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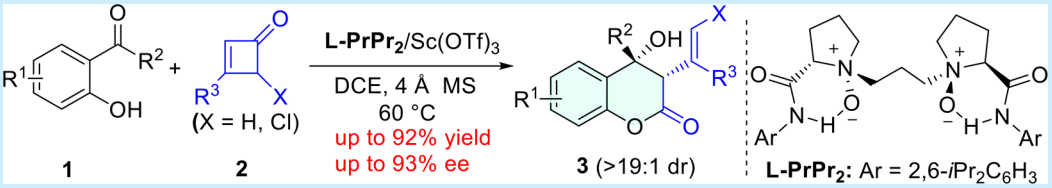
Enantioselective Synthesis of 4-Hydroxy-dihydrocoumarins via Catalytic Ring Opening/Cycloaddition of Cyclobutenones

Hang Zhang, Yao Luo, Dawei Li, Qian Yao, Shunxi Dong, Xiaohua Liu,* and Xiaoming Feng*

Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China

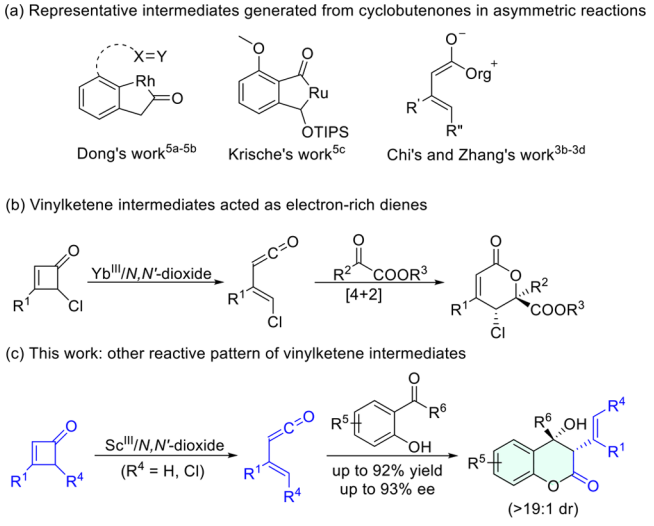
Supporting Information



ABSTRACT: A highly diastereo- and enantioselective ring-opening/cycloaddition reaction of cyclobutenones with 2-hydroxyacetophenones or salicylaldehyde was achieved by employing a chiral *N,N′*-dioxide-scandium(III) complex as the catalyst. It provided various 3-phenylvinyl-4-hydroxy-dihydrocoumarins in good yields (up to 92%), high enantioselectivities (up to 93% ee), and excellent diastereoselectivities (>19:1 dr). Moreover, a possible catalytic cycle was proposed based on the control experiments and previous reports.

Cyclobutenones, readily available unsaturated cyclic compounds with high ring strain, have proven valuable in organic synthesis.[1] The unique core skeleton provides them with multiple reactive patterns, depending on the nature of the reaction partners,[2] the activation modes of different catalysts,[3] and the reaction conditions as well.[1b] Of the patterns reported to date, distinctive ring opening/cycloaddition has attracted considerable interest.[1b,4] In this regard, most of the enantioselective reactions were promoted by either transition metal catalyst[5] or nucleophilic organocatalyst[3b−d] (Scheme 1a). In addition, photolysis and thermolysis of cyclobutenones could afford the important vinylketene intermediates which possess multiple reactive patterns similar to disubstituted ketenes.[6] Previous reports mainly focused on the nucleophilic addition[2f−h] or formal [2 + 2] cycloadditions with electron-rich alkenes and alkynes.[2a−e] Recently, we disclosed that chiral Lewis acids could activate cyclobutenones to generate the aforementioned vinylketene intermediates under mild conditions, which subsequently acted as electron-rich dienes[6a] in formal [4 + 2] cycloaddition reaction with *β,γ*-unsaturated *α*-ketoesters (Scheme 1b).[7] Despite that these vinylketene intermediates are potentially useful in the rapid construction of structurally attractive and biologically important molecules,[2e] such kinds of multiple transformations are still rare.[1b,2f]

Scheme 1. Multiple Reactive Patterns of Cyclobutenones



3,4-Dihydrocoumarins are core structures of various biologically active compounds and natural products.[8] They are also widely used as important intermediates in organic synthesis.[9] In the past decade, many efforts have been devoted to their enantioselective synthesis.[10] Among them, only a few examples were related to the synthesis of optically active 4-hydroxy-chroman-2-one.[10a] We hypothesized that the reaction of ketenes with 2-hydroxyacetophenones or salicylaldehyde might provide a new access to optically active dihydrocoumarin derivatives via a formal [2 + 4] process. Mechanistically, in the presence of a Lewis acid, cyclobutenone is activated to generate a vinylketene intermediate, which is subsequently captured by the hydroxyl group of 2-hydroxyacetophenone to afford a Lewis-acid-bonded dienolate intermediate. If a stereoselective intramolecular nucleophilic addition of a dienolate intermediate with the carbonyl group occurs, chiral 4-hydroxy-3,4-dihydrocoumarins could be readily provided.

