Ring Opening in the Hydroamination of Methylenecyclopropanes Catalyzed by Palladium

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The carbon–nitrogen bond formation is one of the most important processes in organic synthesis. In particular, the addition of the nitrogen–hydrogen bond of amines to carbon–carbon multiple bonds, that is hydroamination, is an ideal and challenging method for this purpose.[1] The *intermolecular* hydroamination reactions catalyzed by iridium,[2] rhodium,[3] lanthanide,[4] or actinide complexes[5] were reported by several groups. The catalytic cycle of these reactions involves the insertion process of a carbon–carbon double bond into the N–M bond. On the other hand, the palladium-catalyzed *intermolecular* hydroamination of 1,3-dienes,[6] allenes,[7] and enynes[8] proceeded through the insertion of the double bond to the H–M bond. We were interested in assessing the reactivity of other types of alkenes in the palladium-catalyzed hydroamination reactions.

The palladium-catalyzed hydrostannation[9] and rhodium-catalyzed hydrosilylation[10] of methylenecyclopropanes proceed through the anti-Markovnikov-type addition **1** followed
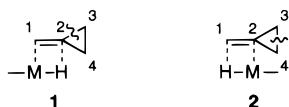
by proximal bond cleavage (C-2 and C-3) of the cyclopropane ring, whereas the palladium-catalyzed hydrocarbonation mainly proceeds through the Markovnikov-type addition **2** followed by distal bond cleavage (C-3 and C-4) except for the reaction of benzylidenecyclopropane.[11] We report herein that the palladium-catalyzed hydroamination of methylenecyclopropanes mainly proceeds via mode **2** (eq 1).
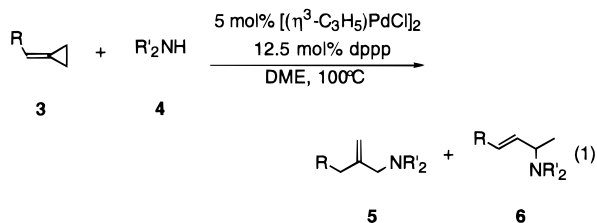
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Table 1. Palladium-Catalyzed Addition of 4 to 3[a]

entry	3	4	yield of **5** (%)[b]	yield of **6** (%)[b]
1	**3a** (R=PhCH₂CH₂CH₂)	Bn₂NH **4a**	**5a** (91)	-
2	**3a**	Et₂NH **4b**	**5b** (31)	
3	**3a**	⬠NH **4c**	**5c** (64)[c]	-
4	**3a**	(Boc)₂NH **4d**	**5d** (68)	
5	**3b** (R=PhCH₂CH₂)	Bn₂NH **4a**	**5e** (82)	-
6	**3c** (R=cyclohexyl)	**4a**	**5f** (72)	-
7	**3d** (R=Ph)	**4a**	-	**6a** (19)[d]
8	**3d**	(phthalimide NH) **4e**	-	**6b** (84)

[a] The reaction of **3** (1.0 mmol) with **4** (0.5 mmol) was carried out in the presence of 5 mol % of [(η³-C₃H₅)PdCl]₂ and 12.5 mol % of dppp in DME at 100 °C for 3 days. [b] Isolated yield. [c] 10 mol % of [(η³-C₃H₅)PdCl]₂ and 25 mol % of dppp were used. [d] The trans configuration of the double bond of **6a** was confirmed by the coupling constant of the olefinic protons (16.2 Hz).

The results are summarized in Table 1. The reaction of (4-phenylbutylidene)cyclopropane (**3a**) with dibenzylamine (**4a**) in the presence of catalytic amounts of allylpalladium chloride dimer (5 mol %) and 1,3-bis(diphenylphosphino)-propane (dppp, 12.5 mol %) gave the corresponding hydroamination product **5a** in 91% yield (entry 1). The use of Pd₂(dba)₃·CHCl₃, Pd(PPh₃)₄, or PdCl₂(PPh₃)₂ as a catalyst gave **5a** in lower yields, and Pd(OAc)₂ did not promote the reaction at all. Although the reaction of **3a** with diethylamine (**4b**) gave **5b** in low yield (entry 2), the reaction with pyrrolidine (**4c**) afforded the hydroamination product **5c** in good yield (entry 3). The carbamate **4d** reacted with **3a** very smoothly (entry 4). The reaction of 3-phenylpropylidenecyclopropane (**3b**) with **4a** gave **5e** in 82% yield (entry 5), and the reaction of cyclohexylmethylenecyclopropane (**3c**) with **4a** afforded **5f** in 72% yield (entry 6). In the above reactions, no trace amounts of product **6** were detected. On the other hand, the reactions of benzylidenecyclopropane (**3d**) led exclusively to a different type of hydroamination products **6**; **6a** was obtained from **4a** in 19% yield (entry 7) and **6b** in 84% yield from **4e** (entry 8).

