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Cobalt(II)-Catalyzed Intermolecular Diels–Alder Reaction of Piperine

Kun Wei, Wei Li, Kazuo Koike, and Tamotsu Nikaido*

*Faculty of Pharmaceutical Sciences, Toho University, Miyama 2-2-1,
Funabashi, Chiba 274-8510*

nikaido@phar.toho-u.ac.jp

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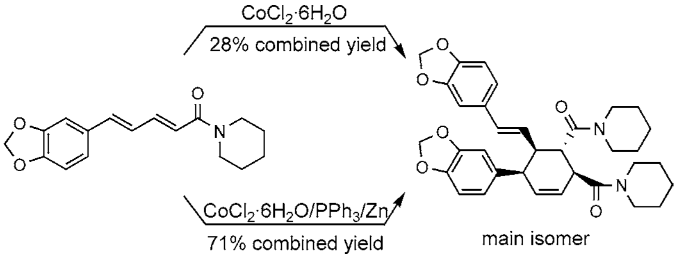
ABSTRACT



An intermolecular cobalt–phosphine-catalyzed Diels–Alder reaction of piperine is described. The dimerization of piperine in the presence of cobalt–phosphine complexes gave much better yields than that in the presence of only cobalt, which, combined with the result under the purely thermal conditions, indicates that addition of phosphine ligands changes the inhibition of cobalt to the reaction into promotion. For elucidation of the distinction, different cobalt-catalyzed mechanisms were proposed for the Diels–Alder dimerization of piperine.

Since the discovery of the Diels−Alder reaction in 1928, it has been one of the most important bond-forming reactions in organic synthesis for obtaining cyclic systems and excellent stereoselectivity.[1,2] The provocative biosynthetic proposals of some secondary metabolites suggest that this valuable reaction also plays an important role in nature.[3] Recently, we have reported a novel family of cyclohexene-type dimeric amide alkaloids from the roots of *Piper nigrum*.[4] On the basis of a biosynthetic hypothesis by the intermolecular Diels−Alder reaction, we chose piperine (**1**) as substrate to perform the biomimetic synthesis of the dimers.

It is well-known that Lewis acid can ameliorate the conditions of the Diels−Alder reaction and enhance reactivity and selectivity,[1,3] which was considered through the coordination of the metal atom to carbonyl or other polarized groups either to lower LUMO$_{dienophile}$ energy to result in the decrease of the LUMO$_{dienophile}$−HOMO$_{diene}$ gap (normal electron demand Diels−Alder reaction) or reduce LUMO$_{diene}$ energy to result in the decrease of the LUMO$_{diene}$−HOMO$_{dienophile}$ gap (inverse electron demand Diels−Alder reaction) based on frontier molecular orbital (FMO) model.[4] However, in the presence of Lewis acids, the Diels−Alder dimerization of piperine gave much lower combined yields than that in a purely thermal reaction and harsh reaction conditions were still required.[4] A straightforward route (path A) is proposed for explaining the low yield (Scheme 1, taking the cobalt-catalyzed reaction as an example). In this pathway, both carbonyls of piperine as diene and dienophile were coordinated to the cobalt atom. This may give rise to the increase of the LUMO−HOMO gap, thereby generating a higher barrier for the catalyzed process.

With the development of transition metal catalysts, the strategy through the coordination of metal complexes to the π-bonds of dienophile and diene has become a solution for the cycloaddition reaction between electronically similar diene and dienophile, which are processed under more extreme reaction conditions,[7] such as the Ni(COD)$_2$-mediated

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[1] Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, 1990.

[2] For reviews: (a) Ichihara, A.; Oikawa, H. *Curr. Org. Chem.* **1998**, *2*, 365−394. (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698. (c) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650−1667.

[3] Stocking, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078−3115.

[4] Wei, K.; Li, W.; Koike, K.; Chen, Y. J.; Nikaido, T. *J. Org. Chem.* **2005**, *70*, 1164−1176.

