Highly Regioselective Synthesis of 2,3,5-Trisubstituted Furans via Phosphine-Catalyzed Ring-Opening Cycloisomerization Reactions of Cyclopropenyl Dicarboxylates

Jie Chen,[a] Shengjun Ni,[a] Shengming Ma*[a,b]

[a] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. of China

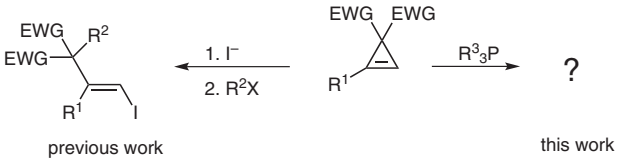
[b] Shanghai Key Laboratory of Green Chemistry and Chemical Process, Department of Chemistry, East China Normal University, 3663 North Zhongshan Road, Shanghai 200062, P. R. of China
Fax +86(21)62609305; E-mail: masm@sioc.ac.cn

Received 3 December 2010

Dedicated to Professors Xiyan Lu and Lixin Dai

Abstract: Different 2,3,5-trisubstituted furans have been regioselectively synthesized through a ring-opening cycloisomerization of functionalized cyclopropenyl carboxylates with moderate to excellent yields by using tri(2-furanyl)phosphine as the catalyst.

Key words: furans, regioselectivity, ring-opening cycloisomerization, cyclopropenes, tri(2-furanyl)phosphine



Scheme 1

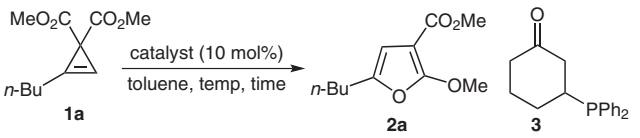
Organophousphorus compounds have been widely used in synthetic organic chemistry.[1] For example, phosphines have been extensively used as ligands in the transition-metal-catalyzed reactions.[2] They are also used as reagents in the Wittig reaction,[3] Staudinger reaction,[4] and Mitsunobu reaction,[5] etc. Furthermore, phosphines can be used as a class of nucleophilic organocatalysts, which was first reported in late 1960s.[6] Recently, since two types of phosphine-catalyzed reactions, that is, the isomerization of α,β-ynones and the [3+2] cycloaddition of 2,3-butadienoates or 2-butynoates with electron-deficient olefins, were independently developed by Lu's group and Trost's group, reports of phosphines as nucleophilic catalysts have grown significantly.[7] Cyclopropenes, highly strained but readily accessible carbocyclic molecules, have been shown to possess interesting reactivities in organic synthesis.[8] There are many reports on the ring-opening reactions of cyclopropenes in the literature. Transition metals, such as Rh, Ru, Pd, Cu, Au, Fe, Ag, etc. have been found to be good catalysts in these reaction.[9] In 2003, we reported an X^- (X = I, Br) triggered ring-openging coupling reaction of functionalized cyclopropenes with organic halides, imines, or 1,1-bis(phenylsulfonyl)ethylene (Scheme 1).[10] However, to the best of our knowledge, the ring-opening reaction of cyclopropenes catalyzed by organocatalyst has not been reported so far.[11] Herein, we wish to report the first phosphine-catalyzed ring-opening cycloisomerization reaction of cyclopropenyl dicarboxylates for the highly regioselective synthesis of 2,3,5-trisubstituted furans.

Initial attempt to promote ring-opening cycloisomerization of readily available cyclopropene **1a** led to disappointing results using triphenylphosphine as the catalyst in toluene at 100 °C; no reaction occurred and **1a** was recovered in 84% yield as determined by ^{1}H NMR spectroscopic analysis (Table 1, entry 1). Trialkylphosphine derivatives, such as trimethylphosphine and tricyclohexylphosphine, are ineffective in this reaction at 100 °C (Table 1, entries 3 and 4). Under the similar conditions, when tris(*o*-tolyl)phosphine, tris(4-methoxyphenyl)phosphine, 3-(diphenylphosphino)cyclohexanone **3**, or diphenylphosphine was employed as catalyst, the corresponding furan **2a** could not be obtained either (Table 1, entries 5–8). To our delight, trace of product **2a** was observed with tri(1-naphthyl)phosphine as the catalyst (Table 1, entry 9). When tri(2,4,6-trimethoxyphenyl)phosphine was used, the yield was slightly higher (Table 1, entry 10). Gratifyingly, the use of tri(2-furanyl)phosphine led to formation of **2a** in 78% yield with **1a** being recovered in 10% yield (Table 1, entry 11). By conducting the reaction at 150 °C, complete conversion of **1a** was reached, and the corresponding product **2a** was obtained in 90% isolated yield (Table 1, entry 12). Formation of product **2a** was not observed when nitrogen-containing nucleophilic catalysts, such as DMAP, DBU, and DABCO, were employed (Table 1, entries 13–15). The reaction could not occur without any catalyst (Table 1, entry 2).

