JACS ARTICLES

Published on Web 05/07/2010

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

Ryo Shintani,* Takaoki Tsuji, Soyoung Park, and Tamio Hayashi*

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

Received March 24, 2010; E-mail: shintani@kuchem.kyoto-u.ac.jp; thayashi@kuchem.kyoto-u.ac.jp

Abstract: Mechanistic studies for the palladium-catalyzed decarboxylative cyclization reactions of γ-methylidene-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-methylidene-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

(1) (a) Galan, B. R.; Rovis, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 2830. (b) Varela, J. A.; Saá, C. *Synlett* **2008**, 2571. (c) Shibata, T. *Adv. Synth. Catal.* **2006**, *348*, 2328. (d) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (e) Wender, P. A.; Gamber, G. G.; Williams, T. J. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005; p 263. (f) Mandai, T. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; p 925. (g) Kobayashi, S., Jørgensen, K. A., Eds. *Cycloaddition Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002.

(2) (a) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792. (b) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1988**, *110*, 7933. (c) Trost, B. M.; Fandrick, D. R. *J. Am. Chem. Soc.* **2003**, *125*, 11836. (d) Larksarp, C.; Alper, H. *J. Am. Chem. Soc.* **1997**, *119*, 3709. (e) Butler, D. C. D.; Inman, G. A.; Alper, H. *J. Org. Chem.* **2000**, *65*, 5887.

(3) (a) Fujinami, T.; Suzuki, T.; Kamiya, M.; Fukuzuka, S.; Sakai, S. *Chem. Lett.* **1985**, 199. (b) Trost, B. M.; Angle, S. R. *J. Am. Chem. Soc.* **1985**, *107*, 6123. (c) Shim, J.-G.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 3067. (d) Shim, J.-G.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 1053. For a review, see: (e) Courillon, C.; Thorimbert, S.; Malacrìa, M. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: Hoboken, NJ, 2002; p 1795.

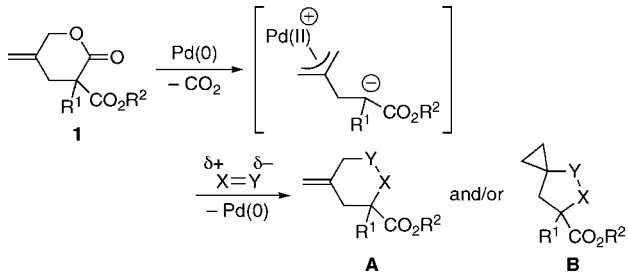
(4) (a) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6429. (b) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2315. (c) Trost, B. M.; MacPherson, D. T. *J. Am. Chem. Soc.* **1987**, *109*, 3483. (d) Trost, B. M.; Seoane, P. R. *J. Am. Chem. Soc.* **1987**, *109*, 615. (e) Trost, B. M.; Stambuli, J. P.; Silverman, S. M.; Schwörer, U. *J. Am. Chem. Soc.* **2006**, *128*, 13328. (f) Trost, B. M.; Silverman, S. M.; Stambuli, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 12398. (g) Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 6330. (h) Shintani, R.; Park, S.; Duan, W.-L.; Hayashi, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5901. See also: (i) Shimizu, I.; Ohashi, Y.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 5183. (j) Inoue, Y.; Ajioka, M.; Toyofuku, M.; Mori, A.; Fukui, T.; Kawashima, Y.; Miyano, S.; Hashimoto, H. *J. Mol. Catal.* **1985**, *32*, 91.

(5) For reviews, see: (a) Chan, D. M. T. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, Germany, 2002; p 57. (a) Ogoshi, S. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: Hoboken, NJ, 2002; p 1995.

