## Cobalt Porphyrin Catalyzed [3+2] Cycloaddition of Cyclopropanes and Carbonyl Compounds

Takahiro Shiba,<sup>a</sup> Daiki Kuroda,<sup>a</sup> Takuya Kurahashi,<sup>\*a,b</sup> Seijiro Matsubara<sup>\*a</sup>

<sup>a</sup> Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan Fax +81(75)3832438; E-mail: kurahashi.takuya.2c@kyoto-u.ac.jp; E-mail: matsubara.seijiro.2e@kyoto-u.ac.jp

<sup>b</sup> JST, ACT-C, 4-1-8 Honcho, Kawaguchi, Saitama, 332-0012, Japan

Received: 19.05.2014; Accepted after revision: 09.06.2014

**Abstract:** A cobalt porphyrin efficiently catalyzed the formal [3+2] cycloaddition of alkyl-/aryl-substituted cyclopropanes and carbonyl compounds such as aldehydes and ketones to afford the corresponding substituted tetrahydrofurans. The use of the cobalt porphyrin complex as a Lewis acid to catalyze the reaction via the electrophilic activation of cyclopropanes was demonstrated. The high functional-group tolerance and robustness of the catalyst were also demonstrated. Further, the potential utility of the catalyst was demonstrated by performing the cycloaddition of cyclic ketones and cyclopropanes to afford spiro tetrahydrofurans.

Key words: aldehydes, catalysis, cycloaddition, furans, ketones

Efficient synthesis of tetrahydrofurans is one of the most important research topics in organic synthesis because they are privileged scaffolds in many natural products and bioactive compounds.<sup>1–3</sup> Among various synthetic methods, Lewis acid catalyzed [3+2] cycloadditions have emerged as one of the most powerful tools for the synthesis of tetrahydrofurans in the last decades; cycloadditions of malonate-derived cyclopropanes and aldehydes catalyzed by Lewis acids such as Sc(OTf)<sub>3</sub>, SnCl<sub>4</sub>, and MgI<sub>2</sub> have been reported.<sup>4–8</sup> Herein, we report the cobalt porphyrin catalyzed regio- and stereoselective intermolecular [3+2] cycloaddition of cyclopropanes with carbonyl compounds. The cycloaddition of cyclopropanes and ketones catalyzed by cobalt porphyrin to afford the corresponding substituted tetrahydrofurans was achieved.

Porphyrins have emerged as useful ligands for Lewis acid catalysts in organic reactions that are difficult to perform using other ligands.<sup>9</sup> One of the distinct properties of porphyrin ligands can be attributed to their characteristic structure; metals can be rigidly coordinated in the porphyrin plane, thus stabilizing the high-valent Lewis acidic metal center. During our study on metalloporphyrin-catalyzed organic reactions, we found that a cobalt porphyrin efficiently catalyzes the [3+2] cycloaddition of malonate-derived cyclopropanes with aldehydes to afford the corresponding substituted tetrahydrofurans in high yields regio- and stereoselectively (Table 1).<sup>10,11</sup> The reaction of cyclopropane **1a** with benzaldehyde (**2a**) catalyzed by 2 mol% [Co(TPP)]SbF<sub>6</sub> (TPP: *meso*-tetraphenylporphyrin) in 1,2-dichloroethane at 60 °C for four hours afforded cy-

© Georg Thieme Verlag Stuttgart · New York

cloadduct **3aa** in 82% yield and with a diastereomeric ratio of 20:1 (Table 1, entry 1).



