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Diastereo- and Enantioselective Construction of the Hexahydrocoumarin Scaffold via an Organocatalytic Asymmetric [3 + 3] Cyclization

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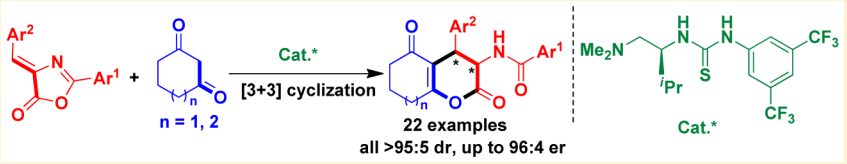
Supporting Information



ABSTRACT: The first catalytic asymmetric construction of the biologically important hexahydrocoumarin scaffold has been established, which takes advantage of chiral thiourea−tertiary amine-catalyzed enantioselective transformations. Besides, this reaction also realized the first catalytic asymmetric [3 + 3] cyclization of 4-arylidene-2-aryloxazol-5(4*H*)-ones with cyclohexane-1,3-diones, which afforded structurally diverse 3-aminohexahydrocoumarin derivatives in excellent diastereoselectivities and high enantioselectivities (all >95:5 dr, up to 96:4 er). The investigation on the activation mode suggested that the chiral thiourea−tertiary amine catalyst simultaneously activated the two substrates via hydrogen-bonding interaction. Moreover, this reaction could be applied to a large scale synthesis of enantioenriched hexahydrocoumarin. This approach will not only provide an efficient method for the construction of the chiral hexahydrocoumarin scaffold but also enrich the research areas of asymmetric organocatalysis and catalytic enantioselective [3 + 3] cyclizations.

INTRODUCTION

Coumarin derivatives are abundant in natural products and bioactive compounds.[1−4,5a] As shown in Figure 1, splitomycin[2]

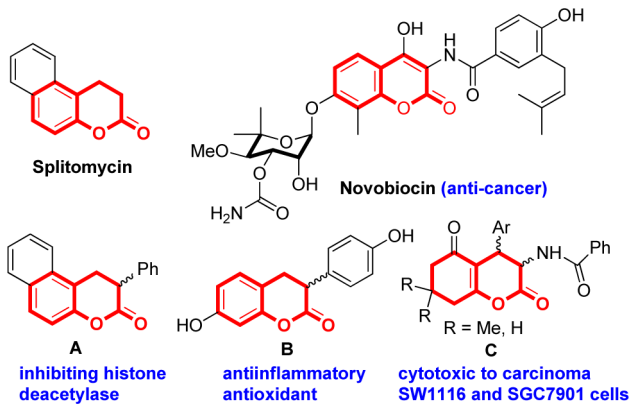


Figure 1. Natural products and bioactive compounds containing the coumarin scaffold.

and novobiocin[3] are natural products containing dihydrocoumarin and coumarin scaffolds, respectively. Besides, dihydrocoumarin compounds **A** and **B** possess important bioactivities such as inhibiting histone deacetylase, anti-inflammatory, and antioxidant.[4] More significantly, the series of hexahydrocoumarin compounds **C** exhibit moderate to strong cytotoxicity toward carcinoma SW1116 and SGC7901 cells, which are promising anticancer candidates.[5a] As a result, the syntheses of coumarin derivatives, especially those in an enantioselective fashion, have received great attention from the chemistry community, because the two enantiomers may have distinct bioactivities from each other or from the racemates.[6]

In this context, a number of catalytic asymmetric reactions have been developed to access enantioenriched coumarin derivatives.[7,8] However, despite these elegant approaches, most of them are focused on the synthesis of enantioenriched 3,4-dihydrocoumarins in the presence of chiral metal catalysts[7] or organocatalysts[8] (eq 1). *In sharp contrast, no catalytic asymmetric approaches have been available yet for the enantioselective synthesis of hexahydrocoumarins* (eq 2), although this type of coumarin derivatives as exemplified by compounds **C** is pharmaceutically important.[5a] Very surprisingly, even the syntheses of racemic hexahydrocoumarins were sporadically found in the literature, which just included two approaches. One made use of the reaction of 1,3-dicarbonyls with *N*-methyl-1,3-oxazolium-5-olate derivatives,[5b] and another took advantage of a microwave-assisted reaction of dimedone or cyclohexane-1,3-dione with 4-arylidene-2-phenyloxazol-5(4*H*)-ones.[5a] Therefore, developing catalytic asymmetric methods for the synthesis of enantioenriched hexahydrocoumarins has become an urgent task.

Chiral thiourea−tertiary amines belong to a class of privileged bifunctional organocatalysts, which have enabled a variety of catalytic asymmetric transformations.[9,10] Catalytic asymmetric

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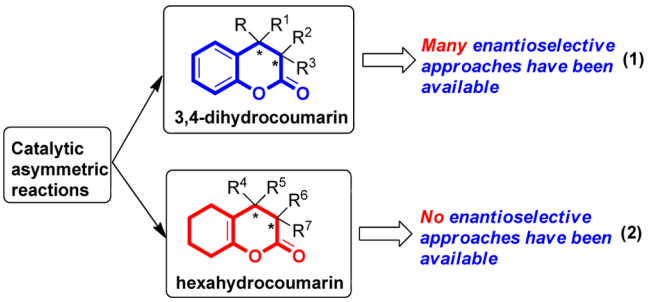
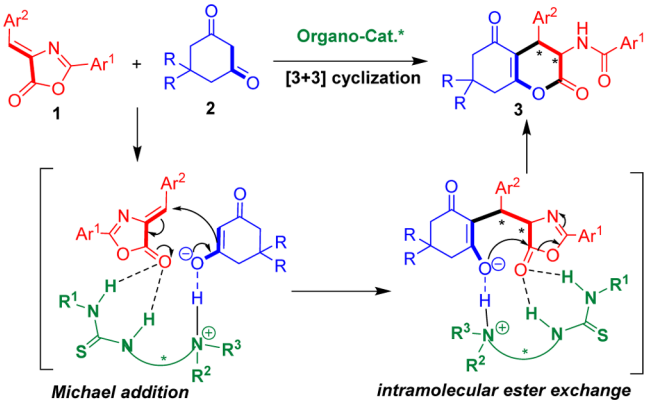


[3 + 3] cyclization is a powerful method to construct six-membered rings with optical purity.[11] For the purpose to construct the hexahydrocoumarin framework in an enantioselective way, and as a continuation of our efforts in synthesizing enantioenriched heterocycles with biological relevance via asymmetric organocatalysis,[12] we designed a thiourea−tertiary amine-catalyzed [3 + 3] cyclization of 4-arylidene-2-aryloxazol-5(4*H*)-ones **1** with cyclohexane-1,3-diones **2** to realize the catalytic asymmetric synthesis of hexahydrocoumarins **3** (Scheme 1).

Scheme 1. Design of the Reaction



In this design, chiral thiourea−tertiary amine catalyst would activate both of the substrates via hydrogen-bonding interaction to facilitate a tandem Michael addition/intramolecular ester exchange sequence, thus constructing the hexahydrocoumarin skeleton in a diastereo- and enantioselective style.

Herein, we report the first catalytic asymmetric construction of biologically important hexahydrocoumarin scaffold, which takes advantage of chiral thiourea−tertiary amine-catalyzed enantioselective transformations. Besides, this reaction also realized the first catalytic asymmetric [3 + 3] cyclization of 4-arylidene-2-aryloxazol-5(4*H*)-ones with cyclohexane-1,3-diones, which afforded structurally diverse 3-aminohexahydrocoumarin derivatives in excellent diastereoselectivities and high enantioselectivities (all >95:5 dr, up to 96:4 er).

