ACCOUNTS
of chemical research

Direct Functionalization of Nitrogen Heterocycles via Rh-Catalyzed C−H Bond Activation

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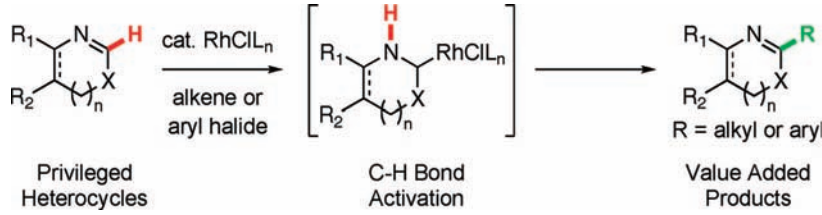
RECEIVED ON FEBRUARY 4, 2008

CONSPECTUS



Nitrogen heterocycles are present in many compounds of enormous practical importance, ranging from pharmaceutical agents and biological probes to electroactive materials. Direct functionalization of nitrogen heterocycles through C−H bond activation constitutes a powerful means of regioselectively introducing a variety of substituents with diverse functional groups onto the heterocycle scaffold. Working together, our two groups have developed a family of Rh-catalyzed heterocycle alkylation and arylation reactions that are notable for their high level of functional-group compatibility. This Account describes our work in this area, emphasizing the relevant mechanistic insights that enabled synthetic advances and distinguished the resulting transformations from other methods.

We initially discovered an intramolecular Rh-catalyzed C-2 alkylation of azoles by alkenyl groups. That reaction provided access to a number of di-, tri-, and tetracyclic azole derivatives. We then developed conditions that exploited microwave heating to expedite these reactions. While investigating the mechanism of this transformation, we discovered that a novel substrate-derived Rh−*N*-heterocyclic carbene (NHC) complex was involved as an intermediate. We then synthesized analogous Rh−NHC complexes directly by treating precursors to the intermediate [RhCl(PCy$_3$)$_2$] with *N*-methylbenzimidazole, 3-methyl-3,4-dihydroquinazoline, and 1-methyl-1,4-benzodiazepine-2-one.

Extensive kinetic analysis and DFT calculations supported a mechanism for carbene formation in which the catalytically active RhCl(PCy$_3$)$_2$ fragment coordinates to the heterocycle before intramolecular activation of the C−H bond occurs. The resulting Rh−H intermediate ultimately tautomerizes to the observed carbene complex. With this mechanistic information and the discovery that acid cocatalysts accelerate the alkylation, we developed conditions that efficiently and intermolecularly alkylate a variety of heterocycles, including azoles, azolines, dihydroquinazolines, pyridines, and quinolines, with a wide range of functionalized olefins. We demonstrated the utility of this methodology in the synthesis of natural products, drug candidates, and other biologically active molecules.

In addition, we developed conditions to directly arylate these heterocycles with aryl halides. Our initial conditions that used PCy$_3$ as a ligand were successful only for aryl iodides. However, efforts designed to avoid catalyst decomposition led to the development of ligands based on 9-phosphabicyclo[4.2.1]nonane (phoban) that also facilitated the coupling of aryl bromides. We then replicated the unique coordination environment, stability, and catalytic activity of this complex using the much simpler tetrahydrophosphepine ligands and developed conditions that coupled aryl bromides bearing diverse functional groups without the use of a glovebox or purified reagents. With further mechanistic inquiry, we anticipate that researchers will better understand the details of the aforementioned Rh-catalyzed C−H bond functionalization reactions, resulting in the design of more efficient and robust catalysts, expanded substrate scope, and new transformations.

Published on the Web 07/11/2008 www.pubs.acs.org/acr
10.1021/ar800042p CCC: $40.75

Introduction

Nitrogen heterocycles are present in many compounds of enormous practical importance, ranging from pharmaceutical agents and biological probes to electroactive materials. Tailoring the properties of these compounds to satisfy their specific functions necessitates the development of synthetic methods capable of regioselectively introducing a variety of substituents bearing diverse functional groups to the desired heterocycle scaffold. Direct functionalization of nitrogen heterocycles through C−H bond activation constitutes a powerful means to accomplish this important goal.[1]

This approach provides an atom-economical alternative to conventional procedures using halogenated or metallated starting materials.[2] However, a potential catalyst must activate a relatively inert C−H bond in the presence of other C−H bonds and then efficiently functionalize the metallated carbon in order to provide the desired product.[3] Despite these demanding requirements, a number of reactions that exploit directing groups,[4] repulsive steric interactions,[5] electron-rich substrates,[6] C−H bond acidity,[7] radical stability,[8] and even enzymes[9] to selectively activate and functionalize a specific C−H bond with a transition metal catalyst have been developed. When applicable to a particular substrate class, these methods reduce reaction byproducts, increase the number of available substrates, and decrease the synthetic effort required for formation of the desired C−C bond.

Selecting the appropriate catalyst for a desired substrate can seem daunting. However, understanding the mechanisms of the individual transformations provides a rational approach to addressing this problem as well as a framework for the application and continued discovery of new transformations. Working together, principally via jointly supervised co-workers, our two groups have extensively applied this strategy toward the development of a family of Rh-catalyzed heterocycle alkylation and arylation reactions that are notable for the high level of functional group compatibility that is achieved. This Account describes our work in this area, emphasizing the relevant mechanistic insights that enabled synthetic advances and distinguished the resulting transformations from other methods.

Intramolecular Alkylation of Azoles

The prevalence of 2-alkyl azoles in drugs led to our interest in developing a catalytic method for the alkylation of azoles at the 2-position.[10] At the time we began our investigations in this area, a number of researchers had demonstrated the feasibility of directly arylating the 2-position of azoles with aryl halides using Pd catalysis[11] and acylating this same site using

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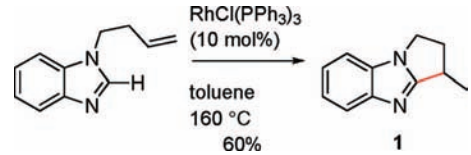

