Multicomponent Reactions

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Enantioselective Synthesis of β-Iodo Morita–Baylis–Hillman Esters by a Catalytic Asymmetric Three-Component Coupling Reaction**

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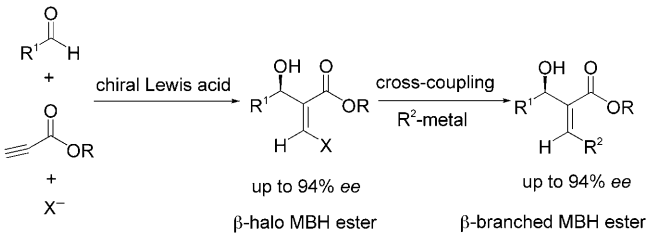
Dedicated to Professor Sung Ho Kang on the occasion of his 60th birthday

Optically active α-methylene-β-hydroxy carbonyl derivatives can be prepared by the asymmetric Morita–Baylis–Hillman (MBH) reaction.[1] These derivatives are useful chiral building blocks for biologically active molecules and natural products because of their multifunctional composition.[2] Even with recent advances in this area, asymmetric synthesis of β-substituted MBH products such as β-branched MBH ketones or esters have not been successful by this method.[2] One efficient route to give various β-branched MBH products[3] can be achieved through the cross-coupling reaction of chiral β-halo MBH products (Scheme 1). The presence of a halogen



Scheme 1. Enantioselective synthesis of *Z*-selective β-branched MBH esters through β-halo MBH esters.

atom in the β position is beneficial for numerous further transformations on the products and is useful for the rapid construction of complex organic molecules.[4] Consequently, the development of efficient methods for enantioselective and *E*/*Z*-stereocontrolled synthesis of β-halo MBH products can provide efficient entry to give various optically active β-substituted MBH products. Although racemic *E*-[5] or *Z*-stereocontrolled[6] synthetic approaches to give β-halo MBH esters or ketones have been reported by our research group and others, methods for asymmetric conversion[7] are currently limited. Li et al. have reported the asymmetric synthesis of β-iodo MBH ketones by using an aldol reaction between preformed silyl allenolates and aldehydes that was catalyzed by *N*-heptafluorobutyryl oxazaborolidine.[7a] They also reported a catalytic, asymmetric synthetic method to give β-iodo MBH esters, which are more useful than their ketone counterparts.[7b] However, there have been no reports of highly enantioselective and *E*/*Z*-stereocontrolled synthetic methods to give optically active β-halo MBH esters.

We report herein the highly enantioselective and *Z*-stereocontrolled three-component coupling reaction of α,β-acetylenic esters, aldehydes, and trimethylsilyl iodide (TMSI) using chiral cationic oxazaborolidinium catalysts (Scheme 1). The reaction provides the optically active β-iodo MBH esters with good to excellent yield and enantioselectivity in a straightforward way. In addition, the subsequent metal-catalyzed cross-coupling of these esters are performed directly to access the synthetically more useful β-branched MBH esters through a single step (Scheme 1). The stereochemical course of the reaction and its high *Z* selectivity are rationalized by the preassembly of the transition state, shown in Scheme 3.

The chiral oxazaborolidinium salts (**1** and **2**; Scheme 2) behave as powerful Lewis acids and have been proven to be effective catalysts for enantioselective Diels–Alder reactions,[8a,e,f] cyanosilylations,[8b,c] and Michael reactions.[8d] There is much evidence for the formation of the complex between catalyst **1** and aldehydes.[8a,b] We applied these oxazaborolidinium catalysts in a three-component coupling reaction involving an aldehyde, an alkyl propiolate, and TMSI.

Scheme 2. Catalysts screened for enantioselective synthesis of β-iodo MBH esters.

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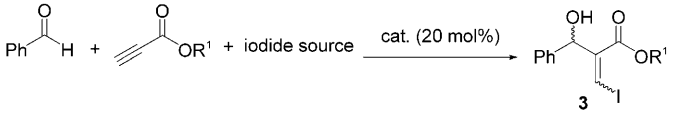
Benzaldehyde was selected as a model substrate for the initial optimization (Table 1). The three-component coupling reaction between benzaldehyde, ethyl propiolate, and nBu$_4$NI, using 0.2 equivalents of catalyst **1a** in CH_2Cl_2 at

Table 1: Enantioselective *Z* stereocontrolled three-component coupling between benzaldehyde, alkyl propiolate, and TMSI[a]



