Organic LETTERS

Letter

pubs.acs.org/OrgLett

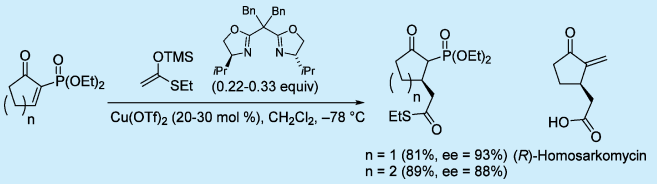
Enantioselective Mukaiyama–Michael Reaction of Cyclic α-Alkylidene β-Keto Phosphine Oxide and Phosphonate and Asymmetric Synthesis of (*R*)-Homosarkomycin

Kotaro Nagatani, Atsushi Minami, Haruka Tezuka, Yunosuke Hoshino, and Masahisa Nakada*

Department of Chemistry and Biochemistry, School of Advanced Science and Engineering, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan

Supporting Information

ABSTRACT: The asymmetric Mukaiyama–Michael reaction of cyclic α-alkylidene β-oxo phosphates and phosphine oxides that proceeds in a highly enantioselective manner is described. It is possible to carry out these reactions using a catalytic amount of a bisoxazoline–Cu(II) complex without decreasing the enantioselectivity, and one of the products has been successfully used for the first enantioselective synthesis of (*R*)-homosarkomycin.



Alkenes bearing two electron-withdrawing groups have been widely used as electrophiles in a variety of transformations including catalytic asymmetric reactions such as cycloadditions,[1] Michael reactions,[2] and Friedel–Crafts[3] reactions due to their electron-deficient properties. Owing to their greater reactivity, alkenes bearing two electron-withdrawing groups have been employed as key intermediates in natural product synthesis.[4] However, catalytic asymmetric reactions of α-alkylidene β-oxo esters are difficult to establish because the two electron-withdrawing groups present in these molecules act as a bidentate ligand for the used chiral catalyst; therefore, the reacting alkene might be located far from the chiral ligand. Although a number of catalytic asymmetric reactions of α-alkylidene β-oxo esters have been described, successful examples are limited.[2]

Catalytic asymmetric reactions of α-alkylidene β-oxo phosphates and phosphine oxides have not yet been reported; however, they are interesting because phosphates and phosphine oxides are bulky electron-withdrawing groups; thus, their reactions are expected to give different results compared with those of α-alkylidene β-oxo esters. Moreover, the resulting products can undergo Horner–Wadsworth–Emmons or Horner–Wittig olefinations, which are useful transformations in natural product synthesis.

Herein, we report a highly enantioselective Mukaiyama–Michael reaction of cyclic α-alkylidene β-oxo phosphates and phosphine oxides and its successful application to the synthesis of (*R*)-homosarkomycin.[5]

To investigate the utility of α-alkylidene β-oxo phosphates and phosphine oxides, compounds **1a** and **1b** were prepared from 6-bromo-1,4-dioxa-spiro[4.4]non-6-ene,[6] and **1c** was prepared according to reported methods.[7] Silyl enol ether **2**[8] was used in this study since the product derived from **2** was expected to be useful in a variety of transformations such as the Fukuyama reduction[9] and the Liebeskind–Srogl coupling reaction.[10]

First, the Mukaiyama–Michael reactions of **1a** and **2** using a stoichiometric amount of $Cu(OTf)_2$ and ligands **L1–5** were examined to explore the feasibility of this enantioselective transformation (Table 1, entries 1–5). Reactions conducted in the presence of **L1–4** at −78 °C were completed within 10 min to afford **3a**. The yields ranged from 50% to quantitative, and the enantioselectivity depended on the structure of the ligands. Thus, the ee of **3a** was 17% when **L1** was used (Table 1, entry 1), while it increased when the ligand substituents R^2 were bulkier (**L2**, 51% ee (Table 1, entry 2); **L3**, 65% ee (Table 1, entry 3)). The reaction in the presence of **L4** afforded **3a** in 93% ee (Table 1, entry 4), and interestingly, the enantioface selectivity was reversed. The reaction with **L5** was slow even at room temperature, and the yield and enantioselectivity were low probably because **L5** is a tridentate ligand that can reduce the Lewis acidity of the $Cu(OTf)_2$ complex (Table 1, entry 5).