Then the solvent effect was examined, and different solvents provided different outcomes for this reaction (Table 2). No reaction occurred in $MeNO_2$, MeCN, Et_2O, CH_2Cl_2, or THF (Table 2, entries 2–6). Low conversion was observed in NMP, DCE, or dioxane (Table 2, entries

SYNLETT 2011, No. 7, pp 0931–0934
Advanced online publication: 10.03.2011
DOI: 10.1055/s-0030-1259904; Art ID: W32910ST

Table 1 Cycloisomerization of **1a** under Different Reaction Conditions with Organocatalysts[a]



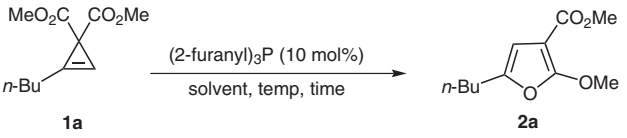
Entry	Catalyst	Temp (°C)	Time (h)	Yield (%)	Recovery of **1a** (%)
1	Ph_3P	100	60	n.r.	84
2	–	100	48	n.r.	84
3	Me_3P	100	48	n.r.	80
4	Cy_3P	100	48	n.r.	66
5	$(2\text{-}MeC_6H_4)_3P$	100	48	n.r.	88
6	$(4\text{-}MeOC_6H_4)_3P$	100	48	n.r.	87
7	Ph_2PH	100	48	n.r.	81
8	**3**	100	25	n.r.	83
9	$(1\text{-naphthyl})_3P$	100	48	8	53
10	$[2,4,6\text{-}(MeO)_3C_6H_2]_3P$	100	48	17	52
11	$(2\text{-furanyl})_3P$	100	96	78	10
12	$(2\text{-furanyl})_3P$	150	31	89 (90[b])	–
13	DMAP	100	48	n.r.	71
14	DBU	100	48	n.r.	71
15	DABCO	100	48	n.r.	53

[a] The reaction was conducted in a Schlenk tube with a screw cap and the yield was determined by ^1H NMR spectroscopic analysis with $MeNO_2$ as the internal standard.
[b] The numbers in the parenthesis are the isolated yields of **2a**.

7–9). Using DMF as the solvent the reaction was complicated and 12% yield of **1a** was recovered (Table 2, entry 10). In conclusion, toluene is the optimal solvent for this transformation (Table 2, entry 1).

With the optimized conditions in hand (Table 2, entry 1), the scope of the reaction was explored (Table 3). With R being alkyl (Table 3, entries 1–3), cyclohexyl (Table 3, entry 4), Bn (Table 3, entry 5), $PhCH_2CH_2$ (Table 3, entry 6), protected alcohol, such as $TBSOCH_2CH_2$ (Table 3, entry 7), $TBSOCH_2CH_2CH_2$ (Table 3, entry 8), and $THPOCH_2CH_2$ (Table 3, entry 9), the reaction proceeded smoothly to afford the corresponding 2,3,5-trisubstituted furans in excellent yields. However, with R bearing the unprotected hydroxyl group, the reaction could not occur and cyclopropene **1i** was recovered in 66% yield as determined by ^1H NMR spectroscopic analysis (Table 3, entry 10). Interestingly, for substrates with R being relatively bulky *t*-Bu, the reaction could also occur in 86% yield (Table 3, entry 12). For cyclopropenyl dicarboxylates, differently substituted aryl group R has an important influence on the reaction. For example, with R being Ph, the