MeO₂C Ph	Ph CO <sub>2</sub> Me O + Ph H 1a 2a	Pn N M <sup>+</sup> metalloporphyrin [M(TPP)]X (2 solvent, 4	Ph n catalyst mol%)	Ph MeO <sub>2</sub> C CO <sub>2</sub> Me Ph <b>3aa</b>
Entry	Catalyst	Solvent	Temp (	(°C) Yield (%) <sup><math>a,b</math></sup>
1	[Co(TPP)]SbF <sub>6</sub>	DCE	60	82 (20:1)
2	[Fe(TPP)]SbF <sub>6</sub>	DCE	60	<1
3	[Mn(TPP)]SbF <sub>6</sub>	DCE	60	<1
4	[Cr(TPP)]SbF <sub>6</sub>	DCE	60	<1
5	[Co(TPP)]Cl	DCE	60	<1
6	[Co(TPP)]OTf	DCE	60	<1
7	[Co(TPP)]BF <sub>4</sub>	DCE	60	<1
8	[Co(TPP)]PF <sub>6</sub>	DCE	60	<1
9	[Co(TPP)]TFPB	DCE	60	99 (13:1)
10	NaTFPB	DCE	60	<1
11	[Co(TPP)]TFPB	DCE	55	99 (20:1)
12	[Co(TPP)]TFPB	DCE	50	49 (20:1)
13	[Co(TPP)]TFPB	$CH_2Cl_2$	55	99 (20:1)
14	[Co(TPP)]TFPB	toluene	55	82 (20:1)
15	[Co(TPP)]TFPB	THF	55	<1

<sup>a</sup> Isolated yields.

<sup>b</sup> Ratios of diastereomers.

Among various metalloporphyrins, such as  $[Fe(TPP)]SbF_6$ ,  $[Mn(TPP)]SbF_6$ , and  $[Cr(TPP)]SbF_6$ , only  $[Co(TPP)]SbF_6$  catalyzed the cycloaddition (Table 1, entries 1–4). We also examined the effect of counteran-

*SYNLETT* 2014, 25, 2005–2008 Advanced online publication: 04.08.2014 DOI: 10.1055/s-0034-1378394; Art ID: st-2014-u0436-1

ions such as Cl<sup>-</sup>, OTf<sup>-</sup>, BF<sub>4</sub><sup>-</sup>, and PF<sub>6</sub><sup>-</sup>, which act as axial ligands, on the cationic nature of Co<sup>3+</sup> (Table 1, entries 5–8). When tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (TFPB) was used as the counteranion, **3aa** was obtained in 99% isolated yield (Table 1, entry 9). The reaction failed when the sodium salt of TFPB (NaTFPB) was used as the catalyst (Table 1, entry 10). Further, **3aa** was obtained diastereoselectively in 99% yield when the reaction was performed at a lower reaction temperature (Table 1, entry 11). Among the reaction solvents examined, nonpolar solvents such as dichloromethane and toluene were suitable for the reaction, whereas polar solvents such as tetrahydrofuran resulted in poor yields (Table 1, entries 13–15).

To determine the substrate scope of this cycloaddition, we carried out the reactions of various malonate-derived cyclopropanes 1 with benzaldehyde (2a) under the optimized reaction conditions (Table 2). The reactions of aryl-substituted cyclopropanes such as 1b, 1c, and 1d with 2a afforded the corresponding substituted tetrahydrofurans (Table 2, entries 2–4).<sup>12</sup> The reaction of cyclopropane 1e, with a 2-furyl moiety, with 2a afforded 3ea (Table 2, entry 5). The reaction of vinyl cyclopropane 1f with 2a afforded vinyl-substituted tetrahydrofuran 3fa in excellent yield (Table 2, entry 6). The reaction of cyclopropane 1g, containing a phthalimide moiety, with 2a afforded 3ga in 61% yield (Table 2, entry 7). The reaction of gem-dimeth-yl-substituted cyclopropane 1h with 2a afforded 3ha in 68% yield (Table 2, entry 8).

