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Rhodium Catalyzed Chelation-Assisted C–H Bond Functionalization Reactions◇

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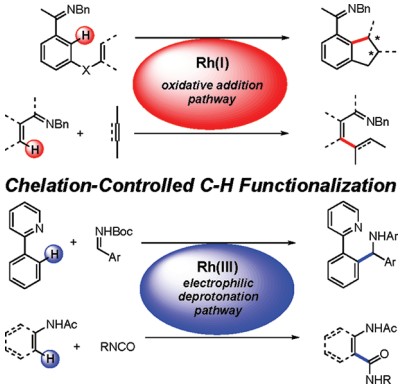
CONSPECTUS

Over the last several decades, researchers have achieved remarkable progress in the field of organometallic chemistry. The development of metal-catalyzed cross-coupling reactions represents a paradigm shift in chemical synthesis, and today synthetic chemists can readily access carbon–carbon and carbon–heteroatom bonds from a vast array of starting compounds. Although we cannot understate the importance of these methods, the required prefunctionalization to carry out these reactions adds cost and reduces the availability of the starting reagents.



The use of C–H bond activation in lieu of prefunctionalization has presented a tantalizing alternative to classical cross-coupling reactions. Researchers have met the challenges of selectivity and reactivity associated with the development of C–H bond functionalization reactions with an explosion of creative advances in substrate and catalyst design. Literature reports on selectivity based on steric effects, acidity, and electronic and directing group effects are now numerous.

Our group has developed an array of C–H bond functionalization reactions that take advantage of a chelating directing group, and this Account surveys our progress in this area. The use of chelation control in C–H bond functionalization offers several advantages with respect to substrate scope and application to total synthesis. The predictability and decreased dependence on the inherent stereoelectronics of the substrate generally result in selective and high yielding transformations with broad applicability. The nature of the chelating moiety can be chosen to serve as a functional handle in subsequent elaborations.

Our work began with the use of Rh(I) catalysts in intramolecular aromatic C–H annulations, which we further developed to include enantioselective transformations. The application of this chemistry to the simple olefinic C–H bonds found in α, β-unsaturated imines allowed access to highly substituted olefins, pyridines, and piperidines. We observed complementary reactivity with Rh(III) catalysts and developed an oxidative coupling with unactivated alkenes. Further studies on the Rh(III) catalysts led us to develop methods for the coupling of C–H bonds to polarized π bonds such as those in imines and isocyanates. In several cases the methods that we have developed for chelation-controlled C–H bond functionalization have been applied to the total synthesis of complex molecules such as natural products, highlighting the utility of these methods in organic synthesis.

Introduction

The ability to directly transform unfunctionalized precursors into complex molecules is an important goal of synthetic organic chemistry. The use of transition metal catalysis in the elaboration of organic molecules has revolutionized the field of organic synthesis over the past several decades and has become an indispensible tool. Many of the most far-reaching advances in transition metal catalysis involve the coupling of two appropriately prefunctionalized precursors to give products in a predictable and highly selective manner. The predictable nature of these reactions, however, comes with a price. The necessity for prefunctionalization adds cost and reduces the availability of starting materials, in addition to producing potentially toxic waste streams. In light of the liabilities of traditional cross coupling reactions, the use of C–H bond activation has become

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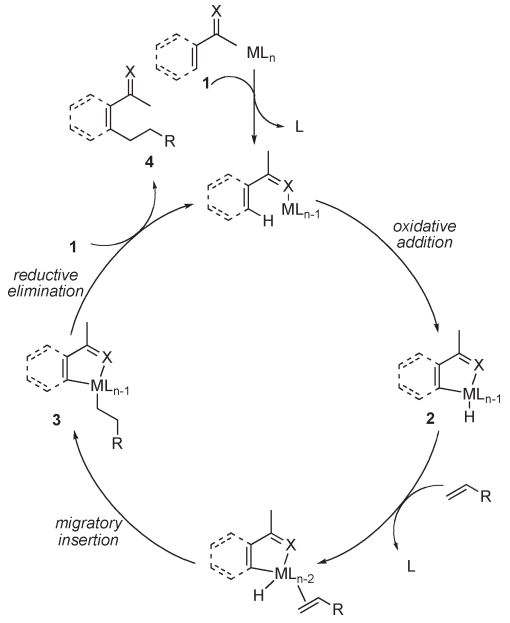
FIGURE 1. Chelation-assisted C–H bond activation.

SCHEME 1. Mechanism of Chelation-Assisted C–H Alkylation



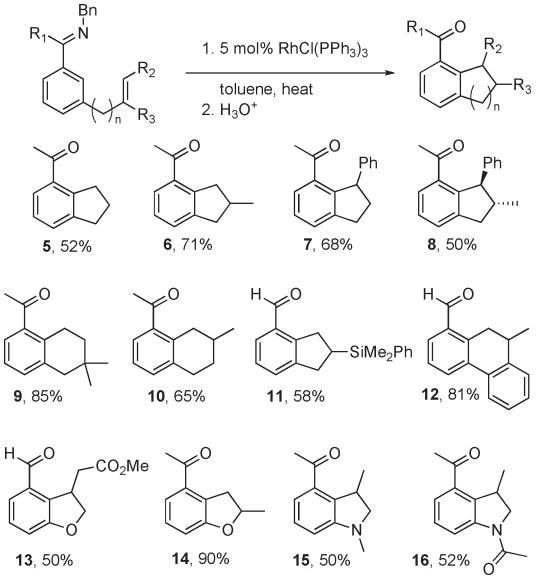
increasingly attractive to the synthetic chemist, and has enjoyed demonstrated success in the synthesis of complex molecules. However, by eliminating prefunctionalization, certain key challenges are introduced, namely, selectivity and overfunctionalization through the competing reactivity of multiple C–H bonds.

Accordingly, a great deal of effort in the past two decades has been devoted to the achievement of selectivity in C–H bond functionalization reactions.[1,2] A rich array of catalysts have emerged that exploit subtle differences in the reactivity of specific C–H bonds within a molecule. One approach that has seen widespread use involves taking advantage of a chelating heteroatom to facilitate reactivity at a proximal site (Figure 1). With respect to functional group tolerance and efficiency, rhodium-based catalysts have emerged as leading candidates for this type of transformation, and over the past decade our group has developed several methods for the efficient functionalization of sp^2 C–H bonds that utilize this approach.

