

Mechanistic Investigation of the Palladium-Catalyzed Decarboxylative Cyclization of γ -Methyldiene- δ -valerolactones with Isocyanates: Kinetic Studies and Origin of the Site Selectivity in the Nucleophilic Attack at a (π -Allyl)palladium

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Abstract: Mechanistic studies for the palladium-catalyzed decarboxylative cyclization reactions of γ -methyldiene- δ -valerolactones **1** with isocyanates **2** are described. The reactions can be effectively catalyzed by palladium triarylphosphine complexes to give piperidones **3** and/or azaspiro[2.4]heptanones **4**. Through kinetic studies using NMR spectroscopy, it has been determined that the oxidative addition of lactones **1** to palladium(0) is the turnover-limiting step of the catalytic cycle. By changes in the electronic properties of the triarylphosphine ligands, the product distribution between **3** and **4** can be easily controlled, and an explanation for the origin of this selectivity is provided. The selectivity between **3** and **4** is also influenced by the nature of the nitrogen substituent on isocyanates **2**, and more electron-rich substituents tend to give higher selectivity toward azaspiro[2.4]heptanones **4**. These studies represent the first systematic investigation into the selectivity between terminal attack and central attack at (π -allyl)palladium species by nitrogen-based nucleophiles.

Introduction

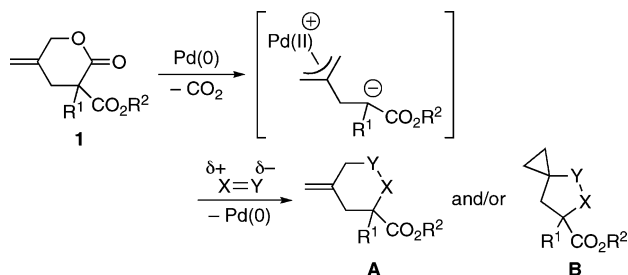
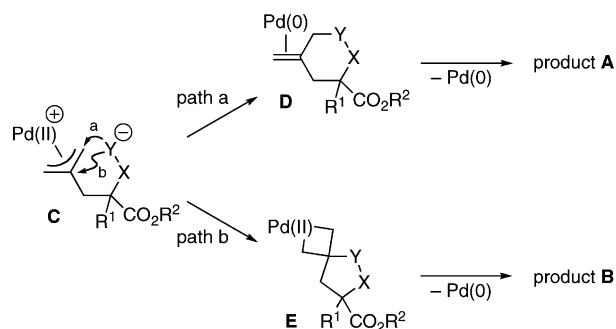
Intermolecular cycloadditions catalyzed by transition-metal complexes are powerful methods for convergent synthesis of cyclic compounds.¹ The development of new and efficient intermolecular cycloaddition reactions is therefore an important objective in synthetic organic chemistry in order to expand the accessibility to a wide variety of carbo- and heterocyclic materials. In this regard, reactions of catalytically generated electrophilic (π -allyl)palladium species bearing a pendant nucleophile with carbon–carbon or carbon–heteroatom unsaturated bonds represent an efficient and attractive approach. For example, vinyl epoxides and aziridines are often utilized for the construction of oxygen- and nitrogen-

containing heterocycles,^{2,3} and 2-((trimethylsilyl)methyl)-2-propenyl acetate and its derivatives are used as effective precursors for palladium trimethylenemethane species in the context of catalytic [3 + n] cycloaddition reactions.^{4,5}

