ORGANIC LETTERS

2010
Vol. 12, No. 22
5088−5091

Highly Enantioselective Mukaiyama Aldol Reactions Catalyzed by a Chiral Oxazaborolidinium Ion: Total Synthesis of (−)-Inthomycin C

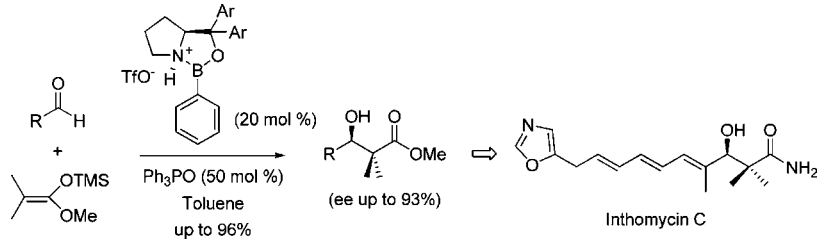
Bidyut Kumar Senapati,[†] Lizhu Gao,[†] Sung Il Lee,[†] Geum-Sook Hwang,[*,‡] and Do Hyun Ryu[*,†]

Department of Chemistry, Sungkyunkwan University, Suwon, 440-746, Korea, and Korea Basic Science Institute and Graduate School of Analytical Science and Technology, Chungnam National University, Seoul, 136-713, Korea

dhryu@skku.edu; gshwang@kbsi.re.kr

Received July 9, 2010

ABSTRACT



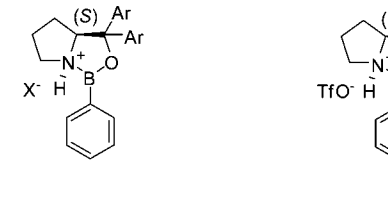
A cationic oxazaborolidinium-catalyzed asymmetric Mukaiyama aldol reaction of (1-methoxy-2-methyl-propenyloxy)-trimethylsilane with various aldehydes including α,β-disubstituted acroleins has been developed in high yields and enantioselectivities. The synthetic utility of this methodology was demonstrated in the first short synthesis of naturally occurring inthomycin C in high enantiopurity.

The asymmetric Mukaiyama aldol reaction between enolsilanes and aldehydes is a powerful and versatile synthetic method for the stereoselective construction of optically active β-hydroxy carbonyl derivatives under mild conditions.[1] These derivatives are useful chiral building blocks for the synthesis of many biologically active compounds and natural products.[2] The reaction is typically catalyzed by Lewis acids, and notable asymmetric versions of the reaction have been explored over the past 20 years.[3] While important contributions have come from numerous research groups,[4] typically high catalyst loadings are required. However, Carreira et al. have developed a chiral titanium catalyst which could be used at relatively low catalyst loading (0.5−5 mol %).[3] A complementary approach using chiral Lewis bases has been described by Denmark et al.[5] Recently, hydrogen-bonding Brønsted acid catalysis has been developed for asymmetric Mukaiyama aldol reactions,[6] and an elegant and powerful

[†] Sungkyunkwan University.
[‡] Korea Basic Science Institute, Chungnam National University.

(1) Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1990**, 1455.
(2) Trost, B. M.; Fleming, I. In *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 1.
(3) (a) Carreira, E. M.; Kvaerno, L. *Classics in Stereoselective Synthesis*; Wiley-VCH: Weinheim, 2009. (b) Anada, M.; Washio, T.; Watanabe, Y.; Hashimoto, S. *Heterocycles* **2010**, *80*, 1489. (c) Nishiyama, Y.; Kaiba, K.; Umeda, R. *Tetrahedron Lett.* **2010**, *51*, 793.
(4) (a) Kobayashi, S.; Furuya, M.; Ohtsubo, A.; Mukaiyama, T. *Tetrahedron: Asymmetry* **1991**, *2*, 635. (b) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041. (c) Parmee, E. R.; Tempkin, O.; Masamune, S.; Abiko, A. *J. Am. Chem. Soc.* **1991**, *113*, 9365. (d) Ishitani, H.; Yamashita, Y.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 5403. (e) Reetz, M. T.; Raguse, B.; Marth, C. F.; Hügel, H. M.; Bach, T.; Fox, D. N. A. *Tetrahedron* **1992**, *48*, 5731. (f) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907. (g) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039. (h) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837. (i) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814.
(5) Denmark, S. E.; Wynn, T.; Beutner, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 13405.

