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Intermolecular Coupling of Alkenes to Heterocycles via C−H Bond Activation

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The intermolecular coupling of unactivated alkenes to a range of heterocycles using a Rh(I) catalyst was investigated. A variety of functional groups were incorporated into the alkene, including esters, nitriles, acetals, and phthalimide. Furthermore, the heterocycle tolerated substitution with both electron-rich and electron-deficient groups. The intermolecular coupling became possible after it was discovered that weak acids dramatically increase the rate of both the inter- and intramolecular reactions. An extensive optimization of additives was performed, and HCl·PCy_3 (Cy = cyclohexyl) and HCl·P-*t*-Bu_2Et were in general found to be the best additives for the reaction.

Introduction

Metal-catalyzed C−H bond activation[1] reactions have become important methods for the formation of carbon−carbon bonds.[2] The addition of aryl C−H bonds to alkenes, known as hydroarylation, has been a rapidly developing field. Two major approaches have been developed to accomplish hydroarylation:[3] nondirected C−H activation and directed C−H activation by a pendant functional group or embedded heteroatom. Nondirected C−H activation processes have the benefit of not requiring a functional handle on the starting material; however, the regioselectivity of the functionalization is a major challenge in this area. Periana has developed Ir catalysts that couple benzene derivatives to alkenes.[4] While Periana's Ir-based catalysts have shown good turnover numbers and alkene generality, the process has suffered from modest regioselectivity on both the arene and alkene component. Recently, Gunnoe reported a Ru catalyst for this process, which functions at a lower temperature.[5] Several groups have used electrophilic C−H activation catalysts to perform hydroarylations with electron-rich aromatics.[6] Fujiwara has demonstrated that electron rich aromatics will undergo nondirected coupling to electron deficient alkenes and alkynes at room temperature.[7] Sames extended the scope of this methodology to an intramolecular cyclization using a Ru(III) catalyst, allowing access to chromanes, tetralins, and terpenoids.[8]

Several groups have focused on directed C−H activation to increase both the selectivity and reactivity of these processes. In 1993, Murai reported that a ketone could be used to direct C−H activation at the ortho position of an aromatic ring, and subsequent coupling to an alkene yielded the ortho alkylated product.[9] Since this initial report, several groups have expanded the scope of this reaction to include a variety of directing groups such as imines,[10] nitriles,[11] ketones,[12] esters,[13] pyridines,[14] and other heterocycles. The Bergman and Ellman labs have developed an intramolecular cyclization using an imine

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(7) (a) Jia, C. G.; Piao, D. G.; Oyamada, J. Z.; Lu, W. J.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992−1995. (b) Fujiwara, Y.; Jia, C. G. *Pure Appl. Chem.* **2001**, *73*, 319−324.

(8) Youn, S. W.; Pastine, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581−584.

(9) (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529−531. (b) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Pure Appl. Chem.* **1994**, *66*, 1527−1534. (c) Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62−83.

(10) Jun, C. H.; Hong, J. B.; Kim, Y. H.; Chung, K. Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 3440.

(11) Kakiuchi, F.; Sonoda, M.; Tsujimoto, T.; Chatani, N.; Murai, S. *Chem. Lett.* **1999**, 1083−1084.

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(13) Trost, B. M.; Imi, K.; Davies, I. W. *J. Am. Chem. Soc.* **1995**, *117*, 5371−5372.

(14) (a) Lim, Y. G.; Kim, Y. H.; Kang, J. B. *Chem. Commun.* **1994**, 2267−2268. (b) Lim, Y. G.; Kang, J. B.; Kim, Y. H. *Chem. Commun.* **1996**, 585−586. (c) Lim, Y. G.; Kang, J. B.; Kim, Y. H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 699−707.

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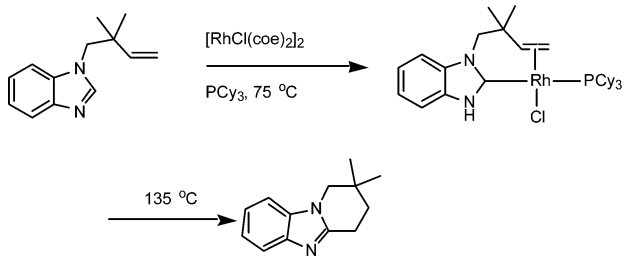
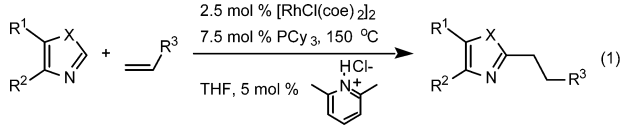
SCHEME 1



directing group,[10] which has allowed access to a variety of functionalized carbo- and heterocyclic products.[15]