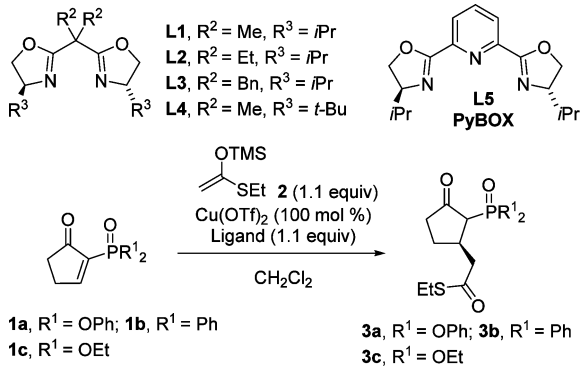
The Mukaiyama–Michael reactions of **1b** and **2** in the presence of **L1–4** at −78 °C smoothly afforded **3b** in good to high yields (Table 1, entries 6–9). The enantioselectivity trend was similar to that observed in entries 1–4; i.e., the ee depended on the bulkiness of the ligand substituents R^2, and the enantioface selectivity was reversed in the reaction using **L4** (Table 1, entry 9). The yield and enantioselectivity of the reaction with **L5** were also poorer than those with **L1–4** (Table 1, entry 10).

The Mukaiyama–Michael reactions of **1c** and **2** in the presence of **L1–4** at −78 °C were completed within 10 min to afford **3c** in high to excellent yields (Table 1, entries 11–14), and interestingly, the ee values were higher than those observed in the corresponding reactions of **1a** and **1b**, although the

Received: December 21, 2016

DOI: 10.1021/acs.orglett.6b03798
Org. Lett. XXXX, XXX, XXX–XXX

Table 1. Enantioselective Mukaiyama−Michael Reaction of 1a−c and 2



1a, R^1 = OPh; **1b**, R^1 = Ph
1c, R^1 = OEt

3a, R^1 = OPh; **3b**, R^1 = Ph
3c, R^1 = OEt

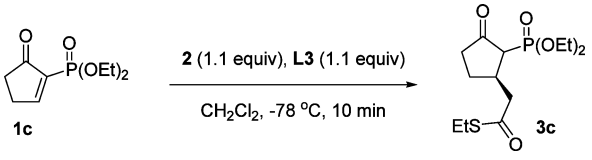
entry	1	ligand	temp (°C)	time (min)	yield[a] (%)	ee[b] (%)
1	**1a**	**L1**	−78	10	quant	17
2	**1a**	**L2**	−78	10	71	51
3	**1a**	**L3**	−78	10	97	65
4	**1a**	**L4**	−78	10	93	−93[c]
5	**1a**	**L5**	rt	720	50	31
6	**1b**	**L1**	−78	10	74	57
7	**1b**	**L2**	−78	10	81	49
8	**1b**	**L3**	−78	10	79	65
9	**1b**	**L4**	−78	10	54	−80[c]
10	**1b**	**L5**	rt	720	10	24
11	**1c**	**L1**	−78	10	quant	72
12	**1c**	**L2**	−78	10	83	87
13	**1c**	**L3**	−78	10	91	91
14	**1c**	**L4**	−78	10	86	−79[c]
15	**1c**	**L5**	rt	720	15	62

[a]Isolated yields. [b]Determined by HPLC; see the Supporting Information. [c]A minus sign indicates reversal of the enantioselectivity.

substituents on the phosphorus atom were smaller ethoxy groups. The reaction of **1c** with **L4** afforded **3c** with an ee comparable to that of **3b** and a reversal enantioface selectivity was again observed. The reaction with **L5** afforded **3c** with 62% ee, although the yield was only 15% (Table 1, entry 15).