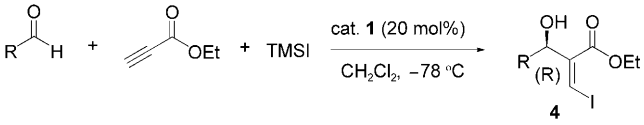
Entry	Cat.	R^1	Reaction conditions	Yield [%][b]	Z/E[c]	*ee* [%][d]
1	**1a**	Et	nBu$_4$NI, CH_2Cl_2, −40 °C, 10 h	26	85:15	20
2	**1a**	Et	TMSI, CH_2Cl_2, −40 °C, 3 h	68	90:10	77
3	**1a**	Et	TMSI, CH_3CH_2CN, −40 °C, 10 h	38	88:12	69
4	**1a**	Et	TMSI, toluene, −78 °C, 5 h	85	92:8	84
5	**1b**	Et	TMSI, CH_2Cl_2, −78 °C, 3 h	92	94:6	67
6	**1a**	Me	TMSI, CH_2Cl_2, −78 °C, 1.5 h	92	99:1	84
7	**1a**	*t*Bu	TMSI, CH_2Cl_2, −78 °C, 10 h	0	–	–
8	**1a**	Et	TMSI, CH_2Cl_2, −78 °C, 2 h	93	>99:1	87[e]
9	**2**	Et	TMSI, CH_2Cl_2, −78 °C, 2 h	90	>99:1	87[f]
10	**1c**	Et	TMSI, CH_2Cl_2, −78 °C, 1 h	95	>99:1	94[e]

[a] Reactions run with 1.0 mmol of benzaldehyde, 2.0 mmol of ethylpropiolate, 1.5 mmol of the iodide source, and 0.2 mmol of catalyst. [b] Yield of isolated product. [c] Determined after separation by column chromatography. [d] Determined by HPLC on a chiral stationary phase. [e] The absolute configuration of **3** was determined to be *R* enriched. For details see the Supporting Information. [f] The absolute configuration of **3** was determined to be *S* enriched.

−40 °C gave the desired product (26% yield) with a poor enantioselectivity (20% *ee*) for the *Z* isomer (Table 1, entry 1). Replacement of nBu$_4$NI by TMSI under similar reaction conditions produced the desired product with an improved yield and *ee* value (Table 1, entry 2). The resulting *Z* and *E* isomers of **3** could be easily separated by column chromatography on silica gel. The *Z* configuration of the major product was determined unambiguously by 2D ROESY analysis, as mentioned in our previous report.[6g] The reaction conditions were then optimized by varying the reaction parameters and catalysts. During our investigation, it emerged that catalyst **1a** provided better *ee* values than **1b** in CH_2Cl_2 compared to toluene or propionitrile. The *Z* selectivity of product **3** was excellent (>99:1) at −78 °C compared to −40 °C (compare Table 1, entries 2 and 8). This high stereoselectivity obtained at low temperature is due to the multicoordinating Lewis acidic catalyst **1**, which prefers the chairlike transition state **5a** to give the kinetically favored *Z* product (Scheme 3).[6g,7a] Both ethyl and methyl propiolates provided high enantioselectivity under similar conditions (Table 1, entries 6 and 8). However, in the case of *tert*-butyl propiolate a coupling product could not be isolated (Table 1, entries 7). Both catalysts **1a** and **2** were effective at providing (*R*)- and (*S*)-β-iodo MBH esters in high yield and *ee*, respectively (Table 1, entries 8 and 9). The use of mexyl-substituted catalyst **1c** improved the *ee* value of **3** up to 94% (Table 1, entry 10).

After optimization of the reaction parameters for *Z* stereoselective, asymmetric three-component coupling reactions, the scope of this methodology was studied (Table 2). Reactions with various aldehydes provided the corresponding *Z*-selective β-iodo MBH esters **4** in high to excellent enantio-

Table 2: Results of the catalytic enantioselective synthesis of *Z*-selective β-iodo MBH esters.[a]



