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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

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

The occurrence of cyclobutane frameworks in many natural products and biologically active compounds (Figure 1),[1]

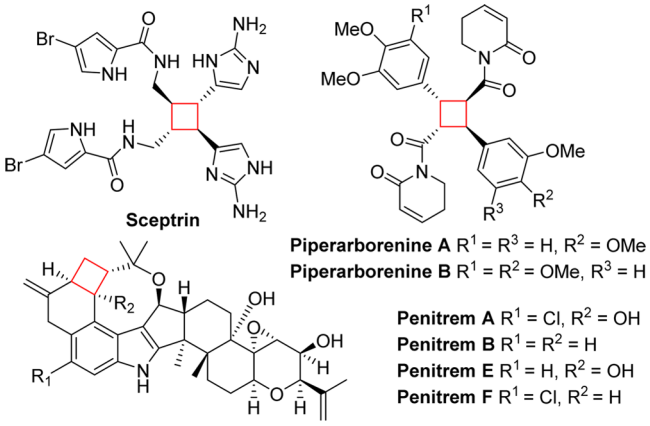

Figure 1. Bioactive natural products containing cyclobutane frameworks.

as well as the possibility to transform cyclobutanes bearing multiple functional groups to various synthetically useful and architecturally complex structures,[2] has aroused great interest in building these fascinating structures.[3] Although enantioselective protocols have achieved remarkable breakthroughs,[4−6] successful examples of asymmetric cyclobutanation are still limited because 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 [2 + 2] cycloadditions with electron-rich alkenes to form donor−acceptor (D−A) cyclobutanes in the presence of Lewis acid catalysts since 1983.[2a,b,8] Recently, Parsons and Johnson,[2a] Moustafa and Pagenkopf,[2b] and de Nanteuil and Waser[8d] independently developed racemic cyclobutanation reactions using $Sc(OTf)_3$, $Yb(OTf)_3$, or $FeCl_3{\cdot}Al_2O_3$ as the catalyst. However, to the best of our knowledge, an 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 fact that the resulting optically active D−A cyclobutanes are 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)/bisoxazoline (BOX)-catalyzed [2 + 2] cycloaddition of methylidenemalonate with multisubstituted alkenes that furnishes tri- and tetrasubstituted cyclobutanes with high diastereoselectivities and excellent ee's. In addition, optically active (+)-piperarborenine B was synthesized with this newly developed method in eight steps from methylidenemalonate and olefin in 17% overall yield with >99/1 dr and 99% ee. Herein we report these preliminary results.

We began our study by using side-arm-modified BOX (SaBOX) ligand **L1** with two pendant benzyl groups as side arms[9−11] and copper perchlorate as the 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 was complete within a few minutes but without any chiral induction (entries 1 and 2). Lowering the reaction temperature resulted in a dramatic increase in the enantioselectivity. Notably, when the reaction was carried out at −70 °C, 69% ee was obtained with a significant decrease in the yield, despite full consumption of **2a** (entry 3). However, further study of this reaction showed that this result was difficult to reproduce (entry 3). Interestingly, when **3a** with 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, but only **3a** with 62% ee was observed, and no cross-cyclobutanation compound was detected (eq 2). These results suggest that the cyclobutane product **3a** probably decomposes into a pair of zwitterions at room temperature in

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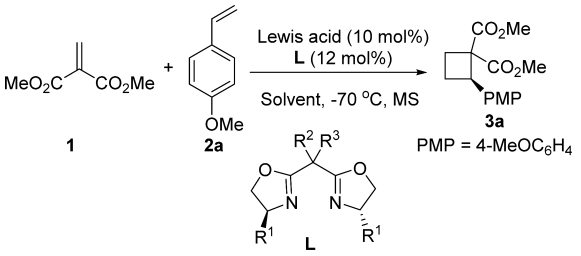
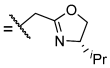
Table 1. Reaction Optimization[a]