Catalysis by Rh(I)

Early reports of Rh-catalyzed C–H bond functionalization reactions employed Rh(I) catalysts, which demonstrate reactivity that is mechanistically distinct from the Rh(III)

CHART 1. Intramolecular Alkylation of Aryl Imines



pathways that will be discussed at the end of this Account. A mechanism for chelation-assisted C–H bond functionalization, using alkylation as a representative example, is given in Scheme 1. Although the mechanistic details may vary from case to case, this classical pathway is similar for most chelation-driven processes. The initial coordination of the transition metal to the heteroatom of **1** followed by facile C–H bond activation provides the metallacyclic intermediate **2**. Ligand exchange to coordinate the olefin, followed by alkene insertion into the M–H bond, gives **3**. Reductive elimination from **3** forms a new C–C bond, and dissociation of the product **4** closes the catalytic cycle. In most C–H alkylation reactions, the reductive elimination step is rate limiting, and one of the beneficial effects of chelation is to stabilize **3** to facilitate reductive elimination.[3,4]

Intramolecular Annulation of Arenes

Stemming from the seminal reports by Murai and co-workers on the intermolecular *ortho*-alkylation of aryl ketones with alkenes using a ruthenium catalyst,[5] Jun demonstrated that the scope and efficiency of this transformation could be greatly improved through the use of an imine directing group and a Rh-based catalyst such as Wilkinson's catalyst.[3a] Despite these improvements in reactivity, the scope of imine-directed alkylation was still limited with respect to the olefinic component, and with few exceptions only monosubstituted terminal olefins served as coupling partners. Our group therefore set out to demonstrate a more widespread applicability in the intramolecular annulation of arenes.

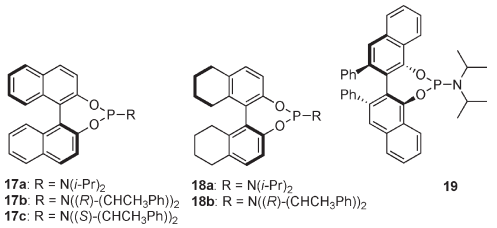


FIGURE 2. Phosphoramidite ligands for enantioselective olefin hydroarylation.

We demonstrated the annulation of aryl ketimines with mono (**5**), 1,1-di- (**6**), 1,2-di- (**7**), and even trisubstituted (**8**) olefins tethered to the *meta* position to provide the indane derivatives shown in Chart 1.[6] In addition to indane derivatives, extensions of the tethered chain provided the tetralin derivatives **9** and **10**. In the substrate used to produce tetralin **10**, the double bond has the potential to isomerize to the internal position and then cyclize to give an indane derivative, but no evidence for the formation of this product was observed.

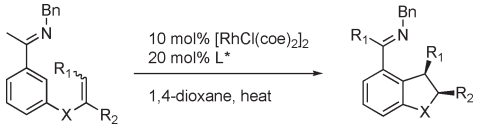
Aryl aldimines reacted efficiently using Wilkinson's catalyst (Chart 1, **11**–**13**). Heteroatoms could also be incorporated into the tether, generating dihydrobenzofuran (**13** and **14**) and dihydroindole (**15** and **16**) derivatives, broadening the range of accessible structural motifs. This advancement in particular improves the potential applicability of C–H bond functionalization to pharmaceutical and industrial targets, where heterocycles are prominent.

Enantioselective Intramolecular Alkylation

In the realm of transition metal catalysis, the development of methods for the catalytic enantioselective functionalization of organic molecules is often emphasized as a means to produce chiral molecules that do not rely on the chiral pool or expensive auxiliaries. In contrast to other catalytic methods, enantioselective approaches to C–H bond functionalization have been slow to develop.[7] The advancement of these methods is hindered, in part, by the substrate scope observed for C–H bond alkylation reactions where efficient reactivity is only seen with linear α-olefins.

The tolerance of more highly substituted alkenes in intramolecular annulations provided a platform on which to develop catalytic systems for enantioselective C–H bond functionalization.[8] Through the use of chiral phosphines, we hoped to bias the coordination of the rhodium-hydride complex to one diastereoface of the alkene, which would provide the stereocontrol required in the subsequent stereodetermining insertion step. Our investigation of this transformation led to the application of monodentate chiral phosphoramidite ligands for use in C–H bond functionalization reactions (Figure 2).[9] These ligands, when combined with a Rh precatalyst, gave high conversion and selectivities in the cyclization of 1,2- and 1,1-di-, and trisubstituted olefins to give chiral indanes and benzofurans with both aryl and alkyl substituents (Table 1). *N*-Allylic indoles were also competent substrates (entry 3), though these challenging substrates required higher temperatures and gave modest enantiometric excesses (ee's) (see also Scheme 4).

TABLE 1. Enantioselective Annulation of Aryl Imines

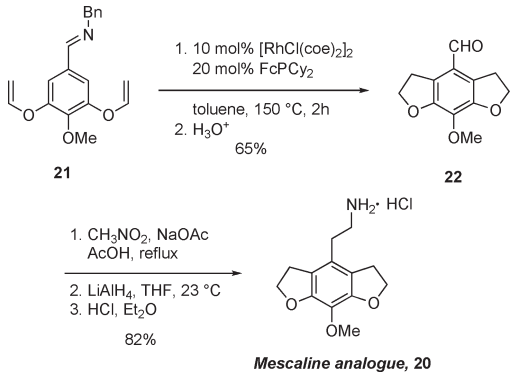


Entry	Substrate	Product	L*	T (°C)	% Yield[a]	% ee[b]
1			**17b**	50	94	95
2			**17c**	75	98	90
3			**17c**	125	99	68
4			**17c**	50	99	95
5			**18a**	75	93	87
6			**18a**	75	69	90
7			**18b**	50	80	93
8			**18b**	75	50	90

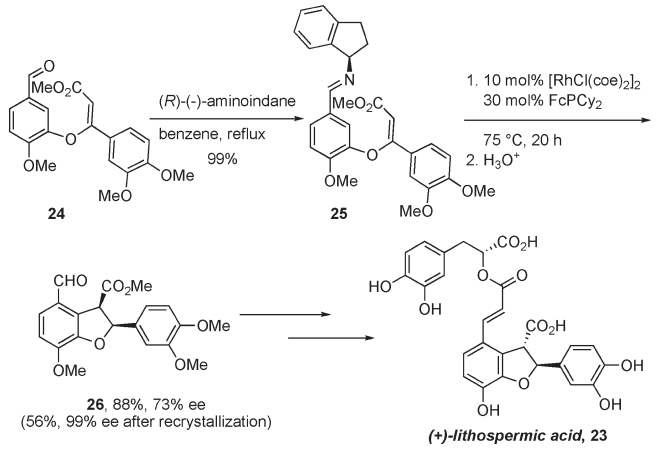
[a]Yield of *N*-benzylimine product determined by ^{1}H NMR using 2,6-dimethoxytoluene as an internal standard. [b]ee's determined after hydrolysis of products with silica gel or HCl/H_2O-dioxane using chiral HPLC.