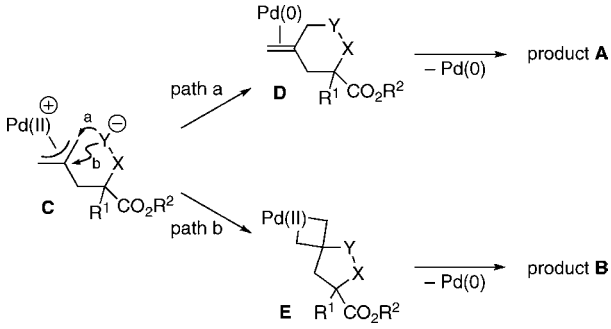
(6) (a) Shintani, R.; Murakami, M.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12356. (b) Shintani, R.; Park, S.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 14866. (c) Shintani, R.; Park, S.; Shirozu, F.; Murakami, M.; Hayashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 16174. (d) Shintani, R.; Murakami, M.; Hayashi, T. *Org. Lett.* **2009**, *11*, 457. (e) Park, S.; Shintani, R.; Hayashi, T. *Chem. Lett.* **2009**, *38*, 204. (f) Shintani, R.; Hayashi, S.; Murakami, M.; Takeda, M.; Hayashi, T. *Org. Lett.* **2009**, *11*, 3754. (g) Shintani, R.; Murakami, M.; Tsuji, T.; Tanno, H.; Hayashi, T. *Org. Lett.* **2009**, *11*, 5642.

 10.1021/ja1023223

Scheme 1. Schematic Representation for the Palladium-Catalyzed Decarboxylative Cyclization of γ-Methylidene-δ-valerolactones **1** with X=Y

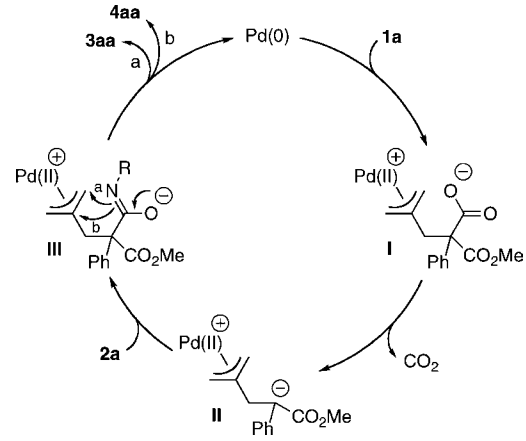


Scheme 2. Proposed Pathways for the Formation of Products **A** and **B**



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 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]

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



In this article, we employ isocyanates[14] 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 $Pd(PPh_3)_4$ 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-

(7) (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) Tunge, J. A.; Burger, E. C. *Eur. J. Org. Chem.* **2005**, 1715. (d) You, S.-L.; Dai, L.-X. *Angew. Chem., Int. Ed.* **2006**, *45*, 5246.

(8) For leading references, see: (a) Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113. (b) Rayabarapu, D. K.; Tunge, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13510. (c) Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 14860. (d) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180. (e) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924. (f) Patil, N. T.; Huo, Z.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 6991.

(9) For recent reviews on palladium-catalyzed allylic alkylation reactions, see: (a) Trost, B. M.; Fandrick, D. R. *Aldrichim. Acta* **2007**, *40*, 59. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (c) Hayashi, T. *J. Organomet. Chem.* **1999**, *576*, 195. (d) Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203. (e) Negishi, E., Ed. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley: Hoboken, NJ, 2002; Vol. 2.

(10) Hoffmann, H. M. R.; Otte, A. R.; Wilde, A.; Menzer, S.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 100.

(11) (a) Hegedus, L. S.; Darlington, W. H.; Russell, C. E. *J. Org. Chem.* **1980**, *45*, 5193. (b) Hoffmann, H. M. R.; Otte, A. R.; Wilde, A. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 234. (c) Wilde, A.; Otte, A. R.; Hoffmann, H. M. R. *J. Chem. Soc., Chem. Commun.* **1993**, 615. (d) Otte, A. R.; Wilde, A.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1280.

(12) (a) Formica, M.; Musco, A.; Pontellini, R.; Linn, K.; Mealli, C. *J. Organomet. Chem.* **1993**, *448*, C6. (b) Satake, A.; Nakata, T. *J. Am. Chem. Soc.* **1998**, *120*, 10391. (c) Satake, A.; Koshino, H.; Nakata, T. *Chem. Lett.* **1999**, 49. (d) Satake, A.; Kadohama, H.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 3597. (e) Liu, W.; Chen, D.; Zhu, X.-Z.; Wan, X.-L.; Hou, X.-L. *J. Am. Chem. Soc.* **2009**, *131*, 8734.

