Communication

Enantioselective Construction of Cyclobutanes: A New and Concise Approach to the Total Synthesis of Piperarborenine B

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Enantioselective Construction of Cyclobutanes: A New and Concise Approach to the Total Synthesis of (+)-Piperarborenine B

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Supporting Information Placeholder

ABSTRACT: A highly diastereoselective and enantioselective Cu(II)/SaBOX catalyzed [2 + 2] cycloaddition of methylidenemalonate with multisubstituted alkenes was developed to furnish the optically active cyclobutanes in high yields with >99/1 dr and up to >99% ee. By applying the newly developed method, the total synthesis of (+)-piperarborenine B was completed in 8 steps from methylidenemalonate and olefin with 17% overall yield, >99/1 dr and 99% ee.

The occurrence of cyclobutane frameworks in many natural products and biologically active compounds (Figure 1) ,[1] as well as the possibility to transform cyclobutanes bearing multiple functional groups to various synthetically useful and architecturally complex structures,[2] has aroused great interests to build these fascinating structures.[3] Although enantioselective protocols have achieved remarkable breakthroughs,[4-6] successful examples of asymmetric cyclobutanation are still limited due to the fact that some of these methods still suffer from limitations such as moderate diastereoselectivity and/or high catalyst loading, as well as limited substrate scope. Accordingly, the appeal of developing new and effective enantioselective methods for the construction of new-fashioned cyclobutanes is urgent and necessary. Methylidenemalonate, which was first prepared by Perkin in 1886,[7] has been found to be a very reactive candidate in the [2 + 2] cycloaddition with electron-rich alkenes to form donor-acceptor (D-A) cyclobutanes in the presence of Lewis acid catalysts since 1983.[2a,2b,8] Recently, Johnson et al.,[2a] Pagenkopf et al.[2b] and Waser et al.[8d] independently developed racemic cyclobutanation reactions, using $Sc(OTf)_3$, $Yb(OTf)_3$, or $FeCl_3{\cdot}Al_2O_3$ as catalysts. However, to the best of our knowledge, the enantioselective version of this reaction has not been realized yet. This can probably be ascribed to the high symmetry of the methylidenemalonate molecule, the remote chiral delivery to the prostereogenic olefin, and the resulting optically active D-A cyclobutanes being likely to decompose into the racemic zwitterions promoted by Lewis acids, which makes the enantioselective cyclobutanation reaction a challenging problem. In this work, we have developed a Cu(II)/BOX (bisoxazoline) catalyzed [2 + 2] cycloaddition of methylidenemalonate with multisubstituted alkenes, furnishing tri- and tetra- substituted cyclobutanes with high diastereoselectivities and excellent ees. In addition, optically active (+)-piperarborenine B was synthesized by employing this newly developed method in 8 steps from methylidenemalonate and olefin with 17% overall yield, >99/1 dr and 99% ee. Herein, we report these preliminary results.

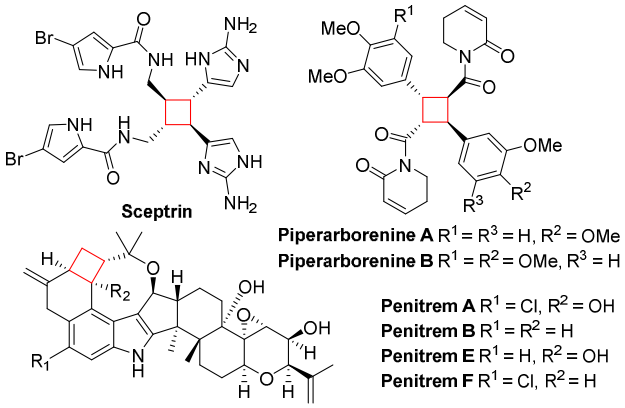
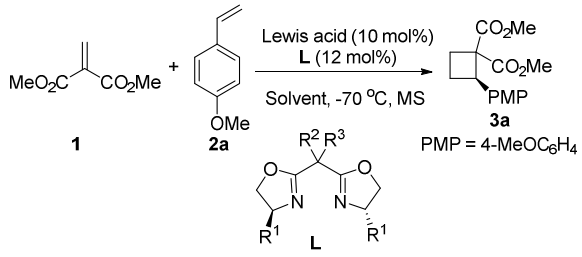


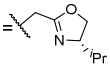
Figure 1. Bioactive natural products containing cyclobutane frameworks.