Synthetic Applications. The total synthesis of natural products and biologically relevant molecules serves as a platform for the demonstration of the range and utility of catalytic methods in complex and less predictable situations. The Rh-catalyzed annulation of aryl imines has been utilized in the synthesis of several natural products and

SCHEME 2. Synthesis of Mescaline Analogue **20**



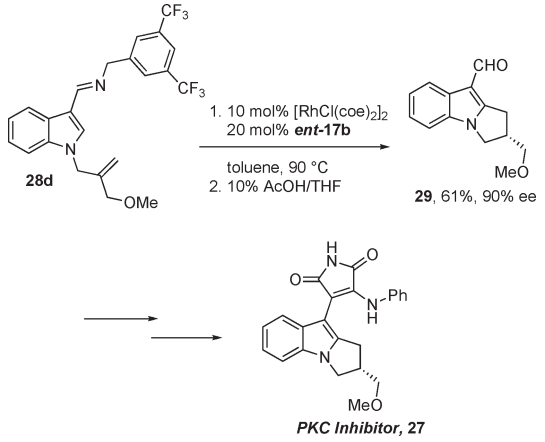
SCHEME 3. Cyclization of **25** in the First Synthesis of (+)-Lithospermic Acid



drug candidates. This transformation was first employed in a tandem alkylation reaction to produce **20**, an analogue of mescaline with interesting biological properties (Scheme 2).[10,11] The reaction of **21** using Wilkinson's catalyst was sluggish and proceeded in low yields. However, electron-donating ligands were much more active in this transformation and the ferrocenyl-based ligand, (dicyclohexylphosphinyl)ferrocene ($FcPCy_2$), produced the desired product **22** in good yield. The tricyclic aldehyde **22** could then be easily elaborated to give **20**.

We next turned to the challenging structural motif found in the natural product (+)-lithospermic acid **23** (Scheme 3), requiring the stereoselective intramolecular *ortho*-alkylation of the densely functionalized trisubstituted alkene in aryl aldimine **25**.[12] Initial experiments on the use of chiral catalysts in the cyclization of **25** did not provide satisfactory yields and enantioselectivities, which prompted us to explore alternative approaches for accomplishing an asymmetric annulation.

SCHEME 4. Enantioselective Cyclization and Synthesis of **27**

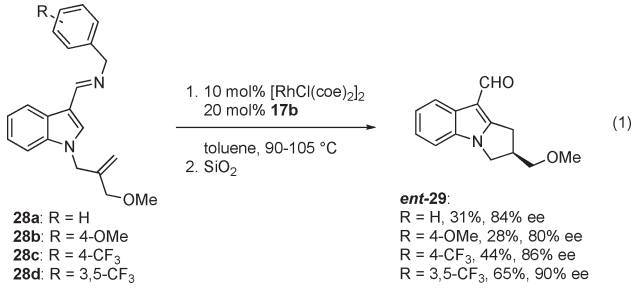


Because of the proximity of the substituent on the imine nitrogen to the metal center, the use of a chiral amine auxiliary that could later be cleaved by hydrolysis was an attractive alternative to enantioselective catalysis. Chiral non-racemic amines were condensed with aldehyde **24** and the resultant imines were tested for their efficiency and diastereoselectivity in the Rh-catalyzed cyclization (Scheme 3). The *syn* diastereomer **26** was formed in the Rh-catalyzed cyclization reaction through *syn* alkene insertion followed by reductive elimination proceeding with retention. This product then underwent epimerization under basic conditions to the more thermodynamically favorable and desired *anti*-isomer. In the initial synthesis, the imine generated from (*R*)-aminoindane **25** provided the highest yield of cyclized product with good diastereoselectivity and resulted in the first synthesis[13] of this natural product in only 10 steps from commercially available starting materials (Scheme 3).

In a subsequent study, the effect of substituents on the aminoindane auxiliary on the efficiency and stereoselectivity of the annulation reaction was evaluated.[14] Substituents at the 7-position provided superior results, with 7-fluoro-1-aminoindane leading to **26** in 70% yield and with 90% ee.

To demonstrate the power of the enantioselective annulation method in organic synthesis, we next embarked on a rapid synthesis of the tricyclic indole core of the protein kinase C inhibitor **27** (Scheme 4).[15] We envisioned that the indole tricyclic core **29** could be generated by the enantioselective annulation of imine **28a** (eq 1), which could be prepared in just two steps from indole carboxaldehyde. Although the *N*-benzyl imine had routinely exhibited good reactivity in C–H bond functionalization reactions, **28a** showed very poor conversion when the chiral phosphoramidite ligand **17b** was used with a Rh precatalyst (eq 1).

Optimization of this reaction through ligand and catalyst screening did not lead to an improvement in the observed reactivity, and so we began to consider substrate modifications that might lead to a more efficient reaction.



We envisioned that by reducing the electron-donating ability of the imine nitrogen, a more electron deficient metal center could be generated that would lower the barrier for reductive elimination, which has been shown to be rate limiting in C–H bond functionalization reactions.[2,3c] Indeed, use of the more electron-rich substrate **28b** resulted in decreased reaction efficiency relative to **28a**. 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 **28d** providing ***ent*-29** in 65% yield and 90% ee (eq 1). Although ligand **17b** provided the enantiomer of the desired product **29**, the enantiomer of **17b** (***ent*-17b**) is also commercially available and was used to produce **29** with the correct sense of induction (Scheme 4). The desired target **27** was produced in just four subsequent steps.

