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Palladium-Catalyzed Addition of Nitrogen Pronucleophiles to Alkylidenecyclopropanes

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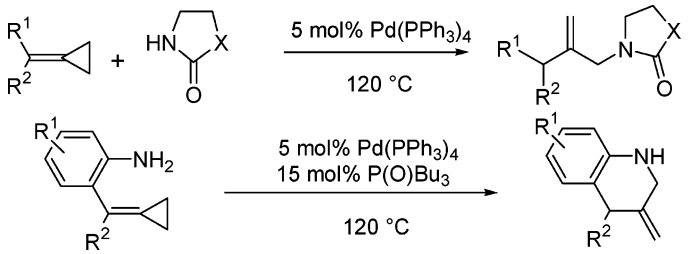

The inter- and intramolecular additions of cyclic amides (nitrogen pronucleophiles) to methylenecyclopropanes proceeded smoothly in the presence of catalytic amounts of $Pd(PPh_3)_4$, affording the corresponding hydroamination products in good to high yields with high regioselectivities. The ring opening of methylenecyclopropanes occurred at the distal position of the cyclopropane ring.

Introduction

Methylenecyclopropanes are interesting substrates for transition metal-catalyzed reactions; they are stable, easily accessible, and easy to handle despite a high level of ring strain.[1] In early 1970, transition metal-catalyzed [3+2] cycloaddition of alkylidenecyclopropanes with olefins was well investigated and became a powerful tool in constructing five-membered carbocycles.[2] The transition metal-catalyzed reactions of methylenecyclopropane are summarized in Scheme 1. Proximal bond cleavage proceeds through the β-carbon elimination of the cyclopropylcarbinylpalladium species **2** or **3** formed by the addition of H-Pd or R−Pd intermediates to the double bond of **1** (paths A and B). This type of reaction takes place with $H-SiR_3$,[3] $H-SnR_3$,[4] and organic halides (R−X).[5] Oxidative addition of the proximal bond to the transition metal catalysts leading to **4** can also be a key process to cleave a proximal bond (path C). The reaction with a multiple bond (X = Y)[2a,6] or with an organometallic compound[7] (for example, Si−CN, B−B, or B−Si,) proceeds through this process. On the other hand, distal bond cleavage takes place through the addition of a H−Pd−Nu complex to the double bond of **1** in a manner opposite to the case of path A, followed by the β-carbon elimination of the resulting cyclopropylpalladium complex **5** (path D), or through the formation of palladacyclobutane species **6** (path E). In general, the reaction with carbon,[8] nitrogen,[9] and oxygen[10] pronucleophiles proceeds via path D or E. The selectivity of the respective ring-opening position depends primarily on the combination

