J|A|C|S COMMUNICATIONS

Published on Web 08/21/2009

[4+2] Cycloaddition of *o*-Xylylenes with Imines Using Palladium Catalyst

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o-Xylylenes, which are 1,3-cyclohexadienes bearing two exo-methylenes at the 5- and 6-positions, are often used as diene substrates for the Diels−Alder reaction.[1] The [4+2] cycloaddition of *o*-xylylenes with alkenes or alkynes has been intensively studied. As with the carbon dienophiles, imines might be another attractive dienophile for the *o*-xylylene cycloaddition. The hetero-Diels−Alder reaction[2] will afford tetrahydroisoquinoline frameworks, which are found in many useful biologically active compounds. Nevertheless, only a few reports have been made on the reaction with imines.[3] In these works, the *o*-xylylenes were generated from the thermal ring-opening reaction of benzocyclobutenes. Herein, we describe a new approach to the [4+2] cycloaddition of *o*-xylylene with imines.

We previously reported a unique protocol for the *o*-xylylene cycloaddition with C−C double bonds using a palladium catalyst.[4] In the palladium catalysis, *o*-{(trimethylsilyl)methyl}benzyl carbonates **1** were employed as formal *o*-xylylene precursors. In our initial attempt, a mixture of **1a** and *N*-tosylimine **2a** in DMF was heated at 120 °C for 24 h in the presence of 3.0% Pd(η^3-C_3H_5)Cp-DPPE catalyst, which is the most effective for the cycloaddition with methyl acrylate. However, the desired tetrahydroisoquinoline **3a** was obtained in only 11% yield. The catalyst efficiency was significantly affected by the distance between the phosphorus atoms of bidentate ligand. Use of DPPPent[5,6] in place of DPPE brought about the improved yield of **3a**. Gradual decomposition of the catalyst into palladium black was observed in the course of the cycloaddition. Owing to the catalyst decomposition, the prolonged reaction was ineffective in enhancing the yield. The undesirable formation of palladium black was avoided by increasing the amount of DPPPent. When the ligand was used in 2.2 mol equiv with palladium, the reaction of **1a** with **2a** successfully produced **3a** in 92% isolated yield, but it required 48 h for the complete conversion of **1a** (Scheme 1).

The reaction rate of the catalytic cycloaddition was dramatically enhanced by stoichiometric potassium fluoride, which activated the C−Si bond.[7] The reaction of **1a** with **2a** finished within 3 h, affording the cycloaddition product **3a** in 85% isolated yield. The choice of the fluoride source was crucial for the catalytic reaction. Use of cesium or tetrabutylammonium fluoride led to immediate disappearance of **1a** but failed to produce **3a**. The reactive fluoride sources induced the rapid generation of free *o*-xylylene from **1a** without the involvement of palladium catalysis.[8] The *o*-xylylene decomposed before it reacted with **2a**. In contrast, potassium fluoride was less reactive to **1a** because of its low solubility in organic solvent. The low reactivity caused a selective acceleration of forming an organopalladium species equivalent to *o*-xylylene in the catalytic cycle. Although potassium fluoride is known to be effective for the generation of *o*-xylylene from **1a**,[9,10] little formation of **3a** was observed when a mixture of **1a** and **2a** was treated with potassium fluoride in the absence of Pd(η^3-C_3H_5)Cp.[11] The observation suggests that the formation of **3a** proceeds not through the concerted [4+2] cycloaddition of *o*-xylylene with **2a** but through a reaction pathway involving palladium catalysis.

