Synthetic Methods

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Palladium-Catalyzed Decarboxylative Intramolecular Aziridination from 4*H*-Isoxazol-5-ones Leading to 1-Azabicyclo[3.1.0]hex-2-enes**

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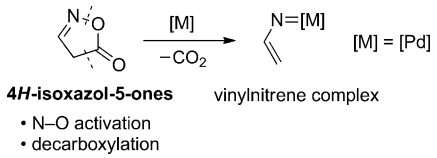
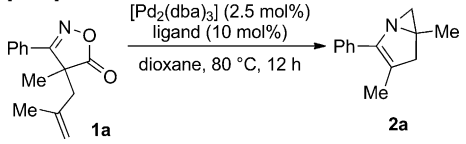
Transition-metal-catalyzed nitrene-transfer reactions are powerful methods for incorporating nitrogen atoms directly into organic molecules.[1,2] Organic azides[2a,b] and *N*-sulfonyliminoiodinanes[2c–e] are highly reactive nitrene precursors, and have been widely used for such reactions as olefin aziridination and C–H amination. However, they must be handled carefully or prepared immediately before use because of their high reactivity. Therefore, the development of catalytic nitrene-transfer reactions that use stable precursors under mild reaction conditions is an important topic. Our research interest has been focused on 4*H*-isoxazol-5-ones, five-membered cyclic oxime esters, as candidates for stable vinylnitrene equivalents (Scheme 1). They can be readily prepared from β-ketoesters[3] and are generally thermally stable. We envisioned that the reaction of a 4*H*-isoxazol-5-one with a palladium catalyst would give a nitrene complex,[4] which is formed by the activation of the N–O bond by a low-valent palladium species[5] followed by decarboxylation. Herein, we report a palladium-catalyzed decarboxylative intramolecular aziridination reaction of alkene-tethered 4*H*-isoxazol-5-ones to form N-fused bicyclic aziridines.



Scheme 1. 4*H*-isoxazol-5-ones as a vinylnitrene equivalent.

During the course of our investigations of several nitrene-transfer reactions using 4*H*-isoxazol-5-ones, we found that the reaction of 4*H*-isoxazol-5-one **1a**, which possesses a methallyl group at the 4-position, in the presence of 2.5 mol% of $[Pd_2(dba)_3]$ (5 mol% Pd) and 10 mol% of PPh_3 in 1,4-dioxane at 80 °C for 12 h gave the expected 1-azabicyclo[3.1.0]hex-2-ene **2a**[6] in 84% yield (Table 1, entry 1). Various triarylphosphine ligands were examined for this decarboxylative intramolecular aziridination reaction (Table 1, entries 2–9). The use of more electron-donating triarylphosphines resulted in similar or lower yields (Table 1, entries 2–4), whereas the use of more electron-withdrawing triarylphosphines increased the yields (Table 1, entries 5 and 6) up to 95% yield (87% yield upon isolation). However, the reactions with the more electron-deficient $P(C_6F_5)_3$ or *ortho*-substituted triarylphosphines did not proceed well (Table 1, entries 7–9). Trialkylphosphines or bidentate phosphine ligands were not effective for this reaction (Table 1, entries 10–14).[7]

Table 1: Palladium-catalyzed intramolecular aziridination giving azabicyclo[3.1.0]hexene **2a**.[a]



Entry	Ligand	Conversion [%][b]	Yield [%][b]
1	PPh_3	98	84
2	$P(4\text{-}MeC_6H_4)_3$	91	76
3	$P(4\text{-}MeOC_6H_4)_3$	98	83
4	$P(2\text{-furyl})_3$	81	69
5	$P(4\text{-}FC_6H_4)_3$	100	92
6	$P(4\text{-}CF_3C_6H_4)_3$	100	95 (87[c])
7	$P(C_6F_5)_3$	0	0
8	$P(2\text{-}MeC_6H_4)_3$	14	11
9	$P(2\text{-}MeOC_6H_4)_3$	9	0
10	PBu_3	0	0
11	PCy_3	3	0
12	$P(t\text{Bu})_3$	7	6
13[d]	dppb	11	0
14[d]	*rac*-binap	15	0