 Table 2
 Cobalt Porphyrin Catalyzed [3+2] Cycloaddition of Cyclopropanes 1 and Benzaldehyde (2a)

MeO <sub>2</sub> C R <sup>1</sup> R <sup>2</sup>	1	Ph P	PP)]TFPB CE, 55 °C,	(2 mol%) ★ , 4 h	$\begin{array}{c} MeO_2C  CO_2Me \\ & & Ph \\ R^1  CO_2  Ph \\ R^2  R^2  3 \end{array}$
Entry	1	$\mathbb{R}^1$	$\mathbb{R}^2$	3	Yield (%) <sup>a,b</sup>
1	1a	Ph	Н	3aa	99 (20:1)
2	1b	$4-MeC_6H_4$	Н	3ba	92 (13:1)
3	1c	$2-MeC_6H_4$	Н	3ca	69 (17:1)
4	1d	$4-MeOC_6H_4$	Н	3da	60 (2:1)
5	1e	2-furyl	Н	3ea	30 (3:1)
6	1f	vinyl	Н	3fa	90 (2:1)
7	1g	PhthN <sup>c</sup>	Н	3ga	61 (10:1)
8	1h	Me	Me	3ha	68

a Isolated yields.

<sup>b</sup> Ratios of diastereomers.

° PhthN: phthalimido.

We next examined the cycloaddition of **1a** with diverse aldehydes **2**, and the results are summarized in Table 3. The reaction of tolualdehyde **2b** afforded tetrahydrofuran **3ab**  in 61% yield (Table 3, entry 2), and the reactions of anisaldehydes 2c and 2d afforded the corresponding tetrahydrofurans 3ac and 3ad in 91% and 95% yields, respectively (Table 3, entries 3 and 4).<sup>13</sup> However, the reaction with o-anisaldehyde failed, probably because of the steric hindrance or coordination of the ortho-methoxy moiety to the cobalt porphyrin. Benzaldehydes, containing functional groups such as bromo, fluoro, acetyl, and acetoxy, afforded the corresponding tetrahydrofurans 3 diastereoselectively (Table 3, entries 5-8). Furyl and thienyl substituents were also tolerated under the reaction conditions to afford the corresponding substituted tetrahydrofurans (Table 3, entries 9-11). Furthermore, cyclopropane 1a also underwent reaction with aliphatic aldehydes to afford the corresponding tetrahydrofurans 3; the reaction of cyclohexanecarboaldehyde 21 with 1a afforded 3al in 77% yield (Table 3, entry 12). Notably, the reaction of cyclopropanecarboaldehyde 2m with 1a afforded 3am in excellent yield (Table 3, entry 13).

 Table 3
 Cobalt Porphyrin Catalyzed [3+2] Cycloaddition of Cyclopropane 1a and Aldehydes 2

MeO <sub>2</sub> C	CO <sub>2</sub> Me	O II [Co(TPP)]TF		
Ph		R <sup>3</sup> H DCE, 5	<b>5</b> °C, 4 h	
	1a	2		Ph 3
Entry	2	R <sup>3</sup>	<b>3</b> <sup>14</sup>	Yield (%) <sup>a,b</sup>
1	2a	Ph	<b>3</b> aa	99 (20:1)
2	2b	$4-MeC_6H_4$	3ab	61 (20:1)
3	2c	$4-MeOC_6H_4$	3ac	91 (2:1)°
4	2d	$3-MeOC_6H_4$	3ad	95 (10:1)
5	2e	$4-BrC_6H_4$	3ae	80 (20:1)
6	2f	$4-FC_6H_4$	3af	88 (20:1)
7	2g	$4-AcC_6H_4$	3ag	41 (20:1)
8	2h	$4-AcOC_6H_4$	3ah	90 (20:1) <sup>c</sup>
9	2i	2-furyl	3ai	80 (3:1)
10	2j	3-furyl	3aj	70 (20:1)
11	2k	2-thienyl	3ak	42 (20:1)
12	21	cyclohexyl	3al	77 (20:1)
13	2m	cyclopropyl	3am	99 (10:1)

<sup>a</sup> Isolated yields.

<sup>b</sup> Ratios of diastereomers.

<sup>c</sup> Reaction temperature: 70 °C.