10.1021/ol102234k
Published on Web 10/19/2010



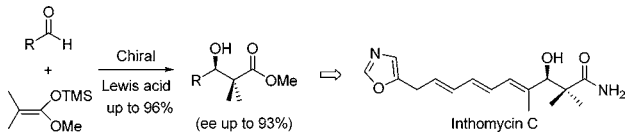
1a Ar = Ph, X = TfO
1b Ar = Ph, X = Tf_2N
1c Ar = mexyl (3,5-dimethylphenyl), X = TfO

Figure 1. Catalysts screened for enantioselective Mukaiyama aldol reaction.

chiral disulfonamide derivative was very recently reported by List et al. to catalyze this reaction.[7] However, highly activated and selected substrates are generally required with these systems. Therefore, a focus of the latest research in this area has been to develop practical and broadly applicable catalytic systems.

Herein, we report the enantioselective Mukaiyama aldol reaction of silyl ketene acetals and aldehydes promoted by chiral cationic oxazaborolidinium catalysts. A variety of aldehydes, aromatic, aliphatic, and α,β-disubstituted acroleins have been successfully reacted to provide the corresponding β-hydroxy carbonyl derivatives in high yields and enantioselectivities. Indeed, the utility of this methodology is illustrated by an expedient synthesis of (−)-inthomycin C (Scheme 1).

Scheme 1. Enantioselective Synthesis of Inthomycin C



The chiral oxazaborolidinium salts (**1** and **2**, Figure 1)[8] behave as powerful Lewis acids and have proven to be effective catalysts for enantioselective Diels−Alder reactions,[8a−d,h] cyanosilylations,[8e,f] Michael reactions,[8g] a three-component coupling reaction,[8i] and 1,3-dipolar cycloadditions.[8j] There is substantial evidence for the formation of a complex between catalyst **1** and aldehydes.[8a,b,e] We have examined the application of these oxazaborolidinium catalysts to the asymmetric aldol reaction of aldehydes with silyl ketene acetals. The absolute stereochemical course of the reaction can be predicted by the precedented mechanistic pathway shown in Figure 2.

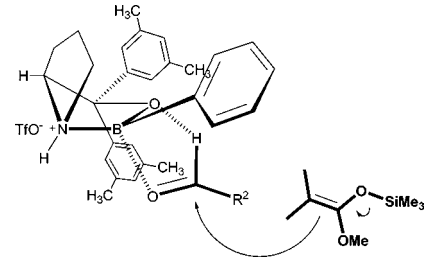
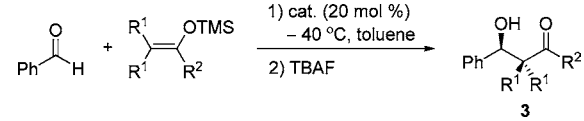


Figure 2. Transition state model for asymmetric Mukaiyama aldol reaction.

Our initial studies to optimize the reaction conditions were performed using benzaldehyde and (1-methoxy-2-methylpropenyloxy)-trimethylsilane (Table 1). In initial experiments using only 0.2 equiv of catalyst **1a** in toluene at −40 °C, the desired product was obtained in 95% yield although with poor ee (Table 1, entry 1). To suppress probable competing pathways of carbonyl activation through cationic silicon species[9] that would result in racemic products, triph-

Table 1. Enantioselective Mukaiyama Aldol Reaction between Benzaldehyde and Silyl Ketene Acetal[a]



3

entry	cat.	R^1	R^2	additive (mol %)	time (h)	yield (%)[b]	ee (%)[c]
1[d]	**1a**	Me	OMe	–	1	95	20
2	**1a**	Me	OMe	Ph_3PO (30)	12	92	55
3[e]	**1a**	Me	OMe	Ph_3PO (50)	20	90	87
4	**2**	Me	OMe	Ph_3PO (50)	20	82	40
5	**1b**	Me	OMe	Ph_3PO (50)	20	93	83
6	**1a**	Me	OEt	Ph_3PO (50)	35	80	81
7	**1a**	Me	O^{i}Pr	Ph_3PO (50)	20	50	40
8	**1a**	H	OEt	Ph_3PO (50)	20	55	45
9	**1c**	Me	OMe	Ph_3PO (50)	20	92	93[f]

[a] Reactions were run with 1.0 mmol of benzaldehyde, 1.2 mmol of silyl ketene acetal, and 0.2 mmol of catalyst, and deprotection of silylated product was carried out with TBAF. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC analysis. [d] Similar results were obtained when the reactions were run at −78 °C. [e] Reactions run with 60 mol % of Ph_3PO did not improve the ee. [f] The absolute configuration of **3** was assigned as (*R*)-enriched.

