Concise Report

[2+2] Cyclization, Cyclobutane, Copper catalyst, Asymmetric catalysis, Diastereoselectivity, Enantioselecticity

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Highly Stereoselective Direct Construction of Diaryl-Substituted Cyclobutanes†

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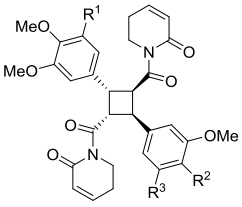
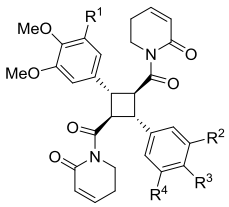
Summary of main observation and conclusion A copper catalyzed stereoselective [2+2] cyclization has been developed, providing a concise protocol to the direct construction of diaryl-substituted cyclobutanes in up to 99% yield with up to >95/5 dr. Meanwhile, the enantioselective version of this reaction has also been achieved, leading to a series of optically active diaryl-substituted cyclobutanes with up to 94% ee.

Background and Originality Content

Diaryl-substituted cyclobutanes are core structures of a number of biologically active natural products.[1] For example, a family of cyclobutanoid amides (Figure 1) isolated from the stem of piper arborescens were found potent *in vitro* cytotoxicity against cancer cell lines (P-388, HT-29, and A549, IC_{50} < 4 μg/mL),[1c,1e] and thus arouse broad research interests of organic chemists towards the construction of multi-substituted cyclobutanes.



Piplartine-dimer A
$R^1 = R^2 = R^3 = OMe$
Piperarborenine A
$R^1 = R^3 = H$, $R^2 = OMe$
Piperarborenine B
$R^1 = R^2 = OMe$, $R^3 = H$
Piperarboresine
$R^1 = OMe$, R^2, $R^3 = OCH_2O$



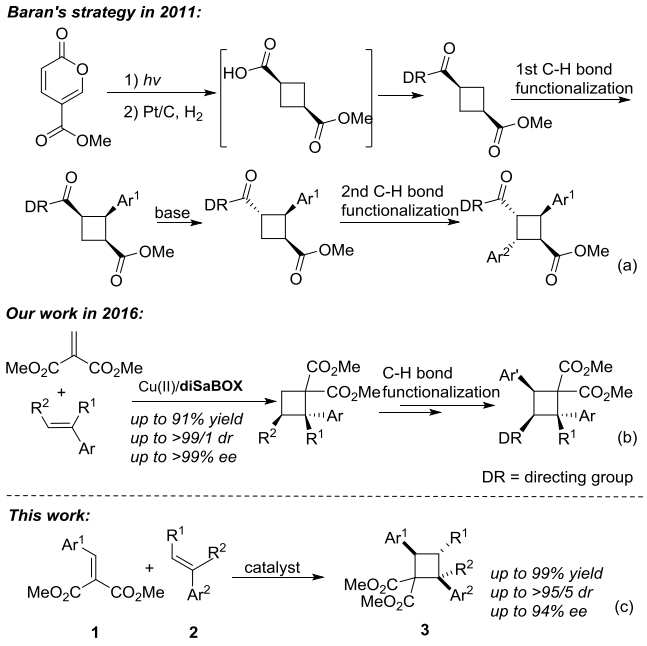
Piperarborenine C $R^1 = R^2 =$ OMe, R^3, $R^4 =$ OMe
Piperarborenine D $R^1 = R^2 = R^3 =$ OMe, $R^4 = H$
Piperarborenine E $R^1 = H$, $R^2 =$ OMe, R^3, $R^4 = OCH_2O$

Figure 1 Biologically active cyclobutanoid amides.

Many efficient methods have been established aiming to the building of cyclobutanes,[2] including the ring expansion reactions from cyclopropanes,[3] the ring contraction reactions from five or six membered rings,[4] the photo promoted [2+2] cycloaddition reactions,[5] as well as the [2+2] tandem cyclizations.[6] However, owing to the unique structure of cyclobutanoid amide natural products, bearing two aryl groups on the 2,4-positions of the cyclobutanes, there are still very limited protocols to construct such multi-substituted cylcobutane unit.