The cobalt porphyrin catalyzed cycloaddition of cyclopropane **1a** with acetone **2n** afforded *gem*-dimethyl-substituted tetrahydrofuran **3an** in 73% yield with prolonged reaction time (Scheme 1). The reaction is also applicable to the synthesis of spiro tetrahydrofurans from cyclic ketones. For example, the reaction of **1a** with cyclopenta-



Scheme 1 Cobalt porphyrin catalyzed [3+2] cycloaddition of cyclopropane 1a and ketones 2

none **2o** in the presence of cobalt porphyrin catalyst afforded spiro tetrahydrofuran **3ao** in 82% yield. It was found that the reaction of **1a** with **2n** and **2o** with  $Sc(OTf)_3$  in place of cobalt porphyrin catalyst afforded cycloadducts in moderate yields. These results clearly highlight the excellent reactivity of the cobalt porphyrin for the cycloaddition of cyclopropanes with carbonyl compounds compared to other Lewis acid catalysts. The cycloaddition with cyclohexanone **2p** and cycloheptanone **2q** also afforded the corresponding spiro tetrahydrofurans **3ap** and **3aq**.

The cycloaddition of optically active cyclopropane 1a (99% ee) with 2a afforded tetrahydrofuran 3aa with 77% enantiomeric excess (Scheme 2). However, optically active cyclopropane 1a gradually racemized in the presence of cobalt catalyst, indicating that the Lewis acidic cobalt porphyrin catalyst initially facilitates the ring opening of the cyclopropane to generate a cationic intermediate, which reacts with 2a to afford tetrahydrofuran by stepwise reaction mechanism.<sup>13</sup>





Scheme 2 Cobalt porphyrin catalyzed [3+2] cycloaddition of chiral cyclopropane 1a and benzaldehyde (2a)

In summary, an efficient access to tetrahydrofuran derivatives was developed by a cobalt porphyrin catalyzed [3+2] cycloaddition of malonate-derived cyclopropanes and aldehydes. The use of the cobalt porphyrin catalyst also allows ketones to react with cyclopropanes. Efforts to expand the substrate scope of the reaction and the development of an asymmetric variant of the reaction with chiral cobalt porphyrins are under way.

## Acknowledgment

This work was supported by JST, ACT-C and Grants-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan. T.K. acknowledges the Asahi Glass Foundation, the Uehara Memorial Foundation, Tokuyama Science Foundation, and Kurata Memorial Hitachi Science and Technology Foundation. We thank Rigaku Corporation for the valuable help in X-ray crystal structural analysis.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

## **References and Notes**

- For reviews on the synthesis of tetrahydrofurans, see:

   (a) Harmange, J.-C.; Figadére, B. *Tetrahedron: Asymmetry* 1993, 4, 1711.
   (b) Bellur, E.; Feist, H.; Langer, P. *Tetrahedron* 2007, 63, 10865.
   (c) Wolfe, J. P.; Hay, M. B. *Tetrahedron* 2007, 63, 261.
- (2) For selected reviews on the synthesis of natural products with tetrahydrofuran skeletons, see: (a) Fual, M. M.; Huff, B. E. *Chem. Rev.* 2000, *100*, 2407. (b) Kang, E. J.; Lee, E. *Chem. Rev.* 2005, *105*, 4348. (c) Li, N.; Shi, Z.; Tang, Y.; Chen, J.; Li, X. *Beilstein J. Org. Chem.* 2008, *4*, 1. (d) Lorente, A.; Lamariano-Merketegi, J.; Albericio, F.; Álvarez, M. *Chem. Rev.* 2013, *113*, 4567.
- (3) For selected recent examples of tetrahydrofuran synthesis, see: (a) Fries, P.; Halter, D.; Kleinschek, A.; Hartung, J. J. Am. Chem. Soc. 2011, 133, 3906. (b) Vasconcelos, R. S.; Silva, L. F. Jr.; Giannis, A. J. Org. Chem. 2011, 76, 1499. (c) Arthuis, M.; Beaud, R.; Gandon, V.; Roulland, E. Angew. Chem. Int. Ed. 2012, 51, 10510. (d) Miller, Y.; Miao, L.; Hosseini, A. S.; Chemler, S. R. J. Am. Chem. Soc. 2012, 134, 12149. (e) Hashimoto, Y.; Itoh, K.; Kakehi, A.; Shiro, M.; Suga, H. J. Org. Chem. 2013, 78, 6182. (f) Touchet, S.; Macé, A.; Roisenel, T.; Carreeaux, F.; Bouillon, A.; Carboni, B. Org. Lett. 2013, 15, 2712. (g) Grandjean, J.-M. M.; Nicewicz, D. A. Angew. Chem. Int. Ed. 2013, 52, 3967. (h) Minuti, L.; Bonaccorosi, A. P. M.; Di Gioia, M. L.; Leggio, A.; Siciliano, C.; Temperini, A. Org. Lett. 2013, 15, 3906. (i) Trost, B. M.; Bringley, D. A. Angew. Chem. Int. Ed. 2013, 52, 4466.

