Communication

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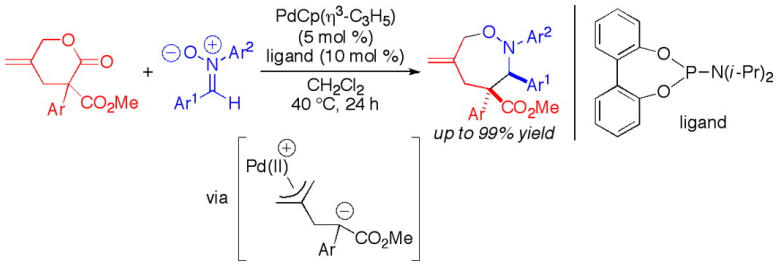

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γ-Methylidene-δ-valerolactones as a Coupling Partner for Cycloaddition: Palladium-Catalyzed [4 + 3] Cycloaddition with Nitrones

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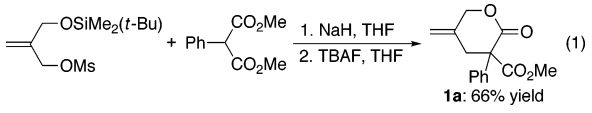
Intermolecular cycloadditions catalyzed by transition-metal complexes are useful methods for convergent synthesis of cyclic materials.[1] The development of a new and efficient intermolecular cycloaddition reaction is, therefore, of high value in organic chemistry. In this context, Trost described the use of palladium−trimethylenemethane (TMM) complexes as a 1,3-dipole-like three-carbon unit in the formation of a cyclic framework almost 30 years ago (Figure 1a).[2] Since then, this method has been applied to the construction of a variety of cyclic compounds,[3] and some asymmetric variants have also been reported.[4] In this Communication, we introduce a new type of reagent, γ-methylidene-δ-valerolactones, which serves as a four-carbon unit in the palladium-catalyzed cycloaddition through the formation of a 1,4-zwitterionic species (Figure 1b),[5] and demonstrate its utility in the [4 + 3] cycloaddition with nitrones to provide highly functionalized 1,2-oxazepines,[6] including the asymmetric variant with high enantioselectivity.

In an initial investigation, we prepared γ-methylidene-δ-valerolactone **1a** as a model reagent for our study in two steps from known compounds, as shown in eq 1, and examined its utility for a [4 + 3] cycloaddition reaction with nitrone **2a** in the presence of 5 mol % of palladium catalyst at 40 °C (Table 1). To our delight, the reaction proceeded smoothly by the use of PPh_3 as a ligand, giving the desired 1,2-oxazepine **3aa** in 95% yield as a mixture of two diastereomers (72/28; entry 1). The use of other ligands such as $P(Oi\text{-}Pr)_3$ and phosphoramidite **4**[7] also gave **3aa** in high yield (97−99% yield; entries 2 and 3),[8] and high diastereoselectivity (90/10) was achieved with ligand **4**. Under these conditions with **4** as the ligand, several other γ-methylidene-δ-valerolactones underwent cycloadditions with **2a** as well, giving the corresponding 1,2-oxazepines in high yield with good to excellent diastereoselectivity (87/13−94/6; entries 4−7).[9] The cycloaddition also proceeded with nitrones having a substituted aryl group at their electrophilic carbon atoms with high diastereoselectivity (92/8−94/6; entries 8−10).



A proposed catalytic cycle of this process is illustrated in Figure 2. Thus, oxidative addition of the allyl ester moiety of **1** to palladium(0), followed by decarboxylation,[10,11] gave 1,4-zwitterionic species **A**. The anionic carbon of **A** then attacked the electrophilic carbon of **2** to give intermediate **B**, which underwent a ring closure through a nucleophilic attack of the oxygen atom to the π-allylpalladium moiety, leading to the formation of 1,2-oxazepine **3** along with regeneration of palladium(0).