We began our study by using sidearm-modified bisoxazoline (SaBOX) ligand **L1** with two pendent benzyl groups as sidearms[9,10,11] copper perchlorate as catalyst, and 4-methoxystyrene **2a** as a model substrate (Table 1). When performed at room temperature or 0 °C, the reaction proceeded very fast and completed within a few minutes but without any chiral induction (entries 1, 2). Lowing the reaction temperatures resulted in a dramatic increase of the enantioselectivity. Notably, when the reaction was carried out at −70 °C, 69% ee was obtained with a significant decrease of the yield, despite a full consumption of **2a** (entry 3). However, further study of this reaction has shown that this result was difficult to reproduce (entry 3). Interestingly, when **3a** with a 96% ee was subjected to the above reaction conditions, **3a** was recovered after 2 h in 80% yield but with only 50% ee (Scheme 1, eq. 1). A cross experiment of **3a** (96% ee) with **2m** was also carried out, however, only **3a** with 62% ee was observed and no cross cyclobutanation compound was detected (eq. 2). These results suggest that the cyclobutane product **3a** is probably decom-

posed into a pair of zwitterions at room temperature in the presence of Lewis acids,[2a] resulting in the racemization of **3a**.

Table 1. Reaction Optimization[a]



L1: R^1= ^{i}Pr, R^2 = R^3 = Bn
L2: R^1= ^{sec}Bu, R^2 = R^3 = Bn
L3: R^1= ^{t}Bu, R^2 = R^3 = Bn
L4: R^1= Ph, R^2 = R^3 = Bn
L5: R^1= ^{i}Pr, R^2 = Me, R^3 = Bn
L6: R^1= ^{i}Pr, R^2 = R^3 = Me
L7: R^1= ^{i}Pr, R^2 = R^3 = H
L8: R^1= ^{i}Pr, R^2 = Me, R^3 = 
L9: R^1= ^{i}Pr, R^2 = R^3 = 2-$BrC_6H_4CH_2$
L10: R^1= ^{i}Pr, R^2 = R^3 = 3-$BrC_6H_4CH_2$
L11: R^1= ^{i}Pr, R^2 = R^3 = 4-$BrC_6H_4CH_2$

