JOC*Note*

Synthesis of 5-Azaindolizine Derivatives by the Palladium-Catalyzed Intermolecular Formal [3+2] Cycloaddition of Alkylidenecyclopropanes with 1,2-Diazines

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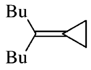
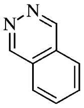
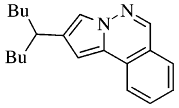
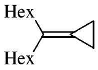
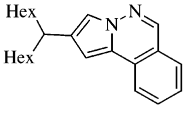
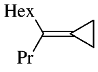
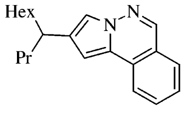
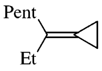
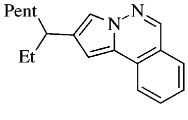
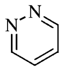
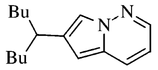
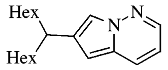
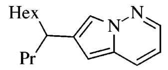
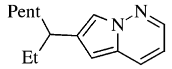
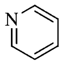
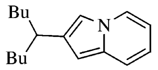
Abstract: The palladium-catalyzed formal [3+2] cycloaddition reaction of alkylidenecyclopropanes with 1,2-diazines proceeded smoothly to give the corresponding 5-azaindolizine derivatives in good to allowable yields. For example, in the presence of 5 mol % of Pd(PPh$_3$)$_4$, the reaction of 1-propylhexylidenecyclopropane with phthalazine or with pyridazine proceeded at 120 °C without solvent, and the corresponding 2-(1-butylpentyl)pyrrolo[2,1-*a*]phthalazine or 6-(1-butylpentyl)pyrrolo[1,2-*b*]pyridazine was obtained in 61% or 49% yield, respectively.

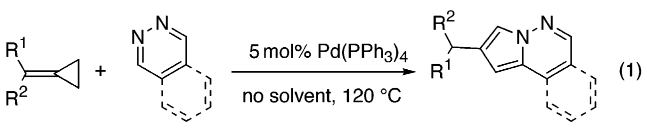
Azaindolizine derivatives have been widely utilized in various fields, such as material science, pharmaceutical, and agricultural chemstry.[1] Therefore, highly efficient and short syntheses of these compounds are of great interest for organic chemists. Recently the catalytic synthesis of azaindolizine derivatives by *intramolecular* cyclization has been reported.[2] To the best of our knowledge, however, the catalytic *intermolecular* reaction to yield 5-azaindolizines has not been reported until today. Recent investigations have demonstrated that formal [3+2] cycloadditions of alkylidenecyclopropanes to alkenes, alkynes, carbon dioxide, and keteneimines are a powerful tool in constructing five-membered carbo- and heterocyclic compounds.[3] More recently, we found that palladium-catalyzed hetero [3+2] cycloaddition of alkylidenecyclopropanes with aldehydes[4] and imines[5] produced tetrahydrofurans and pyrrolidines in good to high yields.

TABLE 1. Palladium-Catalyzed [3+2] Cycloaddition of Alkylidenecyclopropanes 1 with 1,2-Diazines 2[a]

entry	1	2	3	yield/ %[b]
1	 **1a**	 **2a**	 **3a**	57
2	 **1b**	**2a**	 **3b**	55
3	 **1c**	**2a**	 **3c**	61
4	 **1d**	**2a**	 **3d**	52
5	**1a**	 **2b**	 **3e**	38
6	**1b**	**2b**	 **3f**	34
7	**1c**	**2b**	 **3g**	49
8	**1d**	**2b**	 **3h**	43
9	**1a**	 **2c**	 **3i**	6

[a] The reaction of **1** (0.5 mmol) with **2** (2.5 mmol) was carried out in the presence of 5 mol % of Pd(PPh$_3$)$_3$ without solvent at 120 °C for 42−48 h. [b] Isolated yield based on **1**.

Herein, we report that palladium-catalyzed formal [3+2] cycloaddition of the alkylidenecyclopropanes **1** with the 1,2-diazines **2** proceeds smoothly to give the 5-azaindolizine derivatives **3** in good to satisfying yields (eq 1).



