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Catalytic Enantioselective Carbon Insertion into the β-Vinyl C−H Bond of Cyclic Enones

Sung Il Lee,[†,‡] Geum-Sook Hwang,[*,‡] and Do Hyun Ryu[*,†]

[†]Department of Chemistry, Sungkyunkwan University, Suwon 440-746, Korea
[‡]Seoul Center, Korea Basic Science Institute, Seoul 136-713, Korea

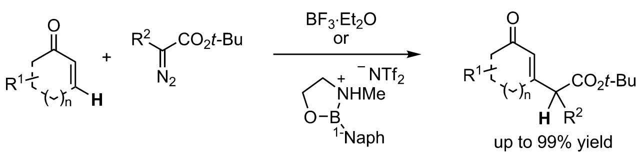
Supporting Information

ABSTRACT: Chiral oxazaborolidinium ion-catalyzed C_{sp^2}−H functionalization of enones using diazoacetate has been developed. Various β-substituted cyclic enones were synthesized in high yield (up to 99%) with high to excellent enantioselectivity (up to 99% ee). The synthetic utility of this reaction was demonstrated by the formal synthesis of (+)-epijuvabione.

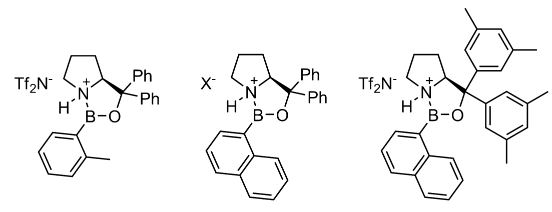
Direct C−H functionalizations provide potential advantages to the synthetic strategies for making complex molecules,[1] and related methodologies have been extensively investigated.[2] Despite the recent progress in C−H functionalization, the development of an enantioselective method with a chiral catalyst still remains one of the most challenging topics in current organic synthesis. Transition-metal-catalyzed asymmetric C−H functionalizations with diazo compounds via intra-[3] and intermolecular[4] methods have been reported during the past decade. In addition, recent research has revealed that a chiral Lewis acid catalyst is suitable for an enantioselective formyl C_{sp^2}−H functionalization.[5]

We recently developed a boron Lewis acid-catalyzed C_{sp^2}−H functionalization of cyclic enones using diazoacetates.[6] $BF_3 \cdot Et_2O$ and the newly designed achiral oxazaborolidinium ion successfully catalyzed the C−H functionalization reaction and afforded C−H-inserted cyclic enones in moderate to high yields (Scheme 1). We believe that the development of an asymmetric carbon insertion reaction of a cyclic enone would be highly valuable for generating useful chiral building blocks in the synthesis of biologically active molecules and pharmaceuticals.

Scheme 1. Boron Lewis Acid-Catalyzed Carbon Insertion Reaction of Cyclic Enones



The chiral oxazaborolidinium ions **1** (Figure 1), which are generated from the corresponding oxazaborolidines by protonation with strong Brønsted acids, behave as powerful Lewis acids and have proven to be effective catalysts for asymmetric Diels−Alder reactions,[7a] cyanosilylations,[7b] a tandem Michael−aldol reaction,[7c] cyclopropanation,[7d] and the Roskamp reaction.[5b] There is substantial evidence for the formation of a complex between oxazaborolidinium ions and α,β-unsaturated ketones.[8] We anticipated that an oxazaborolidinium ion would be a suitable Lewis acid catalyst for the enantioselective C−H functionalization reaction. In this communication, we present the first case of highly enantiocontrolled catalytic carbon insertion into the β-vinyl C−H bond of cyclic enones using diazoacetates.



1a **1b** (X = Tf_2N) **1c** (X = TfO) **1d**

Figure 1. Structures of oxazaborolidinium ions **1**.