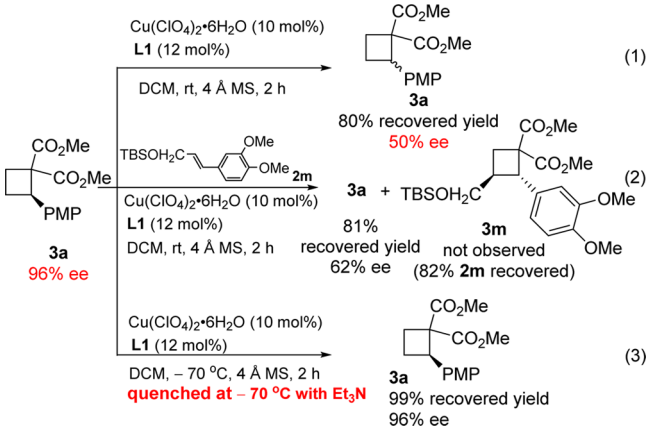


L1: R^1= ^{i}Pr, R^2 = R^3 = Bn
L2: R^1= ^{sec}Bu, R^2 = R^3 = Bn
L3: R^1= ^{t}Bu, R^2 = R^3 = Bn
L4: R^1= Ph, R^2 = R^3 = Bn
L5: R^1= ^{i}Pr, R^2 = Me, R^3 = Bn
L6: R^1= ^{i}Pr, R^2 = R^3 = Me
L7: R^1= ^{i}Pr, R^2 = R^3 = H
L8: R^1= ^{i}Pr, R^2 = Me, R^3 = 
L9: R^1= ^{i}Pr, R^2 = R^3 = 2-$BrC_6H_4CH_2$
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 acid	solvent	L	yield (%)[b]	ee (%)[c]
1[d,f]	$Cu(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2	**L1**	48	0
2[e,f]	$Cu(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2	**L1**	91	0
3[f,g]	$Cu(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2	**L1**	19	63−69
4[f]	$Cu(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2	**L1**	28	72
5[f]	$Cu(OTf)_2$	CH_2Cl_2	**L1**	41	70
6[f]	$Ni(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2	**L1**	29	0
7	$Cu(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2	**L1**	45	72
8	$Cu(ClO_4)_2{\cdot}6H_2O$	THF	**L1**	41	93
9	$Cu(ClO_4)_2{\cdot}6H_2O$	THF	**L2**	7	71
10	$Cu(ClO_4)_2{\cdot}6H_2O$	THF	**L3**	7	56
11	$Cu(ClO_4)_2{\cdot}6H_2O$	THF	**L4**	10	63
12	$Cu(ClO_4)_2{\cdot}6H_2O$	THF	**L5**	39	92
13	$Cu(ClO_4)_2{\cdot}6H_2O$	THF	**L6**	22	82
14	$Cu(ClO_4)_2{\cdot}6H_2O$	THF	**L7**	48	83
15	$Cu(ClO_4)_2{\cdot}6H_2O$	THF	**L8**	trace	–
16	$Cu(ClO_4)_2{\cdot}6H_2O$	THF	**L9**	82	97
17	$Cu(ClO_4)_2{\cdot}6H_2O$	THF	**L10**	77	95
18	$Cu(ClO_4)_2{\cdot}6H_2O$	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 phase. [d]The reaction was performed at room temperature. [e]The reaction was performed at 0 °C. [f]4 Å MS was used as an additive. [g]Without Et_3N quench.

Scheme 1. Mechanistic Studies



the presence of Lewis acids,[2a] resulting in the racemization of **3a**.

Thus, it was envisioned that poisoning the catalyst would inhibit the racemization. As expected, the ee of cyclobutane **3a** was maintained under the reaction conditions for 2 h after quenching with NEt_3 at −70 °C (eq 3). On the basis of these results, we improved the workup 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, providing a promising solution in the enantioselective catalysis involving enantiolabile compounds.