RESULTS AND DISCUSSION

Initially, the reaction of 4-phenylidene-2-phenyloxazol-5(4*H*)-one **1a** with dimedone **2a** was employed as a model reaction to screen a variety of chiral thiourea−tertiary amine catalysts and to perform condition optimization (Table 1). The screening of thiourea−tertiary amine catalysts **4a**−**g** with different chiral backbones verified that this type of bifunctional catalysts could indeed promote the designed [3 + 3] cyclization reaction to afford the desired hexahydrocoumarin product **3aa** (entries 1−7), although the yield and the enantioselectivity were very low. The preliminary results revealed that catalysts **4c** and **4g** could deliver the product **3aa** at a relatively higher yield and better enantioselectivity than other thiourea−tertiary amine catalysts (entries 3 and 7 vs entries 1, 2, and 4−6). Besides, several chiral squaramide−tertiary amine catalysts were also employed to the model reaction, but none of them exhibited better catalytic activity than **4c** and **4g** in terms of yield and enantioselectivity (see the Supporting Information for details). Then, in the presence of catalyst **4c**, a series of representative solvents were screened (entries 8−12), which found that using toluene as a solvent could greatly improve the yield although the enantioselectivity was still very low (entry 10). Gratifyingly, when we tentatively lowered the reaction temperature to 30 °C, the enantioselectivity was remarkably increased to 83:17 er albeit with a decreased yield (entry 13). Under this condition, the replacement of catalyst **4c** by **4g** resulted in a further improved enantioselectivity of 89:11 er, but the yield dropped to a lower level (entry 14). Fortunately, carefully modulating the molar ratio of the two reactants (see the Supporting Information for details) disclosed that the yield could be elevated to 53% and the enantioselectivity could be enhanced to 94:6 er when the molar ratio of **1a** to **2a** was 2:1 (entry 15). Subsequently, *o*-, *m*-, and *p*-xylenes as analogues of toluene were utilized as solvents (entries 16−18), which found that *m*-xylene was a more suitable solvent for the reaction compared with toluene (entry 17 vs 15). Next, the evaluation of molecular sieves (MS) led to the finding that using 5 Å MS as additives could improve the yield to 66% with a retained enantioselectivity (entry 20 vs entries 17 and 19). The action of the MS in the reaction was to prevent the hydrolysis of substrate **1a**. Finally, properly increasing the catalyst loading to 25 mol % with a prolonged reaction time resulted in the best yield of 77% with a high enantioselectivity of 96:4 er (entry 22). Notably, during the process of condition optimization, the diastereoselectivity of the reaction was always kept in an excellent level of >95:5 dr.

With the optimal conditions known, we then investigated the substrate scope of 4-arylidene-2-aryloxazol-5(4*H*)-ones **1** by the [3 + 3] cyclizations with dimedone **2a**. As shown in Table 2, this protocol was amenable to a wide range of substrates **1** bearing different aromatic R^1/R^2 groups, delivering structurally diverse hexahydrocoumarins **3** in generally excellent diastereoselectivities (all >95:5 dr) and moderate to good enantioselectivities (84:16 to 96:4 er). In detail, a variety of electronically different phenyl groups could serve as competent R^1 substituents for substrates **1** (entries 1−8), which took part in the [3 + 3] cyclizations in considerable yields (47−91%) and high stereoselectivities (all >95:5 dr, 88:12 to 96:4 er). In addition, a wide scope of ortho-, meta-, para-, and multisubstituted phenyl groups could be successfully utilized as aromatic R^2 substituents (entries 9−19), affording the [3 + 3] cyclization products **3** in uniformly excellent diastereoselectivities of >95:5 dr and overall good enantioselectivities ranging from 90:10 to 95:5 er. Notably, substrate **1t** bearing a heteroaromatic 2-thiophenyl group could also participate in the desired [3 + 3] cyclization to give the corresponding product **3ta** in an acceptable stereoselectivity (>95:5 dr, 84:16 er) albeit with a low yield (entry 20). Nevertheless, this would enlarge the applicability of this reaction. Finally, we also tried to employ aliphatic R^1/R^2 groups for substrates **1** (entries 21 and 22). However, these substrates **1u**,**v** exhibited extremely low reactivity, and no reaction (N.R.) occurred under the standard conditions. Besides, to further demonstrate the synthetic utility of this protocol, we tried to recrystallize some [3 + 3] cyclization products **3**, which could afford the corresponding products **3** with a higher er value after recrystallization (Table 2, in parentheses).

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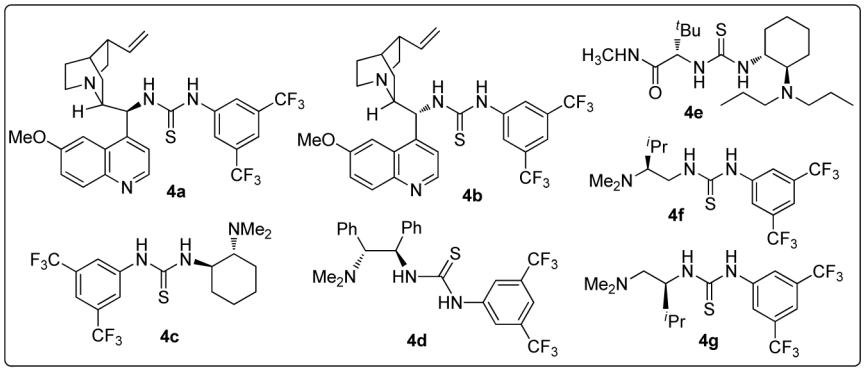
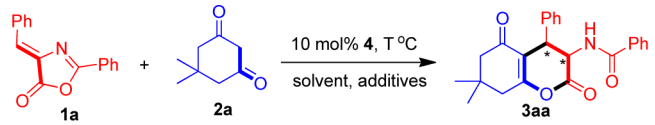
Table 1. Screening of Catalysts and Condition Optimization[a]

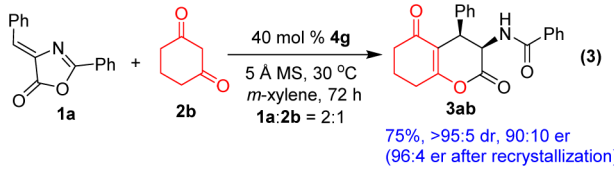




entry	cat.	solvent	T (°C)	yield (%)[b]	dr[c]	er[d]
1	**4a**	THF	50	20	>95:5	48:52
2	**4b**	THF	50	27	>95:5	61:39
3	**4c**	THF	50	40	>95:5	68:32
4	**4d**	THF	50	8	>95:5	57:43
5	**4e**	THF	50	8	>95:5	58:42
6	**4f**	THF	50	13	>95:5	54:46
7	**4g**	THF	50	37	>95:5	66:34
8	**4c**	CH_2Cl_2	50	80	>95:5	64:36
9	**4c**	AcOEt	50	77	>95:5	53:47
10	**4c**	toluene	50	69	>95:5	69:31
11	**4c**	acetone	50	73	>95:5	62:38
12	**4c**	MeCN	50	55	>95:5	60:40
13	**4c**	toluene	30	46	>95:5	83:17
14	**4g**	toluene	30	34	>95:5	89:11
15[e]	**4g**	toluene	30	53	>95:5	94:6
16[e]	**4g**	*o*-xylene	30	55	>95:5	94:6
17[e]	**4g**	*m*-xylene	30	59	>95:5	96:4
18[e]	**4g**	*p*-xylene	30	59	>95:5	95:5
19[e,f]	**4g**	*m*-xylene	30	50	>95:5	95:5
20[e,g]	**4g**	*m*-xylene	30	66	>95:5	96:4
21[e,g,h]	**4g**	*m*-xylene	30	67	>95:5	96:4
22[e,g,h,i]	**4g**	*m*-xylene	30	77	>95:5	96:4

[a]Unless otherwise indicated, the reaction was carried out at the 0.1 mmol scale in the presence of 10 mol % **4** in a solvent (1 mL) with 3 Å MS (100 mg) as additives for 48 h, and the molar ratio of **1a**:**2a** was 1:1. [b]Isolated yields. [c]The dr value was determined by ^{1}H NMR and HPLC. [d]The er value was determined by HPLC. [e]The molar ratio of **1a**:**2a** was 2:1. [f]Using 4 Å MS (100 mg) as additives. [g]Using 5 Å MS (100 mg) as additives. [h]The reaction was 72 h. [i]In the presence of 25 mol % **4g**.

Moreover, cyclohexane-1,3-dione **2b** could smoothly undergo the catalytic asymmetric [3 + 3] cyclization with substrate **1a** to generate the hexahydrocoumarin **3ab** at a good yield of 75% with a high stereoselectivity of >95:5 dr and 90:10 er (eq 3).



Fortunately, the enantioselectivity of product **3ab** could also be improved to 96:4 er after recrystallization.

