Communication

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

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/ja402873b • Publication Date (Web): 02 May 2013

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

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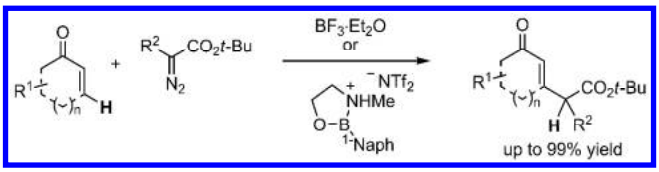
Supporting Information Placeholder

ABSTRACT: Chiral oxazaborolidinium ion catalyzed C_{sp2}-H functionalization of enones using diazoacetate has been developed. Various β-substituted cyclic enones are synthesized with high yield (up to 99%) and high to excellent enantioselectivity (up to 99%). The synthetic utility of this reaction was demonstrated by 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, development of an enantioselective method with a chiral catalyst still remains one of the most challenging topic in current organic synthesis. Transition metal catalyzed asymmetric C-H functionalizations with a diazo compound were reported via intra-[3] and intermolecular[4] methods during the last decade. In addition, recent research reveals that the chiral Lewis acid catalyst is suitable for an enantioselective formyl C_{sp2}-H functionalization.[5]

Recently, we developed a boron Lewis acid catalyzed C_{sp2}-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 a moderate to high yield (Scheme 1). We believed development of an asymmetric carbon insertion reaction of a cyclic enone is 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 ion **1**, which is generated from the corresponding oxazaborolidine by protonation with strong Brønsted acids, behaves as powerful Lewis acid and has proven to be an effective catalyst for asymmetric Diels-Alder reactions,[7a] cyanosilylations,[7b] tandem Michael-aldol reaction,[7c] cyclopropanation[7d], and Roskamp reaction[5b] (Figure 1). There is substantial evidence for the formation of a complex between oxazaborolidinium ion and α,β-unsaturated ketones.[8] We anticipated that the oxazaborolidinium ion is 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 with diazoacetates.

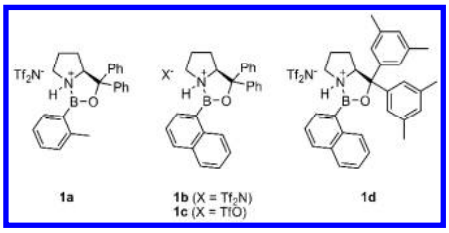
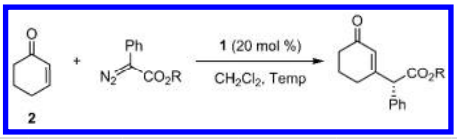


Figure 1. Structure of oxazaborolidinium ion.

Initially, the asymmetric C-H functionalization reaction between 2-cyclohexen-1-one (**2**) and various alkyl phenyldiazoesters was examined in the presence of 20 mol% of the oxazaborolidinium **1a**, which was prepared by activation of its precursor with triflic imide. With methyl and benzyl ester, the desired C-H inserted cyclohexenone was obtained in 44% and 68% yields, respectively, with poor ee (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% (Table 1, entry 3). Our focus then moved to the screening for a suitable catalyst structure. We found 1-naphthyl substituent at the boron center of oxazaborolidinium catalyst (**1b**) effectively produced a C-H insertion product without a decline of stereoselectivity (Table 1, entry 4). Triflic acid activated oxazaborolidinium (**1c**) brought about a significant decrease in yield (Table 1, entry 5). At -20 ºC, the carbon insertion reaction of diazoacetate was successfully carried out and furnished 2-substituted cyclohexenone with improved enantioselectivity (Table 1, entry 6).

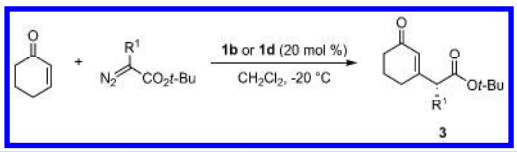
Table 1. Screening of the Reaction Conditions for Oxazaborolidinium Ion-Catalyzed Enantioselective Carbon Insertion Reaction of 2-Cyclohexen-1-one[a].



Entry	Cat	R	Temp. (ºC)	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-cyclohexen-1-one. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

Table 2. Substructure Scope of the Chiral Oxazaborolidinium Ion Catalyzed Carbon Insertion Reaction of 2-Cyclohexen-1-one[a].

