J|A|C|S
COMMUNICATIONS

Published on Web 11/05/2002

Intermolecular Coupling of Isomerizable Alkenes to Heterocycles via Rhodium-Catalyzed C−H Bond Activation

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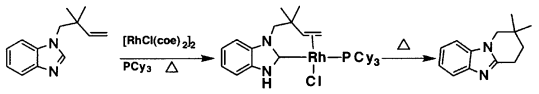
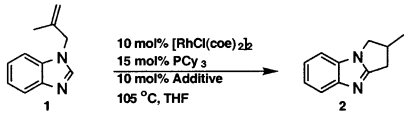
Received August 12, 2002

Metal-mediated C−H bond activation reactions have become important methods for the formation of carbon−carbon bonds.[1] The selective functionalization of heterocycles is of particular importance due to the ubiquity of these structures in natural products as well as pharmaceutical agents. In the course of developing C−H activation processes to reach this goal, our group has demonstrated the intermediacy of an *N*-heterocyclic carbene[2] Rh(I) complex in the intramolecular coupling of an alkene to a benzimidazole core (eq 1).[3] We recognized from this intermediate that a broad range of heterocycles could function under this mechanism, thereby increasing the scope of the C−C bond-forming reaction dramatically. However, the intramolecular system limits heterocycle generality because it requires a tethered alkene proximal to the site of C−H activation. Herein, we describe the first intermolecular coupling of unactivated alkenes, including isomerizable alkenes, to heterocycles.[4] A wide range of heterocycles was employed in the reaction, and a variety of functional groups can be incorporated, including esters, nitriles, and acetals. The intermolecular coupling became possible after it was discovered that weak acids dramatically increase the rate of both the inter- and intramolecular reactions.



(1)

Initial attempts to couple neo-hexene to benzimidazole, using the optimized conditions previously reported, afforded low yields of the desired product. In an effort to accelerate the rate of the reaction, an additive screen was undertaken. The intramolecular cyclization of compound **1** was used as the model substrate (eq 2). The reaction was performed at 105 °C (55 °C lower than previously reported). The initial screen provided the following information (Table 1):[5] (a) weak Brønsted acids have a dramatic impact on the rate of the reaction; (b) the most effective additives are Lewis acids such as $MgBr_2$, which produce the highest conversions at 105 °C; (c) noncoordinating anions for both Lewis and Brønsted acids led to either low yields or decomposition of the starting material. Since with both the Lewis and Brønsted acids the counterion had a profound effect on the reactivity, we believe the reaction requires a balance between acidity of the additive and Lewis basicity of the X group. We are currently investigating the mechanism of the additive effect more closely, to determine the origin of the rate acceleration.



(2)

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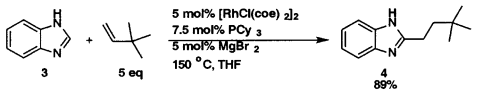
Table 1. Additive Effects[a]

additive	% **1**	% **2**	additive	% **1**	% **2**
none	77	<7	YCl_3	19	69
NH_4Cl	66	11	$Mg(OTf)_3$	85	14
Lut.[b] Cl^-	32	49	MgI_2	50	18
Lut.[b] pTSA	50	28	$MgBr_2$	12	69
Bu_4NCl	70	8	$MgCl_2$	47	27
$CuCl_2$	72	6	MgF_2	72	−
$ZnCl_2$	72	12	LiBr	58	24
$Al(OTf)_3$	76	trace	$CaCl_2$	68	13
$ScCl_3$	44	33			

[a] Run at 0.15 M substrate; yields by ^{1}H NMR. [b] Lut.=lutidinium.

With the increase in reactivity provided by the most effective additives, intermolecular coupling of benzimidazole and neo-hexene was explored in more detail. With addition of 5% $MgBr_2$ the desired linearly coupled product was isolated in 89% yield (eq 3).



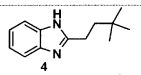
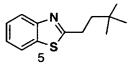
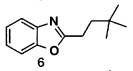
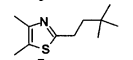
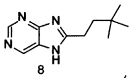
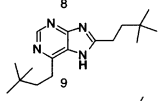
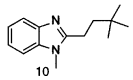
(3)

However, when other heterocycles were used, incomplete conversion occurred in many cases, presumably due to catalyst decomposition. Further exploration of the effect of additives on the intermolecular coupling revealed that lutidinium chloride consistently gave the highest yields. Using this additive, heterocycle generality was expanded to include benzthiazole, benzoxazole, 4,5-dimethylthiazole, and purine (Table 2, entries 2−5). 1-Methylbenzimidazole also participated in the reaction, although higher catalyst loading was required to obtain high conversion (Table 2, 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 neo-hexene and either pyrimidine or indole, which is expected since these compounds are not known to form *N*-heterocyclic carbenes. Isoxazole and 1-phenylpyrazole also did not couple with neo-hexene, 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 to the decreasing acidity of the salt.[6] We believe this may also explain the lack of reactivity of 1-phenylpyrazole and isoxazole. Interestingly, purine was found to undergo multiple alkylations, unlike the other heterocycles tested.[7] 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 2, entry 5).

