ORGANIC LETTERS

2012
Vol. 14, No. 9
2326–2329

Palladium-Catalyzed Asymmetric 6-Endo Cyclization of Dienamides with Substituent-Driven Activation

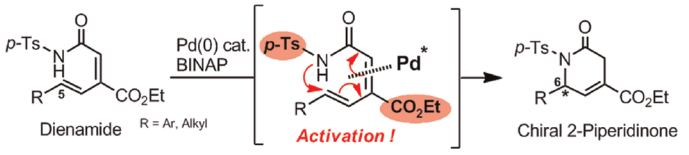
Hiroshi Tsuchikawa,*,† Yuya Maekawa, and Shigeo Katsumura*

School of Science and Technology, Kwansei Gakuin University, Gakuen 2-1, Sanda, Hyogo 669-1337, Japan

h-tsuchi@chem.sci.osaka-u.ac.jp; katsumura@kwansei.ac.jp

Received March 22, 2012

ABSTRACT



Chiral 2-piperidinone compounds with various C-6 substituents were successfully synthesized via a Pd-catalyzed asymmetric 6-*endo* cyclization of dienamides, which were evidently activated by both *N*-*p*-toluenesulfonyl and C-3 ester substituents.

Nitrogen-containing six-membered heterocycles, such as pyridine, piperidine, and piperidinone, are often found as the core structural motif in naturally occurring bioactive compounds and synthetic drugs.[1] Among them, 2-piperidinone (δ-lactam) has especially attracted much attention in the synthetic community, because it can be a versatile precursor of highly functionalized piperidines.[2] Various synthetic approaches to 2-piperidinones have currently been developed,[3] for example, through the aza-Diels–Alder reaction,[3c,d] ring closing metathesis,[3e,f] and metal-catalyzed C–H bond amination.[3g,h] However, the cyclization of activated C–C bonds with a tethered amide,[3a,b] which seems to be the most conventional route, has not been well documented probably due to the lower nucleophilicity of the amide nitrogen compared to amines.[4] Herein, we report a Pd-catalyzed 6-*endo* type cyclization of the dienamide with the appropriate substituents at the nitrogen atom and the C-3 position to obtain 2-piperidinones with various C-6 substituents. Moreover, we present its enantioselective variants using the BINAP-Pd complex catalyst, which must provide a valuable synthon for the multisubstituted chiral piperidinone and piperidine compounds.

Over the past 10 years, we have developed efficient synthetic methods for 2,4-disubstituted pyridine and chiral piperidine compounds based on rapid 6π-azaelectrocyclization from 1-azatrienes (Scheme 1).[5] This rapid cyclization

† Department of Chemistry, Graduate School of Science, Osaka University, 1-1 Machikaneyama, Toyonaka, Osaka 560-0043, Japan.

(1) For example: (a) Joule, J. A.; Smith, G.; Mills, K. *Heterocyclic Chemistry*, 3rd ed.; Chapman and Hall: London, 1995; pp 72–119. (b) Roth, H. J., Kleemann, A., Eds. *Pharmaceutical Chemistry, Vol. 1: Drug Synthesis*; John Wiley: New York, 1988. (c) Strunz, G. M.; Findlay, J. A. *The Alkaloids*; Brossi, A., Ed.; Academic Press: London, 1985; Vol. 26, pp 89–183. (d) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon Press: New York, 1999; Vol. 13, pp 1–161.

(2) (a) Escolano, M.; Amat, M.; Bosch, J. *Chem.—Eur. J.* **2006**, *12*, 8198–8207. (b) Agami, C.; Dechoux, L.; Hebbe, S.; Ménard, C. 60 *Tetrahedron* **2004**, *60*, 5433–5438. (c) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843–9873.

(3) For example: (a) Patil, N. T.; Huo, Z.; Bajracharya, G. B.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 3612–3614. (b) Obika, S.; Yasui, Y.; Yanada, R.; Takemoto, Y. *J. Org. Chem.* **2008**, *73*, 5206–5209. (c) 65 Chen, Z.; Lin, L.; Chen, D.; Li, J.; Liu, X.; Feng, X. *Tetrahedron Lett.* **2010**, *51*, 3088–3091. (d) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4796–4798. (e) Fiorelli, C.; Savoia, D. *J. Org. Chem.* **2007**, *72*, 6022–6028. (f) Lee, J. H.; Shin, S.; Kang, J.; Lee, S. *J. Org. Chem.* **2007**, *72*, 7443–7446. (g) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058–14059. (h) Inamoto, K.; Saito, T.; Hiroya, K.; Doi, T. *J. Org. Chem.* **2010**, *75*, 3900–3903.