In 2011, Baran and coworkers reported a synthesis of cyclobutane by employing a photo promoted process, and then in the use of C—H bond functionalization strategy to introduce the two aryl groups on the four-membered ring (Scheme 1a).[7] In 2016, we have developed a copper catalyzed highly diastereoselective and enantioselective formal [2+2] cycloaddition of methylidenemalonate with styrene, which provided a mono-aryl substituted cyclobutane in high yield with excellent dr and ee value. Furthermore, by the same strategy of Baran, the second aryl group was assembled by C—H bond functionalization *via* introducing and removing a directing group (Scheme 1b).[8] To the best of our knowledge, efficient synthetic methods in the direct construction of the important diaryl-substituted cyclobutane unit, are still barely been demonstrated. Recently, we have realized the copper catalyzed stereoselective [2+2] cyclizations of arylmethylidenemalonates with substituted styrenes, furnishing a series of multi-substituted cyclobutanes bearing two aryl groups on the 2,4-positions in good to high yields with up to >95/5 dr (Scheme 1c). Meanwhile, the enantioselective version of this reaction was also achieved in the presence of a chiral bisoxazoline (BOX) ligand with up to 94% ee. Herein, we report the preliminary results.

Scheme 1 Construction of diaryl-substituted cyclobutanes



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† Dedicated to Professor Mingyuan He on the occasion of his 80th birthday.

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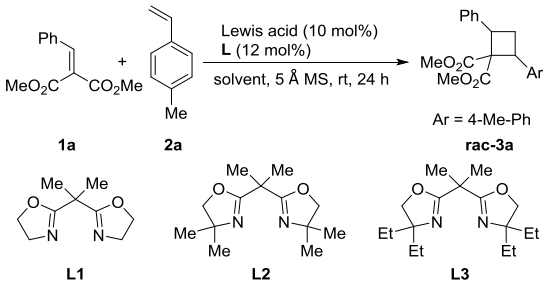
Results and Discussion

Initially, the $Cu(SbF_6)_2$/**L1** complex was *in-situ* generated with $CuBr_2$, $AgSbF_6$ and BOX, which was employed as a catalyst to promote the synthesis of cyclobutane **3a** in the [2+2] cyclization reaction (11% yield, 61/39 dr, Table 1, entry 1). A simple screening of the BOX ligand showed that **L2** though gave only 8% yield, the diastereoselectivity was the best among **L1**—**L3** (entries 1—3).

Table 1 Optimization of racemic reaction conditions



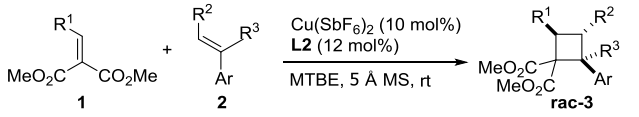
Entry[a]	Lewis acid	L	Solvent	Yield[b]/%	dr[c]
1	$Cu(SbF_6)_2$	**L1**	THF	11	61/39
2	$Cu(SbF_6)_2$	**L2**	THF	8	67/33
3	$Cu(SbF_6)_2$	**L3**	THF	NR	—
4	$Cu(ClO_4)_2·6H_2O$	**L2**	THF	NR	—
5	$Cu(OTf)_2$	**L2**	THF	NR	—
6	$Cu(SbF_6)_2$	**L2**	1,4-dioxane	12	70/30
7	$Cu(SbF_6)_2$	**L2**	Et_2O	83	70/30
8	$Cu(SbF_6)_2$	**L2**	MTBE	83	88/12
9	$Cu(SbF_6)_2$	**L2**	toluene	7	65/35
10	$Cu(SbF_6)_2$	**L2**	DCM	trace	—
11	$Cu(SbF_6)_2$	**L2**	CH_3CN	trace	—
12[d]	$Cu(SbF_6)_2$	**L2**	MTBE	31	88/12

[a] Carried out at rt under argon atmosphere: Lewis acid (0.02 mmol), **L** (0.024 mmol), **1a/2a** = 1/2.0 (**1a**, 0.2 mmol), 5 Å MS (25.0 mg), solvent (1.0 mL). [b] Yields were determined by ^{1}H NMR spectra with 1,1,2,2-tetrachloroethane (TTCE) as internal standard. [c] The dr values were determined by ^{1}H NMR spectra of the crude reaction mixtures. [d] Without 5 Å MS.

Counterion was found to influence the reactivity. For example, when $Cu(ClO_4)_2·6H_2O$ and $Cu(OTf)_2$ were used as Lewis acid, the cyclobutanation did not occur (entries 4—5). Ethers were found as suitable solvents in this reaction. 1,4-Dioxane could slightly improve the diastereoselectivity to give 70/30 dr (entry 6). When diethyl ether was employed, the yield of this reaction was increased dramatically (83% yield, entry 7). With methyl *tert*-butyl ether (MTBE) as solvent, the diastereoselectivity was further improved and 88/12 dr was obtained (entry 8). Toluene was also used as solvent, but both the yield and dr value were unsatisfied (entry 9). With other solvents such as dichloromethane (DCM) and acetonitrile, only trace amount of desired product was obtained (entries 10—11). The 5 Å molecular sieve (MS) was found quite important to obtain good yield, without which the reaction only gives 31% yield (entry 12).

