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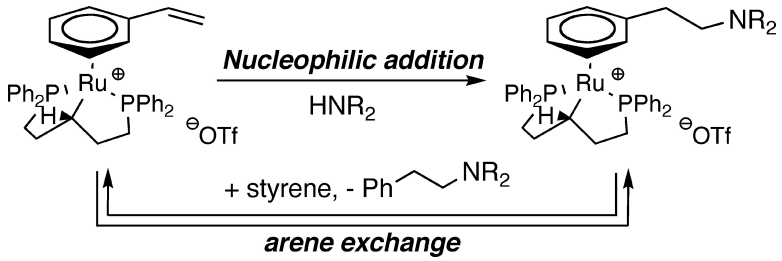

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Mechanistic Studies of Ruthenium-Catalyzed Anti-Markovnikov Hydroamination of Vinylarenes: Intermediates and Evidence for Catalysis through π-Arene Complexes

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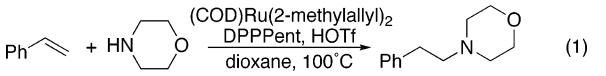
Catalytic hydroamination of alkenes is an addition process that allows control of regiochemistry and stereochemistry.[1] Several mechanisms for hydroamination of alkenes have been elucidated. One pathway occurs by activation of alkenes toward nucleophilic attack;[2] two additional pathways include N−H activation;[3] a third pathway occurs by imido complexes that undergo [2 + 2] reactions with olefins,[4] and a fourth pathway includes nucleophilic attack of an amine on an (η^3-arylethyl)Pd complex.[5]

Seeming unrelated to hydroamination at first, the stoichiometric reactivity of π-arene ligands has been widely investigated as a means to elaborate aromatic structures.[6] Although catalytic versions of these transformations of π-arene ligands would be highly desirable, only one catalytic process involving modification of an arene ligand was cited in a recent review describing π-arene complexes as catalysts.[7]

We report evidence that catalytic hydroamination and the reactions of π-arene complexes converge at our anti-Markovnikov addition of alkylamines to vinylarenes catalyzed by the combination of Ru(COD)(2-methylallyl)$_2$, DPPPent,[8] and TfOH (eq 1).[9] We show that these catalyst precursors generate an η^6-styrene complex, and we provide evidence that the anti-Markovnikov hydroamination catalyzed by this ruthenium system occurs by attack of amine on this η^6-styrene complex and exchange of π-arene ligands.



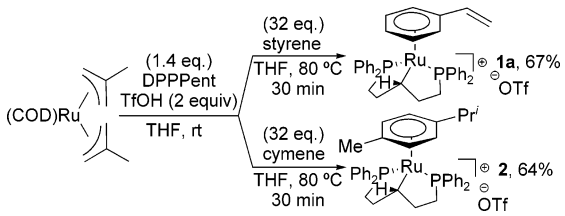
(1)

To deduce the mechanism of the hydroamination of vinylarenes catalyzed by Ru(COD)(2-methylallyl)$_2$, DPPPent, and TfOH, we studied the products generated by various combinations of the catalyst components, styrene, and morpholine. A mixture of Ru(COD)(2-methylallyl)$_2$, DPPPent, and TfOH and an excess of styrene in THF at 80 °C generated the new (η^6-styrene)ruthenium complex **1a** in Scheme 1. This complex was isolated in 67% yield as a pale yellow, crystalline solid. An analogous (η^6-cymene)-ruthenium complex **2** was prepared in 64% yield by the same reaction with cymene instead of styrene. A combination of protonolysis of the allyl groups, replacement of COD by the DPPPent ligand, metalation of the central carbon of the pentane backbone of the DPPPent ligand, and coordination of the arene to the PCP−ruthenium fragment generates **1a** and **2**.

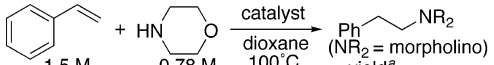
Complexes **1a** and **2** were characterized by ^{1}H, ^{13}C, and multinuclear 2D NMR spectroscopy, and **1a** was characterized by X-ray diffraction. The aromatic protons of **1a** resonated at 5.3−6.8 ppm, which is typical of transition-metal−arene complexes. The methine proton of the ligand backbone was unusually downfield (4.8 ppm), presumably from deshielding by the styrene ring.[10]

The structure of **1a** by X-ray diffraction (Figure S1) reveals the cyclometalated structure of the PCP ligand and the presence of the η^6-vinylarene ligand. The Ru−C(23) (2.198(3) Å) and Ru−styrene (2.253(3)−2.289(3) Å) bond lengths are similar to those of previous Ru−pincer and Ru−arene complexes.[11] The dihedral angle between the plane of the olefin and of the arene is only 3.7°, implying that the olefin remains conjugated with the arene.