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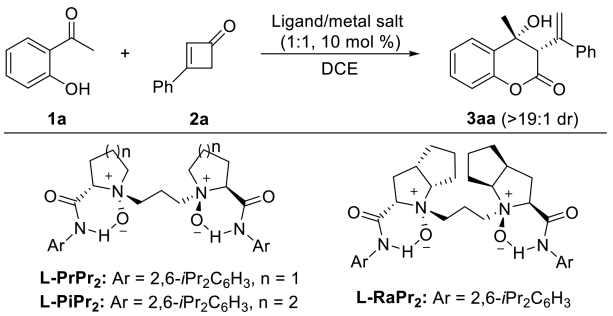
Herein, we demonstrate our contribution to this area. The chiral *N*,*N*′-dioxide−scandium(III) complex[11] developed by our group was found to be a suitable catalyst to promote the titled cascade reaction, furnishing enantioenriched dihydrocoumarin derivatives in good to excellent results (>19:1 dr, up to 92% yield, and 93% ee).

Initially, the cycloaddition of cyclobutenone **2a** with 2-hydroxyacetophenone **1a** was selected as the model reaction to optimize the reaction conditions (Table 1). A variety of metal salts were examined by coordinating with L-proline-derived *N*,*N*′-dioxide **L-PrPr$_2$** in ClCH$_2$CH$_2$Cl at 50 °C. It was found that the complexes of Mg(OTf)$_2$, La(OTf)$_3$, or Yb(OTf)$_3$ could promote the reaction smoothly with low enantioselectivity (entries 1−3). In sharp contrast, the use of Sc(OTf)$_3$/**L-PrPr$_2$** was able to achieve high enantioselectivity (entry 4; 90% ee). We next chose Sc(OTf)$_3$ as the central metal to screen chiral *N*,*N*′-dioxide ligands. It was found that both the chiral backbones and the amine moieties in ligands displayed an obvious effect on the enantioselectivity of the reaction (for details, see SI). **L-PrPr$_2$** and **L-RaPr$_2$** were superior to **L-PiPr$_2$** derived from L-pipecolic acid in terms of enantioselectivity (entries 4−6). In addition, we investigated other commercially available ligands, such as chiral Box ligand, Pybox ligand, and Salen ligand, while no better results were obtained (see SI for details). It was worth noting that some acidic byproducts were detected by HRMS which might inhibit this reaction (see SI and entries 7−8). Finally, after preparing the catalyst Sc(OTf)$_3$/**L-PrPr$_2$** in anhydrous methanol, decreasing the amount of 4 Å molecular sieves, and performing the reaction under N$_2$ atmosphere for 72 h, the product **3aa** could be obtained in a higher yield (entry 9 vs entry 6; 72% yield). Using an excessive amount of cyclobutenone **2a** (1.5 equiv) could further increase the yield to 84% (entry 10). Finally, the adjustment of the reaction concentration and the reaction temperature (from 50 to 60 °C) resulted in the optimal conditions, and the product **3aa** was isolated in 91% yield, 91% ee, and >19:1 dr (entry 11).

Under the optimized reaction conditions, the substrate scope was then investigated (Table 2). With respect to the substrate **1**, the effect of different group R^1 was first examined.

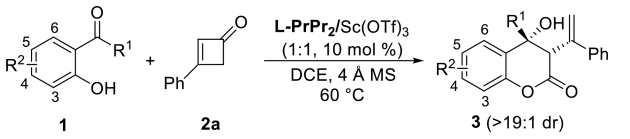
Table 1. Optimization of the Reaction Conditions

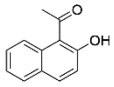


entry[a]	metal salt	ligand	yield (%)[b]	ee (%)[c]
1	Mg(OTf)$_2$	**L-PrPr$_2$**	43	0
2	La(OTf)$_3$	**L-PrPr$_2$**	44	0
3	Yb(OTf)$_3$	**L-PrPr$_2$**	72	9
4	Sc(OTf)$_3$	**L-PrPr$_2$**	58	90
5	Sc(OTf)$_3$	**L-PiPr$_2$**	46	70
6	Sc(OTf)$_3$	**L-RaPr$_2$**	55	90
7[d]	Sc(OTf)$_3$	**L-RaPr$_2$**	18	45
8[e]	Sc(OTf)$_3$	**L-RaPr$_2$**	24	65
9[f,g]	Sc(OTf)$_3$	**L-PrPr$_2$**	72	91
10[f,g,h]	Sc(OTf)$_3$	**L-PrPr$_2$**	84	91
11[f,g,h,i]	Sc(OTf)$_3$	**L-PrPr$_2$**	91	91

