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Desymmetrization Process by Mg(II)-Catalyzed Intramolecular Vinylogous Michael Reaction

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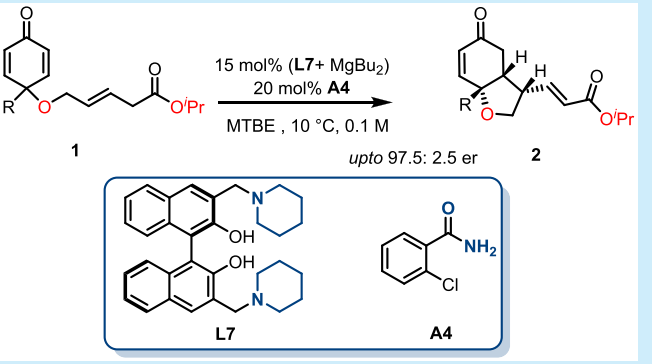
ABSTRACT: Chiral magnesium catalyzed intramolecular vinylogous Michael reaction of novel cyclohexadienones via a desymmetrization process is reported. (*R*)-BINOL derived ligand and an achiral amide were employed in the current in situ generated magnesium catalyst, giving the corresponding hydrogenated benzofuranone skeletons in good to excellent enantioselectivities with high yields. This simple and efficient strategy could be utilized for the synthesis of aromatized α,β-unsaturated ester and Br-substituted hydrogenated benzofuranone in good yields under mild conditions.



The hydrogenated benzofuranone skeletons were widely found in natural products and biologically significant molecules, such as isoambrox, haterumaimide I, incarviditone, and millingtonini A (Figure 1).[1] Asymmetric synthesis of such skeletons with cyclohexadienones including the Stetter reaction,[2] the Rauhut–Currier reaction,[3] and the cascade reaction[4] have attracted extensive attention of many chemists in the past decades. However, the intramolecular vinylogous reactions still have limited applications in this area, especially for the direct use of allylic esters. Herein, by integrating the desymmetrization and intramolecular vinylogous Michael reaction, we designed a series of symmetric cyclohexadienones modified by a linear allylic ester for the efficient asymmetric synthesis of hydrogenated benzofuranone structures. Notably, linear allylic esters are less reactive, compared with other linear allylic carbonyl compounds.[5] Thus, in the well-documented literature, activated enolization methods were often adopted to overcome this problem.[6] There are still very few studies on the direct activation of linear allylic esters in catalytic asymmetric reactions. Of those studies, with use of chiral copper catalysts and base additives, Yin's group reported the direct asymmetric vinylogous adol reaction of allylic esters.[7] Recently, we reported a kinetic resolution reaction of a novel allylic ester substrate.[8]

Desymmetrization reactions are highly attractive manners for the rapid synthesis of optical compounds.[9] Inspired by these works, we have designed novel substrates for the construction of the desired hydrogenated benzofuranone skeletons via a desymmetrization pathway. In these, the symmetric cyclohexadienones could be efficiently obtained by oxidation and olefin metathesis reactions using simple substituted phenols (Figure 1). Bifunctional magnesium

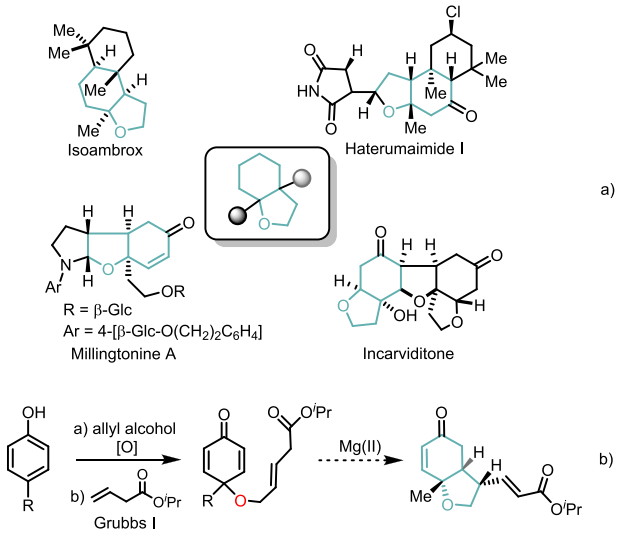


Figure 1. (a) *cis*-Hydrobenzofurans as structural motifs in natural products and b) the designed symmetric substrates to the hydrobenzofurans via desymmetrization process.