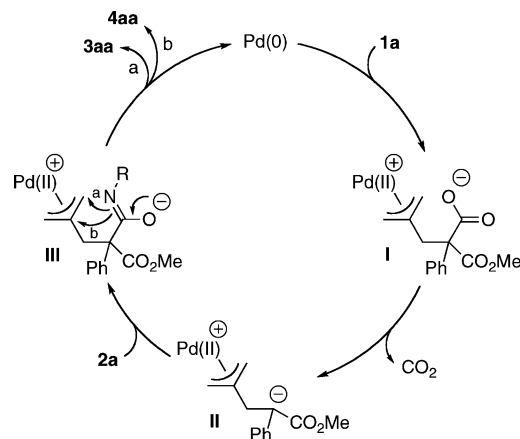
To enhance the utility of palladium-catalyzed intermolecular cycloaddition chemistry, we recently devised γ -methyldiene- δ -valerolactones (**1** in Scheme 1) as new reagents for decarboxylative addition/cyclization reactions with several reaction partners to produce various cyclic compounds under mild palladium catalysis.⁶ These lactones **1** were originally designed

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Scheme 1. Schematic Representation for the Palladium-Catalyzed Decarboxylative Cyclization of γ -Methylidene- δ -valerolactones **1** with X=Y**Scheme 2.** Proposed Pathways for the Formation of Products **A** and **B**

to serve as precursors for 1,4-zwitterionic species through oxidative addition to palladium(0) and successive decarboxylation,^{7,8} thereby introducing a four-carbon unit in a newly formed cyclic framework (product **A**; Scheme 1). During the course of our studies, however, we encountered some cases (particularly with electron-deficient olefins^{6b} or isocyanates^{6c} as the reaction partner) where they provide three carbons in a cyclic framework with a spirocyclopropane moiety (product **B**). Both products **A** and **B** are presumably formed through the common intermediate **C** in Scheme 2, and the position of the subsequent nucleophilic ring closure dictates the structure of the products. Namely, a prototypical Tsuji–Trost-type intramolecular nucleophilic attack at one of the two terminal carbons of the (π -allyl)palladium moiety leads to **A** through **D** (path a),⁹ whereas an attack to the central carbon gives palladacyclobutane **E**,¹⁰ reductive elimination of which leads to **B** (path b).^{10,11} Cyclopropane formation through the latter mode of the reaction pathway was first disclosed by Hegedus and co-workers in the context of

Scheme 3. Proposed Catalytic Cycle for the Palladium-Catalyzed Decarboxylative Cyclization of **1a** and **2a**

stoichiometric reactions with ester enolates.^{11a} Since then, several examples have been reported, including catalytic reactions,^{12,13} but most of them rely on the use of carbon-based nucleophiles such as ester enolates. In contrast, the use of nitrogen-based nucleophiles is very rare for this type of cyclopropanation.¹³

In this article, we employ isocyanates¹⁴ as the reaction partner for the palladium-catalyzed decarboxylative cyclization of γ -methylidene- δ -valerolactones^{6c} and describe the results of our mechanistic investigation, mainly focused on the kinetic studies and the origin of the site selectivity in the nucleophilic attack of nitrogen-based nucleophiles at (π -allyl)palladium species.

Results and Discussion

The reaction of γ -methylidene- δ -valerolactone **1a** with 4-methoxyphenyl isocyanate (**2a**) was conducted in the presence of 5 mol % of Pd(PPh₃)₄ as a catalyst in toluene at 30 °C (eq 1). The reaction was completed within 6 h, and the expected piperidone **3aa** was obtained along with the formation of azaspiro[2.4]heptanone **4aa** with a **3aa/4aa** ratio of 91/9 (94% combined yield). A proposed catalytic cycle of this process is illustrated in Scheme 3. Thus, initial oxidative addition of the allyl ester moiety of **1a** to palladium(0) gives the allylpalladium carboxylate **I**, decarboxylation of which leads to the 1,4-