Under the optimized reaction conditions (Table 1, entry 8), the substrate scope of the racemic cyclobutanation was investigated. As shown in Table 2, arylmethylidenemalonates bearing different electron deficient substituents at the aryl group reacted smoothly, such as 4-F, 4-Cl, 4-Br, 4-NO_2, 4-CN, and 4-CF_3, leading to the corresponding [2+2] cyclization products (**rac-3b**—**3g**) in 80%—99% yields with 70/30—88/12 dr (Table 2, entries 2—7).[12] With a methyl ester group at the *para*-position of a benzene ring,

Table 2 Substrate scope of racemic reactions



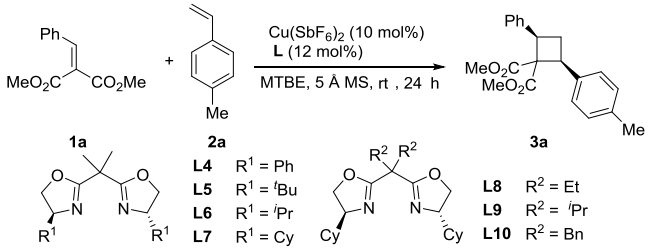
Entry[a]	R^1	R^2	R^3	Ar	3	*t*/h	Yield[b]/%	dr[c]
1	Ph	H	H	4-MeC_6H_5	**rac-3a**	24	83	88/12
2	4-FC_6H_5	H	H	4-MeC_6H_5	**rac-3b**	50	99	81/19
3	4-ClC_6H_5	H	H	4-MeC_6H_5	**rac-3c**	67	80	86/14
4	4-BrC_6H_5	H	H	4-MeC_6H_5	**rac-3d**	67	83	85/15
5	4-$NO_2C_6H_5$	H	H	4-MeC_6H_5	**rac-3e**	47	96	71/29
6	4-CNC_6H_5	H	H	4-MeC_6H_5	**rac-3f**	47	96	74/26
7	4-$CF_3C_6H_5$	H	H	4-MeC_6H_5	**rac-3g**	30	99	70/30
8	4-$MeO_2CC_6H_5$	H	H	4-MeC_6H_5	**rac-3h**	47	98	74/26
9	4-PhC_6H_5	H	H	4-MeC_6H_5	**rac-3i**	68	59	88/12
10	Me	H	H	4-MeC_6H_5	**rac-3j**	17	55	>95/5
11	Et	H	H	4-MeC_6H_5	**rac-3k**	61	51	90/10
12	^{n}Pr	H	H	4-MeC_6H_5	**rac-3l**	53	58	92/8
13	Cy	H	H	4-MeC_6H_5	**rac-3m**	78	99	91/9
14	$BnCH_2$	H	H	4-MeC_6H_5	**rac-3n**	23	94	93/7
15	CH_2Br	H	H	4-MeC_6H_5	**rac-3o**	17	91	80/20
16	Ph	H	H	4-^{t}BuC_6H_5	**rac-3p**	85	44	84/16
17	Ph	H	H	2-MeC_6H_5	**rac-3q**	76	16	>95/5
18	Ph	H	Me	Ph	**rac-3r**	85	61	>95/5
19	Ph	Me	H	4-$MeOC_6H_5$	**rac-3s**	55	82	>95/5

[a] Carried out at rt under argon atmosphere: $CuBr_2$ (0.02 mmol), $AgSbF_6$ (0.04 mmol), **L2** (0.024 mmol), **1/2** = 1/2.0 (**1**, 0.2 mmol), 5 Å MS (25.0 mg), MTBE (1.0 mL). [b] Isolated yield. [c] The dr values were determined by ^{1}H NMR spectra of the crude reaction mixtures.