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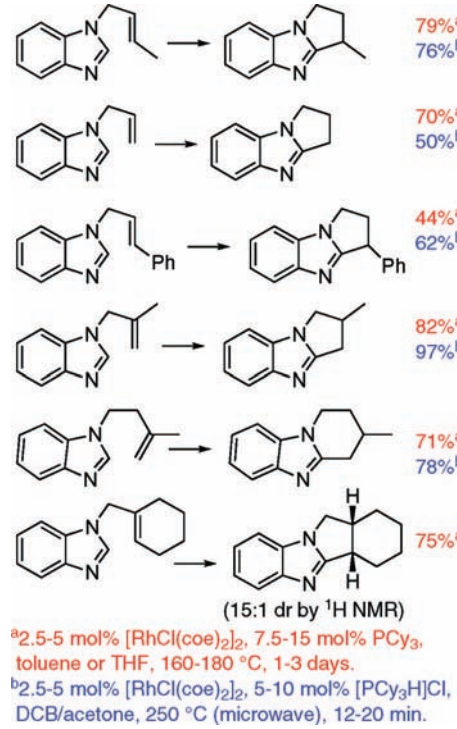
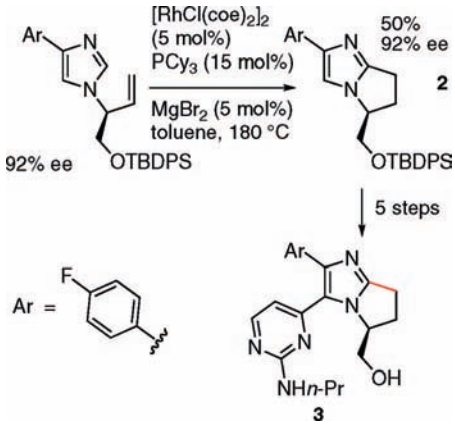


Ru catalysis.[12] We envisioned that the analogous alkylation reaction might be accomplished by formal hydroheteroarylation of an olefin by an azole in the presence of a transition metal catalyst.[13]

A number of late transition metal complexes were screened for their ability to catalyze the intramolecular alkylation of a benzimidazole bearing a pendant olefin, which led to the finding that Wilkinson's catalyst ($RhCl(PPh_3)_3$) provided a single cyclization product **1** in 60% isolated yield (Scheme 1). Optimization of the reaction parameters led to the identification of $[RhCl(coe)_2]_2$ (coe = cyclooctene) as a highly effective Rh precatalyst and PCy_3 as the optimal phosphine. This catalyst system was then applied toward the synthesis of a range of bi-, tri-, and tetracyclic 2-alkylimidazoles (Scheme 2, conditions a). In general, the cyclization provides products containing a five-membered ring as the major isomer unless an overriding steric bias, such as geminal alkene substitution or allylic α-dibranching, prevails. This preference is observed for both allyl- and homoallyl-substituted imidazoles due to rapid, competi-

SCHEME 3



tive olefin isomerization that generates an allyl-substituted cyclization precursor regardless of the initial olefin position.

Extensive efforts to improve the efficiency of this reaction led to the discovery that Lewis and Brønsted acid additives, including 2,6-dimethylpyridinium chloride and magnesium bromide, provided marked increases in reaction rate and conversion.[14] It was subsequently found that $[PCy_3H]Cl$ could be conveniently utilized to provide both the additive and the phosphine. This modification simplifies the reaction setup and renders the phosphine air stable for long-term storage.

In a collaborative effort with researchers at Abbott Laboratories, the cyclization reactions described above were reinvestigated using $[PCy_3H]Cl$ and a simplified protocol employing microwave heating (Scheme 2, conditions b).[15] The use of a microwave reactor allows convenient access to the high temperatures needed to reduce reaction times to 20 min, and the initial reaction mixtures were assembled using only a N_2 line to degas the solvent and reaction vessel prior to heating.[16] A microwave procedure was also developed using commercially available Wilkinson's catalyst in place of $[RhCl(coe)_2]_2/PCy_3$. Even with this suboptimal catalyst, the desired cyclized products were obtained in moderate yields (data not shown).

The intramolecular alkylation reaction has subsequently been applied to the synthesis of complex bioactive compounds. For example, the potent c-Jun N-terminal kinase inhibitor **3**, originally prepared in 14 linear steps and 6% overall yield,[17] was prepared in 11 linear steps and 13% overall yield by relying on our C−H functionalization reaction as the key step in the sequence (Scheme 3).[18] More highly substituted derivatives **4**, ent-**4**, and **5**, which would be very difficult to prepare by alternative methods, could be readily synthesized just as rapidly in 15% and 17% overall yields, respectively, and resulted in the identification of even more potent inhibitors (Figure 1).

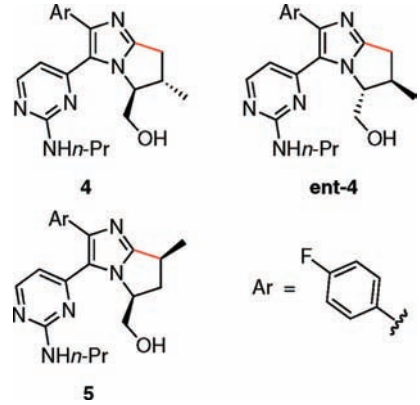


FIGURE 1. Methylated derivatives of kinase inhibitor **3**.

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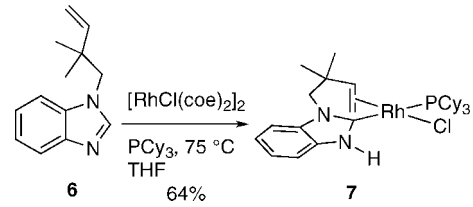


Investigation of the Mechanism of C−H Activation. Having established the utility of this new method for the intramolecular alkylation of imidazoles, we undertook an investigation of the mechanism of this novel transformation.[19] Initial deuterium tracer and crossover experiments revealed that rapid H/D exchange occurred between the heterocycle 2-position and pendant and external olefins. In order to shed further light on this exchange and to minimize the number of concurrent processes, the nonisomerizable substrate **6** was heated in the presence of stoichiometric quantities of $[RhCl(coe)_2]_2$ and PCy_3 at a temperature substantially below that required for cyclization in the absence of acid cocatalysts (Scheme 4).

A single compound, assigned as the square-planar Rh(I)−*N*-heterocyclic carbene (NHC) complex **7** by X-ray crystallography (Figure 2), formed under these conditions. This result was surprising, given that literature precedent generally indicates the formation of Rh(III)− or Ir(III)−hydride complexes following C−H bond activation by neutral Rh(I) or Ir(I) species.[3] Nonetheless, **7** catalyzed the cyclization of benzimidazole

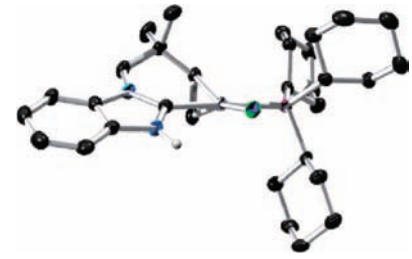
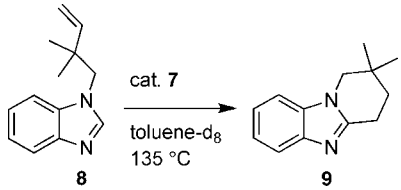
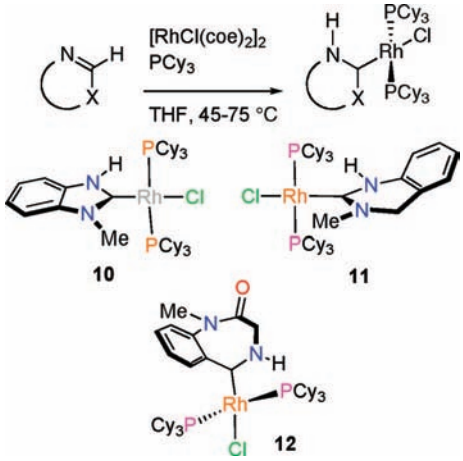


FIGURE 2. ORTEP diagram of **7**.