Furthermore, we employed 1,3-cyclopentanedione, 1,3-cycloheptanedione, and acetylacetone as 1,3-diones to the reaction (Scheme 2). In the case of 1,3-cyclopentanedione **2c**, under the standard reaction conditions (eq 4), no reaction occurred and no desired product **3ac** was detected. We also tried some other conditions (see the Supporting Information for details), but no reaction occurred in all cases. These results indicated that the reactivity of 1,3-cyclopentanedione was extremely low in this [3 + 3] cyclization. Gratifyingly, in the case of 1,3-cycloheptanedione **2d**, this substrate could smoothly take part in the desired [3 + 3] cyclization under the standard conditions (eq 5), which afford the corresponding product **3ad** in an excellent diastereo- and enantioselectivity (>95:5 dr, 90:10 er) albeit with a moderate yield of 48%. This result will enlarge the synthetic applicability of this catalytic asymmetric [3 + 3] cyclization. Finally, we tried to use acetylacetone **2e** as a 1,3-dione substrate to the [3 + 3] cyclization under the standard conditions (eq 6). However, this acyclic 1,3-dione also exhibited extremely low reactivity and no reaction occurred. To find a suitable condition

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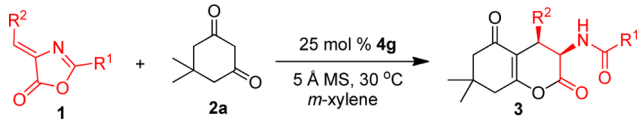
Table 2. Substrate Scope of 4-Arylidene-2-aryloxazol-5(4*H*)-ones 1[a]



entry	3	R^1/R^2 (1)	yield (%)[b]	dr[c]	er[d]
1	**3aa**	Ph/Ph (**1a**)	77	>95:5	96:4 (99:1)[f]
2	**3ba**	2-FC_6H_4/Ph (**1b**)	47	>95:5	93:7
3	**3ca**	2-BrC_6H_4/Ph (**1c**)	91	>95:5	90:10 (98:2)[f]
4	**3da**	3-$OMeC_6H_4$/Ph (**1d**)	74	>95:5	91:9 (99:1)[f]
5[e]	**3ea**	4-BrC_6H_4/Ph (**1e**)	52	>95:5	88:12
6	**3fa**	4-MeC_6H_4/Ph (**1f**)	84	>95:5	90:10 (97:3)[f]
7	**3ga**	4-$OMeC_6H_4$/Ph (**1g**)	57	>95:5	93:7
8	**3ha**	2-naphthyl/Ph (**1h**)	74	>95:5	88:12 (98:2)[f]
9	**3ia**	Ph/2-FC_6H_4 (**1i**)	49	>95:5	90:10 (96:4)[f]
10[e]	**3ja**	Ph/2-ClC_6H_4 (**1j**)	59	>95:5	90:10 (>99:1)[f]
11	**3ka**	Ph/2-$OMeC_6H_4$ (**1k**)	73	>95:5	90:10 (99:1)[f]
12	**3la**	Ph/3-FC_6H_4 (**1l**)	81	>95:5	91:9
13	**3ma**	Ph/3,4-$Cl_2C_6H_3$ (**1m**)	48	>95:5	95:5
14	**3na**	Ph/3-Cl,4-FC_6H_3 (**1n**)	72	>95:5	90:10 (96:4)[f]
15	**3oa**	Ph/3,4,5-$F_3C_6H_2$ (**1o**)	41	>95:5	92:8
16	**3pa**	Ph/4-ClC_6H_4 (**1p**)	57	>95:5	91:9 (99:1)[f]
17[e]	**3qa**	Ph/4-BrC_6H_4 (**1q**)	40	>95:5	92:8 (99:1)[f]
18[e]	**3ra**	Ph/4-MeC_6H_4 (**1r**)	64	>95:5	90:10 (95:5)[f]
19[e]	**3sa**	Ph/2-naphthyl (**1s**)	42	>95:5	90:10
20	**3ta**	Ph/2-thiophenyl (**1t**)	31	>95:5	84:16
21	**3ua**	Et/Ph (**1u**)	N.R.	–	–
22	**3va**	Ph/*n*-Bu (**1v**)	N.R.	–	–

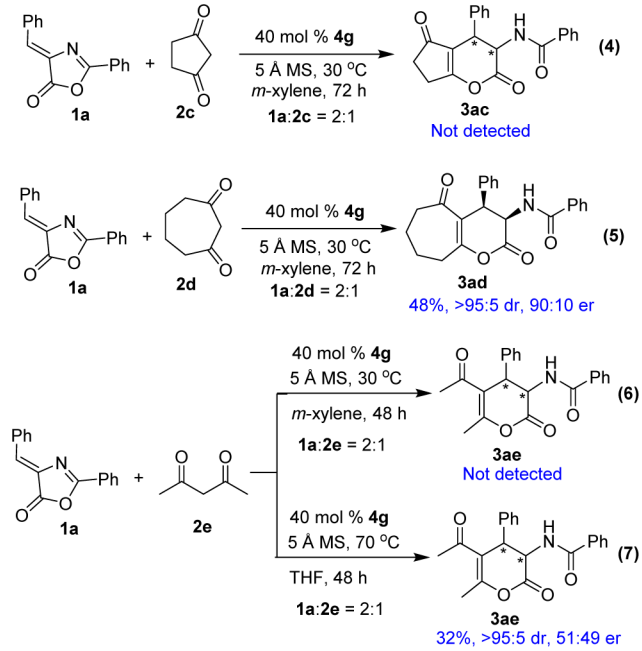
[a]Unless indicated otherwise, the reaction was carried out at the 0.1 mmol scale in the presence of 25 mol % **4g** in *m*-xylene (1 mL) at 30 °C with 5 Å MS (100 mg) as additives for 72 h, and the molar ratio of **1**:**2a** was 2:1. [b]Isolated yields. [c]The dr value was determined by ^{1}H NMR. [d]The er value was determined by HPLC. [e]In the presence of 40 mol % **4g**. [f]The er value was determined after recrystallization of *ent*-**3aa**.

for the reaction, we reoptimized the reaction conditions (see the Supporting Information for details), which found that the [3 + 3] cyclization could occur in THF to give the product **3ae** in 32% yield and 51:49 er (eq 7). This result implied that controlling the reactivity and the enantioselectivity of the acyclic 1,3-diones in the [3 + 3] cyclization was very difficult.

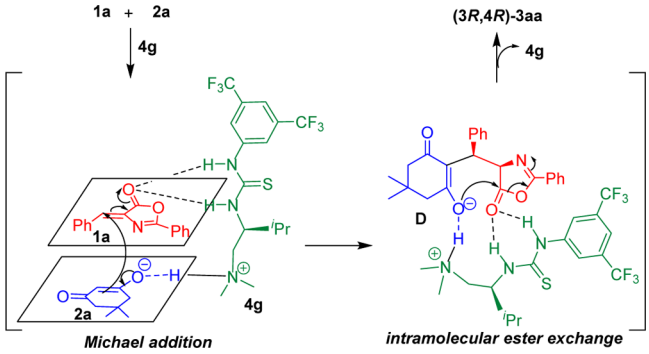
The absolute configuration of product **3ka** (99:1 er after recrystallization) was unambiguously determined to be (3*R*,4*R*) by single crystal X-ray diffraction analysis (see the Supporting Information for details).[13] Besides, the relative configuration of compound **3ka** was also identified to be cis by its single crystal structure. So, the relative and absolute configurations of other hexahydrocoumarins **3** were assigned by analogy with product **3ka**.

On the basis of the experimental results and previous theoretical investigation on thiourea-catalyzed reactions,[14] we suggested a possible transition state and activation mode of the [3 + 3] cyclization (Scheme 3). As exemplified by the formation of product **3aa**, in the first step of Michael addition, the thiourea functionality of the catalyst **4g** generated two hydrogen bonds with the carbonyl group of substrate **1a**. At the same time, the tertiary amine functionality of the catalyst **4g** served as a Brønsted base to deprotonate the OH group and formed a hydrogen bond with the enolate of dimedone **2a**. So, the dual activation of the chiral thiourea−tertiary amine catalyst to the two substrates facilitated an enantioselective Michael addition of

Scheme 2. Using 1,3-Cyclopentanedione, 1,3-Cycloheptanedione, and Acetylacetone as 1,3-Dione Substrates



Scheme 3. Suggested Transition State and Activation Mode



dimedone **2a** to substrate **1a**, leading to the generation of a transient intermediate **D**, which further performed an intramolecular ester exchange reaction again under the promotion of the same catalyst **4g** to afford the final hexahydrocoumarin product **3aa** with (3*R*,4*R*)-configuration.

To verify our suggested activation mode, we performed some ^{1}H NMR control experiments to investigate the interaction between the catalyst **4g** and the two substrates. As illustrated in Scheme 4, in the mixture of catalyst **4g** and dimedone **2a**, the peak of the enolized OH group (10.97 ppm) in dimedone **2a** disappeared. Besides, the peak of the two *N*-methyl groups in catalyst **4g** shifted from 2.21 to 2.28 ppm (see the Supporting Information). These phenomena indicated that the tertiary amine functionality of the catalyst **4g** might act as a Brønsted base to deprotonate the enolized OH group of dimedone **2a**. The disappeared signal of the OH group suggested that a deprotonation of the OH group might occur by the action of the Brønsted basic tertiary amine functionality. In the mixture of catalyst **4g** and substrate **1a**, the peak of the Ar−H in ortho-position of the thiourea functionality shifted from 8.02 to 8.04 ppm. Moreover, the peaks of the phenyl groups in substrate **1a** also had some slight shifts (see the Supporting Information).