- (4) For reviews on malonate-derived donor-acceptor (D-A) cyclopropanes and their synthetic applications, see:
  (a) Reissig, H.-U. *Top. Curr. Chem.* **1988**, *144*, 73.
  (b) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.
  (c) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151.
  (d) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321.
  (e) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem. Int. Ed.* **2014**, *53*, 2. (f) Davies, H. M. L.; Denton, J. R. *Chem. Soc. Rev.* **2009**, *38*, 3061. (g) Cavitt, M. A.; Phunt, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 804. (h) De Simone, F.; Waser, J. *Synthesis* **2009**, 3353. (i) Tang, P.; Qin, Y. *Synthesis* **2012**, 2969.
- (5) For metal-mediated cycloaddition of cyclopropanes with aldehydes, see: (a) Han, Z.; Uehira, S.; Tsuritani, T.; Shinokubo, H.; Oshima, K. *Tetrahedron* 2001, *57*, 987.
  (b) Christie, S. D. R.; Cummins, J.; Elsegood, M. R.; Dawson, G. *Synlett* 2009, 257; see also ref. 7a,b.
- (6) For Lewis acid catalyzed cycloaddition of cyclopropanes with aldehydes, see: (a) Pohlhaus, P. D.; Johnson, J. S. J. Org. Chem. 2005, 70, 1057. (b) Sanders, S. D.; Ruiz-Olalla, A.; Johnson, J. S. Chem. Commun. 2009, 5135. (c) Campbell, M. J.; Johnson, J. S. J. Am. Chem. Soc. 2009, 131, 10370. (d) Campbell, M. J.; Johnson, J. S.; Parsons, A. T.; Polhous, P. D.; Sanders, S. D. J. Org. Chem. 2010, 75, 6317. (e) Smith, A. G.; Slade, M. C.; Johnson, J. S. Org. Lett. 2011, 13, 1996. (f) Yang, G.; Shen, Y.; Li, K.; Sun, Y.; Hua, Y. J. Org. Chem. 2011, 76, 229. (g) Yang, G.; Sun, Y.; Shen, Y.; Chai, Z.; Zhou, S.; Chu, J.; Chai, J. J. Org. Chem. 2013, 78, 5393. (h) Christie, S. D. R.; Davoile, R. J.; Elsegood, M. R.; Fryatt, R.; Jone, R. C. F.; Pritchard, G. J. Chem. Commun. 2004, 2474; see also ref. 7c–e.
- (7) For cycloaddition of cyclopropanes with ketones, see:
  (a) Sugita, Y.; Kawai, K.; Yokoe, I. *Heterocycles* 2000, 53, 657. (b) Sugita, Y.; Kawai, K.; Yokoe, I. *Heterocycles* 2001, 55, 135. (c) Gupta, A.; Yadav, V. K. *Tetrahedron Lett.* 2006, 47, 8043. (d) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* 2008, *130*, 8642. (e) Xing, S.; Pan, W.; Liu, C.; Ren, J.; Wang, Z. *Angew. Chem. Int. Ed.* 2010, 49, 3215. (f) Mei, L.-Y.; Wei, Y.; Xu, Q.; Shi, M. *Organometallics* 2013, *32*, 3544. (g) Benfatti, F.; de Nateuil, F.; Waser, J. *Chem. Eur. J.* 2012, *18*, 4844. (h) Hu, B.; Xing, S.; Ren, J.; Wang, Z. *Tetrahedron* 2010, 60, 5671.
- (8) For Lewis acid catalyzed asymmetric cycloaddition of cyclopropanes with aldehydes, see: (a) Pohlhaus, P. D.; Johnson, J. S. J. Am. Chem. Soc. 2005, 127, 16014.
  (b) Pohlhaus, P. D.; Johnson, J. S. J. Am. Chem. Soc. 2009, 131, 3122.