98% yield with 74/26 dr was obtained after 47 h (entry 8). With a biphenyl substituted methylenemalonate as substrate, the corresponding cyclobutane **rac-3i** was produced in moderate yield with 88/12 dr (entry 9). Alkyl lidenemalonates were also found to be suitable reaction candidates. For example, when R^1 was methyl, ethyl or *n*-propyl group, moderate yields (51%-58%) with excellent diastereoselectivity (90/10 –> 95/5 dr) were achieved (entries 10—12). When cyclohexyl- and $BnCH_2$-methylenemalonates were employed, the corresponding **rac-3m** and **rac-3n** were furnished in 99% and 94% yields with 93/7 dr (entries 13 and 14). With $BrCH_2$ as substituent, the cyclobutane **rac-3o** was afforded in 91% yield with 80/20 dr (entry 15). Various olefins, including not only terminal olefins such as 4-^{t}Bu-styrene, 2-Me-styrene and α-methylstyrene, but also internal olefin (*E*)-anethol, were tolerated in the current reaction system, giving the [2+2] products (**rac-3p-s**)[9] in moderate to good yields with up to >95/5 dr (entry 16—19).

The asymmetric version of this [2+2] cyclization reaction was also investigated. As summarized in Table 3, a variety of chiral bisoxazolines (BOX) were screened as chiral ligands.[10] When *L*-phenylglycinol derived BOX ligand **L4** was used, the reactivity of the catalytic reaction was slashed dramatically, and only trace amount of the desired product was observed (Table 3, entry 1). *tert*-Butyl group substituted chiral BOX ligand **L5** could deliver the cyclubutane **3a** in 50% yield with 83/17 dr and poor enantioselectivity (entry 2). With *L*-valinol derived BOX ligand **L6**, both the diastereo- and enantioselectivity were increased (92/8 dr and 82% ee, entry 3). By finely tuning the chiral environment, changing the backbone of chiral BOX from ^{i}Pr group to cyclohexyl (Cy) group,

Table 3 Optimization of asymmetric reaction conditions



Entry[a]	L	Yield[b]/%	dr[c]	ee[d]/%
1	**L4**	trace	—	—
2	**L5**	50	83/17	9
3	**L6**	51	92/8	82
4	**L7**	93	93/7	89
5	**L8**	21	94/6	93
6	**L9**	49	90/10	84
7	**L10**	40	85/15	85
8[e]	**L8**	95	92/8	93

[a] Carried out at rt under argon atmosphere: $CuBr_2$ (0.02 mmol), $AgSbF_6$ (0.04 mmol), **L** (0.024 mmol), **1/2** = 1/2.0 (**1**, 0.2 mmol), 5 Å MS (25.0 mg), MTBE (1.0 mL). [b] Isolated yield. [c] The dr values were determined by ^{1}H NMR spectra of the crude reaction mixtures. [d] The ee values were determined by HPLC with a chiral stationary phase. [e] After 132 h.

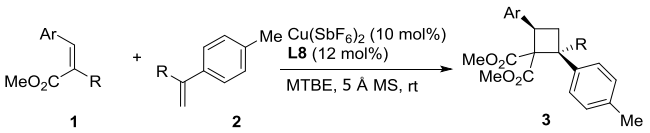
reactivity of the enantioselective cyclobutanation was further improved with slightly increase of both the dr and ee value (entry 4). Further modification on the chiral ligand **L7** led to ligand **L8**—**10**.[11] Among these ligands, **L8** delivered the best dr diastereo- and enantio-selectivity (94/6 dr and 93% ee), but led to a dramatic decline of the reactivity (entry 5). To our delight, the yield of this reaction could be further improved to 95% yield by prolonging the reaction time (92/8 dr and 93% ee, entry 8).

With the optimized reaction condition in hand, the substrate scope of this asymmetric catalytic cyclobutanation was explored. As shown in Table 4, several different methylenemalonates with various substituents at the Ar groups were proved to be suitable substrates, affording the corresponding cyclobutanes in good to excellent yields with up to 94% ee. For example, when 4-FC_6H_5 was chosen as Ar group, although the yield was poor, excellent enantioselecticity (92% ee) could be achieved (entry 2). With 4-BrC_6H_5 as Ar group, both excellent yield and excellent enantioselectivity were afforded (entry 3). Methylenemalonates, bearing strong electron-withdrawing groups such as nitro-, cyano- and triflormethyl-groups, also worked well in 93%—97% yields with 79/21—87/13 dr and 85%—94% ee (entries 4—6).[12] Chiral cyclobutane **3h** containing ester groups could also be produced in 96% yield with 89/11 dr and 92% ee (entry 7). Biphenyl substrate was tolerated in this catalytic system to give the product **3i** in 76% yield with 85/15 dr and 92% ee (entry 8). When α-methylstyrene was employed as substrate, 51% yield with >95/5 dr and 61% ee was obtained (entry 9).