With the reproducible reaction conditions in hand, we turned our focus on further optimization of the Lewis acid, solvents, and ligands (Table 1). It was found that both $Cu(OTf)_2$ and $Ni(ClO_4)_2$ could afford the desired product (entries 5 and 6).[12] Interestingly, the yield was promoted to 45% without any loss of enantioselectivity when 5 Å molecular sieves (MS) was used instead of 4 Å MS as an additive (entry 7). Notably, when tetrahydrofuran (THF) was employed as the solvent, a significant improvement in the enantiocontrol was obtained (93% ee), but still with a moderate yield (entry 8). We then switched to THF as the solvent to study the influence of the ligand.[12] As can be seen from Table 1, the substituent of the BOX 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 in both the yield and enantioselectivity (entries 8−10). **L4** bearing an aromatic R^1 group could not give 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 effect of the ligand side arm was clearly revealed.[10] For ligands **L6** and **L7** without side-arm groups, a decrease in enantioselectivity was observed (entries 13 and 14). In addition, trisoxazoline (TOX) ligand **L8** containing an L-valinol-derived oxazolinyl group as the side arm could barely promote the reaction (entry 15). Since the side arms of the ligands play a key role in the enantiocontrol of the cyclobutanation, we modified the side arms by synthesizing ligands **L9**−**L11** with different pendant groups R^2 and R^3.[12] All of 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 side arms gave the best results, 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). With methylidenemalonate **1**, a broad range of alkenes worked well. For substituted styrenes **2a**−**c**, with electron-donating groups such as MeO or BnO at the para position of the phenyl group, the corresponding D−A cyclobutanes **3a** and **3b** were isolated in 82−91% yield with 96% ee, respectively. 3,4-Disubstituted piperonyl alkene **2c** worked well in this reaction with the same enantioselectivity. Thienyl-substituted cyclobutane **3d** was also furnished with 95% ee. The absolute configuration of **3d** was confirmed by single-crystal X-ray analysis.[13] For 1,1-disubstituted alkenes **2e** and **2f**, the desired products were obtained in up to 72% yield with up to 96% ee when the reaction was carried out at −80 °C using $Cu(OTf)_2$ as the catalyst. Notably, a variety of trans-disubstituted alkenes **2g**−**k** proved to be suitable substrates for the current catalytic system, giving the corresponding products in good yields with excellent diastereoselectivities and enantioselectivities (93/7 to >99/1 dr, 97 to >99% ee). To

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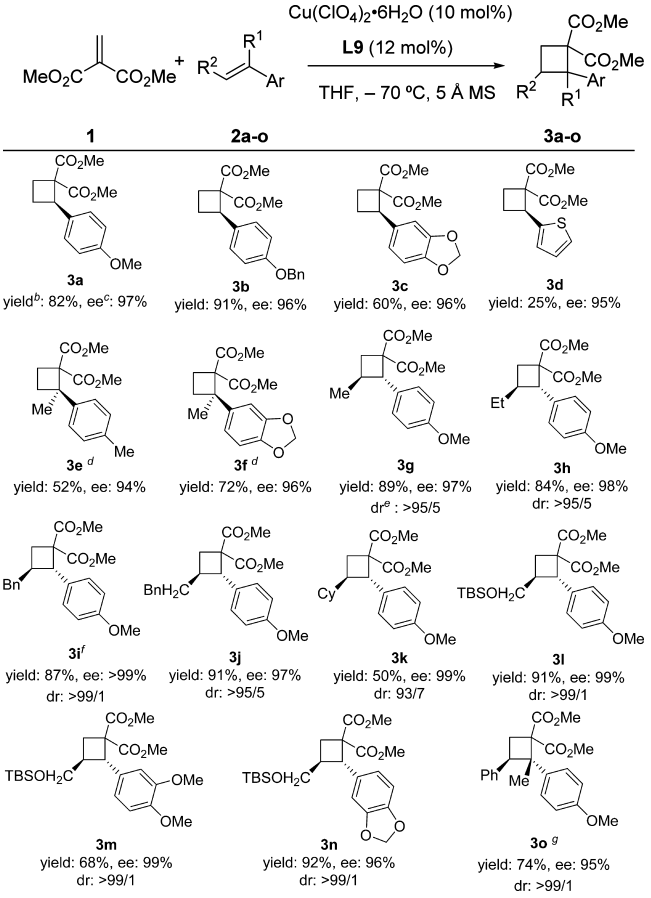
Table 2. Substrate Scope[a]

