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Palladium-Catalyzed Synthesis of 4-Oxaspiro[2.4]heptanes via Central Attack of Oxygen Nucleophiles to π-Allylpalladium Intermediates

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ABSTRACT

A palladium-catalyzed decarboxylative cyclopropanation of γ-methylidene-δ-valerolactones with aromatic aldehydes has been developed to give 4-oxaspiro[2.4]heptanes with high selectivity. The site of nucleophilic attack to a π-allylpalladium intermediate has been controlled with a sterically demanding phosphine ligand. The course of the reaction is highly dependent on ligands and solvents, and selective formation of methylenetetrahydropyrans has also been realized.

Palladium-catalyzed cyclopropanation through a nucleophilic attack at the central carbon of a π-allylpalladium intermediate represents an interesting way of constructing cyclopropanes, although it requires suppression of the competitive allylic substitution process that is usually more prone to take place.[1] Since the first discovery of such a cyclopropanation by Hegedus and co-workers in stoichiometric reactions with ester enolates,[2] several effective catalytic variants have been developed, most of which rely on the use of enolate-based carbon nucleophiles.[3,4] Other nucleophiles that can be employed for this type of cyclopropanation are currently limited to carbonyl-attached nitrogen nucleophiles in the ring-forming processes.[5] In this context, here we describe the development of a palladium-catalyzed synthesis of 4-oxaspiro[2.4]heptanes from

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(4) For examples of stoichiometric reactions, see: (a) Hoffmann, H. M. R.; Otte, A. R.; Wilde, A. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 234. (b) Wilde, A.; Otte, A. R.; Hoffmann, H. M. R. *J. Chem. Soc., Chem. Commun.* **1993**, 615. (c) Otte, A. R.; Wilde, A.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1280. (d) Hoffmann, H. M. R.; Otte, A. R.; Wilde, A.; Menzer, S.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 100.

(5) (a) Grigg, R.; Kordes, M. *Eur. J. Org. Chem.* **2001**, 707. (b) Shintani, R.; Park, S.; Shirozu, F.; Murakami, M.; Hayashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 16174. (c) Shintani, R.; Tsuji, T.; Park, S.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 7508. (d) Shintani, R.; Moriya, K.; Hayashi, T. *Chem. Commun.* **2011**, *47*, 3057.

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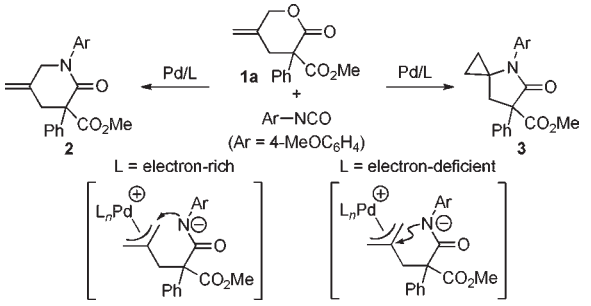
γ-methylidene-δ-valerolactones and aldehydes by the successful use of oxygen nucleophiles for a central attack to π-allylpalladium intermediates.[6]

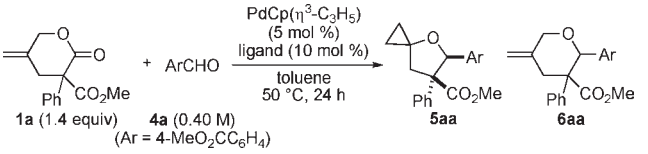
In 2010, we described a palladium-catalyzed decarboxylative cyclization of γ-methylidene-δ-valerolactone **1a** with 4-methoxyphenyl isocyanate to give piperidone **2** and/or azaspiro[2.4]heptanone **3** (Scheme 1).[5c] In this reaction, selective formation of compound **2** was achieved by the use of electron-rich phosphine ligands such as P(4-$MeOC_6H_4)_3$ through a usual allylic substitution pathway from the π-allylpalladium intermediate, whereas the formation of compound **3** became dominant by employing electron-deficient phosphine ligands such as P(4-$CF_3C_6H_4)_3$ through a nucleophilic attack at the central carbon of the same intermediate.

