthesis of Vasicoline



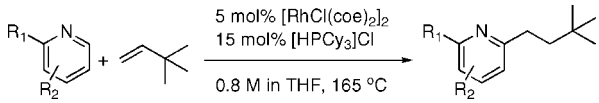
Scheme 17. Synthesis of Vasicoline



substrate **213**, which would lead directly to vasicoline. Unfortunately, no desired product was obtained from this reaction under Rh catalysis. The authors speculate that the proximity of the basic dimethylaniline substituent of **213** to the desired site of C−C bond formation led to catalyst entrapment, shutting down reactivity.

To avoid the interaction of the basic *ortho*-substituent with the catalyst, a less basic chloro substituent was employed, which could later be converted to the appropriate amine functionality. The requisite alkyl bromide **214** was prepared in three steps from *o*-chlorocinnamic acid (Scheme 17). Alkylation of dihydroquinazoline with **214** generated the necessary cyclization substrate **215**. It was anticipated that the cyclization of **215** would be challenging, since cinnamyl substituted azoles had previously been demonstrated to cyclize sluggishly.[76] Initial investigations into the cyclization of **215** using tricyclohexylphosphine did not meet with success. Fortunately, the 9-cyclohexylbicyclo[3.3.1]-9-phosphanonane (Cy-[3.3.1]-Phoban) ligand **217** (Figure 12)[77] proved active in this transformation, producing **218** in 60% yield. Use of the more readily available 2:1 isomeric mixture of [3.3.1] (**217**) and [4.2.1] (**216**) Cy-Phoban ligands also generated **218** with no reduction in yield.

Table 10. Heterocycle Scope for the Alkylation of Pyridine Derivatives



Entry	Heterocycle	R	Yield[a]
1		**a**: Me	59%
2		**b**: *i*-Pr	83%
3	**220**	**c**: TIPS	64%
4		**a**: OMe	96%
5		**b**: H	98%
6	**221**	**c**: CO_2Me	96%

[a] Isolated yield

Although **218** would not succumb to amination using a variety of ammonia equivalents and coupling conditions, amidation was achieved using Buchwald's Cu-mediated conditions (Scheme 17). Hydrolysis of the amide produced aniline **219**. The methylation of **219** was nontrivial; nucleophilic methylation methods could not be used because the amidine functionality was more nucleophilic than the aniline, and standard reductive amination methods would reduce the amidine functionality. Mild reductive amination using KH-$Fe(CO)_4$ under an atmosphere of CO ultimately generated **212**.[78]

4.5. Alkylation of Pyridine Derivatives

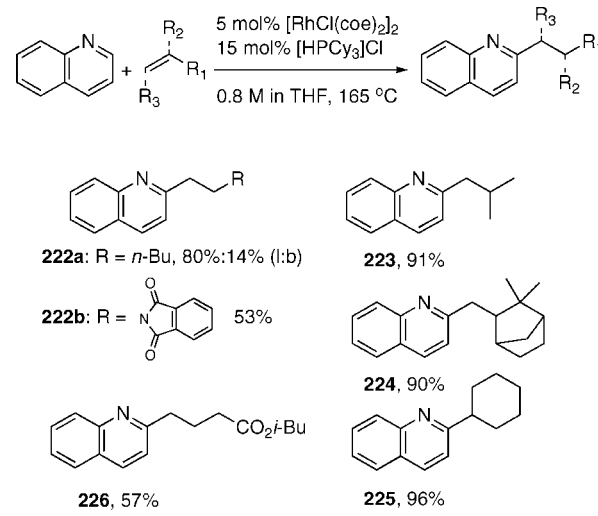
A key attribute of all of the substrates amenable to heteroatom-directed Rh-catalyzed alkylation in early reports was that the reactive carbon was flanked by two heteroatoms, both of which acted to stabilize the organometallic intermediates. The formation of an *N*-heterocyclic carbene (NHC) has been implicated as a key intermediate along the reaction pathway for these substrates (vide infra, section 4.6). Based on reports of stable NHC complexes displaying only a single stabilizing heteroatom,[79] the Rh-catalyzed alkylation of pyridine and quinoline derivatives was explored.[80] In prior heteroatom-stabilized C−H bond functionalization reactions, electron-rich heterocycles were primarily employed, and the alkylation of these electron-deficient heterocycles is a testament to the broad applicability of the Rh/[$HPCy_3$]Cl catalyst system.[81]

Catalyst optimizations of the alkylation of 2-picoline (**220a**) with neohexene revealed a dependence on Brønsted acid additives, either in the form of lutidinium salts as additives or more conveniently as [$HPCy_3$]Cl as the source of phosphine ligand (Table 10). In addition, yields were remarkably improved upon increasing the reaction concentration from 0.1 M in substrate to 0.8 M. Under these reaction conditions, neohexene underwent hydroarylation with *ortho*-substituted pyridines **220a**−**c**, in addition to quinolines **221a**−**c**, in high yields. In particular, the silyl-substituted pyridine **220c** can easily undergo protiodesilylation using HF, expanding the utility of this transformation.