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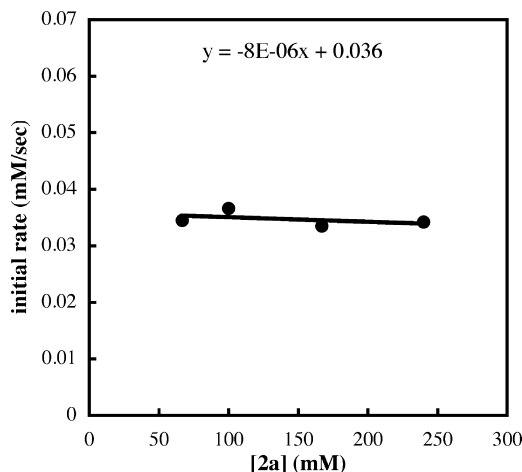
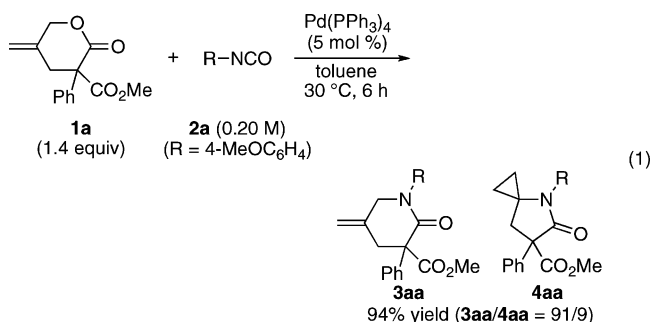


Figure 1. Plot of the initial rate (mM/sec) vs concentration of isocyanate **2a** (mM) ([Pd]₀ = 4 mM, [1a]₀ = 160 mM, [2a]₀ = 67–240 mM).

zwitterionic species **II**. The anionic carbon of **II** then attacks the electrophilic carbon of **2a** to give intermediate **III**. From this intermediate, **3aa** is obtained by a ring closure through a nucleophilic attack of the nitrogen atom at the terminal carbon of the (π -allyl)palladium moiety (path a), whereas **4aa** is generated through a nucleophilic attack at the central carbon followed by reductive elimination (path b).



Kinetic Studies on the Decarboxylative Cyclization of 1a with 2a. A series of NMR experiments were carried out for the kinetic studies of the reaction of lactone **1a** with isocyanate **2a** in toluene-*d*₈ in the presence of Pd(PPh₃)₄ as a catalyst at 25 °C. As shown in Figure 1, the initial concentration of isocyanate **2a** has no influence on the initial rate of the production of **3aa**, indicating that the reaction is zero order in [2a]. In contrast, the reaction rate shows first-order dependency both on the initial concentration of lactone **1a** and on that of palladium catalyst, as illustrated in Figures 2 and 3. These results indicate that the oxidative addition of **1a** to palladium(0) (Pd(0) → **I** step in Scheme 3) is the turnover-limiting step and successive decarboxylation and reaction with **2a** occur much more quickly.

Effect of the Electronic Nature of Ligands for Palladium. Interesting trends were observed by conducting a reaction of lactone **1a** with isocyanate **2a** in the presence of a palladium catalyst possessing several electronically different triarylphosphine ligands. The use of tris(4-methoxyphenyl)phosphine as the ligand smoothly and selectively provided **3aa** in 87% yield with no formation of **4aa** (Table 1, entry 1). By changing the ligand to more electron-deficient triarylphosphines, the reactivity became gradually lower and the selectivity toward **4aa** gradually became higher, reaching **3aa/4aa** = 5/95 with tris(4-(trifluoromethyl)phenyl)phosphine (entry 4).

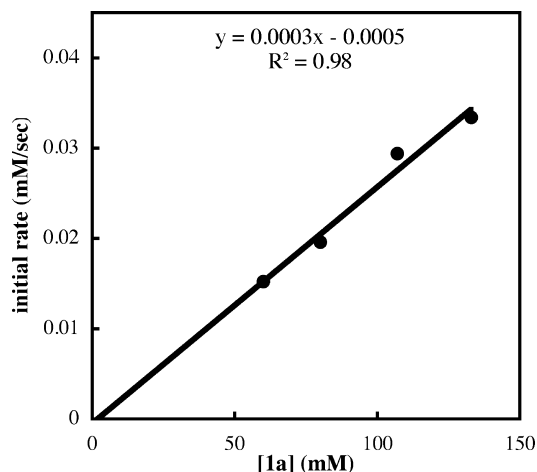


Figure 2. Plot of the initial rate (mM/sec) vs concentration of lactone **1a** (mM) ([Pd]₀ = 4 mM, [1a]₀ = 60–133 mM, [2a]₀ = 100 mM).