1 **2** (5 equiv) **3** (1)

The results are summarized in Table 1. In the presence of 5 mol % of Pd(PPh$_3$)$_4$, the reaction of 1-butylpentyl-

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(1) For a review, see: (a) Flitsch, W. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, UK, 1984; Vol. 4, p 443. (b) Greenhill, J. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, UK, 1984; Vol. 5, p 305. (c) Montgomery, J. A.; Secrist, J. A., III In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, UK, 1984; Vol. 5, p 607. (d) Uchida, T.; Matsumoto, K. *Synthesis* **1976**, 209.

(2) (a) Kel'in, A. V.; Stomek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (b) Kim, J.; Gevorgyan, V. *Org. Lett.* **2002**, *4*, 4697.

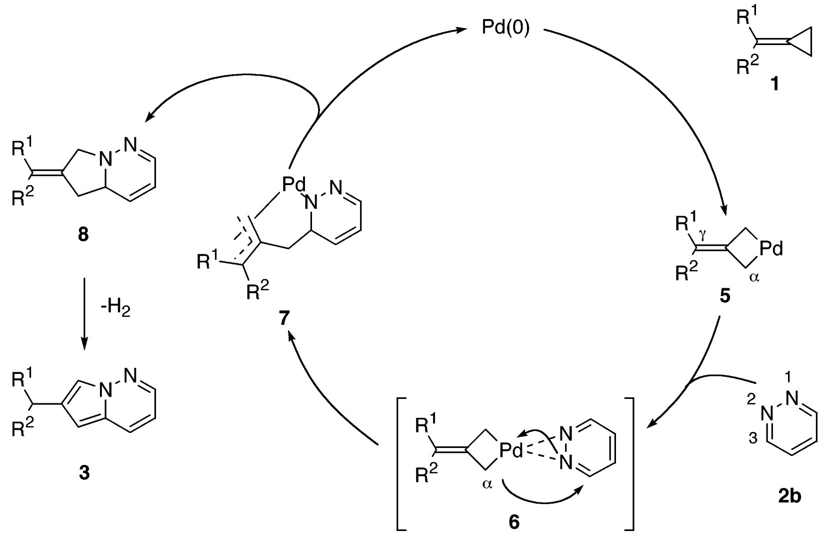
(3) For a review, see: (a) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213. (b) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111. (c) Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589.

(4) Nakamura, I.; Oh, B.; H. Saito, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1298.

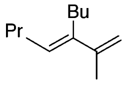
(5) Oh, B. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6203.

10.1021/jo035810i CCC: $27.50

SCHEME 1



idenecyclopropane **1a** with 5 equiv of phthalazine **2a** proceeded at 120 °C and the corresponding 5-azaindolizine derivative **3a** was obtained in 57% yield (entry 1). With the use of smaller amounts of **2a**, the yield of **3a** decreased. In the absence of palladium catalysts, the reaction of **1a** with 5 equiv of **2a** at 120 °C without solvent did not proceed at all. The reaction of **1a** and **2a** with $Pd(OAc)_2$ and PPh_3 as a catalyst gave **3a** in 20% yield. Other catalysts, such as $PdCl_2(PPh_3)_2$, $Pt(PPh_3)_4$, and $Ni(PPh_3)_4$, did not promote this reaction. The use of organic solvents decreased the yield of the reaction of **1a** and **2a**; the reaction of **1a** and **2b** in THF gave **3a** in 16% yield. The reaction of 1-hexylheptylidenecyclopropane **1b** with **2a** gave **3b** in 55% yield (entry 2). The reaction of unsymmetrical alkylidenecyclopropanes **1c** and **1d** with **2a** produced **3c** and **3d** in good yields (entries 3 and 4). The reaction of pyridazine **2b** with **1a** gave **3e** in 38% yield along with a small amount of the diene **4** as a byproduct (entry 5).[7b] The reaction of **2b** with **1b**, **1c**, and **1d** afforded **3f**, **3g**, and **3h** in 34%, 49%, and 43% yield, respectively (entries 6−8). The reaction of pyridine **2c** and **1a** proceeded sluggishly, producing 2-(1-butyl)pentylindolizine **3i** in 6% yield only with a considerable amount of **4** (entry 9).