SCHEME 5



SCHEME 6



derivative **8** at the same rate as $[RhCl(coe)_2]_2/PCy_3$ (Scheme 5). Furthermore, a kinetic investigation of the cyclization of **8** catalyzed by complex **7** indicated that the reaction was zero-order in concentration of **8** and first-order in concentration of **7**. These results are consistent with a mechanism in which the resting state of the catalyst contains a single molecule of bound substrate. Carbene complex **7** forms at a lower temperature than that at which cyclization occurs and is observed throughout the reaction, leading to the conclusion that **7** is the resting state of the catalyst.

Similar Rh−NHC complexes have been obtained from the reaction of $[RhCl(coe)_2]_2$ and PCy_3 with a number of additional heterocycles, including benzimidazole,[20] 3,4-dihydroquinazoline,[21] and a 1,4-benzodiazepine-2-one[22] (Scheme 6, Figure 3). Prior to these examples, the direct formation of metal−NHC complexes from the corresponding heterocycles had not been reported. The novelty of this transformation, in addition to its centrality to our alkylation chemistry, led us to explore its mechanism in greater detail.

Closer examination of the reaction of 3-methyl-3,4-dihydroquinazoline **13**, $[RhCl(coe)_2]_2$, and PCy_3 at 45 °C in THF revealed the initial formation of a N-bound Rh-heterocycle complex, **14** (Scheme 7).[21] The structure of this complex was established unambiguously by extensive multidimensional NMR experiments on a variety of ^2H-, ^{13}C-, and ^{15}N-labeled 3-methyl-3,4-dihydroquinazolines. Upon further heating at 75 °C, this material was converted to the Rh−NHC complex **11**.

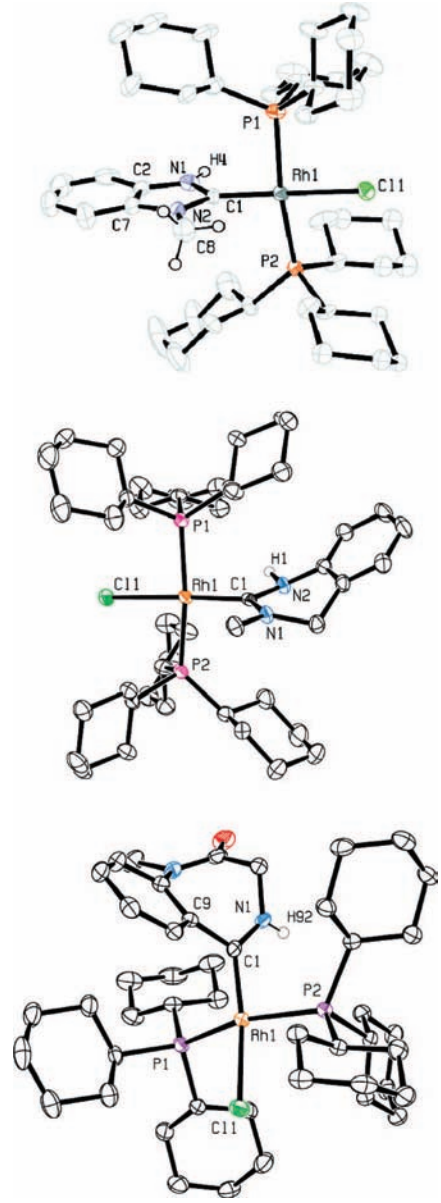
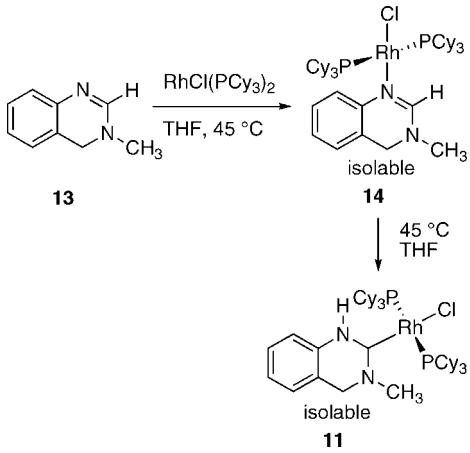


FIGURE 3. ORTEP diagrams of **10**−**12**.

Careful kinetic analysis established the N-bound complex **14** as an intermediate in the formation of **11**.

Deuterium-labeling tracer experiments using C2-D-**13** led to formation of the carbene complex possessing 88% deuterium at the N1 position. In addition, a double-labeling crossover experiment carried out using equal amounts of C2-D-**13** and $^{15}N1$-**13** revealed only a minor amount of crossover product ($^{14}N1$-H-**11**/$^{15}N1$-D-**11**). Together, these data are consistent with an intramolecular H-transfer in the conversion of **14** to **11**. The deuterium kinetic isotope effect on rate of conversion of **14** to **11** was measured, and the observed k_H/k_D (1.8 ± 0.1) is consistent with cleavage of the C2−H bond during or prior to the rate-limiting step. Activation parameters

SCHEME 7



($\Delta H^{\ddagger} = 26.0 \pm 0.3$ kcal/mol and $\Delta S^{\ddagger} = -10.3 \pm 0.8$ cal/(mol·K)) were also obtained and reveal the dramatic extent to which metal-mediation facilitates heterocycle-to-NHC tautomerization.

In an effort to gain further insight into the microscopic steps of C−H activation, these detailed mechanistic data were augmented with DFT calculations. A model system using 3-methyl-3,4-dihydropyrimidine in place of **13** and PMe_3 in place of PCy_3 was constructed based upon the structures of **14** and **11**. Conversion of starting complex **A**, the structure of which is in agreement with all spectroscopic data for **11**, to **I** was most consistent with a mechanism shown in Figure 4. Importantly, this mechanism indicated that the aforementioned Rh(III)−hydride complex (**G** in Figure 4) does indeed lie on the reaction coordinate but that the NHC tautomer is thermodynamically more stable and readily accessible via an intramolecular H migration.

