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# Annulation of Aromatic Imines via Directed C−H Bond Activation

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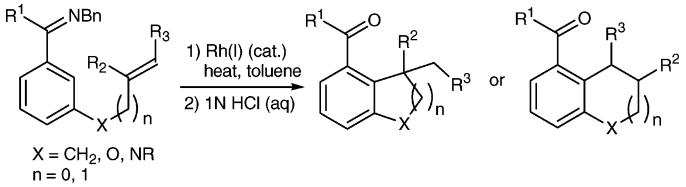


A directed C−H bond activation approach to the synthesis of indans, tetralins, dihydrofurans, dihydroindoles, and other polycyclic aromatic compounds is presented. Cyclization of aromatic ketimines and aldimines containing alkenyl groups tethered at the *meta* position relative to the imine directing group has been achieved using $(PPh_3)_3RhCl$ (Wilkinson's catalyst). The cyclization of a range of aromatic ketimines and aldimines provides bi- and tricyclic ring systems with good regioselectivity. Different ring sizes and substitution patterns can be accessed through the coupling of monosubstituted, 1,1- or 1,2-disubstituted, and trisubstituted alkenes bearing both electron-rich and electron-deficient functionality.

## Introduction

In contemporary organic synthesis, one of the most attractive methods for carbon−carbon bond formation is the transition-metal-catalyzed activation and functionalization of otherwise unreactive carbon−hydrogen bonds.[1,2] Because C−H bonds are among the most ubiquitous chemical linkages in nature, the direct conversion of C−H bonds to C−C bonds represents an efficient and economical strategy for fine chemical production. The greatest challenge in this field of research is the development of both mild and selective methods for transforming the relatively inert C−H bonds into other chemical functionalities. Murai's 1993 discovery of a highly efficient and selective catalytic addition of C−H bonds to simple olefins represents a breakthrough in this field.[3] In this seminal work, chelation-assisted ruthenium-catalyzed C−H bond activation of aromatic ketones followed by olefin addition provided exclusively *ortho*-alkylated products.[4] Since that publication, Brookhart has developed a rhodium complex $[Cp^*Rh(C_2H_3SiMe_3)_2]$ that catalyzes the same reaction,[5] and the ruthenium-catalyzed olefin hydroarylation reaction has been extended to include various aromatic compounds, such as thiophene, furan, pyrrole, and electron-deficient aromatic esters.[6] Olefinic C−H bonds at the $\beta$-position of $\alpha,\beta$-unsaturated ketones[7] and esters[8] can also be added to carbon−carbon double bonds. A range of functional

(1) For reviews on stoichiometric C−H activation, see: (a) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (c) Shilov, A.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (d) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154. (e) Ryabov, A. *Chem. Rev.* **1990**, *90*, 403.

(2) For reviews on catalytic C−H activation, see: (a) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1699. (b) Guari, Y.; Sabo-Etienne, S.; Chaudret, B. *Eur. J. Inorg. Chem.* **1999**, *7*, 1047. (c) Kakiuchi, F.; Murai, S. In *Topics in Organometallic Chemistry*; Murai, S., Ed.; Springer-Verlag: Berlin Heidelberg, 1999; Vol. 3, p 47. (d) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102 (5)*, 1731. (e) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (f) Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2003**, *680*, 3. (g) Jia, C. G.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633.

(3) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.

(4) Bis-alkylation occurs in substrates where both *ortho* positions are unsubstituted. The ratio of mono- to bis-alkylation is determined by the number of olefin equivalents and the reaction time.

(5) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616.

(6) (a) Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62. (b) Murai, S.; Kakiuchi, F.; Sekine, S.; Yanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Pure Appl. Chem.* **1994**, *66*, 1527. (c) Murai, S.; Chatani, N.; Kakiuchi, F. *Pure Appl. Chem.* **1997**, *69*, 589. (d) Sonoda, M.; Kakiuchi, F.; Kamatani, A.; Chatani, N.; Murai, S. *Chem. Lett.* **1996**, 109.

(7) Kakiuchi, F.; Tanaka, Y.; Sato, T.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, 679.

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

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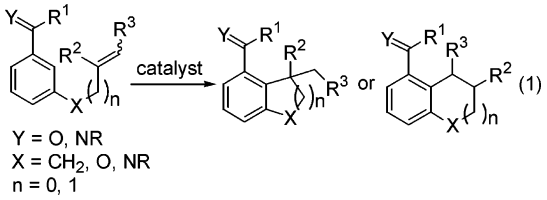
groups on the aromatic component are tolerated, including ethers, esters, amides, and nitriles.[2c,9]

The primary factor that hinders the utility of this chemistry is the limited olefin substrate scope.[6a] Generally, vinylsilanes, vinylsiloxanes, and *tert*-butyl ethylene couple efficiently, but other olefins such as internal olefins, dienes, and olefins with electron-withdrawing or electron-donating groups show a low reactivity toward *ortho*-alkylation. In addition, terminal alkenes that can undergo olefin isomerization do not serve as effective coupling partners.

