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Catalytic Asymmetric [2+2] Cycloaddition between Quinones and Fulvenes and a Subsequent Stereoselective Isomerization to 2,3-Dihydrobenzofurans

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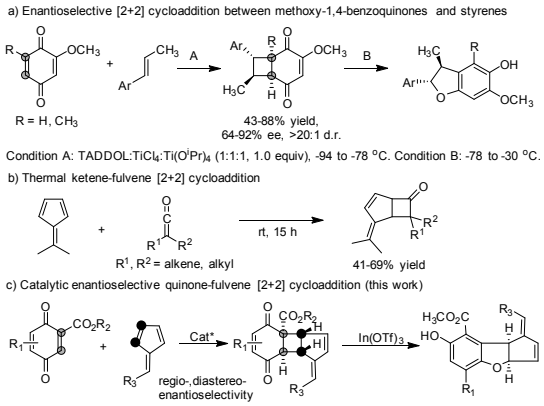
The first catalytic enantioselective [2+2] cycloaddition between quinones and fulvenes was addressed by the use of a chiral copper(II) complex catalyst. The transformation afforded a series of enantiomerically enriched [6,4,5]-tricyclic cyclobutane derivatives in good yields with excellent regio- and stereoselectivities. Furthermore, the [2+2] adducts could be easily converted to formal [3+2] adducts efficiently and stereoselectively.

Cyclobutane motif is present in a number of natural products,[1] and is also a type of useful intermediate with diversity of reactions.[2] One of the principal strategies for the synthesis of enantiomerically enriched cyclobutane derivatives involves catalytic enantioselective [2+2] cycloadditions.[3] Many variants have been established, such as photochemical approach,[4] polarized [2+2] cycloadditions between α,β-unsaturated carbonyl compounds or allenes and electron-rich alkenes catalyzed by sigma Lewis acids[5] or π-philic Lewis acids,[6] as well as amine-catalyst-based formal [2+2] cycloadditions of α,β-unsaturated aldehydes.[7] Despite of these efforts, the π-partners for catalytic enantioselective [2+2] cycloadditions remain extremely limited, and the scope of the process is worth of further extending in order to access to various cyclobutane derivatives.

The use of quinones as the π-component in cycloadditions is a major advance and challenge since the reactions might result in several different products, and the quinone subcategory could transform into densely functionalized aromatic rings.[8] Early in 1991, Engler and coworkers used chiral TADDOL/$TiCl_4$/$Ti(O^iPr)_4$ catalyst for the enantioselective [2+2] cycloaddition between 2-methoxy-1,4-benzoquinones and styrenes. The corresponding cyclobutane adducts were obtained in good yields and high ee, although stiochiometric amount catalyst were required (Scheme 1a).[8a] On the other side, fulvenes are useful synthons as 2π, 4π, and 6π components in a variety of cycloadditions to construct polycyclic structures.[9] [2+2] Cycloaddition of fulvenes was firstly reported by Huston and coworkers in 1982 using ketene as the electro-poor 2π partner (Scheme 1b).[9b] In spite of these efforts, no catalytic enantioselective [2+2] cycloaddition involving quinones and fulvenes have been reported to date. The key element is finding an appropriate Lewis acid that could activate the desired [2+2] cycloaddition, but weaken the competitive formal [3+2] cycloaddition,[8a,9f,11] [4+2] cycloaddition,[9f] polycondensation of quinones[10] and dimerization of fulvenes[9e].



Scheme 1. [2+2] Cycloaddition related to quinones or fulvenes.

Herein, we utilized a chiral *N*,*N*′-dioxide-Cu(OTf)$_2$ catalyst[12] for the mentioned [2+2] cycloaddition (Scheme 1c). Moreover, the formed [6,4,5]-tricyclic structures can be easily and stereoselectively converted into [6,5,5]-dihydro-1H-cyclopenta[b]benzofuran structures assisted by In(OTf)$_3$. Through these ways, the useful cyclobutane and cylcopenta[b]benzofuran structures both can be obtained in good yields with excellent regio- and stereoselectivities.

