

Organometallic Chemistry - 4571

Name: _____

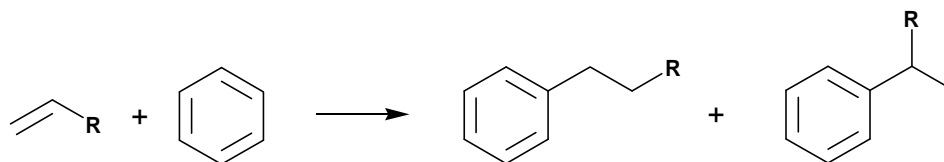
Homework # 4 - Due: May 1, 2007 (by Noon)

Signature: _____

Group: _____

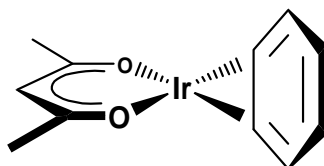
Check the box to the right if you want your graded homework to be placed out in the public rack outside Prof. Stanley's office. Otherwise you will have to pick up your homework from Prof. Stanley in person:

1. (20 pts) Write out a catalytic cycle for the hydrophenylation of alkenes to produce alkylated arenes:



The starting catalyst is shown below and you are to use benzene as the arene and ethylene (ethene) as the alkene. The catalysis proceeds by the following reaction steps: 1) arene C-H oxidative addition, 2) alkene addition, 3) migratory insertion, 4) reductive elimination. The exact ligands involved in step 3 is not specified, you are to choose the most likely ligands to do this reaction. Ligand dissociation of the initial ligands is allowed if necessary, but I have not indicated when this may (or may not) happen. Clearly sketch out each metal complex with proper geometries. [Periana et al., *JACS*, **2000**, *122*, 7414-7415]

Ir(acac)(η^4 -benzene)



Read the attached paper from the *Journal of the American Chemical Society* (Bergman, 2001, 123, 2685-2686) and answer the following questions about it.

2. (10 pts) The catalyst precursor used is listed as $[\text{RhCl}(\text{coe})_2]_2$. What is coe? Sketch out the structure of $[\text{RhCl}(\text{coe})_2]_2$ – you can abbreviate the coe ligand as:



coe = _____

3. (15 pts) From Table 2 calculate the following:

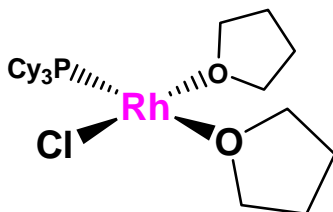
a) maximum # of turnovers (TON): _____

b) average turnover frequency (TOF hr^{-1}) for entry # 1 (assume 85% conversion to product) = _____

c) using the last catalytic run from Table 1, calculate the average TOF for this run = _____

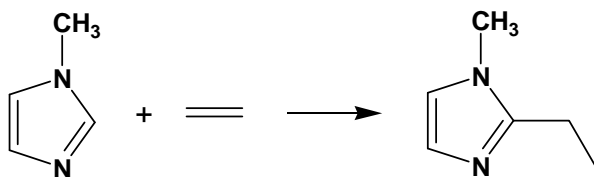
4. (10 pts) In the scheme on the first page, column 2, substrate **1** can be isomerized to **2** or **3**. Clearly, **1** can be converted to the product **4**. Can **2** or **3** directly cyclize to form **4**? Explain your answer for **2** and **3**.

5. (25 pts) Sketch out a catalytic cycle for **1** being converted to **4** (no isomerization). You only have to draw the imidazole ring and N-alkenyl group on **1**. Start with the catalyst shown below. The first step is coordination of **1** via the less substituted N lone pair. The second step is activation (but label this with the more correct mechanistic term) of the adjacent C-H bond. Based on this initial information, complete the cycle. Clearly label each step with what is happening mechanistically.



6. (10 pts) At what point in the catalytic cycle is the alkene isomerization discussed in question # 4 (and the paper) most likely to happen. Sketch out the isomerization of **1** to **2** and label each step (once again, you don't have to draw out the arene ring on **1** and **2**).

7. (5 pts) Given the catalytic conditions (temp, catalyst loading, TOF), do you think the following similar reaction is likely to be catalyzed by the best catalyst discussed in this paper? Fully discuss.



8. (5 pts) The authors add some excess PCy₃, but I've only drawn the catalyst with one PCy₃ ligand. Why didn't I use two PCy₃ ligands on the catalyst?