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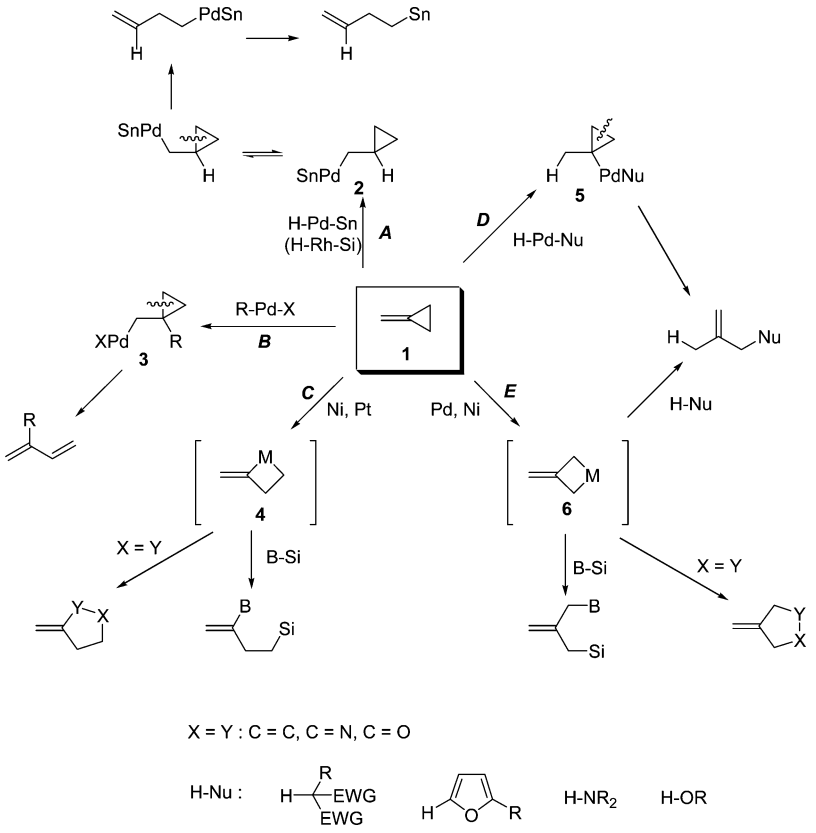
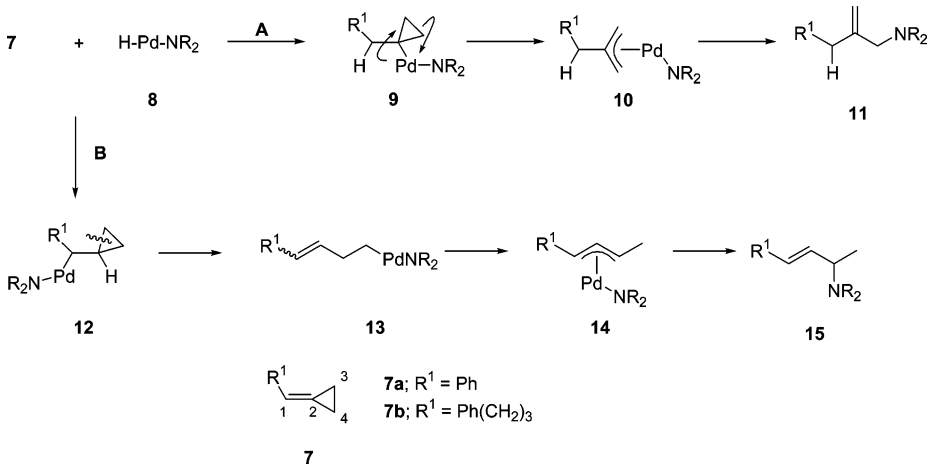
SCHEME 1. Transition Metal-Catalyzed Reactions of Methylenecyclopropane 1



SCHEME 2. A Plausible Mechanism for the Hydroamination of 7



of substrates and catalysts. While the crucial factors that determine the mode of ring opening are unknown, the difference of the ease of oxidative addition of a substrate to a transition metal complex plays an important role. Substituents on the methylenecyclopropane skeleton often affect the reactivity and the regioselectivity. Especially, if the C-1 position of the olefinic moiety of **1** is substituted with two alkyl groups, the reaction with less reactive pronucleophiles, such as furan, amines, and alcohols, gives the ring opening products in higher yields than that of monosubstituted methylenecyclopropanes. Further, substitution on the cyclopropane ring tends to decrease the chemical yields of the addition products of less reactive pronucleophiles.

We previously reported that the Pd-catalyzed hydroamination of methylenecyclopropanes **7** mainly proceeds through a π-allylpalladium intermediate formed by distal bond cleavage.[9] A proposed mechanism for the hydroamination of **7** is shown in Scheme 2. Oxidative addition of a nitrogen−hydrogen bond of amines onto a zerovalent palladium produces the hydridopalladium species **8**,[11] which reacts with methylenecyclopropanes **7** in two different orientations; hydropalladation in which Pd is linked toa C2 carbon (path A) leads to the cyclo-