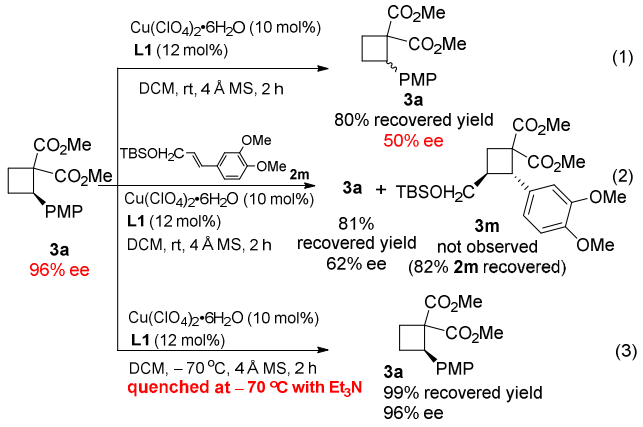
entry	Lewis acids	solvent	L	yield (%)[b]	ee (%)[c]
1[d,f]	$Cu(ClO_4)_2·6H_2O$	CH_2Cl_2	**L1**	48	0
2[e,f]	$Cu(ClO_4)_2·6H_2O$	CH_2Cl_2	**L1**	91	0
3[f,g]	$Cu(ClO_4)_2·6H_2O$	CH_2Cl_2	**L1**	19	63~69
4[f]	$Cu(ClO_4)_2·6H_2O$	CH_2Cl_2	**L1**	28	72
5[f]	$Cu(OTf)_2$	CH_2Cl_2	**L1**	41	70
6[f]	$Ni(ClO_4)_2·6H_2O$	CH_2Cl_2	**L1**	29	0
7	$Cu(ClO_4)_2·6H_2O$	CH_2Cl_2	**L1**	45	72
8	$Cu(ClO_4)_2·6H_2O$	THF	**L1**	41	93
9	$Cu(ClO_4)_2·6H_2O$	THF	**L2**	7	71
10	$Cu(ClO_4)_2·6H_2O$	THF	**L3**	7	56
11	$Cu(ClO_4)_2·6H_2O$	THF	**L4**	10	63
12	$Cu(ClO_4)_2·6H_2O$	THF	**L5**	39	92
13	$Cu(ClO_4)_2·6H_2O$	THF	**L6**	22	82
14	$Cu(ClO_4)_2·6H_2O$	THF	**L7**	48	83
15	$Cu(ClO_4)_2·6H_2O$	THF	**L8**	trace	-
16	$Cu(ClO_4)_2·6H_2O$	THF	**L9**	82	97
17	$Cu(ClO_4)_2·6H_2O$	THF	**L10**	77	95
18	$Cu(ClO_4)_2·6H_2O$	THF	**L11**	54	95

[a]Reaction conditions: Lewis acid (0.04 mmol), L (0.048 mmol), 5 Å MS (100 mg), **1** (1.0 mmol), and **2a** (0.4 mmol) in 4.0 mL of solvent, After **1** or **2a** was consumed, Et_3N was added to quench the reaction at the reaction temperature. [b]Isolated yields. [c]Determined by HPLC using a chiral stationary. [d]Reaction performed at room temperature. [e]Reaction performed at 0 °C. [f] 4 Å MS was used as additive. [g] Without Et_3N quench.

Thus, it was envisioned that poisoning the catalyst may inhibit the racemization. As expected, the ee of cyclobutane **3a** was maintained under the reaction conditions for 2 h after being quenched by NEt_3 at – 70 °C (eq. 3). On the basis of these results, we improved the work-up procedure by quenching the reaction with NEt_3 at – 70 °C after the reaction was completed. Under these conditions, the ee was enhanced slightly and could be readily reproduced (entry 7). Remarkably, by means of quenching the reaction at low temperature, the racemization of the resulting D-A cyclobutanes was effectively suppressed, which provides a promising solution in the enantioselective catalysis involving enantio-labile compounds.

With the reproducible reaction conditions in hand, we turned our focus on further optimization of the Lewis acid, solvents