Conclusions

In conclusion, we have developed a diastereo- and enantioselective catalytic asymmetric [2+2] cyclization of arylmethylidenemalonate with substituted styrene. In the presence of copper(II)/BOX complex as catalyst, various arylmethylidenemalonates, as well as many different styrene with substituents at different position reacted smoothly, providing a facile approach to the construction of multisubstituted cyclobutanes. Furthermore,

Table 4 Substrate scope of asymmetric reactions



Entry[a]	Ar	R	**3**	*t*/h	Yield[b]/%	dr[c]	ee[d]/%
1	Ph	H	**3a**	132	95	92/8	93
2	4-FC_6H_5	H	**3b**	138	27	89/11	92
3	4-BrC_6H_5	H	**3d**	70	93	70/30	89
4	4-$NO_2C_6H_5$	H	**3e**	81	97	79/21	89
5	4-CNC_6H_5	H	**3f**	28	93	81/19	85
6	4-$CF_3C_6H_5$	H	**3g**	16	97	87/13	94
7	4-$MeO_2CC_6H_5$	H	**3h**	62	96	89/11	92
8	4-PhC_6H_5	H	**3i**	56	76	85/15	92
9	Ph	Me	**3r**	117	51	>95/5	61

[a] Carried out at rt under argon atmosphere: $CuBr_2$ (0.02 mmol), $AgSbF_6$ (0.04 mmol), **L8** (0.024 mmol), **1/2** = 1/2.0 (**1**, 0.2 mmol), 5 Å MS (25.0 mg), MTBE (1.0 mL). [b] Isolated yield. [c] The dr values were determined by ^{1}H NMR spectra of the crude reaction mixtures. [d] The ee values were determined by HPLC with a chiral stationary phase.

by employing chiral BOX as ligand, the asymmetric version of this transformation delivered a series of optically active cyclobutanes in up to 97% yield with up to 92/8 dr and up to 94% ee. Further application of the useful method to the construction of biologically active molecules is ongoing in our laboratory.

Experimental

Typical procedure for the cyclobutation (**3a** as an example): A mixture of $CuBr_2$ (4.4 mg, 0.02 mmol), $AgSbF_6$ (13.8 mg, 0.04 mmol), **L8** (5.8 mg, 0.024 mmol) and 25 mg 5 Å molecular sieve in DCM (1 mL) was stirred at room temperature for 2—3 h under the atmosphere of nitrogen. Pumped out the DCM with a vacuum pump, then added the MTBE (1 mL). Ultrasound to bring the catalyst into solvent, substrate **1a** (0.2 mmol) was added immediately without interval at room temperature, then substrate **2a** (0.4 mmol) was added and stirred at room temperature. After the reaction was completed (monitored by TLC), the reaction was filtered through a glass funnel with thin layer (30 mm) of silica gel (100—200 mesh) and eluted with DCM/ethyl acetate. The filtrate was concentrated under reduced pressure, purified by flash chromatography (petroleum ether/ethyl acetate = 20/1) to afford the product **3a** as a colorless oil, in 95% yield with 92/8 dr and 93% ee [Chiralpak ID, *n*-hexanes/^{i}PrOH = 95/5, 0.7 mL/min, λ = 230 nm: t_R (minor) = 12.5 min, t_R (major) = 14.3 min); $[\alpha]_D^{31}$ = + 12.1° (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 (d, *J* = 7.2 Hz, 2H), 7.29—7.28 (m, 4H), 7.21—7.18 (m, 2H), 7.10 (d, *J* = 7.6 Hz, 2H), 4.16—4.08 (m, 2H), 3.91 (s, 3H), 3.15 (q, *J* = 11.2 Hz, 1H), 3.06 (s, 3H), 2.56 (q, *J* = 9.2 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.3, 167.9, 139.1, 136.1, 135.9, 128.6, 127.9, 127.1(8), 127.1(5), 126.5, 65.7, 52.6, 51.4, 42.2, 42.1, 25.7, 21.0; IR (KBr) *v*: 1728.3, 1516.2, 1497.9, 1432.8, 1262.3, 1199.0, 1181.7, 1083.7, 1039.9, 877.6, 823.8, 761.7, 697.4 cm^{-1}; HRMS-ESI: Exact mass calcd. for $C_{21}H_{22}O_4Na^+$ $[M+Na]^+$: 361.1410; Found: 361.1403.

Supporting Information

Experimental procedures and characterization data for all products and crystallographic data are included. The supporting information for this article is available on the WWW under

https://doi.org/10.1002/cjoc.201900456.

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