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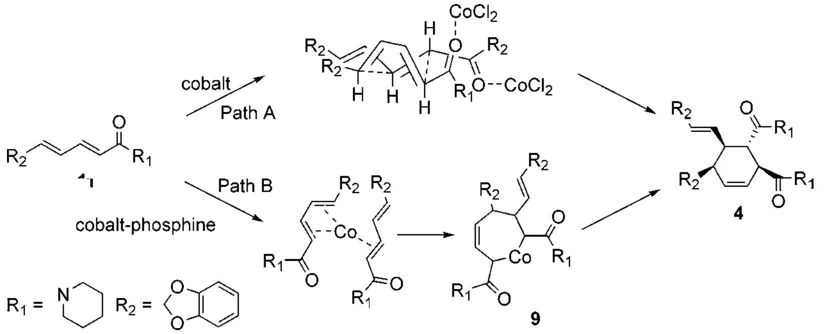
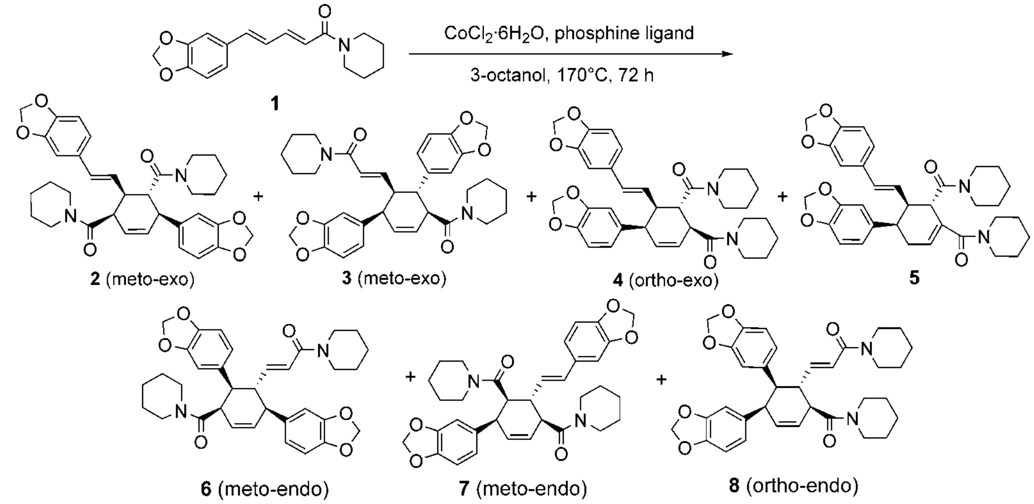
Scheme 1



intramolecular [4 + 2] diene−allene cyaloaddition and cobalt(I)-catalyzed intermolecular Diels−Alder reaction of alkynyl sulfides with acyclic 1,3-dienes. On the basis of this consideration, the intermolecular Diels−Alder dimerization reaction could also be catalyzed through this strategy, but no example of the cobalt(II)−phosphine-catalyzed reaction

Table 1. Optimization of the Cobalt-Catalyzed Diels−Alder Reaction of Piperine



1

2 (meto-exo)

3 (meto-exo)

4 (ortho-exo)

5

6 (meto-endo)

7 (meto-endo)

8 (ortho-endo)

entry	catalyst[b]	yield[c] (%)	cycloadduct (ratio, %)						
			2	**3**	**4**	**5**	**6**	**7**	**8**
1	$CoCl_2 \cdot 6H_2O$	28	15	3	41	41	0	0	0
2	$CoCl_2 \cdot 6H_2O/PPh_3$ (1:1)	48	12	7	72	5	3	0	1
3	$CoCl_2 \cdot 6H_2O/PPh_3$(1:2)	65	12	5	62	14	2	2	3
4	$CoCl_2 \cdot 6H_2O/PPh_3$(1:10)	54	12	6	76	2	1	1	2
5	$CoCl_2 \cdot 6H_2O/PPh_3$(1:20)	53	11	9	74	4	0	0	2
6	$CoCl_2 \cdot 6H_2O$/dpph (1:1)	45	13	5	77	3	1	0	1
7	$CoCl_2 \cdot 6H_2O$/dpph (1:2)	41	12	4	81	0	0	1	2
8	$CoCl_2 \cdot 6H_2O$/dppe (1:1)	33	11	5	79	2	1	1	1
9	$CoCl_26H_2O$/dppe (1:2)	48	11	5	78	3	1	0	2
10	$CoCl_2 \cdot 6H_2O$/dppb (1:1)	52	11	4	72	7	2	1	3
11	$CoCl_26H_2O$/dppb (1:2)	45	11	5	74	4	1	0	5
12	$CoCl_2 \cdot 6H_2O/PPh_3/Zn$ (1:10:5)	58	12	5	64	14	2	1	2
13	$CoCl_2 \cdot 6H_2O/PPh_3/Zn$ (1:10:10)	71	11	5	57	24	1	0	2
14	$CoCl_2 \cdot 6H_2O/PPh_3/Zn$ (1:10:20)	57	12	5	59	20	1	1	2
15	$CoCl_2 \cdot 6H_2O/PPh_3/Zn$ (1:1:10)	50	11	5	56	24	2	0	2
16	$CoCl_2 \cdot 6H_2O/PPh_3/Zn$ (1:2:10)	69	12	6	46	30	2	2	2
17	$CoCl_2 \cdot 6H_2O/PPh_3/Zn$ (1:4:10)	70	13	6	37	40	1	1	2