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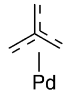
A plausible mechanism for the reaction of an alkylidenecyclopropane **1** with pyridazine **2b** is shown in Scheme 1.[7] Oxidative addition of a distal bond of **1** to palladium(0) would give the palladacyclobutane intermediate **5**. Since **5** is a sort of σ-allylmetal species, the α-allylation of allylpalladium reagent at the 3 position of pyridazine **2b** would occur to form the π-allylpalladium complex **7**. Reductive elimination would give 2-methylenetetrahydroindolizine species **8**. Subsequent isomerization and dehydrogenation would give the 2-alkyl-5-azaindolizine **3**.

Alternatively, there may be the possibility that the present reaction proceeds through formation of the trimethylenemethanepalladium species **9**.[8] However, this possibility is considered less likely since the reactions of the trimethylenemethane precursor **10** with phthalazine **2a** and pyridazine **2b**, using the same conditions as mentioned above, did not produce the [3+2] cycloadducts at all, but gave a complicated mixture of unidentified products.



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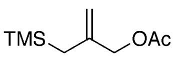
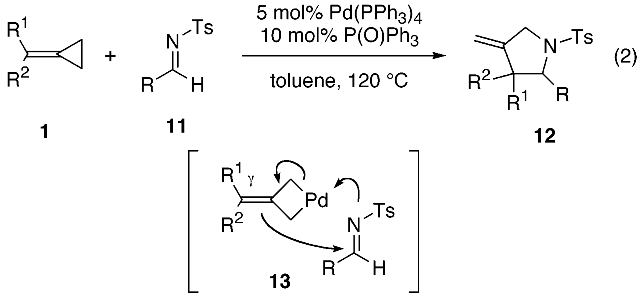


10

Recently we reported that the palladium-catalyzed hetero [3+2] cycloaddition of alkylidenecyclopropanes **1** with imines **11** gave the corresponding 3-methylenepyrrolidines **12** in good to high yields (eq 2). It is a marked



contrast that the reaction of alkylidenecyclopropanes **1** with imines **11** proceeds through allylation of imines **11** at the γ-position of the palladacyclobutane **5**, while the allylation of 1,2-diazines **2** occurred at the α-position of the palladacyclobutane as shown in **6** of Scheme 1.

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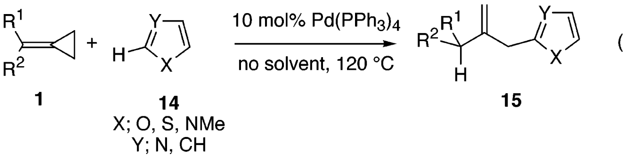
(6) Fujimoto, H.; Suzuki, T. *Inorg. Chem.* **2000**, *39*, 1113.

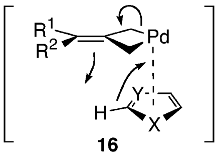
(7) This mode of cycloaddition of methylenecyclopropanes has previously been observed by Binger et al.: Binger, P.; Wedemann, P.; Kozhushkov, S. I.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, 113 and references therein.

(8) (a) Noyori, R.; Odagi, T.; Takaya, H. *J. Am. Chem. Soc.* **1970**, *92*, 5780. (b) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6432.

Perhaps the intermediate **6** of the [3+2] cycloaddition of the palladacycle with pyridazine **2b** is rigid due to bidentate coordination of **2b** to the palladium of **5**. Therefore, attack of palladacyclobutane **5** to **2b** can occur only at the α-position of the palladacyclobutane **5**. Meanwhile, the allylation of imines occurs at the γ-position since the intermediate **13** is much more flexible than **6** and the γ-position of the palladacyclobutane **5** is more reactive than the α-position.