[a]Reactions were performed with **1a** (0.10 mmol), **2a** (0.10 mmol), 4 Å MS (50 mg), and ligand/metal salt (1:1, 10 mol %) in ClCH$_2$CH$_2$Cl (1.0 mL) at 50 °C for 48 h. [b]Yield of the isolated product. [c]Determined by chiral HPLC analysis. [d]With 3-ClC$_6$H$_4$COOH (10 mol %). [e]With PhCH$_2$CH$_2$COOH (10 mol %). [f]The catalyst **L-PrPr$_2$**/Sc(OTf)$_3$ (1:1) was prepared in CH$_3$OH. [g]Performed with **1a** (0.15 mmol), **2a** (0.15 mmol), 4 Å MS (30 mg), and catalyst **L-PrPr$_2$**/Sc(OTf)$_3$ (10 mol %) in ClCH$_2$CH$_2$Cl (1.5 mL) at 50 °C under N$_2$ atmosphere for 72 h. [h]**2a** (1.5 equiv). [i]ClCH$_2$CH$_2$Cl (1.2 mL) and at 60 °C for 72 h.

Table 2. Substrate Scope with Respect to the 2-Hydroxyacetophenones



entry[a]	R^1	R^2	yield (%)[b]	ee (%)[c]
1	Me	H	91 (**3aa**)	91
2	Et	H	80 (**3ba**)	90
3	CH$_2$Br	H	83 (**3ca**)	93
4[d]	nPr	H	61 (**3da**)	86
5[d]	CH$_2$CH$_2$Ph	H	63 (**3ea**)	85
6	Ethynyl	H	54 (**3fa**)	85
7[d,e]	CO$_2$Et	H	57 (**3ga**)	90
8	Ph	H	90 (**3ha**)	20
9	Me	4-Me	86 (**3ia**)	88
10	Me	4-F	51 (**3ja**)	90
11	Me	4-Cl	74 (**3ka**)	89
12	Me	5-Me	88 (**3la**)	89
13	Me	5-F	84 (**3ma**)	92
14	Me	5-Cl	89 (**3na**)	92
15	Me	5-Br	89 (**3oa**)	91
16	Me	5-MeO	92 (**3pa**)	90
17	Me	4,5-Me$_2$	91 (**3qa**)	87
18	Me	6-MeO	86 (**3ra**)	87
19	Me	3,5-Me$_2$	90 (**3sa**)	55
20			80 (**3ta**)	91

[a]Reactions were performed with **1** (0.15 mmol), **2a** (0.23 mmol), 4 Å MS (30 mg), and catalyst **L-PrPr$_2$**/Sc(OTf)$_3$ (10 mol %) in ClCH$_2$CH$_2$Cl (1.2 mL) at 60 °C for 72 h. [b]Yield of the isolated product. [c]Determined by chiral HPLC analysis. [d]4 Å MS (50 mg) and **L-PrPr$_2$**/Sc(OTf)$_3$ (15 mol %). [e]At 50 °C.

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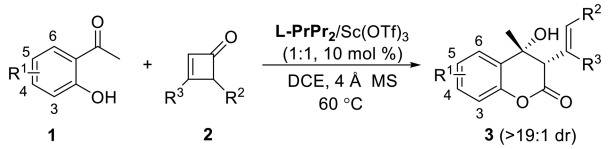
All the alkyl-substituted ketones, ethynyl ketone, and α-ketone ester could be converted into the corresponding products **3aa**−**3ga** in 54−91% yields and 85−93% ee (entries 1−7). When R^1 was a phenyl group, the product **3ha** was obtained in 90% yield with only 20% ee, which might be due to the steric hindrance (entry 8). Next, various C4-, C5-, and C6-substituted 2-hydroxyacetophenones were tested, and all the reactions proceeded smoothly and gave the desired products **3ia**−**3ra** in moderate to good yields with high enantioselectivities (entries 9−18; 51−92% yield and 87−92% ee). When 3,5-dimethyl-2-hydroxyacetophenone was used, the product **3sa** was given in lower ee value (entry 19). In addition, 1-(2-hydroxynaphthalen-1-yl)ethan-1-one was also tolerated well in this reaction, providing **3ta** in 80% yield with 91% ee value (entry 20).