Scheme 1. Mechanistic studies

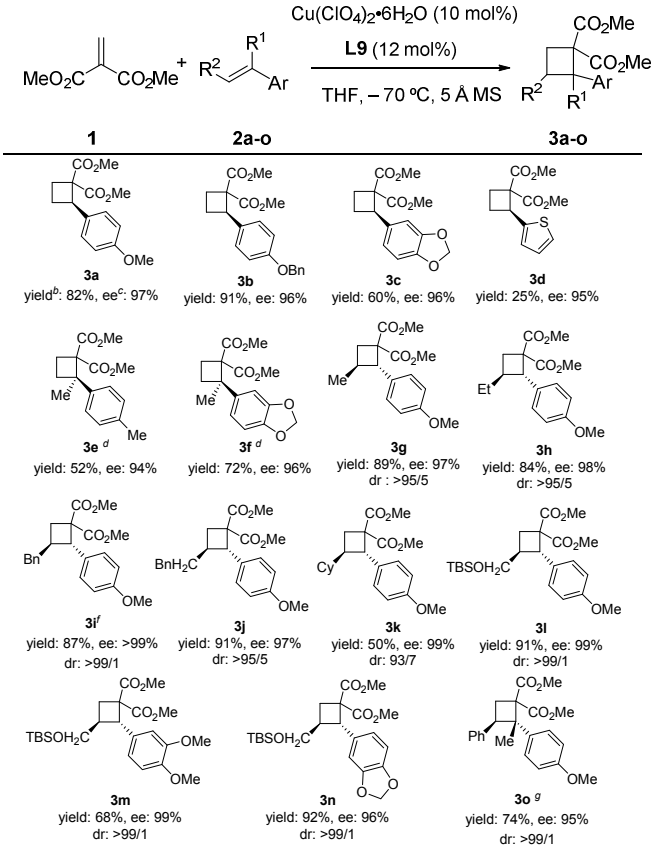


and ligands (Table 1). It was found that both $Cu(OTf)_2$ and $Ni(ClO_4)_2$ could afford the desired product (entries 5, 6).[12] Interestingly, the yield was promoted to 45% without any loss of the enantioselectivity, when 5 Å MS (molecule sieves) was used instead of 4 Å MS as additive, (entry 7). Notably, when THF was employed as solvent, a significant improvement of the enantiocontrol was obtained with a 93% ee, but with a still moderate yield (entry 8). We then switched to THF as solvent to study the influence of ligands.[12] As can be seen from Table 1, the substituent of the BOX (bisoxazoline) ligand has a great impact on the stereocontrol. It was found that increasing the steric demand of the R^1 group led to a dramatic decrease of both yield and enantioselectivity (entries 8-10). **L4** bearing an aromatic R^1 group could not give a better enantioselectivity (entry 11). Thus, the chiral BOX ligand **L1** derived from *L*-valinol was found to be best in terms of both ee value and yield (41% yield, 93% ee, entry 8). When ligands **L5**-**L7** were applied in the reaction, the sidearm effect of the ligands was clearly revealed.[10] For ligands **L6** and **L7** without sidearm groups, a decrease of enantioselectivity was observed (entries 13-14). In addition, trisoxazoline (TOX) **L8** containing a *L*-valinol derived oxazolinyl group as sidearm could barely promote the reaction (entry 15). Since the sidearms of the ligands played a key role in the enantiocontrol of the cyclobutanation, we tried to modify the sidearms and synthesized ligands **L9**-**L11** with different pendant groups R^2 and R^3.[12] All these ligands showed increased ee values and yields (entries 16-18) in comparison with **L1**. Of the ligands tested, **L9** bearing 2-$BrC_6H_4CH_2$ groups as sidearms gave the best result, leading to the desired product in 82% yield with 97% ee (entry 16).

Under the optimized conditions, the substrate scope was next explored (Table 2). Using methylidenemalonate **1**, a broad range of alkenes worked well. For substituted styrenes **2a**-**2c**, with electron-donating groups such as MeO- or BnO- in *para*-position of the phenyl, the corresponding D–A cyclobutanes (**3a**, **3b**) were isolated in 82–91% yields with 96% ee, respectively. 3,4-Disubstituted piperonyl alkene **2c** worked well in this reaction with the same enantioselectivity. Thienyl substituted cyclobutane **3d** could also be furnished in 95% ee. The absolute configuration of **3d** was confirmed by single-

crystal X-ray analyses.[13] For 1,1-disubstituted alkenes **2e-2f**, the desired products were obtained with up to 72% yields and up to 96% ee, when the reaction was carried out at – 80 °C,

Table 2. Substrate Scope[a]