Annulation of Alkenyl-Substituted Heterocycles via Rhodium-Catalyzed Intramolecular C–H Activated Coupling Reactions

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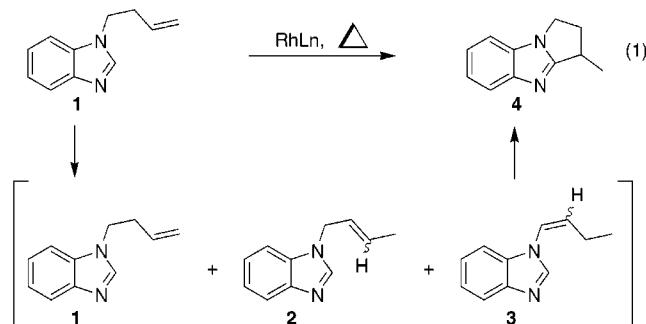
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Transition metal catalyzed C–H bond activation has been developing rapidly as a method for the formation of carbon–carbon bonds.¹ One of the most useful transformations of this type is directed C–H bond activation exemplified by the regioselective *ortho* alkylation of aromatic carbonyl compounds with ruthenium catalysts by Murai.² Subsequently, several groups have expanded the scope of intermolecular alkylation of arenes by incorporating a variety of directing groups such as imines, pyridines, and esters.³ Although broadly applicable, this intermolecular coupling occurs predominantly at the terminus of the alkenyl chain, and thus gives only linear products. We report here an intramolecular⁴ variant of this methodology that couples a vinyl carbon in a tethered alkene to imidazole rings via a novel and a selective C–H bond activation at the position α to the heteroatom.^{5–8} This reaction is successful with a wide range of substrates, allowing for the synthesis of a variety of annulated heterocycles in good yield. In a significant departure from earlier work, disubstituted and even trisubstituted alkenes have been cyclized in a regioselective manner, yielding complex fused heterocyclic/carbocyclic skeletons with stereogenic centers.

In an effort to expand the scope of catalytic C–H activation and direct coupling to alkenes, we began by investigating the cyclization of *N*-homoallyl benzimidazole **1**. Although attempts to cyclize **1** with $\text{RuH}_2\text{CO}(\text{PPh}_3)_3$, $\text{Cp}^*\text{Rh}(\text{C}_2\text{H}_2\text{SiMe}_3)_2$, $[\text{Rh}(\text{Diphos})_2]\text{ClO}_4$, and $[\text{RhCl}(\text{coe})_2]_2$ proved unsuccessful, benzimidazole **1** was converted to carbocycle **4** in 60% ¹H NMR yield

with 10 mol % $(\text{Ph}_3\text{P})_3\text{RhCl}$ (Wilkinson's catalyst) at 160 °C. Monitoring the reaction by ¹H NMR spectroscopy demonstrated that **1** undergoes double bond positional isomerization rapidly under the reaction conditions, leading to an initial mixture of alkenes with the disubstituted isomer **2** predominating (eq 1). Over time the mixture was converted to tricyclic product **4** and decomposition products, contaminated only with trace amounts of **1**, **2**, and **3**.



To optimize the reaction conditions, a range of phosphine additives with varying steric and electronic properties were surveyed (Table 1). With $[\text{RhCl}(\text{coe})_2]_2$ as the catalyst precursor, the use of $\text{P}(p\text{-tolyl})_3$ resulted in 56% ¹H NMR yield at 160 °C after 40 h. Although the addition of $\text{P}(t\text{-Bu})_3$ did not improve the yield, the addition of the electron-rich but less sterically encumbering PCy_3 effected the cyclization of alkene **1** to carbocycle **4** in 86% yield in 3.5 h at 160 °C as determined by ¹H NMR spectroscopy. Isomerization to an intermediate mixture of alkenes **1** and **2** was observed, with **2** predominating, and again both isomers were cleanly converted to product with further heating (eq 1). Upon optimization of the conditions, it was found that **1** cyclized to **4** in 79% isolated yield, with a reduction of catalyst loading to 5 mol % $[\text{RhCl}(\text{coe})_2]_2$ and 7.5 mol % PCy_3 (Table 2, entry 1).

Table 1. Survey of Phosphine Effects on Cyclization^a

phosphine	time, h	¹ H NMR yield, %
PPh_3	3.5	22 (61) ^b
$\text{P}(o\text{-tolyl})_3$	3.5	<5 (<5) ^b
$\text{P}(t\text{-Bu})_3$	3.5	20 (57) ^b
$\text{P}(p\text{-tolyl})_3$	3.5	20 (56) ^b
PCy_3	3.5	86

^a Reactions were preformed with 10 mol % $[\text{RhCl}(\text{coe})_2]_2$ and 30 mol % PR_3 at 160 °C in *d*₈-toluene. ^b ¹H NMR yield at complete conversion.