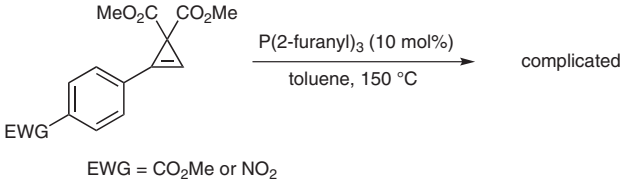
Table 2 Cycloisomerization of **1a** in Different Solvent[a]



Entry	Solvent	Temp (°C)	Time (h)	Yield (%)	Recovery of **1a** (%)
1	toluene	150	31	89 (90[b])	–
2	$MeNO_2$	100	72	n.r.	82
3	MeCN	100	72	n.r.	82
4	Et_2O	70	96	n.r.	80
5	CH_2Cl_2	70	72	n.r.	85
6	THF	100	96	n.r.	68
7	NMP	100	72	2	84
8	DCE	100	72	4	79
9	dioxane	100	96	22	53
10	DMF	100	72	complicated	12

[a] The reaction was conducted in a Schlenk tube with a screw cap, and the yield was determined by ^1H NMR spectroscopic analysis with $MeNO_2$ as the internal standard.
[b] The numbers in the parenthesis are the isolated yield of **2a**.

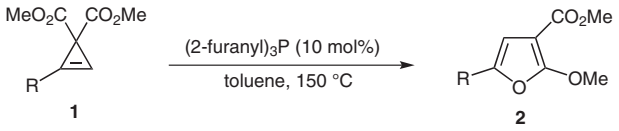
product was obtained in 39% yield (Table 3, entry 13); with R being $4\text{-}MeC_6H_4$, the product was obtained in 62% yield (Table 3, entry 14); with R being $4\text{-}MeO_2CC_6H_4$ or $4\text{-}O_2NC_6H_4$, the reaction was complicated and no excepted product was obtained (Scheme 2). In addition, to test the practicability of the catalytic system, the reaction was carried out in gram scale (5.0 mmol) of **1a** in the presence of 10 mol% of tri(2-furanyl)phosphine. The desired product was obtained in 95% yield (Table 3, entry 2).



Scheme 2

A plausible mechanism for this ring-opening cycloisomerization reaction is depicted in Scheme 3. Initial attack of the tri(2-furanyl)phosphine at the 2-position of cyclopropene **1a** results in the formation of zwitterionic phosphonium adduct **I**. Isomerization from **I** gives intermediate **II**, which allows the cyclization to generate the cyclic zwitterion **III**.[12] Finally, elimination of the phosphine catalyst furnishes the furan product **2a**.[13] The product is the same as the one which was obtained in

Table 3 The Scope of Phosphine-Catalyzed Cycloisomerization Reactions of Cyclopropenyl Dicarboxylates[a]



Entry	R	Time (h)	Isolated yield of **2** (%)
1	**1a** *n*-Bu	31	**2a** 90
2	**1a** *n*-Bu	18	**2a** 95[b]
3	**1b** *n*-C_8H_{17}	24	**2b** 81
4	**1c** cyclohexyl	24	**2c** 94
5	**1d** Bn	19.5	**2d** 90
6	**1e** $PhCH_2CH_2$	24	**2e** 94
7	**1f** $TBSOCH_2CH_2$	24	**2f** 92
8	**1g** $TBSOCH_2CH_2CH_2$	24	**2g** 90
9	**1h** $THPOCH_2CH_2$	25	**2h** 86
10	**1i** $HOCH_2CH_2$	24	–[c]
11	**1j** *n*-Bu[d]	24	**2j** 85
12	**1k** *t*-Bu	19	**2k** 86
13	**1l** Ph	34	**2l** 39
14	**1m** 4-MeC_6H_4	24	**2m** 62

[a] The reaction was conducted by using **1** (0.20 mmol) and tri(2-furanyl)phosphine (0.02 mmol) in toluene (0.1 M) at 150 °C in a Schlenk tube with a screw cap.
[b] Conditions: 5.0 mmol of **1a** were used in this reaction.
[c] No expected product was obtained and cyclopropene **1i** was recovered in 66% yield as determined by ^{1}H NMR spectroscopic analysis.
[d] Diethyl 2-butylcycloprop-2-ene-1,1-dicarboxylate (**1j**) was used.

