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Palladium-catalyzed [3+2] cycloaddition of alkylidenecyclopropanes with imines

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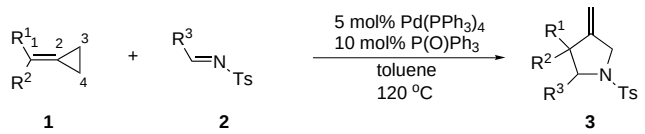
Abstract—Alkylidenecyclopropanes react with *N*-tosylimines in toluene in the presence of a catalytic amount of $Pd(PPh_3)_4$ to afford the corresponding [3+2] cycloaddition products, pyrrolidine derivatives, in good to excellent yields.

Transition-metal-catalyzed [3+2] cycloaddition reactions are one of the most effective methods for constructing five-membered carbo- and heterocycles.[1] Methylenecyclopropanes are particularly useful 'three-carbon components' for [3+2] cycloaddition reactions.[1] The synthesis of carbocycles via the intermolecular [3+2] cycloaddition reaction of methylenecyclopropanes with a carbon–carbon multiple bond[1,2] and its intramolecular version has been reported by several groups.[3] However, catalytic hetero [3+2] cycloaddition of methylenecyclopropanes with a carbon–heteroatom multiple bond is limited to the reaction with heterocumulenes such as carbon dioxide[4] and keteneimines.[5] Recently, we reported on the palladium-catalyzed [3+2] cycloaddition of methylenecyclopropanes with aldehydes.[6] To the best of our knowledge, there has been no report on the catalytic [3+2] cycloaddition between methylenecyclopropanes and the carbon–nitrogen double bond of imines. The [3+2] cycloaddition of electron-deficient imines with trimethylenemethane (TMM), generated in situ from 2-acetoxymethyl-3-allyltrimethylsilane and a palladium catalyst, was reported by Trost and Marrs.[7]

We now report that the reaction of methylenecyclopropanes **1** with *N*-tosylimines **2** in the presence of 5 mol% of [$Pd(PPh_3)_4$] and 10 mol% of triphenylphosphine oxide at 120°C gives the corresponding [3+2] cycloadducts, the pyrrolidine derivatives **3**, in good to excellent yields (Eq. (1)).



1 **2** **3** (1)

The results are summarized in Table 1. In the presence of catalytic amounts of $Pd(PPh_3)_4$ (5 mol%) and triphenylphosphine oxide (10 mol%), the reaction of 2-butylpentylidenecyclopropane **1a** (1 mmol) and 2-furyl-*N*-tosylimine **2a** (0.5 mmol) in toluene at 120°C for 16 h gave the corresponding cycloadduct **3a** in 89% yield (entry 1). The use of other solvents, such as THF, DMF, 1,4-dioxane and CH_3CN, also gave the cycloaddition product **3a** in good or moderate yields, while the use of CH_2Cl_2 as a solvent did not afford the cyclized product. Without a palladium catalyst, the reaction of **1a** and **2a** did not proceed at all. The catalytic system $Pd(dba)_2/PPh_3$ was less effective, and $Pd_2(dba)_3CHCl_3$ or $Pd(PPh_3)_2Cl_2$ did not promote the reaction of **1a** and **2a** at all. The combination of $Pd(PPh_3)_4$ with phosphine ligands such as PPh_3, $P(O)Bu_3$, $P(o\text{-tolyl})_3$ gave **3a** in good to high yields. However, even in the presence of a $Pd(PPh_3)_4$ catalyst, if bidentate ligands such as bis-(diphenylphosphanyl)methane (dppm), 1,2-bis(diphenylphosphanyl)ethane (dppe) and 1,1′-bis(diphenylphosphanyl)ferrocene (dppf) were used as a ligand, only trace amounts of **3a** were obtained. The reaction of 2-hexylheptylidenecyclopropane **1b** with **2a**, and 2-methyl-4-phenylbutylidenecyclopropane **1c** with **2a** afforded **3b** and **3c** in yields of 88 and 91%, respectively (entries 2 and 3). The spiro compound **3d** was obtained in 71% yield from the reaction of **1d** with **2a** (entry 4). The reaction of **1a** with **2b** proceeded smoothly and