While *N*-heterocyclic carbenes are commonly utilized as ancillary ligands on transition metal complexes,[23] the results highlighted above marked the first time that such complexes had been implicated as intermediates in a catalytic reaction.[24] More significantly, the known formation of stable metal−NHC complexes derived from myriad metals and carbene precursors, most notably azoles,[23] nonaromatic heterocycles,[25] heterocycles with only a single heteroatom,[26] and even certain acyclic molecules,[27] suggested that a number of additional substrates might also be compatible with Rh-catalyzed alkylation reaction conditions. Taken together with our synthesis of metal−NHC complexes directly from a variety of heterocycles, these precedents provided strong evidence that a greatly expanded substrate scope of Rh-catalyzed alkylation could be realized.

Intermolecular Alkylation of Heterocycles

Azoles. Initial efforts to achieve this goal focused on the intermolecular alkyation of various azoles with alkenes. Reaction conditions were initially evaluated for the intermolecular alkylation of benzimidazole using 3,3-dimethyl-1-butene, which proceeded efficiently with catalytic amounts of $[RhCl(coe)_2]_2$ and either $[PCy_3H]Cl$ or PCy_3 and 2,6-dimethylpyridinium chloride (LutCl) (Scheme 8).[14] Heterocycles capable of stabilizing M−NHC complexes served as effective substrates, including 1-methylbenzimidazole, benzthiazole, benzoxazole, 4,5-dimethylthiazole, and purine. Moreover, a broad functional group tolerance on the heterocycle was observed, and a variety of terminal olefins were compatible with the reaction conditions. In particular, both electron-rich and electron-poor olefins underwent coupling efficiently, and numerous functional groups, including silyl ethers, esters, acetals, phthalimides, and nitriles, were tolerated.

3,4-Dihydroquinazolines. Quinazoline-derived metal−carbene complexes are less well represented in the literature than their azole congeners, but the results of our study of complex **11** provided ample motivation to explore the Rh-catalyzed alkylation of this heterocycle class.[28] Furthermore, the quinazoline skeleton, in its various oxidation states, is a common structural motif in natural products and pharmaceuticals with a range of biological activities.[29] We initially investigated the alkylation of 3,4-dihydroquinazoline because it can be readily converted to the analogous quinazolines, quinazolinones, or 1,2,3,4-tetrahydroquinazolines by choice of an appropriate oxidant or reductant.[30]

Analysis by ^{1}H NMR spectroscopy established that quantitative C2 alkylation of 3,4-dihydroquinazoline occurred with *n*-hexene in the presence of our Rh catalyst. To simplify product analysis, oxidation of the crude alkylation product to the corresponding alkylated quinazoline was accomplished using MnO_2 (Scheme 9). In contrast to the azole alkylation discussed above, both styrene and methylenecyclohexane, a 1,1-disubstituted alkene, coupled efficiently, and *N*-methyldihydroquinazoline also proved to be a viable substrate.

Intramolecular dihydroquinazoline alkylation is also of interest because the process can be used to form ring-fused pyrrolo[2,1-*b*]quinazolines, a common scaffold for medically relevant natural products.[29] To demonstrate the applicability of this method, we undertook a total synthesis of vasicoline (Scheme 10). Cyclization of **15** proved to be particularly challenging, but a conformationally rigid cyclohexylphoban ligand, which had previously provided ruthenium alkylidene cata-

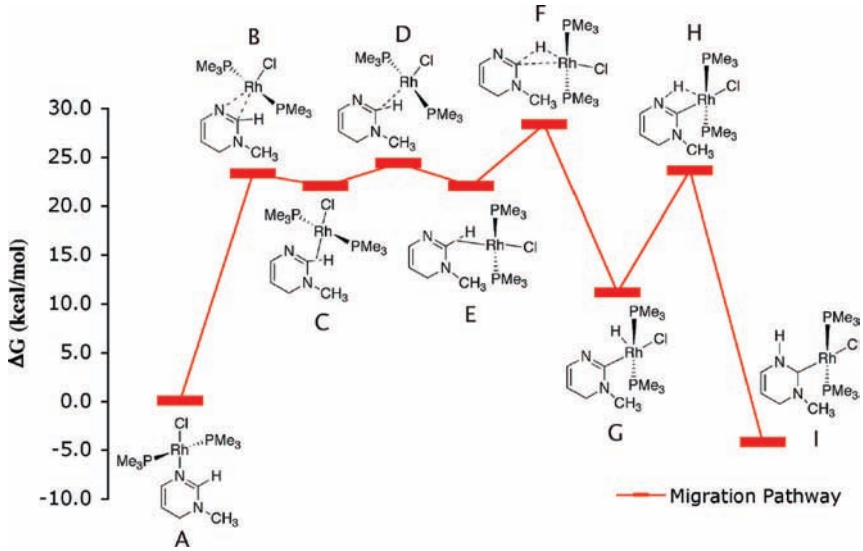
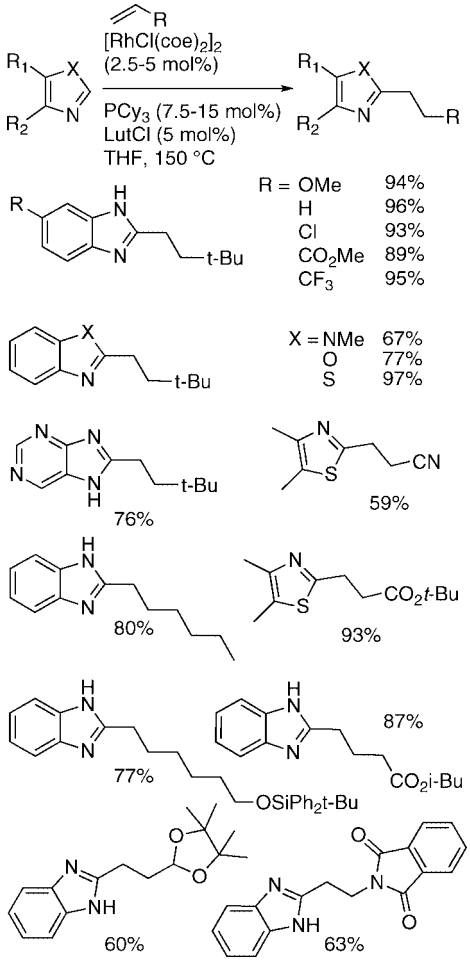


FIGURE 4. Calculated reaction coordinate for carbene formation.