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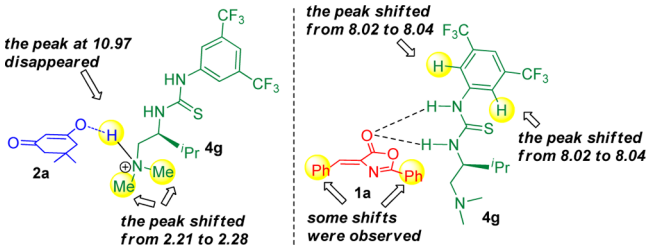
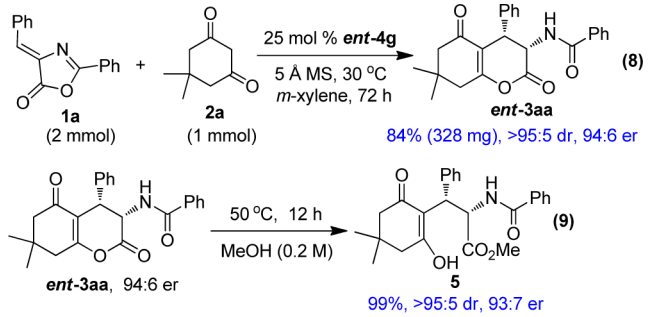
Scheme 4. ^{1}H NMR Control Experiments



These results indicated that the thiourea functionality of the catalyst **4g** might have some interactions with substrate **1a**.

Finally, to demonstrate the synthetic utility of this protocol, the model reaction was performed on a large scale (1 mmol) under the optimal conditions using *ent*-**4g** as a catalyst (eq 8).



Delightfully, compared with the small scale reaction (Table 2, entry 1), this large scale reaction afforded the hexahydrocoumarin *ent*-**3aa** at a higher yield of 84%, an excellent diastereoselectivity of >95:5 dr, and a nearly maintained enantioselectivity of 94:6 er. In addition, the generated *ent*-**3aa** was further subjected to alcoholysis (eq 9), which led to compound **5** at a quantitative yield of 99% and almost retained stereoselectivity (>95:5 dr, 93:7 er).

CONCLUSIONS

In summary, we have established the first catalytic asymmetric construction of biologically important hexahydrocoumarin scaffold, which takes advantage of chiral thiourea−tertiary amine-catalyzed enantioselective transformations. Besides, this reaction also realized the first catalytic asymmetric [3 + 3] cyclization of 4-arylidene-2-aryloxazol-5(4*H*)-ones with cyclohexane-1,3-diones, which afforded structurally diverse 3-amino-hexahydrocoumarin derivatives in excellent diastereoselectivities and high enantioselectivities (all >95:5 dr, up to 96:4 er). The investigation on the activation mode suggested that the chiral thiourea−tertiary amine catalyst simultaneously activated the two substrates via hydrogen-bonding interaction. Moreover, this reaction could be utilized to a large scale synthesis of the enantioenriched hexahydrocoumarin. This approach will not only provide an efficient method for the construction of chiral hexahydrocoumarin scaffold but will also enrich the research areas of asymmetric organocatalysis and catalytic enantioselective [3 + 3] cyclizations.

EXPERIMENTAL SECTION

General Information. ^{1}H and ^{13}C NMR spectra were measured at 400 and 100 MHz, respectively. The solvents used for NMR spectroscopy were $CDCl_3$, methanol-d_4, and DMSO-d_6, using tetramethylsilane as the internal reference. HRMS (ESI) was determined by a HRMS/MS instrument. Enantiomeric ratios (er) were determined by chiral high-performance liquid chromatography (chiral HPLC). The chiral columns used for the determination of enantiomeric ratios by chiral HPLC were Chiralpak AD-H and IC columns. Optical rotation values were measured with instruments operating at λ = 589 nm, corresponding to the sodium D line at the temperatures indicated. The X-ray source used for the single crystal X-ray diffraction analysis of compound **3ka** was Cu Kα (λ = 1.54178). Analytical grade solvents for the column chromatography were used after distillation. All starting materials commercially available were used directly. Substrates **1** were synthesized according to the literature method.[15]

Typical Experimental Procedure for the Synthesis of Products 3. To the mixture of 4-arylidene-2-aryloxazol-5(4*H*)-ones **1** (0.2 mmol), cyclohexane-1,3-diones **2** (0.1 mmol), chiral catalyst **4g** (0.025 mmol), and 5 Å MS (100 mg) was added *m*-xylene (1 mL). After being stirred at 30 °C for 72 h, the reaction mixture was filtered to remove the molecular sieves and the solid powder was washed with ethyl acetate. The resultant solution was concentrated under reduced pressure to give the residue, which was purified through flash column chromatography on silica gel to afford pure products **3**.

***N*-((3*R*,4*R*)-7,7-Dimethyl-2,5-dioxo-4-phenyl-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)benzamide (3aa).** Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; >95:5 dr; yield: 77% (30.0 mg); white solid; mp 135.7−136.9 °C; $[\alpha]_D^{20}$ = −98.7 (*c* 0.23, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.66−7.58 (m, 2H), 7.53−7.45 (m, 1H), 7.43−7.35 (m, 2H), 7.34−7.27 (m, 3H), 7.13−7.02 (m, 2H), 6.27 (d, *J* = 7.6 Hz, 1H), 5.37 (t, *J* = 7.6 Hz, 1H), 4.63 (d, *J* = 7.6 Hz, 1H), 2.70−2.52 (m, 2H), 2.43−2.23 (m, 2H), 1.19 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.3 (C═O), 167.1 (═C), 166.5 (C═O), 164.8 (C═O), 135.4 (ArC), 133.2 (ArC), 132.1 (ArC), 129.3 (ArC), 128.7 (ArC), 128.4 (ArC), 128.0 (ArC), 127.1 (ArC), 116.1 (═C), 52.6 (CH), 50.4 (CH_2), 40.7 (CH_2), 39.3 (CH), 32.7 (C), 28.6 (CH_3), 28.2 (CH_3); IR (KBr): 2925, 2360, 2342, 1792, 1733, 1653, 1540, 1489, 1377, 1261, 1161, 1089, 1050, 698, 556 cm^{-1}; ESI FTMS exact mass calcd for $(C_{24}H_{23}NO_4 + Na)^+$ requires *m*/*z* 412.1525, found *m*/*z* 412.1537; enantiomeric ratio (er) value: 96:4, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm): t_R = 9.297 min (major), t_R = 15.813 min (minor).

***N*-((3*R*,4*R*)-7,7-Dimethyl-2,5-dioxo-4-phenyl-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)-2-fluorobenzamide (3ba).** Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; >95:5 dr; yield: 47% (19.1 mg); white solid; mp 139.2−140.8 °C; $[\alpha]_D^{20}$ = −175.3 (*c* 0.29, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.13−8.00 (m, 1H), 7.53−7.41 (m, 1H), 7.32−7.27 (m, 3H), 7.26−7.20 (m, 1H), 7.13−7.09 (m, 2H), 7.08−7.00 (m, 1H), 6.90−6.79 (m, 1H), 5.49−5.33 (m, 1H), 4.60 (d, *J* = 7.6 Hz, 1H), 2.61 (s, 2H), 2.40−2.20 (m, 2H), 1.19 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.3 (C═O), 166.0 (═C), 164.8 (C═O), 163.2 (C═O), 163.1 (ArC),160.7 (d, *J* = 247.6 Hz, ArC), 135.2 (ArC), 134.0 (d, *J* = 9.3 Hz, ArC), 132.0 (d, *J* = 1.8 Hz, ArC), 129.3 (ArC), 128.4 (ArC), 127.9 (ArC), 124.8 (d, *J* = 3.3 Hz, ArC), 119.9 (d, *J* = 11.1 Hz, ArC), 116.2 (d, *J* = 24.3 Hz, ArC), 116.1 (═C), 52.7 (CH), 50.4 (CH_2), 40.8 (CH_2), 39.3 (CH), 32.7 (C), 28.6 (CH_3), 28.2 (CH_3); IR (KBr): 3433, 2960, 2923, 2360, 1801, 1654, 1614, 1518, 1477, 1374, 1348, 1162, 1116, 1089, 1074, 1029, 757, 543 cm^{-1}; ESI FTMS exact mass calcd for $(C_{24}H_{22}FNO_4 + Na)^+$ requires *m*/*z* 430.1431, found *m*/*z* 430.1409; enantiomeric ratio (er) value: 93:7, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm): t_R = 11.057 min (major), t_R = 21.037 min (minor).

