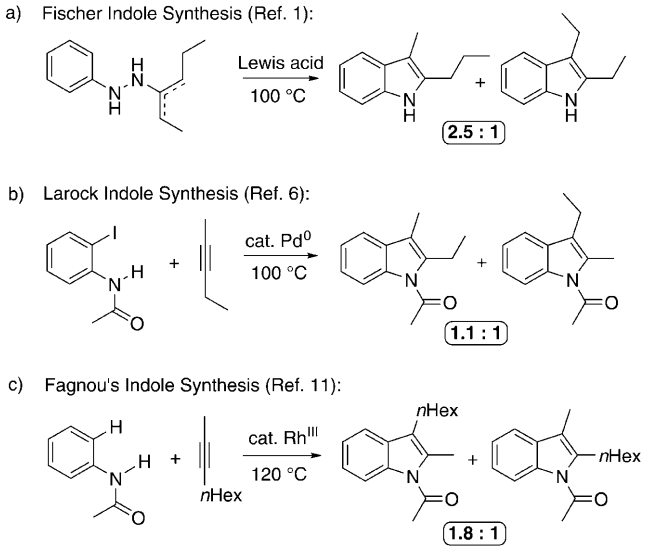
Heterocycles

DOI: 10.1002/anie.201006381

The Vinyl Moiety as a Handle for Regiocontrol in the Preparation of Unsymmetrical 2,3-Aliphatic-Substituted Indoles and Pyrroles**

Malcolm P. Huestis, Lina Chan, David R. Stuart, and Keith Fagnou†*

Since their introduction in the 1880s, the Fischer indole synthesis[1] (Scheme 1a) and the Paal–Knorr pyrrole synthesis[2] have ranked among the most utilized reactions in heterocyclic chemistry.[3] However, the general importance of these heterocycles have driven chemists to continue developing novel methods to access differentially substituted indoles[4] and pyrroles.[5] Over 100 years later, Larock's indole synthesis[6] (Scheme 1b) aptly highlighted the utility of transition-metal catalysis in the formation of aromatic heterocycles.[7] In the subsequent decade, palladium has continued to play a central role in this diverse reaction class.[8]



Scheme 1. Challenges in the synthesis of 2,3-aliphatic indoles.

More recently, an increasing number of examples have appeared in the literature featuring a transition metal catalyzed oxidative C–H bond functionalization event as a fundamental step in the formation of various heterocycles.[9] This mode of reactivity is particularly desirable since the cost to install activating functionality, such as halides, is obviated. A particular focus has been placed on annulative couplings of nitrogen-substituted aryl or vinyl groups with internal alkynes catalyzed by rhodium(III) complexes.[10] Our group has previously exploited this approach, developing reactions forming indoles[11,12a] (Scheme 1c), pyrroles,[12a] isoquinolines,[13a] and isoquinolones.[14a]

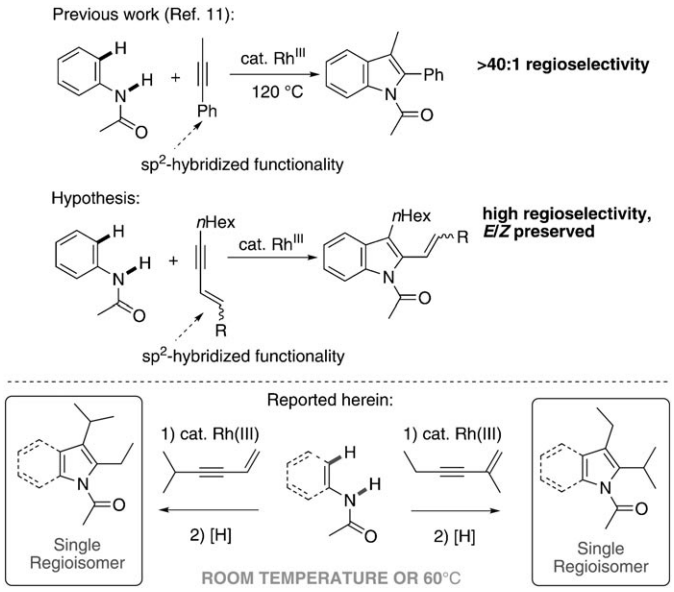
Despite these recent advances, a pharmaceutically relevant target[15] that continues to represent a significant synthetic challenge is the unsymmetrical 2,3-aliphatic-substituted indole (Scheme 1). To the best of our knowledge, all methods for constructing indoles with 2,3-aliphatic substitution other than methyl require multistep procedures, and the opposite C2/C3 regioisomer cannot be accessed by the same method.[4] In the context of rhodium(III)-catalyzed annulations, the difficulties associated with this substrate class derive from poor regioselectivity in the 1,2-migratory insertion across unsymmetrical aliphatic-substituted internal alkynes as well as rate inhibition by dialkyl-substituted internal alkynes.[12a]