More recently, Jun and co-workers reported a more general reaction involving the *ortho*-alkylation of aromatic ketimines using Wilkinson's catalyst, $(PPh_3)_3RhCl$.[10,11] Ketimines efficiently coupled with a range of olefins to afford selectively the linearly-alkylated products. Isomerizable alkenes, 1,1-disubstituted alkenes, 1,2-disubstituted alkenes, and $\alpha,\omega$-dienes couple with moderate to good efficiency,[10] as do $\alpha,\beta$-unsaturated carbonyl systems.[11] Interestingly, internal olefins undergo reaction after isomerization to the terminal olefin. The rhodium-catalyzed *ortho*-alkylation of ketimines is believed to occur by a mechanism analogous to that of the Murai reaction.[12]

Despite the advancements achieved through the imine-directed reaction, there remain several limitations to this chemistry. First, aldimines are not effective directing groups for the coupling reaction, a fact that significantly confines the synthetic versatility of the products.[13] Second, the formation of only linear alkylated products precludes the general use of this chemistry in the synthesis of chiral products.[6] Finally, heteroatom-containing olefins, such as vinyl ethers, allylic ethers, and allylic amines, do not react with the ketimine.[6]

Prior to our research group's studies on intramolecular hydroarylation reactions,[14] there were surprisingly few examples of intramolecular C−H activation/olefin insertion chemistry.[15,16] The development of an intramolecular variant of the Murai reaction (eq 1), in which the alkene

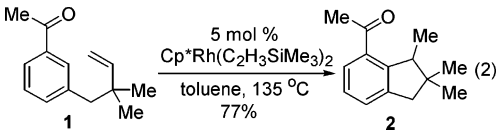



is tethered *meta* to the carbonyl or imine directing group, was expected to broaden the substrate scope to include less reactive olefins due to the lower entropic barrier of reaction. Substrates with electron-rich or electron-deficient olefins, highly substituted olefins, and heteroatom-containing olefins would allow access to synthetically useful compounds that are not otherwise readily prepared. Furthermore, the construction of aromatic compounds in which new stereocenters are generated would allow the development of asymmetric catalytic C−H bond activation/olefin insertion chemistry.

We have developed an intramolecular variant of the chelation-assisted C−H bond activation/olefin insertion reaction that is much more versatile than the intermolecular reaction and have published our preliminary results in a previous communication.[17] Since then, we have demonstrated its application to the synthesis of a biologically important molecule[18] and have recently communicated a highly enantioselective variant of the annulation reaction using chiral phosphoramidite ligands.[19] Herein, the details of our studies on the annulation using achiral catalysts are reported.

## Results and Discussion

The reactions of aromatic ketones with an alkene tethered at the *meta* position (eq 2) were initially ex-




amined. $Cp^*Rh(C_2H_3SiMe_3)_2$ cleanly converts ketone **1**, containing allylic geminal substitution, into indan **2** in good yield and high regioselectivity (11.5:1 five- to six-membered ring product ratio by GC).[20] However, the scope of the carbonyl-directed/$Cp^*Rh(C_2H_3SiMe_3)_2$-catalyzed reaction was not general, as substrates bearing isomerizable olefins did not undergo annulation.

We refocused our efforts to the annulation of aromatic imines shortly after the report by Jun appeared in the literature describing a broader reaction scope with respect to the olefin coupling partner. The cyclization of an acetophenone imine with a tethered isomerizable olefin was initially examined. Treatment of imine **3**

(9) (a) Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. *J. Organomet. Chem.* **1995**, *504*, 151. (b) Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 3117.

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

(11) Lim, S.-G.; Ahn, J.-A.; Jun, C.-H. *Org. Lett.* **2004**, *6*, 4687−4690.

(12) Jun, C. H.; Moon, C. W.; Hong, J.-B.; Lim, S.-G.; Chung, K. Y.; Kim, Y.-H. *Chem. Eur. J.* **2002**, *8*, 485.

(13) (a) Lim has shown that aldimines can be coupled to isomerizable alkenes using $[RhCl(coe)_2]_2/Cy_3P$ 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. (b) 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.

(14) For intramolecular heterocyclic C−H activation/olefin insertions, see: (a) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 2685. (b) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 3202. (c) Tan, K. L.; Vasudevan, A.; Bergman, R. G.; Ellman, J. A.; Souers, A. J. *Org. Lett.* **2003**, *5*, 2131. (f) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 13964. (g) Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 1685. (h) Lewis, J. C.; Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 35.

(15) Fujii, N.; Kakiuchi, F.; Yamada, A.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1998**, *285*, 5.