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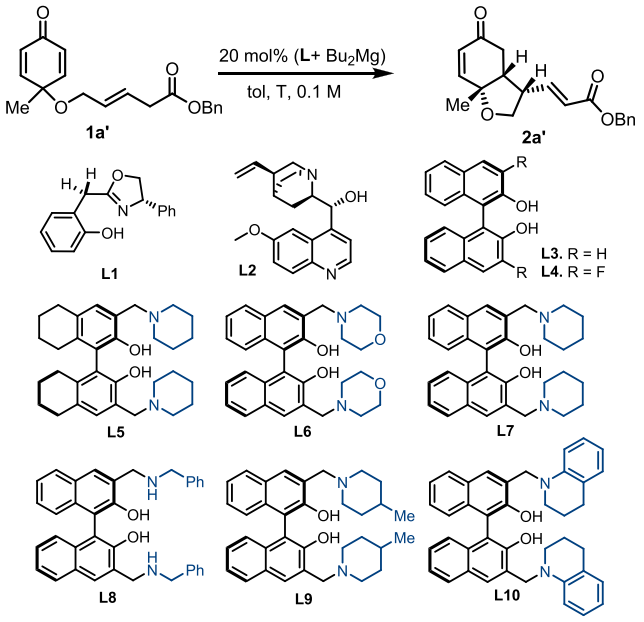
catalysts[10] are selected to mediate the current desymmetrization reaction, for which magnesium is widely distributed in nature, present a wide range of low toxicity, and represent an attractive catalyst source.

We began the experiments by evaluating a series of chiral ligands in the Mg(II)-mediated desymmetrization of cyclohexadienone **1a'** at 60 °C. As illustrated in Table 1, reactions

Table 1. Optimization of the Ligands Participating in the Desymmetrization Reaction[a]



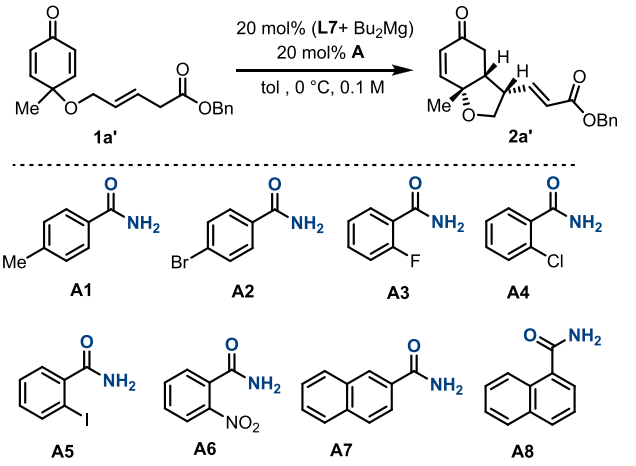
entry	L	T (°C)	yield[b] (%)	er[c] (%)
1	**L1**	60	-	-
2	**L2**	60	65	58:42
3	**L3**	60	-	-
4	**L4**	60	-	-
5	**L5**	60	30	64.5:35.5
6	**L6**	60	33	76.5:23.5
7	**L7**	60	51	81:19
8	**L8**	60	39	52:48
9	**L9**	60	45	77:23
10	**L10**	60	11	-
11	**L7**	0	58	84:16

[a]Reactions were performed with **1a'** (0.1 mmol) in the presence of chiral ligands (20 mol %, 0.02 mmol) and Bu_2Mg (20 mol %, 0.02 mmol) in toluene (1.0 mL) overnight. [b]Isolated yields. [c]Enantiomeric excesses were analyzed by stationary phase HPLC, "-" indicates no detected.