(13) Grigg, R.; Kordes, M. *Eur. J. Org. Chem.* **2001**, 707.

(14) For leading references on transition metal-catalyzed cycloadditions using isocyanates, see: (a) Reference 2. (b) Baeg, J.-O.; Bensimon, C.; Alper, H. *J. Am. Chem. Soc.* **1995**, *117*, 4700. (c) Duong, H. A.; Cross, M. J.; Louie, J. *J. Am. Chem. Soc.* **2004**, *126*, 11438. (d) Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Takagishi, H.; Okuda, S.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 605. (e) Tanaka, K.; Wada, A.; Noguchi, K. *Org. Lett.* **2005**, *7*, 4737. (f) Tanaka, K.; Hagiwara, Y.; Hirano, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2734. (g) Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2782. (h) Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 12370. (i) Yu, R. T.; Friedman, R. K.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 13250.

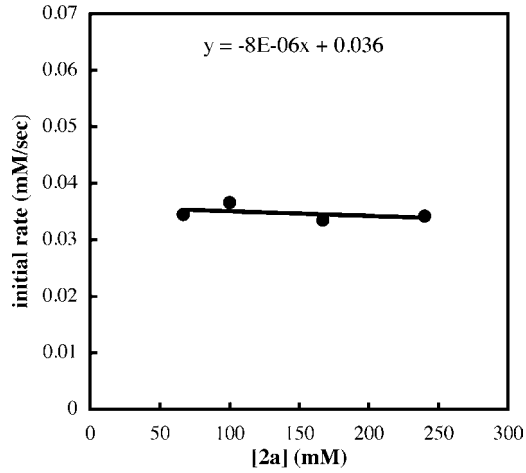
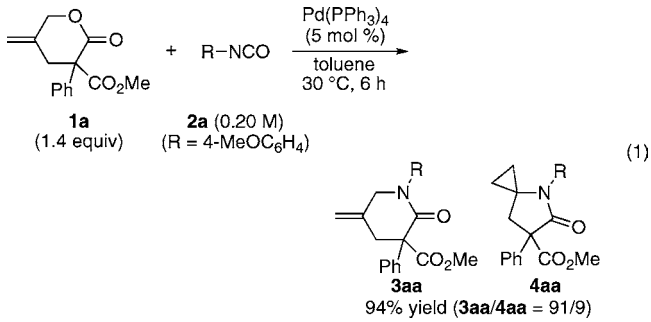


Figure 1. Plot of the initial rate (mM/sec) vs concentration of isocyanate **2a** (mM) ([Pd]$_0$ = 4 mM, [**1a**]$_0$ = 160 mM, [**2a**]$_0$ = 67−240 mM).

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).



(1)

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(PPh$_3$)$_4$ 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).

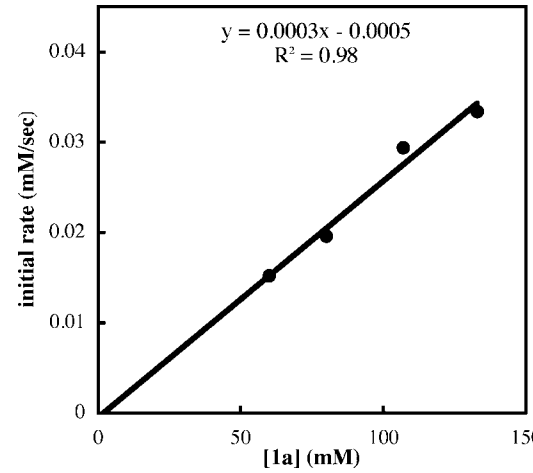


Figure 2. Plot of the initial rate (mM/sec) vs concentration of lactone **1a** (mM) ([Pd]$_0$ = 4 mM, [**1a**]$_0$ = 60−133 mM, [**2a**]$_0$ = 100 mM).