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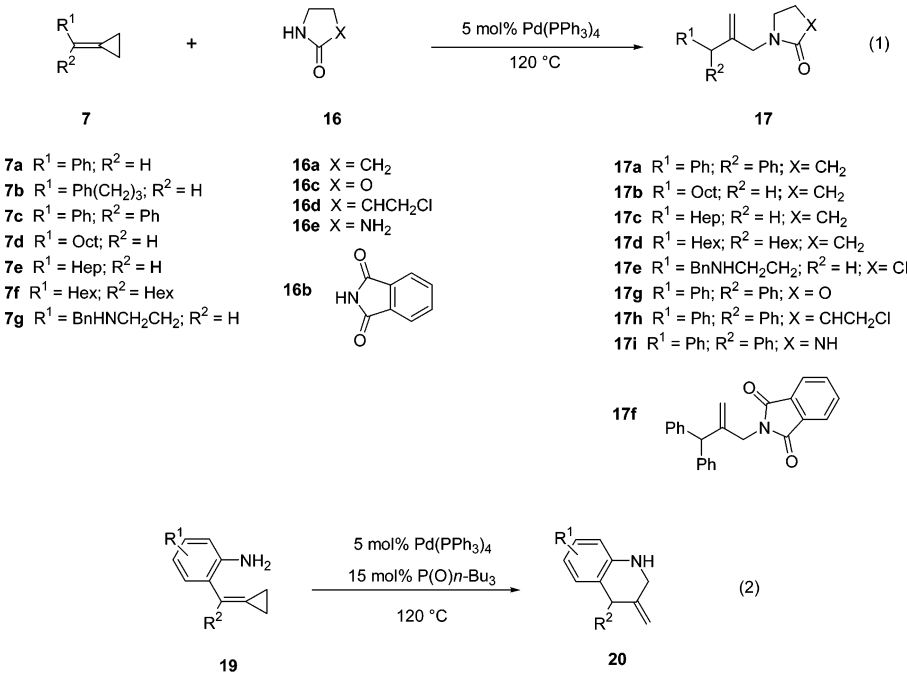

propylpalladium **9**, whereas the hydropalladation in an opposite manner (path B) gives the cyclopropylcarbinylpalladium **12**.[12] The distal bond cleavage of **9** affords the π-allylpalladium intermediate **10**, leading to **11** and Pd(0) upon reductive coupling. The proximal bond cleavage of **12** gives the homoallylpalladium **13**,[13] which undergoes migration to the π-allylpalladium **14**,[14] and subsequent reductive coupling produces **15** and Pd(0).

The regioselectivity and reactivity of the hydroamination reaction were considerably affected by the substitution pattern of methylenecyclopropanes. Alkyl substituents on the double bond tend to decrease the electron density at the C-1 carbon of **7** and the hydropalladation leads to the cyclopropylpalladium species **9**.[12] On the contrary, in the reaction of phenyl-substituted methylenecyclopropane **7a**, the phenyl group increases the electron density at the C-1 carbon and the hydropalladation leads to cyclopropylcarbinylpalladium intermediate **12**. AM1 calculations predicted higher negative charges on the C-1 carbon of **7a**, compared to the C-1 carbon of **7b**. On the other hand, a substituent on the cyclopropane ring decreased the reactivity toward the hydroamination reaction. However, the influence of the structure of amines upon the regioselectivity was not thoroughly studied. We now report that the regioselective distal bond cleavage of **7** was accomplished, irrespective of the structure of the substituent R^1, by using the cyclic amides **16** (eq 1). Furthermore, we found an interesting intramolecular hydroamination of **19** that gave the six-membered nitrogen heterocycles **20** (eq 2).