The reaction scope was quite general with respect to substitution at the alkenyl group (Table 2). In an unprecedented direct coupling of a C–H bond with a trisubstituted double bond, tetracycle **12** was formed from **5** in good yield and high diastereoselectivity for the *cis*-ring fusion (15:1 by ¹H NMR) as established by X-ray crystallographic analysis (Table 2, entry 2).⁹ Cyclization of 1,2-disubstituted alkene **6** yielded the five-membered ring **13** in good yield with no other cyclic products observed (Table 2, entry 3). Six-membered rings were accessible with the appropriate substitution as demonstrated for products **14** and **15** (Table 2, entries 4 and 5). Apparently, internal geminal alkene substitution or allylic α,α -dibranching leads to the

(9) This result was unexpected, since insertion into the trisubstituted alkene is believed to initially form the *trans*-ring juncture. However, the rapid isomerization seen in previous cases suggests that the *cis*- or *trans*-ring juncture would be accessible, and our observations indicate that the *cis* adduct reductively eliminates more rapidly than the *trans* adduct (refer to Figure S-2 in the Supporting Information for the mechanism).

† The Center for New Directions in Organic Synthesis is supported by Bristol-Myers Squibb as Sponsoring Member.

(1) For reviews, see: (a) Kakiuchi, F.; Murai, S. Activation of Unreactive C–H Bonds. In *Top. Organomet. Chem.* **1999**, *3*, 47–79. (b) Guari, Y.; Sabotier, S.; Chaudret, B. *Eur. J. Inorg. Chem.* **1999**, 1047–1055. (c) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1699–1712. (d) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879–2932.

(2) (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Pure Appl. Chem.* **1994**, *66*, 1527–1534. (b) Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62–83.

(3) (a) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616–6623. (b) Lim, Y. G.; Kang, J. B.; Kim, Y. H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2201–2206. (c) Lim, Y. G.; Kim, Y. H.; Kang, J. B. *J. Chem. Soc., Chem. Commun.* **1994**, 2267–2268. (d) Jun, C. H.; Hong, J. B.; Kim, Y. H.; Chung, K. Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 3440–3441. (e) Trost showed that alkenes could also be functionalized in similar fashion. Trost, B. M.; Imai, K.; Davies, I. W. *J. Am. Chem. Soc.* **1995**, *117*, 5371–5372.

(4) Murai has demonstrated directed intramolecular cyclization of 1,5 and 1,6 dienes. Fujii, N.; Kakiuchi, F.; Yamada, A.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 285–298.

(5) Jordan and Taylor showed the coupling of pyridine to propene. Jordan, R. F.; Taylor, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 778–779.

(6) Fujiwara has successfully cyclized electron-deficient alkenes and alkynes to aromatic rings with palladium. Jia, C. G.; Piao, D. G.; Oyama, J. Z.; Lu, W. J.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992–1995.

(7) Murai and Moore have shown the selective acylation of heteroaromatics with $\text{Ru}_3(\text{CO})_{12}$. (a) Moore, E. J.; Pretzer, W. R.; O'Connell, T. J.; Harris, J.; Labounty, L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc.* **1992**, *114*, 5888–5890. (b) Chatani, N.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1996**, *118*, 493–494. (c) Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1997**, *62*, 2604–2610. (d) Fukuyama, T.; Chatani, N.; Tatsumi, J.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1998**, *120*, 11522–11523.

(8) Intermolecular addition of C–H bonds in imines to alkenes has been reported by Suggs et al. and Jun et al. (a) Suggs, J. W. *J. Am. Chem. Soc.* **1979**, *101*, 489–489. (b) Jun, C. H.; Lee, H.; Hong, J. B. *J. Org. Chem.* **1997**, *62*, 1200–1201.