We became interested in further developing our hydroarylation methodology using heterocycles as the coupling partner. The selective functionalization of heterocycles is of particular importance due to the ubiquity of these structures in natural products, as well as in pharmaceutical agents. Prior to our initial communication, the only account of a catalytic hydroarylation of a heterocycle at the ortho position was by Taylor and Jordan, who reported the ortho alkylation of pyridine with ethylene and propene using a Zr catalyst.[16] We initially developed an intramolecular cyclization of alkenes to benzimidazole and imidazole scaffolds.[17] This methodology allowed for the cyclization of numerous substituted alkenes, yielding a variety of heterocyclic scaffolds. In the course of studying the mechanism of this reaction, an *N*-heterocyclic carbene Rh(I) complex was identified and characterized (Scheme 1).[18] The intermediacy of this NHC complex suggested that a broad range of heterocycles could function under this mechanism, thereby increasing the scope of the C−C bond-forming reaction dramatically.[19] Due to the limitations of the intramolecular reaction, which requires a tethered alkene proximal to the site of C−H activation, we were interested in exploring conditions for a general intermolecular coupling reaction. After an initial screening of additives, it was discovered that addition of weak Lewis and Brønsted acids dramatically accelerated the rate of the reaction, thus making the intermolecular coupling of alkenes to heterocycles possible (eq 1).[20]



In this paper, a detailed study of the intermolecular coupling reaction of heterocycles to alkenes is reported. In addition to an examination of substrate scope, we provide an account of the optimization of the additive and phosphine, as well as postulate a rationale of the additive effect.

Results and Discussion

Intermolecular Coupling of Neohexene to Heterocycles. In earlier work, we had reported the intramolecular coupling of alkenes to benzimidazole, using $[RhCl(coe)_2]_2$ (coe = *cis*-cyclooctene) and PCy_3 (Cy = cyclohexyl) as the catalyst. Application of this catalyst system to the intermolecular coupling of benzimidazole to neohexene resulted in no reaction. However, the addition of certain Lewis or Brønsted acids resulted in a dramatic increase in the rate of the cyclization chemistry and made the intermolecular coupling accessible.[21] Though several Lewis and Brønsted acids accelerated the reaction, weak Brønsted acids afforded the highest yields for the largest range of heterocycle substrates. Using lutidinium chloride as a cocatalyst, the heterocycle generality was expanded to include benzthiazole, benzoxazole, 4,5-dimethylthiazole, and purines (Table 1). 1-Methylbenzimidazole also functioned as a coupling partner, although higher catalyst loading was required to obtain high conversion (Table 1, entry 6). The success of the reaction with these substrates is consistent with the formation of an *N*-heterocyclic carbene complex as a critical intermediate on the catalytic cycle. No reaction was observed between neohexene and either pyrimidine or indole, which is expected since these compounds are not known to form *N*-heterocyclic carbenes. However, isoxazole, indazole, and 1-phenylpyrazole also did not couple with neohexene, even though they could form carbene complexes. Recently, Herrmann and co-workers showed that in the formation of Rh(I) carbene complexes with azolium salts the reaction rate decreased in the order benzimidazole > triazole > imidazole > pyrazole, which correlates with the decreasing acidity of the salt.[22] We believe this may also explain the lack of reactivity of 1-phenylpyrazole, indazole, and isoxazole in our system. Interestingly, purine was found to undergo multiple alkylations, unlike the other heterocycles tested. Monitoring the reaction by ^{1}H NMR spectroscopy established that the reactions proceed sequentially, with initial alkylation occurring at the 8 position, followed by reaction at the 6 position (Table 1, entry 5).[23]

Survey of the Functional Group Compatibility on the Alkene Coupling Partner. With these encouraging results, a survey of alkene generality was undertaken using benzimidazole as the model heterocycle. One of the major limitations in the C−H coupling to alkenes thus far has been the lack of success with isomerizable alkenes. We were delighted to find that with the new conditions for intermolecular coupling, 1-hexene reacts efficiently with benzimidazole giving the linearly coupled product **9** in 80% isolated yield (Table 2, entry 2). Attempts at coupling cyclohexene with benzimidazole

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(16) (a) Jordan, R. F.; Taylor, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 778−779. (b) Dagorne, S.; Rodewald, S.; Jordan, R. F. *Organometallics* **1997**, *16*, 5541−5555. (c) Jordan, R. F.; Bradley, P. K.; Lapointe, R. E.; Taylor, D. F. *New J. Chem.* **1990**, *14*, 505−511.