Effect of the counteranion of the Cu(II) salt in the presence of **L3** was examined (Table 2). All of the reactions using $Cu(BF_4)_2$ (Table 2, entry 2), $Cu(PF_6)_2$ (Table 2, entry 3), and $Cu(SbF_6)_2$ (Table 2, entry 4) afforded **3c** in excellent yields; however, the ee was low in all cases when compared with the reaction using $Cu(OTf)_2$ (Table 2, entry 1). The reason for this low ee could be attributed to a background reaction,[8] which

Table 2. Effect of the Counteranion of the Cu(II) Salt



1c **3c**

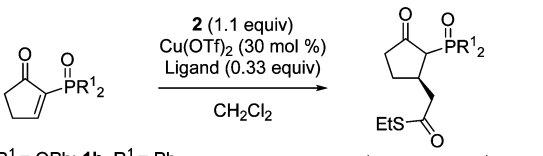
entry	Cu(II) (100 mol %)	yield[a] (%)	ee[b] (%)
1	$Cu(OTf)_2$	91	91
2	$Cu(BF_4)_2$	89	57
3	$Cu(PF_6)_2$	98	−9[c]
4	$Cu(SbF_6)_2$	quant	42

[a]Isolated yields. [b]Determined by HPLC; see the Supporting Information. [c]A minus sign indicates reversal of the enantioselectivity.

was proposed to proceed due to catalysis by a silyl cation generated from silyl enol ether **2**.

Next, we further examined the catalytic asymmetric reactions of **1a−c** with **2** (Table 3). Since the reaction of **1a** using a

Table 3. Catalytic Asymmetric Mukaiyama−Michael Reaction of 1a−c and 2



1a, R^1 = OPh; **1b**, R^1 = Ph
1c, R^1 = OEt

3a, R^1 = OPh; **3b**, R^1 = Ph
3c, R^1 = OEt

entry	1	ligand	temp/time (°C/h)	yield[a] (%)	ee[b] (%)
1	**1a**	**L4**	−78/4, then −60/48	35	−83[c]
2	**1a**	**L4**	−78/3.5, then, 0/1	79	−36[c]
3	**1b**	**L4**	−30/120	36	−53[c]
4	**1c**	**L3**	−78/5	79	92
5[d]	**1c**	**L3**	−78/7 then −60/14	81	92
6[e]	**1c**	**L3**	−78/4	81	93

[a]Isolated yields. [b]Determined by HPLC; see the Supporting Information. [c]A minus sign indicates reversal of the enantioselectivity. [d]$Cu(OTf)_2$ (20 mol %) and ligand (0.22 equiv) were used. [e]**2** (2.0 equiv) was used.

stoichiometric amount of **L4** and $Cu(OTf)_2$ afforded **3a** with high enantioselectivity, its reaction using 30 mol % of $Cu(OTf)_2$ and 0.33 equiv of **L4** was examined (Table 3, entry 1). The reaction was slow at −78 °C; hence, it was then conducted at −60 °C but required 48 h to afford **3a** in 35% yield and 83% ee. The same reaction at 0 °C (Table 3, entry 2) was completed within 1 h affording **3a** in 79% yield, although the ee decreased to 36%.

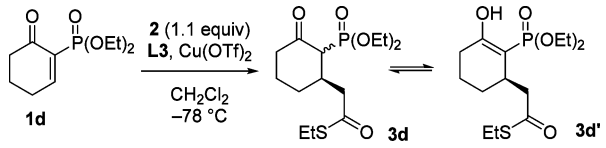
The reaction of **1b** using 30 mol % of $Cu(OTf)_2$ and 0.33 equiv of **L4** was very slow even at −30 °C (Table 3, entry 3) and required 5 days to afford **3b** in 36% yield. The ee decreased to 53% compared with the corresponding stoichiometric reaction (80% ee). The catalytic asymmetric reaction using less bulky **1c** was efficient and was completed after stirring at −78 °C for 5 h using **L3** to afford **3c** in 79% yield and 92% ee (Table 3, entry 4). The reaction went to completion after stirring at −78 °C for 7 h and then at −60 °C for 14 h, using 20 mol % of $Cu(OTf)_2$ and 22 mol % of **L3** to afford **3c** in 81% yield and 92% ee (Table 3, entry 5). The same reaction of **1c** using 2.0 equiv of **2** was completed within 4 h at −78 °C to give results similar to those of entry 5 (Table 3, entry 6).