with oxazoline-OH, commercial chiral BINOL, or some simple BINOL derivatives did not give promising cyclization product (Table 1, entries 1, 3, and 4). Although the transformation proceeded smoothly in the presence of quinine **L2**, only 58:42 er was obtained. Next, we examined chiral ligands derived from BINOL by introducing C_2-symmetric Brønsted bases on the naphthol ring, considering that heterocyclic rings on the ligands should not only act as a steric hindrance function but also as Brønsted bases to activate the linear allylic esters. It was observed that **L7** equipped with a piperidine ring on the phenol gave more potential results, compared with H_8-BINOL-derived ligand **L5**. Other experiments with various substituents of C_2-symmetric Brønsted based on the naphthols did not give better results.

Further optimizations were operated by introducing achiral amide additives (Table 2). It was found that the addition of *O*-

Table 2. Achiral Ligands' Influence in the Current Desymmetrization Reaction[a]



entry	A	yield[b] (%)	er[c] (%)
1	**A1**	75	84:16
2	**A2**	71	85.5:14.5
3	**A3**	79	87.5:12.5
4	**A4**	85	90:10
5	**A5**	69	86:14
6	**A6**	78	85.5:14.5
7	**A7**	84	84:16
8	**A8**	81	87:13

[a]Reactions were performed with **1a'** (0.1 mmol) in the presence of chiral ligand **L7** (20 mol %, 0.02 mmol), achiral ligands **A** (20 mol %, 0.02 mmol) and Bu_2Mg (20 mol %, 0.02 mmol) in toluene (1.0 mL) overnight. [b]Isolated yields. [c]Enantiomeric excesses were analyzed by stationary phase HPLC.

chlorobenzamide obviously improved the enantioselectivity of the desymmetrization reaction compared with other amide additives. With regard to this, a control experiment of NMR analysis was carried out, showing that the introduction of the benzamide additive to the **L7**−Mg complex results in obvious shifts for the hydrogen atom of the amide and broadened peaks were also generated.[11b] Herein, the benzamide was supposed to play a stabilizing effect via hydrogen bonding between the **L7** and benzamide as well as the coordination of oxygen atom to the magnesium center.[11]

After obtaining the optimized conditions, we explored the scope of this Mg(II)-mediated intramolecular vinylogous Michael desymmetrization reaction. Cyclohexadienones furnished with different alkyl substituents were employed in the current catalysis system, providing corresponding hydrogenated benzofuranones with different fundamental groups at the opposite position of carbonyl in good yields and good to excellent enantioselectivities. Then a series of arkyl-substituted cyclohexadienones were synthesized and participated in the desymmetrization reaction. As the results shown in Scheme 1, aryl-substituted cyclohexadienones with electron-donating or -withdrawing groups were tolerable in the reaction, leading to the corresponding products with moderate to good enantio-