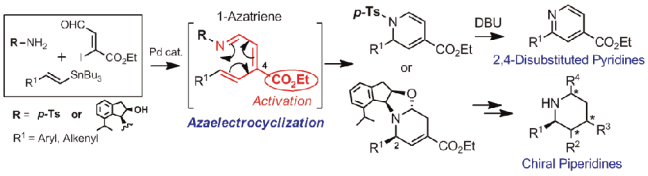
(4) Some analogous reactions to give γ-lactams and oxazolidinones are reported. (a) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2892–2895. (b) Overman, L. E.; Remarchuk, T. P. *J. Am. Chem. Soc.* **2002**, *124*, 12–13. (c) Hayashi, T.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1988**, *29*, 99–102.

(5) (a) Sakaguchi, T.; Kobayashi, T.; Hatano, S.; Tsuchikawa, H.; Fukase, K.; Tanaka, K.; Katsumura, S. *Chem.—Asian J.* **2009**, *4*, 1573–1577. (b) Kobayashi, T.; Takeuchi, K.; Miwa, J.; Tsuchikawa, H.; Katsumura, S. *Chem. Commun.* **2009**, 3363–3365. (c) Kobayashi, T.; Hatano, S.; Tsuchikawa, H.; Katsumura, S. *Tetrahedron Lett.* **2008**, *49*, 4349–4351. (d) Kobayashi, T.; Hasegawa, F.; Tanaka, K.; Katsumura, S. *Org. Lett.* **2006**, *8*, 3813–3816. (e) Tanaka, K.; Mori, H.; Yamamoto, M.; Katsumura, S. *J. Org. Chem.* **2001**, *66*, 3099–3110.

10.1021/ol300737t
Published on Web 04/24/2012

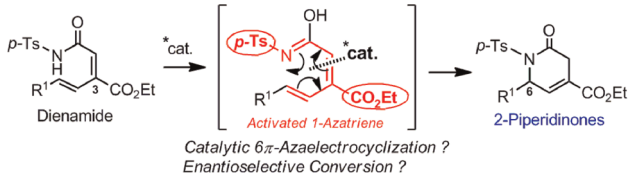
was realized by the remarkable substituent effect due to the enhancement of the HOMO−LUMO interaction in the 6π-electron system mainly derived from the C-4 ester substituent,[5e] and the additional electron withdrawing group at the nitrogen.[5a,c,e]

Scheme 1. Synthetic Methods for 2,4-Disubstituted Pyridines and Chiral Piperidines via the Rapid 6π-Azaelectrocyclization



In order to further develop our synthetic methodology using this "substituent-driven activation", we next focused on the more challenging variant, catalytic 6π-azaelectrocyclization.[6] Because the difficulty of the catalytic activation of a simple triene system has already been known,[6c,d] we carefully designed and devised the substrate (Scheme 2). Thus, we expected that the addition of a catalyst to the dienamide compound with the C-3 ester and *N*-*p*-Ts groups would lead to generation of the activated 1-azatriene form followed by an immediate azaelectrocyclization to give the 2-piperidinone compound. Hence, we envisioned that we could not only realize the catalytic cyclization with substituent-driven activation but also develop the novel synthetic strategy for substituted 2-piperidinones. Moreover, utilizing a chiral catalyst might lead to the promising enantioselective conversion.