Previous studies on the mechanism of our indole-forming reaction revealed that, while there is little influence from steric effects in the alkyne insertion event, this step is largely controlled by electronic effects.[12a] Therefore, in cases we have investigated in which there is one aryl (or sp^2 hybridized) substituent on the alkyne, this group is delivered proximal to the indole nitrogen atom with very high regioselectivity.[16] On the basis of these results a working hypothesis was conceived in which an enyne would function as a coupling partner with a bias for highly regioselective alkyne insertion leading to the production of a C2-vinyl-substituted heterocycle (Scheme 2). Herein, we report the realization of this goal, namely the ability to control which regioisomer is obtained by employing the appropriate enyne, and formation of unsymmetrical 2,3-aliphatic-substituted indoles and pyrroles by facile hydrogenation of the resulting alkene at the C2 position of the heterocycle. The nonhygroscopic, bench-weighable complex $[Cp^*Rh(MeCN)_3](SbF_6)_2$ catalyzed the annulation reaction under mild reaction conditions (20–60 °C), required no inert atmosphere, and displayed broad substrate scope with respect to the formation of both indoles and pyrroles.[17]

Our studies were initiated by the reaction of an enyne with acetanilide under our first-generation reaction conditions.[11] Despite a low yield of the isolated product (11%), the reaction yielded exclusively the desired 2-alkenyl indole regioisomer (Table 1, entry 1). The incompatibility of enynes with acetanilide under more mild reaction conditions (entry 2) led us to examine a wide variety of anilides,[18]

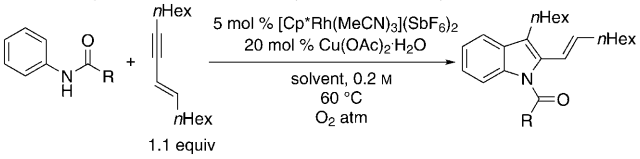
[*] M. P. Huestis,[+] L. Chan, D. R. Stuart, Prof. Dr. K. Fagnou
Department of Chemistry, University of Ottawa
10 Marie Curie, Ottawa, ON K1N 6N5 (Canada)
E-mail: malcolm.huestis@gmail.com
[+] Current address: Discovery Chemistry, Genentech, Inc.
1 DNA Way, South San Francisco, CA 94080 (USA)
[†] Deceased November 11, 2009.

[**] NSERC, University of Ottawa, The Sloan Foundation, Merck-Frosst, Amgen, Eli Lilly, and AstraZeneca are acknowledged for financial support. We thank Derek J. Schipper is for valuable discussions.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201006381.



Scheme 2. The vinyl moiety as an element of regiocontrol.

Table 1: Optimization of indole synthesis with enynes.[a]