(16) For reports on related, nondirected intramolecular C−H activation/alkene insertion reactions, see: (a) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055. (b) Pastine, S. J.; Youn, S. W.; Sames, D. *Tetrahedron* **2003**, *59*, 8859. (c) Youn, S. W.; Pastine, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581−584.

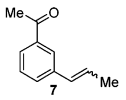
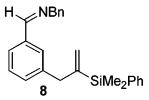
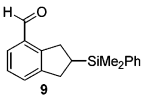
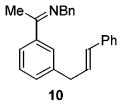
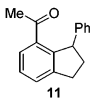
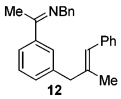
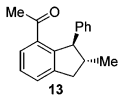
(17) Thalji, R. K.; Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 9692.

(18) Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1301.

(19) Thalji, R. K.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 7192.

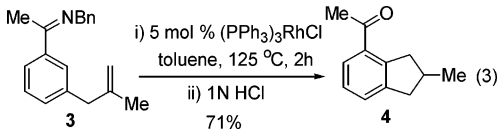
(20) Murai's most successful catalyst for the analogous intermolecular reaction, $RuH_2(CO)(PPh_3)_3$, gave a poor yield (~20% NMR yield) of the five-membered ring product, and $Ru_3(CO)_{12}$ was ineffective.

**TABLE 1. Synthesis of Indan Derivatives**[a]

| Entry | Substrate | Temp (°C) | Time (h) | Product | % Yield[b] |
|---|---|---|---|---|---|
| 1 |  **5** | 125 | 1 |  **6**  **7** | 52 **6**:**7** = 3:1 |
| 2 |  **8** | 150 | 36 |  **9** | 58 |
| 3 |  **10** | 150 | 16 |  **11** | 68 |
| 4 |  **12** | 150 | 36 |  **13** | 50 7:1 *trans*:*cis*[c] |

[a] Conditions: 5 mol % $(PPh_3)_3RhCl$, toluene, heat; then 1 N HCl. [b] Isolated yields of purified products after silica gel chromatography. [c] *trans*-Isomer determined to be the major product by NOESY experiment and X-ray crystallography.

with Wilkinson's catalyst at elevated temperature, followed by aqueous acid workup, provided the indan product **4** in high yield (eq 3). No double-bond isomer was



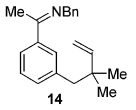
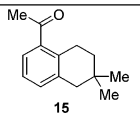
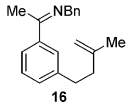
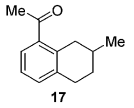
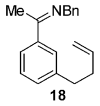
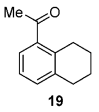
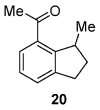
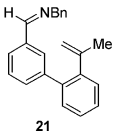
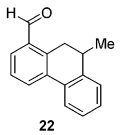

detected.[21] Encouraged by this initial result, the substrate generality of the annulation reaction was explored.

**Synthesis of Indan Derivatives.** A variety of other indans are readily accessed with this methodology, as outlined in Table 1. Cyclization of the allyl-substituted ketimine **5** occurs, providing a 52% yield of **6** (entry 2). Competing olefin isomerization takes place in this case, forming the styrenyl isomer **7** in addition to the desired product (**6**:**7** = 3:1). As might be expected from the estimated exothermicity of the reaction (~18 kcal/mol[22]), the imine corresponding to product **6** does not react with Wilkinson's catalyst, establishing that isomer **7** and the indan product are not in equilibrium. This result suggests that the ratio of products formed by the reaction of ketimine **5** is kinetically determined.

(21) The remainder of the mass balance for the reaction of this substrate and others is presumably lost to oligomerization and/or polymerization of starting material. An evaluation of the reaction concentration revealed that performing the reaction at a substrate concentration of 0.1 M afforded higher yields than performing the same reaction at either higher or lower concentrations.

(22) This value was calculated using the heats of formation of compounds **5** and **6** estimated by the Benson group equivalent method (Benson, S. W. *Thermochemical Kinetics*, 2nd ed., Wiley: New York, 1976; <http://webbook.nist.gov/chemistry/grp-add/ga-app.shtml>). The entropy change counteracts this exothermicity to a significant extent at 125 °C, but the free energy change is still predicted to be negative at this temperature.

**TABLE 2. Synthesis of Tetralin Derivatives**[a]

| Entry | Substrate | Temp (°C) | Time (h) | Product(s) | % Yield[b] |
|---|---|---|---|---|---|
| 1 |  **14** | 125 | 2 |  **15** | 85 |
| 2 |  **16** | 150 | 8 |  **17** | 65 |
| 3 |  **18** | 150 | 48 |  **19**  **20** | 50 **19**:**20** = 1:1 |
| 4 |  **21** | 150 | 6 |  **22** | 81 |

[a] Conditions: 5 mol % $(PPh_3)_3RhCl$, toluene, heat; then 1 N HCl. [b] Isolated yields of purified products after silica gel chromatography.