Subsequently, we turned our attention to the generality of cyclobutenones **2**. As shown in Table 3, all the reactions

Table 3. Substrate Scope for Cyclobutenones



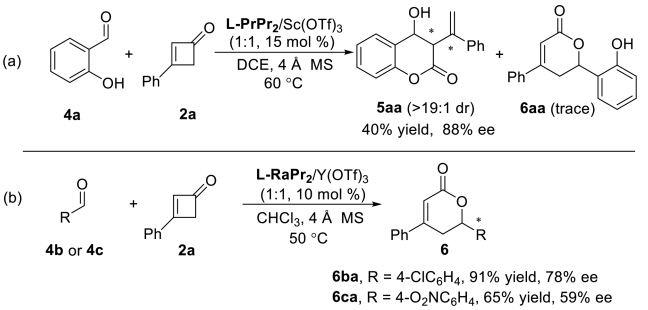
entry[a]	R^1; R^2; R^3	yield (%)[a]	ee (%)[a]
1	H; H; 3-MeC_6H_4	92 (**3ab**)	91
2	H; H; 2-FC_6H_4	80 (**3ac**)	92
3	H; H; 3-FC_6H_4	86 (**3ad**)	89
4	H; H; 4-FC_6H_4	89 (**3ae**)	90
5	5-MeO; H; 4-MeC_6H_4	68 (**3nf**)	91
6[b]	5-MeO; H; 4-MeOC_6H_4	88 (**3ng**)	90
7	H; Cl; 4-MeC_6H_4	68 (**3ah**)	59
8	H; Cl; 3-MeC_6H_4	64 (**3ai**)	53

[a]Unless otherwise stated, all reactions were the as same as the footnote in Table 2. [b]4 Å MS (50 mg) and **L-PrPr$_2$**/Sc(OTf)$_3$ (15 mol %, 1:1).

proceeded smoothly and gave the 3-vinyl-substituted dihydrochromans **3ab**−**3nf** in moderate to good yields with high enantioselectivities (entries 1−5; 68−92% yields and 89−92% ee). When R^3 was replaced by an electron-rich aryl group, for instance, 4-MeOC_6H_4, a lower yield of **3ng** was obtained. This issue could be addressed by increasing the loading of the catalyst and molecular sieve (entry 6; 88% yield with 90% ee). The reaction was also applicable to cyclobutenones **2h** and **2i** (R^2 = Cl), and the desired products **3ah** and **3ai** were obtained in moderate yields but with moderate ee values (entries 7 and 8).

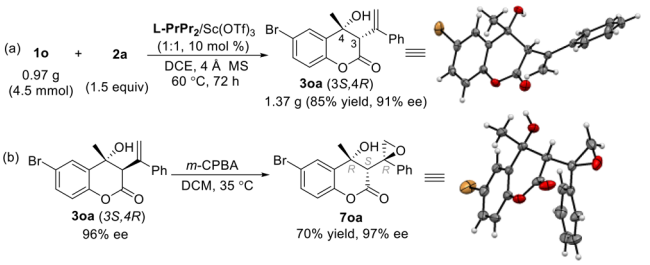
Salicylaldehyde **4a** was also tolerated in this ring-opening/cycloaddition process after slight modification of reaction conditions, and the desired product **5aa** was isolated as the major product in 40% yield with 88% ee (Scheme 2a). It was worth mentioning that a trace amount of oxa-Diels−Alder reaction product **6aa** was detected where cyclobutenone participated in the reaction as a diene. When aldehydes as **4b** and **4c** without a hydroxyl group were employed, racemic β,γ-unsaturated δ-lactones **6ba** and **6ca** were produced in moderate yields under the standard catalytic conditions. After the newly optimized reaction conditions by the use of **L-RaPr$_2$**-Y(OTf)$_3$ as the catalyst, the oxa-Diels−Alder products could be delivered in good yields with moderate enantioselectivities (Scheme 2b).

Scheme 2. Reactions of Cyclobutenone with Aldehydes



To evaluate the synthetic potential of the catalytic system, a gram-scale synthesis of **3oa** was carried out. As shown in Scheme 3, 4.5 mmol of **1o** reacted smoothly with 6.8 mmol of

Scheme 3. Gram-Scale Synthesis of the Product 3oa and Its Transformation



2a under the optimized reaction conditions, delivering the corresponding product **3oa** in 85% yield (1.37g) with 91% ee. Furthermore, the absolute configuration of **3oa** was determined to be (3*S*,4*R*) by the X-ray crystallographic analysis. In addition, 3,4-dihydrocoumarin **3oa** (96% ee) could also be oxidized by *m*-CPBA to generate the expected epoxide **7oa** as a single diastereomer with maintained ee value (70% yield, 97% ee).