With these encouraging results, a survey of the alkene generality was undertaken using benzimidazole as the model heterocycle. One of the major hurdles in the C−H coupling to alkenes has been the lack of success with isomerizable alkenes.[8] We were delighted to find that under the optimized conditions, 1-hexene reacts efficiently with benzimidazole, giving the linearly coupled product **11** in 80%

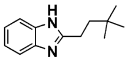
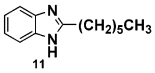
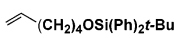
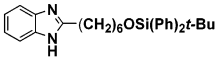
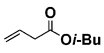
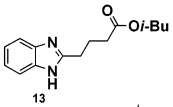
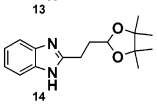
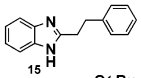
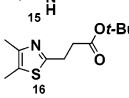
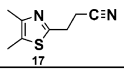
10.1021/ja0281129 CCC: $22.00

Table 2. Heterocycle Generality

Entry	Heterocycle	Product	Yield (%)[a]
1		 **4**	96
2		 **5**	97
3		 **6**	77
4		 **7**	99
5		 **8**	76
		 **9**	17
6		 **10**	67[b]

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

Table 3. Alkene Generality

Entry	Alkene	Product	Yield (%)
1		 **4**	96[a]
2		 **11**	80[a]
3		 **12**	77[a]
4		 **13**	87[b]
5		 **14**	60[b]
6		 **15**	19[b]
7		 **16**	93[b]
8		 **17**	59[b]

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

isolated yield (Table 3, entry 2). Attempts at coupling cyclohexene with benzimidazole were unsuccessful, suggesting that highly substituted alkenes are poor substrates. A silyl-protected alcohol was stable under the C−H/alkene coupling conditions (Table 3, entry 3). Ester **13** was synthesized by coupling a β,γ-unsaturated ester to benzimidazole, although an increase in the catalyst loading was necessary to obtain a high yield (Table 3, entry 4). This result was surprising since the alkene could rearrange to its conjugated isomer to shut down the reaction. The acetal of acrolein reacted with benzimidazole to give the functionalized heterocycle **14** (Table 3, entry 5). The pinacol protecting group was used because other acetals, such as acrolein dimethyl acetal and 2-vinyl-1,3-dioxolane, led to decomposition or poor yields. We believe the steric bulk of the pinacol hinders isomerization and provides a more robust protecting group, thereby allowing the coupling to compete with decomposition. A poor yield was observed when styrene was used as the coupling partner (Table 3, entry 6).[9] Polymerization of stryene was observed under the conditions which may have accelerated the catalyst decomposition.[10] Since α,β-unsaturated esters reacted with benzimidazole by hydroamination rather than by the desired C−H coupling, we 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, showing that electron-deficient alkenes are suitable substrates for the reaction (Table 3, entries 7 and 8). The use of acrylonitrile gave mostly the linear isomer, but a smaller amount of branched isomer was also observed (l:b = 3.8:1).

In summary, the discovery of the profound effects of additives on this reaction has led to (a) a significant lowering of the reaction temperature required for the intramolecular cyclization of alkenes with benzimidazole and (b) the first intermolecular coupling of unactivated alkenes to heterocycles. The reaction functions with a variety of heterocycles as well as alkenes. A large breadth of functional groups can be introduced easily and from readily available starting materials. The potential of this reaction in drug discovery and process chemistry is evident. We are currently working on improving the catalyst stability and performance.

Acknowledgment. This work was supported by a fellowship (to K.L.T.) from Bristol-Myers Squibb, by the NIH Grant GM5050353 (to J.A.E.), and by the Director, Office of Energy Research, Office of Basic Energy Sciences, Chemical Sciences Division, U.S. Department of Energy, under Contract No. DE-AC03-76SF00098 (to R.G.B). Bristol-Myers Squibb is the founding member of the UC Berkeley Center for New Directions in Synthesis.

Supporting Information Available: Experimental details, including analytical data for all compounds described, X-ray diffraction data for **9**, and a table of all additives screened (PDF/CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Complete list of additives screened available in Supporting Information.

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

(7) Regiochemistry of the bis-alkylated purine was determined by X-ray crystallography. X-ray diffraction data are available in Supporting Information.

(8) Kakiuchi, F.; Murai, S, *Acc. Chem. Res.* **2002**, ASAP June 21, 2002.

(9) A small amount of the branched isomer was isolated from the reaction. GC−MS analysis of the crude mixture showed a 25:1 linear:branched ratio.

(10) At the reaction completion some styrene remains, indicating that poor conversion did not simply result from consumption of styrene.

JA0281129