[a] The reaction was carried out with isoxazolone **1a** (0.20 mmol), $[Pd_2(dba)_3]$ (2.5 mol%), and ligand (10 mol%) in 1,4-dioxane (1.3 mL). [b] The yields were determined by ^{1}H NMR spectroscopy of the crude products (see the Supporting Information). [c] Yield of the isolated product. [d] 5 mol% of ligand was used. binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl ,Cy = cyclohexyl, dba = dibenzylideneacetone, dppb = bis(diphenylphosphanyl)butane.

The present intramolecular aziridination reaction is applicable to a variety of 4*H*-isoxazol-5-ones possessing a range of substituents. Table 2 summarizes the substrate scope of this reaction, using 5 mol% or 10 mol% of the palladium catalyst $[Pd_2(dba)_3]/P(4\text{-}CF_3C_6H_4)_3$. 4*H*-Isoxazol-5-ones **1b** and **1c**, bearing a 2-naphthyl group and a (*p*-trifluoromethyl)phenyl group instead of a phenyl group, gave 1-azabicyclo[3.1.0]hexenes **2b** and **2c** in 83% and 80% yields, respectively (Table 2, entries 2 and 3). The use of isoxazolone **1d**, having two phenyl groups on the five-membered ring

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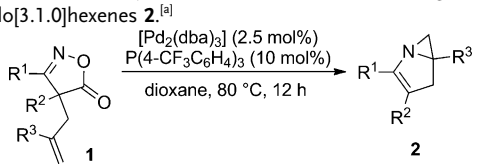
Table 2: Palladium-catalyzed intramolecular aziridination giving azabicyclo[3.1.0]hexenes **2**.[a]

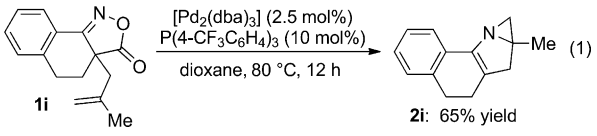


1 **2**

Entry	Isoxazolone	R^1	R^2	R^3		Yield [%][b]
1	**1a**	Ph	Me	Me	**2a**	87
2	**1b**	2-naphthyl	Me	Me	**2b**	83
3	**1c**	4-$CF_3C_6H_4$	Me	Me	**2c**	80[c]
4	**1d**	Ph	Ph	Me	**2d**	88[c]
5	**1e**	Ph	Me	*n*-hexyl	**2e**	80
6	**1f**	*n*Pr	Me	*n*-hexyl	**2f**	63[c]
7	**1g**	Me	Bn	Me	**2g**	64[c]
8	**1h**	Me	methallyl	Me	**2h**	40[c]

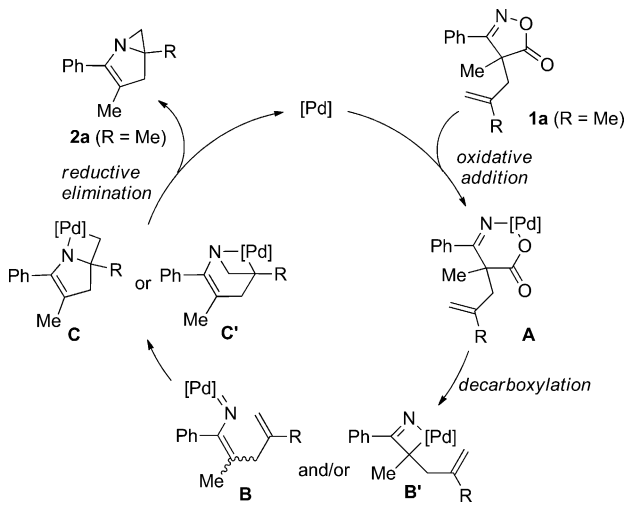
[a] The reaction was carried out with isoxazolone **1a** (0.20 mmol), $[Pd_2(dba)_3]$ (2.5 mol%), and $P(4\text{-}CF_3C_6H_4)_3$ (10 mol%) in 1,4-dioxane (1.3 mL). [b] Yield of the isolated product. [c] $[Pd_2(dba)_3]$ (5 mol%), and $P(4\text{-}CF_3C_6H_4)_3$ (20 mol%) were used.