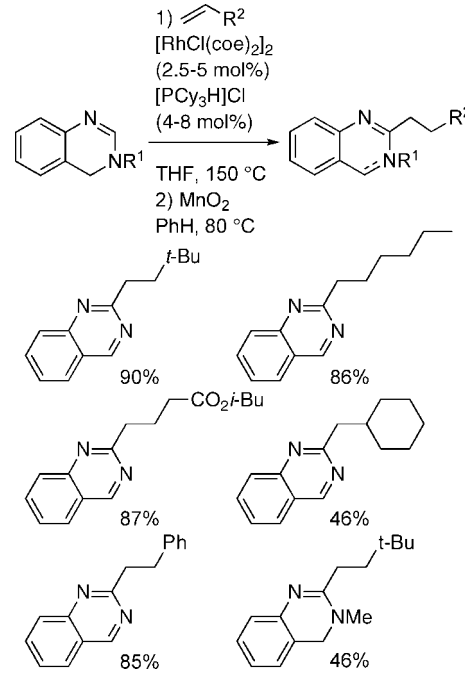
SCHEME 8



lysts with enhanced stability,[31] proved to be an effective ligand to facilitate the desired reaction.

Azolines. Nonaromatic azolines were next targeted as potential substrates since the wealth of literature on azoline-

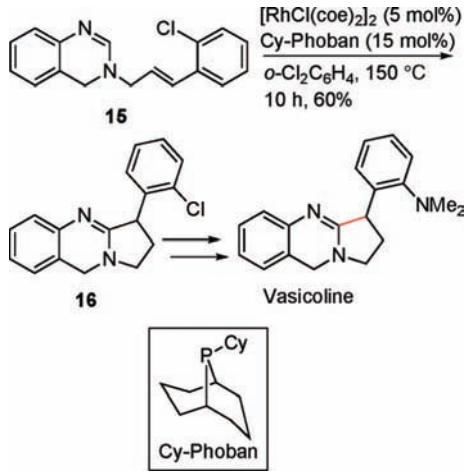
SCHEME 9



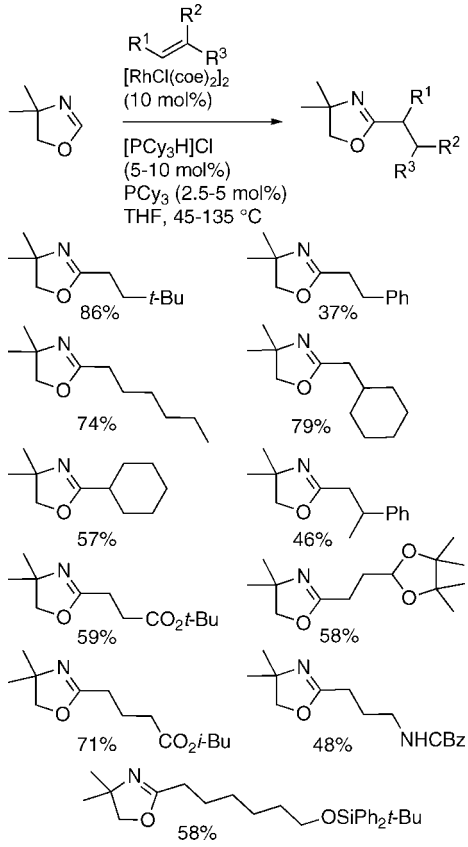
derived carbene ligands suggested that the corresponding azolines should be compatible with our NHC mechanism.[25] We were particularly interested in the alkylation of oxazolines as such a method would constitute a formal C1 olefin homologation without the use of toxic CO gas. The alkylated oxazolines could subsequently be converted to carboxylic acids or esters using well-known chemistry.[32]

Alkylation of 4,4-dimethyl-2-oxazoline was achieved with a large number of alkenes displaying a range of functionality in the presence of our Rh−phosphine catalyst (Scheme 11).[33] Under optimal conditions the alkylation could often be performed at 45 °C, a temperature significantly lower than

SCHEME 10



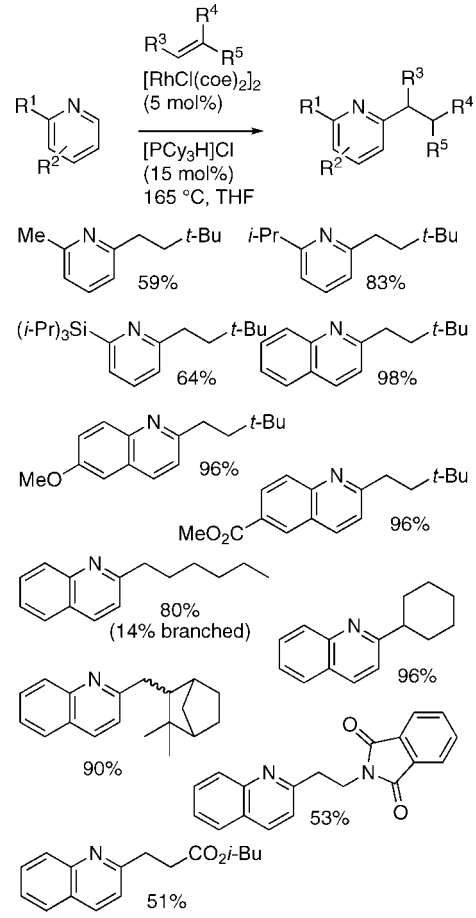
SCHEME 11



that used in the coupling of aromatic azoles. Both 1,1- and 1,2-disubstituted alkenes were effective coupling partners, and cyclohexene and methylenecylcohexane underwent coupling with good to moderate yield. Even α-methylstyrene, which results in a new stereocenter, coupled with modest efficiency.

Pyridines. In all of the substrates compatible with the Rh-catalyzed alkylation chemistry discussed thus far, the reactive carbon atom is flanked by two heteroatoms. This motif presumably stabilizes the proposed Rh−NHC intermediates

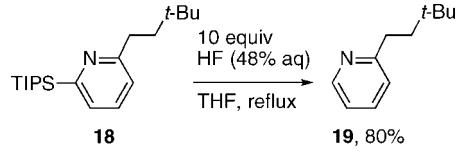
SCHEME 12



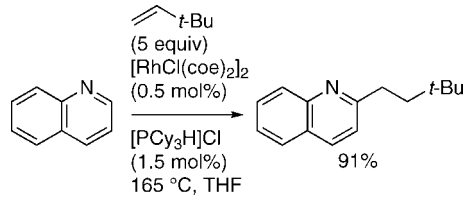
common to this family of reactions.[23] However, a number of groups have investigated the formation of NHC complexes in which two donating heteroatoms are not required.[26,27] While these complexes were not necessarily formed via the activation of a C−H bond, they did indicate the possibility that such complexes could function as catalytic intermediates. The Carmona and Esteruelas groups recently reported the synthesis of 2-substituted-pyridine- and quinoline-based Os−, Ru−, and Ir−NHC complexes directly from the corresponding heterocycles and a late transition metal complex.[26] The authors propose mechanisms similar to those shown in Figure 4 but emphasize the necessity of substitution *ortho* to the heterocycle ring nitrogen in order to drive the equilibrium from N-bound to the desired NHC complexes (Scheme 7, Figure 4). We therefore sought to determine whether our Rh/PCy_3 catalyst system could be used to not only activate but also alkylate these heterocycles.