The annulation of vinylsilane substrate **8** (entry 3) illustrates a method of introducing a hydroxyl functionality in the product, as the phenyldimethylsilyl group can be converted to an alcohol using oxidation conditions developed by Fleming[23] and Tamao.[24] The cyclization of cinnamyl-tethered substrate **10** demonstrates, for the first time, the direct coupling of an acyclic 1,2-disubstituted alkene to an aromatic ring.[25] Even the sterically hindered alkene **12** could be cyclized with good yield and high diastereoselectivity. In this case, the observed preference for *trans* substitution is presumably a result of a *syn* addition of the Rh−H bond to the olefin. The minor *cis* indan product observed is most likely due to in situ double bond isomerization of **12** to its *cis*-double bond isomer followed by cyclization.

In contrast to the intermolecular variant using Wilkinson's catalyst,[10] aldimines direct the C−H activation/olefin insertion reaction (Tables 1−6). Importantly, this increases the synthetic utility of our annulation strategy due to the facility with which carboxaldehydes can be converted into other functionalities.

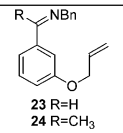
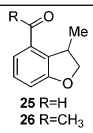
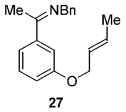
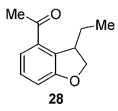
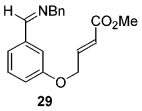
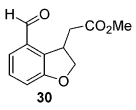
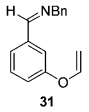
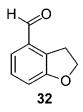
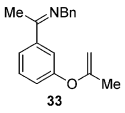
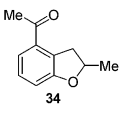
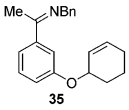
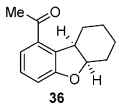
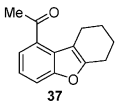
**Synthesis of Tetralin Derivatives.** Various tetralins can also be prepared via rhodium(I)-catalyzed C−H activation/olefin insertion, as shown in Table 2. The presence of allylic α,α-branching (entry 1) and internal geminal alkene substitution (entry 2) directs the reactions to yield exclusively the six-membered ring products. Interestingly, the regioselectivity in the cyclization of imine **14** is opposite to that of ketone **1** (eq 2), which bears

(23) (a) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, *4*, 317. (b) Fleming, I. *Chemtracts: Org. Chem.* **1996**, *9*, 1.

(24) Tamao, K. *Adv. Silicon Chem.* **1996**, *3*, 1.

(25) Murai used $RuH_2(CO)(PPh_3)_3$ to couple aromatic ketones to norbornene and cyclopentene. See ref 6a.

**TABLE 3. Synthesis of Dihydrobenzofuran Products[a]**

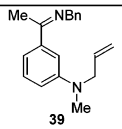
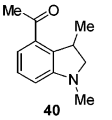
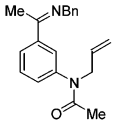
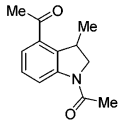
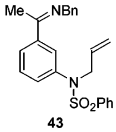
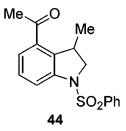
| Entry | Substrate | Temp (°C) | Time (h) | Product | % Yield[b] |
|---|---|---|---|---|---|
| 1 |  **23** R=H **24** R=$CH_3$ | 150 | 20 (R=H) 16 (R=$CH_3$) |  **25** R=H **26** R=$CH_3$ | 52 (**25**) 59 (**26**) |
| 2 |  **27** | 150 | 22 |  **28** | 64 |
| 3 |  **29** | 150 | 48 |  **30** | 50 |
| 4 |  **31** | 150 | 12 |  **32** | 65 |
| 5 |  **33** | 125 | 0.75 |  **34** | 90 |
| 6 |  **35** | 150 | 72 |  **36**  **37** | 41 (**36**) 13 (**37**) |

[a] Conditions: 5 mol % $(PPh_3)_3RhCl$, toluene, heat; then 1 N HCl. [b] Isolated yields of purified products after silica gel chromatography.

the same olefin tether. In the one observed case of a nonregioselective cyclization to a mixture of tetralin and indan products, the ketimine lacks substitution in the alkyl tether (entry 3). Isomerization to the internal olefin occurs in this case, as determined by $^1H$ NMR studies. In addition to bicyclic ring systems, tricyclic products can be prepared with this methodology. Thus, the biaryl aldimine **21** (entry 4) readily yields dihydrophenanthrene **22** under the reaction conditions.