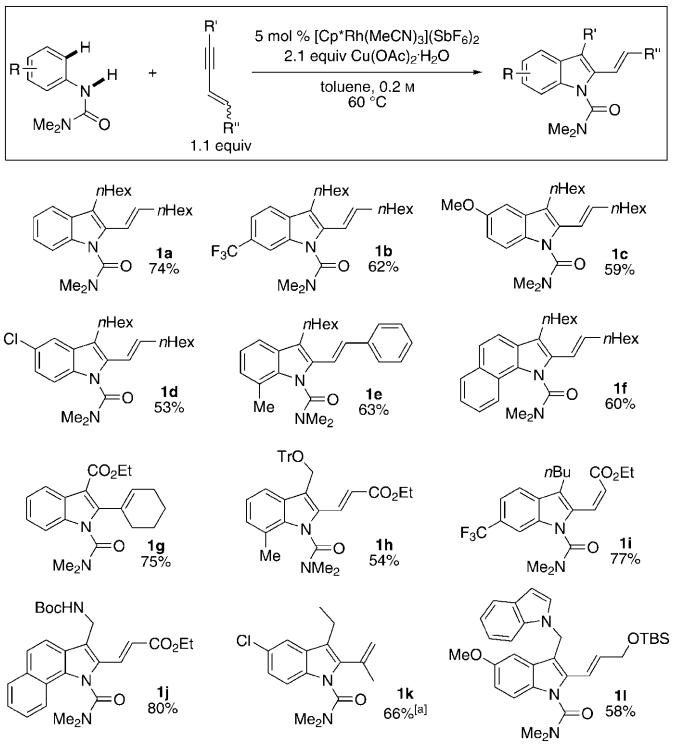


Entry	R	solvent	Yield [%][b]
1	Me	*t*-AmOH	(11)[c]
2	Me	*t*-AmOH	n.r.
3	NHMe	*t*-AmOH	n.r.
4	NEt_2	*t*-AmOH	7[d]
5	NMe_2	*t*-AmOH	16[d] (15)
6	NMe_2	acetone	14
7	NMe_2	*i*PrOAc	35
8	NMe_2	toluene	46 (48)
9	NMe_2	toluene	57[e]
10	NMe_2	toluene	76 (74)[e,f]

[a] Reaction conditions: Anilide (1 equiv), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol%), and $Cu(OAc)_2 \cdot H_2O$ (0.2 or 2.1 equiv) were placed in a test tube, a solution of enyne (1.1 equiv) in solvent (0.2 M) was added. The test tube was capped with a septum, fitted with an oxygen balloon, and the mixture was stirred at 60°C overnight. [b] Yields determined by GC analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard, and the yields of the isolated products are given in parentheses. [c] Reaction performed at 120°C with 2.1 equiv $Cu(OAc)_2 \cdot H_2O$ in place of oxygen atmosphere. [d] Reaction performed at 80°C and yield was determined by ^1H NMR analysis. [e] $Cu(OAc)_2 \cdot H_2O$ was ground with a mortar and pestle. [f] 2.1 equiv of $Cu(OAc)_2 \cdot H_2O$ without an oxygen atmosphere. *t*-AmOH = 2-methyl-2-butanol, n.r. = no reaction.

eventually revealing *N*-aryl ureas as competent substrates for the desired coupling (entries 3–5).[9a] Thus, reaction of *N*,*N*-dimethyl-*N*′-phenylurea afforded the target 2-alkenyl indole in 15% yield as a single regioisomer (entry 5). The reaction outcome was significantly influenced by changes in solvent (entries 5–8), guiding us to a 46% yield with toluene (entry 8). Finely powered copper(II) acetate provided an additional improvement (entry 9), and stoichiometric amounts secured the final reaction conditions (entry 10). Peroxides can also be used in place of metal or atmospheric oxidants.[19]

Under the optimal reaction reaction conditions, a variety of 2-alkenylindoles were constructed (Scheme 3). A number of functional groups were compatible on the benzo ring, such