Results and Discussion

Regioselective Addition of Cyclic Amides: Optimization of the Catalyst−Ligand System. An initial test experiment was carried out with the $[(\eta^3\text{-}C_3H_5)PdCl]_2$-dppp system, which was shown to be the best catalyst in the addition of various amine pronucleophiles, such as dibenzylamine, pyrrolidine, carbamate, phthalimide, benzylamine, and aniline, to alkylidenecyclopropanes.[9a] The reactions of **7a** (phenyl-substituted methylenecyclopropane) and **7b** (alkyl-substituted methylenecyclopropane) with **16a** and **16b** in the presence of 5 mol % of $[(\eta^3\text{-}C_3H_5)PdCl]_2$-dppp system at 100 °C (or even at 120 °C) did not proceed (eq 1). Likewise, the reaction of **7a** or **7b** with **16a** or **16b** in the presence of 5 mol % of $Pd(PPh_3)_4$ at 120 °C gave polymerized mixtures. The reaction of **7c** and **16a** in the presence of different catalytic precursors was chosen for optimizing the reaction conditions. While the reaction of (diphenylmethylene)cyclopropane **7c** (phenyl-disubstituted methylenecyclopropane) with 2-pyrrolidinone **16a** in the presence of 5 mol % of $[(\eta^3\text{-}C_3H_5)PdCl]_2$-dppp at 100 °C did not give the desired product, the same reaction in the presence of 5 mol % of $Pd(PPh_3)_4$ at 120 °C proceeded well producing **17c** in 95% yield (Table 1, entry 1). It was revealed that the previous conditions could not be applied when the cyclic amide **16a** was used. The use of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ with monodentate ligand, PPh_3, or $[(\eta^3\text{-}C_3H_5)PdCl]_2$ without ligand did not give the desired products at all. The other catalyst systems, such as $Pd_2(dba)_3{\cdot}CHCl_3$, gave disappointing results. The use of bidentate ligands such as dppe and dppb gave unsatisfactory results (entries 2−4). The addition of excess PPh_3 or P(*o*-tolyl)$_3$ diminished the yield of **17c** (entries 5 and 6). The use of P(O)*n*-Bu$_3$ was not effective (entry 7). When the reaction was carried out in the absence of $Pd(PPh_3)_4$ catalyst, no reaction was observed and **7c** was recovered, indicating that the alkylidenecyclopropane was stable at 120 °C (entry 8).

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TABLE 1. Optimization of the Catalyst System in the Addition of 16a to 7c[a]

entry	palladium	ligand	yield/%[b]
1	$Pd(PPh_3)_4$		95
2	$Pd(PPh_3)_4$	dppe[c]	43
3	$Pd(PPh_3)_4$	dppp[d]	45
4	$Pd(PPh_3)_4$	dppb[e]	39
5	$Pd(PPh_3)_4$	PPh_3	73
6	$Pd(PPh_3)_4$	P(*o*-tolyl)$_3$	51
7	$Pd(PPh_3)_4$	P(O)-*n*-Bu_3	80
8			NR

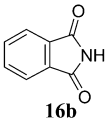
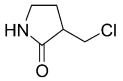
[a] The reaction of **7c** (0.3 mmol) and **16a** (0.6 mmol) was carried out in the presence of 5 mol % of $Pd(PPh_3)_4$ and 10 mol % of the ligand at 120 °C for 2 days. [b] NMR yield with CH_2Cl_2 as an internal standard. [c] dppe = 1,2-bis(diphenylphosphino)ethane. [d] dppp = 1,3-bis(diphenylphosphino)propane. [e] dppb = 1,4-bis(diphenylphosphino)butane.

Various solvents, such as THF, DME, benzene, and acetonitrile, were examined, but we found that addition of solvents gave rather unsatisfactory results. At lower temperatures (60−100 °C) the reaction did not proceed well even after 4−5 days because the reaction mixtures were solid at lower temperatures. In conclusion, the optimized conditions are the following: **7c** (0.3 mmol), **16a** (0.6 mmol), 5 mol % of $Pd(PPh_3)_4$, without solvents, 120 °C, 48 h.