(6) (a) Zhuang, W.; Poulsen, T. B.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 3284. (b) McGilvra, J. D.; Unni, A. K.; Modi, K.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 6130. (c) Gondi, V. B.; Hagihara, K.; Rawal, V. H. *Chem. Commun.* **2010**, *46*, 904.

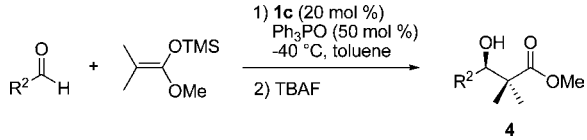
(7) García-García, P.; Lay, F.; García-García, P.; Rabalakos, C.; List, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 4363.

(8) (a) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808. (b) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992. (c) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388. (d) Ryu, D. H.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 4800. (e) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8106. (f) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 5384. (g) Liu, D.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 8160. (h) Lee, M. Y.; Kim, K. H.; Jiang, S.; Jung, Y. H.; Sim, J. Y.; Hwang, G.-S.; Ryu, D. H. *Tetrahedron Lett.* **2008**, *49*, 1965. (i) Senapati, B. K.; Hwang, G.-S.; Lee, S.; Ryu, D. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 4398. (j) Gao, L.; Hwang, G.-S.; Lee, M. Y.; Ryu, D. H. *Chem Commun.* **2009**, 5460. (k) Corey, E. J. *Angew. Chem., Int Ed.* **2009**, *48*, 2100.

enylphosphine oxide[8e,f] was used as an additive. When the reaction was carried out with 30 mol % of Ph_3PO and 20 mol % of **1a** (Table 1, entry 2), the enantioselectivity of the desired product increased to 55%, albeit with a slow reaction rate. To improve the enantioselectivity, careful optimization of the reaction parameters, additives, and catalysts was performed. During our investigation, it emerged that catalyst **1a** in the presence of 50 mol % of Ph_3PO in toluene provided better ee and chemical yields than did catalysts **2** or **1b** (Table 1, entries 3−5) and solvents CH_2Cl_2 or propionitrile. On the other hand, varying the silyl ketene acetal did not improve the yield or ee (Table 1, entries 6−8).[10] The enantioselectivity of product **3** was excellent (93% ee) in the presence of mexyl-substituted catalyst **1c** (Table 1, entry 9).

After optimization of the reaction parameters, the scope and limitations of this methodology were studied using a variety of aldehydes (Table 2). Very good yields and high enantioselectivities were obtained for aromatic as well as aliphatic or unsaturated aldehydes which are typically more challenging substrates in asymmetric carbon−carbon bond forming reactions (Table 2, entries 11−15). The reaction of cyclohexylcarboxaldehyde resulted in a moderate yield of product with 85% ee (Table 2, entry 15).

Table 2. Results of the Catalytic Enantioselective Mukaiyama Aldol Reaction[a]



4

entry		R^2	time (h)	yield (%)[b]	ee (%)[c]
1	**a**	Ph	20	95	93
2	**b**	(4-Me)C_6H_4	15	95	91
3	**c**	(2-Me)C_6H_4	15	91	60
4	**d**	(4-OMe)C_6H_4	30	90	92
5	**e**	(4-Br)C_6H_4	20	80	93
6	**f**	(4-CF_3)C_6H_4	20	83	88
7	**g**	(4-NO_2) C_6H_4	30	92	85
8	**h**	(4-Ph)C_6H_4	20	95	90
9	**i**	2-naphthyl	30	92	90
10	**j**	1-naphthyl	30	96	92
11	**k**	Ph	20	78	90
12	**l**	*n*-Pr	30	75	87
13	**m**	*n*-hexyl	30	72	86
14	**n**		20	86	85[d]
15	**o**	Cy	48	56	85

[a] Reactions were run with 1.0 mmol of aldehyde, 1.2 mmol of silyl ketene acetal, and 0.2 mmol of catalyst, and deprotection of silylated adduct was carried out with TBAF. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC analysis. [d] Determined by chiral GC analysis.

