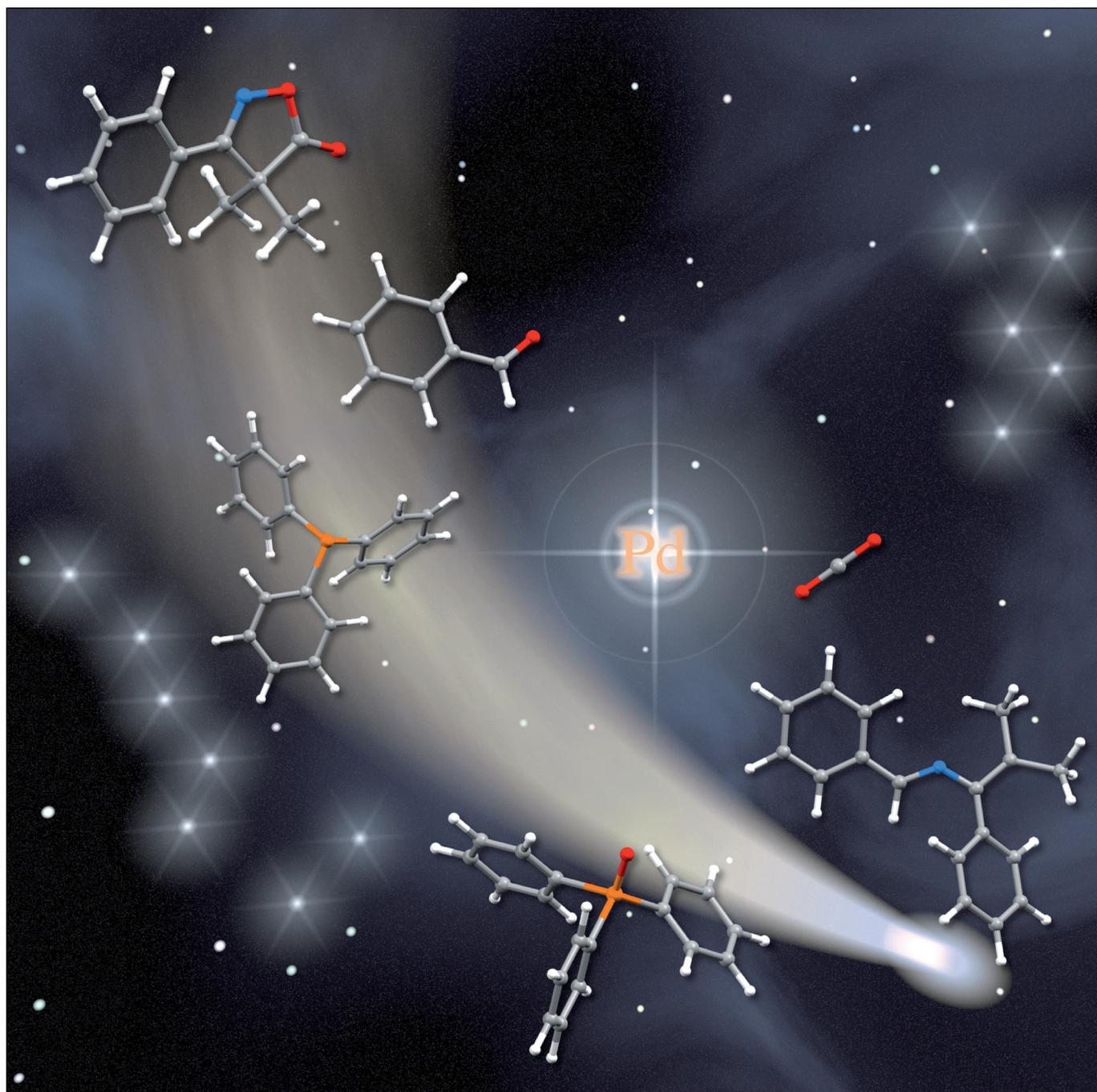


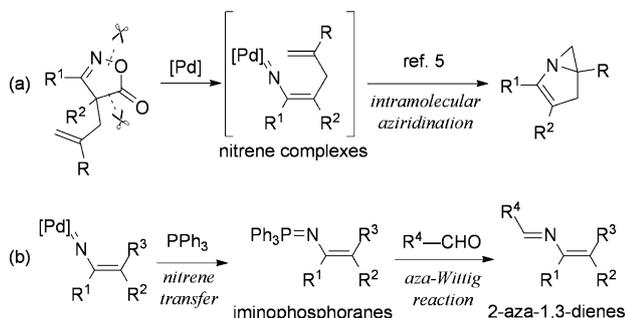
## Synthetic Methods

Palladium-Catalyzed Aza-Wittig-Type Condensation of Isoxazol-5(4*H*)-ones with AldehydesKazuhiro Okamoto,\* Takuya Shimbayashi, Eisuke Tamura, and Kouichi Ohe\*<sup>[a]</sup>

**Abstract:** This paper describes the development of a palladium-catalyzed decarboxylative inter- and intramolecular condensation reaction of isoxazol-5(4*H*)-ones with carbonyl compounds in the presence of PPh<sub>3</sub>, giving various 2-azabuta-1,3-dienes or pyrroles in moderate to high yields.

In 1919, Staudinger and Meyer first reported the reaction of organic azides with phosphines giving iminophosphoranes.<sup>[1]</sup> This is one of the epoch-making discoveries in synthetic organic chemistry, especially because this study triggered the discovery of the Wittig reaction in 1953.<sup>[2]</sup> Nowadays, the Staudinger reaction is widely used as a standard method for the reduction of azides to amines or the aza-Wittig-type condensation.<sup>[3,4]</sup> However, the Staudinger reaction is almost the only method for the generation of iminophosphoranes. Taking the need for careful handling of organic azides into consideration, the development of an alternative method for the formation of iminophosphoranes from more stable precursors is an important issue.

We recently reported a palladium-catalyzed decarboxylative nitrene-transfer reaction of alkene-tethered isoxazol-5(4*H*)-ones affording bicyclic aziridines (Scheme 1a).<sup>[5]</sup> During the course of our investigation aimed at the intermolecular nitrene-transfer reactions, we postulated that the *N*-alkenyliminophosphorane was generated from the decarboxylation of isoxazolone followed by nitrene transfer from palladium to phosphine.<sup>[6,7]</sup> Then the iminophosphorane would react with aldehydes to