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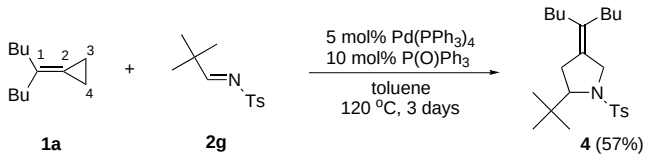
the corresponding cycloadduct **3e** was produced in 91% yield (entry 5). The aryl imines **2c**–**f**, having an electron-donating or electron-withdrawing group at the *para*-position, also reacted smoothly to give **3f**–**i** in excellent yields (entries 6–9).

Interestingly, the reaction of **1a** with *t*-butyl-*N*-tosylimine **2g** gave the regioisomeric [3+2] cycloadduct **4** in 57% yield, in which the three carbon component was derived from the C-2,3,4 carbons of the cyclopropyl group of **1a** (Eq. (2)). This is in marked contrast to the ordinary [3+2] cycloaddition shown in Eq. (1), in which the three carbon component is derived from the C-1,2,3 carbons of **1a**. The formation of the ordinary [3+2] cycloadduct was not detected in the reaction of **2g**.

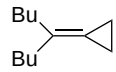
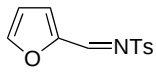
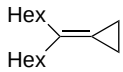
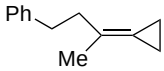
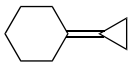
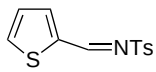
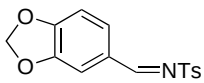
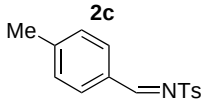
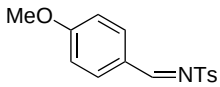
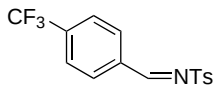


1a **2g** **4** (57%)

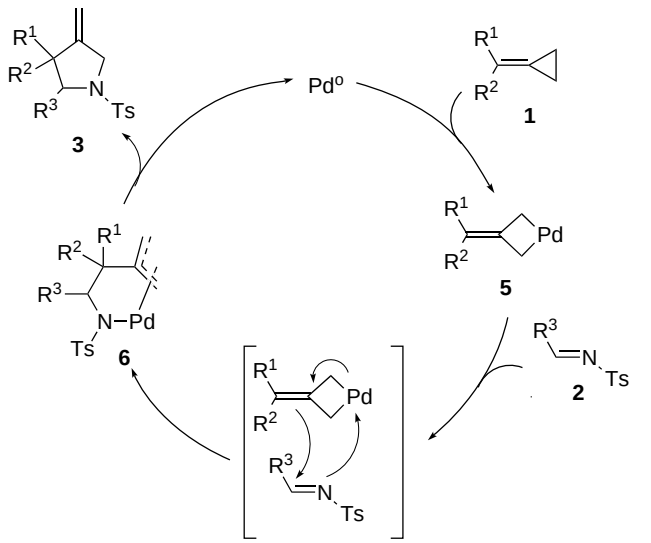
(2)

A plausible mechanism for the ordinary [3+2] cycloaddition is illustrated in Scheme 1. Oxidative addition of palladium(0) to a distal bond of the alkylidenecyclopropane **1** leads to the palladacyclobutane complex **5**,[8] which reacts with the imine **2** to give the π-allylpalladium complex **6**. Reductive elimination of palladium(0) gives the [3+2] cycloadduct **3**. In this case, the σ-allylpalladium complex **5** reacts with the imine **2** in a manner similar to ordinary allylic organometallics such

Table 1. Palladium-catalyzed cycloaddition of alkylidenecyclopropanes **1** and imines **2a**