Scheme 1. [4+2] Cycloaddition of **1a** with **2a**

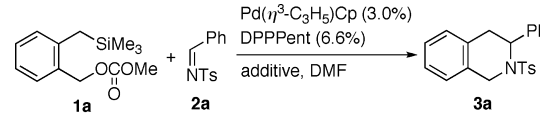
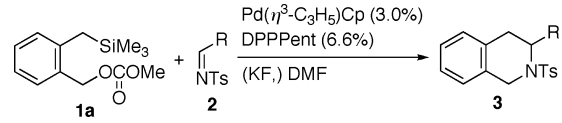


Table 1. [4+2] Cycloaddition of **1a** with *N*-Tosylimines **2**[a]



entry	R (**2**)	condition[b]	time, h	product (**3**)	yield,[c] %
1	2-MeC_6H_4 (**2b**)	A	24	**3b**	84
2	2,6-$Me_2C_6H_3$ (**2c**)	A	24	**3c**	78
3	4-$MeOC_6H_4$ (**2d**)	A	24	**3d**	81
4	4-$CF_3C_6H_4$ (**2e**)	A	48	−	0
5	4-$CF_3C_6H_4$ (**2e**)	B	3	**3e**	67
6	3-$CF_3C_6H_4$ (**2f**)	B	3	**3f**	76
7	1-naphthyl (**2g**)	B	3	**3g**	85
8	2-naphthyl (**2h**)	B	3	**3h**	81

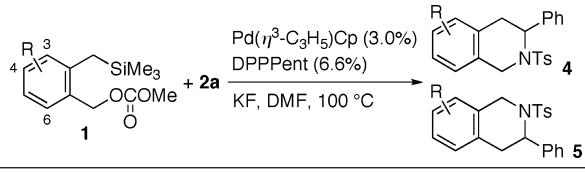
[a] Reactions were conducted in DMF (1.0 mL). The ratio of **1a** (0.15 mmol):**2**:Pd(η^3-C_3H_5)Cp:DPPPent:KF was 100:120:3.0:6.6:150. [b] Condition A: the reactions were carried out at 120 °C without KF. Condition B: the reactions were carried out at 100 °C with KF. [c] Isolated yield.

A range of *N*-tosylimines underwent the cycloaddition with **1a** under the optimized conditions (Table 1). The DPPPent-palladium catalyst transformed electron-rich imines **2b**−**2d** into the desired tetrahydroisoquinolines in good yields (entries 1−3). In these cases, potassium fluoride brought about a marked enhancement of the reaction rate but slightly decreased the yields of **3**. Substituents at the ortho-positions of benzimine scarcely disturbed the formations of **3c** and **3d**. In contrast, the electron-withdrawing group of **2e** severely hampered the catalytic cycloaddition in the absence of potassium fluoride (entry 4). However, the use of the fluoride allows **2e** and **2f** to react with **1a**, affording the cycloadducts **3e** and **3f** (entries 5, 6). The fluoride additive was effective for the reactions of polycyclic aromatic aldimines **2g** and **2h** (entries 7, 8).

o-(Silylmethyl)benzyl carbonates **1b**−**1f**, which have substituents on the aromatic ring, also worked as formal *o*-xylylene precursors in the catalytic cycloaddition with imine **2a** as shown in Table 2. The substituents at the ortho-positions of both reaction sites have no effect on the reactivity of the substrates **1**. The substrate **1b**, which has a phenyl group at the 6-position, was converted into a regioisomeric mixture of **4b** and **5b** in the molar ratio 89:11, when the reaction was carried out with potassium fluoride (entry 1). In the absence of the additive, a mixture of **4b** and **5b** was obtained

10.1021/ja905988e CCC: $40.75

Table 2. [4+2] Cycloaddition of *o*-(Silylmethyl)benzyl Esters **1** with **2a**[a]



entry	R (**1**)	time, h	product	**4**:**5**[b]	yield,[c] %
1	6-Ph (**1b**)	4	**4b**, **5b**	89:11	81
2[d]	6-Ph (**1b**)	72	**4b**, **5b**	89:11	72
3	3-Ph (**1c**)	4	**4c** (= **5b**), **5c** (= **4b**)	10:90	76
4[d]	3-Ph (**1c**)	24	**4c** (= **5b**), **5c** (= **4b**)	11:89	72
5	6-Me (**1d**)	4	**4d**, **5d**	56:44	73
6[d]	3-Me (**1e**)	48	**4e** (= **5d**), **5e** (= **4d**)	43:57	78
7	4,6-Me_2 (**1f**)	3	**4f**, **5f**	88:12	76

[a] Reactions were conducted under condition B in Table 1 unless otherwise noted. [b] Determined by the ^{1}H NMR spectra of the crude products. [c] Isolated yields of the mixtures of **4** and **5**. [d] The reactions were conducted under condition A in Table 1.