In the reported examples of isolated NHC complexes with single heteroatoms, *ortho*-substitution was required to favor the formation of the C−H activated species over the initially formed *N*-bound complex.[79] This substitution was also necessary in the catalyzed alkylation. Under optimum conditions, pyridine underwent alkylation in less than 5% yield.

The scope in olefin was investigated for the alkylation of quinoline (Chart 19). In addition to isomerizable olefins

Chart 19. Investigation of Olefin Scope for Quinoline Alkylation

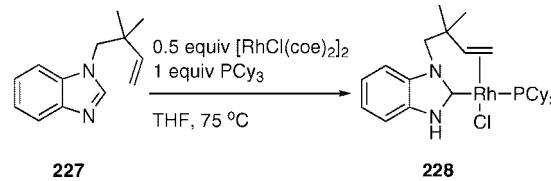


(**222a**), 1,1- (**223**, **224**) and 1,2-disubstituted olefins (**225**) also performed well under these reaction conditions, though *n*-hexene did produce an 80:14 mixture of the linear to branched alkylated products. Ester (**226**) and phthalamide (**222b**) functionalities were also tolerated. It is notable that by simply prolonging the reaction time, the catalyst loading for the reaction between quinoline and neohexene could be reduced to 1% Rh with little change in yield.

4.6. Mechanistic Investigations

The transition-metal-catalyzed alkylation of azoles has been the subject of extensive experimental and computational mechanistic investigations. Deuterium tracer experiments using a C2-deuterated *N*-homoallyl benzimidazole resulted in significant scrambling of the deuterium into the olefinic positions, indicating rapid olefin insertion and β-hydride elimination prior to the formation of product.[69] Crossover experiments provided additional data indicating that H/D exchange occurred between molecules, even though no intermolecular alkylation was observed.

A stoichiometric reaction of **227** with [$RhCl(coe)_2]_2$ and PCy_3 at temperatures below that required for product formation resulted in the formation of Rh(I)−NHC complex **228** (eq 23).[82] The structure of **228** was confirmed spectroscopically as well as by X-ray crystallography. C−H bond activations facilitated by neutral Rh(I) complexes typically result in the formation of Rh(III) hydride species by an oxidative addition pathway (vide supra, Scheme 1 and Figure 9).[83] The preferential formation of the NHC complex represents a mechanistically distinct pathway for C−H bond functionalization reactions.



(23)

When **228** was used as a catalyst in the cyclization of **227**, the rate of the catalytic transformation was identical to that observed when catalytic [$RhCl(coe)_2]_2$/PCy_3 was used. When the reaction was monitored by ^{31}P NMR spectroscopy, the NHC complex **228** was the major phosphine-containing

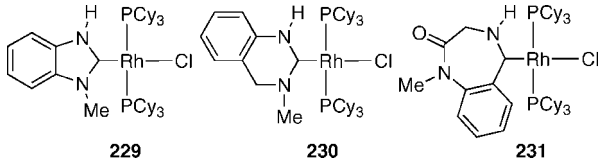
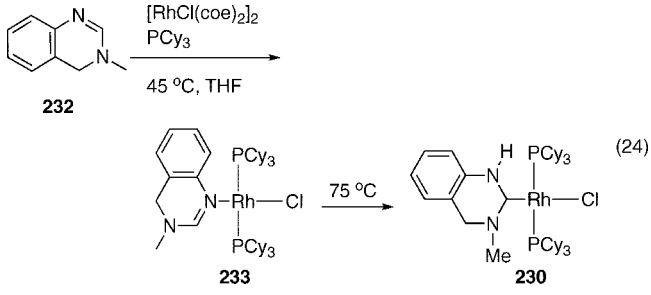


Figure 13. Isolated Rh−NHC complexes.

species throughout the reaction course, indicating that it is most likely the catalyst resting state. The catalytic reaction rate was determined to be zero order in [**227**] and first order in [**228**]. DFT calculations were performed to gain information on the C−C bond-forming steps starting with a simplified version of complex **228**. The results of these calculations indicated that olefin insertion into the Rh−carbene bond, generating a formally zwitterionic intermediate, was rate limiting.