The use of primary amines as nitrogen nucleophiles also gave the corresponding alkylated products. In the reaction of benzylamine **4f** with **3a**, the dialkylated product **7a** was produced as a major product along with a small amount of the monoalkylated **5g**. However, the reaction of aniline **4g** led to only the monoalkylated product **5h** (eq 2). The reaction of the tetrasubstituted alkene **3e** with **4a** proceeded smoothly to give **5i** in 79% yield (eq 3). The methylenecy-
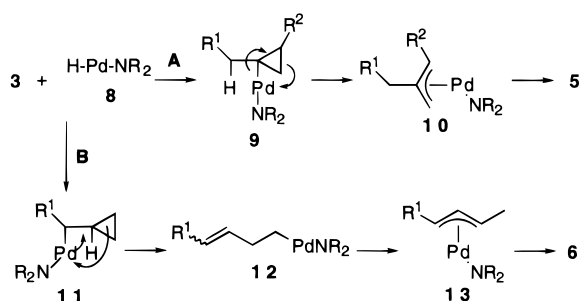
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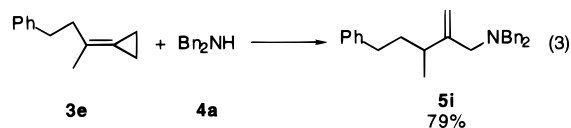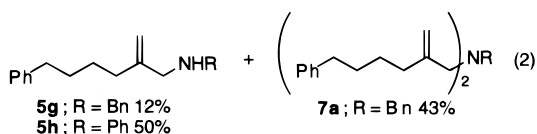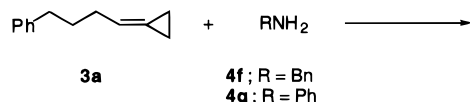(9) Lautens, M.; Meyer, C.; Lorenz, A. *J. Am. Chem. Soc.* **1996,** *118,* 10676.
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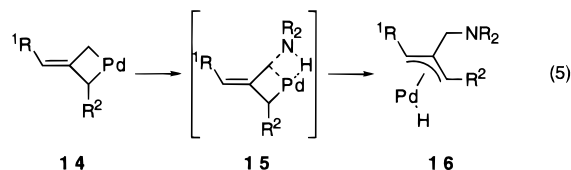
Scheme 1

clopropane **3f** having a substituent on the ring reacted with **4a** to give **5j** (eq 4).



We propose the mechanism shown in Scheme 1 to explain the formation of **5** and **6**. Oxidative addition of zero-valent palladium into the nitrogen−hydrogen bond of amines would produce the hydridopalladium species **8**,[12] which would react with methylenecyclopropanes **3** via two different orientations; the Markovnikov hydropalladation (**A**) would produce **9**, whereas the anti-Markovnikov hydropalladation (**B**) would give **11**.[13] The distal bond cleavage of **9** would afford the π-allylpalladium intermediate **10**, leading to **5** and Pd-(0) upon reductive coupling. The proximal bond cleavage of **11** would give homoallylpalladium **12**,[14] which would undergo migration to π-allylpalladium **13**, and subsequent reductive coupling would produce **6** and Pd(0). The insertion of Pd(0) into the C3−C4 bond (**14**) followed by the addition of an amine to the less substituted carbon (**15**) and subsequent reductive elimination of Pd(0) would produce **5** (eq 5). If this alternative mechanism is operative, the same product (or product ratio) should be obtained from **3b** and **3f** because both reactions proceed via the common intermediate **16**. However, the reaction of **3b** gave **5e**, whereas that of **3f** afforded **5j** (see entry 5 of Table 1 and eq 4). Accordingly, it is not likely that the present ring-opening

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reaction proceeds through the insertion of Pd(0) into the cyclopropane ring of methylenecyclopropanes.

To confirm the hydroamination mechanism, the reactions of deuterated amines **4a**-*d* (D content 86%) and **4e**-*d* (D content 95%) were carried out. The reaction of **3a** with **4a**-*d* under the same conditions as above gave **5a**-*d* in 78% yield in which the deuterium content at the C-1 position was 63% yield (eq 6). Deuterium incorporation did not occur at the
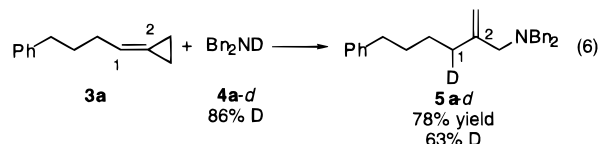
other carbons of **5a**. The result supports the Markovnikov hydropalladation mechanism. The reaction of **3d** with **4e**-*d* afforded **6b**-*d* in 75% yield in which the deuterium content at the C-2 position was 20%, and the other protons were not deuterated at all (eq 7). The loss of deuteriums most
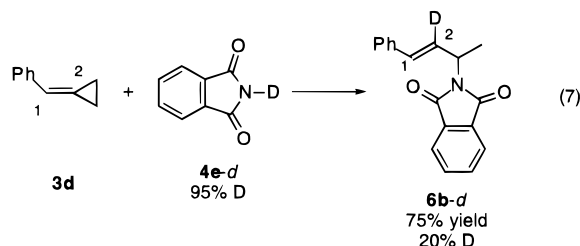
probably occurred on the way from **12** to **13**, which required a sequential process of β-hydride elimination−addition. In the reaction of **3d** with **4a**, 1-phenyl-1,3-butadiene **17** was obtained in 19% yield as a byproduct. This result clearly indicates that **17** was produced via the β-elimination of **12** (R^1 = Ph, R^2 = Bn).
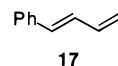
The regioselectivity of the hydropalladation and the ring-opening mode clearly depended on the substituent on the double bond of methylenecyclopropanes. Alkyl substituents on the double bond tend to decrease the electron density at the C-1 carbon of **3**, and the hydropalladation proceeds via the Markovnikov-type **2**. On the contrary, in the reaction of phenyl-substituted methylenecyclopropane **3e**, the phenyl group increases the electron density at the C-1 carbon and the hydropalladation proceeds through the anti-Markovnikov orientation **1**. AM1 calculations predicted higher negative charges on the C-1 carbon of **3e**, compared to the C-1 carbons of **3a**−**c**.

In conclusion, we have reported the first example of the hydroamination of methylenecyclopropanes. This reaction seems to be potentially useful for the synthesis of various types of allylamine derivatives and further seems to be desirable from an ecochemical point of view since most previous syntheses need a substitution process and liberate a leaving group.

Supporting Information Available: Supporting Information Available: Experimental procedures and spectroscopic and analytical data for products **5** and **6** (4 pages).