

Palladium-Catalyzed Decarboxylative [4 + 3] Cyclization of γ -Methylidene- δ -valerolactones with 1,1-Dicyanocyclopropanes

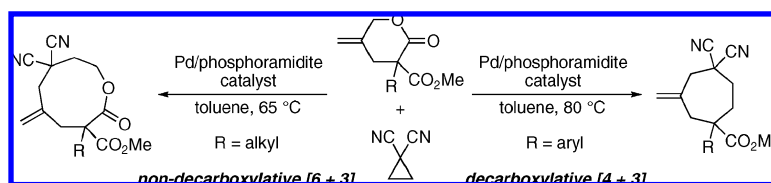
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ABSTRACT



A palladium-catalyzed decarboxylative [4 + 3] cyclization of γ -methylidene- δ -valerolactones with 1,1-dicyanocyclopropanes has been developed to produce cycloheptane derivatives in a convergent manner. This method can be applied to the synthesis of azepanes by reacting with aziridines, and their asymmetric variants have also been described. In addition, selective ring-expansion reactions can be achieved for certain γ -methylidene- δ -valerolactones to give nondecarboxylated nine-membered lactones.

Seven-membered carbocycles represent an important class of cyclic compounds that can be found as a structural motif in many natural products.¹ Considerable efforts have therefore been made for the development of efficient synthetic methods of these compounds,² but it is evidently more difficult than synthesizing five- or six-membered ring systems. A commonly utilized convergent strategy is to employ intermolecular [5 + 2]³ or [4 + 3]⁴ cycloadditions, and various other effective methods also appeared in the past decade.⁵ In addition to achieving the formation of a seven-membered architecture, controlling its absolute

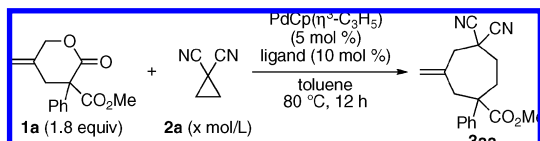
stereochemistry in a catalytic asymmetric fashion is also a subject of importance; a few attractive catalyst systems have been reported to date.⁶ Unfortunately, however,

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accessible structures are still somewhat limited, and it is highly desirable to establish a new catalytic transformation that is amenable to the construction of enantioenriched cycloheptanes. Herein we describe the development of a palladium-catalyzed decarboxylative [4 + 3] cyclization of γ -methylidene- δ -valerolactones with 1,1-dicyanocyclopropanes to produce cycloheptane derivatives, including its application to asymmetric catalysis by using a chiral phosphoramidite ligand.

Table 1. Palladium-Catalyzed Decarboxylative [4 + 3] Cyclization of γ -Methylidene- δ -valerolactone **1a** with 1,1-dicyanocyclopropane (**2a**): Optimization



entry	ligand	x (mol/L)	yield (%) ^a
1	PPh ₃	0.20	9
2	PCy ₃	0.20	15
3	P(O <i>i</i> -Pr) ₃	0.20	7
4 ^b	dppf	0.20	14
5		0.20	24
6		0.40	43
7		0.80	73
8	4a	1.20	83 ^c

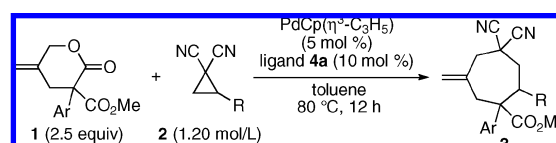
^a Determined by ¹H NMR against an internal standard. ^b 5.5 mol % of ligand was used. ^c Isolated yield.

Although we previously described the use of γ -methylidene- δ -valerolactones (e.g., **1a** in Table 1) in the context of palladium-catalyzed decarboxylative cyclization, the reaction partners had to have unsaturated carbon–carbon or carbon–heteroatom bonds to be successful.⁷ In fact, our initial attempt to utilize cyclopropane **2a** (0.20 mol/L) as a reaction partner for γ -methylidene- δ -valerolactone **1a** under Pd/2PPh₃ catalysis gave only 9% yield of desired seven-membered carbocycle **3aa** even at an elevated temperature with full consumption of **1a** (Table 1, entry 1).⁸ The use of

other ligands such as PCy₃, P(O*i*-Pr)₃, and dppf also resulted in low yield of **3aa** (7–15% yield; entries 2–4), and slightly better yield was obtained by employing phosphoramidite ligand **4a**⁹ (24% yield; entry 5). We subsequently found that the yield of **3aa** was proportionally dependent on the initial concentration of **2a** (entries 5–8), achieving 83% yield at 1.20 mol/L.