[a] All reactions were performed in the presence of 10 mol % of $CoCl_2 \cdot 6H_2O$ in 3-octanol at 170 °C for 72 h. [b] Number in parentheses indicated the molar ratio of reagents in catalytic systems. [c] Combined yields on the basis of isolated products through reversed-phase preparative HPLC.

was reported previously. In our continuing study on the dimerization of piperine, we examined the cycloaddition reaction in the presence of several cobalt−phosphine complexes as catalysts. Herein we describe our new findings in the context of the cobalt system, that is, addition of phosphine ligands gave rise to a very large changes in the combined yields of dimerization of piperine, indicating the change in the catalytic effect of cobalt on the reaction from inhibition to promotion. This suggested that different catalytic mechanisms of the cobalt system for the reaction may exist.

In the present study, we examined the catalytic effect of the cobalt−phosphine complexes on the Diels−Alder reaction formed by $CoCl_2 \cdot 6H_2O$ with several phosphine ligands, including PPh_3, 1,2-bis(diphenylphosphino)ethane (dppe), 1,4-bis(diphenylphosphino)butane (dppb), and 1,6-bis(diphenylphosphino)hexane (dpph) (Table 1). Initially, we performed the reaction of **1** in the presence of $CoCl_2 \cdot 6H_2O$ (10 mol %) and PPh_3 (10 mol %) as catalysts in 3-octanol as solvent at 170 °C for 72 h to afford the expected cycloadducts in 48% combined yield (Table 1, entries 2). Next, the catalytic effects of dppe,dppb, and dpph were also investgated (entries 6−11). These results showed that the combined yields in the presence of cobalt-phosphines were higher than these in the presence of only cobalt (28%). When the amount of ligands was increased to 20 mol %, dimerization of **1** gave higher yield (65%) only in the presence of PPh_3 and showed an increase of the ratio of **5** (entry 3). After that, an increase of the amount of PPh_3 led to a decrease of yields (entries 4 and 5). Comparison of these results (entries 2−11) with that of entry 1 showed that the addition of phosphine ligands to $CoCl_2 \cdot 6H_2O$ surely promoted the cycloaddition of **1**. To explain this behavior, we proposed another mechanism which is shown as path B (Scheme 1). Insertion of a cobalt−phosphine complex molecule into two piperine molecules gives a seven-membered cobaltacycle **9**. A subsequently reductive elimination leads to the desired Diels−Alder adducts. It was obvious that if the cobalt−phosphine complexes catalyzed the dimerization of piperine on the basis of the Lewis acid pattern (path A), the resulting low combined yields were inevitable. However, whether in the presence of only cobalt, the reaction proceeded only via path A has not been ascertained. Additionally, the results of the cobalt-phosphine-catalyzed reactions indicated that the cobalt−PPh_3 system was more effective for the dimerization than other cobalt−phosphine systems. This may be ascribed to the steric effect of dppe, dppb, and dpph.

It has been reported that reduction of Co(II) to Co(I) by zinc dust could effectively promote the formation of bonds.[8] Treatment of a solution of **1** in 3-octanol in the presence of $CoCl_2 \cdot 6H_2O$ (10 mol %), PPh_3 (100 mol %), and zinc (100 mol %) led to a higher combined yield (71%) than that in no zinc systems (Table 1, entry 13) or without extra zinc (5 mol %) and with excess zinc (20 mol %) systems (Table 1, entries 12 and 14). Simultaneously, increase of the ratio of **5** was also observed. Compared to the result in entry 3, the effect of the addition of zinc to cobalt−PPh_3 complexes to promote the increase of combined yields arose from the enhancement of the transformation of **4** to **5** rather than the catalytic result of low-valent cobalt generated from the reduction of high-valent cobalt by zinc dust. It was further observed that under all conditions the reactions gave **4** as the main product. The possible reason was considered as that due to the electronic and steric effects, the activation energies for the reactions favor the ortho-exo transition structure over the others.