Table 2. Rhodium-Catalyzed Cyclization^a

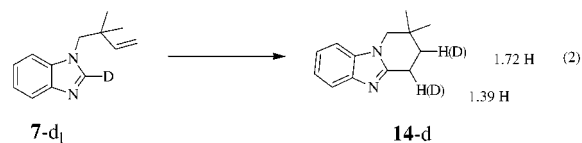
Entry	Alkene	Product	Isolated Yield (%)
1			79
2			75 ^{c,d}
3			11, (59) ^b
4			89
5			71 ^b
6			82
7			25, (70) ^b
8			71

^a Reactions were run with 5% [RhCl(coe)₂]₂ and 7.5% PCy₃ at 160 °C for 20 h in THF unless otherwise noted. ^b Reactions were run with 10% [RhCl(coe)₂]₂ and 15% PCy₃ at 180 °C for 20 h in toluene. ^c Reaction was run with 10% [RhCl(coe)₂]₂ and 15% PCy₃ at 180 °C for 3 days. ^d 75% yield of cis; diastereoselectivity of 15:1 based on ¹H NMR.

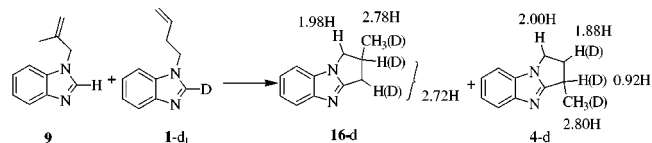
exclusive formation of the larger rings. Geminal substitution may favor the six-membered ring due to the difficulty of cyclizing to form a quaternary center.

In addition to modulating the regioselectivity, the level of substitution at the alkenyl position also has a dramatic impact on the rate of the reaction. Both 1,2-disubstituted alkene **6** and trisubstituted alkene **5** require more vigorous conditions than alkenes **1** and **9** to effect complete cyclization. Interestingly, terminal alkene **10** cyclizes more slowly than geminally substituted alkene **9** and monosubstituted alkene **1**, even though all three yield five-membered carbocycles (Table 1, entries 7, 6, and 1). Monitoring the cyclization of **9** to **16** by ¹H NMR spectroscopy shows that **9** does not undergo much double bond isomerization during the reaction, which may account for at least part of the difference in reactivity of **9** versus **10**. In addition, geminal substitution may provide an enhancement in the overall rate. The successful cyclization of imidazole **11** raises the possibility of extending the scope of this chemistry to other heterocycles.

In an effort to obtain preliminary information about the mechanism of these cyclizations, deuterium tracer (eq 2) and crossover experiments (Figure 1) were undertaken. Treatment of



compound **7-d**₁ with 5 mol % catalyst and 7.5 mol % PCy₃ at 135 °C afforded **14-d** with deuterium incorporated at the two positions indicated in eq 2. This result is consistent with rapid alkene insertion and β -hydride elimination before the formation of the final product.¹⁰ Analysis of **14-d** by electrospray mass spectrometry revealed that deuterium was exchanged between molecules during the course of its formation, since in the mass spectrum of the product, mass ions for **14-d**₀, **14-d**₁, **14-d**₂, and **14-d**₃ were observed. Notably, reaction of alkene **7** under catalytic conditions in *d*₈-toluene showed no deuterium incorporation into **7** or **14**, ruling out exchange of deuterium with the solvent. The proposed intermolecular deuterium exchange was confirmed by the following crossover experiment (Figure 1). Carrying out the catalytic reaction with a 50:50 mixture of **9** and **1-d**₁ gave products **16-d** and **4-d**, which were both shown to have deuterium incorporated by ¹H NMR and mass spectrometry. The crossover could be occurring through an intermolecular alkene insertion followed by rapid β -elimination, allowing for scrambling of deuterium between molecules. In light of the rapid intermolecular deuterium exchange observed here, it is interesting that no intermolecular coupling was observed. Furthermore, attempts to couple *N*-methylbenzimidazole to neo-hexene proved unsuccessful.

**Figure 1.** Deuterium crossover experiment.

In summary, we have developed a general method for carbon–carbon bond formation without necessitating pre-functionalization of the reaction partners. The new carbocyclization can be used to form both five- and six-membered rings via catalytic C–H bond activation. A range of substrates including mono-, di-, and trisubstituted alkenes has allowed the formation of complex structures with stereogenic centers. Mechanistic studies and application to other heterocyclic classes are under way.

Acknowledgment. This work was supported by the NIH GM50353 (to J.A.E), the Director and 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). We thank Dr. Fred Hollander and Dr. Alan Oliver of the UC Berkeley CHEXRAY facility for carrying out the X-ray diffraction studies.

Supporting Information Available: Experimental details, including analytical data for all compounds described in the article, a possible mechanism for formation of **12**, and X-ray diffraction data for **12** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA0058738

(10) Similar results were observed by Murai in ref 4.