($R^1 = R^2 = Ph$), increased the yield of the corresponding aziridines up to 88% (Table 2, entry 4). Isoxazolone **1e**, which possesses an allyl group with a long alkyl chain ($R^3 = n$-hexyl), gave the bicyclic aziridine in 80% yield (Table 2, entry 5). Isoxazolones with aliphatic groups at the imine carbon atom were also used in the present reaction, and the yields of 1-azabicyclo[3.1.0]hexenes **2f**–**2h** were moderate. In the case of isoxazolone **1h**, bearing two methallyl groups, the corresponding aziridine **2h** was obtained in 40% yield, with one of the methallyl groups remaining intact. Furthermore, the reaction of tricyclic isoxazolone **1i** also proceeded well to give tetracyclic compound **2i** in 65% yield [Eq. (1)].

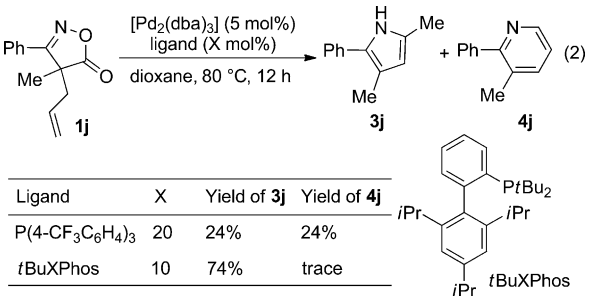


Scheme 2 shows a proposed catalytic cycle for the palladium-catalyzed intramolecular aziridination reaction of methallyl-substituted 4*H*-isoxazol-5-one **1a**. First, the oxidative addition of isoxazolone **1a** to a low-valent palladium center forms the six-membered palladacycle **A**, which readily undergoes decarboxylation[8,9] to give vinylnitrene/palladium complex **B**[10] and/or four-membered azapalladacyclobutene intermediate **B′**.[11] Then, cycloaddition of the tethered alkene gives two possible azapalladacycles **C** and **C′**. Both intermediates can undergo the reductive elimination to produce bicyclic aziridine **2a**, and regenerate the low-valent palladium catalyst.

The palladium-catalyzed reaction of 4*H*-isoxazol-5-one **1j**, possessing an unsubstituted allyl group, did not give a bicyclic aziridine,[12] instead, pyrrole **3j** and pyridine **4j** were obtained in low yields.[13] The selectivity towards the pyrrole was remarkably increased using a bulky monophosphine ligand (*t*BuXPhos).[14] Under the optimized reaction conditions, pyrrole **3j** was obtained in 74% yield together with the trace amount of pyridine **4j** [Eq. (2)].

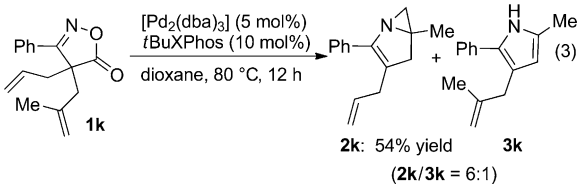


Scheme 2. A proposed catalytic cycle.