The reason behind the low yields obtained in the reactions of **1a** and **1b** is not clear, although it can be postulated that the bulky substituents on the phosphate or the phosphine moieties might prevent either the reaction or the dissociation of the products from the bulky chiral catalysts. The reactions in Table 3 were carried out in the presence of 4 Å MS to exclude water but no improvement in the enantioselectivity was observed in all the cases.

The catalytic asymmetric Mukaiyama−Michael reaction of cyclohexenone derivative **1d**[11] was also examined (Table 4). The reaction using a stoichiometric amount of **L3** and $Cu(OTf)_2$ at −78 °C was completed within 5 min to afford an inseparable mixture of **3d** and its enol form **3d′**[12] in 92% yield. The ee of the product was determined by HPLC of the 3,5-dinitrobenzoate of **3d′** (89% ee, Table 4, entry 1). The

DOI: 10.1021/acs.orglett.6b03798
Org. Lett. XXXX, XXX, XXX−XXX

Table 4. Catalytic Asymmetric Mukaiyama–Michael Reaction of 1d and 2



entry	L3 (equiv)	$Cu(OTf)_2$ (mol %)	time	yield[a] (%)	ee[b] (%)
1	1.1	100	5 min	92	89
2	0.22	20	5 h	89	88

[a]Isolated yields. [b]Determined by HPLC; see the Supporting Information.

catalytic reaction using 20 mol % of $Cu(OTf)_2$ and 22 mol % of **L3** at −78 °C required 5 h to afford 3 d in 89% yield and 88% ee (Table 4, entry 2). The reactions using other ligands gave poorer results in terms of enantioselectivity. The absolute configurations of **3a–d** were determined by X-ray crystallographic analysis of the derivatives[13] (see the SI).

Evans reported the crystal structure of a bisoxazoline–Cu(II)–alkylidene malonate complex in which the alkylidene malonate moiety binds to the complex in a distorted square planar geometry and the two carbonyl groups, alkene carbon, and copper atom form a six-membered ring in a boat conformation.[14] A bent shape of the complex was proposed to rationalize the fact that the reaction of the silyl enol ether occurred at the sterically more accessible convex face. The enantioface selectivity of the reaction of **1c** with **2** using the **L3**–$Cu(OTf)_2$ catalyst could be explained by the conformers of the complex shown in Figure 1, which were generated based on

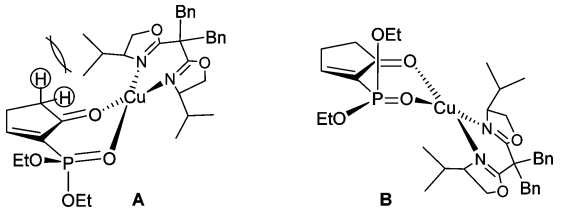


Figure 1. Proposed structures of the **L3**–Cu(II)–**1c** complex.

the model proposed by Evans.[14] Two conformers of the **L3**–$Cu(OTf)_2$–**1c** complex, **A** and **B**, involve the boat conformation of a six-membered ring, which is formed by the carbonyl group, phosphonate, alkene carbon, and copper atom with the alkene carbon and copper atom at the apexes.

A molecular modeling study of the **L3**–$Cu(OTf)_2$–**1c** complex suggests that conformer **B** should be energetically more favorable since the steric repulsion between the isopropyl group of **L3** and the methylene of **1c** is large in conformer **A**, while the corresponding steric repulsion is small in conformer **B**. The bent shape of conformer **B** could allow the reaction of silyl enol ether to proceed at the sterically more accessible convex face (Figure 2). The product derived from the reaction at the convex face of conformer **B** explains the structure of the products in the reaction of **1c** with **2** using **L3**–$Cu(OTf)_2$.