Initially, the asymmetric C−H functionalization reaction between cyclohex-2-en-1-one (**2**) and various alkyl phenyldiazoesters was examined in the presence of 20 mol % oxazaborolidinium ion **1a**, which was prepared by activation of its precursor with triflic imide. With the methyl and benzyl esters, the desired C−H-inserted cyclohexenones were obtained in yields of 44% and 68%, respectively, with poor enantioselectivity (Table 1, entries 1 and 2). Replacement of the ester substituents had a significant impact on the stereoselectivity. For the successful implementation of the diazoester, *tert*-butyl phenyldiazoester was selected for the C−H functionalization reaction, and the enantioselectivity was greatly improved to 80% ee (entry 3). Our focus then moved to the screening for a suitable catalyst structure. We found that oxazaborolidinium ion catalyst **1b** with a 1-naphthyl substituent at the boron center effectively produced a C−H insertion product without a decline in stereoselectivity (entry 4). Using triflic acid-activated oxazaborolidinium ion **1c** brought about a significant decrease in yield (entry 5). At −20 °C, the carbon insertion reaction of diazoacetate using catalyst **1b** was successfully carried out and furnished the β-substituted cyclohexenone with improved enantioselectivity (entry 6).

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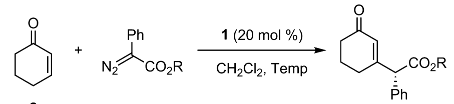
Table 1. Screening of the Reaction Conditions for Oxazaborolidinium Ion-Catalyzed Enantioselective Carbon Insertion Reaction of Cyclohex-2-en-1-one (2)[a]



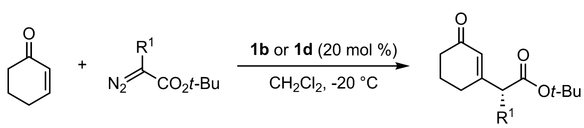
2

entry	cat	R	T (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**1a**	Me	24	16	44	2
2	**1a**	Bn	−20	16	64	8
3	**1a**	*t*-Bu	0	9	25	80
4	**1b**	*t*-Bu	0	6	74	81
5	**1c**	*t*-Bu	0	2	16	79
6	**1b**	*t*-Bu	−20	19	73	85

[a]The reaction was performed using 1.0 equiv of alkyl phenyldiazoester and 1.2 equiv of **2**. [b]Isolated yields. [c]Determined by chiral HPLC analysis.

After optimization of the asymmetric C−H functionalization reaction, the scope of this methodology was investigated with various diazoacetates and cyclic enones. The carbon insertion reaction is more suitable for α-alkyl-substituted *tert*-butyl diazoesters than α-aryl substituted ones (Table 2, entries 2−8). Regardless of the structure of the alkyl group at the α-position of the diazoester, the C−H functionalization reaction proceeded in a highly stereoselective manner, and the corresponding β-substituted cyclohex-2-en-1-one variant **3** was obtained in high yield (entries 2−7). Since the *tert*-butyl isopropyldiazoacetate slowly decomposed in the presence of the oxazaborolidinium ion catalyst, its yield was reduced to 60% under the optimized reaction conditions (entry 8).

Table 2. Substructure Scope of the Chiral Oxazaborolidinium Ion-Catalyzed Carbon Insertion Reaction: Diazoacetates[a]



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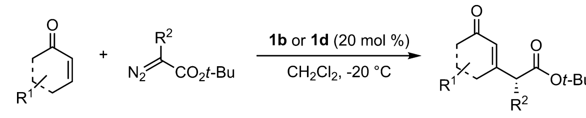
entry	3	1	R[1]	time (h)	yield (%)[b]	ee (%)[c]
1	**3a**	**1b**	Ph	19	73	85
2	**3b**	**1d**	Bn	1	99	95
3	**3c**	**1d**	4-BrBn	1	99	94
4	**3d**	**1d**	allyl	1	99	97
5	**3e**	**1b**	propargyl	1	99	91
6[d]	**3f**	**1d**	Me	<1	97	92
7	**3g**	**1d**	Et	<1	87	96
8	**3h**	**1d**	*i*-Pr	<1	60	97

[a]The reaction was performed using 1.0 equiv of *tert*-butyl diazoester and 1.2 equiv of **2**. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]The absolute configuration was determined to be *R* (see the Supporting Information).