2-Bromo-*N*-((3*R*,4*R*)-7,7-dimethyl-2,5-dioxo-4-phenyl-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)benzamide (3ca). Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; >95:5 dr; yield: 91% (42.5 mg); white solid; mp 172.6−174.3 °C; $[\alpha]_D^{20}$ = −176.2 (*c* 0.61, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.58−7.52 (m, 1H), 7.46−7.39 (m, 1H), 7.36−7.26 (m, 4H), 7.25−7.22 (m, 1H), 7.18−7.12 (m, 2H), 6.30 (d, *J* = 7.2 Hz, 1H), 5.44−5.24 (m, 1H), 4.70 (d, *J* = 7.6 Hz, 1H), 2.60 (s, 2H), 2.41−2.18 (m, 2H), 1.18 (s, 3H), 1.12 (s, 3H); ^{13}C NMR

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(100 MHz, $CDCl_3$) δ (ppm): 195.2 (C═O), 167.2 (═C), 166.0 (C═O), 164.5 (C═O), 136.2 (ArC), 135.4 (ArC), 133.6 (ArC), 131.8 (ArC), 129.7 (ArC), 129.3 (ArC), 128.4 (ArC), 128.2 (ArC), 127.5 (ArC), 119.5 (ArC), 116.3 (═C), 52.8 (CH), 50.4 (CH_2), 40.8 (CH_2), 39.2 (CH), 32.7 (C), 28.5 (CH_3), 28.2 (CH_3); IR (KBr): 3404, 2962, 2925, 2360, 1777, 1676, 1592, 1508, 1369, 1115, 1096, 750, 697 cm^{-1}; ESI FTMS exact mass calcd for $(C_{24}H_{22}BrNO_4 + Na)^+$ requires m/z 490.0630, found m/z 490.0625; enantiomeric ratio (er) value: 90:10, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 11.433 min (major), t_R = 13.703 min (minor).

***N*-((3*R*,4*R*)-7,7-Dimethyl-2,5-dioxo-4-phenyl-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)-3-methoxybenzamide (3da).** Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; >95:5 dr; yield: 74% (31.0 mg); white solid; mp 223.1−224.8 °C; $[\alpha]_D^{20}$ = −212.8 (*c* 0.48, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):7.34−7.26 (m, 4H), 7.24−7.19 (m, 1H), 7.13−7.07 (m, 3H), 7.05−6.98 (m, 1H), 6.23 (d, J = 7.6 Hz, 1H), 5.35 (t, J = 7.6 Hz, 1H), 4.63 (d, J = 7.6 Hz, 1H), 3.81 (s, 3H), 2.70−2.54 (m, 2H), 2.42−2.24 (m, 2H), 1.20 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.2 (C═O), 167.0 (═C), 166.4 (C═O), 164.8 (C═O), 159.8 (ArC), 135.4 (ArC), 134.7 (ArC), 129.7 (ArC), 129.3 (ArC), 128.4 (ArC), 128.0 (ArC), 118.8 (ArC), 118.4 (ArC), 116.1 (═C), 112.3 (ArC), 55.4 (CH_3), 52.6 (CH), 50.4 (CH_2), 40.8 (CH_2), 39.4 (CH), 32.7 (C), 28.6 (CH_3), 28.1 (CH_3); IR (KBr): 3290, 2956, 2928, 2360, 1794, 1647, 1542, 1376, 1340, 1247, 1115, 1028, 893, 812, 695, 545 cm^{-1}; ESI FTMS exact mass calcd for $(C_{25}H_{25}NO_5 + Na)^+$ requires m/z 442.1631, found m/z 442.1610; enantiomeric ratio (er) value: 91:9, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 10.440 min (major), t_R = 18.030 min (minor).

4-Bromo-*N*-((3*R*,4*R*)-7,7-dimethyl-2,5-dioxo-4-phenyl-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)benzamide (3ea). Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; >95:5 dr; yield: 52% (24.5 mg); white solid; mp 135.5−137.9 °C; $[\alpha]_D^{20}$ = −26.3 (*c* 0.48, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.58−7.42 (m, 4H), 7.35−7.27 (m, 3H), 7.15−6.97 (m, 2H), 6.25 (d, J = 7.6 Hz, 1H), 5.40−5.27 (m, 1H), 4.61 (d, J = 7.6 Hz, 1H), 2.60 (s, 2H), 2.39−2.23 (m, 2H), 1.19 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.2 (C═O), 166.4 (═C), 166.1 (C═O), 164.7 (C═O), 135.3 (ArC), 132.0 (ArC), 131.9 (ArC), 129.3 (ArC), 128.7 (ArC), 128.4 (ArC), 127.9 (ArC), 126.9 (ArC), 116.0(═C), 52.7(CH), 50.4 (CH_2), 40.7 (CH_2), 39.2 (CH), 32.7 (C), 28.6 (CH_3), 28.1 (CH_3); IR (KBr): 3735, 2960, 2925, 2360, 2342, 1792, 1669, 1653, 1507, 1481, 1374, 1161, 1111, 1088, 669 cm^{-1}; ESI FTMS exact mass calcd for $(C_{24}H_{22}BrNO_4 + Na)^+$ requires m/z 490.0630, found m/z 490.0634; enantiomeric ratio(er) value: 88:12, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 12.973 min (major), t_R = 26.017 min (minor).

***N*-((3*R*,4*R*)-7,7-Dimethyl-2,5-dioxo-4-phenyl-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)-4-methylbenzamide (3fa).** Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; >95:5 dr; yield: 84% (33.9 mg); white solid; mp 208.8−210.5 °C; $[\alpha]_D^{20}$ = −260.7 (*c* 0.40, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.52 (d, J = 8.0 Hz, 2H), 7.35−7.26 (m, 3H), 7.19 (d, J = 8.0 Hz, 2H), 7.11−7.05 (m, 2H), 6.21 (d, J = 7.6 Hz, 1H), 5.37 (t, J = 7.6 Hz, 1H), 4.63 (d, J = 7.6 Hz, 1H), 2.61 (s, 2H), 2.38 (s, 3H), 2.36−2.25 (m, 2H), 1.20 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.2 (C═O), 167.0 (═C), 166.6 (C═O), 164.7 (C═O), 142.7 (ArC), 135.4 (ArC), 130.4 (ArC), 129.3 (ArC), 129.2 (ArC), 128.3 (ArC), 128.0 (ArC), 127.1 (ArC), 116.2 (═C), 52.6 (CH), 50.4 (CH_2), 40.8 (CH_2), 39.4 (CH), 32.7 (C), 28.6 (CH_3), 28.2 (CH_3), 21.5 (CH_3); IR (KBr): 3424, 2957, 2360, 2342, 1782, 1670, 1540, 1497, 1371, 1090, 701, 565 cm^{-1}; ESI FTMS exact mass calcd for $(C_{25}H_{25}NO_4 + Na)^+$ requires m/z 426.1682, found m/z 426.1681; enantiomeric ratio (er) value: 90:10, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 11.347 min (major), t_R = 23.990 min (minor).

***N*-((3*R*,4*R*)-7,7-Dimethyl-2,5-dioxo-4-phenyl-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)-4-methoxybenzamide (3ga).** Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; >95:5 dr; yield: 57% (24.0 mg); white solid; mp 130.7−132.1 °C; $[\alpha]_D^{20}$ = −21.0 (*c* 0.48, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.65−7.54 (m, 2H), 7.35−7.27 (m, 3H), 7.12−7.04 (m, 2H), 6.92−6.84 (m, 2H), 6.14 (d, J = 7.6 Hz, 1H), 5.37 (t, J = 7.6 Hz, 1H), 4.61 (d, J = 7.6 Hz, 1H), 3.83 (s, 3H), 2.61 (s, 2H), 2.40−2.24 (m, 2H), 1.20 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.3 (C═O), 166.7 (═C), 166.5 (C═O), 164.8 (C═O), 162.7 (ArC), 135.4 (ArC), 129.2 (ArC), 129.0 (ArC), 128.3 (ArC), 128.0 (ArC), 125.5 (ArC), 116.2 (═C), 113.9 (ArC), 55.4 (CH_3), 52.5 (CH), 50.4 (CH_2), 40.8 (CH_2), 39.4 (CH), 32.7 (C), 28.6 (CH_3), 28.2 (CH_3); IR (KBr): 2962, 2375, 1844, 1772, 1706, 1536, 1261, 1160, 1090, 1029, 803, 669, 650 cm^{-1}; ESI FTMS exact mass calcd for $(C_{25}H_{25}NO_5 + Na)^+$ requires m/z 442.1631, found m/z 442.1607; enantiomeric ratio (er) value: 93:7, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 15.367 min (major), t_R = 32.060 min (minor).