Because the step from **A** to **B** creates two contiguous tertiary and quaternary stereocenters, it would be desirable to conduct this reaction in an asymmetric fashion. On the basis of the ligand effect described in Table 1, we employed chiral phosphoramidite ligand (*S*)-**5**[12] in the reaction of **1a** with nitrone **2d**. Under these conditions,

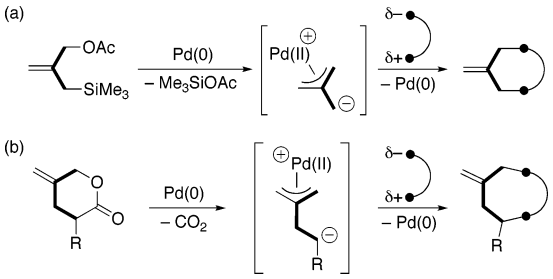
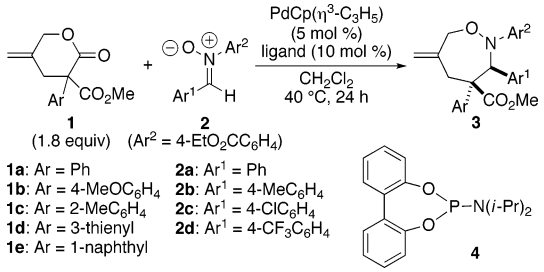


Figure 1. (a) Trost's Pd−TMM complexes for [3 + *n*] cycloadditions. (b) γ-Methylidene-δ-valerolactones for [4 + *n*] cycloadditions.

Table 1. Palladium-Catalyzed [4 + 3] Cycloaddition of γ-Methylidene-δ-valerolactones **1** with Nitrones **2**



entry	1	2	ligand	product	yield (%)[a]	dr[b]
1	**1a**	**2a**	PPh_3	**3aa**	95	72/28
2	**1a**	**2a**	$P(Oi\text{-}Pr)_3$	**3aa**	97	78/22
3	**1a**	**2a**	**4**	**3aa**	99	90/10
4	**1b**	**2a**	**4**	**3ba**	95	93/7
5	**1c**	**2a**	**4**	**3ca**	62	87/13
6	**1d**	**2a**	**4**	**3da**	92	91/9
7	**1e**	**2a**	**4**	**3ea**	96	94/6
8	**1e**	**2b**	**4**	**3eb**	77	92/8
9	**1e**	**2c**	**4**	**3ec**	98	93/7
10	**1e**	**2d**	**4**	**3ed**	98	94/6

[a] Combined yield of two diastereomers. [b] Determined by ^1H NMR.

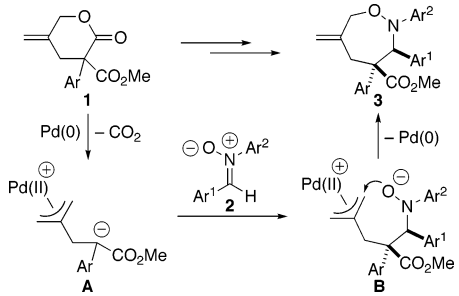


Figure 2. Proposed catalytic cycle for the palladium-catalyzed [4 + 3] cycloaddition of **1** with **2**.

cycloadduct **3ad** was obtained in high yield (98% yield, dr = 85/15), and the enantioselectivity of the major diastereomer was 71% ee (Table 2, entry 1). By changing the nitrogen substituents from