The catalytic asymmetric carbon insertion reaction was also successfully carried out with substituted cyclohexenones (Table 3). The reactions of 5,5-dimethylcyclohex-2-en-1-one with various alkyl diazoacetates furnished the corresponding C−H functionalized products in high yields with high enantioselectivities (entries 1−4), while (*R*)-6-methylcyclohex-2-en-1-one produced the desired products in nearly quantitative yields with high diastereoselectivities (entries 5 and 6). To investigate further the substrate scope of the present catalytic system, we applied the catalytic asymmetric C−H functionalization reaction to cyclic enones of various sizes. The asymmetric carbon insertion reaction using an oxazaborolidinium ion catalyst is a powerful method for the preparation of highly enantiopure β-substituted cyclopent-2-en-1-ones (entries 7 and 8). In addition, cyclic enones with larger ring sizes were subjected to C−H functionalization with a range of alkyl diazoesters, and in all cases, excellent enantioselectivities were observed (entries 9−15). However, the reaction with acyclic enones, such as methyl vinyl ketone, ethyl vinyl ketone, and pent-3-en-2-one produced 2-pyrazoline as a major product.[9]

Table 3. Substructure Scope of the Chiral Oxazaborolidinium-Ion Catalyzed Carbon Insertion Reaction: Cyclic Enones[a]



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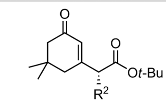
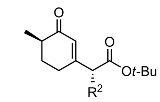
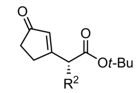
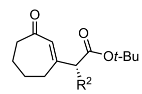
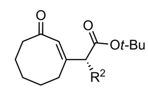
entry	3	1	R[2]	product	time (h)	yield (%)[b]	ee (%)[c]
1[d]	**3i**	**1b**	Bn		8	84	89
2[d]	**3j**	**1b**	allyl		8	97	90
3[d]	**3k**	**1b**	Me		3	82	90
4[d,e]	**3l**	**1b**	Et		3	98	97
5[f]	**3m**	**1b**	Bn		5	99	95[g]
6[f]	**3n**	**1b**	allyl		5	95	96[g]
7	**3o**	**1d**	Bn		5	96	93
8	**3p**	**1b**	*n*-Hex		3	99	86
9[e]	**3q**	**1d**	Bn		8	75	97
10	**3r**	**1d**	4-BrBn		5	68	98
11[e]	**3s**	**1d**	allyl		13	97	95
12	**3t**	**1d**	*n*-Hex		5	91	99
13	**3u**	**1d**	Bn		2	77	96
14	**3v**	**1d**	allyl		2	73	97
15	**3w**	**1d**	*n*-Hex		2	83	98

[a]The reaction was performed using 1.0 equiv of *tert*-butyl diazoester and 1.2 equiv of cyclic enone. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]The reaction was performed at −5 °C. [e]40 mol % oxazaborolidinium ion catalyst was used. [f]The reaction was performed at −30 °C. [g]Diastereomeric excess of the anti isomer (major product) relative to the syn isomer.

The oxazaborolidinium ion-catalyzed C−H functionalization reaction was diastereoselectively performed in the presence of both enantiomers of 6-methylcyclohex-2-en-1-one. Under the optimized reaction conditions, (*R*)-6-methylcyclohex-2-en-1-one reacted faster than the *S* enantiomer and furnished the corresponding anti-β-substituted cyclic enone in excellent yield with a diastereomeric ratio of 87/13 and excellent enantiomeric excess (Scheme 2). Chiral gas chromatography analysis revealed that the remaining (*S*)-6-methylcyclohex-2-en-1-one had 71% ee. A selectivity factor (s) of 16.5 was calculated on the basis of the conversion and the ee of 6-methylcyclohex-2-en-1-one.

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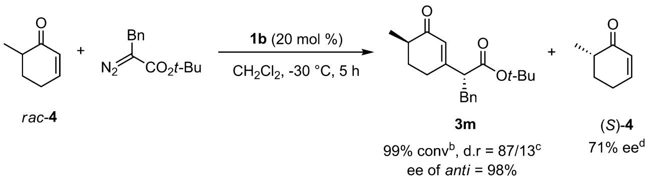
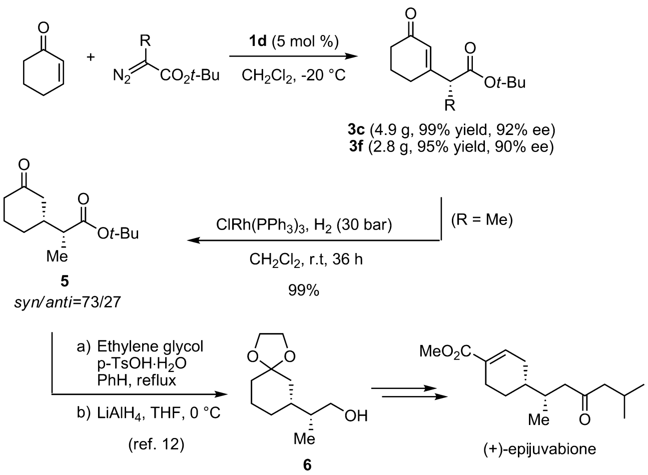
Scheme 2. Enantio- and Diastereoselective Carbon Insertion Reaction of 6-Methylcyclohex-2-en-1-one[a]