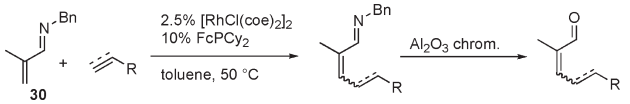
Chelation-Assisted Functionalization of Olefins

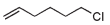
In comparison to the C–H bond functionalization reactions that have been developed with arenes, the reactivity of olefins remains underexplored. This is perhaps because the leading chelating moieties for Rh catalysis, namely, the imine and carbonyl functionalities, serve to activate pendant olefins toward other reactions such as conjugate addition and polymerization.[16]

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-[17] and intramolecular[8] alkylation. Jun was the first to report on the Rh-catalyzed alkylation of an α,β-unsaturated carbonyl derivative, though limited scope and isomeric product mixtures were observed.[18]

Based on our efforts in novel catalyst design for aromatic C–H alkylations, we pursued a method for α,β-unsaturated

TABLE 2. Alkylation of α,β-Unsaturated Aldimines



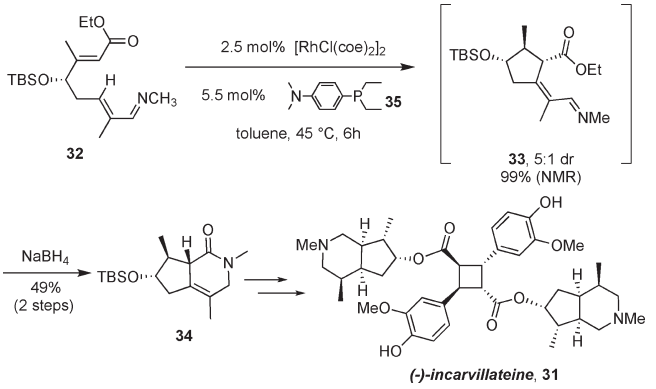
Entry	Alkene(yne)	Time (h)	Imine (*Z*:*E*)	Yield (*Z*:*E*)[a]
1		12	>95:5	91% (10:1)
2[b]		12	>95:5	77% (5:>95)
3		24	10:1	74% (5:1)
4		4	>95:5	78% (5:1)
5[b]		4	>95:5	73% (5:>95)
6		8	>95:5	80% (10:1)
7		4	>95:5	86% (20:1)

[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.

N-benzyl imine alkylation with substantially broadened scope and generality.[19] Although Wilkinson's catalyst was an ineffective catalyst for the alkylation of **30**, electron-donating ligands such as PCy_3 and $FcPCy_2$ produced a much more efficient catalyst, allowing the temperature to be decreased and minimizing subsequent olefin isomerization. Using $FcPCy_2$ as the ligand, the scope of the alkylation included olefins with alkyl (Table 2, entries 1 and 2), aryl (entry 3), ester (entries 4 and 5), and halo substituents (entry 6). In addition, the terminal alkyne *tert*-butylacetylene underwent hydrovinylation to give the dienal product (entry 7). Under acidic hydrolysis conditions, isomerization to the *E* isomer was generally seen (entries 2 and 5). However, concomitant hydrolysis and chromatography on activity III neutral alumina minimized isomerization to afford the trisubstituted *Z* enal products with good stereoselectivity (entries 1, 3, 4, 6, and 7). Although the methacrolein-derived imine was the most efficient substrate, β-substituted aldimines also could be employed to generate the more synthetically challenging β,β-disubstituted tri- and tetrasubstituted enal products stereoselectively and in good yield (not shown).[19] At the current stage of development, more highly substituted alkenes do not couple efficiently. Overcoming this limitation would also enable a catalytic enantioselective method to be pursued.

Synthetic Applications. The synthetic utility of this method was demonstrated in an intramolecular alkylation of an α,β-unsaturated imine in the total synthesis of the potent

SCHEME 5. Diastereoselective Synthesis of (−)-Incarvillateine



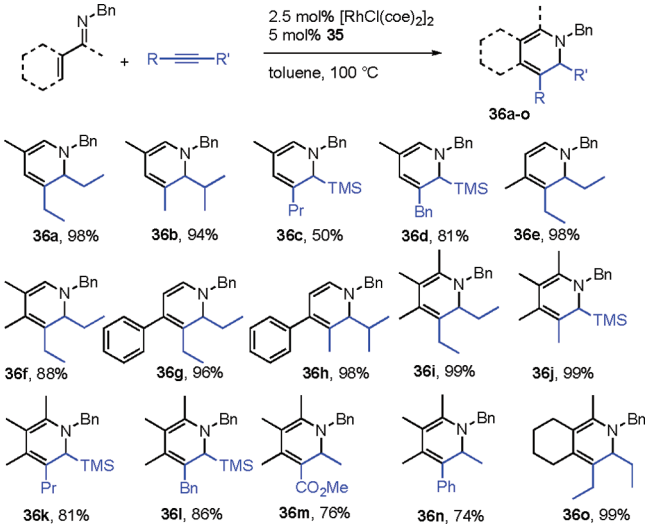
analgesic (−)-incarvillateine **31** (Scheme 5).[20,21] We envisioned that the piperidine functionality could be accessed very efficiently by employing an intramolecular β C–H bond alkylation of substrate **32**. In particular, from substrate **32**, *syn* alkene insertion and reductive elimination would exclusively provide the desired exocyclic double bond geometry and the requisite *anti* relationship of the methyl and ester functionalities.

The requisite imine substrate **32** was prepared enantioselectively in just four steps from commercial reagents. We were particularly interested in the C–H bond functionalization of **32** because it represented the first example of diastereocontrol in intramolecular alkylation arising from a stereocenter on the tether. Ligand screening revealed that electron-donating phosphine ligands were best suited for the desired transformation, and use of the *p*-(*N*,*N*-dimethylaminophenyl)diethylphosphine ((DMAPh)PEt_2, **35**) ligand shown in Scheme 5 provided quantitative conversion to **33** with 5:1 diastereoselectivity.

To avoid the facile tautomerization and epimerization of compound **33**, direct reduction of the crude imine product followed by lactamization provided lactam **34** as a single stereoisomer in 49% overall yield from acyclic precursor **32**. By rapidly generating the piperidine core, (−)-incarvillateine **31** was prepared in only 11 steps and 15.4% overall yield.