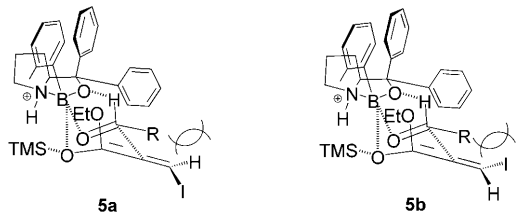
Entry	Catalyst	R	*t* [h]	Yield [%][b]	Z/E[c]	*ee* [%][d]
1	**1c**	Ph	1	95	>99:1	94
2	**1c**	4-FC_6H_4	3	92	>99:1	92
3	**1a**	4-$CF_3C_6H_4$	4	75	99:1	92
4	**1a**	4-ClC_6H_4	2	99	99:1	96
5	**1a**	2-BrC_6H_4	5	95	>99:1	90
6	**1a**	4-BrC_6H_4	5	90	96:4	93
7	**1a**	4-CNC_6H_4	6	91	97:3	95
8	**1a**	4-$NO_2C_6H_4$	30	66	92:8	90
9	**1c**	4-MeC_6H_4	1.5	92	99:1	62
10	**1c**	4-PhC_6H_4	1.5	95	92:8	90
11	**1a**	2-naphthyl	12	65	98:2	91
12[e]	**1b**	*n*Pr	8	72	96:4	93
13[e]	**1b**	*n*-hexyl	12	61	97:3	90
14[e]	**1b**	*i*Pr	12	50	95:5	90

[a] Reactions run with 1.0 mmol of aldehyde, 2.0 mmol of ethylpropiolate, 1.5 mmol of TMSI, and 0.2 mmol of catalyst. [b] Yield of isolated product. [c] Determined after separation by column chromatography. [d] Determined by HPLC on a chiral stationary phase. [e] Reaction run using 2.5 equivalents of ethyl propiolate and 2.0 equivalents of TMSI at −60 °C.

meric excess. For aromatic aldehydes, substitution with electron-withdrawing groups lowered the reaction rate but provided excellent enantioselectivites (90–96% *ee*; Table 2, entries 2–8). The strong electron-withdrawing 4-nitro group can be expected to lower the basicity of the aldehyde carbonyl group and thereby reduce the degree of complexation which results in the catalyst reacting at a slow rate (Table 2, entry 8). Conversely, electron-donating substituents such as *p*-tolualdehyde caused a significant loss in enantioselectivity (62% *ee*; Table 2, entry 9).[9] Similar results were observed for the cyanosilylation of ketones.[8c] 4-Biphenyl and 2-naphthyl carboxaldehyde were also treated under similar reaction condition to produce β-iodo MBH esters with excellent yield and enantioselectivity (Table 2, entry 10 and 11). The reaction rate of aliphatic aldehydes was considerably slow at −78 °C. Optimal results were obtained at −60 °C when **1a** was replaced with the triflimide-activated catalyst **1b** owing to the higher stability of triflimide-activated catalysts[8a] (Table 2, entries 12–14). The reaction of iosobutyraldehyde (Table 2, entry 14) resulted in high enantioselectivities and moderate yield.

The absolute configuration of the major enantiomeric isomer was assigned as *R* by chemical correlations. Product **3** (Table 1, entries 8 or 10) was transformed into (*R*)-2-methoxy-2-phenylacetic acid (see the Supporting Informa-

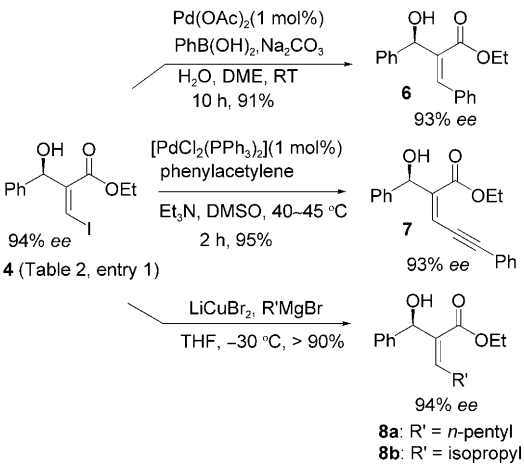
tion) and its ^{1}H NMR spectrum and specific rotation data correlates with those reported earlier.[10] The resulting *Z* geometry and stereochemical course of the three-component coupling reactions (represented in Table 2) can be explained by the asymmetric aldol reaction between trimethylsilyl β-iodo allenoate and aldehydes via a cyclic transition state of pentacoordinated[11] catalyst **1** (Scheme 3).[7a] As



Scheme 3. Transition-state model for the asymmetric Michael-aldol reaction.

serious steric interactions between the I and R groups are obvious in transition state **5b**, therefore transition state **5a** is favored and predominantly affords the *Z* isomer. In terms of *R* chirality, the mode of complexation of the aldehydes is the same as that shown in the enantioselective formation of (*R*)-cyanohydrins from aldehydes and trimethylsilyl cyanide.[8b] The formyl carbon atom is situated above the nearby bulky aryl groups, which effectively shields the *re* face (back) from attack by the β-iodo allenoate intermediate. Thus, nucleophilic attack of the allenoate carbon atom from the *si* face (front) of the formyl carbon atom is facilitated and leads to *R* enantioselectivity. Owing to the greater shielding ability of the mexyl groups, catalyst **1c** provided a 1–7% higher *ee* value than catalyst **1a**.