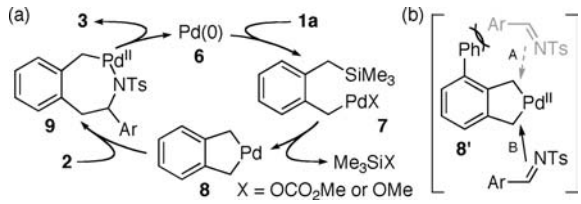


Figure 1. (a) A plausible mechanism of the catalytic cycloaddition of **1a** with **2**. (b) Possible approaches of **2** to **8′** for the 1,2 insertion.

in a similar molar ratio, while a longer reaction time was required for the full conversion of **1b** (entry 2). The reversed regioselectivity was observed in the reaction of 3-substituted substrate **1c** (entries 3 and 4). The observation indicates that the two benzylic reaction sites become equivalent in the course of the catalytic cycloaddition. The good regioselectivity would be caused by the steric hindrance around the 3- or 6-position. The reactions of the methyl-substituted **1d** and **1e** proceeded with low regioselectivities (entries 5, 6). To our surprise, the 4-methyl group of **1f** remarkably magnified the ratio of **4** to **5** (entry 7).

The cycloaddition of **1a** with **2** would proceed through the mechanism in Figure 1a.[4] The benzylic C−O bond of **1a** is cleaved by DPPPent-palladium(0) **6** to form (benzyl)palladium **7**.[12] The silyl group of **7** gives rise to the intramolecular transmetalation, which is facilitated by potassium fluoride.[7c] The intermediacy of 2-palladaindane **8** is consistent with the reversal of the regioselectivities in the reactions of **1b** and **1c**, because the identical intermediate **8′** would be formed from both substrates. A C−Pd bond in **8** undergoes the 1,2 insertion of imine **2**.[13] The reductive elimination from the cyclic (amido)palladium complex **9** produces the desired tetrahydroisoquinoline **3**. Alternatively, it is conceivable that the product **3** is formed through nucleophilic addition of the benzylsilane moiety of **7** to the C−N double bond of **2** and a successive nucleophilic attack of the resulting nitrogen anion to the benzyl ligand on the palladium. However, if the formation of **3** occurred through the nucleophilic addition, regiospecific formation of **4** must be observed in the reactions of **1b**−**1f**. Consequently, the latter pathway is ruled out by the results of Table 2.

The good regioselectivity in the reaction of **1b** or **1c** with **2a** is illustrated as shown in Figure 1b. As described above, both substrates react with **6** to yield the identical palladacycle **8′**. The 1,2 insertion of **2** into the upper C−Pd bond in **8′** leads to the formation of **5b**. However, the approach of **2** to **8′** following arrow A is hampered by the steric bulkiness of the phenyl group. In contrast, the 1,2 insertion into the lower C−Pd bond occurs without serious steric repulsion between the imine and **8′**. Therefore, preferential formation of **4b** was observed in the reactions of entries 1−4 in Table 2. The size of the methyl group in **1d** or **1e** was insufficient for controlling the regiochemistry.

In conclusion, we developed a new method for the [4+2] cycloaddition of *o*-xylylenes with imines.[14] The cycloaddition proceeded in the presence of a DPPPent-ligated palladium complex, providing a range of tetrahydroisoquinolines in good yield. The palladium catalyst allowed the aza-Diels−Alder reaction of the parent *o*-xylylene.

Acknowledgment. This work was supported by KAKENHI (No. 19685008) and a Grant-in-Aid for the Global COE Program, "Science for Future Molecular Systems" from MEXT.

Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA905988E