To get insight into the mechanism of this catalytic reaction, we carried out several control experiments (see SI for details). Only a trace amount of the product **3ga** was detected if Sc(OTf)$_3$ or ligand **L-PrPr$_2$** was absent (Scheme 4a). Furthermore, the ring-opening product **8ga** was not detected by ^{1}H NMR at different reaction time under the catalytic conditions (Scheme 4b). Based on these experiments and the reaction of aldehydes (Scheme 2), we proposed a possible catalytic cycle to explain the catalytic activation process (Scheme 4c). Originally, the *N*,*N*′-dioxide−scandium(III) complex could promote ring opening of cyclobutenone **2a** to generate the vinylketene **A**, which underwent a nucleophilic addition of the hydroxyl group of **1g** to give the dienolate intermediate **B**. From the absolute configuration of the product **3oa**, we speculated that a bidentate dienolate intermediate **C** was formed via coordination with the scandium catalyst in six-membered cyclic transition states. As the steric hindrance of one amide subunit of the ligand shielded the styryl group (see **TS1**), an intramolecular α-nucleophilic addition occurred via the transition state **TS2** from the *Re*−*Re* faces, and then the chiral product **3ga** was generated after protonation procedure accompanied with the regeneration of the catalyst.

In summary, we have developed an efficient asymmetric catalytic synthesis of 4-hydroxy-dihydrocoumarins via ring-opening/cycloaddition reaction of cyclobutenones with 2-

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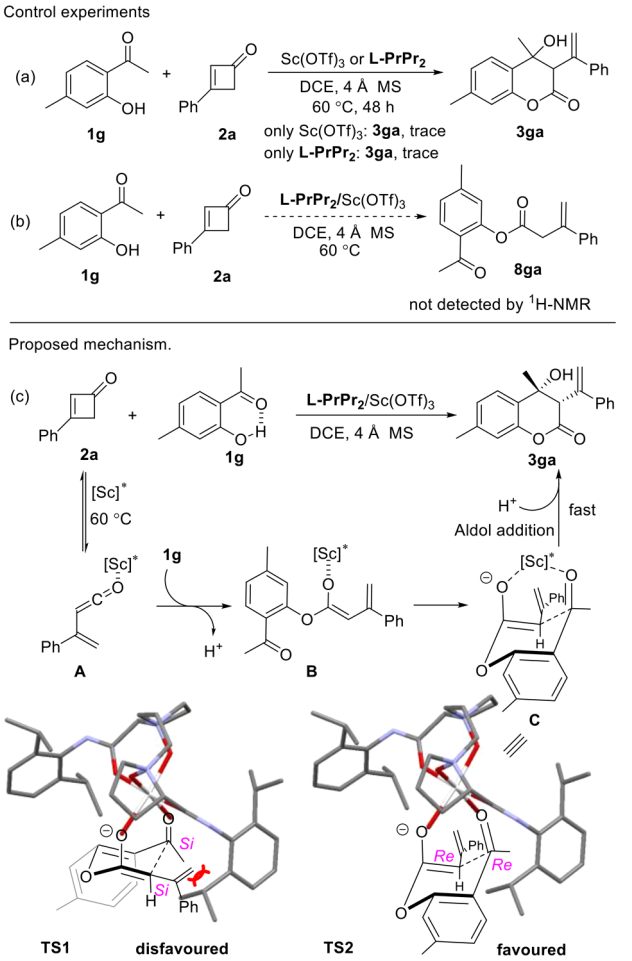
Scheme 4. Control Experiments and Proposed Mechanism



hydroxyacetophenones or salicylaldehyde using $Sc(OTf)_3$/**L-PrPr$_2$** as the catalyst. A range of 3-vinyl-substituted 4-hydroxydihydrocoumarins were obtained in good yields, high enantioselectivities, and excellent diastereoselectivities. A possible catalytic cycle was provided based on the control experiments and previous reports.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00670.

Experimental details and analytical data (NMR, HPLC, HRMS) (PDF)

Accession Codes

CCDC 1884906 and 1884908 contain 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.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: liuxh@scu.edu.cn.
*E-mail: xmfeng@scu.edu.cn.

ORCID

Shunxi Dong: 0000-0002-3018-3085
Xiaohua Liu: 0000-0001-9555-0555
Xiaoming Feng: 0000-0003-4507-0478

Notes

The authors declare no competing financial interest.

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