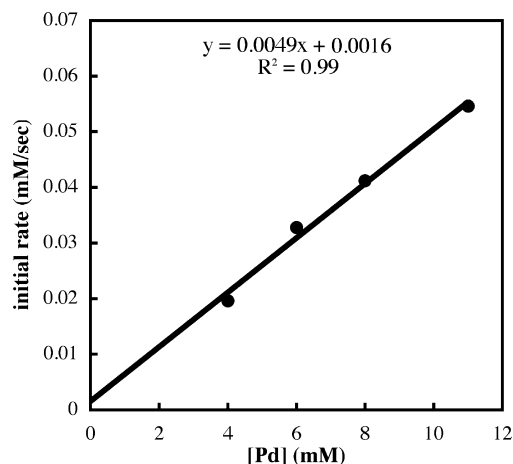


Figure 3. Plot of the initial rate (mM/sec) vs concentration of palladium catalyst (mM) ([Pd]₀ = 4–11 mM, [1a]₀ = 80 mM, [2a]₀ = 100 mM).

Table 1. Palladium-Catalyzed Decarboxylative Cyclization of γ -Methylidene- δ -valerolactone **1a** with 4-Methoxyphenyl Isocyanate (**2a**): Effect of Ligands

entry	Ar	yield (%) ^a	3aa/4aa ^b
1	4-MeOC ₆ H ₄	87	>99/1
2	Ph	85	88/12
3	4-FC ₆ H ₄	71	31/69
4	4-CF ₃ C ₆ H ₄	73 ^c	5/95

^a Combined isolated yield of **3aa** and **4aa**. ^b Determined by ¹H NMR.

^c The reaction was conducted at 50 °C with a 0.67 M concentration of **2a**.

Similarly, under the catalysis of a palladium complex coordinated with tris(4-methoxyphenyl)phosphine, several α -aryl- γ -methylidene- δ -valerolactones **1** smoothly reacted with isocyanate **2a** to provide almost exclusively piperidones **3** in high yield (76–86% yield, **3/4** $\geq$ 97/3; Table 2, entries 1, 3, 5, and 7). The use of tris(4-(trifluoromethyl)phenyl)phosphine as the ligand, on the other hand, led to the

Table 2. Palladium-Catalyzed Decarboxylative Cyclization of **1** with **2a**

entry	1 (Ar)	ligand	product	yield (%) ^a
1 ^b	1b (4-MeOC₆H₄)	P(4-MeOC₆H₄) ₃	3ba/4ba (>99/1)	80
2 ^c	1b	P(4-CF₃C₆H₄) ₃	3ba/4ba (4/96)	64
3 ^b	1c (4-MeC₆H₄)	P(4-MeOC₆H₄) ₃	3ca/4ca (>99/1)	86
4 ^c	1c	P(4-CF₃C₆H₄) ₃	3ca/4ca (5/95)	73
5 ^b	1d (3-MeC₆H₄)	P(4-MeOC₆H₄) ₃	3da/4da (>99/1)	85
6 ^c	1d	P(4-CF₃C₆H₄) ₃	3da/4da (5/95)	62
7 ^b	1e (ferrocenyl)	P(4-MeOC₆H₄) ₃	3ea/4ea (97/3)	76
8 ^c	1e	P(4-CF₃C₆H₄) ₃	3ea/4ea (6/94)	71

^a Combined isolated yield of **3** and **4**. ^b The reaction was conducted at 30 °C with a 0.20 M concentration of **2a**. ^c The reaction was conducted at 50 °C with a 0.67 M concentration of **2a**.