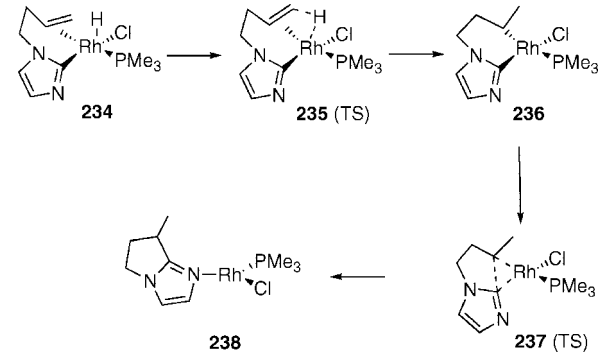
Metal−NHC complexes are traditionally formed starting with cationic azolium salts.[84] In addition to providing mechanistic insight into Rh-catalyzed alkylation reactions, their formation from neutral heterocycles was novel. Following the isolation of complex **228**, several other Rh−NHC complexes have been isolated from the reaction of $[RhCl(coe)_2]_2$ and PCy_3 with heterocycles, including *N*-methylbenzimidazole[85] (**229**), 3,4-dihydroquinazoline[86] (**230**), and a 1,-4-benzodiazepine-2-one[87] (**231**) (Figure 13).

The reactivity of *N*-methyl-3,4-dihydroquinazoline (**232**) with $[RhCl(coe)_2]_2$ and PCy_3 enabled a detailed mechanistic analysis of the Rh-catalyzed alkylation of *N*-heterocycles.[86] At 45 °C in THF, **232** reacted with stoichiometric quantities of $[RhCl(coe)_2]_2$ and PCy_3 to initially generate an *N*-bound complex **233** (eq 24). Although X-ray quality crystals of **233** could not be obtained, the structure was unambiguously established using multidimensional NMR spectroscopy of ^2H, ^{13}C, and ^{15}N labeled *N*-methyldihydroquinazolines. When **233** was heated at 75 °C, clean conversion to the NHC complex **230** was observed. With the aid of kinetic simulations based on numerical integration,[63] careful kinetic analysis established that **233** was an intermediate in the formation of **230**. Deuterium tracer experiments on C2-deuterated-**232** demonstrated that the deuterium at C2 was transferred to N1 in the formation of the carbene complex. In a double-labeling crossover experiment using equimolar amounts of C2-deuterated-**232** and ^{15}N1-**232**, minimal crossover was observed, indicating an intramolecular H-transfer in the formation of **230** from **233**. The deuterium kinetic isotope effect for the conversion of **233** to **230** was determined to be 1.8 ± 0.1, which supports a mechanism involving C−H bond cleavage during or prior to the rate determining step. Additionally, the activation parameters calculated for this transformation ($\Delta H^{\ddagger} = 26 \pm 0.3$ kcal/mol and $\Delta S^{\ddagger} = -10.3 \pm 0.8$ cal/mol·K) reveal the extent to which heterocycle to NHC tautomerization is facilitated by transition-metal mediation.[88]



(24)

Scheme 18. Mechanistic Proposal Excluding an NHC Intermediate

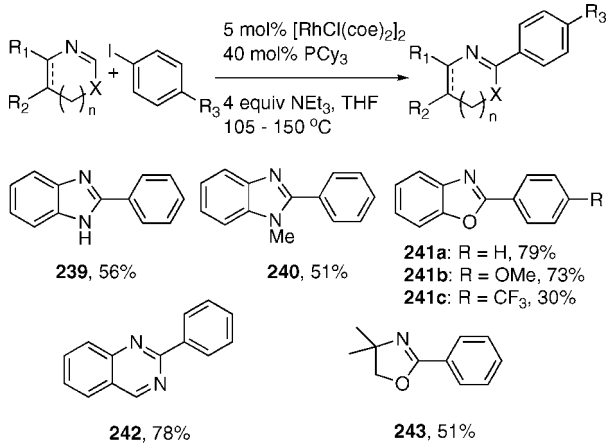


In addition to these detailed experimental mechanistic investigations, DFT calculations were used to predict the complete mechanistic pathway for the formation of **230**.[86] By carrying out the calculations on a simplified system employing 3-methyl-3,4-dihydropyrimidine in place of **232** and PMe_3 in place of PCy_3, a plausible mechanism was elucidated. The DFT calculations predict a mechanism involving initial *N*-coordination of the Rh catalyst, followed by a migration to a σ-complex and formal oxidative addition of the C−H bond to give a Rh-H species. Subsequent proton transfer then produces the NHC complex.[89]

In contrast, as a result of their theoretical studies based on published experimental data, Cavell and Yates proposed a more traditional mechanism that does not include the formation of an NHC intermediate.[90] Their proposed mechanism, summarized in Scheme 18, outlines a pathway analogous to mechanisms that are operative in cross coupling transformations. In their proposed mechanism, initial formation of the Rh-H species occurs via oxidative addition, as was proposed by Ellman and Bergman, to give species **234**. However, rather than proton transfer with subsequent formation of an NHC complex, Cavell and Yates proposed that olefin insertion into the Rh−H bond occurs to give the alkyl complex **236**. Subsequent C−C reductive elimination would produce the *N*-bound Rh-product complex **238**, which could then undergo ligand exchange to close the catalytic cycle. It is to date unclear whether a Rh−NHC complex is involved in the mechanism for heterocycle alkylation or if its formation is a nonproductive side reaction to a mechanism resembling that in Scheme 18. It is equally likely that the operative pathway is dependent upon the substrate or reaction temperature or that both mechanisms are operating in tandem.