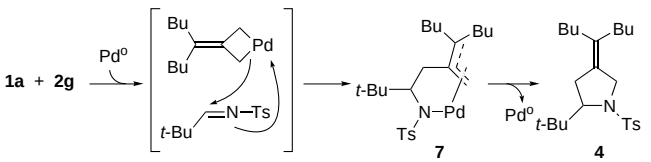
entry	1	2	time / h	3	yield / %[b]
1	 **1a**	 **2a**	16	**3a**	89
2	 **1b**	**2a**	18	**3b**	88
3	 **1c**	**2a**	13	**3c**	91 (56:44)[c]
4	 **1d**	**2a**	20	**3d**	71
5	**1a**	 **2b**	17	**3e**	91
6	**1a**	 **2c**	16	**3f**	93
7	**1a**	 **2d**	12	**3g**	91
8	**1a**	 **2e**	9	**3h**	94
9	**1a**	 **2f**	24	**3i**	88

[a]The reaction of **1** (1 mmol) and **2** (0.5 mmol) was carried out in the presence of 5 mol% of $Pd(PPh_3)_4$ and 10 mol% of triphenylphosphine oxide in toluene at 120 °C. [b]Isolated yield based on **2**. [c]The diastereomeric ratio of **3c**.



Scheme 1. A plausible mechanism for the palladium-catalyzed [3+2] cycloaddition of alkylidenecyclopropanes **1** with imines **2**.

as allylic stannanes; **5** reacts at the γ-position of the allylic unit. On the other hand, the formation of the regioisomeric [3+2] cycloadduct **4**, in the case of *t*-butyl-*N*-tosylimine **2g**, can be explained if **5** reacts with the imine **2g** at the α-position of the allylic unit (Scheme 2). The reaction at the α-position leads to the π-allylpalladium intermediate **7**, which gives **4** upon reductive elimination of Pd(0). Perhaps, steric hindrance by the *t*-butyl group of **2g** forces the allylation reaction to take an alternative pathway through the α-addition.



Scheme 2. A plausible mechanism for the palladium-catalyzed [3+2] cycloaddition of **1a** with **2g**.

The thermal [3+2] cycloaddition reactions of methylenecyclopropane ketals with aldehydes[9] and imines[10] were reported recently. However, these reactions require the use of highly activated methylenecyclopropane derivatives.

In conclusion, we have developed a novel and efficient route to pyrrolidine derivatives through the palladium-catalyzed [3+2] cycloaddition between methylenecyclopropanes and imines. The present atom-economical reaction may be potentially useful for constructing biologically important pyrrolidine skeletons.

References

1. For reviews, see: (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1; (b) Binger, P.; Buch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77; (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.
2. (a) Noyori, R.; Odagi, T.; Takaya, H. *J. Am. Chem. Soc.* **1970**, *92*, 5780; (b) Binger, P.; Schuchardt, U. *Chem. Ber.* **1981**, *114*, 3313.
3. (a) Yamago, S.; Nakamura, E. *J. Chem. Soc., Chem. Commun.* **1988**, 1112; (b) Corlay, H.; Lewis, R. T.; Motherwell, W. B.; Shipman, M. *Tetrahedron* **1995**, *51*, 3303; (c) Lautens, M.; Ren, Y.; Delanghe, P. H. M. *J. Am. Chem. Soc.* **1994**, *116*, 8821.
4. Inoue, Y.; Hibi, T.; Satake, M.; Hashimoto, H. *J. Chem. Soc., Chem. Commun.* **1979**, 982.
5. Weintz, H. J.; Binger, P. *Tetrahedron Lett.* **1985**, *26*, 4075.
6. Nakamura, I.; Oh, B. H.; Saito, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1298.
7. Trost, B. M.; Marrs, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 6636.
8. Suzuki, T.; Fujimoto, H. *Inorg. Chem.* **2000**, *39*, 1113.
9. Yamago, S.; Nakamura, E. *J. Org. Chem.* **1990**, *55*, 5553.
10. Yamago, S.; Nakamura, M.; Wang, X. Q.; Yanagawa, M.; Tokumitsu, S.; Nakamura, E. *J. Org. Chem.* **1998**, *63*, 1694.