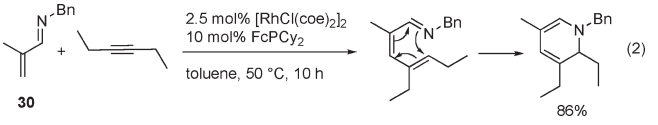
Alkenylation Reactions. Although the reaction of **30** with *tert*-butylacetylene provided the product of β-alkenylation (Table 2, entry 7),[19] reactions with internal alkynes or less bulky alkynes generated alkenylated products that underwent electrocyclization under the reaction conditions to yield 1,2-dihydropyridine (DHP) products (eq 2). This reactivity had been observed previously by Jun and co-workers with benzaldimine substrates,[22] and Odom et al. had also reported a single example of a

CHART 2. Dihydropyridine Synthesis from Imines and Alkynes[a]



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

one-pot hydroamination/C–H alkenylation sequence that generated a 1,2-DHP from the *N*-phenyl imine of 1-acetylcyclohexene.[23]



Extensive catalyst optimization, including the design of novel ligands for C–H bond functionalization, revealed that (DMAPh)PEt_2 ligand **35** (illustrated in Scheme 5) in a 1:1 ratio of L:Rh provided the highest yields of DHP products.[4] Using these optimized conditions, imine **30** reacted cleanly with internal alkynes having alkyl (**36a**,**b**), silyl (**36c**,**d**), or benzyl (**36d**) substituents (Chart 2). Unsymmetrical alkynes typically reacted to give a single regioisomer provided one of the substituents was α-branched. In general, 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. In addition to **30**, β-substituted aldimines reacted to produce highly substituted DHP products in good yields. Ketimines were also very efficient substrates in this chemistry (**36i-o**), and furthermore exhibited clean conversion to DHP products with ester (**36m**) and aryl (**36n**) substituted alkynes.

To gain an understanding of the mechanism of this class of reactions, stoichiometric quantities of imine **30**, the Rh precatalyst, and $FcPCy_2$ were combined and a new complex, **37**, formed immediately upon combination of the reagents

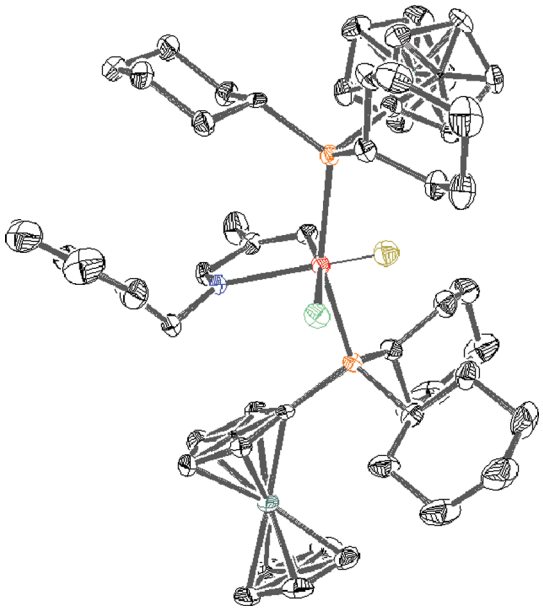
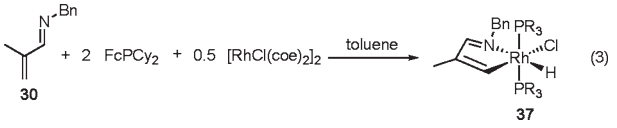


FIGURE 3. X-ray crystal structure (ORTEP diagram) of **37** with thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms distant from the metal center have been omitted for clarity.

at room temperature (eq 3). The crystal structure of **37** shows an azametallacyclopentane formed by chelation and C–H activation of **30** to give a complex with distorted octahedral geometry (Figure 3). Redissolving isolated **37** in toluene-d_8 or THF-d_8 gave a 2:1 equilibrium mixture of **37**:**30**. This demonstrates 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 for related systems.[3b,c]

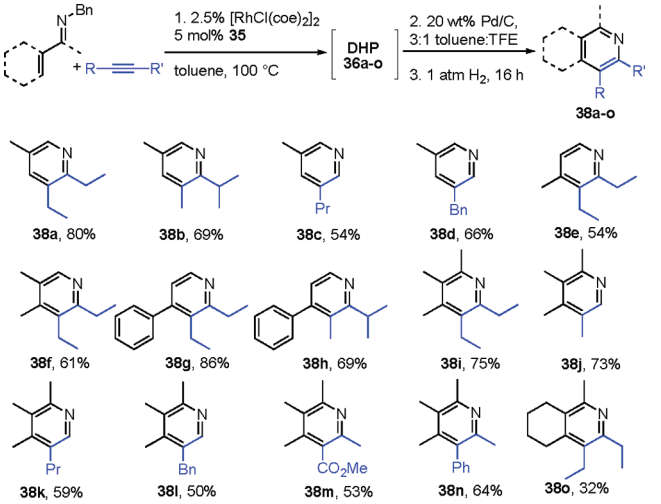
It was further found that reducing the reaction temperature in the catalytic synthesis of **36a** sufficiently slowed the electrocyclization step such that the azatriene intermediate could be observed to grow in and then decay when the reaction was monitored by NMR. This observation argues against a [4 + 2] cycloaddition-based mechanism.



30 37 (3)

Although the high reactivity of dihydropyridines limits their isolation, these compounds have proven to be versatile intermediates for the synthesis of piperidines and pyridines, which are prevalent in natural products, drugs, and materials. We further developed the alkenylation/electrocyclization sequence to include a synthesis of highly substituted

CHART 3. One-Pot Synthesis of Pyridines from Imines and Alkynes[a]



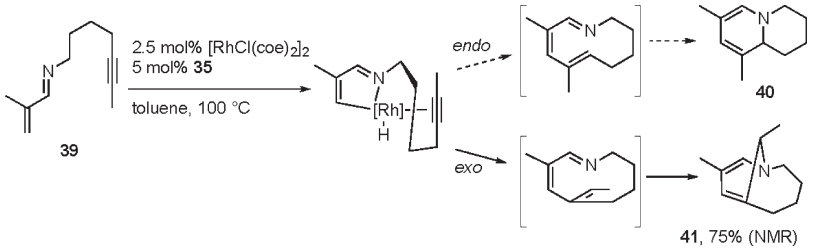
[a]Yields given are isolated yields based on starting imine.

pyridine derivatives that would be difficult to selectively access using other approaches.[24] To achieve this, an oxidation protocol was developed that enabled a one-pot synthesis of pyridines from imines and alkynes (Chart 3).[4] 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. In derivatives that displayed a silyl group α to the nitrogen (**38c**,**d**,**k**,**l**), desilylation occurred. The silyl functionality consequently served as a convenient blocking group that forced bulkier substituents distal to the pyridine nitrogen.