The enantioselectivity was higher when the ligand substituents R^2 were bulky (Table 1). This result supports the hypothesis that the reaction proceeded via conformer **B** because the ligand substituents R^2 would shield the concave face of conformer **B** to increase the enantioselectivity.

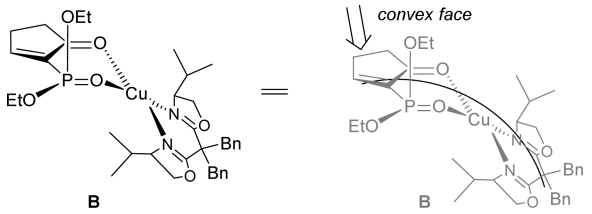


Figure 2. Proposed models for the catalytic asymmetric Michael reaction of the **L3**–Cu(II)–**1c** complex.

Because the steric repulsion between the phosphonate group and the *tert*-butyl group of **L4** is large, the geometry of the **L4**–$Cu(OTf)_2$–**1c** complex could be changed from distorted square planar to tetrahedral (Figure 3).[14] Thus, conformers **A**

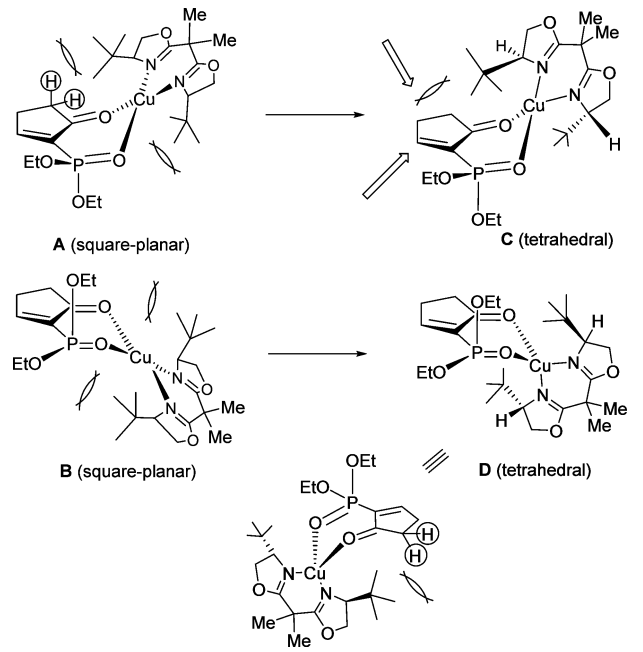


Figure 3. Proposed models for the catalytic asymmetric Michael reaction of the **L4**–Cu(II)–**1c** complex.

and **B** in a square planar geometry were energetically unfavorable when **L4** was used owing to the severe steric repulsion between the ligand substituents and the substrate. Therefore, the corresponding conformers **C** and **D** of the **L4**–$Cu(OTf)_2$–**1c** complex in a tetrahedral geometry would be energetically more favorable when compared with conformers **A** and **B**, respectively. Conformer **C** is more favorable when compared with conformer **D** because the steric repulsion between the *tert*-butyl group of **L4** and the methylene of **1c** could destabilize conformer **D**. The product derived from the reaction at the convex face of conformer **C** explains the reversal enantioface selectivity and the absolute configuration of the products in the reaction of **1a–c** with **2** using **L4**–$Cu(OTf)_2$.

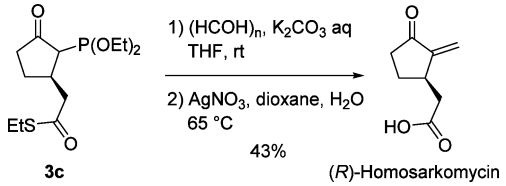
Product **3c** was used for the synthesis of (*R*)-homosarkomycin. To date, two total syntheses of homosarkomycin have been reported but both products were racemates, while no enantioselective synthesis of (*R*)-homosarkomycin has been described.