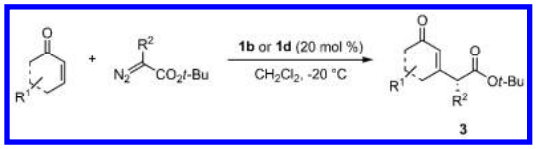


Entry		1	R^1	Time (h)	Yield (%)[b]	ee (%)[c]
1	a	1b	Ph	19	73	85
2	b	1d	Bn	1	99	95
3	c	1d	4-BrBn	1	99	94
4	d	1d	Allyl	1	99	97
5	e	1b	Propargyl	1	99	91
6[d]	f	1d	Me	<1	97	92
7	g	1d	Et	<1	87	96
8	h	1d	iPr	<1	60	97

[a] The reaction was performed using 1.0 equiv of *tert*-butyl diazoester and 1.2 equiv of cyclic enone. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The absolute configuration was determined to be *R*. See supporting information.

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

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

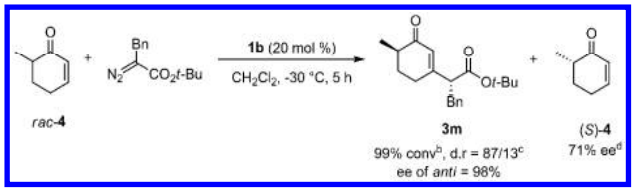


Entry		1	R^2	Product	Time (h)	Yield (%)[b]	ee (%)[c]
1[d]	i	1b	Bn		8	84	89
2[d]	j	1b	Allyl		8	97	90
3[d]	k	1b	Me		3	82	90
4[d, e]	l	1b	Et		3	98	97
5[f]	m	1b	Bn		5	99	95[g]
6[f]	n	1b	Allyl		5	95	96[g]
7	o	1d	Bn		5	96	93
8	p	1b	n-Hex		3	99	86
9[e]	q	1d	Bn		8	75	97
10	r	1d	4-BrBn		5	68	98
11[e]	s	1d	Allyl		13	97	95
12	t	1d	n-Hex		5	91	99
13	u	1d	Bn		2	77	96
14	v	1d	Allyl		2	73	97
15	w	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 yield. [c] Determined by chiral HPLC analysis. [d] Reaction was performed at -5ºC. [e] 40 mol % of oxazaborolidinium catalyst was used. [f] Reaction was performed at -30ºC. [g] Diastereomeric excess of *anti*(major) and *syn*.

Catalytic asymmetric carbon insertion reaction was successfully carried out with substituted cyclohexenone. 5,5-Disubstituted cyclohexenone furnished a corresponding C-H functionalized product with both high yield and enantioselectivities (Table 3, entries 1-4), while *R*-6-methyl-2-cyclohexen-1-one produced the desired product with near quantitative yield and diastereoselectivities (Table 3, entries 5 and 6). To further investigate the substrate scope of the present catalytic system, we applied the catalytic asymmetric C-H functionalization reaction to various sizes of cyclic enones. The asymmetric carbon insertion reaction using an oxazaborolidinium catalyst is a powerful method for preparation of highly enantiopure *β*-substituted 2-cyclopenten-1-one (Table 3, entries 7 and 8). In addition, medium ring sizes of cyclic enones are subjected to C-H functionalization with a range of alkyl diazoesters. In all cases, excellent enantioselectivities are observed (Table 3, entries 9-15). However, the reaction with acyclic enones, for instance methyl vinyl ketone, ethyl vinyl ketone and 3-penten-2-one produced 2-pyrazoline as a major product.[9]

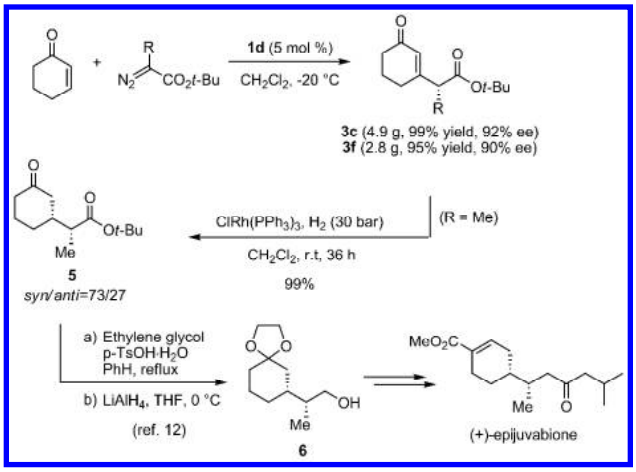
Scheme 2. Enantio- and Diastereoselective Carbon Insertion Reaction of 6-Methyl-2-cyclohexen-1-one[a].



