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Microwave-Assisted C–H Bond Activation: A Rapid Entry into Functionalized Heterocycles

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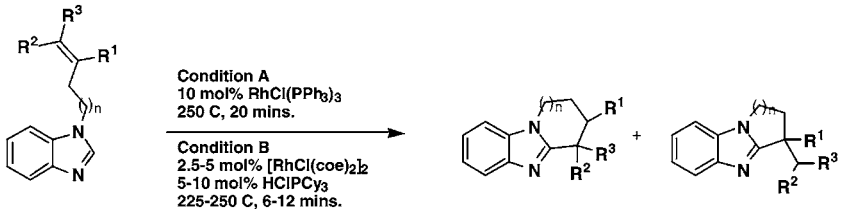
ABSTRACT



Microwave irradiation strongly accelerates the rhodium-catalyzed intramolecular coupling of a benzimidazole C–H bond to pendant alkenes. The cyclic products were formed in moderate to excellent yields with reaction times less than 20 min. Additionally, the use of microwave irradiation allowed the reactions to be performed without any solvent purification and with minimal precautions to exclude air.

Microwave-assisted organic synthesis has emerged as a powerful tool in organic chemistry. The ability to rapidly heat and thermally quench reactions has resulted in dramatic increases in the rates and yields of a variety of chemical transformations.[1] Because of the safe and reproducible heating of sealed vessels in a microwave reactor, both the academic and industrial communities have utilized this technology. Furthermore, automation now enables its use in high-throughput reaction optimization and in rapid analogue synthesis, particularly for drug discovery efforts. The utility of microwave-assisted synthesis is exemplified by its recent successful application to transition metal-mediated reactions such as transfer hydrogenation, allylic alkylation, hydroacylation,[2] Heck-type couplings, and Suzuki, Stille, and Sonogashira couplings.[1]

Recently, we developed both the inter-[3] and intramolecular[4] alkylation of heterocycles by C−H bond activation (Scheme 1).[5] This methodology allows for the rapid func-

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(1) For reviews of microwave applications in organic chemistry, see: (a) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717−727. (b) Wathey, B.; Tierney, J.; Lidstrom, P.; Westman, J. *Drug Discovery Today* **2002**, *7*, 373−380. (c) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95−105. (d) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283.

(2) (a) Jun, C. H.; Chung, J. H.; Lee, D. Y.; Loupy, A.; Chatti, S. *Tetrahedron Lett.* **2001**, *42*, 4803−4805. (b) Loupy, A.; Chatti, S.; Delamare, S.; Lee, D. Y.; Chung, J. H.; Jun, C. H. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1280−1285.

(3) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 13964−13965.

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

(5) For reviews of C−H activation, see: (a) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1699−1712. (b) Jia, C. G.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 844−844. (c) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826−834. (d) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731−1769.

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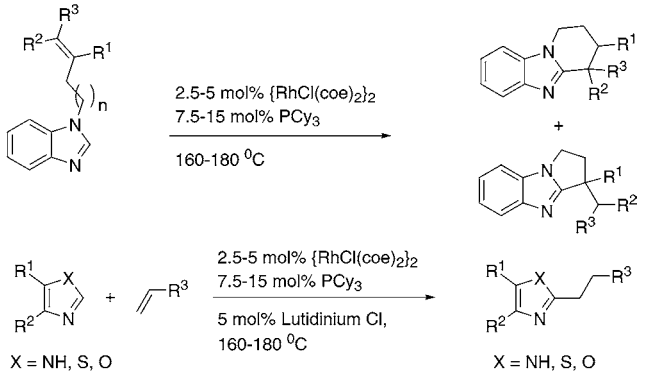
Scheme 1. Intra- and Intermolecular Coupling Reactions



tionalization of a variety of heterocycles, which have proven to be important scaffolds in drug discovery.[6] Furthermore, the use of C−H activation overcomes several limitations of traditional cross-coupling reactions. The coupling of a C−H bond and an alkene obviates the need to prefunctionalize the starting materials, and consequently, fewer byproducts are formed. Because of the simplicity of the starting materials, the pool of commercially available compounds is both vast and inexpensive. However, the air-sensitive nature of the catalyst, as well the high temperatures and long reaction times required, make this methodology difficult to apply to industrial drug discovery applications. Herein, we report a facile microwave-assisted intramolecular C−H bond activation−cyclization that circumvents the limitations described above. This was achieved through the optimization of the catalytic conditions and solvent selection.