Scheme 1. Palladium-Catalyzed Decarboxylative Cyclization of γ-Methylidene-δ-valerolactone **1a** with 4-Methoxyphenyl Isocyanate



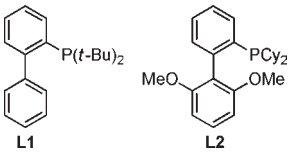
On the basis of this reaction, we initially examined a reaction of γ-methylidene-δ-valerolactone **1a** with aldehyde **4a** in the presence of $PdCp(\eta^3\text{-}C_3H_5)$ (5 mol %) and a phosphine ligand (10 mol %) in toluene at 50 °C (Table 1). As was the case for the reaction of **1a** with 4-methoxyphenyl isocyanate (Scheme 1),[5c] the reaction with electron-rich P(4-$MeOC_6H_4)_3$ as the ligand gave none of the cyclopropanation product **5aa** and methylenetetrahydropyran **6aa** was obtained in 22% yield (entry 1). The use of less electron-rich PPh_3 gave a mixture of **5aa** and **6aa** in a ratio of 30/70 (entry 2). The selectivity of **5aa** became much higher by employing electron-deficient P(4-$CF_3C_6H_4)_3$ as the ligand (**5aa**/**6aa** = 83/17), but the products were obtained only in 10% combined yield (entry 3). In contrast, we were pleased to find that the use of sterically demanding monophosphine ligands could significantly change the reactivity as well as the course of the reaction, preferentially producing 4-oxaspiro[2.4]heptane **5aa** in high yields. Thus, 85% yield of cyclization products was obtained with **5aa**/**6aa** = 82/18 under the catalysis of Pd/P(2-$MeC_6H_4)_3$ (entry 4), and an even higher selectivity of **5aa** was achieved by the use of **L1**[7] as the ligand (**5aa**/**6aa** = 87/13; entry 5). Furthermore, **5aa**/**6aa** = 93/7 was realized in high yield when the ligand was changed to **L2**[8] (entry 6), and the best result was obtained by conducting the reaction at 85 °C instead of 50 °C, giving 88% yield of **5aa**/**6aa** in the ratio of 98/2 (entry 7). The relative configuration of the major diastereomer of **5aa** obtained in entry 7 was established by X-ray crystallographic analysis as shown in Figure 1.[9]

Table 1. Palladium-Catalyzed Decarboxylative Cyclization of γ-Methylidene-δ-valerolactone **1a** with Aldehyde **4a**: Ligand Effect



entry	ligand	yield of **5aa** +**6aa** (%)[a]	**5aa**/**6aa**[a]	dr of **5aa**[a]
1	P(4-$MeOC_6H_4)_3$	23	<1/99	
2	PPh_3	39	30/70	26/74
3	P(4-$CF_3C_6H_4)_3$	10	83/17	50/50
4	P(2-$MeC_6H_4)_3$	85	82/18	91/9
5	**L1**	82	87/13	78/22
6	**L2**	94	93/7	70/30
7[b]	**L2**	88[c]	98/2	83/17

[a] Determined by ^{1}H NMR. [b] Conducted at 85 °C for 3 h. [c] Isolated yield.



