J|A|C|S
COMMUNICATIONS

Published on Web 12/15/2001

Ruthenium-Catalyzed Intramolecular Oxidative Amination of Aminoalkenes Enables Rapid Synthesis of Cyclic Imines

Teruyuki Kondo, Takumi Okada, and Take-aki Mitsudo*

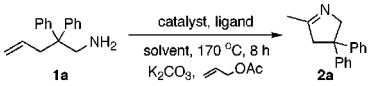
Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

Received September 6, 2001; Revised Manuscript Received November 12, 2001

Transition-metal complex-catalyzed cyclization of aminoalkynes (known as the intramolecular hydroamination) has proven to be a particularly valuable route to a wide variety of unsaturated nitrogen heterocycles such as cyclic imines, enamines, pyrroles, and indoles (Scheme 1, path a).[1] Many transition-metal catalysts[2] as well as lanthanide catalysts[3] can realize this transformation. Similar hydroamination of aminoalkenes to pyrrolidines and piperidines has also been reported (path b);[4,5] however, this cyclization of aminoalkenes is more difficult to achieve than the cyclization of aminoalkynes.[1b] Moreover, a related but less common process is the oxidative amination of alkenes. If intramolecular oxidative amination, instead of simple hydroamination, of aminoalkenes could be accomplished by transition-metal catalysts, synthetically useful cyclic imines could be directly obtained from versatile aminoalkenes without the use of expensive aminoalkynes (path c). Much work has recently been done on the transition-metal complex-catalyzed *intermolecular* oxidative amination of activated and/or electron-deficient alkenes,[6] such as styrenes,[6a,c,d,f] vinylpyridines,[6b] and acrylic compounds;[6e,g,h] however, little is known about the transition-metal complex-catalyzed *intramolecular* oxidative amination of aminoalkenes,[7] except for the catalytic cyclization of 2-vinyl and/or 2-allylanilines to indoles.[8]

Our recent study on the synthesis of novel ruthenium(0) amine complexes[9] and ruthenium-catalyzed hydroamination reactions[10] as well as ruthenium-catalyzed oxidative transformations[11] prompted us to develop the first ruthenium-catalyzed oxidative amination of aminoalkenes to the corresponding cyclic imines (path c). After many trials, we finally found that a novel catalyst system of $[RuCl_2(CO)_3]_2$/dppp (dppp = 1,3-bis(diphenylphosphino)propane) when used concomitantly with K_2CO_3 and allyl acetate in *N*-methylpiperidine is highly effective for the direct synthesis of cyclic imines from general aminoalkenes.

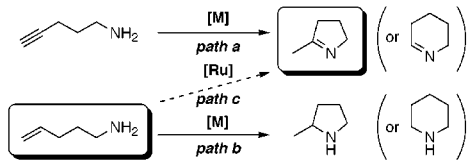
The effects of the solvents, ligands, catalysts, and reaction conditions were first examined in the synthesis of 4,4-diphenyl-2-methyl-1-pyrroline (**2a**) by the oxidative amination of 2,2-diphenyl-4-pentenyl-1-amine (**1a**) (eq 1).



(1)

An appropriate solvent and phosphorus ligand were critical for the success of the present reaction. Among the solvents examined (THF, toluene, acetonitrile, and *N*-methylpiperidine) using our previously reported $RuCl_2(PPh_3)_3$ catalyst with K_2CO_3 and allyl acetate,[11] *N*-methylpiperidine gave the best results.[12] Next, using $RuCl_3 \cdot 3H_2O$ as a catalyst, bidentate phosphine, especially dppp, was found to be the most effective ligand. Several ruthenium complexes, such as $Ru_3(CO)_{12}$ (yield of **2a**, 72%), Ru(η^4-cod)(η^6-cot) [cod = 1,5-cyclooctadiene, cot = 1,3,5-cyclooctatriene] (75%),