[a] Reaction was performed using 1.0 equiv of *tert*-butyl diazoester and 2.1 equiv of *rac*-6-methyl-2-cyclohexen-1-one. [b] Based on diazoacetate. [c] Determined by NMR analysis. [d] Determined by chiral GC analysis.

The oxazaborolidinium catalyzed C-H functionalization reaction was diastereoselectively performed in the presence of both enantiomers of 6-methyl-2-cyclohexen-1-one. Under the optimized reaction condition, *R*-6-methyl-2-cyclohexen-1-one reacts faster than its *S*-enantiomer and furnished the corresponding *anti*-*β*-substituted cyclic enone in 87/13 d.r, excellent yield, and enantiomeric excess. Chiral gas chromatography analysis revealed the remaining *S*-6-methyl-2-cyclohexen-1-one has 71% ee. A selectivity factor was calculated based on conversion and the ee of 6-methyl-2-cyclohexen-1-one (s = 16.5, Scheme 2).

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



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

(+)-Juvabione and (+)-epijuvabione, a natural sesquiterpene exhibiting selective insect juvenile hormone activity was isolated from Balsam fir by Bowers and coworkers.[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] Using the oxazaborolidinium ion catalyzed carbon insertion reaction, *syn*-cyclohexanone **5** was synthesized from simple 2-cyclohexen-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]

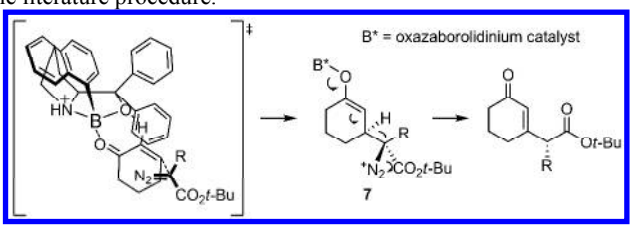


Figure 2. Proposed mechanism for the asymmetric carbon insertion reaction between cyclic enones and *tert*-butyl diazoacetates.

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 coordination mode of the cycloalkenone to an 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 π-π 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 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, approach of the diazoacetate to the front side of the cyclic enone affords the enolate intermediate **7**; subsequent loss of nitrogen molecule by *β*-hydride migration[6] furnishes the (*R*)-*β*-substituted cyclic enone as the major enantiomer.

In conclusion, the first case of highly enantiocontrolled catalytic C_{sp2}-H functionalization reaction of cyclic enones using diazoacetates has been developed. The insertion of a carbon atom of diazoacetates affords *β*-functionalized cyclic enones from simple cyclic enones in a single step, 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 information is available free of charge via the internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This work has supported by grants NRF-2012-R1A6A1040282 (Priority Research Center Program), NRF-2011-0029186 (Mid-career Researcher Program) and the Korea Basic Science Institute (T33409).

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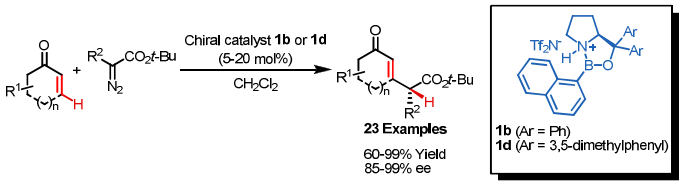
(13) The slower reaction rate of *S*-6-methyl-2-cyclohexen-1-one compared to *R*-enantiomer is likely because the 6-methyl group of *S*-enantiomer interferes with this π-π donor-acceptor interaction (Scheme 2).


Chiral catalyst 1b or 1d
(5-20 mol%)
CH2Cl2
23 Examples
60-99% Yield
85-99% ee
1b (Ar = Ph)
1d (Ar = 3,5-dimethylphenyl)