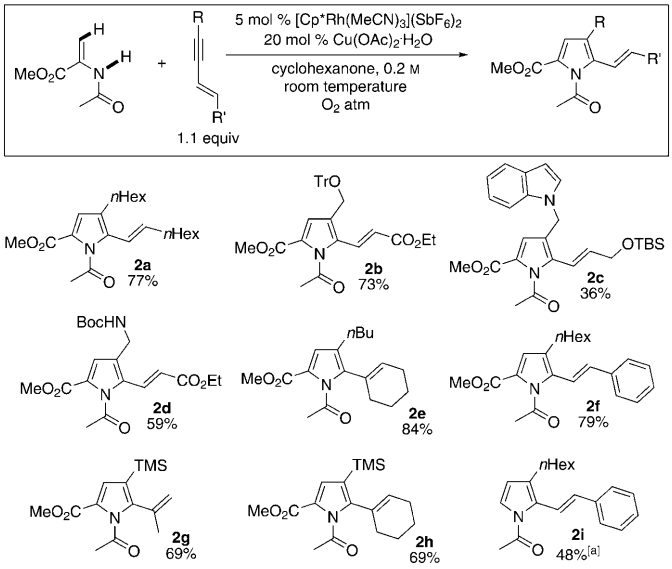


Scheme 3. Scope of the rhodium-catalyzed 2-alkenylindole formation. Reaction conditions: *N*-aryl urea (1 equiv), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol%), and $Cu(OAc)_2 \cdot H_2O$ (2.1 equiv) were placed in a test tube, a solution of enyne (1.1 equiv) in toluene (0.2 M) was added, and the mixture was stirred at 60°C overnight. [a] Employed 3 equiv of enyne. Boc = *tert*-butylcarbamate, TBS = *tert*-butyldimethylsilyl, Tr = triphenylmethyl.

as *m*-trifluoromethyl, *p*-methoxy, *p*-chloro, *o*-methyl, and 1-naphthyl (**1b**–**1f**). Compounds **1g**–**1j** not only demonstrate that α,β-unsaturated esters were tolerated, but also *tert*-butylcarbamate-protected amines and triphenylmethyl ethers. Notably, *Z* alkenes can be employed without evidence of olefin isomerization (**1i**) and 2,2-disubstituted alkenes function as well (**1k**). Finally, an allylic alcohol, protected as the *tert*-butyldimethylsilyl ether, was also installed alongside another aromatic heterocycle (**1l**).

Extension of the enyne chemistry to the synthesis of 2-alkenyl pyrroles was accomplished at room temperature using an enamide coupling partner. During reaction development we found that when the inexpensive cyclohexanone[20] was used as a solvent, it provided superior yields to our previously reported conditions employing acetone.[12a,18] Consistent with the indole chemistry, triphenylmethyl and *tert*-butyldimethylsilyl ethers were well tolerated on the enyne

coupling partner (Scheme 4; **2b** and **2c**), as were *tert*-butylcarbamate-protected amines (**2d**). A pyrrole having a styryl substituent at C2 was also prepared (**2f**), and



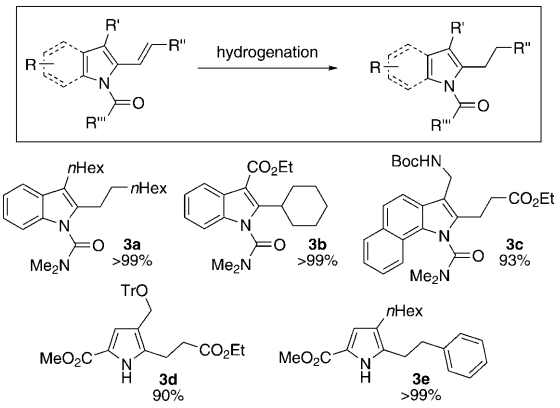
Scheme 4. Scope of the rhodium-catalyzed 2-alkenylpyrrole formation. Reactions conditions: methyl 2-acetamidoacrylate (1 equiv), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol%), and $Cu(OAc)_2.H_2O$ (20 mol%), were placed in a test tube and a solution of enyne (1.1 equiv) in cyclohexanone (0.2 M) was added. The reaction vessel was purged with oxygen and stirred overnight. [a] *N*-Vinylacetamide (3 equiv) was used as coupling partner. TMS = trimethylsilyl.