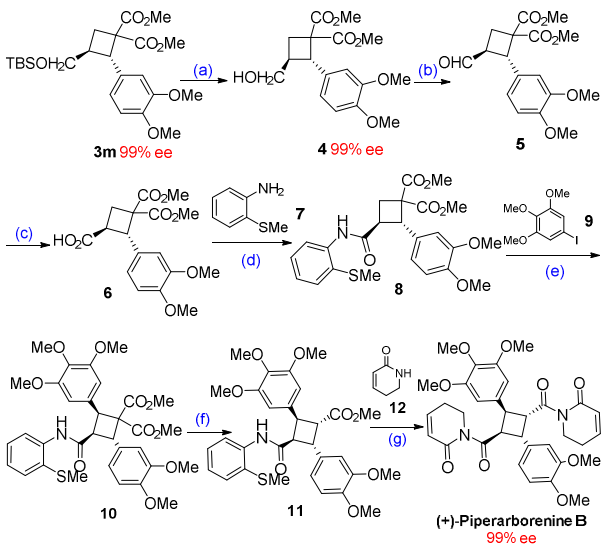


[a]Reaction conditions: $Cu(ClO_4)_2 \cdot 6H_2O$ (0.04 mmol), **L9** (0.048 mmol), 5 Å MS (100 mg), **1** (1.0 mmol), and **2** (0.4 mmol) in 4.0 mL of THF, quenched by Et_3N at –70 °C. [b]Isolated yield. [c]Determined by HPLC using a chiral stationary. [d]$Cu(OTf)_2$ (0.04 mmol), **L1** (0.048 mmol) as catalyst, 2.0 mL THF as solvent, reaction at –80 °C. [e] Determined by ^1H NMR. [f] Reaction at -50 °C. [g]The absolute configuration of **3o** has not been determined.

using $Cu(OTf)_2$ as the catalyst. Notably, a variety of *trans* disubstituted alkenes **2k-2g** proved to be suitable substrates for the current catalytic system, giving the corresponding products in good yields with excellent diastereoselectivity and enantioselectivity (93/7–>99/1 dr, 97–>99% ee). To test the functional group tolerance of the reaction, a TBS protected hydroxyl group was introduced into the substrates, affording **3l-3n** in 68-92% yields with >99/1 dr and 96–>99% ee. The absolute configuration of **3g** was determined by vibrational circular dichroism (VCD).[12] To our delight, the tri-substituted alkene **2o** was also compatible with this reaction, delivering cyclobutane **3o**, bearing a full-carbon chiral center in 74% yield with >99/1 dr and 93% ee. Unfortunately, 2-substituted methylidenemalonate proved to be inert under the current reaction conditions.[12]

Piperarborenine B (Figure 1), which was isolated from the stem of *Piper arborescens* in 2004, has shown *in vitro* cytotoxicity against cancer cell lines (P-388, HT-29, and A549, IC_{50} < 1.46 μg/mL)[1c,1e], and thus has received research interests in the area of organic synthesis.[14] In 2011, Baran and co-workers applied an elegant sequential cyclobutane C-H arylation strategy in their total synthesis of racemic piperarborenine B.[14a,15] With cyclobutane **3m** in hand, we attempted the enantioselective total synthesis of piperarborenine B (Scheme 2). By deprotection of **3m** with TBAF, TBS was removed to give **4** in a quantitative yield. Swern oxidation of **4** resulted in the formation of aldehyde **5** which was further oxidized by oxone to form acid **6**. Condensation of **6** with **7** by EDCI led to amide **8**. With the amide directing group, the 3,4,5-trimethoxylphenyl group could be installed selectively to afford **10**. After removing one of the ester groups in **10** by using LiCl, a single diastereoisomer **11** was obtained. Boc protection of the amideand subsequent hydrolysis of the amide and ester group afforded a diacid which was amidated to give (+)-piperarborenine B. Thus, by employing the current reaction, total synthesis of (+)-piperarborenine B could be acomplished in 8 steps from methylidenemalonate and **2m** with 17% overall yield and 99% ee. During the preparation of this paper, a beautiful work on the enantioselective total synthesis of (+)-piperarborenine B was reported by Fox and co-workers in 10 steps from veratraldehyde with 8% overall yield and 92% ee.[14b]