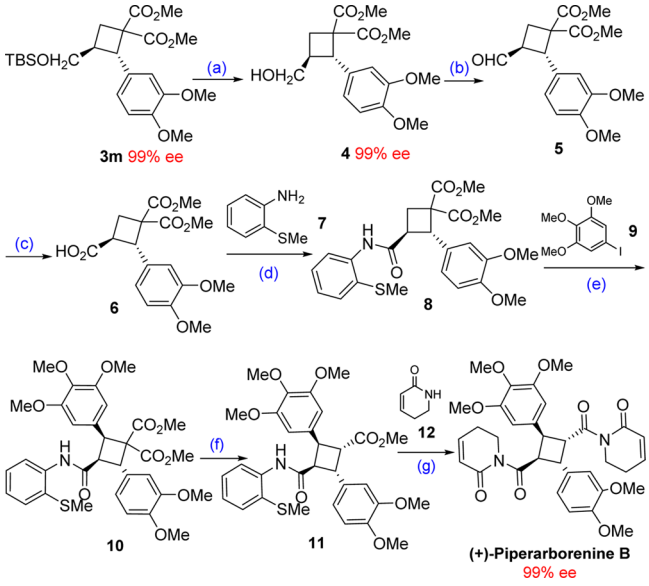


[a]Reaction conditions: $Cu(ClO_4)_2 \cdot 6H_2O$ (0.04 mmol), **L9** (0.048 mmol), 5 Å MS (100 mg), **1** (1.0 mmol), and **2** (0.4 mmol) in 4.0 mL of THF, quenched by Et_3N at −70 °C. [b]Isolated yield. [c]Determined by HPLC using a chiral stationary phase. [d]$Cu(OTf)_2$ (0.04 mmol), **L1** (0.048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

test the functional group tolerance of the reaction, a *tert*-butyldimethylsilyl (TBS)-protected hydroxyl group was introduced into the substrates, affording **3l**−**n** in 68−92% yield with >99/1 dr and 96 to >99% ee. The absolute configuration of **3g** was determined by vibrational circular dichroism (VCD).[12] To our delight, the trisubstituted 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,e] and thus has received research interest 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

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



[a]Reagents 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% over two 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, 72 h, 70% brsm; (f) LiCl (10 equiv), H_2O (10 equiv), DMSO, 130 °C, 48 h, 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, 2 h; **12** (3 equiv), toluene, 4 Å MS, 80 °C, 12 h, 69%.

oxidized by oxone to form acid **6**. Condensation of **6** with **7** using EDCI led to amide **8**. With the amide directing group, the 3,4,5-trimethoxyphenyl group could be installed selectively to afford **10**. Removal of one of the ester groups in **10** using LiCl afforded **11** as a single diastereoisomer. Boc protection of the amide and subsequent hydrolysis of the amide and ester groups afforded a diacid that was amidated to give (+)-piperarborenine B. Thus, by means of the current reaction, the total synthesis of (+)-piperarborenine B could be accomplished in eight steps from methylidenemalonate and **2m** in 17% overall yield with 99% ee. During the preparation of this paper, a beautiful work on the enantioselective total synthesis of (+)-piperarborenine B in 10 steps from veratraldehyde in 8% overall yield with 92% ee was reported by Fox and co-workers.[14b]

In summary, the first asymmetric [2 + 2] cycloaddition of dimethyl methylidenemalonate 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 trisubstituted alkenes all work well. This newly developed method has been applied to the enantioselective total synthesis of (+)-piperarborenine B, which was completed in eight steps from methylidenemalonate and **2m** in 17% overall yield with 99% ee. Further application of this reaction is an ongoing project in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08279.

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Experimental procedures, complete characterization data, NMR spectra, HPLC data, and crystallographic data for **3d** (PDF)

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Notes

The authors declare no competing financial interest.

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