Palladium-Catalyzed Addition of Cyclic Amides 16a−e to Alkylidenecyclopropane Derivatives 7c−g. We then examined the scope of the reaction of the cyclic amide pronucleophiles **16a−e** with alkylidenecyclopropane **7c−g** using the optimized conditions (eq 1 and Table 2). In the presence of 5 mol % of $Pd(PPh_3)_4$ at 120 °C, the reaction of (diphenylmethylene)cyclopropane **7c** with 2-pyrrolidinone **16a** gave the *N*-allylated product **17a** in 91% isolated yield (entry 1). The reaction of (dihexylmethylene)cyclopropane **7d** with **16a** afforded the allylamine **17b** in 82% isolated yield (entry 2). The reaction of monosubstituted **7e** and disubstituted **7f** also afforded the hydroaminated products **17c** and **17d** in moderate yields, respectively (entries 3 and 4). Moreover, **7g** likewise underwent the hydroamination reaction to afford **17e** (entry 5). The reaction of a more acidic nitrogen pronucleophile, such as **16b**, and the carbamate **16c** with **7c** also proceeded smoothly to give **17f** and **17g**, respectively, in high yields (entries 6 and 7, Table 2). Similarly, the use of **16d** afforded **17h** in a high yield (entry 8). The use of **16e** as a nitrogen pronucleophile led to selective formation of the corresponding monoalkylated product **17i** (entry 9).

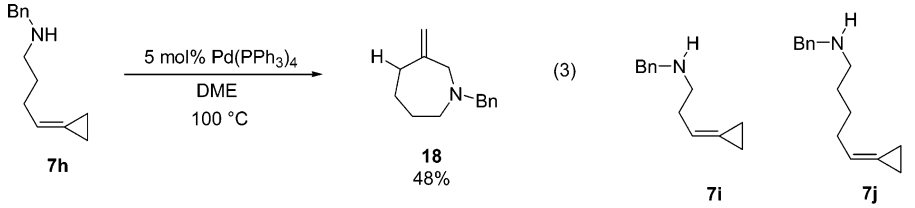
Palladium-Catalyzed Intramolecular Hydroamination of Alkylidenecyclopropanes. We previously reported that the Pd-catalyzed intramolecular hydroamination of methylenecyclopropanes produced cyclic allylamines.[9b] For example, in the presence of 5 mol % of Pd-$(PPh_3)_4$ and DME as a solvent at 100 °C, the reaction of **7h** gave the corresponding azepane derivative **18** in 48%

TABLE 2. Palladium-Catalyzed Addition of Cyclicamides 16 to Alkylidenecyclopropanes 7[a]

Entry	7	16	Yield of 17, %[b]
1	**7c**	 **16a**	**17a**, 91
2	**7d**	**16a**	**17b**, 82
3	**7e**	**16a**	**17c**, 68
4	**7f**	**16a**	**17d**, 64
5	**7g**	**16a**	**17e**, 72
6	**7c**	 **16b**	**17f**, 95
7	**7c**	 **16c**	**17g**, 96
8	**7c**	 **16d**	**17h**, 79
9	**7c**	 **16e**	**17i**, 84

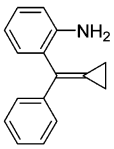
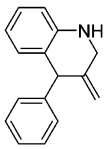
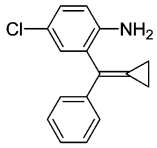
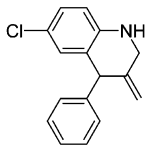
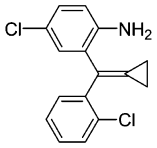
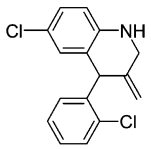
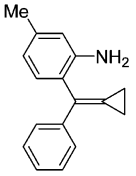
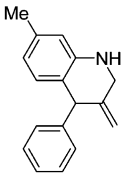
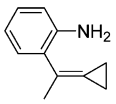
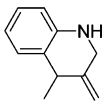
[a] The reaction of **16** (0.6 mmol) with **7** (0.3 mmol) was carried out in the presence of 5 mol % of $Pd(PPh_3)_4$ at 120 °C for 3 days. [b] Isolated yield.