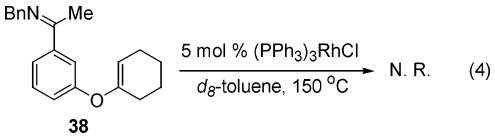
**Synthesis of Dihydrobenzofuran Products.** Allyl ethers couple efficiently, selectively providing dihydrobenzofuran products (Table 3). The formation of a five-membered ring system from the crotyl ether **27** (entry 2) demonstrates direct coupling of an acyclic 1,2-disubstituted alkene to an aromatic ring. Additionally, the α,β-unsaturated ester **29** (entry 3) undergoes this transformation. The successful coupling of allylic ethers is significant because in the intermolecular reactions of aromatic ketones and ketimines these are ineffective substrates. Olefin isomerization occurs in the reactions of substrates **23** and **24** (entry 1), **27** (entry 2), and **29** (entry 3) as observed by $^1H$ NMR, though it is unclear whether cyclization proceeds from the allylic or the vinylic ether. The aryl vinyl ethers **31** and **33** (entries 4 and 5) undergo efficient transformation to the dihydrobenzofuran, suggesting the allylic ethers can cyclize from their internal olefin isomers.

**TABLE 4. Synthesis of Dihydroindole Derivatives[a]**

| Entry | Substrate | Temp (°C) | Time (h) | Product | % Yield[b] |
|---|---|---|---|---|---|
| 1 |  **39** | 150 | 3 |  **40** | 50 |
| 2 |  **41** | 125 | 12 |  **42** | 52 |
| 3 |  **43** | 150 | 26 |  **44** | 53 |

[a] Conditions: 5 mol % $(PPh_3)_3RhCl$, toluene, heat; then 1 N HCl. [b] Isolated yields of purified products after silica gel chromatography.

The cyclohexenyl aryl ether **35** (entry 6) generates the hexahydrodibenzofuran product **36** in modest yield, in addition to a minor amount of tetrahydrodibenzofuran product **37**, presumably due to hydrogen transfer between starting olefin and cyclized product. As observed for the allylic ethers in Table 3, transient olefin isomerization of **35** occurs. In this case, cyclization is believed to occur directly from the allylic double bond because independently synthesized vinyl ether isomer **38** does not undergo reaction in the presence of Wilkinson's catalyst (eq 4). Consistent with a *syn* Rh−H addition to the allylic



**38**

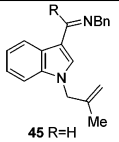
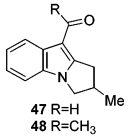
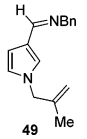
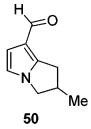
double bond, the *cis*-fused product **36** is obtained exclusively. Direct cyclization of vinyl ether **38** would yield the undetected *trans*-fused product.

**Synthesis of Dihydroindole Derivatives.** Dihydroindoles are synthesized by subjection of aryl allylamine derivatives to the cyclization conditions (Table 4). *N*-Alkyl, *N*-acyl, and *N*-sulfonyl functionalities are tolerated. In all cases, the five-membered ring products are formed in >95:5 selectivity over the six-membered ring products. Although the yields are moderate (50−53% yield), these cyclizations are significant because they represent the first examples of directed C−H activation/olefin insertion using allylamine derivatives as coupling partners.

**Synthesis of Functionalized Heterocycles.** Functionalization of heterocycles with our annulation strategy is demonstrated in Table 5. The C-3 substituted benzyl imine directs C−H activation at the C-2 position of *N*-methallyl indoles (entry 1) and an *N*-methallyl pyrrole (entry 2) to provide the alkylated heterocyclic systems in good to high yield.

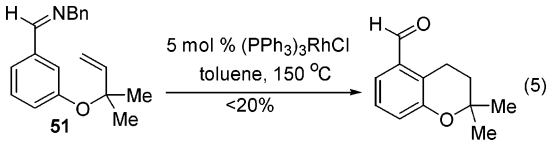
**Limitations.** The intramolecular C−H bond activation/olefin addition strategy provides access to a number of useful polycyclic compounds. We did, however, identify

**TABLE 5. Functionalization of Heterocycles**[a]

| Entry | Substrate | Temp (°C) | Time (h) | Product | % Yield[b] |
|---|---|---|---|---|---|
| 1 |  **45** R=H **46** R=$CH_3$ | 125 | 17 |  **47** R=H **48** R=$CH_3$ | 97 (**47**) |
| | | 125 | 0.5 | | 72 (**48**) |
| 2 |  **49** | 150 | 60 |  **50** | 74 |

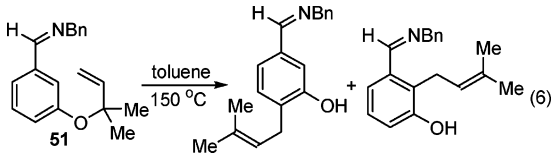
[a] Conditions: 5 mol % $(PPh_3)_3RhCl$, toluene, heat; then $SiO_2$. [b] Isolated yields of purified products.

limitations to this methodology during the course of our studies. For instance, a chroman product was expected from subjection of the *gem*-dialkyl-substituted allylic ether **51** to the cyclization conditions (eq 5), because the




analogous carbon-tethered olefin cyclized to the six-membered ring system in high yield (Table 2, entry 1). However, in the case of the allylic ether, the product yield was low, and efforts to improve the cyclization with increased catalyst loading or decreased temperature were unsuccessful.