Recently we demonstrated that the palladium-catalyzed reaction of five-membered heteroaromatics **14**, such as furans, thiophenes, thiazoles, and pyrroles, with alkylidenecyclopropanes gave the α-allylated products **15** in good to high yields (eq 3).[9] It is remarkable that the reaction of *electron-deficient* six-membered heteroaromatics (e.g., pyridazine **2b**) with alkylidenecyclopropanes proceeded through [3+2] cycloaddition, while the reaction of *electron-rich* five-membered heteroaromatics (e.g., furans) proceeded through C−H activation. Perhaps the coordination of pyridazine **2b** to the palladacyclobutane intermediate **6** occurs at a lone pair on a nitrogen atom of pyridazine **2b**, leading to the nucleophilic attack of the σ-allylpalladium **5** to pyridazine **2b** at the 3-position as shown in **6**. On the contrary, the coordination of the electron-rich five-membered heterocycles **9** to the palladacyclobutane intermediate **5** occurs most probably at the π-electron cloud of five-membered ring (as shown in **16**) leading to C−H activation at the α-position of the heterocycles.





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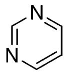
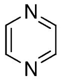
The reaction of 1,2-diazines gave the [3+2] cycloadducts in higher yields than the reaction of pyridine (Table 1, entries 1, 5, and 9) and pyrimidine **17** and pyrazole **18** did not react with alkylidenecyclopropanes **1**. One nitrogen atom of 1,2-diazines might work as an electron-withdrawing group of the other nitrogen atom, which facilitates nucleophilic attack of σ-allylpalladium to a C═N bond of the 1,2-diazine (Scheme 1, **6** to **7**). Bidentate coordination of 1,2-diazines is also the key to this reaction proceeding.



17



18

Now we are at a position to construct the 5-azaindolizine framework in an atom-economic manner. Since the present reaction is free from (i) multistep conversion, (ii) the use of a stoichiometric amount of strong bases, and (iii) formation of undesired byproducts, this methodology has a high potential for synthesizing important azaindolizine compounds, such as antibacterial agents[10] and potential adrenoceptor antagonists.[11]

Experimental Section

General Procedure of Palladium-Catalyzed [3+2] Cycloaddition of the Alkylidenecyclopropanes 1 with the 1,2-Diazines 2. To $Pd(PPh_3)_4$ were added alkylidenecyclopropanes **1** (0.5 mmol) and 1,2-diazines **2** (2.5 mmol) under Ar atmosphere in a pressure vial. After being heated for 42−48 h, the reaction mixture was filtered through a short florisil column with ethyl acetate as an eluent. Separation through a florisil column (hexane as an eluent) and purification by middle-pressure liquid column chromatography (silica gel) with hexane as an eluent afforded the products **3**.

2-(1-Butylpentyl)pyrrolo[2,1-*a*]phthalazine (3a). IR (neat) 2955, 2925, 2856, 1621, 1538, 1506, 1455, 1376, 1322, 1266, 1217, 1174, 1143, 1118, 1031, 948, 898, 859, 791, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, $J = 6.9$ Hz, 6H), 1.17−1.35 (m, 8H), 1.53−1.71 (m, 4H), 2.61−2.67 (s, 1H), 6.70 (s, 1H), 7.34−7.42 (m, 2H), 7.65 (t, $J = 7.7$ Hz, 2H), 7.89 (d, $J = 8.1$ Hz, 1H), 8.25 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.9, 29.9, 36.9, 38.3, 97.3, 115.8, 119.6, 121.1, 125.4, 127.5, 128.0, 131.2, 131.8, 142.5. Anal. Calcd for $C_{20}H_{26}N_2$ (294.43): C, 81.59; H, 8.90; N, 9.51. Found: C, 81.59; H, 8.90; N, 9.23. HRMS (EI) calcd for $C_{20}H_{26}N_2$ *m*/*z* 294.2096, found *m*/*z* 294.2109.

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.

JO035810I

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[9] (a) Nakamura, I.; Saito, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 2661. (b) Nakamura, I.; Siriwardana, A. I.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 3445.

[10] Ruxer, J. M.; Lachoux, C.; Ousset, J. B.; Torregrosa, J. L.; Mattioda, G. *J. Heterocycl. Chem.* **1994,** *31*, 409.

[11] Barlocco, D.; Cignarella, G.; Montesano, F.; Leonardi, A.; Mella, M.; Toma, L. *J. Med. Chem.* **1999**, *42*, 173.