N-vinylacetamide also participates as the enamide component, providing direct access to 2,3-disubstituted pyrroles, albeit in diminished yield (**2i**). Access to pyrroles not possessing functionality at C3 was possible through the use of TMS-functionalized enynes (**2g** and **2h**).[21]

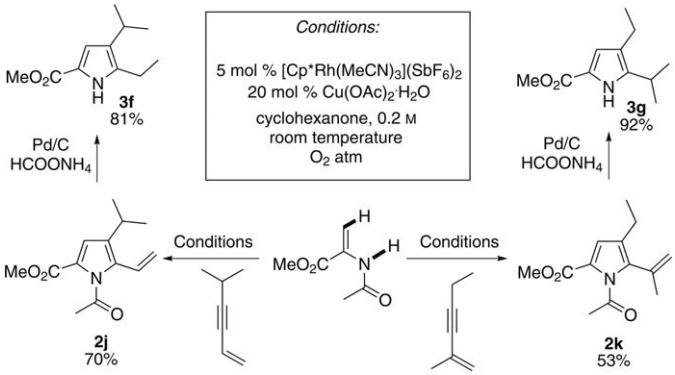
In accordance with our desired goal of obtaining single regioisomers of unsymmetrical 2,3-aliphatic-substituted indoles and pyrroles, we secured conditions for the efficient hydrogenation of the resultant compounds having alkene substituents at C2 (Scheme 5). Reduction of the 2-alkenylindoles proved to be facile under standard hydrogenation conditions with Pd/C and H_2 atmosphere in ethanol at room temperature (Scheme 5; **3a**–**3c**). For the reduction of the 2-alkenylpyrroles, ammonium formate was employed as the hydrogen source in refluxing ethanol (**3d**–**3e**). In these cases, loss of the *N*-acetyl group occurs concomitantly with alkene hydrogenation.

To additionally establish the power of the methodology, two members of the regioisomeric series represented in Scheme 6 were prepared as single regioisomers. Coupling of the enamide with 5-methylhex-1-en-3-yne or 2-methyl-1-en-3-yne provided pyrrole **2j** or **2k**, respectively, as single regioisomers. Hydrogenation under our established conditions then provided 2-ethyl-3-isopropylpyrrole (**3f**) or 3-ethyl-2-isopropylpyrrole (**3g**) as single regioisomers.[22]

Finally, conditions for removal of the robust dimethylurea protecting group from the indole series were developed.[23]

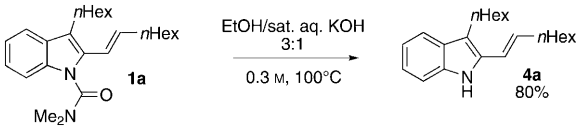


Scheme 5. Hydrogenation of C2-alkenylindoles and pyrroles. Reaction conditions: Indole (1 equiv) and 10% Pd/C (5 mol%), were dissolved in EtOH under an atmosphere of hydrogen (1 atm) and stirred overnight, or pyrrole (1 equiv), 10% Pd/C (5 mol%) and ammonium formate (10 equiv) were dissolved in EtOH and refluxed overnight under an argon atmosphere.



Scheme 6. Preparation of a C2/C3 regioisomeric series.

After considerable optimization, we found that heating compound **1a** in ethanol/saturated aqueous potassium hydroxide (3:1) in a sealed vessel delivered the 2-alkenyl indole **4a** in 80% yield [Eq. (1)].



(1)

In conclusion, unsymmetrical 2,3-aliphatic-substituted indoles and pyrroles may be accessed under mild conditions by the rhodium-catalyzed union of enynes with simple nitrogen-containing starting materials, and subsequent facile hydrogenation. The mild nature of the reaction (room temperature or 60 °C) should facilitate its practical application in settings that feature multiple labile functional groups. This method also provides direct access to 2-alkenyl indoles and pyrroles, scaffolds whose value is demonstrated by the recent interest in direct C2 alkenylations.[24]

Received: October 11, 2010
Published online: December 29, 2010

Keywords: enynes · homogeneous catalysis · nitrogen heterocycles · regioselectivity · rhodium

[1] a) E. Fischer, F. Jourdan, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241 – 2245; b) E. Fischer, O. Hess, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 559 – 568; c) S. Banerjee, E. Barnea, A. L. Odom, *Organometallics* **2008**, *27*, 1005 – 1014.

[2] a) L. Knorr, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2863 – 2870; b) C. Paal, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2756 – 2767; c) L. Knorr, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 299 – 311; d) C. Paal, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 367 – 371.

[3] a) *Name Reactions in Heterocyclic Chemistry* (Ed.: J.-J. Li), Wiley, Hoboken, New Jersey, **2005**; b) *Heterocyclic Chemistry* (Eds.: J. A. Joule, K. Mills), Blackwell Science, Oxford, **2000**.