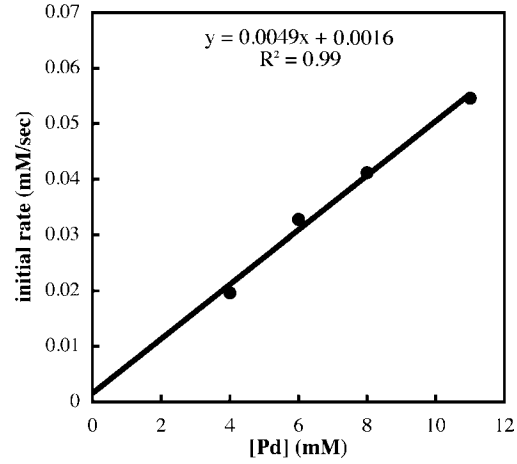
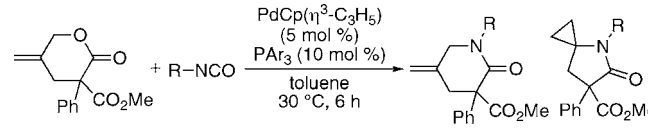


Figure 3. Plot of the initial rate (mM/sec) vs concentration of palladium catalyst (mM) ([Pd]$_0$ = 4−11 mM, [**1a**]$_0$ = 80 mM, [**2a**]$_0$ = 100 mM).

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

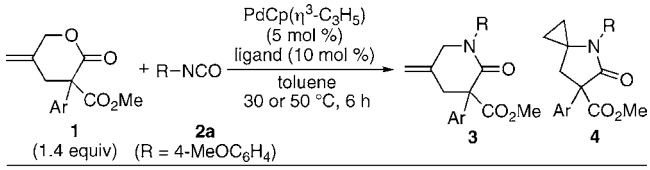


entry	Ar	yield (%)[a]	**3aa**/**4aa**[b]
1	4-MeOC$_6$H$_4$	87	>99/1
2	Ph	85	88/12
3	4-FC$_6$H$_4$	71	31/69
4	4-CF$_3$C$_6$H$_4$	73[c]	5/95

[a] Combined isolated yield of **3aa** and **4aa**. [b] Determined by ^{1}H 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** ≥ 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-$MeOC_6H_4$)	P(4-$MeOC_6H_4$)$_3$	**3ba**/**4ba** (>99/1)	80
2[c]	**1b**	P(4-$CF_3C_6H_4$)$_3$	**3ba**/**4ba** (4/96)	64
3[b]	**1c** (4-MeC_6H_4)	P(4-$MeOC_6H_4$)$_3$	**3ca**/**4ca** (>99/1)	86
4[c]	**1c**	P(4-$CF_3C_6H_4$)$_3$	**3ca**/**4ca** (5/95)	73
5[b]	**1d** (3-MeC_6H_4)	P(4-$MeOC_6H_4$)$_3$	**3da**/**4da** (>99/1)	85
6[c]	**1d**	P(4-$CF_3C_6H_4$)$_3$	**3da**/**4da** (5/95)	62
7[b]	**1e** (ferrocenyl)	P(4-$MeOC_6H_4$)$_3$	**3ea**/**4ea** (97/3)	76
8[c]	**1e**	P(4-$CF_3C_6H_4$)$_3$	**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**.

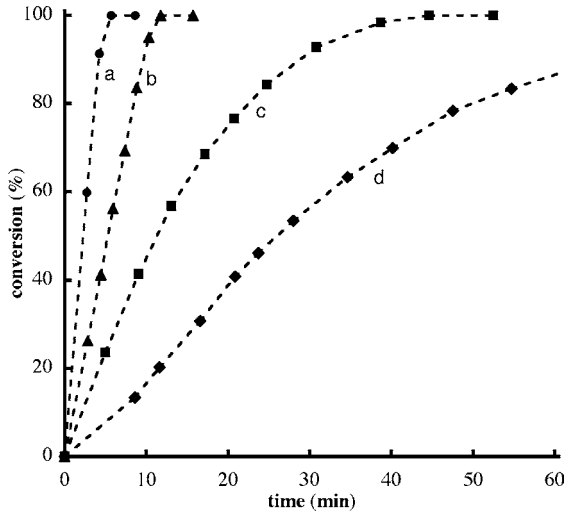


Figure 4. Plot of conversion of **1a** vs time for the reaction of **1a** ($[\mathbf{1a}]_0$ = 0.080 M) with **2a** ($[\mathbf{2a}]_0$ = 0.100 M) in toluene-d_8 (0.60 mL) in the presence of $PdCp(\eta^3\text{-}C_3H_5)/2PAr_3$ ($[Pd]_0$ = 0.004 M). Reaction conditions: (a) Ar = 4-$MeOC_6H_4$ at 30 °C; (b) Ar = Ph at 30 °C; (c) Ar = 4-FC_6H_4 at 50 °C; (d) Ar = $CF_3C_6H_4$ at 80 °C.