Scheme 2. Strategy for 2-Piperidinone Synthesis via the Catalyzed 6π-Azaelectrocyclization



We first chose 3-ethoxycarbonyl-5-phenyl-*N*-*p*-toluenesulfonyldienamide **1** as a substrate for the cyclization (Table 1).[7] As a catalyst, we selected tris(dibenzylideneacetone)-dipalladium [$Pd_2(dba)_3$] which seemed to have a favorable affinity to 1-azatriene.[5b,d] The dienamide **1** and a catalytic amount of $Pd_2(dba)_3$ were stirred at 70 °C in dioxane for 6 h only to give the starting material (entry 1). Next, although trifurylphosphine or triphenylphosphine was added as an additive, the desired piperidinone **1P** was not obtained (entries 2 and 3). However, after changing dioxane to toluene, surprisingly, the cyclization partly proceeded to afford the expected 2-piperidinone **1P** in 38% yield (entry 4). Encouraged by this result, we finally found when the bidentate phosphine ligands {1,2-bis(diphenylphosphino)-ethane (DPPE), 1,3-bis(diphenylphosphino)propane (DPPP), or 1,4-bis(diphenylphosphino)butane (DPPB)} were used, the reaction smoothly proceeded to produce the desired piperidinone in 85%, 85%, and 75% yields, respectively (entries 5 to 7). Meanwhile, utilizing other catalysts, such as palladium(II) chloride (entry 8), Lewis acid [$Sc(OTf)_3$, entry 9] ,or base (1,8-diazabicyclo[5.4.0]undec-7-ene: DBU, entry 10) induced no cyclization. These results obviously showed that the combination of $Pd_2(dba)_3$ with the bidentate phosphine ligands was the best for this cyclization reaction.

To broaden the utility of this reaction, we next examined the cyclization with dienamide substrates having various C-5 substituents (Table 2). As shown in entries 1 to 6, the established set of conditions in Table 1 was successfully applied to the substrates with some aryl and heteroaromatic substituents to afford the corresponding 2-piperidinones in good yields. Moreover, in the case of acyclic substituents, such as the methoxymethyl and siloxymethyl derivatives **7** and **8**, cyclic products **7P** and **8P** were found to occur in significant yields (entries 7 and 8). These results have shown that this reaction has a high generality for the C-5-substituents and is a novel approach for the 2-piperidinones with various C-6 substituents. Furthermore, regarding this reaction as an amide cyclization, it is, to the best of our knowledge, an unprecedented example of the Pd-catalyzed intramolecular 1,6-addition of an amide.[8]

Since promising results of the catalytic cyclization were obtained, we next focused on the enantioselective conversion (Scheme 3). Taking into consideration the results above, chiral bidentate phosphine ligands, such as (*R*,*R*)-1,2-bis[(2-methoxyphenyl)phenylphosphino]ethane (DIPAMP), (−)-1,2-bis[(2R,5R)-2,5-dimethylphospholano]-benzene (Me-DUPHOS), (4*R*,5*R*)-*trans*-4,5-bis[(diphenylphosphino)methyl]-2,2-dimethyl-1,3-dioxalane (DIOP), (*R*)-[(5,6),(5′,6′)-bis(ethylenedioxy)biphenyl-2,2′-diyl]bis-(diphenylphosphine) (SYNPHOS), and (*S*)-2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl (BINAP) were examined (Scheme 3A). Among them, gratifyingly, all ligands showed certain enantioselectivities, and especially those with an axial chirality produced a significant increase in the enantiomeric excess; SYNPHOS was 68% ee and BINAP was 76% ee, along with 68% and 78% chemical yields, respectively. In addition, the enantioselective cyclization using BINAP exhibited generality at the C5-substituents

(6) There are a few reports about the catalyzed 6π electrocyclization: (a) Müller, S.; List, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9975–9978. (b) Maciver, E. E.; Thompson, S.; Smith, M. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 9979–9982. (c) Tantillo, D. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 31–32. (d) Bishop, L. M.; Barbarow, J. E.; Bergman, R. G.; Trauner, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8100–8103.

(7) For the synthesis of all substrates **1**–**8**, see the Supporting Information.

