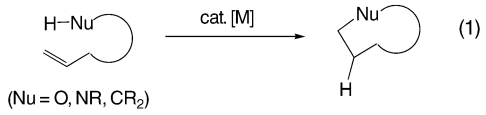
Alkene Functionalization

Anti-Markovnikov Hydrofunctionalization of Olefins Mediated by Rhodium–Porphyrin Complexes**

*Melanie S. Sanford and John T. Groves**

The development of catalysts for the anti-Markovnikov addition of H-Nu (H-Nu = H-NR_2, H-OR) to olefins could provide an atom-economical approach to amines, ethers, and heterocyclic compounds [Eq. (1)].[1] These products are of



(1)

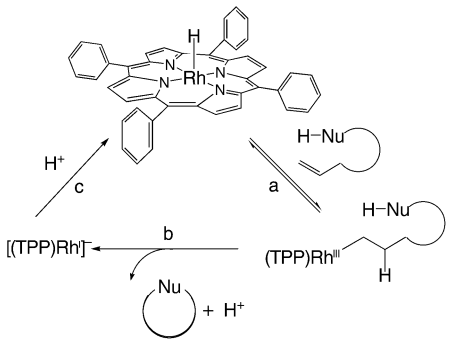
significant utility to both the chemical and pharmaceutical industries, and as a result the development of new catalysts for this type of transformation has been identified as one of the "top ten challenges for catalysis".[2] However, despite considerable effort in this area over the past two decades,[3–5] general and selective processes and catalysts for such transformations have remained elusive. This report describes the rational design of a new mechanistic pathway, which offers a potentially general solution to anti-Markovnikov olefin hydrofunctionalization.

We envisaged a three-step catalytic cycle for intramolecular anti-Markovnikov olefin hydrofunctionalization involving: a) olefin insertion into a [Rh]–H bond, b) intramolecular functionalization of the resulting σ-alkyl adduct, and c) protonation of the resulting $[Rh^I]^-$ species to regenerate the starting [Rh]-H complex (Scheme 1). We anticipated that the regioselectivity of the reaction would be dictated by the olefin-insertion step, which should favor the less-substituted metal σ-alkyl species[6] and thereby selectively provide the anti-Markovnikov product. We report herein that (TPP)Rh-H (TPP = tetraphenylporphyrin) efficiently mediates each step of this postulated catalytic cycle to afford heterocyclic products with extremely high (>97%) anti-Markovnikov regioselectivity. The functionalization step serves as a rare and unusually general example of direct $C(sp^3)$–heteroatom bond-forming reductive elimination.[7,8]

[*] Dr. M. S. Sanford, Prof. J. T. Groves
Department of Chemistry, Princeton University
Princeton, NJ 08544 (USA)
Fax: (+1) 626-564-9297
E-mail: jtgroves@princeton.edu

[**] This research was supported by the National Science Foundation (CHE 9814301). M.S.S. also thanks the NIH for a postdoctoral fellowship (GM64158-02).

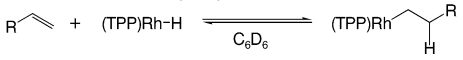
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

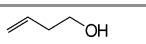
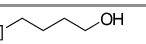
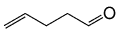
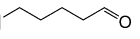
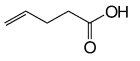
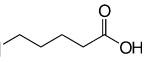
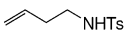
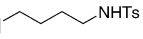
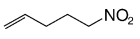
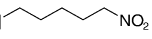


Scheme 1. Rhodium–porphyrin-mediated olefin hydrofunctionalization.

The first step of the process involves a reversible olefin insertion into (TPP)Rh-H to produce a σ-alkyl rhodium complex (Scheme 1, step a).[9] As summarized in Table 1, the desired reaction proceeded efficiently (within 1 h at 25 °C) to afford a variety of stable rhodium–alkyl products.[10] This transformation was highly regioselective, and in all cases the less-substituted metal–alkyl species was the only insertion product observed by ^{1}H NMR spectroscopy.[10] Furthermore, yields remained excellent in the presence of a diverse array of functional groups, including alcohols, aldehydes, carboxylic acids, sulfonamides, and nitroalkanes (Table 1, entries 1–5). This extraordinary functional-group tolerance is particularly notable because the insertion mechanism involves reactive Rh^{II} radicals as intermediates.[9,11]

Table 1: Olefin insertion into (TPP)Rh-H.[a]



Entry	Substrate	Product	Yield [%][b]
1			88
2			74
3			91
4			76
5			83

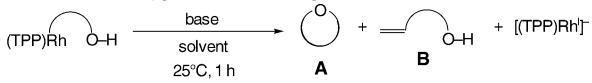
[a] Conditions: 25 °C; 12 h; [Rh] ~ 0.01 M; [olefin] ~ 0.10 M. In all cases the yield of the reaction was >90% as measured by ^{1}H NMR spectroscopy. [b] Yield of isolated product.