Cavell and Yates also performed a full computational analysis of the reaction pathway in the presence of an acid additive (H^+ and HCl), which had been shown experimentally to accelerate Rh-catalyzed azole alkylations (vide supra).[71,74−76] The results of their calculations indicated that the origin of the rate acceleration with acid additives was largely based on the coordinating anion, rather than on acid activation of the azole. Simulated mechanisms employing noncoordinating anions did not benefit significantly from protic activation. Based on previous experimental work,[91] the authors suggested that HCl initially undergoes oxidative addition to the Rh precatalyst, generating a coordinatively unsaturated active catalyst. The protonated azolium salt then binds to generate an *N*-bound complex with subsequent C−H oxidative addition to generate the Rh−NHC complex directly. Olefin insertion into the Rh−H bond, followed by reductive elimination then produces the product. Overall,

Chart 20. Arylation of *N*-Heterocycles



substantially lower energy barriers were predicted for the entire process when an acid additive was included.

5. Arylation of N-Heterocycles

In the past decade, methods for heterocycle arylation have enjoyed rapid growth and development, with numerous Pd-[92] and Cu-catalyzed[93] methods appearing in the literature. The unique mode of activation and functional group tolerance that Rh catalysts offer has led to expanded substrate scope and regioselectivity which differs from that observed for other catalysts.

5.1. Azole Arylation

Initial investigations into the Rh-catalyzed arylation of azoles explored the reaction between benzimidazole and aryl iodides using the conditions optimized for Rh-catalyzed heterocycle alkylation (vide supra, section 4.1).[94] It was quickly determined that, in contrast to heterocycle alkylation, which was accelerated by acid, a base additive was required to achieve good yields of arylated products, presumably to neutralize the strong acid (HI) generated as the sole byproduct (Chart 20). Under optimized conditions, an array of heterocycles including benzimidazoles (**239**, **240**), benzoxazoles (**241a**), dihydroquinazoline (**242**), and oxazolines (**243**) underwent arylation using phenyl iodide in good yield. For 3,4-dihydroquinazoline, the fully aromatic quinazoline **242** was isolated. Interestingly, when the parent quinazoline was subjected to the arylation conditions, no arylated product was detected. It is therefore probable that arylation precedes aromatization for the 3,4-dihydroquinazoline substrate. In addition, an electron-rich aryl iodide (**241b**) reacted efficiently with benzoxazole, whereas an electron-poor aryl iodide (**241c**) gave a lower yield.

Even under the optimized conditions given in Chart 20, extensive hydrodehalogenation of the aryl iodide was observed, with the dehalogenated arene comprising the mass balance of the aryl iodide coupling partner.[95] Additionally, when $(PCy_3)_2RhCl$ was heated in THF, Rh-H species were observed by ^1H NMR spectroscopy. The authors therefore proposed that the Rh center undergoes either cyclometalation or intermolecular C−H activation of the phosphine ligands, followed by β-hydride elimination, to generate a Rh−dihydride complex (**244**, Scheme 19).[96] Reductive elimination of HCl, followed by oxidative addition of the aryl iodide, would produce **245**, and subsequent reductive elimination of the arene would yield **246**, which is proposed to be catalytically

Scheme 19. Proposed Mechanism for Hydrodehalogenation

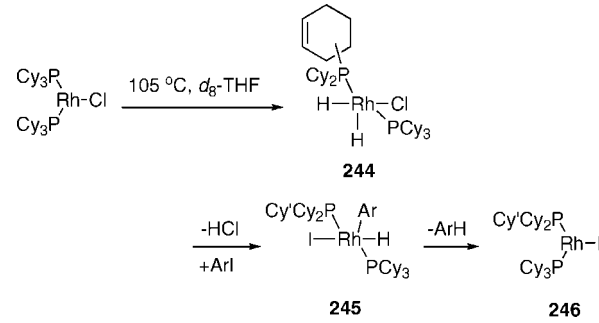
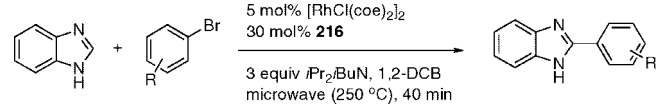


Table 11. Scope in Aryl Bromide



entry	R	yield[a]
1	4-CF_3	77% (60%)[b]
2	4-CN	90%
3	4-Cl	67%
4	4-COEt	77% (59%)[b]
5	4-$CONH_2$	60%
6	4-Ph	81%
7	4-H	80% (28%)[b]
8	4-Me	91%
9	4-OMe	54% (24%)[b]
10	3-CO_2Et	70%
11	3-Me	79%
12	3-OEt	46%