[a]The reaction was performed using 1.0 equiv of *tert*-butyl diazoester and 2.1 equiv of (*rac*)-6-methylcyclohex-2-en-1-one. [b]Based on diazoacetate. [c]Determined by NMR analysis. [d]Determined by chiral GC analysis.

The feasibility of reducing the catalyst loading and increasing the reaction scale to a multigram scale was examined (Scheme 3). The loading of catalyst **1d** could be reduced to 5 mol % while maintaining excellent yields and enantioselectivities.

Scheme 3. Multigram-Scale Carbon Insertion Reactions Using Lower Catalyst Loading and the Stereoselective Formal Synthesis of (+)-Epijuvabione



(+)-Juvabione and (+)-epijuvabione, a natural sesquiterpene exhibiting selective insect juvenile hormone activity, were isolated from Balsam fir by Bowers and co-workers.[10] (+)-Juvabione and (+)-epijuvabione have been the target of numerous synthetic investigations because of their interesting continuous stereogenic centers on a ring and side chain.[11] With the oxazaborolidinium ion-catalyzed carbon insertion reaction, *syn*-cyclohexanone **5** was synthesized from simple cyclohex-2-en-1-one in two steps (Scheme 3). Cyclohexanone **5** could be converted to a known intermediate for the synthesis of (+)-epijuvabione (**6**) according to the literature procedure.[12]

The observed stereochemistry of the oxazaborolidinium ion-catalyzed asymmetric carbon insertion reaction can be explained by the transition state model shown in Figure 2. The mode of the cycloalkenone coordination to the oxazaborolidinium ion is the same as that previously shown for the absolute configuration of chiral Diels–Alder adducts[8a−c] and Michael products[8d] from α,β-unsaturated enones. In that complex, the electron-deficient α,β-enone subunit attracts the phenyl or 3,5-dimethylphenyl group by a $\pi-\pi$ donor–acceptor interaction,[7a,13] and the double bond of the cyclic enone is situated above the phenyl or 3,5-dimethylphenyl group. This effectively shields the back of the cyclic enone from approach

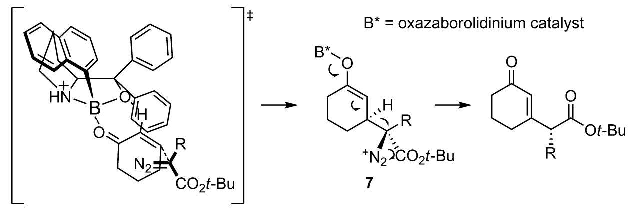


Figure 2. Proposed mechanism for the asymmetric carbon insertion reaction between cyclic enones and *tert*-butyl diazoacetates.

by the diazoacetate. Since the dipole–dipole interaction between two carbonyl groups increases the transition state energy, the *tert*-butyl ester group is placed away from the ketone group. In addition, the sterically bulkier R group is situated on the same side of hydrogen. As a result, the approach of the diazoacetate to the front side of the cyclic enone affords enolate intermediate **7**; subsequent loss of N_2 by β-hydride migration[6] furnishes the (*R*)-β-substituted cyclic enone as the major enantiomer.

In conclusion, the first case of a highly enantiocontrolled catalytic C_{sp^2}–H functionalization reaction of cyclic enones using diazoacetates has been developed. The insertion of a carbon atom of the diazoacetate affords β-functionalized cyclic enones from simple cyclic enones in a single step in excellent yields and enantioselectivities. We believe that the resulting chiral β-functionalized cyclic enones could be highly valuable for the synthesis of useful complex molecules.

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

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

Notes

The authors declare no competing financial interest.

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(13) It is likely that (*S*)-6-methylcyclohex-2-en-1-one reacts slower than the *R* enantiomer because the 6-methyl group of the *S* enantiomer interferes with this $\pi-\pi$ donor−acceptor interaction (Scheme 2).