To extend the application of the resulting β-iodo MBH adducts, we performed various cross-coupling reactions to generate chiral (*Z*)-β-branched MBH adducts without the need to protect the chiral alcohol (Scheme 4). Suzuki coupling of **4** (Table 2, entry 1) with phenyl boronic acid in



Scheme 4. Synthesis of *Z*-selective β-branched chiral MBH esters by a direct cross-coupling reaction. DME = 1,2-dimethoxyethane, DMSO = dimethyl sulfoxide.

the presence of $Pd(OAc)_2$ under known reaction conditions proceeded smoothly to give (*Z*)-β-phenyl MBH ester **6** with a 91% yield without an obvious loss of enantiopurity.[12] Sonogashira coupling with phenyl acetylene and $[PdCl_2(PPh_3)_2]$ produced **7** in a 95% yield.[13] Similarly, organocuprate-promoted conjugate addition of Grignard reagent provided exclusively (*Z*)-β-branched allylic alcohols **8** with an excellent yield without loss of enantiopurity.[14]

In summary, we have developed a highly enantioselective, catalytic three-component coupling reaction between an aldehyde, ethyl propiolate, and TMSI to give chiral (*Z*)-β-iodo MBH esters. Both the enantiomers of (*Z*)-β-iodo MBH esters (*R*/*S*) could be obtained enantioselectively by using an *S*- or *R*-oxazaborolidinium catalyst (**1** or **2**). These esters can be directly converted into the optically active (*Z*)-β-branched derivatives with retention of configuration. The absolute configuration of the product was that predicted by the transition state model **5a**. We believe that these results should be useful in the synthesis of various optically active (*Z*)-β-branched Morita–Baylis–Hillman esters. Further optimization of this catalytic asymmetric reaction, extension of the scope, and synthetic applications are in progress.

Experimental Section

Synthesis of **4**: A freshly prepared solution of triflic acid in CH_2Cl_2 (0.200 M solution, 0.690 μL, 0.138 mmol) was added dropwise to an aliquot of oxazaborolidine precursor **1c** (0.166 mmol, ca. 20 mol%, theoretical) in of CH_2Cl_2 (1.5 mL) at −40 °C under nitrogen. During the addition, the catalyst solution turned orange in color but then became clear instantaneously. Towards the end of the reaction, a small amount of orange precipitate was observed. After stirring for 15–20 min at −40 °C, the orange precipitate disappeared and a colourless homogeneous solution of catalyst was obtained. Benzaldehyde (0.691 mmol, 70.5 μL) was then added dropwise to the cooled (−78 °C) solution of catalyst. After 20 min of stirring at −78 °C, ethyl propiolate (1.383 mmol, 140 μL) and TMSI (1.04 mmol, 148 μL) were quickly added to the mixture sequentially. After stirring for 1 h at −78 °C, the reaction mixture was quenched with H_2O (2 mL) and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and the solvent removed under vacuum to produce the crude product. Purification by flash column chromatography on silica gel (eluent: 1:10 EtOAc/hexanes) afforded the corresponding β-iodo MBH ester **4** as a colourless oil in 95% yield (218 mg, 94% *ee* ; Table 2, entry 1).

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[1] For recent reviews on the Morita-Baylis–Hillman reaction, see a) G. Masson, C. Housseman, J. Zhu, *Angew. Chem.* **2007**, *119*, 4698; *Angew. Chem. Int. Ed.* **2007**, *46*, 4614; b) Y.-L. Shi, M. Shi, *Eur. J. Org. Chem.* **2007**, 2905; c) D. Basavaiah, K. V. Rao, R. J. Reddy, *Chem. Soc. Rev.* **2007**, *36*, 1581.

[2] a) D. Basavaiah, A. J. Rao, T. J. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811; b) K. Y. Lee, K. Y. Gowrisankar, J. N. Kim, *Bull. Korean Chem. Soc.* **2005**, *26*, 1481.