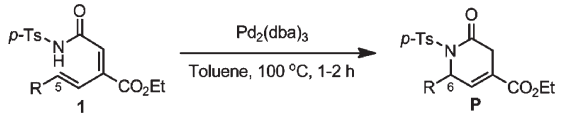
(8) The intramolecular 1,6-addition of a carboxylic acid or an amide was quite rare. See: (a) Günes, M.; Speicher, A. *Tetrahedron* **2003**, *59*, 8799–8802. (b) Mali, R. S.; Jagtap, P. G.; Patil, S. R.; Pawar, P. N. *J. Chem. Soc., Chem. Commun.* **1992**, 883–884. (c) Bellinger, G. C. A.; Campbell, W. E.; Giles, R. G. F.; Tobias, J. D. *J. Chem. Soc., Perkin. Trans.* **1982**, 2819–2825. (d) Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1982**, *23*, 5151–5154. (e) Deyanov, A. B.; Konshin, M. E. *Chem. Heterocycl. Compd.* **2005**, *41*, 511–514.

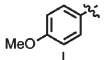
Table 1. Screening of Reaction Conditions for Cyclization Using 3-Ethoxycarbonyl-5-phenyl-*N*-*p*-toluenesulfonyldienamide **1**

entry	catalyst (equiv)	additive	solvent	temp (°C)	time (h)	result
1	$Pd_2(dba)_3$ (0.3)	–	dioxane	70	6	no reaction
2	$Pd_2(dba)_3$ (0.3)	$P(2\text{-furyl})_3$ (1.2)	dioxane	100	7	no reaction
3	$Pd_2(dba)_3$ (0.2)	Ph_3P (0.8)	dioxane	100	7	no reaction
4	$Pd_2(dba)_3$ (0.2)	Ph_3P (0.8)	toluene	100	1	38
5	$Pd_2(dba)_3$ (0.2)	DPPE (0.4)	toluene	100	1	85
6	$Pd_2(dba)_3$ (0.2)	DPPP (0.4)	toluene	100	1	85
7	$Pd_2(dba)_3$ (0.2)	DPPB (0.4)	toluene	100	1	75
8	$PdCl_2$ (0.2)	–	toluene	100	1	no reaction
9	$Sc(OTf)_3$ (0.5)	–	toluene	100	1	no reaction[a]
10	DBU (2.0)	–	toluene	100	1	no reaction

[a] Partly decomposed.

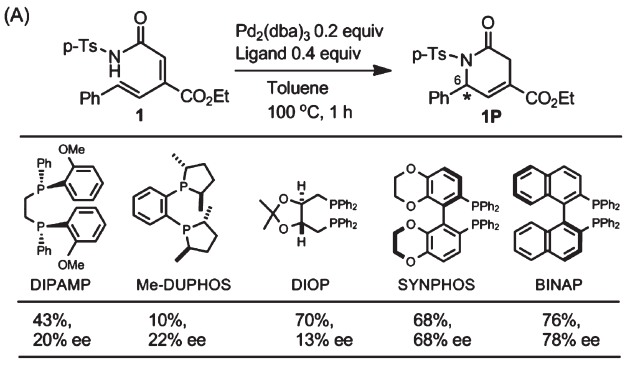
Table 2. Cyclization Using 3-Ethoxycarbonyl-*N*-*p*-toluenesulfonyldienamides with Various C5-Substituents



entry	R	additive	product	yield (%)
1[b]	 1	DPPE	**1P**	85
2[a]	 2	DPPE	**2P**	70
3[b]	 3	DPPE	**3P**	90
4[b]	 4	DPPB	**4P**	80
5[a]	 5	DPPE	**5P**	83
6[a]	 6	DPPE	**6P**	78
7[b]	 7	DPPE	**7P**	72
8[b]	 8	DPPE	**8P**	63

[a] $Pd_2(dba)_3$ 0.15 equiv, additive 0.3 equiv. [b] $Pd_2(dba)_3$ 0.2 equiv, additive 0.4 equiv.

Scheme 3. (A) Screening of Chiral Ligands for Enantioselective Cyclization; (B) Generality at the C5-Substituents for the Enantioselective Cyclization

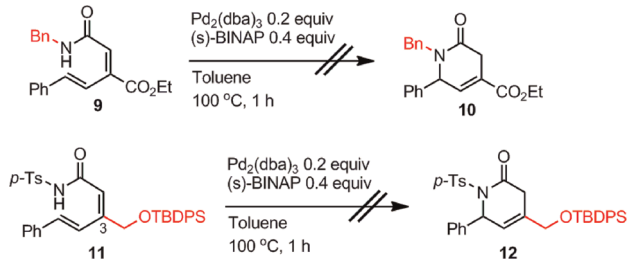


[a] The reaction condition was moderately optimized {$Pd_2(dba)_3$ 0.05 equiv, BINAP 0.1 equiv}.