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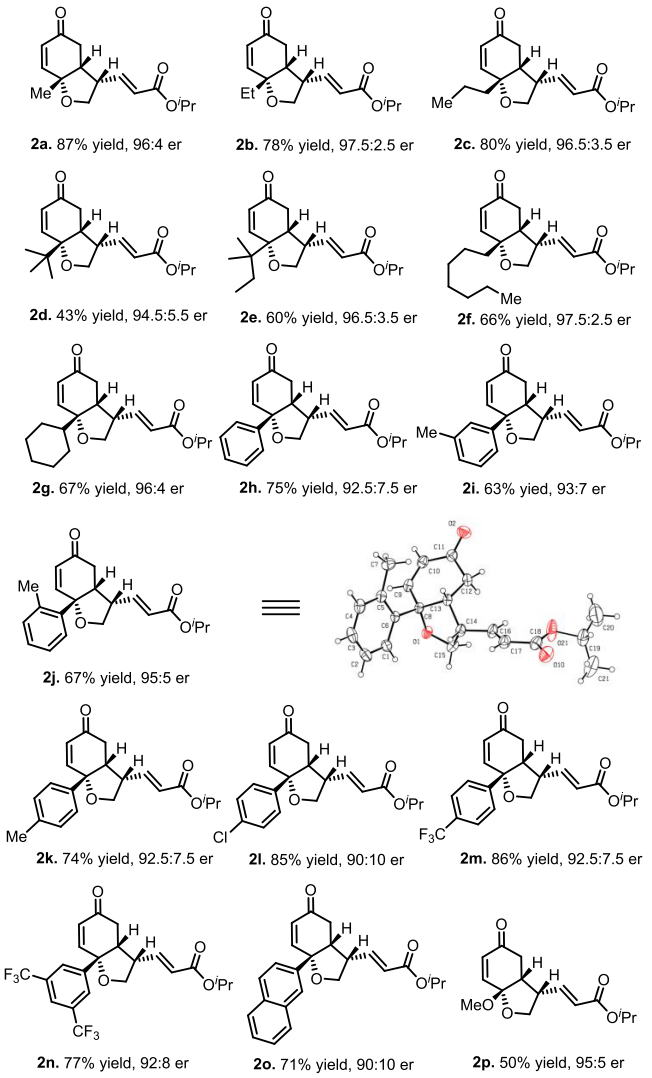
Scheme 1. Substrate Scope of the Desymmetrization Product[a]



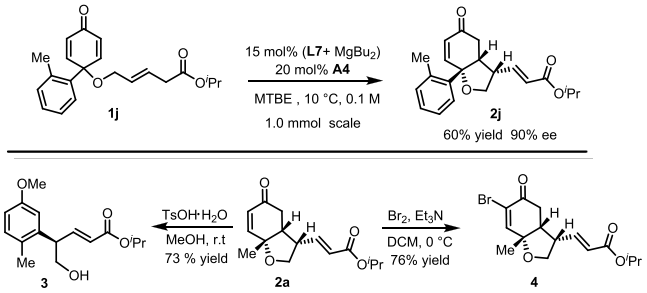
[a]Reactions were performed with **1** (0.1 mmol) in the presence of chiral ligands **L7** (15 mol %, 0.015 mmol), achiral ligands **A4** (20 mol %, 0.02 mmol), and Bu_2Mg (15 mol %, 0.015 mmol) in MTBE (1.0 mL) at 10 °C overnight.

selectivities. The absolute configuration was determined by the X-ray crystallographic analysis of **2j** (Scheme 1).

Furthermore, the desymmetrization process mediated by the Mg(II)-catalyzed intramolecular vinylogous Michael reaction was carried out on a 1 mmol scale, leading to the hydrogenated benzofuranone products **2j** in good yield and enantioselectivity. Then, by simple treatment of $TsOH{\cdot}H_2O$, the desymmetrization product **2a** was transformed to aromatized product **3** in good yield under mild conditions. And using the Br_2 as the source of halogen, Br-substituted hydrogenated benzofuranone on the α-C(sp^2) atom was obtained in a satisfactory yield (Scheme 2).

In summary, we have reported a desymmetrizative vinylogous Michael reaction of cyclohexadionones, mediated by an in situ generated magnesium catalyst. The introduction of achiral *O*-chlorobenzamide could significantly improve the enantioselectivity of the reaction. Under the current system, a series of significant hydrogenated benzofuranone compounds

Scheme 2. 1 mmol Scale Synthesis and Further Transformations



were obtained in good yields and good to excellent enantioselectivities. Moreover, the catalytic desymmetrization reaction could be performed on scaled reaction. And the enantioenriched products were further transformed to aromatized products and other functionalized cyclohexanones in good yields under mild conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03417.

Experimental procedures and spectroscopic data for all new compounds and copies of ^1H, ^{13}C NMR and and HPLC spectra (PDF)

Accession Codes

CCDC 2014891 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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