(17) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 2685−2686.

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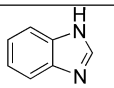
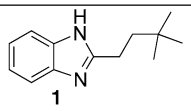
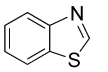
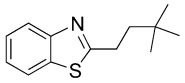
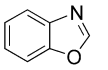
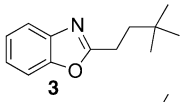
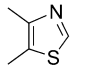
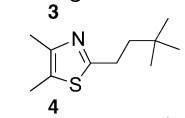
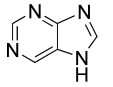
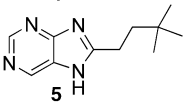
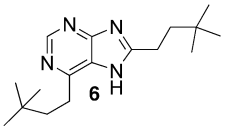
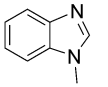
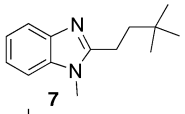
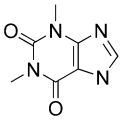
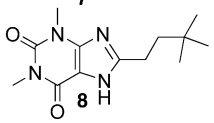
(21) Addition of Bu_4NCl did not result in acceleration of the reaction showing that the additive effect is not a result of ionic strength of the medium.

(22) Kocher, C.; Herrmann, W. A. *J. Organomet. Chem.* **1997**, *532*, 261−265.

(23) The regioselectivity of the alkylation of **6** was determined by X-ray crystallography.

TABLE 1. Intermolecular Coupling of Neohexene to Heterocycles

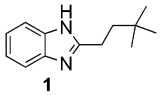
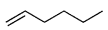
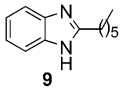
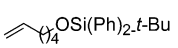
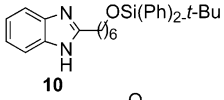
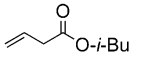
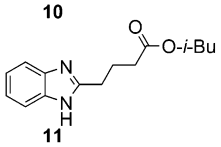
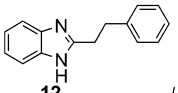
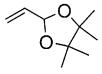
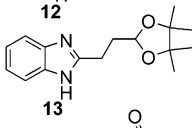
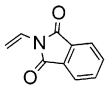
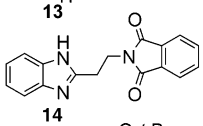
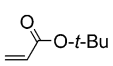
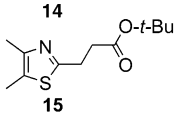
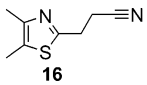
Entry	Heterocycle	Product	Yield (%)
1		 1	96[a]
2		 2	97[a]
3		 3	77[a]
4		 4	99[a]
5		 5	76[a]
		 6	17[a]
6		 7	67[b]
7		 8	15[c]

[a] 2.5 mol % $[RhCl(coe)_2]_2$, 7.5 mol % PCy_3, 5 mol % lutidinium Cl^-, and 5 equiv of neohexene, at 150 °C in THF. [b] 5 mol % $[RhCl(coe)_2]_2$, 15 mol % PCy_3, 5 mol % lutidinium Cl^-, and 5 equiv of neohexene at 150 °C in THF. [c] 5 mol % $[RhCl(coe)_2]_2$, 10 mol % $HClPCy_3$, and 5 equiv of neohexene, at 150 °C in THF.

were unsuccessful, suggesting that only terminal alkenes are effective substrates.

With this initial success, we explored the electronic requirements of the alkene and the functional group compatibility of the substrates under the reaction conditions. A silyl-protected alcohol was stable under the C−H/alkene coupling conditions (Table 2, entry 3). Ester **11** was synthesized by coupling an allylic ester to benzimidazole, although an increase in the catalyst loading was necessary to obtain a high yield (Table 2, entry 4). A poor yield was observed when styrene was used as the coupling partner (Table 2, entry 5). Polymerization of styrene was observed under the conditions, which may have accelerated the catalyst decomposition. The acetal of acrolein reacted with benzimidazole to give the functionalized heterocycle **13** (Table 2, entry 6). The pinacol protecting group was used because other acetals, e.g., acrolein dimethyl acetal and 2-vinyl-1,3-dioxolane, led either to decomposition or poor yields. The steric bulk of the pinacol may hinder isomerization and provides a more robust protecting group, thereby eliminating potential decomposition pathways. While reaction with alkenes incorporating a carbamate protecting group resulted in decomposition or poor yields, use of a vinyl phthalimide as a coupling partner resulted in good yields