Scheme 1



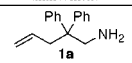
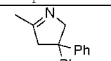
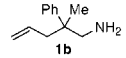
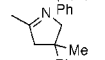
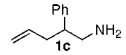
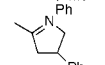
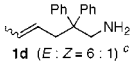
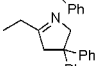
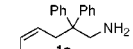
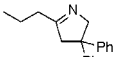
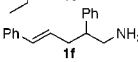
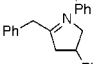
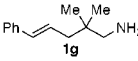
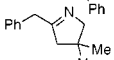
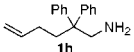
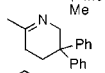
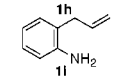
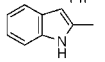
$[Ru(\eta^6\text{-}C_6H_6)Cl_2]_2$ (71%), $[Cp^*RuCl_2]_2$ (69%), and $CpRuCl(CO)_2$ (51%), also showed good to high catalytic activities under the present reaction conditions (with dppp in *N*-methylpiperidine). Ultimately, treatment of **1a** with 2 mol % of $[RuCl_2(CO)_3]_2$ and 5 mol % of dppp in the presence of K_2CO_3 and allyl acetate in *N*-methylpiperidine at 140 °C for 8 h gave the corresponding cyclic imine **2a** in quantitative yield (>99%). In addition to ruthenium, only $[RhCl(CO)_2]_2$ showed moderate catalytic activity (43%). With $PdCl_2$ and K_2PtCl_4[4e] catalysts, the *N*,*N*-diallylation of aminoalkene **1a** with allyl acetate predominantly proceeded, and the desired **2a** was not obtained at all.

The concomitant use of K_2CO_3 and allyl acetate is indispensable for the present reaction. For example, in the absence of allyl acetate, competitive olefin isomerization of **1a** to (*E*)-2,2-diphenyl-3-pentenyl-1-amine (**3a**), which is totally unreactive toward both simple intramolecular hydroamination and oxidative amination reactions, constitutes the major reaction. In the absence of K_2CO_3, the corresponding acetamide (**4a**) was obtained by acetylation of **1a** with allyl acetate. Na_2CO_3 and/or NEt_3 in place of K_2CO_3 drastically decreased both the yield and selectivity of **2a**.

The results obtained in the $[RuCl_2(CO)_3]_2$/dppp-catalyzed oxidative amination of several aminoalkenes (**1**) are summarized in Table 1. The only byproduct was a small amount of the corresponding nitriles which was obtained by the dehydrogenation of aminoalkenes (vide infra). The present process can regioselectively form five- and six-membered cyclic imines. Interestingly, a dramatic rate enhancement was observed in *gem*-disubstituted aminoalkenes at the 2-position, and almost no reaction occurred with 5-phenyl-4-pentenyl-1-amine, which has no substituent at the 2-position, due to nonbonding interactions in the acyclic form relative to the cyclic form. The present ring-size dependence of cyclization rates and product yield follows the order 5 > 6 ≫ 7, which is consistent with trends expected for sterically controlled ring-forming transition states. These observations strongly support a turnover-limiting alkene insertion/isomerization mechanism (vide infra).[13] The stereochemistry of the olefinic moieties in aminoalkenes (*E* and *Z*) did not affect the reaction. This process can be applied to the synthesis of 2-methylindole from 2-allylaniline. After run 1 in Table 1, propene was evolved in the gas phase in 43% yield, and we believe that allyl acetate operates as an effective hydrogen acceptor, as in our previous work.[11] No propyl acetate, a simple hydrogenated product of allyl acetate, was detected by careful GC analysis.

10.1021/ja017012k CCC: $22.00 © 2002 American Chemical Society

Table 1. $[RuCl_2(CO)_3]_2$/dppp-Catalyzed Oxidative Amination of Aminoalkenes[a]

run	aminoalkene	product	yield (%) [b]
1	 **1a**		**2a** >99 (87)
2	 **1b**		**2b** 89 (81)
3	 **1c**		**2c** (73)
4	 **1d** ($E:Z = 6:1$) [c]		**2d** 90 (87)
5[d]	 **1e**		**2e** 55 (38)
6	 **1f**		**2f** 47 (40)
7[d]	 **1g**		**2g** 76
8	 **1h**		**2h** 94 (87)
9	 **1i**		**2i** 78 (74)

[a] Aminoalkene (2.5 mmol), $[RuCl_2(CO)_3]_2$ (0.050 mmol), dppp (0.10 mmol), K_2CO_3 (5.0 mmol), allyl acetate (7.5 mmol), and *N*-methylpiperidine (4.0 mL) at 140 °C for 8 h under an argon atmosphere. [b] Determined by GLC (isolated yield). [c] Determined by ^1H NMR. [d] At 120 °C for 22 h.