**Scheme 1.** Palladium-catalyzed decarboxylative transformation via hypothetical palladium-nitrene complexes.

afford a 2-aza-1,3-diene as a product (Scheme 1b).<sup>[8,9]</sup>

An initial experiment was performed with isoxazolone **1a**, 3.0 equivalents of benzaldehyde **2m**, an equimolar amount of

**Table 1.** Palladium-catalyzed decarboxylative condensation of isoxazolone **1a** with aldehyde **2m**.<sup>[a]</sup>

	Catalyst precursor	Acid [mol%] <sup>[b]</sup>	Yield [%] <sup>[b]</sup>
1	[Pd(PPh <sub>3</sub> ) <sub>4</sub> ]	none	4
2	[Pd(PPh <sub>3</sub> ) <sub>4</sub> ]	PhCO <sub>2</sub> H (10)	34
3	[Pd(PPh <sub>3</sub> ) <sub>4</sub> ]	PhCO <sub>2</sub> H (20)	91 (81) <sup>[c]</sup>
4	[Pd(PPh <sub>3</sub> ) <sub>4</sub> ]	PhCO <sub>2</sub> H (30)	71
5	[Pd(PPh <sub>3</sub> ) <sub>4</sub> ]	PhCO <sub>2</sub> H (100)	17
6 <sup>[d]</sup>	[Pd(PPh <sub>3</sub> ) <sub>4</sub> ]	PhCO <sub>2</sub> H (20)	15
7 <sup>[e]</sup>	[Pd(PPh <sub>3</sub> ) <sub>4</sub> ]	PhCO <sub>2</sub> H (20)	26
8	[Pd(PPh <sub>3</sub> ) <sub>4</sub> ]	Ph <sub>2</sub> P(O)OH (20)	85
9	[Pd(PPh <sub>3</sub> ) <sub>4</sub> ]	PPTS (20)	0
10	[Pd(PPh <sub>3</sub> ) <sub>4</sub> ]	HCl (20)	0
11	[Pd(PPh <sub>3</sub> ) <sub>4</sub> ]	ZnCl <sub>2</sub> (20)	3
12 <sup>[f]</sup>	Pd(OAc) <sub>2</sub>	PhCO <sub>2</sub> H (20)	91
13 <sup>[f]</sup>	[Pd <sub>2</sub> (dba) <sub>3</sub> ]	PhCO <sub>2</sub> H (20)	76
14 <sup>[f]</sup>	PdCl <sub>2</sub>	PhCO <sub>2</sub> H (20)	0