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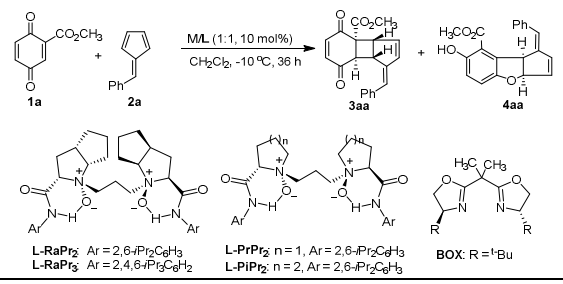
Table 1. Optimization of the [2+2] cycloaddition reaction conditions.[a]



entry	L/Metal salt	Yield (**3aa**)(%) [b]	Dr [c]	Er [d]
1	**L-RaPr$_2$**/Mg(OTf)$_2$	53	94:6	87:13
2	**L-RaPr$_2$**/Ni(OTf)$_2$	62	73:27	72:28
3	**L-RaPr$_2$**/Zn(OTf)$_2$	25	64:36	50:50
4	**L-RaPr$_2$**/Cu(OTf)$_2$	31	94:6	90:10
5	**BOX**/Cu(OTf)$_2$	trace	-	-
6	**L-PiPr$_2$**/Cu(OTf)$_2$	41	72:28	50:50
7	**L-PrPr$_2$**/Cu(OTf)$_2$	25	95:5	94:6
8	**L-RaPr$_3$**/Cu(OTf)$_2$	56	94:6	94:6
9[e]	**L-RaPr$_3$**/Cu(OTf)$_2$	56	94:6	97:3
10[e,f]	**L-RaPr$_3$**/Cu(OTf)$_2$	74	94:6	98.5:1.5
11[e–g]	**L-RaPr$_3$**/Cu(OTf)$_2$	82	94:6	98.5:1.5

[a] Unless otherwise noted, the reactions were performed with **L–M** (1:1, 10 mol%), **1a** (0.1 mmol) and **2a** (0.15 mmol) in CH_2Cl_2 (1.0 mL) at −10 °C for 36 h. [b] Isolated yield. [c] The dr value was determined by ^{1}H NMR and HPLC analysis. [d] Determined by HPLC analysis on chiral stationary phases. [e] At −40 °C. [f] CH_3CN as the solvent. [g] The ratio of **M/L** was 1:1.1, and 3 Å molecular sieves (10 mg) was added.

Initial studies used 6-phenylfluvene **2a** and unsubstituted 1,4-benzoquinone as the reactants. After efforts toward optimization of the chiral catalysts, we got the related [2+2]-product in moderate yield with poor enantioselectivity (for detail see Supporting Information). Next, we introduced an ester group into the quinone structure to enhance the coordination between the catalyst and quinone via a bidentate-binding manner.[13] Table 1 summarizes the results between 2-ester-substituted quinone **1a** and fluvene **2a**. The [2+2] cycloaddition occurred from electron-deficient double bond rather than sterically more accessible double bond bearing two hydrogens.[8a] The product **3aa** was obtained as the major product, accompanying trace amount of the formal [3+2] adduct **4aa**[11,9f] and the [4+2] cycloaddition product was suppressed in this reaction temperature. By using Mg(OTf)$_2$-**L-RaPr$_2$** catalyst, the [2+2] adduct **3aa** was obtained in 53% yield, 94:6 dr and 87:13 er, meanwhile the byproduct **4aa** was obtained in 21% yield with poor enantioselectivity (Table 1, entry 1). Encouraged by this promising result, a detailed optimization of metal salts was done firstly. Pleasingly, Cu(OTf)$_2$ afforded a better result in terms of enantioselectivity (entries 2-4). Subsequent evaluation focused on various chiral ligands, including chiral bisoxazoline **BOX**, and several chiral *N*,*N*′-dioxides (entries 5-8). In the presence of **BOX** ligand, trace adducts (**3aa**/**4aa**) were obtained which was contributed to the polycondensation of quinone. Luckily, it was found that the ligand **L-RaPr$_3$** provided an obvious increase in terms of reactivity and enantioselectivity (entry 8). Decreasing the reaction temperature from −10 to −40 °C led to a further increase in enantioselectivity (entry 9). Of the solvents tested for the reaction, CH_3CN proved optimal with respect to the yield (entry 10). Moreover, by adding 3 Å molecular sieves and changing the ratio of the metal salt and ligand, the best results of 82% yield, 94:6 dr and 98.5:1.5 er for **3aa** were obtained with trace byproduct **4aa** (entry 11).