TABLE 2. Survey of Functional Group Tolerance on the Alkene Coupling Partner

Entry	Alkene	Product	Yield(%)
1		 1	96[a]
2		 9	80[a]
3		 10	77[a]
4		 11	87[b]
5		 12	19[b]
6		 13	60[b]
7		 14	63[c]
8		 15	93[b]
9		 16	59[b]

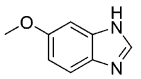
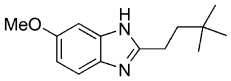
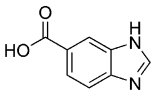
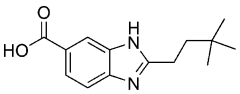
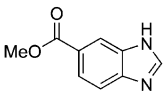
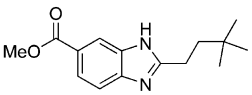
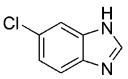
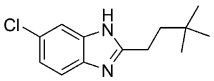
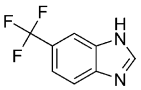
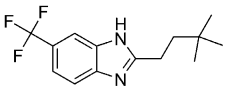
[a] Reactions run with 2.5 mol % $[RhCl(coe)_2]_2$, 7.5 mol % PCy_3, 5 mol % lutidinium Cl^-, and 5 equiv of alkene at 150 °C, in THF. [b] Reactions run with 5 mol % $[RhCl(coe)_2]_2$, 15 mol % PCy_3, 5 mol % lutidinium Cl^-, and 5 equiv of alkene at 150 °C, in THF. [c] Reactions run with 5 mol % $[RhCl(coe)_2]_2$, 10 mol % $HClPCy_3$, and 5 equiv of alkene at 150 °C, in THF.

of the desired amine-protected product **14** (Table 2, entry 7).[24] This reaction is also notable because it demonstrates that electron-rich alkenes are effective coupling partners. Investigation of electron deficient α,β-unsaturated esters with benzimidazole as a coupling partner resulted in hydroamination rather than the desired C−H coupling products. We then tested the Michael acceptors with 4,5-dimethylthiazole, which is unable to undergo the hydroamination reaction. Acrylonitrile and *tert*-butyl acrylate both underwent coupling to 4,5-dimethylthiazole, demonstrating that electron-deficient alkenes are also suitable substrates for the reaction (Table 2, entries 8 and 9). Acrylonitrile provided mostly the desired linear isomer, but a small amount of branched isomer was also observed (L/B = 3.8:1).

Survey of the Functional Group Compatibility on the Heterocycle Coupling Partner. The functional group tolerance on the heterocycle component was also

(24) A carbamate protecting group was used successfully in the coupling with an oxazoline derivative; see ref 20c.

TABLE 3. Functional Group Compatibility on the Heterocycle Coupling Partner

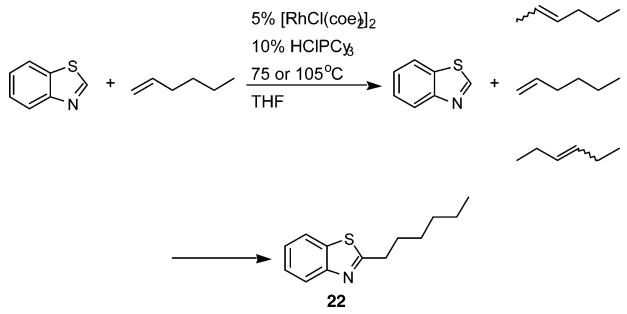
Entry	Heterocycle	Product	Yield(%)
1		 **17**	94[a]
2		 **18**	66[b]
3		 **19**	89[a]
4		 **20**	93[a]
5		 **21**	95[a]

[a] Reactions run with 2.5 mol % $[RhCl(coe)_2]_2$, 5 mol % $HClPCy_3$, and 5 equiv of alkene at 150 °C, in THF. [b] Reactions run with 5 mol % $[RhCl(coe)_2]_2$, 10 mol % $HClPCy_3$, and 5 equiv of alkene at 150 °C, in THF.