[a] Reaction conditions: isoxazolone **1a** (0.20 mmol), aldehyde **2m** (0.60 mmol), [Pd] (5 mol% Pd) and acid in toluene (1.3 mL). [b] Determined by <sup>1</sup>H NMR spectroscopy (see the Supporting Information). [c] Isolated yield. [d] Without additional PPh<sub>3</sub>. [e] The reaction was performed at 60 °C. [f] 1.2 equivalents of PPh<sub>3</sub> was used.

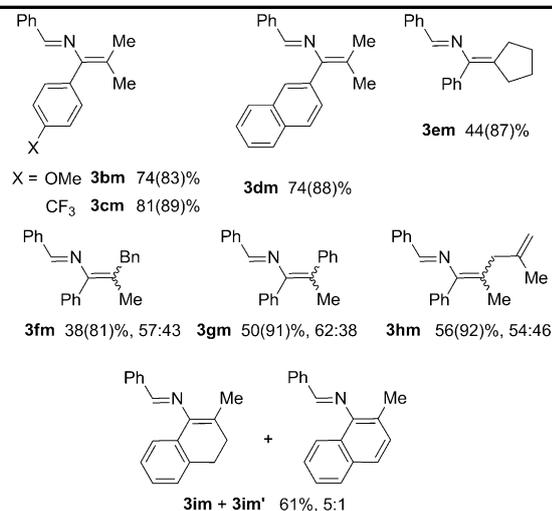
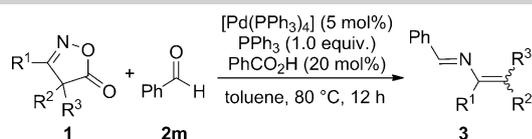
PPh<sub>3</sub>, and 5 mol% of [Pd(PPh<sub>3</sub>)<sub>4</sub>] in toluene at 80 °C for 12 h. The expected azadiene **3am** was observed in the <sup>1</sup>H NMR spectrum of the crude mixture, but the yield was only 4% (Table 1, entry 1). The use of 10 mol% of benzoic acid (PhCO<sub>2</sub>H) as an additive dramatically improved the reactivity, and the yield of **3am** was 34% (entry 2). When the amount of PhCO<sub>2</sub>H was varied from 10 to 100 mol% (entries 2–5), the highest yield was obtained with 20 mol% loading of PhCO<sub>2</sub>H (91% yield determined by NMR spectroscopy; entry 3). When the reaction was performed without additional PPh<sub>3</sub>, the observed yield (15%) was almost equal to the amount of PPh<sub>3</sub> (20%) included in the palladium catalyst. This result indicates that this reaction requires the stoichiometric amount of phosphine in this aza-Wittig-type condensation (entry 6).<sup>[10]</sup> Lowering the reaction temperature to 60 °C remarkably decreased the yield of the product (26%; entry 7). The screening of several other Brønsted or Lewis acids showed that diphenylphosphinic acid (Ph<sub>2</sub>P(O)OH), possessing a similar acidity to PhCO<sub>2</sub>H, also worked well to give the product in relatively high yield, whereas other acids were not effective for the current reaction (entries 8–11). As an alternative precursor, Pd(OAc)<sub>2</sub> also showed the same catalytic activity as [Pd(PPh<sub>3</sub>)<sub>4</sub>]; however, other precursors were less or scarcely reactive (entries 12–14).