- (9) For examples of the use of metalloporphyrins in nonoxidative bond formation, see: (a) Suda, K.; Baba, K.; Nakajima, S.-I.; Takanami, T. *Chem. Commun.* 2002, 2570. (b) Suda, K.; Kikkawa, T.; Nakajima, S.-I.; Takanami, T. *J. Am. Chem. Soc.* 2004, *126*, 9554. (c) Suda, K.; Baba, K.; Nakajima, S.-i.; Takanami, T. *Tetrahedron Lett.* 1999, *40*, 7243. (d) Chen, J.; Che, C.-M. *Angew. Chem. Int. Ed.* 2004, *43*, 4950. (e) Li, Y.; Chan, P. W. H.; Zhu, N.-Y.; Che, C.-M.; Kwong, H.-L. *Organometallics* 2004, *23*, 54. (f) Schmidt, J. A. R.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* 2005, *127*, 11426. (g) Zhou, C.-H.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* 2006, *8*, 325.
- (10) (a) Fujiwara, K.; Kurahashi, T.; Matsubara, S. J. Am. Chem. Soc. 2012, 134, 5512. (b) Wakabayashi, R.; Kurahashi, T.; Matsubara, S. Org. Lett. 2012, 14, 4794. (c) Ozawa, T.; Kurahashi, T.; Matsubara, S. Org. Lett. 2012, 14, 3008.
- (11) For some selected examples on the synthesis and properties of cobalt-porphyrin complexes, see: (a) Satoh, M.; Ohba, Y.; Yamauchi, S.; Iwaizumi, M. *Inorg. Chem.* 1992, *31*, 298.
  (b) Sakurai, T.; Yamamoto, K.; Naito, H.; Nakamoto, N. *Bull. Chem. Soc. Jpn.* 1976, *49*, 3042. (c) Fukuzumi, S.; Okamoto, K.; Tokuda, Y.; Gros, C. P.; Guilard, R. *J. Am. Chem. Soc.* 2004, *126*, 17059.
- (12) The [3+2] cycloaddition afforded tetrahydrofuran 3da (Table 2, entry 4) and 3ac (Table 3, entry 3) with low diasteroselectivity. These reactions proceed in high diasteroselectivity at initial stage, however, epimerization occurs upon completion of the reaction probably because electron-donating methoxy group facilitate the ring opening by stabilizing benzylic cation intermediate. For epimerization of the tetrahydrofurans with Lewis acid, see ref. 6e.
- (13) For the computational studies on the [3+2] cycloaddition of the malonate-derivered cyclopropanes with aldehydes, see: Zhang, J.; Shen, W.; Li, M. Eur. J. Org. Chem. 2007, 4855.
- (14) General Procedure for the [3+2] Cycloaddition The reaction was performed in a 15 mL sealed tube equipped with a Teflon-coated magnetic stirrer bar. An aldehyde 2 (0.15 mmol) was added to a solution of cyclopropane 1 (0.1 mmol) and [Co(TPP)]TFPB (3.1 mg, 4  $\mu$ mol) in DCE (1 mL) in a dry box. The sealed tube was taken outside the dry box and heated at 55 °C for the indicated time under argon atmosphere. The resulting reaction mixture was cooled to ambient temperature and filtered through a silica gel pad, concentrated in vacuo. The residue was purified by flash silica gel column chromatography (20 g, 2 × 15 cm; hexane– EtOAc, 5:1) to give the products **3**.

Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.