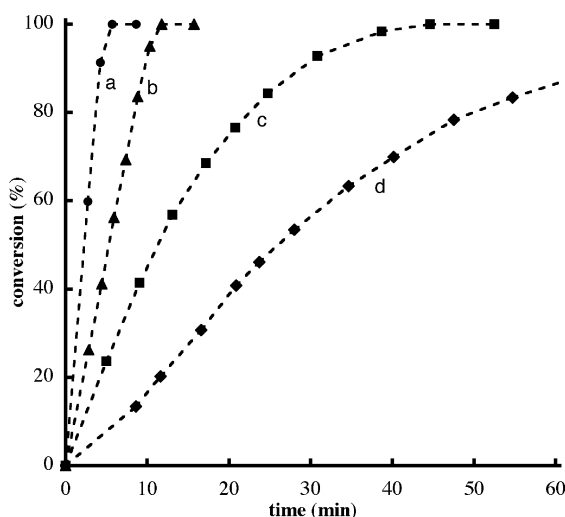


Figure 4. Plot of conversion of **1a** vs time for the reaction of **1a** ($[1a]_0 = 0.080$ M) with **2a** ($[2a]_0 = 0.100$ M) in toluene-*d*₈ (0.60 mL) in the presence of PdCp(η^3 -C₃H₅)/2PAr₃ ($[Pd]_0 = 0.004$ M). Reaction conditions: (a) Ar = 4-MeOC₆H₄ at 30 °C; (b) Ar = Ph at 30 °C; (c) Ar = 4-FC₆H₄ at 50 °C; (d) Ar = CF₃C₆H₄ at 80 °C.

formation of azaspiro[2.4]heptanones **4** with high selectivity (62–73% yield, **3/4** ≤ 6/94; entries 2, 4, 6, and 8).

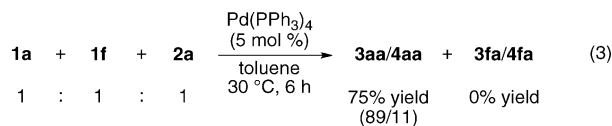
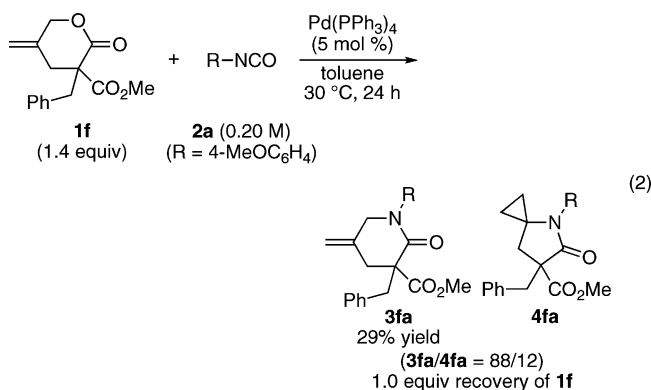
The reactivity difference, dependent on the electronic nature of phosphine ligands, is visualized in Figure 4 by monitoring the reactions in toluene-*d*₈ using NMR spectroscopy. The trend that more electron-rich triarylphosphines provide more reactive catalysts is consistent with the conclusion of the kinetic studies that the turnover-limiting step in the catalytic cycle is the step of oxidative addition, which is known to become more facile with electron-rich ligands on palladium.¹⁵

With regard to the site selectivity of the nucleophilic attack, the central carbon of (π -allyl)metal complexes is known to be more positively charged than the terminal carbons,¹⁶ and the formation of a metallacyclobutane through a nucleophilic attack at the central carbon atom is kinetically controlled.¹⁷ In addition, a theoretical investigation indicates that the site selectivity of

the nucleophilic attack to (π -allyl)metal complexes can be altered by subtle changes of the reaction parameters, due to the possible closeness in energy level of the two empty orbitals derived from the allyl moiety (*n* and π^* orbitals).^{16,18} It has also been proposed that higher nucleophilicity (higher HOMO) of the incoming nucleophile provides a better overlap of its filled orbital with the π^* -derived empty orbital of the (π -allyl)metal species without significant repulsive interaction, leading to the formation of a metallacyclobutane.¹⁸ Furthermore, in the event of a nucleophilic attack to a cationic (π -allyl)palladium(II) complex, the rate is known to become faster with electron-deficient triarylphosphine ligands such as tris(4-(trifluoromethyl)phenyl)phosphine than with electron-rich counterparts such as tris(4-methoxyphenyl)phosphine.¹⁹