A related synthesis of pyridines from ketoxime derivatives and alkynes using Wilkinson's catalyst in which the DHP intermediates undergo aromatization through dehydration has also been reported, though this transformation was not demonstrated to proceed with aldoxime substrates.[25]

By applying the alkenylation chemistry to a substrate that has an alkyne tethered to the imine nitrogen (e.g., **39**, Scheme 6), an interesting result was obtained.[26] Depending on the direction of the migratory insertion step, two different products could be obtained, **40** or **41**. Under all conditions explored, substrate **39** produced the highly strained bicyclic enamine **41** exclusively. Presumably, the formation of **40** is not observed because *endo* migratory insertion would lead to an unfavorable *trans*-double bond within the [6.3.0] metallacyclic fused ring intermediate.

SCHEME 6. Possible Reaction Pathways for **39**



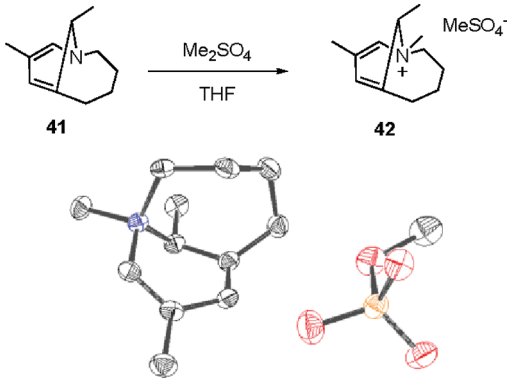
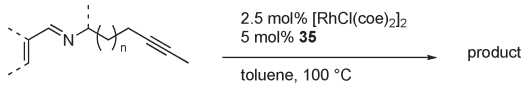


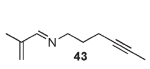
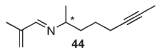
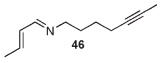
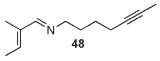
FIGURE 4. Methylation of **41**. ORTEP diagram of **42** with thermal ellipsoids drawn at the 50% probability level.

Product **41** possesses unique structural characteristics, namely, a bridgehead enamine functionality that lacks the proper geometry for conjugation and a bridgehead double bond in a nine-membered ring. Accordingly, **41** underwent methylation with dimethyl sulfate to provide the *N*-methylated product **42**, as opposed to the *C*-alkylated product that is normally obtained from enamine alkylation. X-ray quality crystals of **42** were obtained, validating the highly strained structure of this bicycle (Figure 4).

A series of substrates were prepared in order to evaluate the effect of changing substituents and tether length on this transformation (Table 3). Substrate **43**, displaying a shorter tether, underwent alkenylation, but the resulting azatriene decomposed without cyclizing, presumably due to the strain required to form a smaller ring with a bridgehead double bond. Substrate **44**, with a methyl group α to the nitrogen on the tether chain, underwent alkenylation and slow electrocyclization with complete atropodiastereoselectivity to give a single product stereoisomer, **45**. Substrates with β-substituents on the α,β-unsaturation (**46** and **48**) produced products with exocyclic double bonds. Isomerization likely occurs under the reaction conditions in order to relieve ring strain.

TABLE 3. C–H Bond Functionalization of Imines with Tethered Alkynes



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

[a]Isolated yields.

Catalysis by Rh(III) Complexes

Insertion into Alkenes. Complementary to the coupling with alkynes, similar alkenylated products could also be accessed through the oxidative coupling of alkenes using Rh(III) catalysts. In contrast to the Rh(I) complexes discussed previously, Rh(III) catalysts activate C–H bonds via an electrophilic deprotonation pathway to produce an aryl-Rh intermediate (**50**, Scheme 7).[27] Insertion of an alkene into the newly formed bond generates an alkyl-Rh complex (**51**) that likely β-hydride eliminates to yield the Heck-type product (**52**). An oxidant then regenerates the Rh(III) catalyst.[28]

One limitation of these Heck-type couplings with Rh(III) and related Pd(II) catalysts[29] is that they only proceed with activated alkenes such as acrylates and styrenes.[30] We hoped to be able to expand the scope to include a broader range of olefins.[31] Initial screens using methyl oximes and 1-hexene showed that the addition of a halide abstractor

SCHEME 7. Proposed Mechanism for the Rh(III) Catalyzed Oxidative Coupling of Alkenes

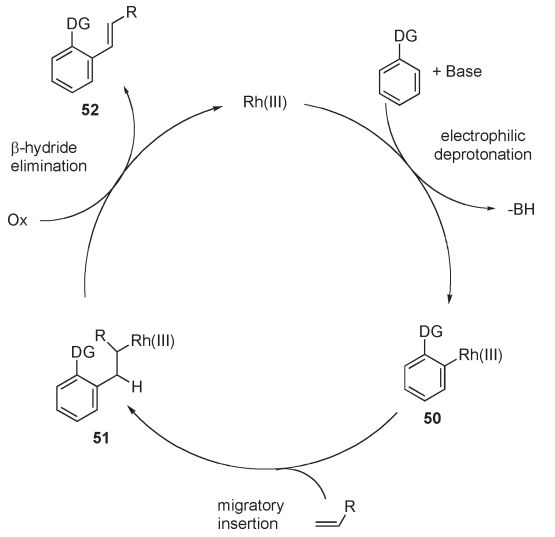
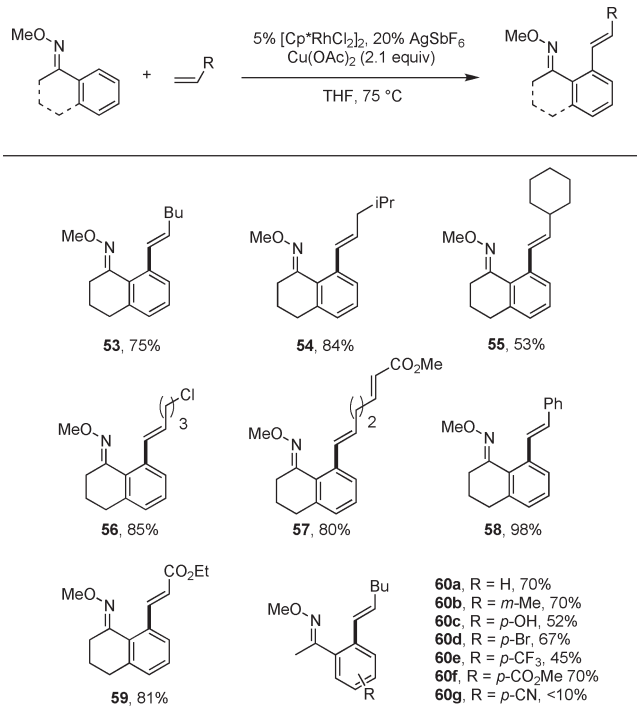
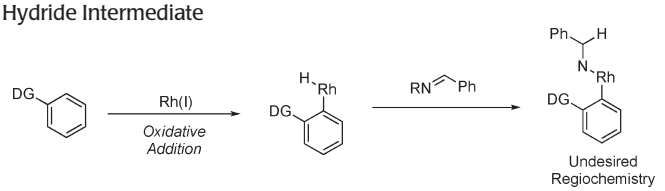