[3] For other routes to β-branched MBH products, see: a) T. Kataoka, H. Kinoshita, S. Kinoshita, T. Iwamura, S. Watanabe, *Angew. Chem.* **2000**, *112*, 2448; *Angew. Chem. Int. Ed.* **2000**, *39*, 2358; b) P. Ramachandran, M. T. Rudd, T. E. Burghardt, M. V. R. Reddy, *J. Org. Chem.* **2003**, *68*, 9310; c) T. E. Reynolds, A. R. Bharadwaj, K. A. Scheidt, *J. Am. Chem. Soc.* **2006**, *128*, 15382; d) T. E. Reynolds, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 7952; *Angew. Chem. Int. Ed.* **2007**, *46*, 7806; e) E. Tarsis, A. Gromova, D. Lim, G. Zhou, C. Guoqiang, D. M. Coltart, *Org. Lett.* **2008**, *10*, 4819; f) A. J. Mueller, M. P. Jennings, *Org. Lett.* **2008**, *10*, 1649.

[4] For the transformation of vinyl halides, see: a) G. S. Zweifel, M. H. Nantz in *Modern Organic Synthesis: An Introduction*, W. H. Freeman and Company, New York, **2007**, pp. 290–358; b) J. Tsuji in *Palladium Reagents and Catalysts*, Wiley, New York, **2004**, pp. 109–176; c) M. C. Walczak, R. S. Coleman, *Org. Lett.* **2005**, *7*, 2289.

[5] a) Q. Li, M. Shi, J. M. Lyte, G. Li, *Tetrahedron Lett.* **2006**, *47*, 7699; b) S. Lee, G.-S. Hwang, S. C. Shin, T. G. Lee, R. H. Jo, D. H. Ryu, *Org. Lett.* **2007**, *9*, 5087.

[6] For a review on (*Z*)-β-halo MBH synthesis, see: a) G. Li, J. Hook, H.-X. Wei in *Recent Research Developments in Organic & Bioorganic Chemistry*; Transworld Research Network, *Vol. 4*, **2001**, pp. 49–61; b) T. Kataoka, Y. Banno, S. Watanabe, T. Iwamura, H. Shimizu, *Tetrahedron Lett.* **1997**, *38*, 1809; c) S. Watanabe, K. Yamamoto, Y. Itagaki, T. Kataoka, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2053; d) G. Li, H.-X. Wei, T. D. Caputo, *Tetrahedron Lett.* **2000**, *41*, 1; e) G. Li, J, Gao, H.-X. Wei, M. Enright, *Org. Lett.* **2000**, *2*, 617; f) C. Timmons, A. Kattuboina, S. Banerjee, G. Li, *Tetrahedron Lett.* **2006**, *62*, 7151; g) S. Lee, G.-S. Hwang, D. H. Ryu, *Synlett* **2007**, 59.

[7] a) G. Li, H.-X. Wei, B. S. Phelps, D. W. Purkiss, S. H. Kim, *Org. Lett.* **2001**, *3*, 823; b) D. Chen, C. Timmons, J. Liu, A. Headley, G. Li, *Eur. J. Org. Chem.* **2004**, 3330; c) D. Chen, G. Li, Guo, S. R. S. S. Kotti, G. Li, *Tetrahedron: Asymmetry* **2005**, *16*, 1757.

[8] a) D. H. Ryu, E. J. Corey, *J. Am. Chem. Soc.* **2003**, *125*, 6388; b) D. H. Ryu, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 8106; c) D. H. Ryu, E. J. Corey, *J. Am. Chem. Soc.* **2005**, *127*, 5384; d) D. Liu, S. Hong, E. J. Corey, *J. Am. Chem. Soc.* **2006**, *128*, 8160; e) J. Y. Sim, G.-S. Hwang, K. H. Kim, E. M. Ko, D. H. Ryu, *Chem. Commun.* **2007**, 5064; f) M. Y. Lee, K. H. Kim, S. Jiang, Y. H. Jung, J. Y. Sim, G.-S. Hwang, D. H. Ryu, *Tetrahedron Lett.* **2008**, *49*, 1965.

[9] 4-Methoxybenzaldehyde was found to be incompatible under our catalytic conditions; it gave a complex mixture. The 4-methoxy group might be causing problems through some kind of complexation with the boron atom of the oxazaborolidinium catalyst.

[10] E. Boyd, S. Chavada, J. Eames, Y. Yohannes, *Tetrahedron: Asymmetry* **2007**, *18*, 476.

[11] T. Ooi, D. Uraguchi, N. Kagoshima, K. Maruoka, *J. Am. Chem. Soc.* **1998**, *120*, 5327.

[12] N. A. Bumagin, V. V. Bykov, *Tetrahedron* **1997**, *53*, 14437.

[13] Z. Lu, S. Ma, *J. Org. Chem.* **2006**, *71*, 2655.

[14] T. B. Ayed, J. Villiéras, H. Amri, *Tetrahedron* **2000**, *56*, 805.

