Annulation of Aromatic Imines via Directed C−H Activation with Wilkinson's Catalyst

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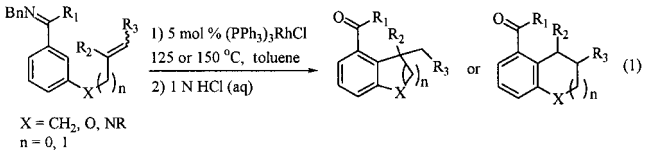
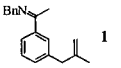
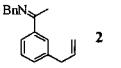
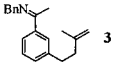
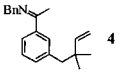
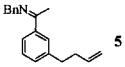
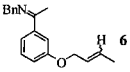
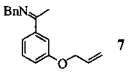
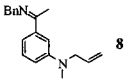
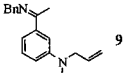
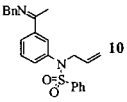
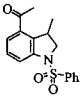
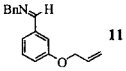
The application of transition metal-mediated C−H activation to C−C bond formation has great potential for the preparation of complex products from simple starting materials.[1] One of the first examples of such a transformation is Murai's regioselective ruthenium-catalyzed ortho alkylation of aromatic ketones with alkenes, which is proposed to involve heteroatom-directed C−H activation of the ortho-site.[2] Brookhart has used $Cp^*Rh(C_2H_3SiMe_3)_2$ ($Cp^* = C_5Me_5$) to catalyze this reaction with comparable efficiency,[3a] and several groups have now expanded the scope of these methodologies to include other directing groups such as imines, esters, and pyridines.[3b−e] These reactions, however, give only linear coupling products and are typically limited to terminal alkenes bearing no allylic hydrogens. Recently, Jun reported a more general imine-directed coupling reaction using Wilkinson's catalyst [$(PPh_3)_3RhCl$], that tolerates internal double bonds, yet yields only linear products.[4]

Our group has been interested in intramolecular variants of this methodology and recently reported the annulation of alkenyl-substituted heterocyclic derivatives.[5] Herein, we present the annulation of aromatic imines in which the alkene is tethered meta to the imine (eq 1). Coupling proceeds selectively to the more hindered ortho site to provide functionalized bicyclic ring systems that would be difficult to access by other methods. This intramolecular reaction can provide linear *or* branched coupling products depending on the alkene tether. Our results demonstrate for the first time that allyl ethers and allylamine derivatives function as efficient olefin coupling partners for the directed C−H activation reaction. Remarkably, in contrast to the intermolecular variant employing Wilkinson's catalyst,[4] an aldimine serves as an effective directing group.[6]



(1)

Table 1. Cyclization of Aromatic Imines Using Wilkinson's Catalyst[a]

Entry	Substrate	Temp (°C)	Time (h)	Product	% Isolated Yield (% NMR yield)[b]
1	 **1**	125	4	 **12**	71(89)
2	 **2**	125	1	 **13**	52(76)
				 **14**	(24)
3	 **3**	150	8	 **15**	65
4	 **4**	125	2	 **16**	85
5	 **5**	150	48	 **17**	50[c]
				 **18**	
6	 **6**	150	20	 **19**	64(77)
7	 **7**	150	16	 **20**	59(88)
8	 **8**	150	3	 **21**	50
9	 **9**	125	12	 **22**	52
10	 **10**	150	26	 **23**	53
11	 **11**	150	22	 **24**	50

[a] Reactions were performed using 5 mol % $(PPh_3)_3RhCl$ in toluene (0.1 M). [b] ^1H NMR yields were based on 2,6-dimethoxytoluene internal standard. [c] Yield refers to an isolated mixture of **17** and **18** which appear in a 1:1 ratio by ^1H NMR.

Table 1 summarizes the results of our annulation experiments. Treatment of the aromatic ketimine **1** (entry 1) with 5 mol % $(PPh_3)_3RhCl$ at 125 °C for 4 h affords, after hydrolysis, carbocycle **12** in high yield. The allyl-substituted ketimine **2** (entry 2) is converted to indane **13**, although a double bond isomer **14** is also formed in a kinetic ratio of 3:1.[7] Substrates containing longer alkenyl tethers cyclize to either five- or six-membered rings,

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(1) For reviews on C−H activation, see: (a) Kakiuchi, F.; Murai, S. Activation of Unreactive C−H Bonds. *Top. Organomet. Chem.* **1999**, *3*, 47−79. (b) Guari, Y.; Sabo-Etienne, 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. (e) Arndtsen, B. A.; Bergman, R. G.; Mobley, A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154−162. (f) Ryabov, A. *Chem. Rev.* **1990**, *90*, 403−424. (g) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**. In press.

(2) (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. (d) Murai, S.; Chatani, N.; Kakiuchi, F. *Bull. Chem. Soc. Jpn.* **1997**, *69*, 5589−594.

(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) Trost showed that α,β-unsaturated esters could also be functionalized in a similar fashion. Trost, B. M.; Imi, K.; Davies, I. W. *J. Am. Chem. Soc.* **1995**, *117*, 5371−5372. (e) Jordan and Taylor showed the coupling of pyridine to propene. Jordan, R. F.; Taylor, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 778−779.

(4) Jun, C. H.; Hong, J. B.; Kim, Y. H.; Chung, K. Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 3440−3441.

