Communication

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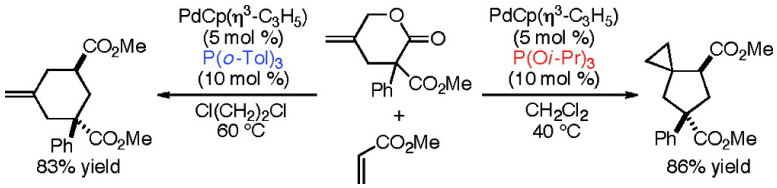

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Palladium-Catalyzed Synthesis of Spiro[2.4]heptanes: Ligand-Dependent Position Control in the Nucleophilic Attack to a π-Allylpalladium Intermediate

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Palladium-catalyzed allylic alkylation is undoubtedly one of the most extensively investigated reactions under transition-metal catalysis.[1] The key elemental step of this process is a nucleophilic attack to a π-allylpalladium intermediate at one of the two terminal carbons of the allylic moiety (Figure 1, left). In contrast, although it is known that a nucleophile can also attack the central carbon to form a cyclopropane ring in the context of stoichiometric reactions (Figure 1, right),[2] catalytic cyclopropanation through this mode of reaction pathway has been scarcely explored. In fact, only a few reports have succeeded in the selective formation of cyclopropanes in a catalytic manner.[3−5] In this Communication, we describe the development of an efficient synthesis of spiro[2.4]heptanes by palladium-catalyzed intermolecular cycloaddition, which involves a nucleophilic ring closure to the central carbon of a π-allylpalladium intermediate.[3d]

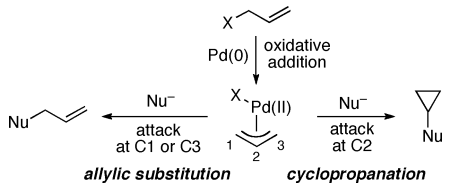
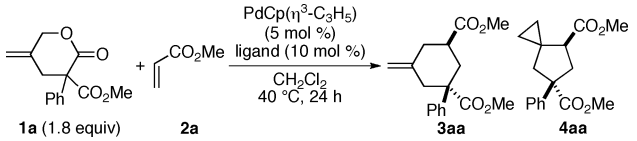


Figure 1. Allylic substitution versus cyclopropanation in the nucleophilic attack to a π-allylpalladium complex.

Recently, we devised γ-methylidene-δ-valerolactones (e.g., **1a**) as new reagents for palladium-catalyzed [4 + 3] cycloaddition reactions with nitrones, demonstrating that these reagents effectively act as a four-carbon unit in an intermolecular cycloaddition reaction.[6] To expand their utility, we attempted a [4 + 2] cycloaddition reaction of **1a** with methyl acrylate (**2a**), an electron-deficient olefin, in the presence of 5 mol % of Pd/2PPh_3 catalyst at 40 °C (Table 1, entry 1). Under these conditions, the expected [4 + 2] cycloadduct (**3aa**) was obtained only in 29% yield and the major product turned out to be spiro[2.4]heptane **4aa** (64% yield). We subsequently determined that the selectivity of **4aa** over **3aa** could be somewhat improved by the use of a bisphosphine ligand such as binap[7] or dppf[8] (**3aa**/**4aa** = 20/80 to 17/83; entries 2 and 3), and the employment of a trialkylphosphite such as $P(OMe)_3$ or $P(Oi\text{-}Pr)_3$ as the ligand further enhanced the selectivity toward the formation of **4aa** (≥95% selectivity; entries 4 and 5).

Under the conditions with $P(Oi\text{-}Pr)_3$ as the ligand, several γ-methylidene-δ-valerolactones can be used for the synthesis of spiro[2.4]heptanes **4** with methyl acrylate in high yield (87−97% yield; Table 2, entries 2−5).[9] With respect to the electron-deficient olefin, other acrylates as well as acrylonitrile are also suitable coupling partners, selectively giving cyclopropanation products **4** (77−92% yield; entries 6−8). In addition, other electron-deficient olefins such as 2-cyclopenten-1-one and 2(5*H*)-furanone undergo the present cycloaddition with **1a** as well to give the corresponding tricyclic spiro[2.4]heptanes in high yield (89−94% yield; entries 9 and 10).[10]

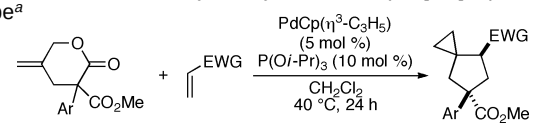
Table 1. Palladium-Catalyzed Cycloaddition of **1a** with Methyl Acrylate (**2a**): Ligand Effect



entry	ligand	% yield of **3aa**[a] (dr)[b]	% yield of **4aa**[a] (dr)[b]
1	PPh_3	29 (83/17)	64 (75/25)
2[c]	binap	14 (81/19)	55 (78/22)
3[c]	dppf	16 (81/19)	77 (77/23)
4	$P(OMe)_3$	4 (−[d])	93 (65/35)
5	$P(Oi\text{-}Pr)_3$	5 (−[d])	86 (79/21)

[a] Combined yield of two diastereomers. [b] Determined by ^{1}H NMR. [c] 5 mol % of ligand was used. [d] The ratio was not determined.