Product **3c** underwent a Horner–Wadsworth–Emmons reaction with formaldehyde using potassium carbonate in aqueous tetrahydrofuran to afford an enone,[15] which was treated with $AgNO_3$ in aqueous dioxane at 65 °C to produce

DOI: 10.1021/acs.orglett.6b03798
Org. Lett. XXXX, XXX, XXX–XXX

the hydrolysis of the thiol ester, affording the corresponding carboxylic acid (43%) (Scheme 1). All of the spectroscopic data

Scheme 1. Enantioselective Synthesis of (*R*)-Homosarkomycin



of the final compound were identical to those of homosarkomycin reported in the literature, indicating that the first synthesis of (*R*)-homosarkomycin was successfully accomplished.

In summary, the asymmetric Mukaiyama−Michael reaction of cyclic α-alkylidene β-oxo phosphates and phosphine oxides has been found to proceed in a highly enantioselective manner. It was possible to carry out these reactions using a catalytic amount of a bisoxazoline−Cu(II) complex, and one of the products was successfully used for the first enantioselective synthesis of (*R*)-homosarkomycin. Further studies on the protocol we developed using α-alkylidene β-oxo phosphates and phosphine oxides are underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03798.

Experimental procedure and characterization of the substrates and products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mnakada@waseda.jp.

ORCID

Masahisa Nakada: 0000-0001-6081-5269

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge support from the Materials Characterization Central Laboratory, Waseda University, for characterization of new compounds. This work was financially supported in part by a Grant-in-Aid for Scientific Research on Innovative Areas 2707 Middle molecular strategy from MEXT and a Waseda University Grant for Special Research Projects.

■ REFERENCES

(1) For selected papers, see: (a) Honda, Y.; Date, T.; Hiramatsu, H.; Yamauchi, M. *Chem. Commun.* **1997**, 1411. (b) Schotes, C.; Mezzetti, A. *J. Am. Chem. Soc.* **2010**, *132*, 3652. (c) Orimoto, K.; Oyama, H.; Namera, Y.; Niwa, T.; Nakada, M. *Org. Lett.* **2013**, *15*, 768. (d) Enomoto, K.; Oyama, H.; Nakada, M. *Chem. - Eur. J.* **2015**, *21*, 2798. (e) Kesava-Reddy, N. K.; Golz, C.; Strohmann, C.; Kumar, K. *Chem. - Eur. J.* **2016**, *22*, 18373.

(2) For selected papers, see: (a) Bernardi, A.; Colombo, G.; Scolastico, C. *Tetrahedron Lett.* **1996**, *37*, 8921. (b) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994. (c) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134. (d) Shizuka, M.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 5049. (e) Zhang, Q.; Xiao, X.; Lin, L.; Liu, X.; Feng, X. *Org. Biomol. Chem.* **2011**, *9*, 5748. (f) Jusseau, X.; Retailleau, P.; Chabaud, L.; Guillou, C. *J. Org. Chem.* **2013**, *78*, 2289. (g) Fraile, J. M.; Garcia, N.; Herrerias, C. I. *ACS Catal.* **2013**, *3*, 2710. (h) Oyama, H.; Orimoto, K.; Niwa, T.; Nakada, M. *Tetrahedron: Asymmetry* **2015**, *26*, 262. (i) Zhang, M. L.; Wu, A. J.; Zhao, J. Q.; Luo, Y.; Xu, X. Y.; Zhang, X. M.; Yuan, W. C. *Org. Lett.* **2016**, *18*, 5110. (j) Guo, S.; Liu, X.; Shen, B.; Lin, L.; Feng, X. *Org. Lett.* **2016**, *18*, 5070. For a recent review of α-alkylidene β-keto esters in asymmetric catalysis, see: Schotes, C.; Mezzetti, A. *ACS Catal.* **2012**, *2*, 528.