***N*-((3*R*,4*R*)-7,7-Dimethyl-2,5-dioxo-4-phenyl-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)-2-naphthamide (3ha).** Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; >95:5 dr; yield: 74% (32.7 mg); white solid; mp 221.2−223.1 °C; $[\alpha]_D^{20}$ = −214.3 (*c* 0.48, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.14 (s, 1H), 7.92−7.79 (m, 3H), 7.76−7.64 (m, 1H), 7.60−7.49 (m, 2H), 7.37−7.28 (m, 3H), 7.16−7.06 (m, 2H), 6.42 (d, J = 7.6 Hz, 1H), 5.44 (t, J = 7.6 Hz, 1H), 4.70 (d, J = 7.6 Hz, 1H), 2.70−2.56 (m, 2H), 2.44−2.23 (m, 2H), 1.21 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.3 (C═O), 167.2 (═C), 166.6 (C═O), 164.8 (C═O), 135.4 (ArC), 135.0 (ArC), 132.5 (ArC), 130.4 (ArC), 129.3 (ArC), 129.0 (ArC), 128.7 (ArC), 128.4 (ArC), 128.0 (ArC), 128.0 (ArC), 127.9 (ArC), 127.8 (ArC), 126.9 (ArC), 123.4 (ArC), 116.2 (═C), 52.8 (CH), 50.4 (CH_2), 40.8 (CH_2), 39.4 (CH), 32.7 (C), 28.6 (CH_3), 28.2 (CH_3); IR (KBr): 3275, 3054, 2960, 2925, 2768, 2360, 2267, 1782, 1653, 1559, 1466, 1375, 1261, 1109, 1088, 864, 820, 734 cm^{-1}; ESI FTMS exact mass calcd for $(C_{28}H_{25}NO_4 + Na)^+$ requires m/z 462.1682, found m/z 462.1683; enantiomeric ratio (er) value: 88:12, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 21.637 min (major), t_R = 38.810 min (minor).

***N*-((3*R*,4*S*)-4-(2-Fluorophenyl)-7,7-dimethyl-2,5-dioxo-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)benzamide (3ia).** Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; >95:5 dr; yield: 49% (20.0 mg); white solid; mp 178.6−179.5 °C; $[\alpha]_D^{20}$ = −110.8 (*c* 0.15, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.62−7.56 (m, 2H), 7.52−7.45 (m, 1H), 7.42−7.34 (m, 2H), 7.30−7.21 (m, 1H), 7.15−6.98 (m, 3H), 6.41 (d, J = 7.2 Hz, 1H), 5.41−5.30 (m, 1H), 4.99 (d, J = 8.0 Hz, 1H), 2.65−2.52 (m, 2H), 2.34 (d, J = 16.4 Hz, 1H), 2.28 (d, J = 16.4 Hz, 1H), 1.19 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.3 (C═O), 167.4 (═C), 166.2 (C═O), 165.1 (C═O), 161.1 (d, J = 245 Hz, ArC), 133.3 (ArC), 132.0 (ArC), 130.5 (d, J = 4.1 Hz, ArC), 130.1 (d, J = 8.4 Hz, ArC), 128.6 (ArC), 127.0 (ArC), 124.9 (d, J = 3.5 Hz, ArC), 122.6 (d, J = 14.2 Hz, ArC), 116.0 (d, J = 22.1 Hz, ArC), 114.3 (═C), 51.8 (CH), 50.4 (CH_2), 40.9 (CH_2), 34.8 (CH), 32.6 (C), 28.5 (CH_3), 28.0 (CH_3); IR (KBr): 3396, 3307, 2962, 2927, 2360, 2342, 1783, 1581, 1527, 1489, 1456, 1374, 1281, 1113, 1079, 757, 714, 559 cm^{-1}; ESI FTMS exact mass calcd for $(C_{24}H_{22}FNO_4 + Na)^+$ requires m/z 430.1431, found m/z 430.1447; enantiomeric ratio(er) value: 90:10, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 11.600 min (major), t_R = 17.453 min (minor).

***N*-((3*R*,4*S*)-4-(2-Chlorophenyl)-7,7-dimethyl-2,5-dioxo-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)benzamide (3ja).** Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; >95:5 dr; yield: 59% (25.0 mg); white solid;

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mp 208.4−210.3 °C; $[\alpha]_D^{20}$ = −59.1 (*c* 0.35, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.67−7.61 (m, 2H), 7.53−7.46 (m, 1H), 7.43−7.36 (m, 3H), 7.25−7.18 (m, 2H), 7.01−6.93 (m, 1H), 6.23 (d, *J* = 8.0 Hz, 1H), 5.51 (t, *J* = 7.6 Hz, 1H), 5.25 (d, *J* = 7.6 Hz, 1H), 2.68−2.55 (m, 2H), 2.38−2.26 (m, 2H), 1.20 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.0 (C═O), 167.6 (═C), 166.2 (C═O), 165.4 (C═O), 135.4 (ArC), 133.5 (ArC), 133.5 (ArC), 132.0 (ArC), 130.5 (ArC), 129.6 (ArC), 128.6 (ArC), 127.8 (ArC), 127.2 (ArC), 116.0 (═C), 52.2 (CH), 50.3 (CH_2), 40.8 (CH_2), 36.0 (CH), 32.7 (C), 28.6 (CH_3), 28.1 (CH_3); IR (KBr): 3305, 2958, 2925, 2360, 1806, 1645, 1529, 1371, 1341, 1162, 1116, 1085, 801, 716, 660 cm^{-1}; ESI FTMS exact mass calcd for ($C_{24}H_{22}ClNO_4$ + Na)$^+$ requires *m*/*z* 446.1135, found *m*/*z* 446.1152; enantiomeric ratio (er) value: 90:10, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm): t_R = 11.327 min (major), t_R = 21.293 min (minor).

***N*-((3*R*,4*R*)-4-(2-Methoxyphenyl)-7,7-dimethyl-2,5-dioxo-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)benzamide (3ka).** Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; >95:5 dr; yield: 73% (30.5 mg); white solid; mp 197.1−198.3 °C; $[\alpha]_D^{20}$ = −108.8 (*c* 0.6, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.52−7.40 (m, 3H), 7.38−7.28 (m, 2H), 7.24−7.15 (m, 2H), 6.92−6.84 (m, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.34 (d, *J* = 7.2 Hz, 1H), 5.35−5.15 (m, 1H), 4.85 (d, *J* = 8.8 Hz, 1H), 3.66 (s, 3H), 2.67−2.41 (m, 2H), 2.33−2.10 (m, 2H), 1.14 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.9 (C═O), 167.2 (═C), 166.2 (C═O), 164.3 (C═O), 157.1 (ArC), 133.6 (ArC), 131.8 (ArC), 129.4 (ArC), 128.5 (ArC), 127.0 (ArC), 123.6 (ArC), 121.3 (ArC), 113.8 (ArC), 110.4 (═C), 54.2 (CH), 50.9 (CH_2), 50.5 (CH_2), 41.0 (CH), 32.6 (C), 28.4 (CH_3), 28.0 (CH_3); IR (KBr): 3447, 3290, 2923, 2360, 2342, 1774, 1663, 1636, 1541, 1497, 1370, 1259, 1162, 1098, 1026, 751, 691, 669 cm^{-1}; ESI FTMS exact mass calcd for ($C_{25}H_{25}NO_5$ + Na)$^+$ requires *m*/*z* 442.1631, found *m*/*z* 442.1620; enantiomeric ratio (er) value: 90:10, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm): t_R = 12.987 min (major), t_R = 17.907 min (minor).

***N*-((3*R*,4*R*)-4-(3-Fluorophenyl)-7,7-dimethyl-2,5-dioxo-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)benzamide (3la).** Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; >95:5 dr; yield: 81% (33.1 mg); white solid; mp 142.5−144.1 °C; $[\alpha]_D^{20}$ = −21.3 (*c* 0.32, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.69−7.61 (m, 2H), 7.56−7.49 (m, 1H), 7.45−7.38 (m, 2H), 7.32−7.27 (m, 1H), 7.02−6.94 (m, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.83−6.76 (m, 1H), 6.33 (d, *J* = 6.8 Hz, 1H), 5.34 (t, *J* = 7.2 Hz, 1H), 4.69 (d, *J* = 7.6 Hz, 1H), 2.62 (s, 2H), 2.37 (d, *J* = 16.4 Hz, 1H), 2.30 (d, *J* = 16.4 Hz, 1H), 1.20 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.2 (C═O), 167.2(═C), 166.3 (C═O), 164.9 (C═O), 163.1 (d, *J* = 246.3 Hz, ArC), 138.0 (ArC), 133.1 (ArC), 132.3 (ArC), 130.8 (d, *J* = 8.2 Hz, ArC), 128.8 (ArC), 127.0 (ArC), 123.8 (d, *J* = 3 Hz, ArC), 115.8 (═C), 115.4 (d, *J* = 20.8 Hz, ArC), 115.0 (d, *J* = 21.6 Hz, ArC), 52.6 (CH), 50.4 (CH_2), 40.7 (CH_2), 39.0 (CH), 32.7 (C), 28.6 (CH_3), 28.2 (CH_3); IR (KBr): 3446, 2963, 2922, 2341, 1791, 1646, 1636, 1540, 1489, 1456, 1373, 1261, 1083, 669 cm^{-1}; ESI FTMS exact mass calcd for ($C_{24}H_{22}FNO_4$ + Na)$^+$ requires *m*/*z* 430.1431, found *m*/*z* 430.1427; enantiomeric ratio (er) value: 91:9, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm): t_R = 9.737 min (major), t_R = 16.513 min (minor).