Control experiments demonstrated substrate **51** undergoes a facile Claisen rearrangement in the absence of catalyst at elevated temperature (eq 6). Interestingly, the unsubstituted allylic ether **23** (Table 3) does not undergo Claisen rearrangement after extended heating at 150 °C, indicating that rearrangement of **51** is promoted by a Thorpe−Ingold (*gem*-dimethyl) effect.




The aryl allyl thioether **52** did not undergo reaction when subjected to Wilkinson's catalyst at elevated temperature (eq 7). We presumed the thioether coordinated too strongly to the rhodium center, poisoning the catalyst. To ascertain if this was the case, a substrate that is known to undergo annulation (aldimine **8**, Table 1) was subjected to the reaction conditions with an equivalent amount of the thioether present (eq 8). Consistent with the above hypothesis, no reaction occurred.

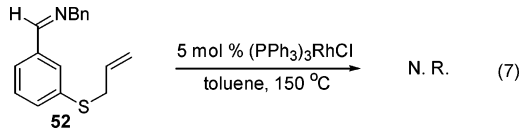
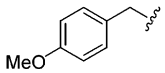
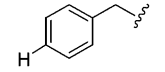
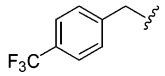
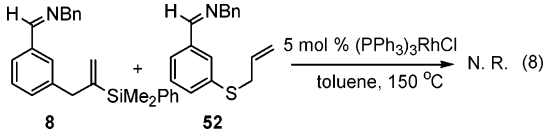


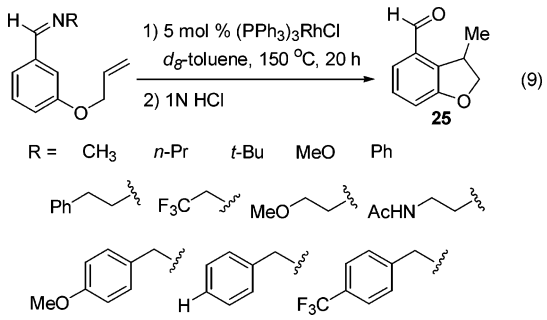

**TABLE 6. Effect of *para*-Substitution of Benzyl Imines on Isolated Yield of 25**

| Entry | R | % Yield[a] |
|---|---|---|
| 1 |  | 38 |
| 2 |  | 50 |
| 3 |  | 60 |

[a] Isolated yield after 1 N HCl hydrolysis.




**Optimization Efforts.** Other imine directing groups were examined. Imines were prepared from a variety of amines and subjected to the cyclization conditions with Wilkinson's catalyst (eq 9). Most of the imines



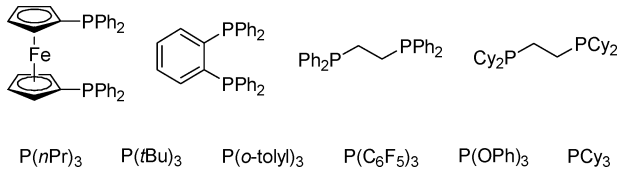

cyclized less efficiently than the benzyl imine, although an interesting trend was observed with *para*-substituted benzyl imines. The electron-donating *p*-methoxy group decreased product yield and the electron-withdrawing *p*-trifluoromethyl group provided a higher yield of cyclized product (Table 6).[26]

In addition to Wilkinson's catalyst, a number of other transition metal complexes were surveyed in the model cyclization reaction of allyl ether **23**, including $(PPh_3)_2Ru(Cp)Cl$, $Ru_3(CO)_{12}$, $RuH_2(CO)(PPh_3)_3$, $(PPh_3)_3RuCl_2$, $(PPh_3)_3CoCl$, $(PPh_3)_2Co(Cp)$, $(PPh_3)_3CoCl_2$, and $[IrCl(coe)_2]_2/PPh_3$. No cyclized product was observed with the cobalt or iridium complexes, and only trace product was detected with the use of $(PPh_3)_2Ru(Cp)Cl$.