Under the optimized reaction conditions, various combinations of isoxazolones and aldehydes could be applied to the present reaction.<sup>[11]</sup> Table 2 summarizes the scope of isoxazolones. The reaction of isoxazolones bearing a methoxy- and trifluoromethyl-substituted phenyl group, and a naphthyl group at the R<sup>1</sup> position, gave azadienes **3bm**, **cm**, and **dm** in good

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<http://dx.doi.org/10.1002/chem.201304211>.

**Table 2.** Palladium-catalyzed decarboxylative condensation of isoxazolone **1** with aldehyde **2m**.<sup>[a]</sup>

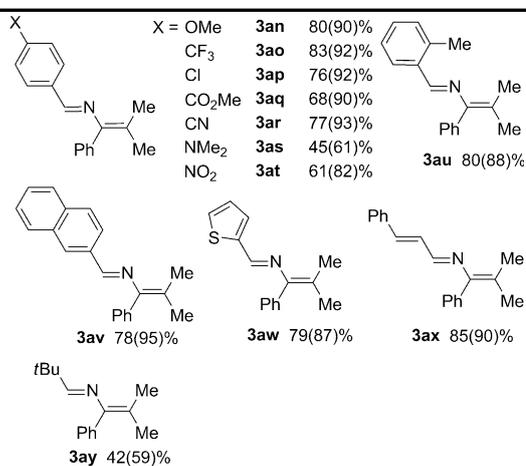
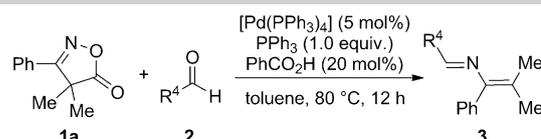


[a] The reaction was performed with isoxazolone **1** (0.20 mmol), aldehyde **2m** (0.60 mmol), [Pd(PPh<sub>3</sub>)<sub>4</sub>] (5 mol%) and benzoic acid (20 mol%) in toluene (1.3 mL). Isolated yields are shown. Yields in parentheses were determined with <sup>1</sup>H NMR spectroscopy using nitromethane as an internal standard. The ratios written following the yield mean the stereoisomeric ratio of *E/Z* mixtures or the ration of two products. The stereochemistry around the C=N bond was determined as *E* form (see the Supporting Information). The stereochemistry around the C=C bond of **3 fm**, **gm**, and **hm** was not determined.

yields. Spirocyclic isoxazolone **1 e** afforded the 2-azadiene **3 em** bearing a cyclopentylidene moiety. In the case of different substituents at the R<sup>2</sup> and R<sup>3</sup> positions, the products were obtained as a mixture of geometrical isomers (**3 fm**, **gm**, and **hm**). It is noteworthy that 2-azadiene **3 hm** was selectively obtained without the formation of the intramolecular aziridination product through the reaction of an alkene moiety.<sup>[12]</sup> Tetrahydronaphthalene-fused isoxazolone **1 i** afforded the corresponding 2-azadiene **3 im** together with the aromatized *N*-naphthylimine **3 im'** in 61% total yield.

The present reaction shows tolerance for various functional groups attached to aldehydes (Table 3). The reaction succeeded with a series of benzaldehyde derivatives bearing *para*-substituents, such as methoxy, trifluoromethyl, chloro, methoxycarbonyl, cyano, dimethylamino, and nitro groups (**3 an–at**). Azadiene **3 as** was obtained in just moderate yield, probably because the dimethylamino group offset the effect of the acid by trapping the proton. The reaction of other aromatic or heteroaromatic aldehydes, such as *ortho*-tolualdehyde, 2-naphthaldehyde, and 2-thiophenecarbaldehyde, afforded the corresponding 2-azadienes in high yields (**3 au–aw**). Cinnamaldehyde also reacted to afford the corresponding azatriene **3 ax** stereoselectively. Pivalaldehyde **2 y** could also be applied as an aliphatic aldehyde. Although other aliphatic aldehydes (R<sup>4</sup> = *n*Bu or Cy)

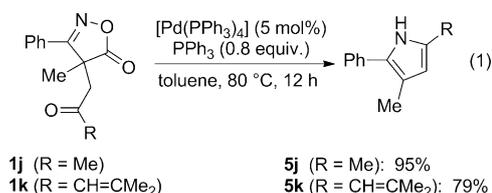
**Table 3.** Palladium-catalyzed decarboxylative condensation of isoxazolone **1a** with aldehyde **2**.<sup>[a]</sup>