yield (eq 3). The hydroamination reaction of **7i** and **7j** was attempted, but the desired cyclic amines were not afforded under the reaction conditions mentioned above. Although only **7h** among **7h−j** was usable for hydroamination, intramolecular hydroamination must be potentially useful for constructing nitrogen heterocycles. Therefore, we continued to research a new intramolecular hydroamination of methylenecyclopropanes and found that the reaction of the aniline-tethered alkylidenecyclopropane **19a** underwent a facile cyclization to give the six-membered exomethylene nitrogen heterocycle **20a** in 86% yield with high regioselectivity (entry 1, Table 3, eq 4). This reaction can be explained by the intramolecular hydropalladation of **19a**. The cyclopropylpalladium species **21** most probably undergoes β-carbon elimination, leading to the π-allylpalladium intermediate **22**. Subsequent reductive elimination of Pd(0) produces **20a** (eq 4).



7h **18** 48% **7i** **7j**

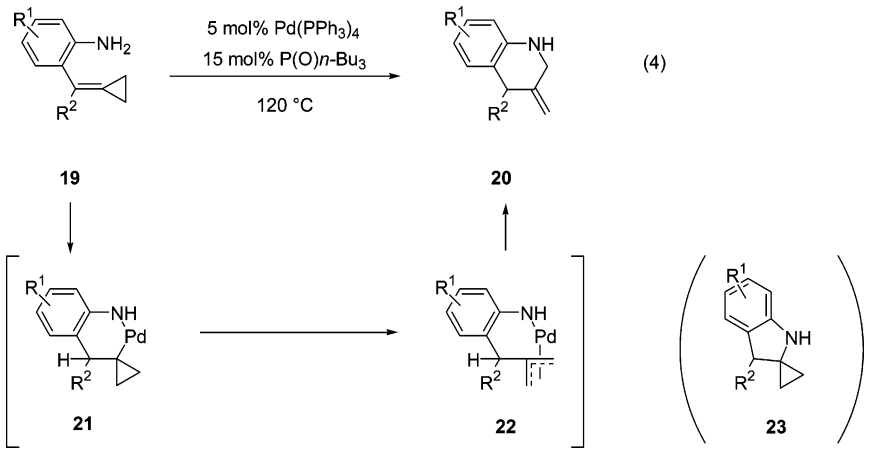
TABLE 3. Palladium-Catalyzed Intramolecular Hydroamination of Alkylidenecyclopropanes 19[a]

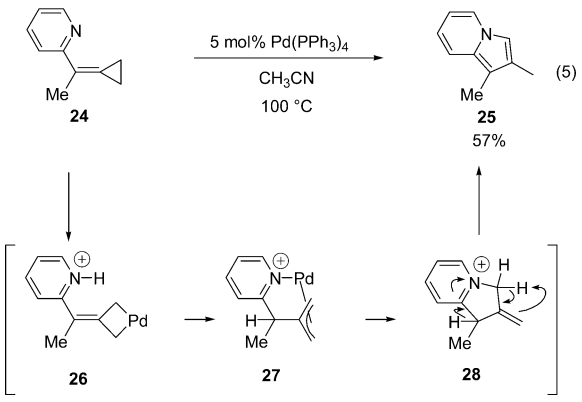
Entry	19		20	Yield of **20**, %[b]
1		**19a**	 **20a**	86
2		**19b**	 **20b**	71[c]
3		**19c**	 **20c**	70
4		**19d**	 **20d**	86
5		**19e**	 **20e**	74

[a] The reaction of **19** (0.5 mmol) was carried out in the presence of 5 mol % of $Pd(PPh_3)_4$, 15 mol % of $P(O)Bu_3$ at 120 °C for 3 days. [b] Isolated yield. [c] The reaction was carried out at 100 °C for 3 days. When the reaction was performed at 120 °C for 3 days, **20b** was isolated in 39% yield.