***N*-((3*R*,4*R*)-4-(3,4-Dichlorophenyl)-7,7-dimethyl-2,5-dioxo-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)benzamide (3ma).** Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; >95:5 dr; yield: 48% (22.0 mg); white solid; mp 218.8−219.7 °C; $[\alpha]_D^{20}$ = −107.7 (*c* 0.14, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.71−7.61 (m, 2H), 7.58−7.49 (m, 1H), 7.47−7.39 (m, 2H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.15 (s, 1H), 6.95−6.86 (m, 1H), 6.43 (d, *J* = 6.8 Hz, 1H), 5.34−5.27 (m, 1H), 4.69 (d, *J* = 7.6 Hz, 1H), 2.62 (s, 2H), 2.37 (d, *J* = 16.4 Hz, 1H), 2.31 (d, *J* = 16.4 Hz, 1H), 1.20 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.1 (C═O), 167.3 (═C), 166.1 (C═O), 165.1 (C═O), 135.8 (ArC), 133.4 (ArC), 132.9 (ArC), 132.6 (ArC), 132.4 (ArC), 131.1 (ArC), 130.0 (ArC), 128.8 (ArC), 127.3 (ArC), 127.1 (ArC), 115.4 (═C), 52.6 (CH), 50.3 (CH_2), 40.7 (CH_2), 38.4 (CH), 32.7 (C), 28.6 (CH_3), 28.1 (CH_3); IR (KBr): 3587, 3567, 3244, 2928, 2360, 2342, 1782, 1637, 1541, 1472, 1363, 1162, 1116, 1088, 1018, 784, 693, 669, 590 cm^{-1}; ESI FTMS exact mass calcd for ($C_{24}H_{21}Cl_2NO_4$ + Na)$^+$ requires *m*/*z* 480.0746, found *m*/*z* 480.0735; enantiomeric ratio (er) value: 95:5, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm): t_R = 8.997 min (major), t_R = 12.830 min (minor).

***N*-((3*R*,4*R*)-4-(3-Chloro-4-fluorophenyl)-7,7-dimethyl-2,5-dioxo-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)benzamide (3na).** Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; >95:5 dr; yield: 72% (31.8 mg); white solid; mp 145.1−146.3 °C; $[\alpha]_D^{20}$ = −40.1 (*c* 0.30, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.71−7.61 (m, 2H), 7.58−7.52 (m, 1H), 7.48−7.37 (m, 2H), 7.14−7.03 (m, 2H), 6.98−6.89 (m, 1H), 6.38 (d, *J* = 6.4 Hz, 1H), 5.36−5.19 (m, 1H), 4.71 (d, *J* = 7.6 Hz, 1H), 2.63 (s, 2H), 2.42−2.25 (m, 2H), 1.21 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.1 (C═O), 167.3(═C), 166.2 (C═O), 165.0 (C═O), 157.9 (d, *J* = 248.7 Hz, ArC), 133.0 (ArC), 132.6 (d, *J* = 3.9 Hz, ArC), 132.4 (ArC), 130.1 (ArC), 128.8 (ArC), 127.8 (d, *J* = 7.3 Hz, ArC), 127.0 (ArC), 121.9 (d, *J* = 17.8 Hz, ArC), 117.3 (d, *J* = 21.1 Hz, ArC), 115.6 (═C), 52.7 (CH), 50.3 (CH_2), 40.7 (CH_2), 38.3 (CH), 32.7 (C), 28.5 (CH_3), 28.2 (CH_3); IR (KBr): 3420, 2963, 2923, 2851, 2360, 2342, 1792, 1653, 1540, 1500, 1373, 1261, 1088, 1025, 802, 692, 669 cm^{-1}; ESI FTMS exact mass calcd for ($C_{24}H_{21}ClFNO_4$ + Na)$^+$ requires *m*/*z* 464.1041, found *m*/*z* 464.1032; enantiomeric ratio (er) value: 90:10, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm): t_R = 8.807 min (major), t_R = 13.407 min (minor).

***N*-((3*R*,4*R*)-7,7-Dimethyl-2,5-dioxo-4-(3,4,5-trifluorophenyl)-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)benzamide (3oa).** Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; >95:5 dr; yield: 41% (18.0 mg); white solid; mp 224.1−225.3 °C; $[\alpha]_D^{20}$ = −45.8 (*c* 0.43, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.70−7.64 (m, 2H), 7.57−7.50 (m, 1H), 7.46−7.40 (m, 2H), 6.74−6.65 (m, 2H), 6.51 (d, *J* = 6.4 Hz, 1H), 5.31−5.23 (m, 1H), 4.71 (d, *J* = 7.6 Hz, 1H), 2.63 (s, 2H), 2.38 (d, *J* = 16.4 Hz, 1H), 2.31 (d, *J* = 16.4 Hz, 1H), 1.20 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.0 (C═O), 167.3 (═C), 166.0 (C═O), 165.2 (C═O), 151.5 (d, *J* = 250.9 Hz,-ArC), 132.7 (ArC), 132.5 (ArC), 132.0 (ArC), 128.9 (ArC), 127.0 (ArC), 115.2 (═C), 112.3 (d, *J* = 6 Hz,-ArC), 112.2 (d, *J* = 5.8 Hz,-ArC), 52.7 (CH), 50.3 (CH_2), 40.7 (CH_2), 38.5 (CH), 32.7 (C), 28.5 (CH_3), 28.2 (CH_3); IR (KBr): 3229, 3059, 2962, 2924, 2850, 2360, 2342, 1786, 1671, 1637, 1528, 1453, 1355, 1262, 1042, 800, 697 cm^{-1}; ESI FTMS exact mass calcd for ($C_{24}H_{20}F_3NO_4$ + Na)$^+$ requires *m*/*z* 466.1242, found *m*/*z* 466.1247; enantiomeric ratio (er) value: 92:8, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm): t_R = 7.250 min (major), t_R = 11.623 min (minor).

***N*-((3*R*,4*R*)-4-(4-Chlorophenyl)-7,7-dimethyl-2,5-dioxo-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)benzamide (3pa).** Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; >95:5 dr; yield: 57% (24.0 mg); white solid; mp 240.0−241.6 °C; $[\alpha]_D^{20}$ = −107.6 (*c* 0.58, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.68−7.61 (m, 2H), 7.57−7.49 (m, 1H), 7.46−7.39 (m, 2H), 7.28−7.26 (m, 2H), 7.04−6.99 (m, 2H), 6.33 (d, *J* = 6.8 Hz, 1H), 5.36−5.29 (m, 1H), 4.68 (d, *J* = 7.6 Hz, 1H), 2.67−2.56 (m, 2H), 2.36 (d, *J* = 16.0 Hz, 1H), 2.29 (d, *J* = 16.0 Hz, 1H), 1.20 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.2 (C═O), 167.2 (═C), 166.3 (C═O), 164.8 (C═O), 134.3 (ArC), 134.0 (ArC), 133.0 (ArC), 132.3 (ArC), 129.4 (ArC), 129.3 (ArC), 128.8 (ArC), 127.1 (ArC), 115.9 (═C), 52.7 (CH), 50.3 (CH_2), 40.7 (CH_2), 38.7 (CH), 32.7 (C), 28.6 (CH_3), 28.1 (CH_3); IR (KBr): 3241, 3064, 2922, 2360, 1782, 1669, 1638, 1545, 1372, 1118, 1087, 1014, 851, 692, 572, 542 cm^{-1}; ESI FTMS exact mass calcd for

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$(C_{24}H_{22}ClNO_4 + Na)^+$ requires m/z 446.1135, found m/z 446.1137; enantiomeric ratio (er) value: 91:9, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 8.547 min (major), t_R = 16.303 min (minor).