Scheme 1



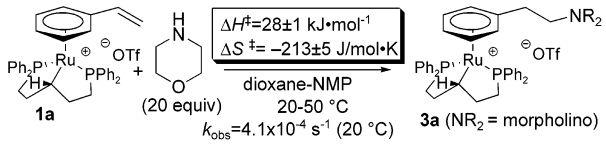
Scheme 2



cat.	15min	30min	1h	2h	5h
1a (5 mol%)	22%	40%	64%	80%	96%
2 (5 mol%)	10%	32%	56%	77%	94%
in situ[b]	9%	18%	40%	63%	87%

[a] Yield by GC. [b] Ru(COD)(2-methylallyl)$_2$ (5 mol %), DPPPent (7 mol %), TfOH (10 mol %).

Scheme 3



Isolated **1a** is competent as a catalyst for the hydroamination. The reaction of styrene with morpholine in the presence of 5 mol % of **1a** in dioxane at 100 °C occurred slightly faster than the reaction catalyzed by Ru(COD)(2-methylallyl)$_2$, DPPPent, and TfOH and afforded the same anti-Markovnikov adduct in high yield (Scheme 2). Cymene complex **2** also catalyzed the hydroamination reaction on a comparable time scale.

Complex **1a** reacted readily with morpholine. This reaction of **1a** with 20 equiv of morpholine in a mixture of dioxane and NMP formed the η^6-morpholinoethylarene complex **3a** at room temperature by nucleophilic attack at the terminus of the vinylarene (Scheme 3). Clearly, the fast rate of attack on the styrene results from the activation of the vinylarene by coordination to the metal. Complex **3a** was characterized by conventional NMR spectroscopic methods and by X-ray diffraction (Figure S2). The structure of the core of **3a** is nearly superimposable with the core of the styrene complex **1a**.

The most likely mechanism for the formation of **3a** is direct nucleophilic attack of morpholine on the terminus of the styrene.[12] Such a nucleophilic addition would occur through a zwitterionic intermediate in which the generated anion could be stabilized by

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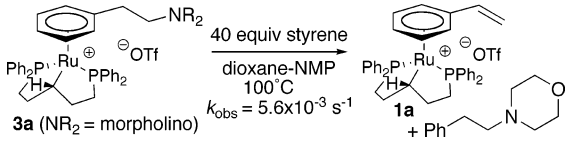
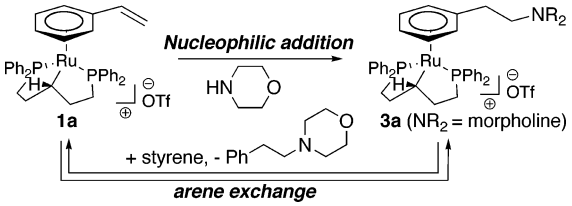
Scheme 4



Scheme 5



an (η^5-alkylidenecyclohexadienyl)ruthenium structure.[13] The reaction of a 15 mM solution of **1a** with 20 equiv of morpholine at 20 °C occurred with a pseudo-first-order k_{obs} of 4.1×10^{-4} s^{-1} (monitored by ^{31}P NMR spectroscopy) and a large $\Delta S^{\ddagger}$ of -213 ± 5 $J \cdot mol^{-1}$ s^{-1} ($T = 20-50$ °C). The large negative entropy of activation is similar to the values for the reaction of alkylamines with nitroalkenes.[14]

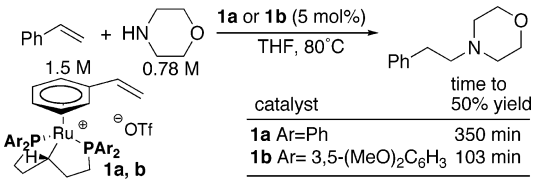
To create a catalytic cycle, the nucleophilic attack must be combined with a mild arene exchange process. This arene exchange was observed in several forms. First, treatment of **3a** with 40 equiv of styrene in a mixture of dioxane and NMP at 100 °C led to a smooth exchange of the free and coordinated arenes to afford styrene complex **1a** in the ratio of **1a**:**3a** of >20:1 (Scheme 4). Second, the reaction of cymene complex **2** with 40 equiv of styrene in a mixture of dioxane and NMP at 100 °C led to nearly complete formation of styrene complex **1a** within 30 min.[15]

A piece of spectroscopic data and two kinetic experiments connect the arene exchange with the catalytic process. First, the ^{31}P NMR spectra of the catalytic reaction of a 10:1 ratio of styrene and morpholine in dioxane and NMP contained resonances at 66.3 and at 67.0 ppm, which correspond to **1a** and **3a**, respectively, in ratio of ~75:25 throughout the reaction. Consistent with the presence of these catalytic intermediates in comparable concentrations, the arene exchange between a 15 mM solution of morpholinoalkylarene complex **3a** and 40 equiv of styrene occurred with a first-order rate constant ($k_{obs} = 5.6 \times 10^{-3}$ s^{-1}) that is comparable to that for nucleophilic addition of morpholine to the η^6-styrene complex **1a** at 100 °C ($k_{obs} = 6.2 \times 10^{-3}$ s^{-1}) deduced from the temperature-dependent rate data. Second, the reaction of styrene with morpholine catalyzed by cymene complex **2** occurred with a clear induction period (Figure S3), but the same reaction catalyzed by **1a** did not.