The other potential product such as the five-membered carbocycle **23** was not produced under the reaction conditions.[3] The reaction of **19a** in the absence of P(O)-*n*-Bu_3 gave **20a** in 70% yield. In the case of **19b**, cyclization proceeded smoothly at 100 °C affording the product **20b** in 71% yield (entry 2). The use of **19c** also gave the intramolecular hydroamination product **20c** in a good yield (entry 3). Moreover, the amine **19d**, having a methyl group on the phenyl ring, also underwent hydroamination reaction to give **20d** (entry 4). Less hindered amine **19e** likewise reacted in the presence of palladium to give the corresponding cyclic amine product **20e** (entry 5).

Additionally, we carried out the intramolecular hydroamination reaction of **24** in the presence of a catalytic amount (5 mol %) of $Pd(PPh_3)_4$. Very interestingly, the corresponding five-membered nitrogen heterocycle **25** was obtained in 57% yield (eq 5). It was perhaps due to the instability of the starting material **24** during the workup of the products with column chromatography. A proposed mechanism for the transformation of **24** to **25** is shown in eq 5. A proton, perhaps coming from moisture (or trace amounts of H_2O in the CH_3CN solvent), adds to the nitrogen of pyridine, and insertion of Pd(0) into the distal bond of the cyclopropane ring of **24** produces the palladacyclobutane intermediate **26**.[15] Since **26** is a sort





of σ-allylpalladium species, an intramolecular palladaene reaction may take place as shown in **26**, giving the π-allylpalladium species **27**. Reductive elimination of Pd(0) from **27** gives the intermediate **28**, which leads to **25** upon deprotonation and bond rearrangement. We tested the effect of proton sources upon the yield of **25** (see the Supporting Information). External addition of H_2O did not exert any significant effects, but the use of CH_3CN as a solvent was a key for the present interesting cyclization. Other solvents, such as DMF and benzene, were not suitable to the present reaction. The use of a strong H^+ source was not suitable perhaps due to facile decomposition of the cyclopropyl derivatives

Conclusion

All cyclic amides reported here reacted with alkylidenecyclopropanes in good to high yields with high regioselectivities. The intermolecular hydroamination of methylenecyclopropanes with amines proceeds smoothly in the presence of palladium catalyst, giving the allylamines **11** or **15** in good to high yields. Here the selectivity of the respective ring-opening position depends on the substituents of methylenecyclopropanes. When the amine pronucleophile was changed to cyclic amides, the highly regioselective products **17** were obtained irrespective of the structure of the substituent of methylenecyclopropanes.

Furthermore, the intramolecular hydroamination of alkylidenecyclopropanes **19** (or **24**) proceeds smoothly in the presence of Pd(0), giving the cyclic amines **20** (or **25**) in good yields. This reaction seems to be potentially useful for the synthesis of various types of quinoline type derivatives (eq 3),[16] azepane type derivatives (eq 4),[17] and indolizine type derivatives (eq 5).[18] This intramolecular hydroamination reaction further seems to be desirable from the eco-chemical point of view since most previous syntheses of cyclic amines need a substitution process and liberate a leaving group.[16−18]

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Experimental Section

Representative Procedure for the Addition of Cyclic Amides 16a to the Alkylidenecyclopropane 7c. To a screw-capped Wheaton microreactor, containing $Pd(PPh_3)_4$ (17.3 mg, 0.015 mmol) and methylenecyclopropane (61.8 mg, 0.3 mmol), was added the cyclic amide (0.045 mL, 0.6 mmol) under Ar atmosphere and the mixture was stirred at 120 °C for the specified time. The reaction progress was monitored with GC-MS. After completion, the turbid reaction mixture was filtered through a short silica column with ethyl acetate as eluent. Separation by passing through a florisil column (hexane as the eluent) and purification by medium-pressure liquid column chromatography (silica gel) with hexane as the eluent afforded the allylation product **17a** in 91% yield.