In an effort to improve the efficiency of the annulation reaction, a diverse set of phosphines was screened in the presence of $[RhCl(coe)_2]_2$ (Chart 1). Bidentate phosphines were unsuccessful for the reaction of allyl ether **23** (Table

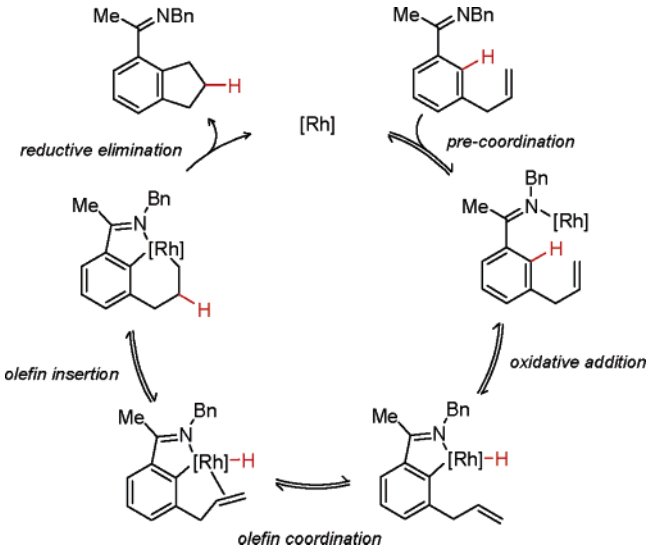
(26) The reason for this trend is unclear; the substituent presumably plays a role in the reaction by altering the basicity of the imine nitrogen or by changing the electrophilicity of the aromatic ring involved in the C−H activation.

**CHART 1. Phosphines Surveyed in the Cyclization of 23**




$P(nPr)_3$ $P(tBu)_3$ $P(o\text{-tolyl})_3$ $P(C_6F_5)_3$ $P(OPh)_3$ $PCy_3$

**SCHEME 1. Postulated Mechanism for the Annulation Reaction**

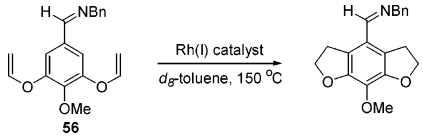



3). This is consistent with the observation that excess phosphine hinders the cyclization reaction. The monodentate phosphines surveyed gave catalysts of comparable or lower efficiency than $PPh_3$ for this model system. However, with certain substrates, the rhodium catalyst generated from $PCy_3$ was found to provide more efficient cyclization than that based on $PPh_3$. For example, the cyclization of **3** using 2.5 mol % $[RhCl(coe)_2]_2$ and 7.5 mol % $PCy_3$ proceeds to completion within 8 h at 80 °C. With more challenging substrates such as **23**, the catalyst decomposes before the reaction is complete.

**Mechanism.** The mechanism of the annulation reaction most likely involves a catalytic cycle analogous to that proposed by Jun et al.[12] for his intermolecular C−H activation/alkene insertion reaction (Scheme 1). Imine precoordination, followed by C−H oxidative addition to the Rh center, would generate a Rh−H complex, as shown in Scheme 1.[27] This step may be followed by coordination of the olefin to the metal. Migratory insertion into the Rh−H bond would provide a metalacycle that can undergo reductive elimination to afford the product. Deuterium labeling studies performed by Jun et al. on the analogous intermolecular reaction indicate that the reductive elimination step is rate-determining.[12] An alternative mechanism for the C−H activation step (not shown) may involve precoordination of both the imine and the olefin, which would form a pincer-type complex that would be well-suited for C−H activation of the hindered *ortho* C−H bond.[28]

(27) Alternatively, reversible *ortho*, *meta*, and *para* C−H activation may precede functional group coordination, which would then serve to trap the *ortho* C−H addition product: Zhang, X.; Kanzelberger, M.; Emge, T. J.; Goldman, A. S. *J. Am. Chem. Soc.* **2004**, *126*, 13192.

**TABLE 7. Optimization of the Tandem C−H Activation/Olefin Insertion Reaction**




| entry | Rh catalyst[a] | $t$ (h) | % yield[b] |
|---|---|---|---|
| 1 | $(PPh_3)_3RhCl$[c] | 20 | 10 |
| 2 | $P(t\text{-Bu})_3$, $[RhCl(coe)_2]_2$ | 3 | 0 |
| 3 | $P(n\text{-Bu})_3$, $[RhCl(coe)_2]_2$ | 17 | 18 |
| 4 | $PCy_3$, $[RhCl(coe)_2]_2$ | 8 | 48 |
| 5 | $FcPPh_2$, $[RhCl(coe)_2]_2$ | 4 | 34 |
| 6 | $FcPCy_2$, $[RhCl(coe)_2]_2$ | 2 | 75 |
| 7 | $FcPCy_2$, $[RhCl(coe)_2]_2$[d] | 5 | 52 |

[a] Reactions were performed using 20 mol % Rh(I) and 20 mol % phosphine. [b] Yields were determined by $^1H$ NMR relative to an internal standard. [c] 20 mol % Wilkinson's catalyst was used. [d] Reaction was performed using 20 mol % Rh(I) and 40 mol % phosphine. Abbreviations: coe = cyclooctene; Fc = ferrocenyl.