On the basis of these precedents, the dependence of selectivity between **3aa** and **4aa** on the electronic nature of ligands could be explained as follows. Thus, by having electron-deficient phosphine ligands on palladium, the reaction pathway is more kinetically controlled and the electron-withdrawing nature of the ligands would facilitate lowering the energy level of the π^* -derived empty orbital. As a consequence, this empty orbital mixes well with the HOMO of the incoming nucleophile, resulting in the preferential formation of a palladacyclobutane, reductive elimination of which gives compound **4aa**. On the other hand, the use of electron-rich phosphine ligands, which slows down the step of nucleophilic attack, leads to a thermodynamically more favorable product (**3aa**) through the usual orbital overlap between the HOMO of the incoming nucleophile and the *n*-derived empty orbital (LUMO) of the (π -allyl)palladium species.

Effect of α -Substituent of Lactones 1. Under the reaction conditions in eq 1, the use of the α -alkyl lactone **1f** resulted in much lower yield of piperidone **3fa** (29% yield after 24 h) with recovery of a significant amount of starting lactone **1f** (1.0 equiv recovery; eq 2). The reactivity difference between the α -phenyl species **1a** and α -benzyl **1f** is further highlighted by the competition experiment in eq 3. Thus, an equimolar mixture of **1a** and **1f** was treated with isocyanate **2a** in the presence of Pd(PPh₃)₄ catalyst at 30 °C. Under these conditions, only the products derived from lactone **1a** (**3aa/4aa**) were obtained in 75% yield with no formation of the **1f**-derived products **3fa/4fa**.



To elucidate the behavior of **1f** during the catalytic reaction, the δ,δ -dideuterio lactone **1f-d**₂ was subjected to the reaction with **2a** and the recovered **1f-d**₂ was analyzed by NMR to show

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that the deuterium content at the δ -position became 120% (out of 200%) and the hydrogens on the *exo*-methylene carbon showed 80% deuterium incorporation (eq 4). This result indicates that oxidative addition of **1f** does occur under these conditions, but successive generation of 1,4-zwitterionic species by decarboxylation becomes less favorable, presumably because the resulting anionic charge on the α -carbon is not well stabilized by the electron-donating alkyl substituent. This hypothesis is further supported by a control experiment using α -phenyl lactone **1a-d₂** in the reaction with **2a** (eq 5). Recovered **1a-d₂** in this case kept its deuterium atoms at the δ -position with essentially no migration to the *exo*-methylene carbon, indicating that the rate-determining oxidative addition is rapidly followed by decarboxylation, which is facilitated by the anion-stabilization ability of the phenyl group at the α -position. On the basis of these experiments, we prepared α -benzyl lactone **1f'** having a more electron-withdrawing phenyl ester, instead of a methyl ester, to accelerate the decarboxylation step (**I** $\rightarrow$ **II** in Scheme 3), and we were pleased to find that the reaction of this lactone **1f'** with isocyanate **2a** did smoothly proceed to give the corresponding decarboxylative cyclization products in high yield (81% yield; eq 6).