[4] a) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875 – 2911; b) K. Krüger (née Alex), A. Tillack, M. Beller, *Adv. Synth. Catal.* **2008**, *350*, 2153 – 2167; c) L. Ackermann, *Synlett* **2007**, 507 – 526.

[5] T. L. Gilchrist, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2849 – 2866.

[6] a) R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6689 – 6690; b) R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* **1998**, *63*, 7652 – 7662; For an analogous pyrrole-formating reaction, see: c) M. L. Crawley, I. Goljer, D. J. Jenkins, J. F. Mehlmann, L. Nogle, R. Dooley, P. E. Mahaney, *Org. Lett.* **2006**, *8*, 5837 – 5840.

[7] a) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127 – 2198; b) L. S. Hegedus, *Angew. Chem.* **1988**, *100*, 1147 – 1161; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1113 – 1126.

[8] a) G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, *104*, 2285 – 2309; b) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873 – 2920; c) T. Sakamoto, Y. Kondo, H. Yamanaka, *Heterocycles* **1988**, *27*, 2225 – 2249.

[9] For examples with Pd^{II}, see: a) C. E. Houlden, C. D. Bailey, J. G. Ford, M. R. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *J. Am. Chem. Soc.* **2008**, *130*, 10066 – 10067; b) C. E. Houlden, M. Hutchby, C. D. Bailey, J. G. Ford, S. N. G. Tyler, M. R. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem.* **2009**, *121*, 1862 – 1865; *Angew. Chem. Int. Ed.* **2009**, *48*, 1830 – 1833; c) S. Würtz, S. Rakshit, J. J. Neumann, T. Dröge, F. Glorius, *Angew. Chem.* **2008**, *120*, 7340 – 7343; *Angew. Chem. Int. Ed.* **2008**, *47*, 7230 – 7233; d) Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding, Y. Cui, N. Jiao, *Angew. Chem.* **2009**, *121*, 4642 – 4646; *Angew. Chem. Int. Ed.* **2009**, *48*, 4572 – 4576; e) Z. Shi, Y. Cui, N. Jiao, *Org. Lett.* **2010**, *12*, 2908 – 2911; f) S. Ding, Z. Shi, N. Jiao, *Org. Lett.* **2010**, *12*, 1540 – 1543; g) Y. Tan, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 3676 – 3677. For an example with Cu^{II}, see: h) R. Bernini, G. Fabrizi, A. Sferrazza, S. Cacchi, *Angew. Chem.* **2009**, *121*, 8222 – 8225; *Angew. Chem. Int. Ed.* **2009**, *48*, 8078 – 8081. For examples with catalytic Rh^{III}, see: i) K. Ueura, T. Satoh, M. Miura, *Org. Lett.* **2007**, *9*, 1407 – 1409; j) K. Ueura, T. Satoh, M. Miura, *J. Org. Chem.* **2007**, *72*, 5362 – 5367; k) N. Umeda, H. Tsurugi, T. Satoh, M. Miura, *Angew. Chem.* **2008**, *120*, 4083 – 4086; *Angew. Chem. Int. Ed.* **2008**, *47*, 4019 – 4022; l) M. Shimizu, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2009**, *74*, 3478 – 3483; m) S. Mochida, M. Shimizu, K. Hirano, T. Satoh, M. Miura, *Chem. Asian J.* **2010**, *5*, 847 – 851; n) Y. Su, M. Zhao, K. Han, G. Song, X. Li, *Org. Lett.* **2010**, *12*, 5462 – 5465. For examples with stoichiometric Rh^{III}, see: o) L. Li, W. W. Brennessel, W. D. Jones, *J. Am. Chem. Soc.* **2008**, *130*, 12414 – 12419; p) L. Li, W. W. Brennessel, W. D. Jones, *Organometallics* **2009**, *28*, 3492 – 3500.

[10] A recent review: T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212 – 11222.

[11] D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 16474 – 16475.

[12] a) D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* **2010**, DOI: 10.1021/ja1082624 ; b) S. Rakshit, F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9585 – 9587.