**Application to the Synthesis of a Mescaline Analogue.** To date, only a few examples of C−H activation in the synthesis of natural products or biologically active molecules have been reported.[29,30] Our interest in mescaline analogue **58**[31] (Scheme 2) was generated by the ability to rapidly assemble the tetrahydrobis(benzofuran) functionality utilizing the catalytic C−H activation/olefin insertion reaction. As outlined in Scheme 2, precursor **56** was prepared from (4′-*O*-methyl)methyl gallate **53**[32] by transformation of the bis-phenol to the bis-vinyl ether **54**[33] followed by ester reduction[34] and conversion of aldehyde **55** to the benzyl imine. Evaluation of a range of catalyst systems (Table 7) led to the identification of conditions (10% $[RhCl(coe)_2]_2$, 20% $FcPCy_2$, 150 °C) that provided the tetrahydrobis(benzofuran) **57** in 65% yield after imine hydrolysis. Compound **57** was subsequently converted to the target mescaline analogue via a Henry reaction followed by reduction of the intermediate nitroalkene. The tetrahydrobis(benzofuran) mescaline analogue **58** was prepared in six steps and 38% overall yield from (4′-*O*-methyl)methyl gallate. This annulation sequence can potentially be applied to the synthesis of other biologically relevant dihydrobenzofurans.

(28) Similar pincer-type cyclometalations have been described by other researchers: (a) Rietveld, M. H. P.; Grove, D. M.; van Koten, G. *New J. Chem.* **1997**, *21*, 751−771. (b) Nemeh, S.; Jensen, C.; Binamira-Soriaga, E.; Kaska, W. C. *Organometallics* **1983**, *2*, 1442−1447.

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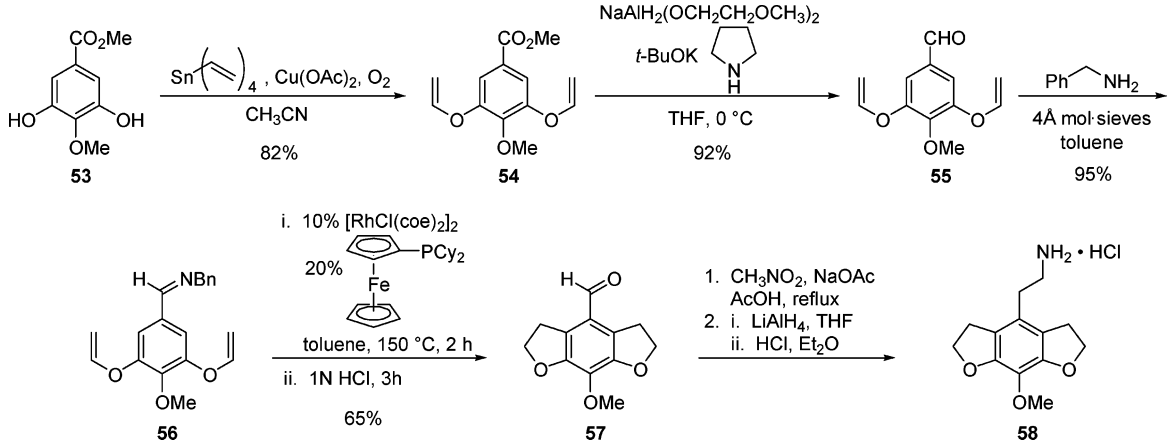
**SCHEME 2. Synthesis of Mescaline Analog 58 Using C−H Activation Methodology**




## Conclusion

A novel method has been developed for the synthesis of functionalized indans, tetralins, dihydrobenzofurans, dihydroindoles, and other polycyclic compounds from simple starting materials using directed C−H bond activation. The cyclizations generally proceed with high selectivity, and the reactions are tolerant of various functional groups, different tether lengths, a number of alkene substitution patterns, and the incorporation of heteroatoms in the tether. Furthermore, the annulation of aldimine substrates provides additional synthetic opportunities due to the facility with which the product carboxaldehydes can be converted into other functionalities.

## Experimental Section

**General Procedure for Cyclization of Benzyl Imino Substrates.** In an inert atmosphere drybox, to a medium-walled glass reaction vessel was added a solution of $(PPh_3)_3$-RhCl (5 mol %) and the benzyl imine in toluene (0.1 M). The vessel was sealed with a Kontes stopcock and placed in an oil bath at 125 or 150 °C. After the noted reaction time, the vessel was removed and cooled to room temperature. The solution was concentrated, 1 N HCl was then added, and the resulting mixture was stirred vigorously for 3 h. The mixture was then diluted with EtOAc, the organic layer was separated, and the aqueous phase was re-extracted. The combined organic extracts were washed with brine, dried, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography.

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**Supporting Information Available:** Full experimental details, including analytical data for all compounds described in the article and X-ray diffraction data for **13** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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