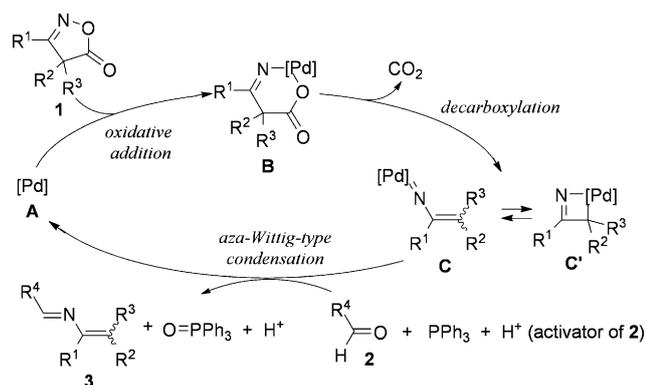
[a] The reaction was performed with isoxazolone **1a** (0.20 mmol), aldehyde **2** (0.60 mmol), [Pd(PPh<sub>3</sub>)<sub>4</sub>] (5 mol%) and benzoic acid (20 mol%) in toluene (1.3 mL). Isolated yields are shown. Yields in parentheses were determined with <sup>1</sup>H NMR spectroscopy using nitromethane as an internal standard.

were also applicable, attempts to isolate the products failed because of the very high sensitivity of the products toward hydrolysis.

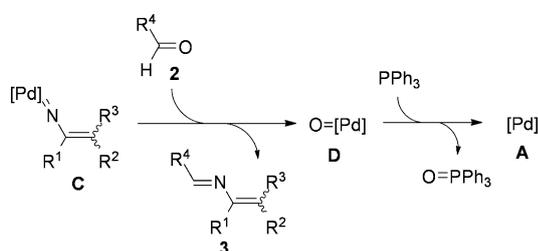
We also attempted to use ketones instead of aldehydes, but the reaction did not proceed. On the other hand, intramolecular condensation of substrate **1 j** successfully proceeded under the standard conditions to afford the corresponding pyrrole **5 j** in 95% isolated yield [Eq. (1)].<sup>[13]</sup> The alkenylated pyrrole **5 k** was also obtained in 79% yield.



A proposed reaction mechanism is shown in Scheme 2. First, the oxidative addition of the N–O bond<sup>[14–16]</sup> in isoxazolone **1** to a zerovalent palladium species **A** is assumed to form a six-membered intermediate **B** that undergoes decarboxylation leading to nitrene–palladium complex **C**.<sup>[17]</sup> Then, nitrene transfer from palladium to PPh<sub>3</sub> followed by the aza-Wittig-type condensation of iminophosphanes with aldehydes would afford the 2-azadiene **3** together with triphenylphosphine oxide (as described in Scheme 1b).<sup>[18]</sup> Alternatively, nitrene-pal-



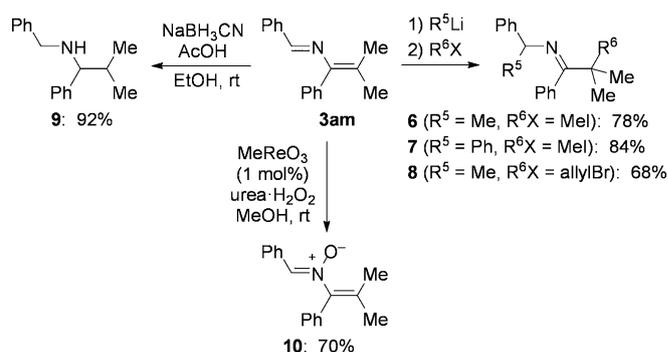
**Scheme 2.** A proposed catalytic cycle for the palladium-catalyzed aza-Wittig reaction using isoxazolones.