Scheme 2. Total Synthesis of (+)-Piperarborenine B[a]



[a]Reagent and conditions: (a) TBAF (1.5 equiv), THF, rt, 99%; (b) DMSO (2.0 equiv), $(COCl)_2$ (1.3 equiv), 92%; (c) Oxone (0.9 equiv), DMF; (d) EDCI (1.2 equiv), DMAP (2.4 equiv), **7** (1.1 equiv), DCM, 79% 2 steps; (e) **9** (2.0 equiv), $Pd(OAc)_2$ (0.3 equiv), Ag_2CO_3 (1.5 equiv), PivOH (1.0 equiv), toluene, 130 °C, 72h, 70% b.r.s.m; (f) LiCl (10 equiv), H_2O (10 equiv), DMSO, 130 °C, 48h, 93%; (g) $(Boc)_2O$ (1.5 equiv), DMAP (0.1 equiv), MeCN; then LiOH (6 equiv), H_2O_2 (10 equiv), THF/H_2O; $(COCl)_2$, DMF, THF, 2h; 12 (3 equiv) , toluene, 4 Å MS, 80 °C, 12h, 69%.

In summary, the first asymmetric [2 + 2] cycloaddition of dimethyl methylidene malonate with polysubstituted olefins has been developed using Cu(II)/SaBOX as the catalyst, giving optically active cyclobutanes in high yields with >99/1 dr

and up to >99% ee. The reaction has a broad substrate scope, in which mono-, di-, and tri-substituted alkenes all work well. This newly developed method has been applied to the enantioselective total synthesis of (+)-piperarborenine B which was completed in 8 steps from methylidenemalonate and **2m** with 17% overall yield and 99% ee. Further application of this reaction is an on-going project in our laboratory.

ASSOCIATED CONTENT

Experimental procedures, complete characterization data, including NMR spectra and HPLC data as well as CIF data of **3d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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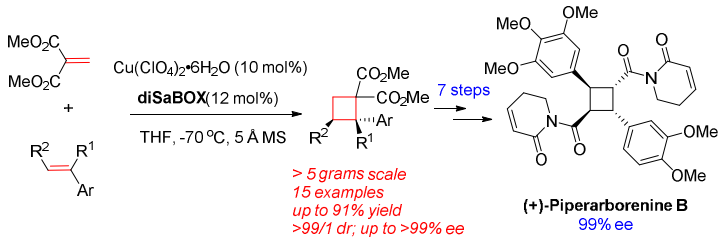
(12) For details, see the Supporting Information.

(13) The crystallographic data of **3d** can be found in Supporting Information.

(14) (a) Gutekunst, W. R.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 19076-19079. (b) Panish, R. A.; Chintala, S. R.; Fox, J. M. *Angew. Chem., Int. Ed.* **2016**, *55*, 4983–4987.

(15) For C-H activation in cyclobutane synthesis, see: (a) Gutekunst, W. R.; Baran, P. S. *J. Org. Chem.* **2014**, *79*, 2430-2452. (b) Chapman, L. M.; Beck, J. C.; Wu, L. Reisman. S. E. *J. Am. Chem. Soc.* **2016** *138*, 9803-9806.


MeO2C
MeO2C
+
R2
R1
Ar
Cu(ClO4)2•6H2O (10 mol%)
diSaBOX(12 mol%)
THF, -70 °C, 5 Å MS
CO2Me
CO2Me
Ar
R2
R1
7 steps
MeO
OMe
MeO
N
O
O
N
O
O
OMe
OMe
> 5 grams scale
15 examples
up to 91% yield
>99/1 dr; up to >99% ee
(+)-Piperarborenine B
99% ee