With the optimal condition in hand, we look into the substrate scope for the synthesis of various cyclobutane derivatives (Table 2). Firstly, substituted quinones were subjected into the [2+2] cycloaddition (entries 1-20). It was found that the steric hindrance of the ester group at 2-carbon position had little effect on the stereoselectivity. Quinones (**1a-1f**) bearing substitutions underwent the reaction well, resulting in 50-82% yields, 96:4-98.5:1.5 er (entries 1-5). The naphalene-1,4-dione derivative **1g** could deliver the product **3ga** in 55% yield, 95:5 dr and 98.5:1.5 er (entry 6). 5-Aryl-substitued quinones (**1h-1m**) with electron-withdrawing or donating substituents on the phenyl group performed the [2+2] reaction with the electron-deficient double bond, giving the related cyclobutene derivatives **1ha-1ma** in 58-68% yields, 90:10-98.5:1.5 er (entries 7-12). Furthermore, 5-alkyl substituted quinones (**1n-1t**) including liner, branched, and cyclic alkyl groups were tolerated to give the cycloadducts **3na-3ua** with 65-82% yields and up to 99:1 er (entries 13-20).

We then examined the substrate scope of fulvenes (Table 2, entries 21-34). 6-Aryl substituted fulvenes **2b–2f** bearing *para*-substituents performed the [2+2] cycloaddition smoothly to generate the desired products **3ab–3af** in good yields (61–77%), and excellent enantioselectivity (97.5:2.5–98.5:1.5er) (entries 21-25). Fulvenes **2g**–**2h** bearing*m*-tolyl or*o*-tolyl substitution made little influence on both the yields and the stereoselectivities (entries 26 and 27). Additionally, fulvenes **2i–2m** containing 6-hetero-aromatic and fused-ring substitutions afforded the corresponding [2+2] products **3ai–3am** in satisfied outcomes, with the yields ranging from 61% to 82%, and the er as high as 90:10 to 99:1 (entries 28-32). Fulvene **2n** bearing a 4-acetylphenylgroup was also tolerable, giving the adduct **3an** in 75% yield, as well as 98.5:1.5 er (entry 33). In addition, multi-conjugated alkene substrate **2o** could afford the desired tricyclic product **3ao** in 81% yield with 97:3 er (entry 34). It is noteworthy that, the diastereoselectivity was excellent and only trace amount of formal [3+2] byproducts **4** were detected in all these cases. Most reaction achieved up to 20:1 dr, and only a few suffered a slightly dropped diastereoselectivity, as the lowest dr as 92:8. Other *ortho*-substituted quinones, substituted fulvenes were found sluggish under the optimal reaction conditions.[14] Furthermore 5,5-dimethylcyclopenta-1,3-diene was also used in this reaction, however the desired [2+2] cycloaddition was not happened and we detected the [4+2] reaction product.