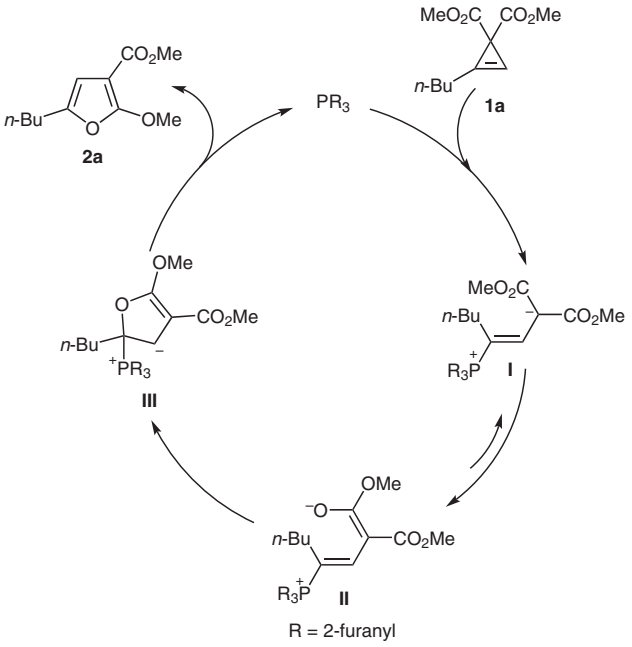
$RuCl_2(PPh_3)_3$-catalyzed cycloisomerization reaction of cyclopropene **1a**.[9o]

In conclusion, we have developed a highly regioselective synthesis 2,3,5-trisubstituted furans[14] via phosphine-catalyzed ring-opening cycloisomerization reactions of cyclopropenyl dicarboxylates.[15] Further studies in this area by using the intermediates formed in Scheme 3 are currently under way in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

Financial support from the Major State Basic Research and Development Program (2009CB825300) and National Natural Science Foundation of China (20732005) is greatly appreciated. We thank Mr. Xiaobing Zhang in this group for reproducing the results in entries 4, 7, and 14 in Table 3.



Scheme 3 Plausible mechanism of phosphine-catalyzed ring-opening cycloisomerization

References and Notes

(1) Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley: New York, **2000**.
(2) (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (b) Börner, A. *Phosphorus Ligands in Asymmetric Catalysis: Synthesis and Applications*; Wiley-VCH: Weinheim, **2008**.
(3) Wittig, G.; Geissler, G. *Justus Liebigs Ann. Chem.* **1953**, *580*, 44.
(4) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635.
(5) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380.
(6) (a) Rauhut, M.; Currier, H. US 3074999, **1963**. (b) Rauhut, M.; Currier, H. *Chem. Abstr.* **1963**, *58*, 11224a. (c) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815.
(7) (a) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (b) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035. (c) Lu, X.; Du, Y.; Lu, C. *Pure Appl. Chem.* **2005**, *12*, 1985. (d) Ye, L.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140. (e) Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.* **2009**, *38*, 3102.
(8) (a) Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77. (b) Nakamura, M.; Isobe, H.; Nakamura, E. *Chem. Rev.* **2003**, *103*, 1295. (c) Fox, J. M.; Yan, N. *Curr. Org. Chem.* **2005**, *9*, 719. (d) Rubin, M.; Rubina, M.; Gevorgyan, V. *Synthesis* **2006**, 1221. (e) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (f) Marek, I.; Simaan, S.; Masarwa, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 7364. (g) Magnus, P.; Littich, R. *Org. Lett.* **2009**, *11*, 3938. (h) Patel, P. R.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 8527.
(9) (a) Weiss, R.; Schlierf, C. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 811. (b) Komendatov, M. I.; Dommin, I. N.; Bulucheva, E. V. *Tetrahedron* **1975**, *31*, 2495. (c) Cho, S. K.; Liebeskind, L. S. *J. Org. Chem.* **1987**, *52*, 2631. (d) Padwa, A.; Kassir, J. M.; Xu, S. L. *J. Org. Chem.* **1991**, *56*, 6971. (e) Semmelhack, M. F.; Ho, S.; Cohen, D.; Steigerwald, M.; Lee, M. C.; Lee, G.; Gilbert, A. M.; Wulff, W. D.; Ball, R.