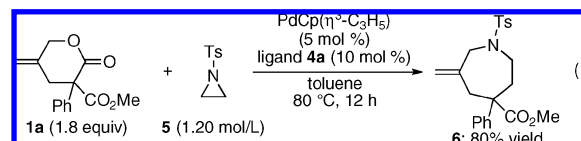
Under the optimized conditions with ligand **4a**, several γ -methylidene- δ -valerolactones **1** bearing an aryl group at the α -position undergo decarboxylative cyclization with **2a** in high yield regardless of their substitution patterns (76–92% yield; Table 2, entries 1–5), and the ferrocenyl group is also tolerated at the α -position of lactone **1** (99% yield; entry 6). The use of 2-phenyl-1,1-dicyanocyclopropane (**2b**) leads to the formation of cycloheptane **3ab** with high regioselectivity (93% yield; entry 7).¹⁰ In addition, not only cyclopropanes but also aziridines can be used as the reaction partner for this decarboxylative cyclization with **1**. For example, a reaction of **1a** with *N*-tosylaziridine (**5**) smoothly proceeds under the same conditions to give azepane **6** in 80% yield (eq 1).¹¹

Table 2. Palladium-Catalyzed Decarboxylative [4 + 3] Cyclization of **1** with **2**: Scope



entry	1	2	product	yield (%) ^a
1 ^b	1a (Ar = Ph)	2a (R = H)	3aa	83
2	1b (Ar = 4-MeOC ₆ H ₄)	2a	3ba	76
3	1c (Ar = 4-MeC ₆ H ₄)	2a	3ca	88
4	1d (Ar = 3-MeC ₆ H ₄)	2a	3da	89
5	1e (Ar = 2-MeC ₆ H ₄)	2a	3ea	92
6 ^b	1f (Ar = ferrocenyl)	2a	3fa	99
7 ^c	1a	2b (R = Ph)	3ab	93 ^d

^a Isolated yield. ^b 1.8 equiv of **1** was used. ^c The reaction was conducted for 40 h. ^d dr = 54/46.



Because phosphoramidite **4a** is highly effective for the present catalysis, we have also begun to explore the development of its asymmetric variant by using a chiral phosphoramidite ligand to construct a quaternary carbon stereocenter.¹² After some investigations, we found that the

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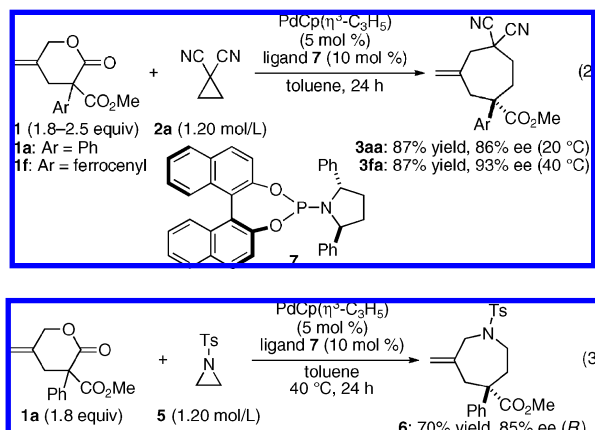
(10) Under the present conditions, 1,1-dicyanocyclopropanes are uniquely effective, and other cyclopropanes such as 1,1-bis(methoxycarbonyl)-cyclopropane and 1,1-diacetylcyclopropane are unreactive toward **1**. To date, the origin of this reactivity difference is unclear.

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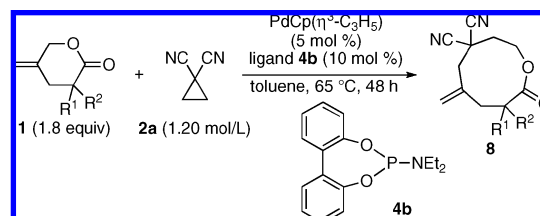
(8) In our previous transformations (ref 7), the reactions were typically conducted at 20–40 °C with 0.20–0.30 mol/L substrate concentration.

reaction of **1a** with **2a** smoothly proceeds at 20 °C in the presence of ligand **7**¹³ to give cycloheptane **3aa** in 87% yield with 86% ee.¹⁴ Similarly, lactone **1f** gives **3fa** in 87% yield with 93% ee at 40 °C, and the same chiral phosphoramidite ligand is also effective for the reaction of **1a** with aziridine **5** to give azepane (*R*)-**6**¹⁵ with 85% ee (eq 3).