Under the conditions using **L2** as the ligand, compound **1a** smoothly reacts with various electron-deficient benzaldehydes **4a**–**g** regardless of their substitution patterns to give 4-oxaspiro[2.4]heptanes **5** selectively in high yield with moderate to good diastereoselectivity (Table 2, entries 1–7). Unfortunately, unsubstituted benzaldehyde (**4h**) shows significantly lower reactivity, but exclusive formation of spirocyclopropane **5ah** was observed with high diastereoselectivity (entry 8). In addition, heteroaromatic aldehydes such as 3-pyridinecarboxaldehyde (**4i**) are also suitable substrates in the present catalysis (entry 9).[10] With

(6) Central attack of phenoxides to 2-halo(π-allyl)palladium intermediates has been reported: (a) Organ, M. G.; Miller, M. *Tetrahedron Lett.* **1997**, *38*, 8181. (b) Ogran, M. G.; Miller, M.; Konstantinou, Z. *J. Am. Chem. Soc.* **1998**, *120*, 9283. (c) Organ, M. G.; Arvanitis, E. A.; Hynes, S. J. *Tetrahedron Lett.* **2002**, *43*, 8989. (d) Kadota, J.; Katsuragi, H.; Fukumoto, Y.; Murai, S. *Organometallics* **2000**, *19*, 979.

(7) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369.

(8) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

(9) CCDC-870014 and CCDC-870020 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(10) Electron-rich or sterically demanding aldehydes, and ketones are not reactive substrates, and aliphatic aldehydes give products in moderate yield with poor diastereoselectivity under the present reaction conditions.

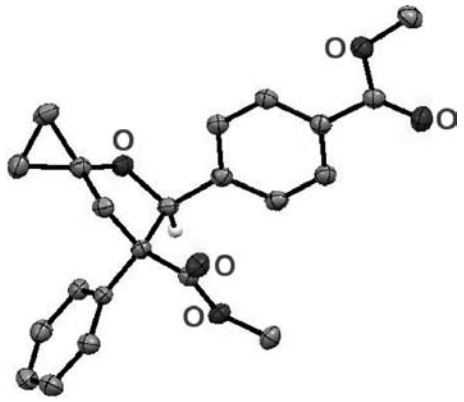
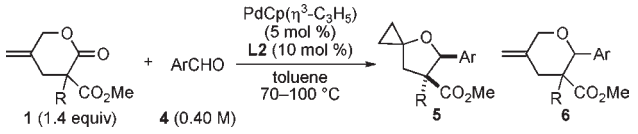


Figure 1. X-ray crystal structure of the major diastereomer of **5aa** (hydrogen atoms except at the stereocenter are omitted for clarity).

Table 2. Palladium-Catalyzed Synthesis of 4-Oxaspiro-[2.4]heptanes **5**: Scope



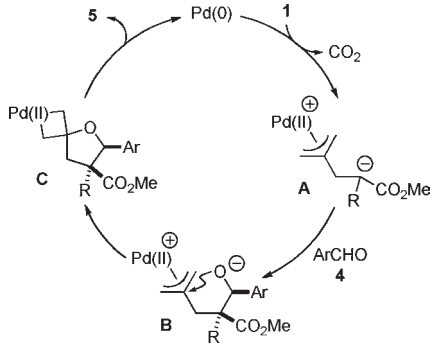
entry	1 (R)	4 (Ar)	yield[a] (%)	5/6[b]	dr of 5[b]
1[c]	**1a** (Ph)	**4a** (4-$MeO_2CC_6H_4$)	88	98/2	83/17
2[c]	**1a**	**4b** (4-$PhCOC_6H_4$)	83	98/2	89/11
3[d]	**1a**	**4c** (4-NCC_6H_4)	86	88/12	71/29
4[c]	**1a**	**4d** (4-$F_3CC_6H_4$)	84	97/3	78/22
5[e]	**1a**	**4e** (4-ClC_6H_4)	82	97/3	88/12
6[e]	**1a**	**4f** (3-ClC_6H_4)	89	94/6	81/19
7[e]	**1a**	**4g** (2-FC_6H_4)	75	97/3	75/25
8[e]	**1a**	**4h** (Ph)	31	>99/1	92/8
9[c]	**1a**	**4i** (3-pyridyl)	87	97/3	79/21
10[c]	**1b** (4-$MeOC_6H_4$)	**4a**	82	88/12	81/19
11[e]	**1b**	**4e**	93	97/3	86/14
12[e]	**1c** (4-MeC_6H_4)	**4e**	82	98/2	86/14
13[c]	**1d** (3-MeC_6H_4)	**4a**	82	96/4	87/13
14[e]	**1d**	**4e**	79	98/2	87/13
15[e]	**1e** (3,4-$(OCH_2O)C_6H_3$)	**4e**	80	96/4	88/12
16[c]	**1f** (2-MeC_6H_4)	**4a**	97	98/2	96/4
17[e]	**1g** (CH_2Ph)	**4e**	81	80/20	52/48