The catalytic cycle in Scheme 5 is consistent with these mechanistic data and accounts for the anti-Markovnikov hydroamination of vinylarenes catalyzed by isolated **1a** and by **1a** generated in situ from Ru(COD)(2-methylallyl)$_2$, DPPPent, and TfOH. This mechanism includes nucleophilic addition of amine on the (η^6-styrene)ruthenium complex **1a** to afford the anti-Markovnikov adduct and arene exchange of free styrene for the coordinated arene in (η^6-(2-phenylethyl)morpholine)ruthenium complex **3a**.

We sought to use these mechanistic data to improve the rates of the catalytic reaction. Our proposed mechanism suggests that a ruthenium complex that contains a ligand analogous to DPPPent, but with more electron-withdrawing aryl groups on the ligand, should undergo faster nucleophilic attack and that an analogous complex with more hindered aryl groups on the ligand should undergo faster arene exchange. To test these hypotheses, we conducted the catalytic reaction with a series of analogues of

Scheme 6



DPPPent. Consistent with our hypotheses, the reaction of styrene with morpholine was faster when catalyzed by the complex generated from a DPPPent analogue containing 3,5-dimethoxyphenyl groups. This reaction in THF at 80 °C was roughly 3.5 times faster with this catalyst **1b** than with the catalyst **1a**.

In summary, our mechanistic data strongly suggest that the ruthenium-catalyzed anti-Markovnikov hydroamination of arenes occurs by a new mechanism involving a rare example of catalytic chemistry through π-arene complexes. These findings suggest that further catalytic processes can be developed through Michael-type additions of nucleophiles other than amines to (η^6-alkenylarene)-metal complexes.[12] Detailed studies on the effect of the electronic and steric properties of phosphine ligand, further modification of the catalyst to improve activity, and the use of this metal fragment for further catalytic reactions through π-arene intermediates are in progress.

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Supporting Information Available: Experimental procedures, product characterization and X-ray diffraction data, and procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675.
(2) (a) Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070. (b) Brunet, J. J.; Cadena, M.; Chu, N. C.; Diallo, O.; Jacob, K.; Mothes, E. *Organometallics* **2004**, *23*, 1264.
(3) (a) Dorta, R.; Egli, P.; Zürcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857. (b) Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1988**, *110*, 6738. (c) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673. (d) Gagne, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275.
(4) (a) Walsh, P. J.; Baranger, A. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 1708. (b) Ackermann, L.; Kaspar, L. T.; Gschrei, C. J. *Org. Lett.* **2004**, *6*, 2515. (c) Anderson, L. L.; Arnold, J.; Bergman, R. G. *Org. Lett.* **2004**, *6*, 2519.
(5) Nettekoven, U.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1166.
(6) Kündig, E. P. *Transition Metal Arene π-Complexes in Organic Synthesis and Catalysts*; Springer-Verlag: Heidelberg, Germany, 2004.
(7) (a) Rigby, J. H.; Kondratenko, M. A. In *Transition Metal Arene π-Complexes in Organic Synthesis and Catalysts*; Kündig, E. P., Ed.; Springer-Verlag: Heidelberg, Germany, 2004. (b) Houghton, R. P.; Voyle, M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 925.
(8) DPPPent = bis(diphenylphosphino)pentane.
(9) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 2702.
(10) Gusev, D. G.; Lough, A. J. *Organometallics* **2002**, *21*, 5091.
(11) de la Ríos, I.; Tenorio, M. J.; Tenorio, M. A. J.; Puerta, M. C.; Valerga, P. *J. Organomet. Chem.* **1996**, *525*, 57.
(12) (a) Semmelhack, M. F.; Seufert, W.; Keller, L. *J. Am. Chem. Soc.* **1980**, *102*, 6584. (b) Davies, S. G.; Furtado, O. M. L. R.; Hepworth, D.; Loveridge, T. *Synlett* **1995**, 69. (c) Gibson, S. E.; Gil, R.; Prechtl, F.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1007. (d) Moriarty, R. M.; Enache, L. A.; Gilardi, R.; Gould, G. L.; Wink, D. J. *Chem. Commun.* **1998**, 1155.
(13) (a) Oh, H. K.; Yang, J. H.; Lee, H. W.; Lee, I. *J. Org. Chem.* **2000**, *65*, 5391. (b) Pipoh, R.; van Eldik, R. *Inorg. Chim. Acta* **1994**, *222*, 207. (c) Popov, A. F.; Perepichka, I. F.; Kostenko, L. I. *J. Chem. Soc., Perkin Trans. 2* **1989**, 395.
(14) See ref 13b.
(15) NMP−dioxane mixed solvent was employed in these stoichiometric reactions since Ru complexes **1a** and **2** were insoluble in dioxane at room temperature.

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