Ligand	X	Yield of **3j**	Yield of **4j**
$P(4\text{-}CF_3C_6H_4)_3$	20	24%	24%
*t*BuXPhos	10	74%	trace

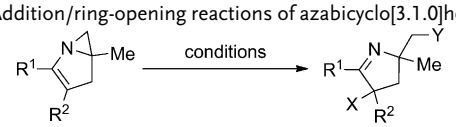
The reaction of isoxazolone **1k**, which possesses both an allyl group and a methallyl group, could result in a mixture of three products (aziridine, pyrrole, and pyridine). Interestingly, the reaction proceeded selectively in the presence of a Pd/*t*BuXphos catalyst to give the corresponding bicyclic aziridine **2k** in 54% yield with a small amount of pyrrole **3k** as a by-product [Eq. (3); **2k**/**3k** = 6:1].



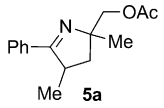
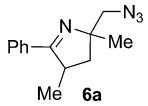
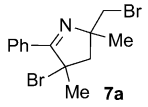
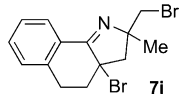
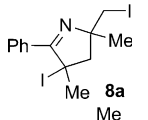
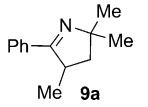
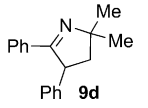
Azabicyclo[3.1.0]hexenes, the products of the present reaction, are highly reactive because of their strained N-fused bicyclic aziridine backbone.[6d,e,15] Of the various addition reactions to the activated olefins of these azabicyclo-[3.1.0]hexenes, protonolysis of the bicyclic aziridines was first examined. The reaction of azabicyclic compound **2a** with an excess amount of acetic acid in dichloromethane pro-

ceeded at room temperature to give ring-opening addition product **5a** in 79% yield (Table 3, entry 1). In this product the electrophile (proton) was introduced at the 3-position on the azabicyclo[3.1.0]hexene backbone, and the nucleophile (acetate anion) was incorporated at the 6-position. This type of reaction also proceeded with other reagents. The use of trimethylsilyl azide and water resulted in the ring-opening addition of hydrogen azide to give the corresponding azidomethyl 1-pyrroline **6a** (Table 3, entry 2; 62% yield). The reaction of azabicyclo[3.1.0]hexene **2a** with molecular bromine (Br_2) afforded a dibrominated 1-pyrroline (**7a**) in 73% yield with a 2:1 d.r. (Table 3, entry 3). Interestingly, the reaction of tetracyclic aziridine **2i** with molecular bromine almost exclusively gave dibromide **7i** in 63% yield (d.r. > 20:1; Table 3, entry 4). Diiodination of aziridine **2a** also gave ring-opened diiodopyrroline **8a** in 67% yield with a 3:1 d.r. (Table 3, entry 5). Catalytic hydrogenation using a heterogeneous palladium catalyst also proceeded to give dihydrogen adduct **9a** in 54% yield (Table 3, entry 6). The diphenyl-substituted bicyclic aziridine **2d** also underwent catalytic hydrogenation to afford the pyrroline **9d** in 61% yield (Table 3, entry 7).

Table 3: Addition/ring-opening reactions of azabicyclo[3.1.0]hexenes **2**.[a]

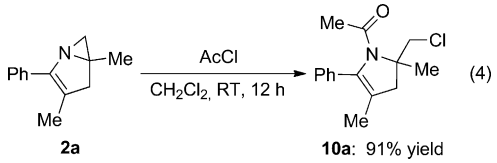


2 **5–9**

Entry	Aziridine	Pyrroline	Conditions	Yield [%][b]	d.r.[c]
1	**2a**	 **5a**	AcOH	79	1:1
2	**2a**	 **6a**	Me_3SiN_3, H_2O	62	1:1
3	**2a**	 **7a**	Br_2	73	2:1
4	**2i**	 **7i**	Br_2	63	> 20:1
5	**2a**	 **8a**	I_2	67	3:1
6	**2a**	 **9a**	H_2, 5% Pd/C	54	–
7	**2d**	 **9d**	H_2, 5% Pd/C	61	–

[a] See the Supporting Information for reaction details. [b] Yield of the isolated product as a mixture of diastereomers. [c] Determined by ^{1}H NMR spectroscopy.