Quinone subcategory has also long served as useful precursors into functionalized aromatic rings.[8a,13] The rearrangement of the cyclobutane adducts could furnish the corresponding 2,3-dihydrobenzofurans, another unique structure in many natural products.[15] Therefore, we next evaluated the condition of the rearrangement from the [2+2] adduct **3** into the formal [3+2] adduct **4**. Preparative scale

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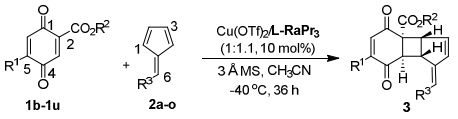
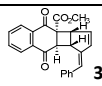
synthesis of the [2+2] cycloadduct **3aa** were carried out, and there was no change in reactivity and stereoselectivity with the cycloaddition underwent from 5 mmol of the substrate **1a**. Enantiomerically pure product **3aa** (99:1 dr and 99.5:0.5 er)

Table 2. Scope of quinones andfulvenes in [2+2] cycloaddition reaction. [a]



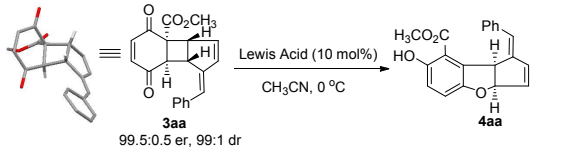
1b-1u 2a-o 3

	Entry	3(R^1, R^2, R^3)	Yield (%)	Dr	er
1		**3ba**: R^2 = Et	67	97:3	97.5:2.5
2	R^1 = H	**3ca**: R^2 = *n*-Pr	60	97:3	97:3
3	R^3 = Ph	**3da**: R^2 = *n*-Bu	70	97:3	98:2
4		**3ea**: R^2 = *i*-Pr	50	97:3	96:4
5		**3fa**: R^2 = *i*-Bu	65	>20:1	98:2
6	 **3ga**		55	95:5	98.5:1.5
7		**3ha**: R^1 = Ph	62	>20:1	95:5
8		**3ia**: R^1 = 3-MeC_6H_4	68	>20:1	98:2
9		**3ja**: R^1 = 2-MeC_6H_4	61	>20:1	90:10
10		**3ka**: R^1 = 4-*t*-BuC_6H_4	60	92:8	98.5:1.5
11		**3la**: R^1 = 4-FC_6H_4	50	>20:1	98.5:1.5
12		**3ma**: R^1 = 4-EtOC_6H_4	60	>20:1	98.5:1.5
13	R^2 = Me	**3na**: R^1 = Me	67	97:3	98:2
14	R^3 = Ph	**3oa**: R^1 = Et	66	95:5	98:2
15		**3pa**: R^1 =*i*-Pr	82	93:7	99:1
16		**3qa**: R^1 =*i*-Bu	83	98:2	99:1
17		**3ra**: R^1 =*t*-Bu	78	95:5	98:2
18		**3sa**: R^1 =*c*-pentyl	65	98:2	99:1
19		**3ta**: R^1 =*c*-hexyl	72	>20:1	98.5:1.5
20		**3ua**: R^1 = $PhCH_2CH_2$	60	95:5	98:2
21		**3ab**: R^3 = 4-FC_6H_4	77	>20:1	98.5:1.5
22		**3ac**: R^3 = 4-ClC_6H_4	75	>20:1	97.5:2.5
23		**3ad**: R^3 = 4-BrC_6H_4	63	>20:1	97.5:2.5
24		**3ae**: R^3 = 4-IC_6H_4	61	>20:1	97.5:2.5
25		**3af**: R^3 = 4-MeC_6H_4	72	>20:1	98:2
26		**3ag**: R^3 = 3-MeC_6H_4	72	>20:1	98.5:1.5
27	R^1 = H	**3ah**: R^3 = 2-MeC_6H_4	70	>20:1	97:3
28	R^2 = Me	**3ai**: R^3 = 2-furyl	61	94:6	99.5:0.5
29		**3aj**: R^3 = 3-thienyl	75	97:3	90:10
30		**3ak**: R^3 = 2-benzo[b]thiophenyl	82	>20:1	98:2
31		**3al**: R^3 = 1-naphthyl	65	>20:1	97:3
32		**3am**: R^3 = 2-naphthyl	78	>20:1	99:1
33		**3an**: R^3 = 4-AcOC_6H_4	75	96:4	98.5:1.5
34		**3ao**: R^3 =PhCH=CH-	81	>20:1	97:3