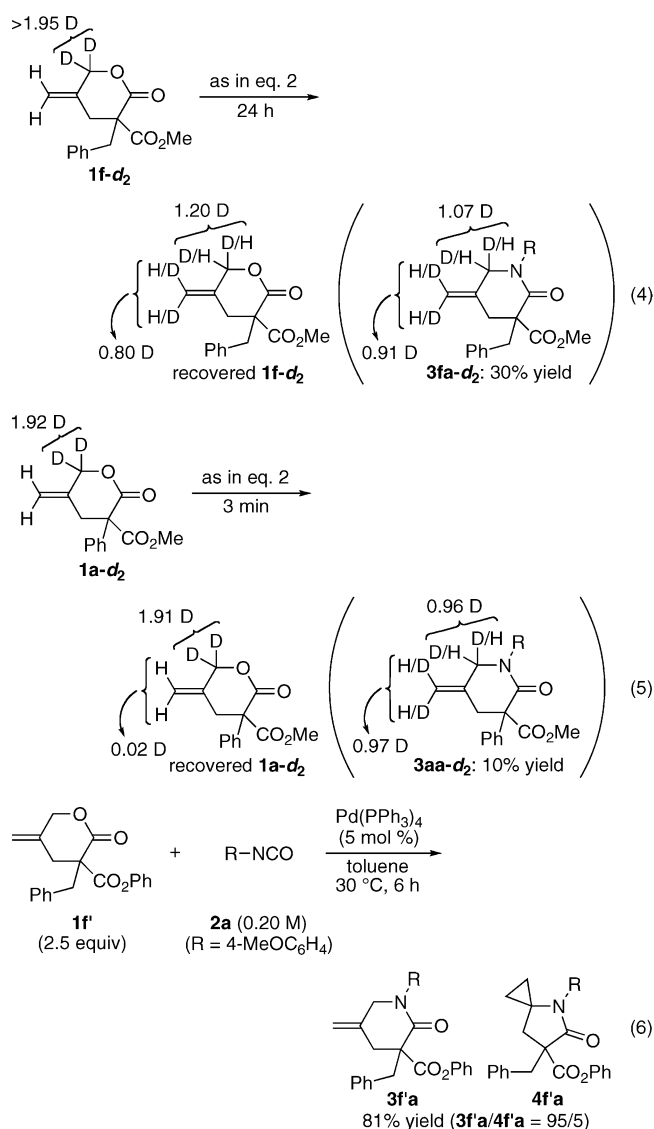


Table 3. Palladium-Catalyzed Decarboxylative Cyclization of **1a** with Isocyanates **2**: Effect of N-Substituents

entry	2 (R)	product	yield (%) ^a
1 ^b	2a (4-MeOC ₆ H ₄)	3aa/4aa (91/9)	94
2 ^b	2b (4-ClC ₆ H ₄)	3ab/4ab (>99/1)	84
3 ^c	2c (1-cyclohexenyl)	3ac/4ac (40/60)	58
4 ^c	2d (CH ₂ Ph)	3ad/4ad (4/96)	55

^a Combined isolated yield of **3** and **4**. ^b 1.4 equiv of **1a** was used. ^c 2.5 equiv of **1a** was used.

(**2a**) provided piperidone **3aa** as the major product under the catalysis of Pd(PPh₃)₄ (**3aa/4aa** = 91/9; Table 3, entry 1) through a preferential nucleophilic ring closure at the terminal carbon of the (π -allyl)palladium intermediate (path a in Scheme 3). The use of electron-deficient aryl isocyanates such as 4-chlorophenyl isocyanate (**2b**) led to further enhancement of selectivity toward product **3** (**3ab/4ab** > 99/1; entry 2). In contrast, the change of nitrogen substituent of the isocyanate to a 1-cyclohexenyl group (**2c**) gave a 40/60 mixture of **3ac/4ac** (entry 3), and the predominant formation of azaspiro[2.4]-heptanone **4ad** was observed with an alkyl isocyanate such as **2d** (**3ad/4ad** = 4/96; entry 4). The results observed here indicate that more stabilized anionic amide nitrogens seem to favor a terminal attack at a (π -allyl)palladium complex, whereas less stabilized counterparts favor a central attack. This trend is similar to that with carbon-based nucleophiles (e.g., ester enolate vs malonate enolate) reported in the literature^{11a,12b} and is consistent with the conclusion of the previous theoretical study.¹⁸