[a] Combined isolated yield of **5** and **6**. [b] Determined by ^1H NMR. [c] Conducted at 85 °C for 3 h. [d] Conducted at 100 °C for 3 h. [e] Conducted at 70 °C for 24 h.

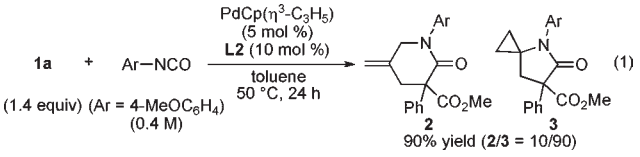
regard to the substituent of γ-methylidene-δ-valerolactones **1**, various aryl groups are tolerated at the α-position in the reactions with aldehydes **4a** and/or **4e** to give cyclopropanation products **5** with high selectivity (entries 10–16). α-Alkyl lactones such as **1g** can also be employed with somewhat reduced chemoselectivity and low diastereoselectivity (entry 17).

A proposed catalytic cycle of the present catalysis is illustrated in Scheme 2. Thus, oxidative addition of the allyl ester moiety of **1** to palladium(0), followed by decarboxylation,[11] gives 1,4-zwitterionic species **A**. The anionic carbon of **A** then attacks the electrophilic carbon of aldehyde **4** to give intermediate **B**. Ring-closing nucleophilic attack of the oxygen atom to the central carbon of the π-allylpalladium moiety of **B** leads to palladacyclobutane **C**. Reductive elimination releases cyclopropanation product **5** along with regeneration of a palladium(0) species.[2−5] The site selectivity in the event of nucleophilic ring closure from intermediate **B** can be controlled by the electronic property of the phosphine ligand on palladium (Table 1, entries 1−3) as was the case for the nitrogen nucleophile (Scheme 1),[5c,d] but the selective formation of 4-oxaspiro[2.4]heptanes **5** by the Pd/**L2** catalyst system shows that this process can also be (more efficiently) controlled by the steric properties of the ligand.[12]

Scheme 2. Proposed Catalytic Cycle for the Palladium-Catalyzed Decarboxylative Cyclopropanation of **1** with **4**



The above-mentioned steric control is also applicable to a selective formation of azaspiro[2.4]heptanone **3** by the reaction of γ-methylidene-δ-valerolactone **1a** with 4-methoxyphenyl isocyanate as shown in eq 1 (see also Scheme 1).[5c] Thus, in the presence of $PdCp(\eta^3\text{-}C_3H_5)$ (5 mol %) and **L2** (10 mol %) in toluene at 50 °C, 90% yield of products **2** and **3** was obtained in the ratio of 10/90.

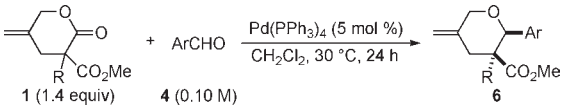


We have also begun to explore the reaction conditions that can selectively provide methylenetetrahydropyrans **6**, rather than 4-oxaspiro[2.4]heptanes **5**, in high yield. On the basis of the ligand effect observed in Table 1,

(11) (a) Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199. (b) Tsuda, T.; Chuji, Y.; Nishi, S.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381. For reviews, see: (c) Reference 1a. (d) Tunge, J. A.; Burger, E. C. *Eur. J. Org. Chem.* **2005**, 1715. (e) You, S.-L.; Dai, L.-X. *Angew. Chem., Int. Ed.* **2006**, *45*, 5246.