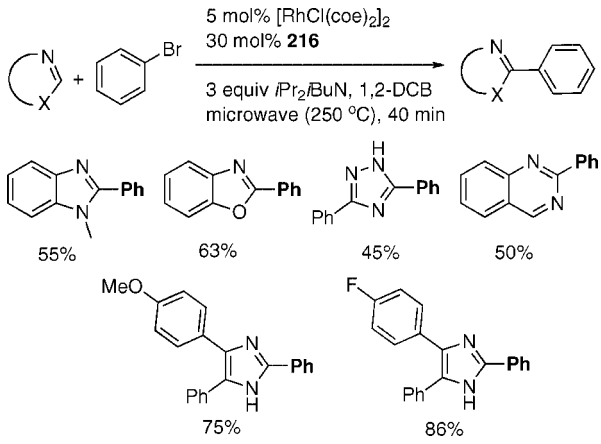
[a] Isolated yields. [b] Yields in parentheses were obtained from in situ NMR spectroscopic analysis of reactions that were conducted in THF-d_8 and conventionally heated at 150 °C for 24 h in a sealed tube.

inactive. This deleterious side reaction was most likely responsible for the moderate yields obtained for the cross-coupling, and extensive investigations into new ligand design were undertaken to circumvent this problem.

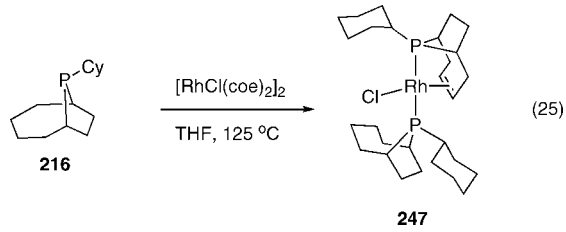
Significant improvements in the yield and scope of the Rh-catalyzed *N*-heterocycle arylation were realized through the use of the 9-cyclohexylbicyclo[4.2.1]-9-phosphanonane (Cy-Phob) ligand **216** (Figure 12).[97] The [3.3.1] isomer **217** was also prepared, but this isomer produced a catalyst that exhibited much lower efficiency in the cross-coupling reaction. The unique structure of the [4.2.1]-Cy-Phob ligand maintains the steric and electronic properties of PCy_3 while presumably reducing its propensity to undergo dehydrogenation. Further optimizations using a more highly hindered amine base (*i*-Pr_2*i*-BuN), and adapting the procedure to a protocol utilizing microwave heating, led to substantial improvements in reaction time and ease of operation. Under these optimized conditions, broad scope was observed. In particular, aryl bromides, which are cheaper and more broadly available than the corresponding iodides, coupled very efficiently (Table 11). Both electron-rich (entries 8, 9, and 11) and electron-deficient (entries 1−5, 10, and 12) aryl bromides coupled with benzimidazole in good to high yields. It is notable that reactive functionalities such as nitrile, ketone, and carboxamide were well tolerated under these reaction conditions. The scope in heterocycle was also broadened to include bis(aryl)imidazoles and a triazole substrate, in addition to benzimidazole, benzoxazole, and 3,4-dihydroquinazoline, which again underwent aromatization to the quinazoline following arylation (Chart 21).

In an effort to understand the increased reactivity afforded by ligand **216**, a stoichiometric reaction between **216** and a

Chart 21. Scope in Heterocycle



Rh precatalyst was performed, which revealed the formation of a P−olefin complex **247** in good yield under the arylation reaction conditions (eq 25).[98] Complex **247** exhibited a high degree of thermal stability, even upon prolonged heating. The stability of this catalyst system stands in stark contrast to the reactivity observed with Rh/PCy_3 systems, which underwent iterative cyclometalation/β-hydride elimination, ultimately resulting in catalyst decomposition. Complex **247** catalyzed the arylation of benzimidazole with a rate and yield similar to those obtained using $[RhCl(coe)_2]_2$/**216** mixtures.



(25)

The enhanced stability of complex **247** arises not only from steric or electronic effects but also from the ability to generate a hemilabile bidentate *P*-olefin ligand in situ. Based on this analysis, a series of (*Z*)-2,3,6,7-tetrahydrophosphepine ligands (e.g., **248**, Chart 22) were prepared and screened for their activity in the direct arylation of azoles.[98] The *tert*-butyl substituted phosphepine **248** provided the highest conversion with essentially no hydrodehalogenation of the aryl bromide during the arylation of benzimidazole. Shortened reaction times were again achieved with microwave heating, and a sterically hindered amine base was necessary to neutralize the HBr produced as the byproduct. Under optimized conditions, a substantial expansion of the substrate scope for the direct arylation of *N*-heterocycles was realized (Chart 22). Functionalities such as sulfoxide, formamide, acetamide, free amine, and free hydroxyl were all tolerated. The compatibility of acidic heteroatom functionalities is particularly notable because these functionalities are often problematic in Pd- and Cu-mediated coupling reactions.[92,93] In addition, electron-rich heteroaryl bromides, such as 3-bromothiophene and 5-bromobenzofuran, 5-bromobenzothiophene, and 5-bromo-1-methylindole coupled in good yield. The scope in heterocycle was also expanded to include 4,5-dimethylthiazole and benzthiazole.