Considering all of our findings, the most plausible mechanism is as follows. The initial step might consist of the predominant coordination and oxidative addition of the amine functionality in aminoalkenes (**1**) to a coordinatively unsaturated active ruthenium center to produce a (hydrido)(amido)ruthenium intermediate.[14] The "Thorpe-Ingold effect"[13] and the formation of a nitrile as a byproduct in the present reaction strongly suggest this direct N−H bond activation/olefin insertion mechanism (vide supra). Neither conversion of aminoalkenes to the corresponding tosylamides[7] nor acidic reaction conditions[4c−e] to decrease the coordination ability of an amine functionality to less than an alkene moiety in aminoalkenes was needed in the present reaction, which also supports this mechanism. Subsequently, insertion of an alkene moiety into the Ru−N bond[15] followed by β-hydride elimination and sequential reductive elimination[16]/isomerization gives the corresponding cyclic imine with the formation of a ruthenium dihydride intermediate, which regenerates a catalytically active ruthenium species via removal of the hydride by hydrogenolysis of allyl acetate (vide supra).

In conclusion, we have developed the practically useful ruthenium-catalyzed intramolecular oxidative amination of aminoalkenes. This process provides an effective and straightforward method for the catalytic synthesis of unsaturated nitrogen heterocycles such as 1-pyrroline and indole derivatives without the use of expensive aminoalkynes.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS). T.K. acknowledges financial support from the Sumitomo Foundation and Yamada Science Foundation. T.O. appreciates Research Fellowships from the Japan Society for the Promotion of Science for Young Scientists.

Supporting Information Available: Complete experimental procedures, lists of spectral data, and elemental analyses for all of the new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Taube, R. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; VCH: New York, 1996; Vol. 1, p 507. (b) Müller, T. E.; Beller, M. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: New York, 1998; Vol. 2, p 316.

(2) For recent examples of intramolecular hydroamination, see: (a) Müller, T. E.; Grosche, M.; Herdtweck, E.; Pleier, A.-K.; Walter, E.; Yan, Y.-K. *Organometallics* **2000**, *19*, 170. (b) Burling, S.; Field, L. D.; Messerle, B. A. *Organometallics* **2000**, *19*, 87. (c) Müller, T. E.; Pleier, A.-K. *J. Chem. Soc., Dalton Trans*. **1999**, 583. For recent examples of intermolecular hydroamination, see: (d) Löber, O.; Kawatsura, M.; Hartwig J. F. *J. Am. Chem. Soc*. **2001**, *123*, 4366. (e) Johnson, J. S.; Bergman R. G. *J. Am. Chem. Soc*. **2001**, *123*, 2923. (f) Tokunaga, M.; Eckert, M.; Wakatsuki, Y. *Angew. Chem., Int. Ed*. **1999**, *38*, 3222. (g) Uchimaru, Y. *Chem. Commun*. **1999**, 1133. (h) Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc*. **1988**, *110*, 6738.

(3) (a) Li, Y.; Marks, T. J. *J. Am. Chem. Soc*. **1998**, *120*, 1757. (b) Bürgstein, M. R.; Berberich, H.; Roesky, P. W. *Organometallics* **1998**, *17*, 1452. (c) Li, Y.; Marks, T. J. *J. Am. Chem. Soc*. **1996**, *118*, 9295. (d) Haskel, A.; Straub, T.; Eisen, M. S. *Organometallics* **1996**, *15*, 3773.

(4) (a) Vogels, C. M.; Hayes, P. G.; Shaver, M. P.; Westcott, S. A. *Chem. Commun*. **2000**, 51. (b) Tamaru, Y.; Hojo, M.; Kawamura, S.; Yoshida, Z. *J. Org. Chem*. **1986**, *51*, 4090. For the stoichiometric reaction under acidic reaction conditions, see: (c) Heathcock, C. H.; Stafford, J. A.; Clark, D. L. *J. Org. Chem*. **1992**, *57*, 2575. (d) Pugin, B.; Venanzi, L. M. *J. Organomet. Chem*. **1981**, *214*, 125. (e) Ambuehl, J.; Pregosin, P. S.; Venanzi, L. M. *J. Organomet. Chem*. **1978**, *160*, 329.

(5) (a) Molander, G. A.; Dowdy, E. D. *J. Org. Chem.* **1998**, *63*, 8983. (b) Roesky, P. W.; Stern, C. L.; Marks, T. J. *Organometallics* **1997**, *16*, 4705. (c) Li, Y.; Marks, T. J. *Organometallics* **1996**, *15*, 3770. (d) Giardello, M. A.; Conticello, V. P.; Brard, L.; Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 10241. (e) Gagné, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc*. **1992**, *114*, 275. (f) Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc*. **1989**, *111*, 4108.