[a] **L-RaPr$_3$**–Cu(OTf)$_2$ (1.1:1, 10 mol%), **1** (0.1 mmol), **2** (1.5 equiv.), 3 Å MS (10 mg) in CH_3CN (1.0 mL) at −40 °C for 36 h. The yield is the isolated yield. The dr was determined by ^{1}H NMR and HPLC analysis, and the er value was determined by HPLC analysis on chiral stationary phases.

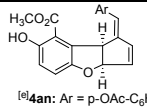
was obtained after simple recrystallization. The absolute configuration of **3aa** was determined to be (3a*R*,3b*R*,7a*R*,7b*S*) by X-ray crystal analysis.[16] Resubjecting **3aa** to various Lewis acid catalysts at 0 °C afforded the related 2,3-dihydrobenzofuran **4aa** (Table 3). Cu(OTf)$_2$ gave only 7% yield, and both the diastereoselectivity and the enantioselectivity of **4aa** dropped a little (entry 1). $BF_3{\cdot}Et_2O$ and Yb(OTf)$_3$ proved either ineffective or less stereoselective (entries 2 and 3). To our delight, In(OTf)$_3$ led to the product **4aa** in 95% yield albeit with a little decrease of stereoselectivity (entry 4). Decreasing the reaction temperature from 0 to −20 °C and increasing the catalyst loading to 15 mol% compensated the loss of stereocontrol, and the formal [3+2] adduct **4aa** could be generated in 95% yield with maintained stereoselectivity (entry 5). Therefore, in the assistance of In(OTf)$_3$, several cyclobutane adducts **3** obtained from the asymmetric [2+2] cycloaddition reaction could efficiently transformed into the related 2,3-dihydrobenzofurans **4**. Good yields (81-95%) were obtained and the diastereo- and enantioselectivities reduced a little but remained satisfying (7:1-99:1 dr, 97.5:1.5-99:1 er).

Table 3. Isomerization of cyclobutane adducts into 2,3-dihydrobenzofurans. [a]

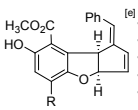


3aa 99.5:0.5 er, 99:1 dr **4aa**

entry	Lewis acid	yield of **4aa** (%)[b]	dr of **4aa**[c]	er of **4aa**[d]
1	Cu(OTf)$_2$	7	90:10	97.5:2.5
2	$BF_3{\cdot}Et_2O$	trace	-	-
3	Yb(OTf)$_3$	36	85:15	54:46
4	In(OTf)$_3$	95	97:3	98.5:1.5
5[e]	In(OTf)$_3$	95	99:1	99.5:0.5



[e]**4an:** Ar = p-OAc-C_6H_4 95% yield, 99:1 dr, 99:1 er (from enantiomeric pure **3an**)



[e] **4pa:** R = *i*-Pr, 82% yield, 7:1 dr, 99:1 er
4qa: R = *i*-Bu, 81%, 7:1 dr, 97.5:2.5 er
4sa: R = *c*-Pentyl, 80% yield, 9:1 dr, 97.5:2.5 er
4ha: R = Ph, 90% yield, 9:1 dr, 98.5:1.5 er
4ua: R = $PhCH_2CH_2$, 85% yield, 7:1 dr, 97.5:2.5 er

[a] Unless otherwise noted, the reactions were performed with Lewis acid (10 mol%), **3** (0.1 mmol) in CH_3CN (1.0 mL) at 0 °C for 0.5 h. [b] Isolated yield. [c] Determined by ^{1}H NMR and HPLC analysis. [d] Determined by HPLC analysis on chiral stationary phases. [e] In(OTf)$_3$ (15 mol%) at −20 °C for 15 min.