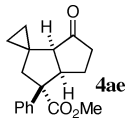
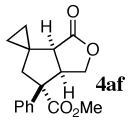
Table 2. Palladium-Catalyzed Synthesis of Spiro[2.4]heptanes: Scope[a]



1a: Ar = Ph
1b: Ar = 4-$MeOC_6H_4$
1c: Ar = 2-MeC_6H_4
1d: Ar = 3-thienyl
1e: Ar = 1-naphthyl

2a: EWG = CO_2Me
2b: EWG = CO_2Et
2c: EWG = CO_2t-Bu
2d: EWG = CN

2e: X = CH_2
2f: X = O

entry	**1**	**2**	product	% yield[b] (dr)[c]
1	**1a**	**2a**	**4aa**	86 (79/21)
2	**1b**	**2a**	**4ba**	91 (74/26)
3	**1c**	**2a**	**4ca**	91 (77/23)
4	**1d**	**2a**	**4da**	87 (72/28)
5	**1e**	**2a**	**4ea**	97 (70/30)
6	**1a**	**2b**	**4ab**	92 (79/21)
7	**1a**	**2c**	**4ac**	77 (90/10)
8	**1a**	**2d**	**4ad**	88 (76/24)
9	**1a**	**2e**	 **4ae**	89 (65/35)
10	**1a**	**2f**	 **4af**	94 (57/43)

[a] The [4 + 2] cycloadducts **3** were obtained in up to 8% yield for all the entries. [b] Combined yield of two diastereomers. [c] Determined by ^{1}H NMR.

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,[11,12] gives 1,4-zwitterionic species **A**. The anionic carbon of **A** then attacks the electrophilic carbon of electron-deficient olefin **2** to give intermediate **B**, which undergoes a ring closure through a nucleophilic attack to the central carbon of the π-allylpalladium moiety to give palladacyclobutane **C**.[2e] Reductive elimination of product **4** then regenerates a palladium(0) species.[2,3]

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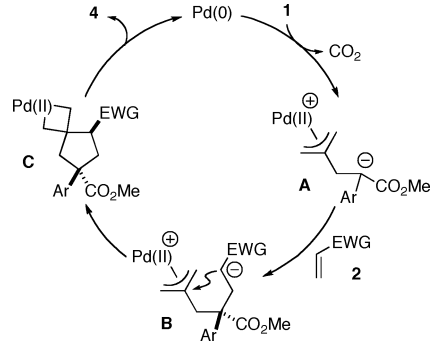


Figure 2. Proposed catalytic cycle for the palladium-catalyzed synthesis of spiro[2.4]heptanes **4** from **1** and **2**.

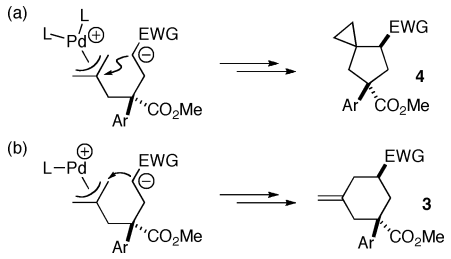
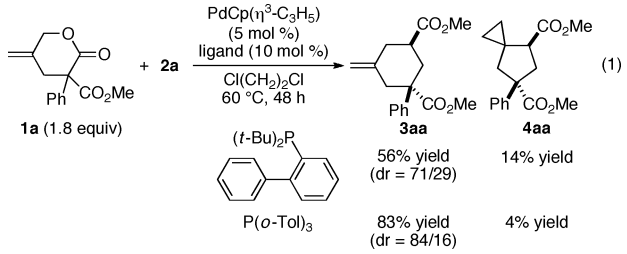


Figure 3. Proposed pathways for the production of (a) spiro[2.4]heptanes **4** and (b) [4 + 2] cycloadducts **3**.



When [4 + 2] cycloadducts **3**, rather than spiro[2.4]heptanes **4**, are the desired products, these can be selectively obtained by employing a bulky tertiary phosphine ligand. For example, the use of $(t\text{-Bu})_2\text{P}(o\text{-PhC}_6\text{H}_4)$[13] in the reaction of **1a** with **2a** at 60 °C gives **3aa** as the major product (**3aa**/**4aa** = 80/20) in 70% combined yield (eq 1), and high yield of **3aa** (83% yield) is achieved by using $\text{P}(o\text{-Tol})_3$ as the ligand with minimal amount of **4aa** (4% yield).[14]

Although it is not entirely clear at this stage, the fact that the use of relatively small phosphine and phosphite ligands as well as bisphosphine ligands tends to give spiro[2.4]heptanes **4** (Table 1) and the use of bulky phosphine ligands preferentially gives [4 + 2] cycloadducts **3** (eq 1) may indicate that Pd(π-allyl)L_2 species is mainly responsible for the ring closure through the central attack in the present catalysis (Figure 3a) and Pd(π-allyl)L_1 species is more responsible for the six-membered ring formation by the terminal attack (Figure 3b).[15,16]

In summary, we have described the development of a palladium-catalyzed intermolecular cycloaddition of γ-methylidene-δ-valerolactones with electron-deficient olefins to produce spiro[2.4]-heptanes with high selectivity through a nucleophilic ring closure to the central carbon of a π-allylpalladium intermediate. We have found that the course of the reaction is dependent on the ligand employed, and selective [4 + 2] cycloadditions can also be achieved by the use of a bulky monophosphine ligand. Future studies will explore more details of the present catalysis including the mechanistic studies as well as the development of an asymmetric variant.

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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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(16) As kindly suggested by one of the reviewers, the observed selectivity may be explained by the steric demand of palladacyclobutane intermediate **C** (Figure 2), the formation of which becomes unfavorable upon using a bulky phosphine ligand.

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