(6) (a) Tillack, A.; Trauthwein, H.; Hartung, C. G.; Eichberger, M.; Pitter, S.; Jansen, A.; Beller, M. *Monatsh. Chem*. **2000**, *131*, 1327. (b) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Müller, T. E. *Eur. J. Inorg. Chem*. **1999**, 1121. (c) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Herwig, J.; Müller, T. E.; Thiel, O. R. *Chem. Eur. J*. **1999**, *5*, 1306. (d) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Müller, T. E.; Zapf, A. *J. Organomet. Chem*. **1998**, *566*, 277. (e) Ragaini, F.; Longo, T.; Cenini, S. *J. Mol. Catal. A: Chemical* **1996**, *110*, L171. (f) Brunet, J.-J.; Neibecker, D.; Philippot, K. *Tetrahedron Lett*. **1993**, *34*, 3877. (g) Hosokawa, T.; Takano, M.; Kuroki, Y.; Murahashi, S.-I. *Tetrahedron Lett*. **1992**, *33*, 6643. (h) Bozell, J. J.; Hegedus, L. S. *J. Org. Chem.* **1981**, *46*, 2561. (i) Graunt, M. J.; Spencer, J. B. *Org. Lett*. **2001**, *3*, 25. (j) Srivastava, R. S.; Nicholas, K. M. *Chem. Commun*. **1996**, 2335.

(7) A few examples of oxidative cyclization/isomerization of aminoalkenes have been reported. All reactions require a tosyl substituent on an amino group. (a) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem*. **1996**, *61*, 3584. (b) Rönn, M.; Bäckvall, J.-E.; Andersson, P. G. *Tetrahedron Lett*. **1995**, *36*, 7749. (c) van Benthem, R. A. T. M.; Hiemstra, H.; Longarela, G. R.; Speckamp, W. N. *Tetrahedron Lett*. **1994**, *35*, 9281. (d) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc*. **1982**, *104*, 2444.

(8) (a) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl*. **1988**, *27*, 1113 and references therein. (b) Krolski, M. E.; Renaldo, A. F.; Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1988**, *53*, 1170.

(9) (a) Suzuki, T.; Shiotsuki, M.; Wada, K.; Kondo, T.; Mitsudo, T. *J. Chem. Soc., Dalton Trans*. **1999**, 4231. (b) Suzuki, T.; Shiotsuki, M.; Wada, K.; Kondo, T.; Mitsudo, T. *Organometallics* **1999**, *18*, 3671.

(10) (a) Kondo, T.; Tanaka, A.; Kotachi, S.; Watanabe, Y. *J. Chem. Soc., Chem. Commun*. **1995**, 413. (b) Kondo, T.; Okada, T.; Suzuki, T.; Mitsudo, T. *J. Organomet. Chem*. **2001**, *622*, 149.

(11) (a) Kondo, T.; Mukai T.; Watanabe, Y. *J. Org. Chem*. **1991**, *56*, 487. (b) Kondo, T.; Kodoi, K.; Mitsudo, T.; Watanabe Y. *J. Chem. Soc., Chem. Commun*. **1994**, 755.

(12) It has been pointed out that ruthenium-catalyzed reactions require highly careful tuning of reaction conditions with substrates to obtain products in high yields and selectivities. *N*-Methylpiperidine was found to be the best solvent for some ruthenium-catalyzed reactions, and may act as a suitable ligand for an active ruthenium species as well as a simple solvent. See: Mitsudo, T.; Kondo, T. *Synlett* **2001**, 309 and references therein.

(13) (a) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; Vol. 11.3c, p 682. (b) Kirby, A. *Adv. Phys. Org. Chem*. **1980**, *17*, 183.

(14) Sappa, E.; Milone, L. *J. Organomet. Chem*. **1973**, *61*, 383.

(15) (a) Cowan, R. L.; Trogler, W. C. *Organometallics* **1987**, *6*, 2451. (b) Cowan, R. L.; Trogler, W. C. *J. Am. Chem. Soc*. **1989**, *111*, 4750.

(16) (a) Baranano, D.; Hartwig, J. F. *J. Am. Chem. Soc*. **1995**, *117*, 2937. (b) Hartwig, J. F. *Angew. Chem., Int. Ed*. **1998**, *37*, 2046.

JA017012K