For aromatic aldehydes, substitution with electron-donating groups provided excellent yields and enantioselectivities (>90% ee) (Table 2, entries 2 and 4) due to the effective coordination between the aldehyde oxygen atom and the boron of the oxazaborolidinium ion (Figure 2). However, *ortho*-tolualdehyde gave the desired aldol product with moderate enantioselectivity (60% ee, Table 2, entry 3). We suspect that the bulkier 2-methyl substituent of *ortho*-tolualdehyde significantly reduces the degree of complexation with the catalyst in the pretransition-state assembly leading to the lower enantioselectivity. Alternatively, strong electron-withdrawing substituents such as a *p*-nitro group caused a small reduction in enantioselectivity (85% ee, Table 2, entry 7), which was to be expected due to the reduced carbonyl basicity and thus diminished degree of aldehyde complexation with the catalyst leading to lower ee. Biphenyl and naphthyl carboxaldehydes were also reacted successfully under similar conditions to provide the corresponding β-hydroxy α,α-dimethyl esters in excellent yields and enantioselectivities (Table 2, entries 8−10).

The absolute configuration of the major enantiomeric isomer has been assigned as (*R*) by measurement of optical rotation and comparison with known substances.[11] The resulting configuration of the aldol reaction products presented in Table 2 can be explained by a cyclic complex between catalyst **1c** and the aldehyde as depicted in Figure 2.

The mode of aldehyde complexation is the same as has previously been postulated in the enantioselective formation of (*R*)-cyanohydrins from aldehydes and trimethylsilyl cyanide.[8e] The observed configuration can be rationalized from the transition state model in which the rear face (back) of the aldehyde is shielded from attack by the silyl ketene acetal by bulky aryl groups from the catalyst. Thus, nucleophilic attack of the silyl ketene acetal from the *si* (front) face of the formyl carbon is facilitated leading to the observed (*R*)-enantioselectivity. Due to the greater shielding ability of a mexyl group, catalyst **1c** provided higher ee (2−6%) than catalyst **1a**.

To further evaluate the broad feasibility of the present catalytic system, α,β-disubstituted acroleins were used as substrates (Table 3). The results are summarized in Table 3.

The synthetic utility of this methodology was further demonstrated by the total synthesis of inthomycin C, which was isolated from *Streptomyces* sp. in 1991.[12] The inthomycins have been shown to be highly specific inhibitors of cellular biosynthesis, displaying selective in vitro antimicrobial activity,[13] and to reduce prostate cancer cell growth.[14] To date, there has been only one reported synthesis of inthomycin C by Taylor and co-workers, which produced

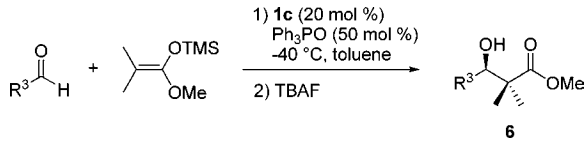
(9) (a) Wang, X.; Adachi, S.; Iwai, H.; Takatsuki, H.; Fujita, K.; Kubo, M.; Oku, A.; Harada, T. *J. Org. Chem.* **2003**, *68*, 10046. (b) Carreira, E. M.; Singer, R. A. *Tetrahedron Lett.* **1994**, *35*, 4323. (c) Hassfeld, J.; Christmann, M.; Kalesse, M. *Org. Lett.* **2001**, *3*, 3561.

(10) The Mukaiyama aldol reaction of benzaldehyde and 1-phenyl-1-(trimethylsilyloxy)ethylene (R1 = H, R2 = Ph) provided β-hydroxy ketone in lower enantiomeric excess (48%) and 40% yield.

(11) (a) Yamashita, Y.; Ishitani, H.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 3292. (b) Fu, F.; Teo, Y.-C.; Loh, T.-P. *Tetrahedron Lett.* **2006**, *47*, 4267.

(12) Henkel, T.; Zeeck, A. *Liebigs Ann. Chem.* **1991**, 367.

Table 3. Asymmetric Mukaiyama Aldol Reaction between α,β-Disubstituted Acroleins and Silyl Ketene Acetal[a]