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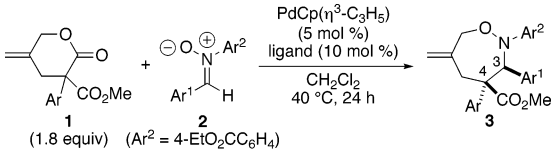
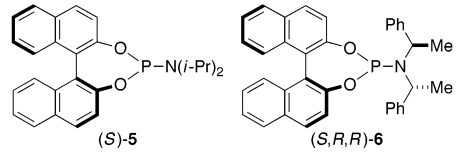
Table 2. Palladium-Catalyzed Asymmetric [4 + 3] Cycloaddition of **1** with **2**





entry	1	2	ligand	product	yield (%)[a]	dr[b]	ee (%)[c]
1	**1a**	**2d**	(*S*)-**5**	**3ad**	98	85/15	71
2	**1a**	**2d**	(*S*,*R*,*R*)-**6**	**3ad**	98	81/19	83
3	**1b**	**2d**	(*S*,*R*,*R*)-**6**	**3bd**	99	86/14	84
4	**1e**	**2d**	(*S*,*R*,*R*)-**6**	**3ed**	98	80/20	96
5[d]	**1e**	**2b**	(*S*,*R*,*R*)-**6**	**3eb**	99	70/30	89[e]
6	**1e**	**2c**	(*S*,*R*,*R*)-**6**	**3ec**	89	72/28	88[f]

[a] Combined yield of two diastereomers. [b] Determined by ^{1}H NMR. [c] The ee of the major diastereomer (determined by chiral HPLC). [d] The reaction was conducted with 10 mol % of catalyst for 48 h. [e] The minor diastereomer was 91% ee. [f] The minor diastereomer was 89% ee.

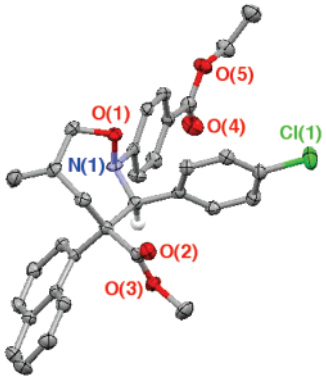
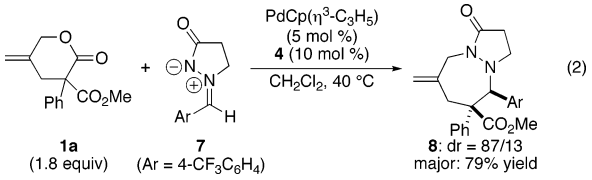


Figure 3. X-ray structure of **3ec** with thermal ellipsoids drawn at the 50% probability level (Flack parameter = −0.01(6)).

isopropyl to (*R*)-1-phenylethyl (ligand (*S*,*R*,*R*)-**6**),[12,13] higher enantioselectivity was observed (83% ee; entry 2). Other γ-methylidene-δ-valerolactones such as **1b** and **1e** also provide the cycloadducts with nitrones **2** with high efficiency in the presence of ligand (*S*,*R*,*R*)-**6** (84−96% ee; entries 3−6). The absolute configuration of **3ec** (entry 6) was determined to be (3*S*,4*R*) by X-ray crystallographic analysis, as shown in Figure 3.

The present catalysis using regent **1** is not limited to the couplings with nitrones. For example, **1a** underwent a cycloaddition with azomethine imine **7**[14,15] to give the corresponding [4 + 3] cycloadduct (**8**) with dr = 87/13, and the major diastereomer was isolated in 79% yield (eq 2).[16]



(2)

In summary, we have described the development of γ-methylidene-δ-valerolactones as a new class of reaction partners in the palladium-catalyzed cycloaddition reaction. These reagents act as a four-carbon unit in a cyclic framework by forming a 1,4-zwitterionic species, and we have demonstrated their utility in the context of stereoselective [4 + 3] cycloaddition with nitrones, including some preliminary results of the asymmetric variant. Future studies will explore further application of these reagents to various other transition-metal-catalyzed cycloaddition reactions.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF) and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Notes: (a) Lactone **1** with alkyl substituents is not a suitable reagent under the present reaction conditions. (b) The use of **1** as the limiting reagent results in lower yield of **3**.

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(16) The relative configuration of **8** was determined by X-ray crystallographic analysis (see Supporting Information for details).

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