Slight modifications to the conditions optimized for azole alkylation enabled the alkylation of a number of 2-substituted pyridines (Scheme 12).[34] Increasing the bulk of the 2-substituent from methyl to isopropyl led to an increase in both alky-

SCHEME 13



SCHEME 14



lation rate and isolated yield of alkylated product, and 2-triisopropylsilylpyridine also proved to be an effective substrate. Consistent with the findings of Carmona and Esteruelas for carbene formation,[26] pyridine was alkylated in less than 5% yield when heated in the presence of excess olefin and catalyst.

A variety of quinolines were also alkylated under the reaction conditions. Parent quinoline was nearly quantitatively converted to the corresponding alkylated quinoline, and both ether and ester substitution were tolerated in the quinoline 6-position. A wide range of olefin substitution patterns were also compatible with the reaction conditions.

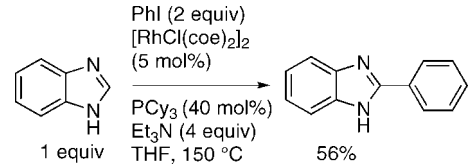
While substitution *ortho* to the pyridine nitrogen was required to obtain high yields of alkylated products, an *ortho*-silyl group serves as a suitable blocking group that can readily be removed to provide monoalkylated pyridines. For example, treatment of **18** with aqueous HF in refluxing THF provided the monoalkylated pyridine product **19** in good yield (Scheme 13).

In a preliminary evaluation of catalyst loading, quinoline was alkylated with neohexene in 91% yield using only 0.5 mol % of the Rh catalyst (Scheme 14).

Rh-Catalyzed Direct Arylation of Heterocycles

Our successes in the area of Rh-catalyzed heterocycle alkylation led us to postulate the feasibility of the corresponding arylation, because such a transformation would provide a highly efficient route to pharmaceutically relevant compounds.[35] At the time we began our research in this area, direct heterocycle arylation had seen only limited literature precedent with Miura's pioneering work using Pd catalysis as the most notable example.[11] Furthermore, we hoped that the novel mode of activation available using Rh catalysis might offer regioselectivity and substrate scope different from those observed with existing Pd- and Cu-based catalysts.[36]

SCHEME 15



Discovery and Optimization of Rh-Catalyzed Heterocycle Arylation. Aryl iodides were identified as suitable coupling partners for the arylation of benzimidazole using catalytic amounts of $[RhCl(coe)_2]_2$ and PCy_3 in the presence of triethylamine (Scheme 15).[20] In promising initial studies, a range of heterocycles, including benzimidazoles, benzoxazoles, 3,4-dihydroquinazoline and 4,4-dimethyl-2-oxazoline, and both electron-rich and electron-poor aryl halides coupled in moderate to good yields.

In addition, hydrodehalogenation of the aryl iodide coupling partner was identified as a key side reaction under the reaction conditions.[37] This process resulted from the dehydrogenation of the cyclohexyl groups of PCy_3, which led to the formation of reactive Rh−hydride complexes and ligand decomposition.[38] Our efforts to find phosphines that would maintain the unique steric and electronic qualities of PCy_3 while reducing the ability of the phosphine to undergo dehydrogenation led to the exploration of P-substituted phobanes as used for the previously discussed dihydroquinazoline alkylation (Figure 5).[28] Superior results were obtained using the [4.2.1] phoban isomers (**22a** and **22b**) as opposed to the [3.3.1] isomer (**21**) used in the alkylation reaction.

Microwave heating was employed to facilitate reaction setup and to conveniently reach the higher temperatures needed to minimize reaction time. Following optimization of the reaction conditions, 2-phenylbenzimidazole was produced from the coupling of benzimidazole and iodobenzene in a 95% yield. More importantly, bromobenzene was also coupled to benzimidazole in 80% isolated yield under the same reaction conditions (Scheme 16).

The direct arylation of heterocycles with aryl bromides using a Rh/**22a/b** catalyst exhibited considerable functional group tolerance[39] and provided access to 2-arylbenzimidazoles incorporating a wide variety of functional groups, includ-

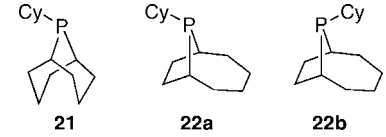
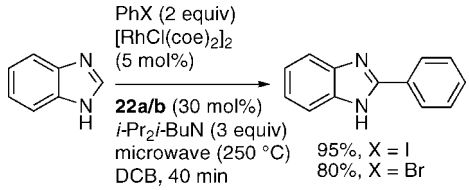
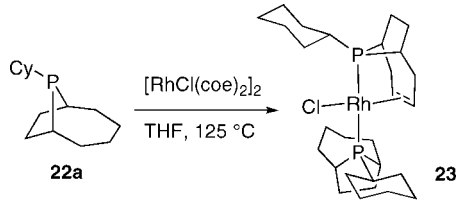


FIGURE 5. Structures of [3.3.1] (**21**), *exo*-[4.2.1] (**22a**), and *endo*-[4.2.1] (**22b**) isomers of 9-cyclohexyl-9-phosphabicyclononane.

SCHEME 16



SCHEME 17



ing nitrile, chloride, alkoxy, ketone, and amide substituents (data not shown). The reaction conditions were compatible with a number of different heterocycles, including *N*-methylbenzimidazole, benzoxazole, 3,4-dihydroquinazoline, and bisarylimidazoles.

Development of New Ligands. Efforts to understand the enhanced arylation activity afforded through the use of **22a/b** revealed the formation of P−olefin complex **23** under the arylation reaction conditions (Scheme 17).[40] This complex was prepared in good yield, and its structure was confirmed by single-crystal X-ray analysis (Figure 6). The structure clearly showed that one of the ligands had been selectively dehydrogenated to generate a P−olefin binding motif, while the second was left intact. The stability of this complex even under extended heating at 125 °C indicated the existence of tighter chelation of the rhodium center relative to the analogous complex formed in situ from Rh/PCy_3, which underwent multiple rounds of cyclometalation/β-hydride elimination ultimately leading to complete decomposition.