Reactions of **1a with Other Substrates.** We previously reported that lactones **1** could undergo decarboxylative cyclization with other reaction partners such as isatins^{6f} and electron-deficient olefins.^{6b} To gain some insight into the reactivity difference of these compounds, we conducted control experiments as follows. The reaction of lactone **1a** with an equimolar mixture of isocyanate **2a** and *N*-methylisatin (**5**) selectively provided the spirooxindole **6a** in 97% yield with no formation of **3aa/4aa** (eq 7). In contrast, the reaction of **1a** with an equimolar mixture of **2a** and methyl acrylate (**7**) produced **3aa/4aa** in 17% combined yield and carbocycles **8a/9a** derived from **7** in 63% combined yield (eq 8). In addition, a reaction of lactone **1a** with an equimolar mixture of *N*-methylisatin (**5**) and methyl acrylate (**7**) selectively provided spirooxindole **6a** with no formation of **8a/9a**. These results establish that the reactivity toward **1a** is in the order of isatin **5** > acrylate **7** > isocyanate **2a**. Because the kinetic studies on the reaction of **1a** with **2a** demonstrated that the oxidative addition of **1a** is the turnover-

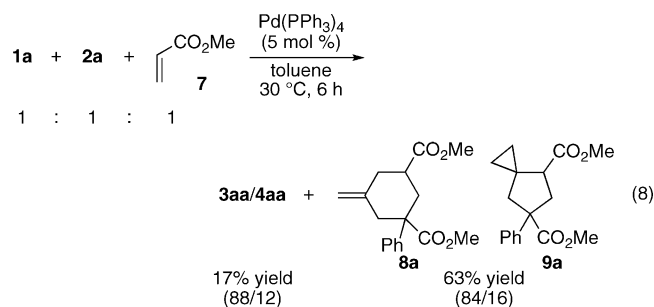
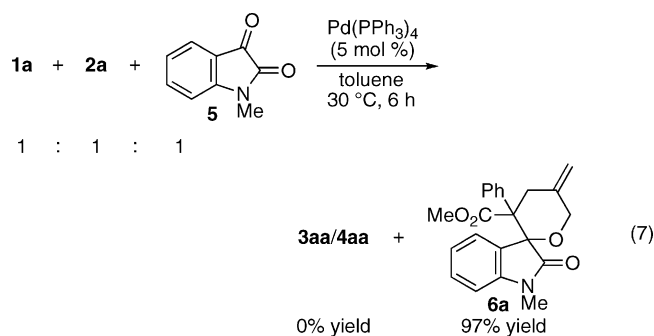
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Effect of N-Substituent of Isocyanates **2.** As described in eq 1, a reaction of lactone **1a** with 4-methoxyphenyl isocyanate

limiting step, the same conclusions could be drawn for more reactive substrates **5** and **7**.



Conclusions

We have described that palladium triarylphosphine complexes can effectively catalyze decarboxylative cyclization reactions

of γ -methylidene- δ -valerolactones **1** with isocyanates **2** to give piperidones **3** and/or azaspiro[2.4]heptanones **4**. Through kinetic studies using NMR spectroscopy, we have determined that the oxidative addition of lactones **1** to palladium(0) is the turnover-limiting step of the catalytic cycle. By changing the electronic property of the triarylphosphine ligands, we have demonstrated that the product distribution between **3** and **4** can be easily controlled. The selectivity between **3** and **4** is also influenced by the nature of the nitrogen substituent on isocyanates **2**, and more electron-rich substituents tend to give higher selectivity toward azaspiro[2.4]heptanones **4**. These studies represent the first systematic investigation on the selectivity between terminal attack and central attack at (π -allyl)palladium species by nitrogen-based nucleophiles under catalytic conditions. We have also shown that other reaction partners such as isatins and acrylates display the same turnover-limiting step in the reaction with γ -methylidene- δ -valerolactones through competition experiments with isocyanates.

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Supporting Information Available: Text and figures giving experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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