(5) (a) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 2685−2686. (b) 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. (c) Fujiwara has successfully cyclized electron-deficient alkenes and alkynes to aromatic rings with palladium. Jia, C. G.; Piao, D. G.; Oyamada, J. Z.; Lu, W. J.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992−1995.

(6) (a) Murai used $Ru_3(CO)_{12}$ to couple aldimines intermolecularly to terminal alkenes with no allylic hydrogens. Kakiuchi, F.; Yamauchi, M.; Chatani, N.; Murai, S. *Chem. Lett.* **1996**, 111. (b) Very recently, Lim has shown that aldimines can be coupled to isomerizable alkenes using $[RhCl(coe)_2]_2/PCy_3$ as the catalyst; however, bis-ortho alkylated products predominate over the desired monoalkylated products. Lim, Y. G.; Han, J. S.; Yang, S. S.; Chun, J. H. *Tetrahedron Lett.* **2001**, *42*, 4853−4856.

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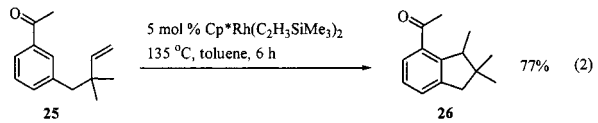
typically with high selectivity. Internal geminal alkene substitution (entry 3) and allylic α,α-dibranching (entry 4) yield exclusively the six-membered ring product. In the one observed case of nonregioselective cyclization (entry 5), the ketimine **5** lacks substitution in the alkenyl tether. All of the tested imines that contain oxygen- and nitrogen-based tethers (entries 6−11) yield the corresponding dihydrobenzofuran and dihydroindole five-membered ring products with high selectivity.[8] The formation of a five-membered ring from crotyl ether **6** (entry 6) demonstrates, for the first time, the direct coupling of an acyclic 1,2-disubstituted alkene to an aromatic ring.[9] It is also noteworthy that a diverse range of nitrogen substituents is compatible with this chemistry. Ketimines that incorporate *N*-alkyl, *N*-acyl, and *N*-sulfonyl functionality in the tether (entries 9−11) all efficiently cyclize. Comparison of the carbon-tethered substrate **5** and the analogous heteroatom-tethered substrates **7**−**10** reveals that the annulation of the heteroatom-linked olefins is more facile.

While most of the substrates are capable of double bond isomerization, the desired cyclic products are still obtained. Monitoring the course of the reactions by ^{1}H NMR reveals the formation of internal alkene isomers from substrates **5** and **7**−**11.** These isomers, however, are eventually consumed to form the corresponding bicyclic products.[10] Only in the case of ketimine **2** (entry 2) were more than trace quantities of the alkene isomer recovered. Not surprisingly, the more highly substituted crotyl ether **6** isomerizes to a much smaller extent than the allyl ethers **7** and **11**. Geminal alkene substitution in **1** and **3** apparently slows double-bond isomerization so that it does not compete significantly with the annulation.

The cyclization of substrate **11** demonstrates that the aldimine is also an effective directing group when applied to the intramolecular reaction.[6] This is notable since the aldimine is ineffective for the analogous intermolecular system using Wilkinson's catalyst.[4]

The ketones corresponding to the imines shown in Table 1 do not cyclize in the presence of Wilkinson's catalyst but instead give double-bond isomers. Interestingly, however, Cp*Rh(C_2H_3-$SiMe_3$)$_2$ cleanly converts ketone **25**, containing allylic geminal substitution, into the indane **26** (eq 2) in good yield and high regioselectivity (11.5:1 five- to six-membered ring product ratio by GC).[11] While the regiochemistry is opposite that observed with the corresponding imine (entry 4), the scope of the carbonyl/Cp*Rh($C_2H_3SiMe_3$)$_2$ reaction is not general; substrates containing isomerizable olefins do not undergo annulation.



In summary, we have developed a novel method for the synthesis of functionalized indane, tetralane, dihydrobenzofuran, and dihydroindole derivatives from simple starting materials using directed C−H bond activation. Cyclization to the bicyclic systems generally proceeds with high selectivity. The reaction tolerates different tether lengths, the incorporation of heteroatoms into the tether, and a number of alkene substitution patterns. Furthermore, the annulation of aldimine substrates provides additional synthetic opportunities due to the facility with which the product carboxaldehyde can be converted into other functionalities. Experiments to establish the scope and to gain further insight into the mechanism of this reaction are currently underway.

Acknowledgment. We dedicate this paper to the memory of our good friend and colleague Andy Dorsey, who passed away suddenly on August 13, 2001. This research was supported by the NIH (Grant no. GM50353 to J.A.E.) and 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.).

Supporting Information Available: Complete experimental details and spectral data for all compounds described in the article (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) This ratio (determined by ^{1}H NMR) was determined to be kinetically controlled by resubjecting the benzylimine of **13** to the reaction conditions and observing no change.

(8) Six-membered ring products were observed in small amounts (<5%).

(9) Murai used $RuH_2(CO)(PPh_3)_3$ to couple aromatic ketones to norbornene and cyclopentene. Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatini, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62−83.

(10) It is unclear whether cyclization proceeds directly from the internal double bond isomer or after rapid equilibration to the terminal isomer.

(11) Murai's most successful catalyst for the analogous intermolecular reaction, $RuH_2(CO)(PPh_3)_3$, gave a poor yield (∼20% NMR yield) of the five-membered ring product, and $Ru_3(CO)_{12}$ was ineffective.