(3) For selected papers, see: (a) Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160. (b) Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030. (c) Yamazaki, S.; Iwata, Y. *J. Org. Chem.* **2006**, *71*, 739. (d) Rasappan, R.; Hager, M.; Gissibl, A.; Reiser, O. *Org. Lett.* **2006**, *8*, 6099. (e) Schätz, A.; Rasappan, R.; Hager, M.; Gissibl, A.; Reiser, O. *Chem. - Eur. J.* **2008**, *14*, 7259. (f) Cao, C.-L.; Zhou, Y.-Y.; Sun, X.-L.; Tang, Y. *Tetrahedron* **2008**, *64*, 10676. (g) Yamazaki, S.; Kashima, S.; Kuriyama, T.; Iwata, Y.; Morimoto, T.; Kakiuchi, K. *Tetrahedron: Asymmetry* **2009**, *20*, 1224. (h) Liu, Y.; Shang, D.; Zhou, X.; Liu, X. H.; Feng, X. *Chem. - Eur. J.* **2009**, *15*, 2055. (i) Liu, L.; Li, J.; Wang, M.; Du, F.; Qin, Z.; Fu, B. *Tetrahedron: Asymmetry* **2011**, *22*, 550. (j) Wu, J.; Wang, D.; Wu, F.; Wan, B. *J. Org. Chem.* **2013**, *78*, 5611. (k) Li, W. *Catal. Lett.* **2014**, *144*, 943. (l) Oyama, H.; Nakada, M. *Tetrahedron: Asymmetry* **2015**, *26*, 195. (m) Ozdemir, H. S.; Sahin, E.; Cakici, M.; Kilic, H. *Tetrahedron* **2015**, *71*, 2882. (n) Zhou, Y.; Liu, X. W.; Gu, Q.; You, S. L. *Synlett* **2016**, *27*, 586.

(4) For example, see: (a) Usui, K.; Kanbe, M.; Nakada, M. *Org. Lett.* **2014**, *16*, 4734. (b) Nakada, M.; Usui, K. *Heterocycles* **2015**, *91*, 332.

(5) (a) Wexler, B. A.; Toder, B. H.; Minaskanian, G.; Smith, A. B., III *J. Org. Chem.* **1982**, *47*, 3333. (b) Tanimori, S.; Kainuki, T.; Nakayama, M. *Biosci., Biotechnol., Biochem.* **1992**, *56*, 1807.

(6) Hanessian, S.; Mainetti, E.; Lecomte, F. *Org. Lett.* **2006**, *8*, 4047. See the Supporting Information..

(7) Snider, B. B.; Yang, K. *J. Org. Chem.* **1992**, *57*, 3615.

(8) Chua, S. S.; Alni, A.; Chan, L. T. J.; Yamane, M.; Loh, T. P. *Tetrahedron* **2011**, *67*, 5079.

(9) (a) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050. (b) Tokuyama, H.; Yokoshima, S.; Lin, S.-C.; Li, L.; Fukuyama, T. *Synthesis* **2002**, *2002*, 1121.

(10) (a) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260. (b) Yu, Y.; Liebeskind, L. S. *J. Org. Chem.* **2004**, *69*, 3554. (c) Villalobos, J. M.; Srogl, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 15734.

(11) Wada, E.; Kanemasa, S.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 860.

(12) Interestingly, the enol forms of **3a−c** were not observed in the NMR spectra.

(13) (a) CCDC 1523414 (**4c**, 3,5-dinitrobenzoate of **3c**) and CCDC 1523097 (**4d**, 3,5-dinitrobenzoate of **3d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.1523414 and www.ccdc.cam.ac.uk/data_request/cif.1523097, respectively.

(14) (a) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460. (b) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559. (c) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134.

(15) Feten, B.; Rafaa, B.; Hassen, A. *Synth. Commun.* **2000**, *30*, 3947.

DOI: 10.1021/acs.orglett.6b03798
Org. Lett. XXXX, XXX, XXX−XXX