CHART 4. Substrate Scope for Oxidative Coupling of Alkenes

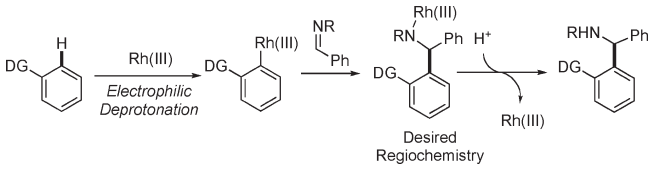


such as $AgSbF_6$ and the solvent choice were important to obtain the desired reactivity. Under optimized conditions, a variety of aliphatic (**53**, **54**, and **60**), branched (**55**), and functionalized (**56**, **57**, and **59**) terminal alkenes could be oxidatively coupled in good yields (Chart 4). More highly substituted alkenes do not react under these conditions, potentially owing to the increased steric interactions encountered during migratory insertion. Future development

SCHEME 8. Regioselectivity of Insertion of Imines into a Rhodium-Hydride Intermediate



SCHEME 9. Rh(III) Catalyzed Arylation of Imines

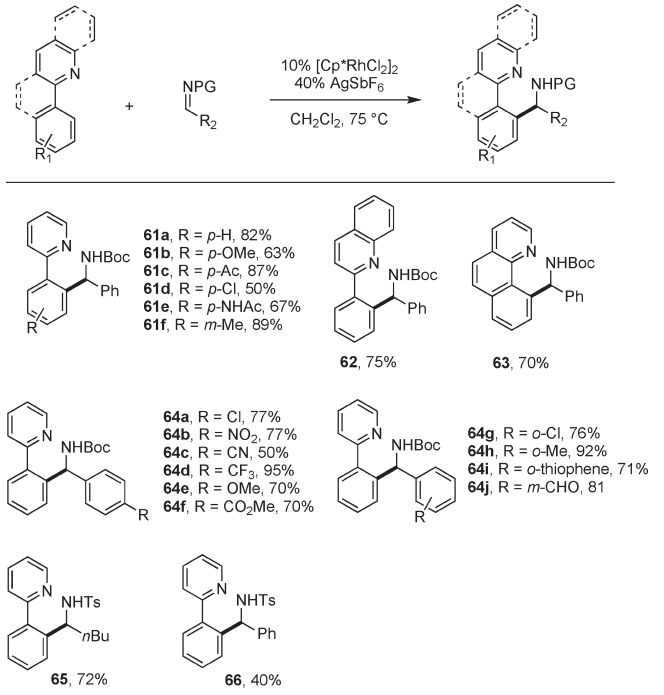


in this area may benefit from the use of less sterically encumbered Rh(III) catalysts. In related work, Fagnou's laboratory recently reported a Rh(III) catalyzed oxidative coupling of unactivated alkenes and alkynes with *N*-alkoxy amides to generate dihydroisoquinolones and isoquinolones, respectively.[32] In this case, as opposed to an external oxidant, the increased oxidation state of the amide is exploited to provide the oxidized products.

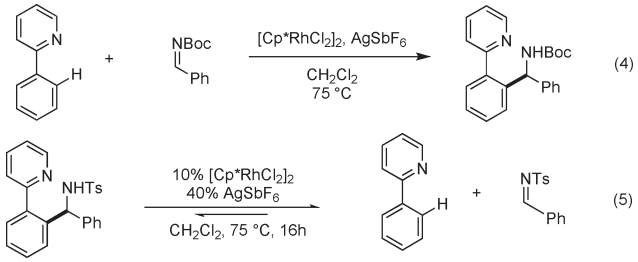
Insertion into Polar π Bonds. While Rh(I) catalysts have been shown to be well suited for couplings with alkenes and alkynes, analogous couplings with carbon-heteroatom π-bonds such as imines, have generally been less successful.[33] One reason for this limitation is that insertion of a prospective imine into the intermediate rhodium hydride is expected to occur with the regiochemistry opposite to that desired to form a C–C bond (Scheme 8).[34] To address this issue of regioselectivity, we looked to Rh(III) catalysts. We hypothesized that imines may be able to insert across the Rh-arene bond generated from initial electrophilic deprotonation with the desired regiochemistry to form a C–C bond. Upon protonolysis, this should directly provide α-branched aryl amines and bypass traditional methods that require arene prefunctionalization (Scheme 9).

To test this, 2-phenylpyridine and the *N*-Boc imine of benzaldehyde were combined in the presence of the Rh(III) catalyst $[Cp^*RhCl_2]_2$ (eq 4).[35,36] During reaction optimization, the addition of $AgSbF_6$ as a halide abstractor was found to be essential to achieve the desired reactivity, possibly by opening up the metal's coordination sphere to allow for binding of both reaction partners and to increase the electrophilicity of the catalyst. The reaction is robust, accommodating electronically diverse 2-arylpyridines and *N*-Boc imines (Chart 5). Reactive