1-(2-Methylene-3,3-diphenylpropyl)pyrrolidin-2-one (17a). IR (neat) 3352, 2939, 1680, 1597, 1490 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.79 (t, J = 5.0 Hz, 2H), 2.26 (t, J = 8.2 Hz, 2H), 3.19 (t, J = 5.4 Hz, 2H), 3.90 (s, 2H), 4.73 (d, J = 16.4 Hz, 2H), 5.15 (s, 1H), 7.12−7.30 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.3, 49.9, 55.2, 61.6, 116.3, 126.5, 128.3, 128.88, 128.89, 141.1, 146.2, 158.2. Anal. Calcd for $C_{20}H_{21}NO$ (291.39): C, 82.44; H, 7.26; N, 4.81; O, 5.49. Found: C, 82.38; H, 7.23; N, 4.79. HRMS (EI) Calcd for $C_{20}H_{21}NO$: *m/z* 291.1623. Found: *m/z* 291.1618.

Representative Procedure for the Intramolecular Hydroamination of Alkylidenecyclopropane 19a. To a mixture of $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol) and $P(O)n\text{-}Bu_3$ (8.4 mg, 0.075 mmol) was added methylenecyclopropane **19a** (110.5 mg, 0.5 mmol), under Ar atmosphere in a screw-capped Wheaton microreactor. After being heated at 120 °C for 2 days, the mixture was filtered through a short florisil column with ethyl acetate as an eluent. Separation by passing though a florisil column (hexane/ethyl acetate as the eluent) and purification by medium-pressure liquid column chromatography (RP-18) with EtOAc as the eluent afforded adducts **20a** in 86% yield.

3-Methylene-4-phenyl-1,2,3,4-tetrahydroquinoline (20a). IR (neat) 3397, 3077−2812, 1653, 1598, 1497, 1450 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.68 (d, J = 12 Hz, 1H), 3.78 (d, J = 12 Hz, 1H), 3.92 (br s, 1H), 4.69 (s, 1H), 5.00 (s, 1H), 5.06 (s, 1H), 6.61 (d, J = 8.0 Hz, 1H), 6.66 (t, J = 7.3 Hz, 1H), 6.87 (d, J = 6.6 Hz, 1H), 7.05 (t, J = 7.4 Hz, 1H), 7.15−7.29 (m, 5H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ 46.1, 50.7, 110.9, 114.5, 117.9, 126.2, 127.4, 128.2, 128.3, 130.3, 144.0, 144.60, 144.64. Anal. Calcd for $C_{16}H_{15}N$ (221.29): C, 86.84; H, 6.83; N, 6.33. Found: C, 86.81; H, 6.85; N, 6.31. HRMS (EI) Calcd for $C_{16}H_{15}N$: *m/z* 221.1204. Found: *m/z* 221.1199.

Representative Procedure for the Intramolecular Hydroamination of Alkylidenecyclopropane 24. To a mixture of $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol) in CH_3CN was added methylenecyclopropane **24** (2.3 mg, 1.0 mmol), under Ar atmosphere in a screw-capped Wheaton microreactor. After being heated at 120 °C for 2 days, the mixture was filtered through a short florisil column with ethyl acetate as an eluent. Separation by passing though a florisil column (hexane/ethyl acetate as the eluent) and purification by medium-pressure liquid column chromatography (RP-18) with EtOAc as the eluent afforded adducts **25** in 57% yield.

1,2-Dimethylindolizine (25). IR (neat) 2919, 1716, 1628, 1434 cm^{-1}. ^1H NMR (C_6D_6, 400 MHz) δ 1.77 (s, 3H), 1.79 (s, 3H), 5.59−5.63 (m, 1H), 5.93−5.97 (m, 1H), 6.31 (s, 1H), 6.70−6.80 (m, 2H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ 8.4, 10.6, 108.8, 110.1, 114.9, 116. 6, 124,4, 128.4, 133.6, 133.8. HRMS (EI) Calcd for $C_{10}H_{11}N$: *m/z* 145.0891. Found: *m/z* 145.0886.

Supporting Information Available: Experimental information including characterization data of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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