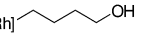
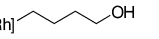
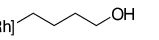
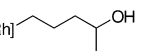
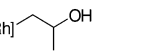
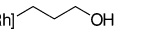
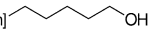
The second step involves reaction of the σ-alkyl–rhodium species with an internal nucleophile (Nu; Scheme 1, step b). C–Nu bond-forming reductive elimination reactions are extremely rare, particularly when the α carbon atom is sp^3 hybridized and/or β hydrogen atoms are present.[6,7,12] We note several previous examples of this transformation that involve methyl–rhodium–porphyrin complexes (e.g., Nu = PPh_3[12a] or Rh^I[12b]).

Initial investigations focused on the intramolecular cyclization of (TPP)Rh$(CH_2)_4$OH to produce THF (Table 2, entries 1-3). The pendant alcohol was not sufficiently nucleophilic to cleave the Rh–alkyl bond under neutral conditions. However, the addition of base led to rapid C–O

  DOI: 10.1002/ange.200351941

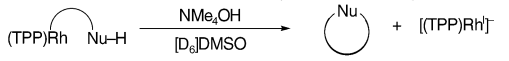
Table 2: Carbon–oxygen bond-forming reductive elimination.[a]

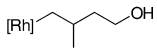
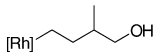
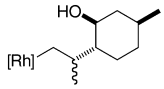
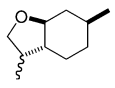
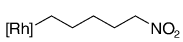
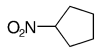
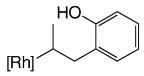
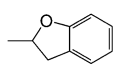
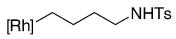
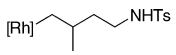
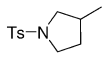
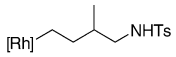
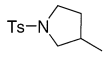


Entry	Substrate	Solvent	Base	Yield [%] A	B
1[b]		C_6D_6	KO*t*Bu	29	71
2[b]		[D$_6$]DMSO	KO*t*Bu	60	40
3[c]		[D$_6$]DMSO	NMe4OH	78	22
4[c]		[D$_6$]DMSO	NMe4OH	70	30
5[b,d]		C_6D_6	KO*t*Bu	>97	<3
6[c,e]		[D$_6$]DMSO	NMe_4OH	<3	>97
7[c]		[D$_6$]DMSO	NMe_4OH	<3	>97

[a] Reactions were quantitative by ^{1}H NMR spectroscopy and were characterized by integration of the ratio of the two organic products. Unless noted, Rh–alkyl substrates were prepared by insertion of the corresponding olefin into (TPP)Rh-H. [b] Conditions: [Rh] = 8.1 mM; [KO*t*Bu] = 16 mM; [[18]crown-6] = 16 mM. [c] Conditions: [Rh] = 8.1 mM; [NMe_4OH] = 24 mM. [d] Substrate prepared according to reference [13]. [e] Substrate prepared by alkylation of (TPP)Rh with $Br(CH_2)_3OH$.

Table 3: Formation of O and N heterocycles and nitropentane.[a]



Entry	Substrate	Product	Yield [%]
1[b]			73
2[b]			>95
3[b]			>95
4[c]			69
5[b,d]			53
6[c]			83
7[c]			92
8[c]			>95

[a] Reactions were monitored by ^{1}H NMR spectroscopy and proceeded quantitatively to give a mixture of the cyclized product and the elimination product (olefin). Yields were determined by integration of the ^{1}H NMR spectrum of the crude reaction mixture. Rh–alkyl substrates were prepared by insertion of the corresponding olefin into (TPP)Rh-H. [b] Conditions: 25 °C; 1 h; [Rh] = 8.1 mM; [NMe_4OH] = 24 mM. [c] Conditions: 70 °C; 12 h; [Rh] = 8.1 mM; [NMe_4OH] = 24 mM. [d] The elimination product was allylphenol.

bond-forming reductive elimination. THF was produced in 78% yield under optimized conditions ([D$_6$]DMSO, NMe_4OH (3 equiv); Table 2, entry 3). The only other organic product identified was 3-buten-1-ol, which is readily recycled under the hydrofunctionalization conditions. The Rh–porphyrin complex was converted into [(TPP)Rh^{I}]$^{-}$ quantitatively. The cyclization of β-hydroxyalkyl–Rh^{III} derivatives to produce epoxides also proceeded in high yield (>97%; Table 2, entry 5).[13] However, attempts to prepare four- and six-membered oxygen heterocycles by using this methodology were unsuccessful. Instead the corresponding olefins were the only organic products formed (Table 2, entries 6 and 7).[14]