Using conventional heating conditions at 175 °C in dioxane, which is most applicable to large-scale reactions, the $[RhCl(coe)_2]_2$ catalyst loading could be reduced to 1%. The arylation procedure was further simplified through the

Chart 22. Improved Scope with Ligand 248

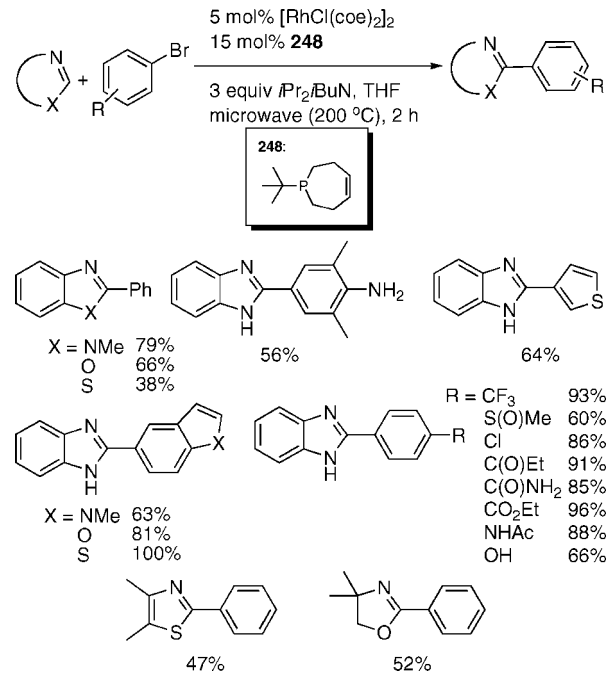
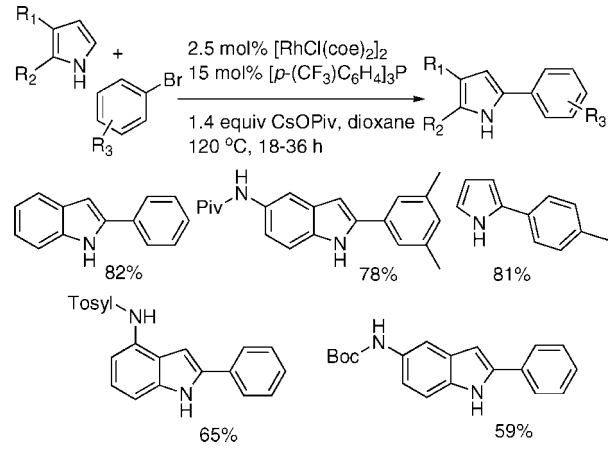


Chart 23. Rh-Catalyzed Indole Arylation

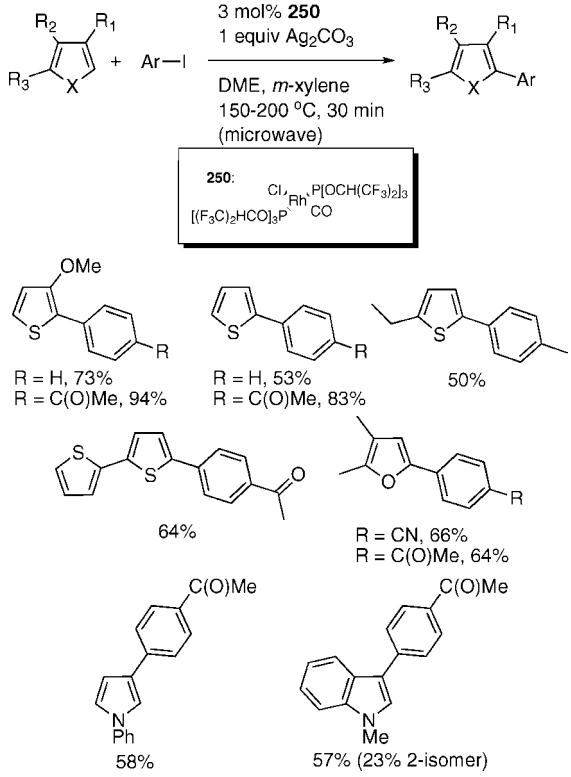


use of [H**248**]BF_4, an air-stable surrogate of **248**, which has been made commercially available, and $[RhCl(cod)]_2$, a less expensive, air-stable Rh source. Using these reagents, the reactions could be assembled outside of a glovebox with minimal reagent purification and with only an N_2 line to purge the reaction vial prior to sealing.