To demonstrate the utility of the [2+2] cycloaddition reaction, preparative scale synthesis of the cycloadducts carried out. The scale synthesis of **ent-3an** was also successful when the enantiomer of the ligand **L-RaPr$_3$** was used instead. The optical pure product *ent*-**3an** was acquired in a 66% totalyield. Next, the catalytic isomerization of the [2+2] adduct *ent*-**3an** at a gram scale performed well, generating the related benzofuranderivative *ent*-**4an** in 95% yield with maintained enantioselectvity. The absolute configuration of *ent*-**4an** was determined after single crystal X-ray analysis.[16] After highly regioselective hydrogenation reaction, the product *ent*-**6an** was obtained in 99% yield (see Supporting Information).

To obtain information about the [2+2] cycloaddition process, static state and Operando IR experiments were carried out (for detail see Supporting Information). As peaks related to the two reactants depleted gradually, the signals of the [2+2] product **3** and the formal [3+2] byproduct **4** increased nearly simultaneously. It indicates that two catalytic reactions occurred synchronal and competitively. The [6,5,5]-tricyclic product **4** is not generated from the isomerization of the [6,4,5]-tricyclic product **3** in the circumstance of the chiral

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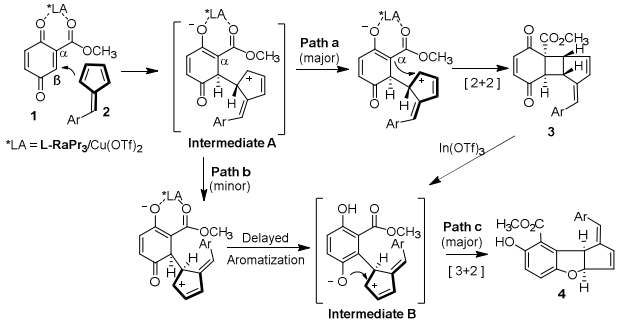
catalytic system. Based on the results mentioned above and our previous work,[12] we proposed possible pathways for the generation of the cycloadducts. As shown in Scheme 3, the chiral **L-RaPr$_3$**-Cu(II) complex bonds the two carbonyl groups of quinone substrate **1**, activating the β-position. Then the nucleophilic ability of the fulvene **2** enables the addition to the β-position of **1**, forming the intermediate **A**, which can get through two reaction pathways to give the cycloadducts. The nucleophilic approach of the α-position of quinone **1** is preferable resulting in enantioselective [2+2] cycloaddition product of [6,4,5]-tricyclic derivative **3** (path a). The



Scheme 3. The proposed reaction processes.

accompanying enantioselective oxygen-nucleophilic addition might be hampered due to the delayed aromatization process (path b), thus the formal [3+2]-product **4** was detected as the minor adduct. Moreover, in the presence of In(OTf)$_3$, the ring-opening of cyclobutane moiety gives the intermediate **B**, which undergoes oxa-addition efficiently and enantioselectively to afford the [6,5,5]-tricyclic product **4**.

In summary, we have developed the catalytic enantioselective [2+2] cycloaddition between quinones and fulvenes. Under a chiral *N*,*N*′-dioxide-copper(II) complex, a variety of quniones and fulvenes smoothly afforded the [6,4,5]-tricyclic cyclobutane derivatives in good yields with excellent regio- and stereoselectivities. Furthermore, the cyclobutane derivatives can be easily, diastereo- and enantioselectively converted into cyclopenta[b]benzofuran structures catalyzed by In(OTf)$_3$. Additionally, based on Operando IR experiments, a conceivable reaction mechanism was also proposed to comprehend the reaction process.

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