A carbon electrophile showed a different reactivity toward the bicyclic aziridine. Azabicyclo[3.1.0]hexene **2a** was treated with acetyl chloride to give the N-acetylated enamide **10a** in 91% yield [Eq. (4)]. This result indicates that the electrophiles first combine with the nitrogen atom followed by the nucleophilic attack of the counter anion to give the ring-opened enamines, and that the enamines readily isomerize into the imines with the exception of acetyl chloride.



2a **10a**: 91% yield (4)

In conclusion, we have developed a palladium-catalyzed intramolecular aziridination reaction using methallyl-substituted 4*H*-isoxazol-5-ones as a vinylnitrene precursor. The resulting N-fused bicyclic aziridines are readily converted into 1-pyrrolines by the addition/ring-opening reaction with various reagents. The pyrrole formation from an allyl-substituted 4*H*-isoxazol-5-one also supports the intermediacy of a vinylnitrene/palladium **B** as well as an azapalladacyclobutane **C**. Enantioselective aziridination and intermolecular nitrene-transfer reactions using the present decarboxylation protocol are in progress.

Experimental Section

General Procedure for Table 2: Isoxazolone **1** (0.20 mmol) was added to a solution of $[Pd_2(dba)_3]$ (4.6 mg, 5.0 μmol) and $P(4\text{-}CF_3C_6H_4)_3$ (9.3 mg, 20 μmol) in 1,4-dioxane (1.3 mL) and the mixture was stirred at 80°C for 12 h. The reaction mixture was filtered through a pad of Florisil and the filtrate was concentrated under vacuum. The residue was chromatographed on silica gel 60 NH_2 (Kanto Chemical, co. ltd.) (hexane/EtOAc = 20:1) to give **2**.

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Keywords: 4*H*-isoxazol-5-ones · cyclization · decarboxylation · homogeneous catalysis · palladium

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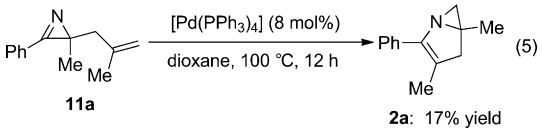

11a **2a**: 17% yield (5)

[11] The decarboxylation of intermediate **A** should give two isomers of vinylnitrene complex **B** (*cis* and *trans*), and only the *cis* isomer can undergo the following insertion. On the other hand, direct insertion of an alkene moiety from azapalladacyclobutene **B′** will not give the aziridination product **2a**. Taking these points into consideration, the two intermediates **B** and **B′** might exist in equilibrium and the *cis* isomer of intermediate **B** might undergo the subsequent steps.

[12] Reactions of isoxazolones possessing other allyl groups (crotyl, cinnamyl, and 2-methyl-3-phenylprop-2-en-1-yl) or a longer tether (3-methylbut-3-en-1-yl group) resulted in low yields of the corresponding aziridines or complex mixtures.

[13] In the case of allyl-substituted isoxazolone **1j** (R = H), intermediate **C** possesses a β hydrogen. β-Hydride elimination from **C** followed by reductive elimination/isomerization will produce pyrrole **3j**. The other intermediate **C′** will undergo double β-hydride elimination to give pyridine **4j**, and generate a palladium dihydride species. See also Ref. [10].

[14] *t*BuXphos was developed by Buchwald and co-workers and widely used for palladium-catalyzed cross-coupling reactions. For examples, see: a) X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653; b) K. W. Anderson, T. Ikawa, R. E. Tundel, S. L. Buchwald, *J. Am. Chem. Soc.* **2006**, *128*, 10694.

[15] M. C. Mcmills, S. C. Bergmeier in *Comprehensive Heterocyclic Chemistry III*, Elsevier, Amsterdam, **2008**, pp. 105–172.