examined. For this series of experiments $HClPCy_3$[25] was employed as both the additive and phosphine. This modification simplifies the reaction setup, and it also renders the phosphine air stable for long-term storage. Under these conditions, a variety of substituted benzimidazoles were successfully coupled to neohexene. Both electron-rich and electron-deficient substituents were tolerated on the ring, and excellent yields were obtained for both types of substitution (Table 3, entries 1 and 5). A free carboxylic acid on the heterocycle resulted in a lower yield of the desired product compared to the other functional groups screened (Table 3, entry 2). The lower yield may be attributed to the poor solubility of the carboxylic acid in THF because replacing the carboxylic acid functionality with a more soluble ester derivative resulted in an excellent yield of the alkylated product (Table 3, entry 3). An aryl chloride was also coupled efficiently, leaving the halide substituent intact for subsequent elaboration via cross-coupling chemistry.

Expanded Solvent and Additive Screen. While the use of $HClPCy_3$ did solve many technical problems, it did not improve the reactivity of the catalyst significantly, which led to an investigation of the causes of the modest reactivity. Monitoring the reaction of benzthiazole with 1-hexene at 75 and 105 °C by ^1H NMR spectroscopy showed that the major impediment to efficient coupling was olefin isomerization (Scheme 2). Within 2 h at 75 and 105 °C, 1-hexene had equilibrated to a mixture of alkene isomers. Under these conditions, only 2−4% (0.1−0.2 equiv) of the initial amount of 1-hexene remained. Though the internal alkene isomers can isomerize back to the terminal alkene and then couple, the concentration of desired 1-hexene is dramatically lowered, thereby causing a large decrease in the overall rate of reaction. At 105 °C, the reaction will go to completion after 2.5 days, demonstrating that the catalyst is robust. These results suggested that the reaction could likely be improved if the rate of coupling was increased relative to the rate of isomerization.

SCHEME 2



Because it was unknown if the use of an additive affected the rate of isomerization and coupling independently, a screen of additives and solvents was undertaken using benzthiazole and 1-hexene as the model compounds at a reaction temperature of 75 °C. A set of Lewis acids and lutidinium bromide was screened in THF, CH_3CN, toluene, 1,2-dichloroethane, and *o*-dichlorobenzene (*o*-DCB) (Figure 1). Generally, the additive effect was most dramatic in THF, with $TiCl_4$·THF providing the highest yield; however, none of the additives were found to be more effective than $HClPCy_3$. Other solvents appeared to suppress the coupling reaction. With these initial leads, several other metal complexes were screened, and a variety of Ti derivatives were evaluated (Table 4). Unfortunately, none of the new metals screened improved the yield of the reaction at this lower temperature. Furthermore, changing the ligands on the Ti center was detrimental to the reaction. Use of the Lewis acidic $Ti(O\text{-}i\text{-}Pr)_4$ gave almost no conversion, demonstrating the importance of the chloride ligand.

Proposed Mechanism for Intermolecular Coupling with $HClPCy_3$ as Additive. The inability to identify a Lewis acid that accelerated the reaction more effectively than $HClPCy_3$ raised the possibility that the Lewis acids screened were themselves simply generating HX in situ rather than acting as Lewis acids. The reactions were performed with dry solvents and reagents; however, the additives may be metallating at the acidic N−H bond of the NHC−Rh intermediate thereby generating HX. A possible mechanism by which a Brønsted acid could accelerate the coupling reaction is via the formation of a Rh(III) hydride (Figure 2). Several groups have reported the isolation of Rh(III) and Ir(III) hydrides from the addition of HCl to Rh(I) and Ir(I) phosphine complexes.[26] We speculate that N-heterocyclic carbene/alkene complex **23** initially forms, which then oxidatively

(25) In our synthesis of $HCl{\cdot}PCy_3$ we found that a variable amount (1−2 equiv) of HCl was incorporated. However, this did not appear to affect the efficiency of the reaction.

(26) (a) Grushin, V. V.; Alper, H. *Organometallics* **1991**, *10*, 1620−1622. (b) Gusev, D. G.; Bakhmutov, V. I.; Grushin, V. V.; Volpin, M. E. *Inorg. Chim. Acta* **1990**, *175*, 19−21. (c) James, B. R.; Preece, M.; Robinson, S. D. *Inorg. Chim. Acta* **1979**, *34*, L219-L221. (d) Intille, G. M. *Inorg. Chem.* **1972**, *11*, 1, 695.