Several pieces of evidence suggest that these unusual reductive eliminations, which involve the formation of a C–O bond, proceed by an S_N2 mechanism. First, the furan/olefin product ratio increased dramatically upon changing the solvent from C_6D_6 to [D$_6$]DMSO (Table 2, entries 1 and 2). Furthermore, modification of the nucleophile from a primary to a secondary alkoxide (Table 2, entries 3 and 4) led to a significant decrease in the ratio of the cyclic product to the 3-buten-1-ol. Both results are indicative of competing S_N2 and E_2 reactions, whereby the S_N2 transition state is favored in more polar solvents[15] and with less sterically hindered nucleophiles. Han has also shown that the cyclization of (TPP)Rh(CDH)CH(CH)$_3$OH (a deuterated analogue of the substrate in Table 2, entry 5) produces [D$_1$]propylene oxide with 100% inversion of stereochemistry at the α carbon atom.[13] This experiment clearly implicates an S_N2 mechanism that proceeds by backside attack at the carbon atom bonded to Rh (as opposed to precoordination of the alkoxide to the Rh center).[7] Importantly, the proposed mechanism is consistent with that of a closely related Rh^{III}/Rh^{I} alkyl-exchange reaction, which proceeds through an S_N2 pathway.[12b]

As summarized in Tables 2 and 3, C(sp^3)–Nu reductive elimination is extremely general in this system and could be applied to the formation of the C–O, C–N, and C–C bonds of a diverse range of cyclic compounds. Once again, the only organic products observed were the desired heterocycle (or carbocycle in the case of Table 3, entry 4) and the corresponding olefin. The Rh complex was quantitatively converted into [(TPP)Rh^{I}]$^{-}$. For example, α-, β-, and γ-substituted Rh–alkyl intermediates with pendant alcohol groups underwent cyclization to produce the corresponding tetrahydrofurans within 1 h at 25 °C (Table 3, entries 1–3). A phenol-substituted rhodium complex underwent facile cyclization at room temperature to give 2,3-dihydro-2-methylbenzofuran (Table 3, entry 5). The modest yield (53%) observed for this system is probably due to the S_N2 mechanism, which requires nucleophilic attack at a sterically hindered tertiary carbon center. Finally, the C–C bonds of cyclopentane (Table 3, entry 4) and C–N bonds of pyrrolidine derivatives (Table 3, entries 6–8) were also constructed readily by using this methodology. Although harsher conditions (70 °C, 12 h) were required relative to the analogous C–O bond-forming reactions, the yields and S_N2/E_2 product ratios remained excellent.

The final step of the catalytic cycle involves protonation of [(TPP)Rh^{I}]$^{-}$ to regenerate the (TPP)Rh-H catalyst (Scheme 1, step c). Nelson and Dimagno recently reported that the pK_a value of (TPP)Rh-H is approximately 11;[12a] therefore, as expected, the addition of excess trifluoroacetic acid to the crude reaction mixtures resulted in quantitative regeneration of (TPP)Rh-H.[16] This transformation com-

pletes the proposed catalytic cycle and makes it possible to recycle the expensive rhodium porphyrin.

In summary, we have developed and implemented a new, rational mechanistic approach to the design of catalysts for the anti-Markovnikov hydrofunctionalization of olefins. We have shown that (TPP)Rh-H mediates each step of the proposed catalytic cycle with high selectivity, and have demonstrated a new and remarkably general carbon–heteroatom bond-forming reductive elimination reaction. The reactions described herein do not yet constitute a working catalytic cycle. Preliminary attempts to carry out these transformations under catalytic conditions (e.g., with several phenol-based substrates and a variety of weak bases) have thus far been hampered by the incompatibility of step a with the polar solvents required for steps b and c. However, the reactions as performed do allow for the facile recycling of the valuable porphyrin–Rh-H complex. Additionally, we anticipate that the design principles presented herein will serve as a valuable foundation for the development of a new generation of regioselective olefin-hydrofunctionalization catalysts. Current efforts in our laboratories are aimed at improving these systems in terms of catalytic turnover through modification of the solvent system, as well as by steric or electronic perturbation of the porphyrin ligands. Efforts to circumvent reaction-medium limitations through the use of solid-supported Rh catalyst systems are also in progress.