Complex **23** catalyzed the arylation of benzimidazole with a rate and final yield similar to those obtained with the use of $[RhCl(coe)_2]_2$/**22a/b**. Thus, the capacity of **22a/b** to form a stable bidentate P−olefin Rh complex and not solely the sterics and electronics of the phosphines themselves is largely responsible for the superior activity of the arylation catalysts derived from phobane ligands. Based on this hypothesis, we sought to simplify the phosphine ligand while maintaining the P−olefin binding motif that conferred the unique activity of **23** through the use of (*Z*)-2,3,6,7-tetrahydrophosphepines (Figure 7).[41]

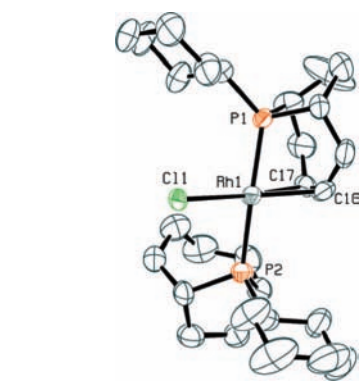


FIGURE 6. ORTEP diagram of **23**.

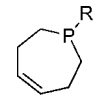
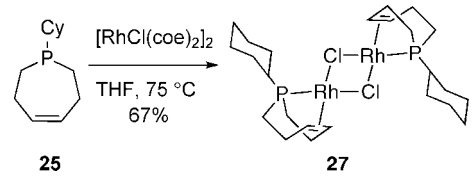


FIGURE 7. (*Z*)-2,3,6,7-Tetrahydrophosphepine skeleton.

SCHEME 18



A family of these ligands was synthesized, and the Rh complex (**27**) of (*Z*)-1-cyclohexyl-2,3,6,7-tetrahydro-1*H*-phosphepine (**25**) was prepared (Scheme 18). The structure of **27** was confirmed by single-crystal X-ray analysis (Figure 8). Notably, the Rh-binding motifs found in **23** and **27** exhibited a great deal of similarity, indicating that removing the two-carbon bridge from **22a** did not significantly alter the desired coordination geometry.

The *tert*-butyl-substituted phosphepine **28** (Figure 7, R = *t*-Bu) provided the highest conversion and essentially no hydrodehalogenation of PhBr during the course of the arylation of benzimidazole, with optimal conditions being microwave heating at 200 °C for 2 h with THF as the solvent.[42] The unique reactivity of these ligands compared with those previously investigated suggests that the hemilabile P−olefin coordination modulates the reactivity of the Rh center to allow the desired heterocycle arylation while reducing off-cycle hydrodehalogenation. At this point, we do not have very much information about the mechanism of the arylation reaction,

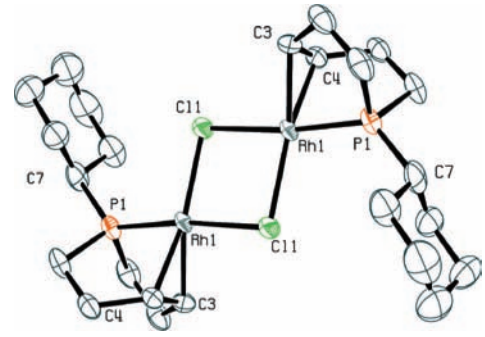
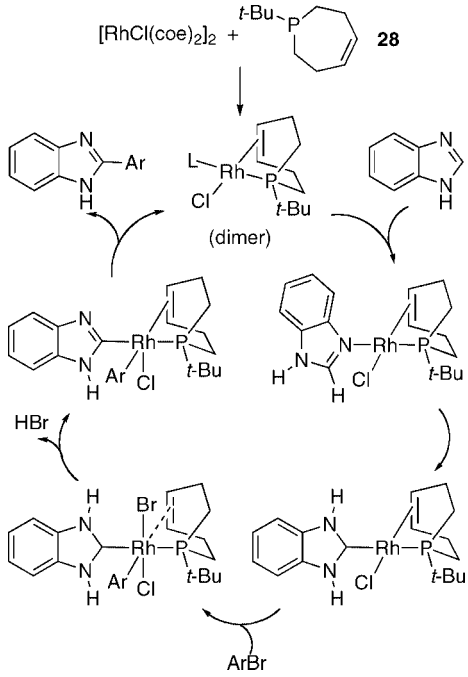


FIGURE 8. ORTEP diagram of **27**.

SCHEME 19

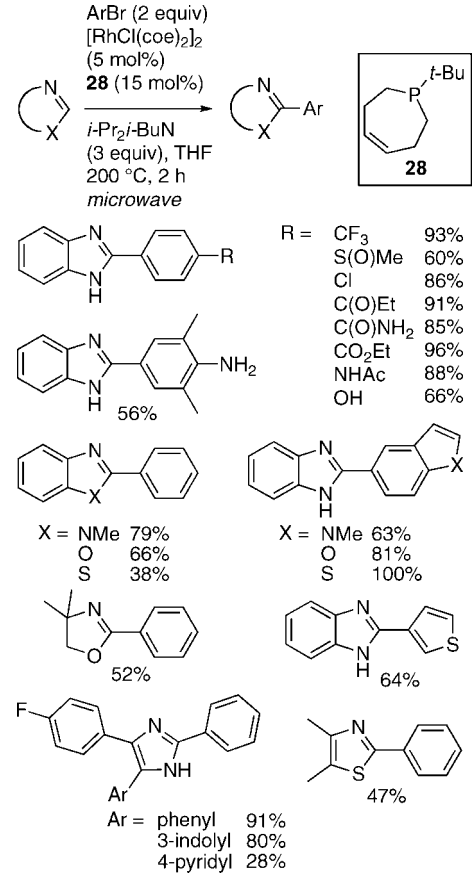


compared with the progress that has been made in the alkylation reactions discussed earlier in this Account. However, if *N*-heterocyclic carbene intermediates are also involved in the arylation, a reasonable hypothesis for the mechanism of the overall process is illustrated in Scheme 19. In this context, the Rh(I)−NHC intermediate is particularly attractive, since the low oxidation state at Rh prepares the metal center for oxidative addition of an aryl halide. However, further mechanistic investigation will be required to determine whether the mechanisms of the alkylation and arylation reactions do proceed by analogous pathways.