5.2. Heterocycles with a Single Heteroatom

Until recently, the majority of Rh-catalyzed heterocycle arylations have required the use of heterocycles with two or more stabilizing heteroatoms (vide supra). Recent advances using electronically disparate Rh catalysts have enabled the arylation of heterocycles possessing only a single heteroatom. In an early example, the Rh-catalyzed arylation of unprotected N−H indoles was accomplished using an electrophilic Rh catalyst generated in situ from $[RhCl(coe)_2]_2$, [*p*-$(CF_3)C_6H_4]_3P$, and a base additive, CsOPiv.[99] Under these conditions, free (NH) indoles and pyrrole underwent clean C2-arylation using aryl iodides with excellent regioselectivity (Chart 23). In addition to the acidic indole NH, protic functional groups such as pivaloyl-, *tert*-butylcarbamoyl-, and tosyl-protected amines were all tolerated.

Chart 24. Arylation of Electron-Rich Heteroarenes



During reaction optimization, it was noted that appreciable yields of arylated products were only obtained using cesium carboxylate bases. A stoichiometric reaction between $[RhCl(coe)_2]_2$, $[p\text{-}(CF_3)C_6H_4]_3P$ (L), and iodobenzene generated a new Rh complex, $[Rh(Ph)(OPiv)_2L_2]$ (**249**, eq 26), resulting from oxidative addition of the iodoarene with subsequent halide displacement by the pivalate anions. The structure of this new complex was confirmed by spectroscopic and X-ray analysis of the tolyl derivative. In catalytic experiments starting with the Rh-precatalyst, complex **249** was observed spectroscopically as the single phosphine-containing species in the reaction mixture and is therefore predicted to be the resting state of the catalyst. Isolated **249** was catalytically competent, producing arylated products at an identical rate and in the same yield as the Rh/L/CsOPiv mixture. A large kinetic isotope effect ($k_H/k_D = 3.0$) is observed at the 2-position of the indole substrate, supporting a mechanism with C−H bond cleavage occurring before or during the rate determining step. A likely role for the pivalate ligands is to assist in the C−H bond cleavage step by serving as an internal base following electrophilic metalation.[100]

The arylation of electron-rich heteroarenes and simple arenes has been reported to proceed using aryl iodides and an electron-deficient Rh catalyst **250** (Chart 24).[101] Complex **250** was readily prepared from $[RhCl(CO)_2]_2$ and was found to be stable to air and moisture. The use of the π-accepting phosphite ligand $P[OCH(CF_3)_2]_3$ was critical to obtaining high yields of arylated products. Even moderate decreases in the π-accepting ability of the ligand significantly attenuated the efficiency of arylation. Silver carbonate was a necessary additive for this transformation, most likely serving as both a base and as a means to sequester iodide anions. Conventionally heated reactions were performed at 150 °C and required lengthy reaction times. By adapting the reaction to a microwave protocol, the temperature could be easily increased, giving full conversion in very short reaction times.

Scheme 20. Arylation of Electron-Rich Arenes

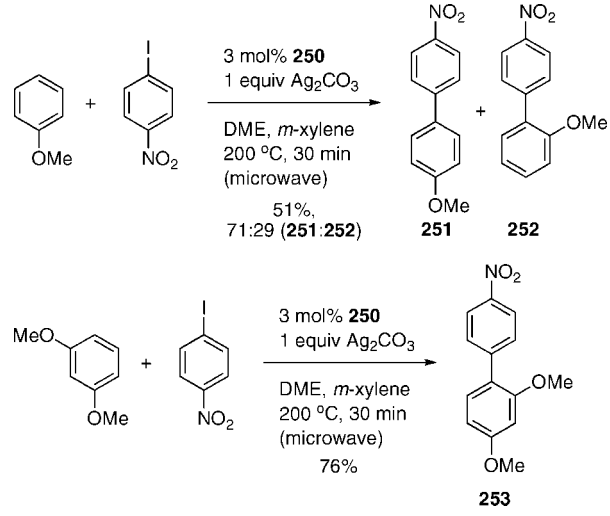
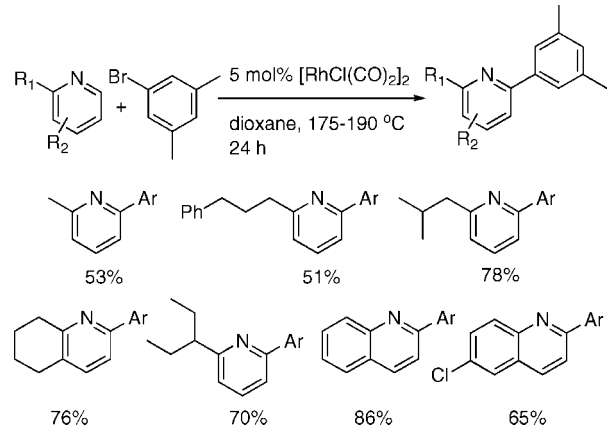
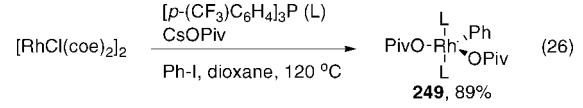