It is worth noting that the course of the reactions between **1** and **2** can be completely switched from decarboxylative [4 + 3] cyclizations to nondecarboxylative formal [6 + 3] cyclizations¹⁶ to give ring-expanded nine-membered lactones¹⁷ simply by changing the electronic nature of the lactone substituents. Thus, a reaction of lactone **1g** having a benzyl group at the α -position with cyclopropane **2a** under the same conditions as in Table 2 (Pd/**4a** catalyst at 80 °C) gave nine-membered lactone **8ga** in 58% yield with no formation of the decarboxylated seven-membered carbocycle (Table 3, entry 1). The yield of **8ga** could be improved to 73% by conducting the reaction with ligand **4b**¹⁸ at 65 °C (entry 2). Under these conditions, other α -alkyl lactones (**1h** and **1i**) as well as lactone **1j** also provide the ring-expanded

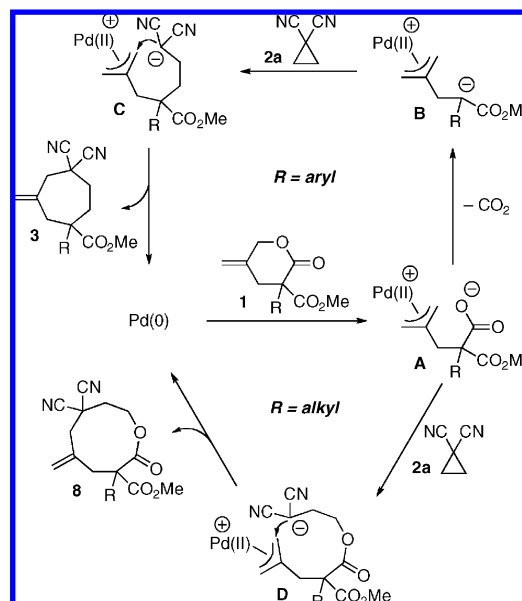
Table 3. Palladium-Catalyzed Ring Expansion of **1** with **2a**



entry	1	product	yield (%) ^a
1 ^b	1g (R ¹ = CH ₂ Ph, R ² = CO ₂ Me)	8ga	58
2	1g	8ga	73
3	1h (R ¹ = Me, R ² = CO ₂ Me)	8ha	78
4	1i (R ¹ = Et, R ² = CO ₂ Me)	8ia	72
5 ^c	1j (R ¹ = R ² = Ph)	8ja	93

^a Isolated yield. ^b The reaction conditions for Table 2, entry 1 (ligand **4a** at 80 °C for 12 h), were employed. ^c 1.0 equiv of **1j** (1.20 mol/L) and 1.4 equiv of **2a** were used.

Scheme 1. Proposed Catalytic Cycles for the Palladium-Catalyzed Cyclizations of **1** with **2a**



nine-membered lactones **8** with complete selectivity (72–93% yield; entries 3–5).

With regard to the reaction pathways for the present catalyses, proposed catalytic cycles for the reaction of lactone **1** with cyclopropane **2a** are illustrated in Scheme 1. Thus, oxidative addition of the allyl ester moiety of **1** to palladium(0) gives π -allylpalladium carboxylate **A**. Successive decarboxylation^{19,20} takes place when R is an aryl group, which can stabilize the resulting anionic charge on the

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(14) See Supporting Information for representative results.

(15) The absolute configuration was determined by X-ray crystallographic analysis (see Supporting Information for details).

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adjacent carbon, to give 1,4-zwitterionic species **B**. The anionic carbon of **B** then attacks the electrophilic carbon of **2** to give intermediate **C**, which undergoes a ring closure through a nucleophilic attack to the π -allylpalladium moiety, leading to the formation of cycloheptane **3** along with regeneration of palladium(0). In contrast, when R is a less stabilizing alkyl group, direct nucleophilic attack of the carboxylate of **A** to **2** occurs faster than decarboxylation to give intermediate **D**, ring closure of which leads to nine-membered lactone **8**.

In summary, we have developed a palladium-catalyzed decarboxylative [4 + 3] cyclization of γ -methylidene- δ -valerolactones with 1,1-dicyanocyclopropanes to produce

cycloheptane derivatives in a convergent manner. This method can be applied to the synthesis of azepanes by reacting with aziridines, and their asymmetric variants have also been described. In addition, we have disclosed that nondecarboxylative ring-expansion reactions selectively proceed for certain γ -methylidene- δ -valerolactones under similar conditions.

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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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