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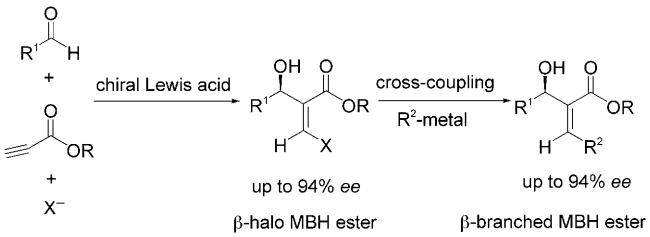
Dedicated to Professor Sung Ho Kang on the occasion of his 60th birthday

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.

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

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

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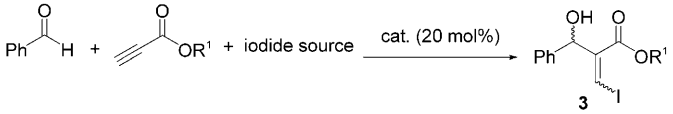
Benzaldehyde was selected as a model substrate for the initial optimization (Table 1). The three-component coupling reaction between benzaldehyde, ethyl propiolate, and nBu$_4$NI, using 0.2 equivalents of catalyst **1a** in CH_2Cl_2 at

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



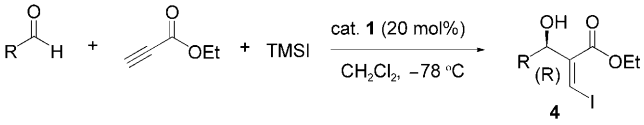
Entry	Cat.	R^1	Reaction conditions	Yield [%][b]	Z/E[c]	*ee* [%][d]
1	**1a**	Et	nBu$_4$NI, CH_2Cl_2, −40 °C, 10 h	26	85:15	20
2	**1a**	Et	TMSI, CH_2Cl_2, −40 °C, 3 h	68	90:10	77
3	**1a**	Et	TMSI, CH_3CH_2CN, −40 °C, 10 h	38	88:12	69
4	**1a**	Et	TMSI, toluene, −78 °C, 5 h	85	92:8	84
5	**1b**	Et	TMSI, CH_2Cl_2, −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]



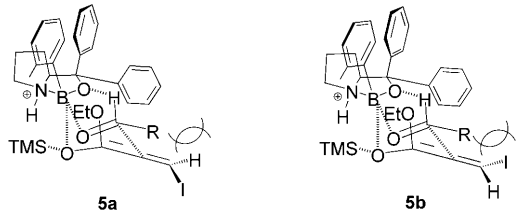
Entry	Catalyst	R	*t* [h]	Yield [%][b]	Z/E[c]	*ee* [%][d]
1	**1c**	Ph	1	95	>99:1	94
2	**1c**	4-FC_6H_4	3	92	>99:1	92
3	**1a**	4-$CF_3C_6H_4$	4	75	99:1	92
4	**1a**	4-ClC_6H_4	2	99	99:1	96
5	**1a**	2-BrC_6H_4	5	95	>99:1	90
6	**1a**	4-BrC_6H_4	5	90	96:4	93
7	**1a**	4-CNC_6H_4	6	91	97:3	95
8	**1a**	4-$NO_2C_6H_4$	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-

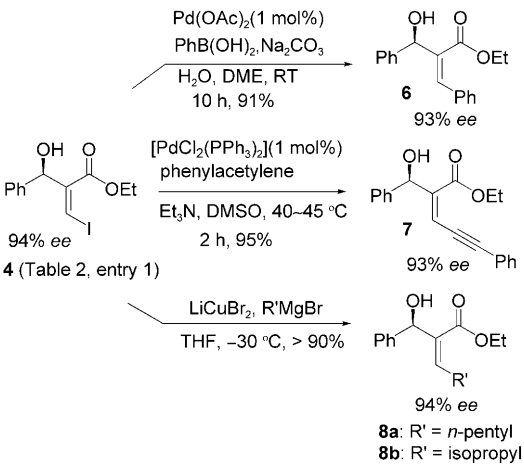
tion) and its ^{1}H NMR spectrum and specific rotation data correlates with those reported earlier.[10] The resulting *Z* geometry and stereochemical course of the three-component coupling reactions (represented in Table 2) can be explained by the asymmetric aldol reaction between trimethylsilyl β-iodo 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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