**Scheme 3.** Another possible pathway for the condensation/catalyst regeneration step.

ladium complex **C** can directly react with an aldehyde to yield 2-azadiene **3** with palladium(II) oxide **D**, which is followed by the reduction by  $\text{PPh}_3$  regenerating the palladium(0) catalyst **A** (Scheme 3). We cannot exclude either of the two possible pathways at the present time. The reason for the low yield of azadiene **3 am** in the reaction using the stoichiometric amount of benzoic acid (Table 1, entry 5) might be deactivation of isoxazolone **1 a** by protonation of its nitrogen atom.

The 2-azadienes obtained in the present reaction could be used as synthetic intermediates for nitrogen-containing molecules. Because 2-azadienes are polarized molecules, unlike the simple 1,3-dienes, and have both the imine moiety and the enamine moiety, they can undergo the addition of organometallic reagents as nucleophiles to generate enamide anions, which is followed by the coupling with alkyl halides as electrophiles.<sup>[19]</sup> Actually, the addition of  $\text{MeLi}$  or  $\text{PhLi}$  followed by quenching with  $\text{MeI}$  or allyl bromide (allylBr) efficiently produced the corresponding 1,4-adducts **6–8** in good yield (Scheme 4, right equation; 68–84% yields). Moreover, treatment of 2-azadiene **3 am** with  $\text{NaBH}_3\text{CN}$  in protic media caused double hydride reduction of 2-azadiene **3 am** to afford saturated amine **9** in one step (Scheme 4, left equation; 92% yield). The transformation of 2-azadiene **3 am** was expanded into not only nucleophilic or reductive reactions, but also *N*-oxidation giving synthetically useful nitrene derivatives. Methyltrioxorhenium-catalyzed oxidation with urea-hydrogen peroxide to afford *N*-alkenylnitrene **10** in 70% yield.<sup>[20]</sup>



**Scheme 4.** Transformation reactions of azadiene **3 am**.

In summary, we have developed a new method for aza-Wittig-type condensation using isoxazol-5(4*H*)-ones as a vinylnitrene source. 2-Aza-1,3-dienes having various substituents were obtained from isoxazolones and aldehydes in the presence of triphenylphosphine and a catalytic amount of benzoic acid. Much less reactive ketone moieties could also be applied for the construction of pyrrole rings by intramolecular condensation. We have also opened up the opportunity for the resulting 2-azadienes to undergo carbon–carbon bond-forming stepwise 1,4-addition reactions leading to various nitrogen-containing organic molecules. Further mechanistic investigations, as well as the development of other transformation reactions by the use of iminophosphoranes, are currently under way.

## Acknowledgements

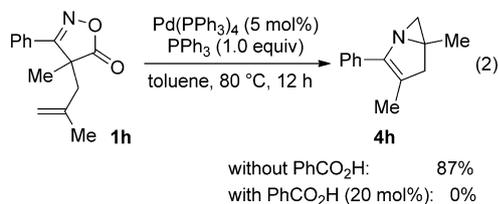
This work was financially supported by Grants-in-Aid for Scientific Research from JSPS and MEXT, Japan. Dr. K. Okamoto also thanks Toray Award in Synthetic Organic Chemistry, Japan.

**Keywords:** aza-wittig · decarboxylation · nitrene transfer · palladium · Staudinger reaction

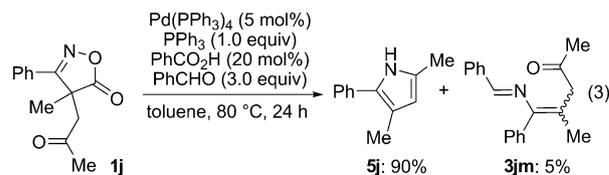
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- [12] As a control experiment, we examined the intramolecular aziridination reaction of **1h** in the absence of PhCHO. As shown in Equation (2), the intramolecular aziridination (see ref. [5]) was completely inhibited in the presence of PhCO<sub>2</sub>H (20 mol%), which is required for the selective conversion of **1h** to azadiene **3hm**.



- [13] The reaction of isoxazolone **1j** with benzaldehyde (**2m**) in the standard reaction conditions gave the corresponding pyrrole **5j** in 90% yield together with a small amount of the corresponding 2-azadiene **3jm** [5% yield; Eq. (3)]. This result indicates that the intramolecular condensation reaction is much faster than intermolecular condensation with aldehyde.



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