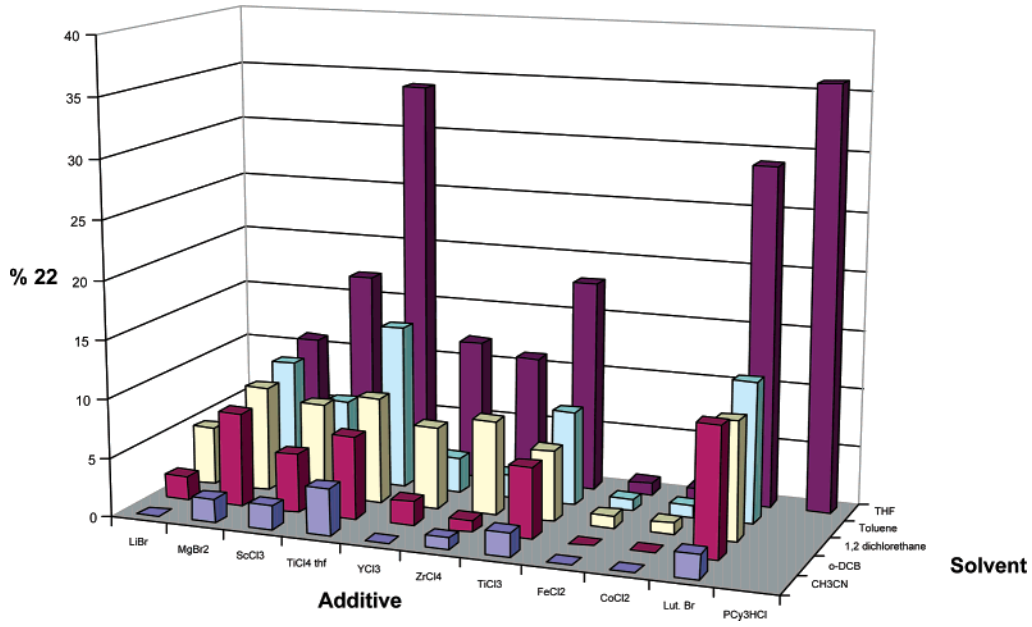


FIGURE 1. Screen of additives and solvents.

TABLE 4. Expanded Screen of Metal Complex Additives

additive	benzthiazole (%)	**22** (%)	total (%)
Lut. Br^-	75	20	95
$AlCl_3$	76	15	92
$(O)MoCl_4$	78	14	92
$MoCl_5$	73	14	87
$(O)VCl_3$	75	18	93
V_2O_5	92	0	92
BCl_3 SMe_2	73	17	90
$TiBr_4$	72	18	91
Cp_2TiCl_2	85	5	90
$CpTiCl_3$	72	20	93
Cp^*TiCl_3	71	22	93
$Ti(O\text{-}i\text{-}Pr)_4$	89	1	90

[a] Reaction carried out with 5 mol % $[RhCl(coe)_2]_2$, 10 mol % PCy_3, and 10 mol % additive in THF at 75 °C; yields were determined by GC versus an internal standard.

adds HCl forming Rh(III) hydride **24** (Figure 2). The hydride then inserts into the alkene yielding Rh alkyl complex **25**. Alkyl migration onto the C-2 position of the heterocycle (complex **26,** Figure 2) followed by β-hydride elimination would yield alkylated product **27**. Alternatively, metal alkyl **25** could reductively eliminate an imidazolium salt, which through proton transfer would reform Rh(III) hydride **28**. Cavell and co-workers have shown that stoichiometric reductive elimination of imidazolium salts occur from Pd(II) complexes,[27] and that Ni(0) complexes can undergo direct oxidative addition to imidazolium C−H bonds.[28]

Screen of Phosphonium Salts in the Coupling of Benzthiazole and 1-Hexene at 75 °C. Because we believe that only Brϕnsted acids accelerate the reaction, a systematic survey of phosphonium salts was undertaken that examined the effects of increasing the size and branching of the phosphine. This screen was limited to bulky trialkylphosphines, which an initial screen had

(27) McGuinness, D. S.; Saendig, N.; Yates, B. F.; Cavell, K. J. *J. Am. Chem. Soc.* **2001**, *123*, 4029−4040.
(28) Clement, N. D.; Cavell, K. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3845−3847.