to some extent as shown in Scheme 3B (60−81% ee for six examples), which suggested that this 6-*endo* asymmetric cyclization could be applied for the multisubstituted chiral piperidinone synthesis. On the other hand, we confirmed the substituent effect at the nitrogen atom and the C-3 position (Scheme 4). As presumed, both the *N*-benzyl substrate **9** and the compound **11** having a 4-*tert*-butyldiphenylsiloxymethyl at the C-3 position led to no reaction under the established conditions. These results showed that both the *N*-*p*-Ts and C-3 ester groups would be essential for the cyclization.

Two pathways would be possible, when considering the mechanism of this reaction. One is the catalytic 6π-aza-electrocyclization as we have described in Scheme 2.[6] Although there is no evidence for the formation of the

Scheme 4. Substituent Effect at the Nitrogen Atom and the C-3 Position



azatriene intermediate, the substituent effects described above may support this mechanism.[10] The other possibility is the Pd(0)-catalyzed intramolecular amidation.[11] There are some reports concerning the amide cyclization to the unsaturated C−C bond using a transition metal catalyst.[3a,b,4] However, in almost all the reports, even containing the broadly investigated intramolecular amination,[12] the cyclization preferentially proceeds in an *exo* mode. Based on these results, the formal Pd(0) catalyzed 6-*endo* cyclization must be unique. It is difficult to judge which mechanism is reasonable; however, we believe that this reaction has a promising perspective.

In summary, we realized a Pd-catalyzed *6-endo* type cyclization of the dienamide with a bidentate phosphine ligand. The reaction was clearly accelerated by both *N-p*-toluenesulfonyl and C-3 ester substituents, which has been one of the most notable examples of our "substituent-driven activation".[13] Moreover, by using the BINAP-Pd catalyst system, we successfully applied this reaction to the synthesis of chiral 2-piperidinone compounds with various C-6 substituents. Further extension of the substrate scope, improvement of the enantiomeric excess, and mechanistic investigations are currently ongoing in our laboratory.

Acknowledgment. This work was financially supported by a Grant-in-Aid for Scientific Research on Innovative Areas 22106541 from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available. The experimental details of reactions and ^{1}H and ^{13}C NMR spectra of the substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

(9) In the case of (*S*)-BINAP, the absolute configuration of **1P** was determined to be 6*S* by converting it to the already-known compound; see the Supporting Information for details.

(10) The probable role of Pd catalyst in this mechanism is that the Pd(II) species generated from the oxidative addition of Pd(0) to the acidic NH might stabilize the transition structure of the intermediary azatriene by a complexation and result in electrostatic acceleration of the electrocyclization as suggested for related reactions by Schleyer et al.; see: Jiao, H.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1995**, *117*, 11529–11535. We are very interested in the computational experiments related to its transition state and plan to report the results in detail.

(11) There can be two pathways. One includes the insertion of alkenes into Pd−N bonds; for example, see: (a) Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 8644–8651. (b) Bertrand, M. B.; Neukom, J. D.; Wolfe, J. P. *J. Org. Chem.* **2008**, *73*, 8851–8860. The other includes the conjugate addition of Pd(0) affording a π-allyl intermediate; for example, see: (c) Custar, D. W.; Le, H.; Morken, J. P. *Org. Lett.* **2010**, *12*, 3760–3763. (d) Yuguchi, M.; Tokuda, M.; Orito, K. *J. Org. Chem.* **2004**, *69*, 908–914.

(12) For recent selected reviews of intramolecular aminations, see: (a) Chemler, S. R. *Org. Biomol. Chem.* **2009**, *7*, 3009–3019. (b) Müller, 115 T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795–3892. (c) Minatti, A.; Muñiz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142–1152.

(13) Quite recently, we also reported the noncatalyst thermal azacyclization of *N*-sulfonyl-2,4-dienamides with a prominent "substituent-driven activation: *Tetrahedron Lett.* **2012**, *53*, 837−841.

The authors declare no competing financial interest.