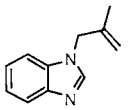
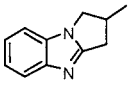
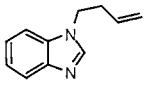
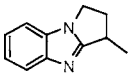
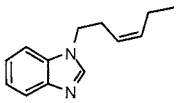
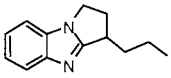
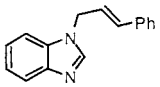
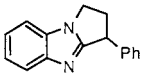
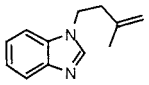
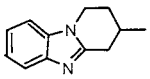
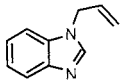
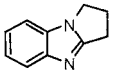
We had previously reported that Wilkinson's catalyst could be used to effect the cyclization of alkene **1** (cf. Table 1) in modest yield when heated to 160 °C in toluene for several hours in a sealed vessel. This commercially available and air-stable catalyst represented a good starting point for the optimization of the microwave conditions. However, the poor microwave absorption characteristics of toluene and THF[7] afforded little to no conversion of compound **1** to **2** when heated at elevated temperatures for 20 min in the microwave reactor.[8] Previous studies with conventional heating demonstrated that commonly used microwave solvents such as water, DMSO, and DMF were poor media for the C−H/alkene coupling reaction. After investigating different solvents and solvent combinations with varying dielectric constants and heating profiles, we found that heating **1** at 250 °C for 20 min in *o*-dichlorobenzene (DCB) afforded efficient conversion to **2**.

Encouraged by this result, we turned our attention toward increasing the reactivity of the system by adjusting the solvent polarity and coordination ability. It was also anticipated that the solubility of most heterocycles in DCB would be limited. We therefore tested the compatibility of cosolvents in the reaction by using mixtures of DCB with varying amounts of THF, CH_3CN, and acetone. The solvent screen was conveniently performed by use of a liquid handler and programmable robotic interface, which allowed for rapid evaluation of solvent mixtures. This effort led to the discovery that both CH_3CN and THF had a negative impact on the reaction rate. However, acetone proved to have a beneficial effect, which not only resulted in a modest improvement in reaction yield but also helped to solubilize the catalyst and starting materials.

The solvent system was further optimized by performing a survey of different ratios of acetone and *o*-dichlorobenzene. The addition of 10−25% of acetone in *o*-dichlorobenzene gave optimal results. The origin of this effect is not easily discerned. Because of the facility with which the target temperature is achieved using the acetone/DCB mixture (relative to neat DCB), combined with the improved solubility of reaction components, a simple thermal effect cannot be ruled out. Interestingly, the addition of as much as 20% water in DCB was also an effective solvent system for the conversion of alkene **1** to product **2**. Because of the high pressures that resulted from the biphasic mixture of water and DCB, the reactions were often interrupted due to built-in safety features in the microwave reactor.

With conditions that were optimal for reactivity and solubility, we next examined the substrate generality by

Table 1. Substrate Generality with $RhCl(PPh_3)_3$[a]

alkene		product		yield(%)
	1		2	64
	3		4	55
	5		6	64
	7		8	42
	9		10	59[b]
	11		12	59

[a] Conditions: 3:1 DCB/acetone, 20 min, 250 °C, 10 mol % $RhCl(PPh_3)_3$. [b] Yield determined by ^1H NMR.

(6) (a) Roth, T.; Morningstar, M. L.; Boyer, P. L.; Hughes, S. H.; Buckheit, R. W.; Michejda, C. J. *J. Med. Chem.* **1997**, *40*, 4199. (b) Wienen, W.; Hauel, N.; Van Meel, J. C. A.; Narr, B.; Ries, U.; Entzeroth, M. *Brit. J. Pharmacol.* **1993**, *110*, 245.

(7) Both toluene and THF have low values of tan ϵ, making them poor microwave solvents. Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM Publishing: Matthews, NC, 2002; pp 29−62.

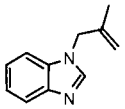
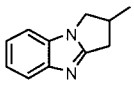
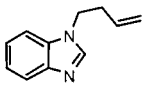
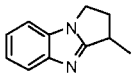
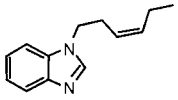
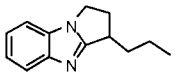
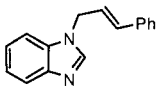
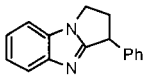
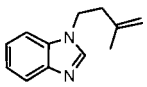
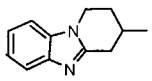
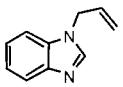
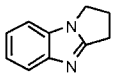
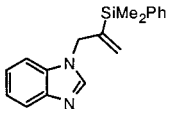
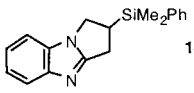
(8) Reactions with THF and toluene solutions were aborted above temperatures of 180 °C due to pressure maxima.

varying the alkene substitution (Table 1). We found that utilization of 10 mol % Wilkinson's catalyst allowed for a wide range of cyclic products to be formed in less than 20 min when the reaction mixture was microwave-heated to 250 °C. The solvents employed for the microwave reactions were used without drying or degassing, and minimal precautions were taken to exclude air from the reaction vessels. The cyclization of alkene **3** afforded product **4** in 55% isolated yield with a regioselectivity of 4:1 (five- vs six-membered ring). Use of the more sterically hindered compound **5** resulted in the exclusive formation of tricycle **6**. Comparable yields were observed under the previously optimized thermal conditions,[4] but a dramatic reduction in reaction time was observed under the microwave conditions. Aryl-substituted alkene **7** could also be cyclized efficiently. Geminally substituted compound **9** favored formation of the terminal six-membered product **10**, probably due to steric factors. Finally, the use of *N*-allyl benzimidazole afforded the product **12** in 59% yield.