[13] a) N. Guimond, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 12050 – 12051; b) T. Fukutani, N. Umeda, K. Hirano, T. Satoh, M. Miura, *Chem. Commun.* **2009**, 5141 – 5143.

[14] a) N. Guimond, C. Gouliaras, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6908 – 6909; b) S. Mochida, N. Umeda, K. Hirano, T. Satoh, M. Miura, *Chem. Lett.* **2010**, *39*, 744 – 746; c) T. K. Hyster, T. Rovis, *J. Am. Chem. Soc.* **2010**, *132*, 10565 – 10569; d) G. Song, D. Chen, C.-L. Pan, R. H. Crabtree, X. Li, *J. Org. Chem.* **2010**, *75*, 7487 – 7490.

[15] Representative commercial drugs with this structural motif: Eccoxolac, see: a) R. Martel, US 4533551, **1985**; b) L. G. Humber, C. A. Demerson, P. Swaminathan, *J. Med. Chem.* **1986**, *29*, 871 – 874; Moban, see: c) M. Finizio, US 4065453, **1977**; d) D. E. Comings, B. Kovacs, J. Macmurry, US 0156078, **2002**; Indosin-SR, see: e) A. Robert, US 4061742, **1977**; f) R. E. Dempski, G. N. Mehta, J. C. Saboe, US 4173626, **1979**; g) R. Brouard, G. Remuzzi, WO 002556, **2000**.

[16] When 1-phenylpropyne is employed as a coupling partner, the regioselectivity for C2-phenyl/C3-phenylindole is $>40:1$ by GC–MS. For 3-phenyl propiolate esters, the phenyl group is delivered proximal to the indole or the pyrrole nitrogen over the ester moiety, see Ref. [12].

[17] $[Cp^*Rh(MeCN)_3](SbF_6)_2$ will be available shortly from Strem Chemicals, Inc., but can be easily prepared in one step from commercially available $[\{Cp^*RhCl_2\}_2]$ and $AgSbF_6$. See the Supporting Information.

[18] For full details of reaction development, see the Supporting Information.

[19] It was later discovered that *tert*-butylhydroperoxide could be used in this reaction instead of metal or atmospheric re-oxidants (70% yield of isolated product, see the Supporting Information).

[20] According to Sigma–Aldrich, ACS reagent grade cyclohexanone is $39 L USD, while acetone is $29 L USD.

[21] For cleavage of the aryl-TMS linkage on compound **2h**, see the Supporting Information.

[22] Use of 2-methylhex-3-yne resulted in a 1:1 mixture of inseparable regioisomers; see the Supporting Information for additional details.

[23] Literature conditions did not preserve the stereochemical integrity of the C2 double bond: C. G. Hartung, A. Fecher, B. Chapell, V. Snieckus, *Org. Lett.* **2003**, *5*, 1899 – 1902.

[24] a) N. P. Grimster, C. Gauntlett, C. R. A. Godfrey, M. J. Gaunt, *Angew. Chem.* **2005**, *117*, 3185 – 3189; *Angew. Chem. Int. Ed.* **2005**, *44*, 3125 – 3129; b) E. M. Beck, N. P. Grimster, R. Hatley, M. J. Gaunt, *J. Am. Chem. Soc.* **2006**, *128*, 2528 – 2529; c) E. M. Beck, R. Hatley, M. J. Gaunt, *Angew. Chem.* **2008**, *120*, 3046 – 3049; *Angew. Chem. Int. Ed.* **2008**, *47*, 3004 – 3007; d) Y. Nakao, K. S. Kanyiva, S. Oda, T. Hiyama, *J. Am. Chem. Soc.* **2006**, *128*, 8146 – 8147; e) A. García-Rubia, R. G. Arrayás, J. C. Carretero, *Angew. Chem.* **2009**, *121*, 6633 – 6637; *Angew. Chem. Int. Ed.* **2009**, *48*, 6511 – 6515; f) D. J. Schipper, M. Hutchinson, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6910 – 6911; g) F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9982 – 9983; h) R. Gao, C. S. Yi, *J. Org. Chem.* **2010**, *75*, 3144 – 3146.