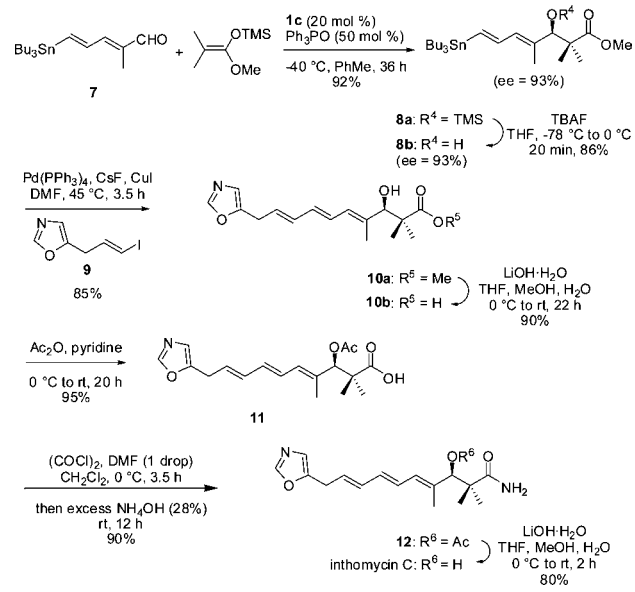
entry		R^3	time (h)	yield (%)[b]	ee (%)[c]
1	**a**	Ph	24	92	89
2	**b**	Me	30	70	73
3	**c**	Et	30	65	84
4	**d**		30	75	74[d]
5	**e**		35	72	74

[a] Reactions were run with 1.0 mmol of aldehyde, 1.2 mmol of silyl ketene acetal, and 0.2 mmol of catalyst, and deprotection of silylated adduct was carried out with TBAF. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC analysis. [d] Determined by chiral GC analysis.

impure (+)-inthomycin C in poor chemical yield and moderate enantioselectivity.[15]

Dienylstannane **7**, which was previously reported as a suitable precursor for the preparation of inthomycin C, was used for the synthesis.[15] The optimized conditions for the catalytic aldol reaction between dienylstannane **7** and (1-methoxy-2-methyl-propenyloxy)-trimethylsilane provided the desired silylated product **8a** in 92% yield. Careful deprotection of **8a** using TBAF afforded alcohol **8b** in 86% yield and 93% ee with only trace levels of destannylated product, a major disadvantage of the previously reported synthesis (Scheme 2).[15] Stille coupling between enantiomerically enriched alcohol **8b** and vinyl iodide **9**[16] using $Pd(PPh_3)_4$/CuI/CsF conditions[17] proceeded in 85% yield, and subsequent saponification gave acid **10b**. Conversion of **10b** to acetate **11** followed by activation with oxalyl chloride and

Scheme 2. Enantioselective Total Synthesis of (−)-Inthomycin C



then treatment with 28% ammonium hydroxide provided amide **12** in high yield. Finally, deprotection of the acetyl group with lithium hydroxide furnished inthomycin C in high enantiopurity, which had spectral properties identical to those previously reported for the natural product. Synthetic inthomycin C was further transformed to 3-*O*-[(*S*)-2-phenylbutyryl] inthomycin C (see Supporting Information), and its ^{1}H NMR and CD data were correlated with reported values.[12]

In summary, a highly efficient and enantioselective Mukaiyama aldol reaction has been developed between (1-methoxy-2-methyl-propenyloxy)-trimethylsilane and various aldehydes using an oxazaborolidinium ion catalyst. These studies revealed that Ph_3PO is an essential additive for high enantioselectivities. Moreover, the catalytic reaction was successfully applied to a short synthesis of (−)-inthomycin C. Application of this methodology to the synthesis of other inthomycins and more complex polyene systems is under investigation.

Acknowledgment. This work was supported by grants NRF-20090094024 (Priority Research Centers Program), NRF-20080058667 (Basic Science Research Program), and NRF-20090076108 (Basic Science Research Program).

Supporting Information Available: Experimental details and chracterization data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102234K

(13) (a) Omura, S.; Tanaka, Y.; Kanaya, I.; Shinose, M.; Takahashi, Y. *J. Antibiot.* **1990**, *43*, 1034. (b) Tanaka, Y.; Kanaya, I.; Shiomi, K.; Tanaka, H.; Omura, S. *J. Antibiot.* **1993**, *46*, 1214.

(14) Kawada, M.; Yoshimoto, Y.; Minamiguchi, K.; Kumagai, H.; Someno, T.; Masuda, T.; Ishizuka, M.; Ikeda, D. *Anticancer Res.* **2004**, *24*, 1561.

(15) Webb, M. R.; Addie, M. S.; Crawforth, C. M.; Dale, J. W.; Franci, X.; Pizzonero, M.; Donald, C.; Taylor, R. J. K. *Tetrahedron* **2008**, *64*, 4778.

(16) Webb, M. R.; Donald, C.; Taylor, R. J. K. *Tetrahedron Lett.* **2006**, *47*, 549.

(17) (a) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132. (b) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Chem.—Eur. J.* **2005**, *11*, 3294.