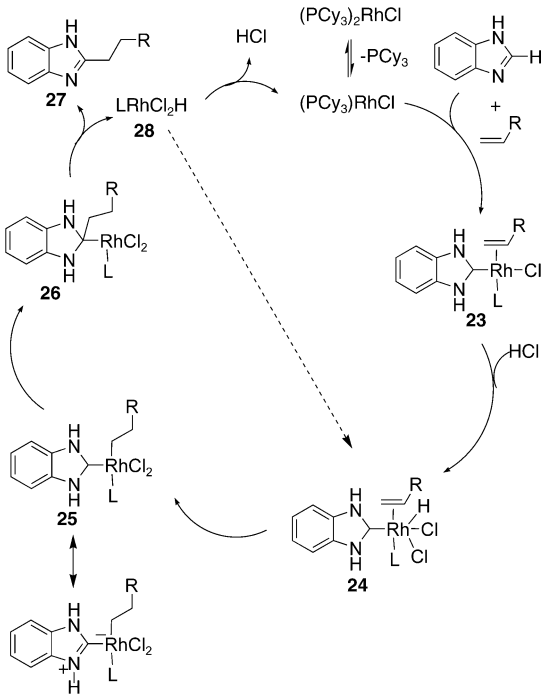


FIGURE 2. Proposed mechanism of reaction with $HClPCy_3$ and $[RhCl(coe)]_2$.

shown to be the most active ligands. The coupling of benzthiazole and 1-hexene at 75 °C for 16 h was used as the model reaction, utilizing GC to determine the yield. The single time point yields were assumed to represent a difference in rates among the reactions, though the increase could potentially be attributed to either an increase in the rate of coupling or a decrease in the rate of isomerization of the alkene. Two independent runs using $HClPCy_3$ (Table 5, entries 1 and 2) showed only minor variation in yield (Table 5). A plot of yield versus the cone angle of the phosphines, which have been used to evaluate steric effects of phosphorus ligands,[29−30]

TABLE 5. Screen of Phosphonium Salts with Benzthiazole and 1-Hexene[a]

entry	PR_3	benzthiazole (%)	**22** (%)
1	$HClPCy_3$	57	36
2	$HClPCy_3$	58	33
3[b]	$HClPCy_3$	54	38
4	$HClPCy_2Me$	103	2
5	$HClPCy_2Et$	71	24
6	$HClPCp_3$	74	18
7	$HClP(i\text{-}Pr)_3$	52	42
8	$HClPCy_2$-*t*-Bu	49	43
9	$HClP(t\text{-}Bu)_2Et$	23	75
10[b]	$HClP(t\text{-}Bu)_2Et$	31	69
11	$HClP(t\text{-}Bu)_2(i\text{-}Pr)$	64	23
12	$HClP(t\text{-}Bu)_3$	82	3
13	$HClPCy_2Biphenyl$	96	2

[a] Reaction performed with 5 mol % $[RhCl(coe)_2]_2$ and 10 mol % $HClPR_3$ in THF at 75 °C for 16 h. Yields were determined by GC. [b] Reaction monitored by ^1H NMR in THF-d_8 and yield determined by ^1H NMR.

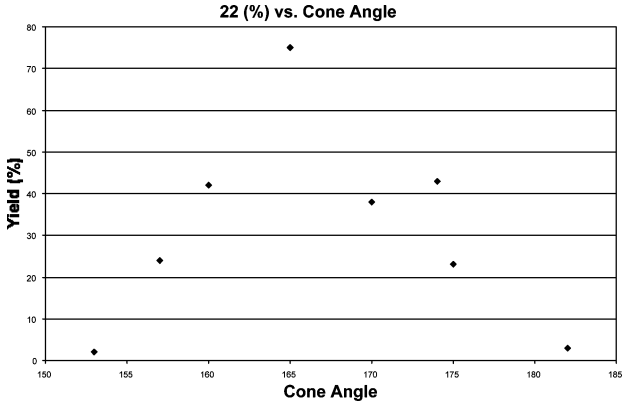


FIGURE 3. Yield of **22** vs cone angle.[30]

demonstrated that there is a significant dependence of the phosphine size on the yield (Figure 3). The data showed that the optimal phosphine size for the coupling was $HClP(t\text{-}Bu)_2Et$ (Table 5, entry 9), and increasing or decreasing the steric bulk of the ligand becomes detrimental to the rate of the reaction.

To verify that these single point yields reflected an increase in the rate of the coupling, two reactions were monitored by ^1H NMR spectroscopy, in which phosphonium salts $HClPCy_3$ and $HClP(t\text{-}Bu)_2Et$ were used. After 16 h, the yield of product corresponded to that observed by GC (Table 5, entries 3 and 10). By monitoring the reaction it was discovered that olefin isomerization occurs rapidly in both cases and the increase in yield can indeed be attributed to an increase in the rate of coupling of 1-hexene to benzthiazole.