In summary, we report the first example of cobalt−phosphine-catalyzed intermolecular Diels−Alder dimerization reaction, that is, piperine as substrate performs the [4 + 2] cycloaddition reaction to afford the corresponding adducts in moderate to good combined yields. The cobalt−phosphine systems appear to be more efficient than that using only cobalt for the reaction. Triphenylphosphine (PPh_3) is the most favorable phosphine ligand of the reaction. Work studying the mechanism of cobalt-catalyzed Diels−Alder dimerization of piperine with the density functional theory is in progress.

Supporting Information Available: General procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) For reviews: (a) Trost, B. M. *Pure Appl. Chem.* **1988**, *60*, 1615−1626. (b) Marko, I. E.; Evans, G. R.; Seres, P.; Chelle, I.; Janousek, Z. *Pure Appl. Chem.* **1996**, *68*, 113−122. (c) Evans, D. A.; Rovis, T.; Johnson, J. S. *Pure Appl. Chem.* **1999**, *71*, 1407−1415. (d) Carmona, D.; Pilar Lamata, M.; Oro, L. A. *Coord. Chem. Rev.* **2000**, *200-202*, 717−772. (e) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335. (f) Mikami, K.; Terada, M.; Matsuzawa, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3554−3571. (g) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217−6254. (h) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453−3516. Also, see ref 2c.

(6) (a) Domingo, L. R.; Arnó, M.; Andrés, J. *J. Org. Chem.* **1999**, *64*, 5867−5875. (b) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558−3588. (c) Avalos, M.; Babiano, R.; Bravo, J. L.; Cintas, P.; Jiménez, J. L.; Palacios, J. C.; Silva, M. A. *J. Org. Chem.* **2000**, *65*, 6613−6619. (d) Roberson, M.; Jepsen, A. S.; Jørgensen, K. A. *Tetrahedron* **2001**, *57*, 907−913. (e) Alves, C. N.; Camilo, F. F.; Gruber, J.; da Silva, A. B. F. *Tetrahedron* **2001**, *57*, 6877−6883. (f) Alves, C. N.; da Silva, A. B. F.; Martí, S.; Moliner, V.; Oliva, M.; Andrés, J.; Domingo, L. R. *Tetrahedron* **2002**, *58*, 2695−2700. (g) García Ruano, J. L.; Clemente, F. R.; González Gutiérrez, L.; Gordillo, R.; Martín Castro, A. M.; Rodríguez Ramos, J. H. *J. Org. Chem.* **2002**, *67*, 2926−2933.

(7) (a) Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432−6434. (b) Jolly, R. S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965−4966. (c) Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1995**, *60*, 2962−2963. (d) Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843−1844. (e) Lautens, M.; Tam, W.; Lautens, J. C.; Edwards, L. G.; Crudden, C. M.; Smith, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 6863−6879. (f) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49−92. (g) Hilt, G.; Lüers, S.; Harms, K. *J. Org. Chem.* **2004**, *69*, 624−630.

(8) (a) Chen, Y.; Kiattansakul, R.; Ma, B.; Snyder, J. K. *J. Org. Chem.* **2001**, *66*, 6932−6942. (b) Chao, K. C.; Rayabarapu, D. K.; Wang, C. C.; Cheng, C. H. *J. Org. Chem.* **2001**, *66*, 8804−8810. (c) Wang, C. C.; Lin, P. S.; Cheng, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 9696−9697. (d) Chang, K. J.; Rayabarapu, D. K.; Cheng, C. H. *Org. Lett.* **2003**, *5*, 3963−3966. (e) Wang, C. C.; Lin, P. S.; Cheng, C. H. *Tetrahedron Lett.* **2004**, *45*, 6203−6206. (f) Chang, K. J.; Rayabarapu, D. K.; Cheng, C. H. *J. Org. Chem.* **2004**, *69*, 4781−4787. (g) Hilt, G.; Luers, S.; Harms, K. *J. Org. Chem.* **2004**, *69*, 624−630.