CHART 5. Scope of 2-Aryl Pyridine Alkylation with Imines

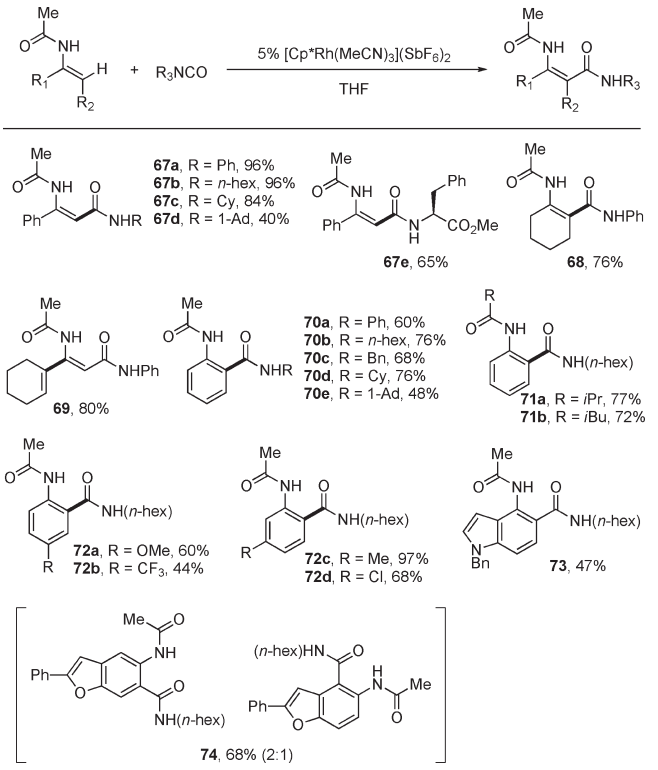


functional groups such as esters (**64f**), amides (**61e**), aldehydes (**64j**), and aryl chlorides (**61d**, **64a** and **g**) were well tolerated under the mild reaction conditions. It was also found that *N*-tosyl imines were suitable reaction partners. Notably, sensitive alkyl *N*-tosyl imines coupled in good yields (**65**). However, the yields for coupling of related aryl *N*-tosyl imines (**66**) were generally lower than those with *N*-Boc imines. Further investigation into the reactivity of aryl *N*-tosyl imines showed that the coupling is reversible under the reaction conditions and the lower yield is due to the equilibrium illustrated in Scheme 5.

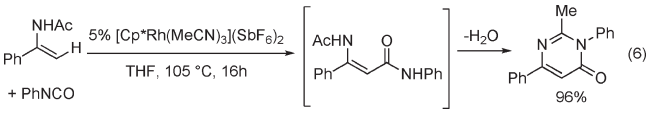


Further exploration of this mode of reactivity revealed that the pyridyl group also directed arylation of the polar carbon–nitrogen π-bond of isocyanates. Moreover, *N*-acyl amino groups also proved to be effective directing groups for the addition of both aryl and vinyl C–H bonds to isocyanates, which is particularly relevant to the synthesis of bioactive drugs and natural products (Chart 6).[37] Variously substituted enamides and anilides could be coupled with isocyanates with diverse steric and electronic properties to

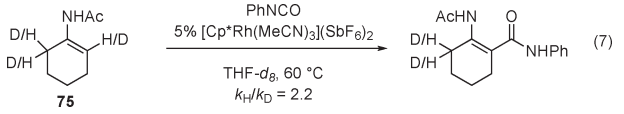
CHART 6. Substrate Scope of *N*-acyl Directed Additions of C–H Bonds to Isocyanates



yield *N*-acyl β-enamine amides and anthranilamides, respectively. Furthermore, the same Rh(III) complex catalyzes the in situ cyclodehydration of select *N*-acyl β-enamine amide products to pyrimidinones simply by increasing the reaction temperature (eq 6).



A normal kinetic isotope effect (eq 7) was observed when initial rates were measured for deuterated and protiated **75**. A normal kinetic isotope effect of comparable magnititude was also observed for a related anilide substrate (not shown). These observations are consistent with the C–H activation mechanism analogous to that proposed in Scheme 9 rather than direct π-bond addition of the enamine to the isocyanate, which should display an inverse kinetic isotope effect.[38] Further mechanistic investigation to confirm this inference is underway.



Continued work is focused on broadening the scope of the Rh(III)-catalyzed transformations to include a wider

range of directing groups and electrophiles, thereby expanding the impact of this chemistry. Additionally, the utility of the developed methods will directly be demonstrated through the synthesis of architecturally complex drugs and nautral products.

Conclusion

The rapid growth of the field of C−H bond functionalization over the last 20 years has established this mode of reactivity as a robust and efficient means for forming new chemical bonds in both simple and very complex targets. Further work toward new catalyst design and optimization promises to improve the selectivity and versatility of these transformations. The rich array of heteroatom directing groups, and the predictability of chelation effects, establishes this approach toward C−H functionalization as a highly effective tool for the synthetic chemist that will only further increase in utility as more efficient catalysts and new types of transformations are developed.

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BIOGRAPHICAL INFORMATION

Denise A. Colby obtained a B.S. in Chemistry and Biochemistry and Molecular Biology in 2004 from Illinois State University under the mentorship of Timothy Lash. She then received her Ph.D. in 2008 from UC Berkeley working in the laboratories of Robert Bergman and Jonathan Ellman, followed by postdoctoral studies in the laboratories of Timothy Jamison at MIT. She is currently a research scientist at Gilead Sciences in California.

Andy S. Tsai received his B.S. in chemistry from the University of Michigan and his Ph.D. from UC Berkeley, under the direction of Jonathan Ellman and Robert Bergman. He is currently a postdoctoral researcher with William Roush at the Scripps Research Institute, Florida.

Robert G. Bergman received his B.A. from Carleton College in 1963 and his Ph.D. from the University of Wisconsin in 1966 under the direction of Jerome Berson, followed by postdoctoral work with Ronald Breslow at Columbia University. His independent career began at CalTech in 1967, and 10 years later he joined the chemistry faculty of UC Berkeley. He has a longstanding interest in mechanistic chemistry and chemical reactivity; his early work on stoichiometric carbon−hydrogen bond activation reactions expanded into catalytic applications of C−H bond activation to organic synthesis in collaboration with Jonathan Ellman.

Jonathan A. Ellman received his B.S. from MIT and his Ph.D. from Harvard University under the direction of David Evans. He carried out postdoctoral research with Peter Schultz at the University of California at Berkeley, and in 1992 he became a member of the chemistry faculty at the same institution. In 2010, he relocated to the departments of pharmacology and chemistry at Yale University. His laboratory is engaged in the design of chemical tools for biological inquiry and in the development of new synthesis methods. He has collaborated with Robert Bergman since 2000 on the study of new C−H bond functionalization reactions.

FOOTNOTES

◇We wish to dedicate this paper to the memory of Keith Fagnou, who made ground-breaking discoveries of new C−H bond activation methods in organic synthesis.
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