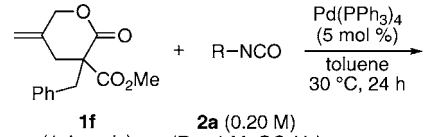
formation of azaspiro[2.4]heptanones **4** with high selectivity (62−73% yield, **3**/**4** ≤ 6/94; entries 2, 4, 6, and 8).

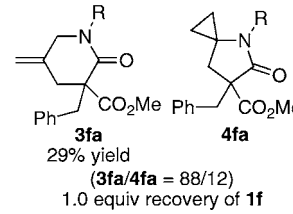
The reactivity difference, dependent on the electronic nature of phosphine ligands, is visualized in Figure 4 by monitoring the reactions in toluene-d_8 using NMR spectroscopy. The trend that more electron-rich triarylphosphines provide more reactive catalysts is consistent with the conclusion of the 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]

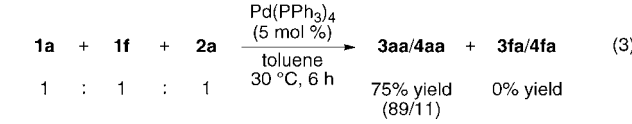
On the basis of these precedents, the dependence of selectivity between **3aa** and **4aa** on the electronic nature of ligands could be explained as follows. Thus, by having electron-deficient phosphine ligands on palladium, the reaction pathway is more kinetically controlled and the electron-withdrawing 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 $Pd(PPh_3)_4$ 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**.





(2)

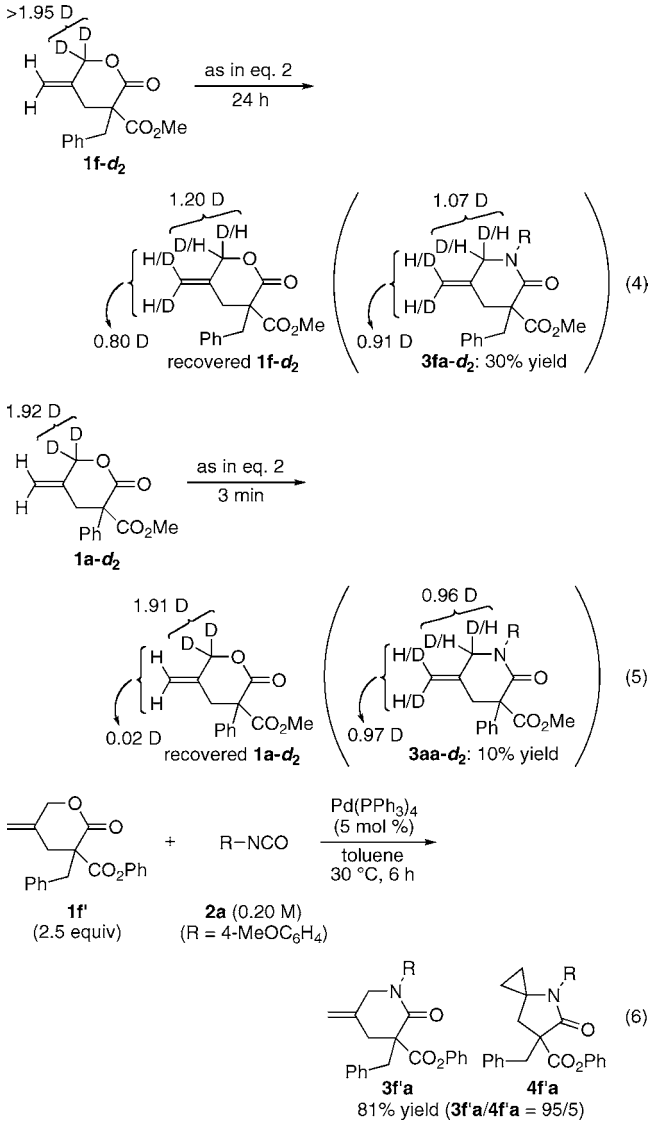


(3)