Screen of Phosphonium Salts in the Coupling of Benzimidazole and 1-Hexene at 105 °C. The encouraging results for coupling with benzthiazole prompted us to conduct a phosphonium salt screen for the coupling of benzimidazole to 1-hexene at 105 °C (Table 6). The optimal phosphonium salt in this case was found to be $HClPCy_3$, and again there was a dependence on phosphine cone angle, such that use of either larger or smaller phosphines led to a decrease in yield. It is worth noting that over the course of these reactions material precipitates from the reaction solution. The differential solubilities of the components in the reaction mixtures of benzimidazole and benzthiazole make it difficult to compare the optimization results. The effect of increasing the ratio of phosphonium salt to $[RhCl(coe)_2]_2$ was also studied, and doubling the amount of phosphonium salt had no significant impact on this reaction.

TABLE 6. Screen of Phosphonium Salts with Benzimidazole and 1-Hexene

PR_3	benzimidazole (%)	**9** (%)	total (%)
$HClPCy_3$	33	40	73
$HClPCy_2Me$	78		78
$HClPCy_2Et$	71	3	74
$HClP(t\text{-}Bu)_2Me$	73	6	79
$HClPCp_3$	58	11	69
$HClP(i\text{-}Pr)_3$	53	16	69
$HClP(t\text{-}Bu)_2Et$	42	17	59
$HClPCy_2$-*t*-Bu	73	3	76
$HClP(t\text{-}Bu)_2$-*i*-Pr	71		71
$HClP(t\text{-}Bu)_3$	72		72
$HClPCy_2Biphenyl$	81		81

[a] Reaction performed with 5 mol % $[RhCl(coe)_2]_2$ and 10 mol % $HClPR_3$ in THF at 105 °C for 16 h. Yields were determined by ^1H NMR spectroscopy

In summary, the discovery of the profound effects of additives on this type of C−H activation reaction has led to an efficient intermolecular coupling of unactivated alkenes to heterocycles. The reaction functions successfully with a variety of heterocycles and alkenes, including both electron-deficient and electron-rich alkenes. Furthermore, the optimized conditions are mild enough to allow for the introduction of a large breadth of functional groups on both the alkene and heterocycle. These improvements suggest a significant potential for drug discovery and process chemistry. We are currently conducting experiments designed to confirm the hypothesis that the active catalyst in the reaction is a Rh(III) hydride. Using the information gained from that work, we hope to identify even more active and robust catalysts.

Experimental Section

General Experimental Procedure for the Hydroarylation Reaction. In air, to an oven-dried vessel with a Kontes stopper was added $[RhCl(coe)_2]_2$ (5−10 mol % Rh), tricyclohexylphosphonium chloride (5−10 mol %), and the heterocycle. The vessel was placed under a nitrogen atmosphere. Under a positive pressure of nitrogen, THF (diluted to 0.1 M in heterocycle) and the alkene (5 equiv) were added to the vessel. The vessel was closed with the Kontes stopper and was subjected to three successive freeze−pump−thaw cycles. The vessel was heated for 15 h at 150 °C. The reaction mixture was dry loaded onto SiO_2 and purified by flash chromatography.

Typical Procedure for Optimization Screens. In a glovebox, a solution of benzthiazole (0.1 M), $[RhCl(coe)_2]_2$ (5 mol % Rh dimer, 10 mol % Rh), PCy_3 (10 mol %), hexamethylbenzene (internal standard), and 1-hexene (5 equiv relative to benzthiazole) in THF was made. To glass vials were distributed the additives (10 mol %) and the above solution (0.5 mL). The vessels were closed and were heated for 16 h at 75 °C. The crude reaction mixtures were loaded onto a silica

(29) The cone angles were either calculated using the procedure described by Tolman or were obtained from the following references: (a) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313−348. (b) Rahman, M. M.; Liu, H. Y.; Eriks, K.; Prock, A.; Giering, W. P. *Organometallics* **1989**, *8*, 1−7.

(30) The cone angles for PCp_3 (Cp = cyclopentyl) was not found, so it was not plotted in Figure 3. Also PCy_2(Biphenyl) is electronically different from the other phosphines screened, and therefore it was not plotted on this figure.

plugs, eluted with 40% EtOAc/hexanes, and analyzed by GC or ^{1}H NMR spectroscopy.

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Supporting Information Available: Experimental details, including analytical data for all compounds described in the article, as well as crystallographic data (CIF) for **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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