(12) As suggested by one of the reviewers, this steric control could be attributed to the formation of a PdL_1 species, which can be regarded as a more electron-deficient palladium complex compared to a PdL_2 species.

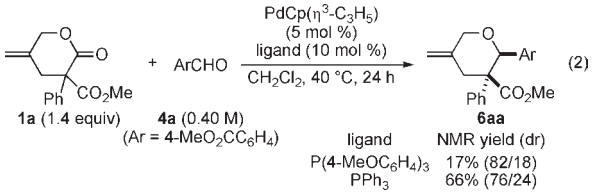
Table 3. Palladium-Catalyzed Synthesis of Methylenetetrahydropyrans **6**: Examples



entry	1	4	product	yield[a] (%)	dr[b]
1	**1a**	**4a**	**6aa**	88	74/26
2	**1a**	**4b**	**6ab**	89	76/24
3	**1b**	**4a**	**6ba**	91	74/26
4	**1e**	**4a**	**6ea**	91	72/28
5[c]	**1f**	**4a**	**6fa**	89	62/38

[a] Isolated yield of **6**. [b] Determined by ^{1}H NMR. [c] Conducted with 1.8 equiv of **1f**.

we reexamined the reaction of **1a** with **4a** using P(4-MeOC$_6$H$_4$)$_3$ and PPh$_3$ as the ligand (eq 2) and found that exclusive formation of **6aa** can be achieved when the reactions are conducted in CH_2Cl_2 instead of in toluene with higher yield using PPh$_3$ (66% NMR yield).[13] We subsequently identified that the use of preformed complex Pd(PPh$_3$)$_4$ under slightly modified conditions gives **6aa** in 88% yield (Table 3, entry 1). Under these conditions, several other substrate combinations can also produce methylenetetrahydropyrans **6** exclusively in high yield (entries 2–5). The relative configuration of the major diastereomer of **6aa** obtained in entry 1 was determined by X-ray crystallographic analysis as shown in Figure 2.[9]



(2)

In summary, we have described a palladium-catalyzed decarboxylative cyclopropanation of γ-methylidene-δ-valerolactones with aldehydes to give 4-oxaspiro[2.4]-heptanes with high selectivity. The site of nucleophilic attack to a π-allylpalladium intermediate has been efficiently controlled by employing sterically demanding phosphine ligand **L2**. We have found that the course of the reaction is highly dependent on both ligands and solvents employed, and selective formation of methylenetetrahydropyrans has also been realized. Future studies will explore further expansion of the reaction scope as well as the mechanistic studies of the present catalysis.

(13) In comparison, the reaction of **1a** with **4a** using **L2** as the ligand in CH_2Cl_2 at 40 °C gave **5aa**/**6aa** = 45/55, confirming that the site selectivity of the nucleophilic ring closure depends on the reaction solvent, but we currently have no good explanation for this solvent effect on the site selectivity.

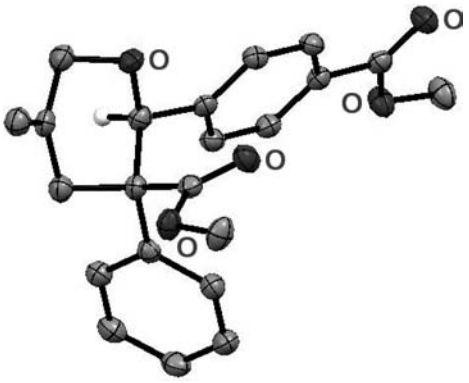


Figure 2. X-ray crystal structure of the major diastereomer of **6aa** (hydrogen atoms except at the stereocenter are omitted for clarity).

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

The authors declare no competing financial interest.