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

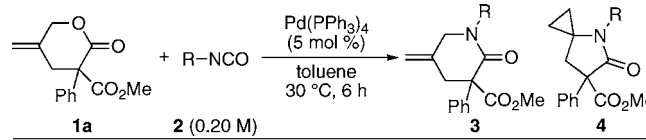
(15) Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. A. *Organometallics* **1995**, *14*, 1818.
(16) Curtis, M. D.; Eisenstein, O. *Organometallics* **1984**, *3*, 887.

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-*d*$_2$** in the reaction with **2a** (eq 5). Recovered **1a-*d*$_2$** 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** → **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).



Effect of N-Substituent of Isocyanates 2. As described in eq 1, a reaction of lactone **1a** with 4-methoxyphenyl isocyanate (**2a**) provided piperidone **3aa** as the major product under the catalysis of $Pd(PPh_3)_4$ (**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]

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



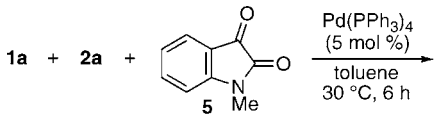
entry	**2** (R)	product	yield (%)[a]
1[b]	**2a** (4-$MeOC_6H_4$)	**3aa**/**4aa** (91/9)	94
2[b]	**2b** (4-ClC_6H_4)	**3ab**/**4ab** (>99/1)	84
3[c]	**2c** (1-cyclohexenyl)	**3ac**/**4ac** (40/60)	58
4[c]	**2d** (CH_2Ph)	**3ad**/**4ad** (4/96)	55

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

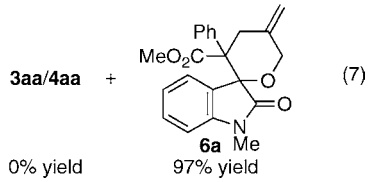
Reactions of 1a with Other Substrates. We previously reported that lactones **1** could undergo decarboxylative cyclization with other reaction partners such as isatins[6f] and electron-deficient olefins.[6b] To gain some insight into the reactivity difference of these compounds, we conducted control 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-

(17) (a) Tjaden, E. B.; Stryker, J. M. *J. Am. Chem. Soc.* **1990**, *112*, 6420. (b) Wakefield, J. B.; Stryker, J. M. *J. Am. Chem. Soc.* **1991**, *113*, 7057.
(18) Carfagna, C.; Galarini, R.; Linn, K.; López, J. A.; Mealli, C.; Musco, A. *Organometallics* **1993**, *12*, 3019.
(19) Evans, L. A.; Fey, N.; Harvey, J. N.; Hose, D.; Lloyd-Jones, G. C.; Murray, P.; Orpen, A. G.; Osborne, R.; Owen-Smith, G. J. J.; Purdie, M. *J. Am. Chem. Soc.* **2008**, *130*, 14471.

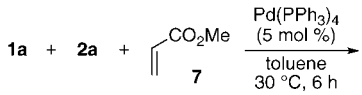
limiting step, the same conclusions could be drawn for more reactive substrates **5** and **7**.



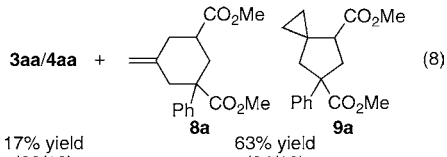
1 : 1 : 1



0% yield 97% yield



1 : 1 : 1



17% yield (88/12) 63% yield (84/16)

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.

Acknowledgment. Support has been provided in part by a Grant-in-Aid for Scientific Research, the Ministry of Education, Culture, Sports, Science and Technology, Japan (the Global COE Program "Integrated Materials Science" on Kyoto University).

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.

JA1023223