Pleased with the initial results using $RhCl(PPh_3)_3$, we next sought to improve the yield and reduce the catalyst loading and reaction time. Previous studies[3] of the intermolecular reaction had demonstrated that addition of Lewis or Br*ϕ*nsted acids to $[RhCl(coe)_2]_2$ (coe = cyclooctene) and PCy_3 increased the rate and yield of the C−H/alkene coupling. We therefore examined the application of this catalyst system to the intramolecular coupling with one variation. Instead of using lutidinium chloride or $MgBr_2$ as an additive, the HCl salt of PCy_3 was employed. By combining the Br*ϕ*nsted acid with the optimal phosphine, the number of required reagents was reduced, enhancing the operational simplicity. Furthermore, the HCl salt also renders the phosphine air stable[9] and soluble in a variety of organic solvents. This allows solutions of catalyst to be prepared for use in high-throughput optimization of reactions with no rigorous glovebox or Schlenk flask manipulations.

Application of the optimal microwave conditions with $[RhCl(coe)_2]_2$ and $HClPCy_3$ as the catalyst system provided the cyclized products with substantial increases in yield. Additionally, lower temperatures, reaction times, and catalyst loadings were implemented (Table 2). As before, the solvents were not degassed or dried before use. The only precaution taken to exclude air was the purging of the reaction vessels with nitrogen after the addition of reagents and before capping the container.[10] The cyclization of **1** proceeded at 225 °C in less than 6 min in excellent yield. The coupling of **3** again led to a mixture of the terminal five- and six-membered ring products with an improved regioselectivity of 8.8:1[11] in favor of **4**. When **11** was cyclized to **12**, the yield of the reaction was 50%, with the isomerized enamine being the major byproduct. Vinylsilane **13**, which contains a functional group handle for further manipulation, cyclized quantitatively in less than 12 min. The major product was the desired heterocycle **14**, but the remainder of the material appeared to be **12** resulting from protodesilyation of the product **14.** The use of Wilkinson's catalyst with this substrate afforded the protodesilylated **12** almost exclusively.

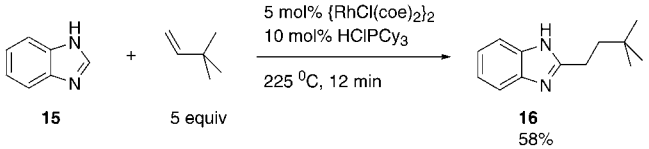
Table 2. Results with $[RhCl(coe)_2]_2$ and $HClPCy_3$

alkene		product		yield(%)
	1		2	97[a]
	3		4	76[a]
	5		6	84[a]
	7		8	62[b]
	9		10	78[a]
	11		12	50[c]
	13		14	74[a]

[a] Conditions: 225 °C, 6−12 min, 3:1 DCB/acetone, 2.5 mol % $[RhCl(coe)_2]_2$, 5 mol % $HClPCy_3$. [b] Conditions: 250 °C, 12 min, 4:1 DCB/acetone, 2.5 mol % $[RhCl(coe)_2]_2$, 5 mol % $HClPCy_3$. [c] Conditions: 250 °C, 12 min, 85:15 DCB/acetone, 5 mol % $[RhCl(coe)_2]_2$, 10 mol % $HClPCy_3$.

Having successfully demonstrated the cyclization of a variety of substrates using microwave irradiation, we attempted to extend the scope to the intermolecular coupling of an untethered alkene to benzimidazole. Initial attempts to couple neohexene to benzimidazole with Wilkinson's catalyst afforded the alkylated product **16** in low yields. *Gratifyingly, implementation of the* $[RhCl(coe)_2]_2$ *and* $HClPCy_3$ *catalyst system afforded the desired compound in 58% yield in 12 min* (Scheme 2). We are currently optimizing the conditions of the reaction and extending this methodology to other heterocycles and alkene substrates.

Scheme 2. Intermolecular Coupling



(9) Though the phosphine hydrochloride is stable to air oxidation, the salt is hydroscopic and should be handled accordingly.

(10) Reactions could be performed in air in many cases. However, for more challenging substrates, modest increases in yield were observed when the vessel was purged with N_2.

(11) Ratio determined by ^1H NMR of the crude reaction mixture.

In conclusion, we have developed an efficient and operationally simple cyclization method utilizing C−H bond activation to rapidly access heterocyclic products that are currently difficult to obtain with alternative methods. The procedure is amenable to high-speed compound synthesis and to rapid reaction optimization for individual substrates. Additionally, we have demonstrated the successful intermolecular coupling of an alkene to benzimidazole. Further studies will be reported in due course.

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

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