G. *J. Am. Chem. Soc.* **1994**, *116*, 7108. (f) Müller, P.; Granicher, C. *Helv. Chim. Acta* **1995**, *78*, 129. (g) Padwa, A.; Kassir, J. M.; Xu, S. L. *J. Org. Chem.* **1997**, *62*, 1642. (h) Ma, S.; Zhang, J. *J. Am. Chem. Soc.* **2003**, *125*, 12386. (i) Chuprakov, S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 4463. (j) Marek, I.; Simaan, S.; Masarwa, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 7364. (k) Wang, Y.; Fordyce, E. A. F.; Chen, F. Y.; Lam, H. W. *Angew. Chem. Int. Ed.* **2008**, *47*, 7350. (l) Hoveyda, A. H.; Lombardi, P. J.; O'Brien, R. V.; Zhugralin, A. R. *J. Am. Chem. Soc.* **2009**, *131*, 8378. (m) Li, C.; Zeng, Y.; Zhang, H.; Feng, J.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 6413. (n) Miege, F.; Meyer, C.; Cossy, J. *Org. Lett.* **2010**, *12*, 4144. (o) Chen, J.; Ma, S. *Chem. Asian J.* **2010**, *5*, 2415.

(10) (a) Ma, S.; Zhang, J.; Cai, Y.; Lu, L. *J. Am. Chem. Soc.* **2003**, *125*, 13954. (b) Ma, S.; Zhang, J.; Lu, L.; Jin, X.; Cai, Y.; Hou, H. *Chem. Commun.* **2005**, 909. (c) Chen, J.; Ma, S. *J. Org. Chem.* **2009**, *74*, 5595. (d) Chen, J.; Xin, N.; Ma, S. *Tetrahedron Lett.* **2009**, *50*, 3175.

(11) In 2007, Gevorgyan and coworkers reported a phosphine-catalyzed sila-Morita–Baylis–Hillman reaction of cyclopropenes, but no ring-opening reaction occurred in this reaction. See: Chuprakov, S.; Malyshev, D. A.; Trofimov, A.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 14868.

(12) (a) Ohe, K.; Fujita, M.; Matsumoto, H.; Tai, Y.; Miki, K. *J. Am. Chem. Soc.* **2006**, *128*, 9270. (b) Peng, L.; Zhang, X.; Ma, M.; Wang, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 1905.

(13) (a) Trost, B. M.; Li, C. *J. Am. Chem. Soc.* **1994**, *116*, 3167. (b) Zhang, C.; Lu, X. *Synlett* **1995**, 645. (c) Du, Y.; Lu, X.; Zhang, C. *Angew. Chem. Int. Ed.* **2003**, *42*, 1035.

(14) Davies, H. M. L.; Romines, K. R. *Tetrahedron* **1988**, *44*, 3343.

(15) **Representative Procedure for the Synthesis of 2-Methoxy-3-methoxycarbonyl-5-butylfuran (2a) in a 5.0 mmol Scale**

To a Schlenk reaction tube with a screw cap, evacuated and backfilled with argon, were added sequentially (2-furanyl)$_3$P (116 mg, 0.50 mmol), cyclopropenyl dicarboxylate **1a** (1.058 g, 4.99 mmol), and toluene (50 mL). The resulting mixture was refluxed at 150 °C. After 18 h the reaction was over (monitored by TLC). Evaporation and column chromatography on silica gel (eluent: PE–EtOAc = 20:1) afforded the desired product **2a**[9o] (1.005 g, 95% yield); oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.15 (t, *J* = 1.0 Hz, 1 H, CH=), 4.05 (s, 3 H, CO_2CH_3), 3.76 (s, 3 H, OCH_3), 2.47 (td, *J* = 7.4, 0.8 Hz, 2 H, $=CCH_2$), 1.60–1.50 (m, 2 H, CH_2), 1.40–1.29 (m, 2 H, CH_2), 0.90 (t, *J* = 7.4 Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.6, 161.0, 146.0, 105.8, 91.2, 57.9, 51.0, 29.5, 27.1, 22.0, 13.7. MS (EI): *m/z* = 212 (19.03) [M^+], 169 (100) [$M^+ - C_3H_7$]. IR (neat): 2955, 2873, 1720, 1607, 1470, 1407, 1278, 1212, 1191, 1138, 1088 cm^{-1}.