Substrate Scope of Heterocycle Arylation Using Rh−Phosphepine Catalyst 28. The optimized reaction conditions exhibited very high functional group tolerance and allowed the use of aryl halides and heterocycles containing acidic NH and OH groups that have yet to be demonstrated as viable azole direct arylation substrates using Pd or Cu catalysis (Scheme 20).[36] In particular, sulfinyl, chloro, acetamide, free hydroxy, and free amine groups were all tolerated; however, ortho substitution was not. Electron-rich heteroaryl bromides, including 5-bromo-1-methylindole, 5-bromobenzoxazole, 5-bromobenzothiazole, and 3-bromothiophene, also underwent coupling in excellent yields. These results are particularly notable given that these heterocycles undergo electrophilic metalation by Pd catalysts, which could cause regioselectivity problems in Pd-catalyzed direct arylations using these substrates.[36c]

A variety of additional heterocycles were also compatible with the Rh-catalyzed arylation conditions. Unprotected N−H

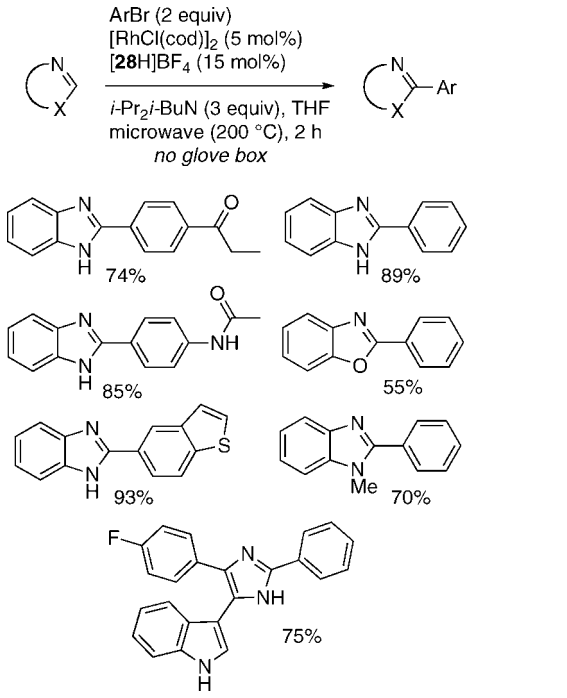
SCHEME 20



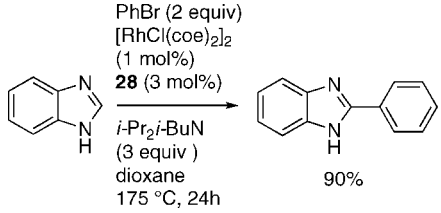
benzimidazoles were optimal, *N*-methylbenzimidazole and benzoxazole coupled in good yield, and benzthiazole was a viable substrate. Pharmaceutically important bisarylimidazoles were also excellent arylation substrates, and both indolyl and pyridyl subsitution, common to a number of known drug candidates, can be present on the imidazole ring.[43] Finally, arylation of 4,5-dimethylthiazole and the nonaromatic 4,4-dimethyloxazoline provided moderate yields of the corresponding arylated products.

The arylation protocol was greatly simplified through the use of [**28**H]BF_4, an air-stable surrogate of **28**[44] that is now commercially available from Sigma-Aldrich, and $[RhCl(cod)]_2$ (cod = cyclooctadiene), a much less expensive, air-stable Rh source (Scheme 21). Using these catalyst precursors, the reaction mixtures can be assembled without the use of a glovebox or reagent purification and with only a N_2 line to provide an inert atmosphere in the microwave vessel. In general, high yields of the desired products were obtained using standard laboratory equipment, so it is anticipated that these conditions would be most suitable for practical applications. Comparable results were obtained with dioxane as solvent (data not shown).

SCHEME 21



SCHEME 22



Preliminary investigation of catalyst loading was also performed under conventional heating, which is most applicable to large-scale reactions. At 1% loading of the $[RhCl(coe)_2]_2$ precatalyst in dioxane at 175 °C, a high yield of arylation product was obtained within 24 h (Scheme 22).

Summary and Outlook

In summary, we have used mechanistic insight to guide the development of efficient, functional group tolerant Rh-catalyzed heterocycle alkylation and arylation reactions. This work commenced with the identification of an intramolecular azole alkylation, using alkenes as the alkylating agents, catalyzed by a Rh(I)−phosphine complex. The discovery that this reaction proceeds via a Rh−NHC intermediate inspired the extension of this reaction to the intermolecular alkylation of a variety of substrates compatible with this intermediate, including azoles, azolines, 3,4-dihydroquinazolines, pyridines, and quinolines.

We then hypothesized that this electron-rich low-valent Rh(I) complex might also be ideally suited to affect the oxidative addition step required in the corresponding heterocycle arylation. Indeed, methods for coupling aryl iodides and ultimately aryl bromides to the previously mentioned heterocycles were developed. These methods were notable in the extremely high functional group tolerance and unique selectivity compared with Cu- and Pd-catalyzed methods.

Further mechanistic inquiry will lead to an increased understanding of the intimate details of the aforementioned Rh-catalyzed C−H functionalization reactions enabling the design of more efficient and robust catalysts. Moreover, many additional classes of nitrogen heterocycles should be capable of undergoing C−H bond activation to provide NHC−metal intermediates, and it is likely that this important new pathway for C−H bond activation will make possible new catalytic C−H bond functionalization methods.

This work was supported by the NIH, Grant GM069559 to J.A.E., and by the Director and Office of Energy Research, Office of Basic Energy Sciences, Chemical Sciences Division, U.S. Department of Energy, under Contract DE-AC03-76SF00098 to R.G.B.

BIOGRAPHICAL INFORMATION

Jared Lewis received his B.S. in chemistry from the University of Illinois working with Eric Oldfield and his Ph.D. from the University of California, Berkeley, under the direction of Jonathan Ellman and Robert Bergman. He is currently an NIH postdoctoral fellow with Frances Arnold at the California Institute of Technology.

Robert Bergman received his chemistry undergraduate degree at Carleton College and his Ph.D. from the University of Wisconsin under the direction of Jerome Berson, followed by postdoctoral work with Ronald Breslow at Columbia University. He joined the faculty of the California Institute of Technology in 1967 and ten years later accepted a professorship at the University of California, Berkeley. At Caltech, his research focused on reaction mechanisms, first on organic systems and gradually moving into the area of organometallic reactions and catalysis. This emphasis continued after his move to Berkeley and has supported his collaboration with Prof. Ellman on catalytic applications of C−H activation reactions.

Jonathan Ellman received his chemistry undergraduate degree from Massachusetts Institute of Technology and his Ph.D. from Harvard University, working with David A. Evans. After carrying out postdoctoral research with Peter G. Schultz at the University of California at Berkeley, he joined the faculty in 1992 and is currently a Professor of Chemistry. His laboratory is primarily engaged in the design of chemical tools for biological studies and in the development of new synthesis methods. He has collaborated with Robert Bergman since 2000 on the study and application of new C−H bond functionalization reactions.

FOOTNOTES

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