Chart 25. Scope in Pyridine and Quinoline Arylation



Under these optimized conditions, thiophenes and 2,3-dimethylfuran were α-arylated with complete regioselectivity (Chart 24). Interestingly, the *N*-heterocycles, *N*-phenylpyrrole and *N*-methylindole, underwent β-arylation preferentially. Simple arenes such as anisole and 1,3-dimethoxybenzene also underwent arylation (Scheme 20). When anisole was used, a 29:71 mixture of *ortho*- and *para*-isomers was obtained, with none of the *meta*-isomer forming.

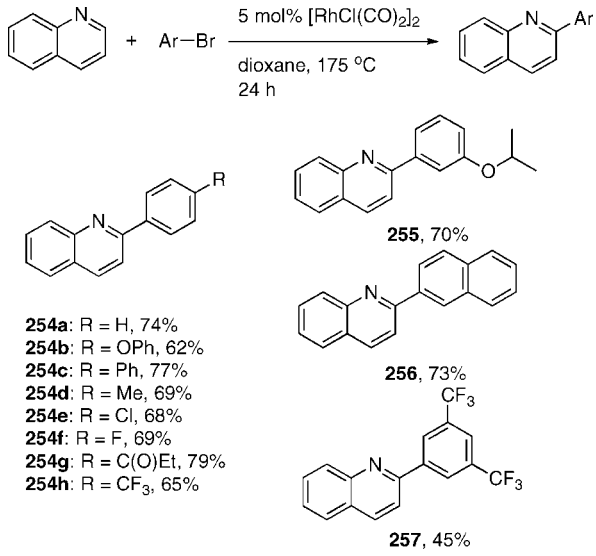


(26)

Based on the observed regioselectivity and the dependence on the use of electron-rich arenes, the mechanism of C−H bond cleavage by **250** most likely involves electrophilic metalation of the electron-deficient Rh catalyst. No deuterium isotope effect was observed when C2-deuterated thiophene was arylated with iodobenzene, which indicates that the C−H bond cleavage step is not rate limiting in the catalytic cycle.

The selective *ortho*-arylation of pyridines has also been demonstrated to proceed with an electron-deficient Rh catalyst.[102,103] Using $[RhCl(CO)_2]_2$ in the absence of any additives, pyridine and quinoline derivatives underwent clean arylation with aryl bromides (Chart 25).[104] As was observed for the alkylation of pyridine derivatives (vide supra, Table 10), the transformation was highly concentration-dependent, with increased yields obtained at higher concentrations.

Chart 26. Scope in Arene for Quinoline Arylation



Optimum yields were obtained using 6 equiv of the heterocycle. The scope in heterocycle was quite good, with *ortho*-alkylated pyridine derivatives performing well under the reaction conditions (Chart 25). Quinoline derivatives were also competent substrates. Pyridine did not undergo arylation using this catalyst system, indicating the necessity for *ortho*-substitution.

The scope in arene was evaluated using quinoline as the heterocycle. A variety of *meta*- and *para*-substituted aryl bromides were competent substrates in this transformation (Chart 26). Both electron-donating (**254b**,**d**) and withdrawing (**254e**−**h**, **255**, **257**) substituents were tolerated, in addition to naphthyl derivatives (**256**). Although the scope was explored using 5 mol % of the dimeric Rh catalyst, it was demonstrated that the catalyst loading could be reduced to 1 mol % of the dimer with only a minor reduction in yield.

The mechanism of the arylation of electron-deficient pyridine and quinoline derivatives is unknown at this time. Electron-rich catalysts were required for the alkylation of pyridine derivatives (vide supra); however, these catalysts displayed poor reactivity in the arylation chemistry. In light of this, it is likely that the two systems proceed by distinctly different mechanisms for C−H bond cleavage and further mechanistic analysis is required.

6. Conclusion

The field of transition-metal-catalyzed C−H bond functionalization reactions has expanded rapidly over the past decade. The unique mode of reactivity of Rh catalysts has led to methods for C−C bond formation that are highly regioselective and demonstrate a broad range of functional group compatibility. Owing in part to their high degree of functional group tolerance, both chelation-assisted and heteroatom-directed C−H bond functionalization methodologies have been employed in the syntheses of complex molecules. With continued mechanistic investigation and methods development, the field of C−H bond functionalization by Rh promises to produce highly active catalyst systems for the mild and selective formation of C−C bonds.

7. Acknowledgments 7

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