Received: May 21, 2003
Revised: October 24, 2003 [Z51941]

Keywords: alkenes · hydroamination · porphyrinoids · reductive elimination · rhodium

[1] B. M. Trost, *Science* **1991**, *254*, 1471 – 1477.
[2] J. Haggin, *Chem. Eng. News* **1993**, *71(22)*, 23.
[3] a) C. M. Jensen, W. C. Trogler, *Science* **1986**, *233*, 1069 – 1071; b) D. Ramprasad, H. J. Yue, J. A. Marsella, *Inorg. Chem.* **1988**, *27*, 3151 – 3155.
[4] a) M. Utsunomiya, R. Kuwano, M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 5608 – 5609; b) M. Beller, C. Breindl, M. Eichberger, C. G. Hartung, J. Seayad, O. R. Thiel, A. Tillack, H. Trauthwein, *Synlett*, **2002**, *10*, 1579 – 1594; c) M. Beller, O. R. Thiel, H. Trauthwein, C. G. Hartung, *Chem. Eur. J.* **2000**, *6*, 2513 – 2522; d) M. Beller, H. Trauthwein, M. Eichberger, C. Breindl, T. E. Muller, *Eur. J. Inorg. Chem.* **1999**, 1121 – 1132; e) M. Beller, H. Trauthwein, M. Eichberger, C. Breindl, J. Herwig, T. E. Muller, O. R. Thiel, *Chem. Eur. J.* **1999**, *5*, 1306 – 1319.
[5] For an alternative approach, see: A. Seayad, M. Ahmed, H. Klein, R. Jackstell, T. Gross, M. Beller, *Science* **2002**, *297*, 1676 – 1678.
[6] R. H. Crabtree, *The Organometallic Chemistry of the Transition Metals*, 2nd ed., Wiley, New York, **2001**, chap. 7.
[7] For recent examples of direct carbon–heteroatom bond-forming reductive elimination under mild conditions, see: a) B. S. Williams, K. I. Goldberg, *J. Am. Chem. Soc.* **2001**, *123*, 2576 – 2587; b) J. F. Hartwig, *Acc. Chem. Res.* **1998**, *31*, 852 – 860; c) S. S. Stahl, J. A. Labinger, J. E. Bercaw, *Angew. Chem.* **1998**, *110*, 2298 – 2311; *Angew. Chem. Int. Ed.* **1998**, *37*, 2181 – 2192.
[8] Reductive elimination induced by oxidation is more common; for a recent example, see: a) B. L. Lin, C. R. Clough, G. L. Hillhouse, *J. Am. Chem. Soc.* **2002**, *124*, 2890 – 2891.
[9] The mechanism of this reaction (involving $[L]Rh^{II}$· intermediates) has been studied, but its scope and functional-group tolerance have not been reported. a) X. F. Fu, L. Basickes, B. B. Wayland, *Chem. Commun.* **2003**, 520 – 521; b) K. W. Mak, F. Xue, T. C. W. Mak, K. S. Chan, *J. Chem. Soc. Dalton Trans.* **1999**, 3333 – 3334; c) D. J. Anderson, R. Eisenberg, *Organometallics* **1996**, *15*, 1697 – 1706; d) R. S. Paonessa, N. C. Thomas, J. Halpern, *J. Am. Chem. Soc.* **1985**, *107*, 4333 – 4334;
[10] Products were identified by ^{1}H NMR spectroscopy based on ^{1}H–Rh coupling and on upfield shifts of the alkyl resonances.[9] The linear product was formed in situ in $>90\%$ yield, whereas the branched isomer was not detected; thus, the lower limit of regioselectivity corresponds to $\sim 97\%$.
[11] a) K. J. Delrossi, X. X. Xhang, B. B. Wayland, *J. Organomet. Chem.* **1995**, *504*, 47 – 56; b) B. B. Wayland, S. J. Ba, A. E. Sherry *J. Am. Chem. Soc.* **1991**, *113*, 5305 – 5311.
[12] a) A. P. Nelson, S. G. Dimagno, *J. Am. Chem. Soc.* **2000**, *122*, 8569 – 8570; b) J. P. Collman, J. I. Brauman, A. M. Madonik, *Organometallics* **1986**, *5*, 215 – 218.
[13] H.-Z. Han, Ph.D. Thesis, Princeton University, 1992.
[14] The origin of this effect is currently under investigation.
[15] K. A. Cooper, M. L. Dhar, E. D. Hughes, C. K. Ingold, B. J. MacNulty, L. I. Woolf, *J. Chem. Soc.* **1948**, 2043 – 2049.
[16] The addition of an excess of trifluoroacetic acid (~5 equiv relative to the base) to the crude cyclization reaction mixtures in C_6D_6 (e.g., Table 2, entry 1) or $[D_7]$DMF resulted in quantitative regeneration of (TPP)Rh-H. The analogous reaction in $[D_6]$DMSO produced a complex mixture of (TPP)Rh products owing to the apparent instability of (TPP)Rh-H in this medium.