***N*-((3*R*,4*R*)-4-(4-Bromophenyl)-7,7-dimethyl-2,5-dioxo-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)benzamide (3qa).** Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; >95:5 dr; yield: 40% (18.8 mg); white solid; mp 246.9−248.3 °C; $[\alpha]_D^{20}$ = −27.7 (*c* 0.50, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.70−7.59 (m, 2H), 7.57−7.47 (m, 1H), 7.47−7.35 (m, 4H), 7.02−6.89 (m, 2H), 6.38 (d, J = 7.2 Hz, 1H), 5.41−5.27 (m, 1H), 4.65 (d, J = 7.6 Hz, 1H), 2.68−2.52 (m, 2H), 2.35 (d, J = 16.4 Hz, 1H), 2.28 (d, J = 16.4 Hz, 1H), 1.19 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.2 (C═O), 167.2 (═C), 166.3 (C═O), 164.9 (C═O), 134.5 (ArC), 133.0 (ArC), 132.3 (ArC), 132.3 (ArC), 129.7 (ArC), 128.8 (ArC), 127.1 (ArC), 122.4 (ArC), 115.8 (═C), 52.6 (CH), 50.3 (CH_2), 40.7 (CH_2), 38.7 (CH), 32.7 (C), 28.6 (CH_3), 28.1 (CH_3); IR (KBr): 3244, 3064, 3027, 2953, 2921, 2360, 2342, 1792, 1781, 1637, 1577, 1542, 1490, 1363, 1120, 1086, 1009, 850, 691 cm^{-1}; ESI FTMS exact mass calcd for $(C_{24}H_{22}BrNO_4 + Na)^+$ requires m/z 490.0630, found m/z 490.0625; enantiomeric ratio (er) value: 92:8, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 8.953 min (major), t_R = 16.353 min (minor).

***N*-((3*R*,4*R*)-7,7-Dimethyl-2,5-dioxo-4-(*p*-tolyl)-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)benzamide (3ra).** Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; >95:5 dr; yield: 64% (26.0 mg); white solid; mp 238.2−239.5 °C; $[\alpha]_D^{20}$ = −218.5 (*c* 0.38, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.71−7.63 (m, 2H), 7.57−7.50 (m, 1H), 7.46−7.39 (m, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.05−6.96 (m, 2H), 6.27 (d, J = 7.6 Hz, 1H), 5.38 (t, J = 7.6 Hz, 1H), 4.61 (d, J = 7.2 Hz, 1H), 2.63 (s, 2H), 2.44−2.35 (m, 1H), 2.33 (s, 3H), 2.29 (s, 1H), 1.22 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.2 (C═O), 167.1 (═C), 166.6 (C═O), 164.6 (C═O), 138.2 (ArC), 133.3 (ArC), 132.2 (ArC), 132.1 (ArC), 130.0 (ArC), 128.7 (ArC), 127.8 (ArC), 127.1 (ArC), 116.3 (═C), 52.6 (CH), 50.4 (CH_2), 40.8 (CH_2), 39.0 (CH), 32.7 (C), 28.6 (CH_3), 28.1 (CH_3), 21.1 (CH_3); IR (KBr): 3254, 2924, 2342, 1783, 1663, 1641, 1543, 1372, 1162, 1118, 1086, 669, 534 cm^{-1}; ESI FTMS exact mass calcd for $(C_{25}H_{25}NO_4 + Na)^+$ requires m/z 426.1682, found m/z 426.1693; enantiomeric ratio (er) value: 90:10, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 8.800 min (major), t_R = 13.523 min (minor).

***N*-((3*R*,4*R*)-7,7-dDimethyl-4-(naphthalen-2-yl)-2,5-dioxo-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)benzamide (3sa).** Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; >95:5 dr; yield: 42% (18.6 mg); white solid; mp 202.8−203.7 °C; $[\alpha]_D^{20}$ = −116.5 (*c* 0.26, acetone);^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.21 (d, J = 8.4 Hz, 1H), 7.88−7.74 (m, 2H), 7.48−7.30 (m, 4H), 7.25−7.03 (m, 5H), 5.98 (d, J = 6.8 Hz, 1H), 5.67−5.47 (m, 2H), 2.69 (s, 2H), 2.38 (d, J = 16.4 Hz, 1H), 2.32 (d, J = 16.4 Hz, 1H), 1.24 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.2 (C═O), 167.7 (═C), 166.3 (C═O), 165.4 (C═O), 134.0 (ArC), 133.2 (ArC), 132.6 (ArC), 131.9 (ArC), 131.8 (ArC), 129.1 (ArC), 128.7 (ArC), 128.3 (ArC), 127.0 (ArC), 126.1 (ArC), 125.4 (ArC), 123.7 (ArC), 123.5 (ArC), 116.8 (═C), 53.4 (CH), 50.4 (CH_2), 40.9 (CH_2), 33.9 (CH), 32.8 (C), 28.6 (CH_3), 28.3 (CH_3); IR (KBr): 3261, 2925, 2342, 1796, 1670, 1647, 1540, 1374, 1161, 1082, 1056, 782, 698, 669 cm^{-1}; ESI FTMS exact mass calcd for $(C_{28}H_{25}NO_4 + Na)^+$ requires m/z 462.1682, found m/z 462.1672; enantiomeric ratio (er) value: 90:10, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 12.643 min (major), t_R = 18.467 min (minor).

***N*-((3*R*,4*R*)-7,7-Dimethyl-2,5-dioxo-4-(thiophen-2-yl)-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)benzamide (3ta).** Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; >95:5 dr; yield: 31% (12.1 mg); white solid; mp 130.5−131.3 °C; $[\alpha]_D^{20}$ = −117.8 (*c* 0.20, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.78−7.69 (m, 2H), 7.56−7.49 (m, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.23−7.16 (m, 1H), 6.98−6.91 (m, 1H), 6.83 (d, J = 3.2 Hz, 1H), 6.56 (d, J = 7.6 Hz, 1H), 5.41−5.27 (m, 1H), 4.92 (d, J = 7.2 Hz, 1H), 2.65−2.50 (m, 2H), 2.41−2.28 (m, 2H), 1.19 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.0 (C═O), 167.1 (═C), 166.1 (C═O), 164.8 (C═O), 137.9 (ArC), 133.2 (ArC), 132.2 (ArC), 128.7 (ArC), 127.7 (ArC), 127.2 (ArC), 126.4 (ArC), 125.7 (ArC), 116.5 (═C), 52.9 (CH), 50.3 (CH_2), 40.7 (CH_2), 34.6 (CH), 32.6 (C), 28.8 (CH_3), 27.9 (CH_3); IR (KBr): 3446, 2924, 2360, 2342, 1734, 1717, 1669, 1653, 1647, 1636, 1559, 1540, 1521, 1507, 1457, 669 cm^{-1}; ESI FTMS exact mass calcd for $(C_{22}H_{21}NO_4S + Na)^+$ requires m/z 418.1089, found m/z 418.1080; enantiomeric ratio (er) value: 84:16, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 11.447 min (major), t_R = 18.633 min (minor).

***N*-((3*R*,4*R*)-2,5-Dioxo-4-phenyl-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)benzamide (3ab).** Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; >95:5 dr; yield: 75% (27.1 mg); white solid; mp 200.7−201.9 °C; $[\alpha]_D^{20}$ = −215.3 (*c* 0.4, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.66−7.58 (m, 2H), 7.55−7.46 (m, 1H), 7.43−7.36 (m, 2H), 7.33−7.27 (m, 3H), 7.14−7.04 (m, 2H), 6.26 (d, J = 7.6 Hz, 1H), 5.37 (t, J = 7.6 Hz, 1H), 4.64 (d, J = 7.6 Hz, 1H), 2.92−2.64 (m, 2H), 2.57−2.33 (m, 2H), 2.24−2.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.4 (C═O), 167.1 (C═O), 166.4(C═O), 135.3 (ArC), 133.2 (ArC), 132.1 (ArC), 129.2 (ArC), 128.7 (ArC), 128.4 (ArC), 128.0 (ArC), 127.1 (ArC), 117.4 (═C), 52.5 (CH), 39.4 (CH), 36.5 (CH_2), 27.0 (CH_2), 20.6 (CH_2); IR (KBr): 3420, 2960, 2924, 2360, 2342, 1734, 1653, 1559, 1489, 1457, 1375, 1262, 1090, 1028, 803, 696 cm^{-1}; ESI FTMS exact mass calcd for $(C_{22}H_{19}NO_4 + Na)^+$ requires m/z 384.1212, found m/z 384.1221; enantiomeric ratio (er) value: 90:10, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 10.970 min (major), t_R = 15.707 min (minor).

***N*-((3*R*,4*R*)-2,5-Dioxo-4-phenyl-2,3,4,5,6,7,8,9-octahydrocyclohepta[*b*]pyran-3-yl)benzamide (3ad).** Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 72 h; >95:5 dr; yield: 48% (18.0 mg); white solid; mp 145.3−146.4 °C; $[\alpha]_D^{20}$ = −152.5 (*c* 0.2, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.66 (d, J = 7.2 Hz, 2H), 7.57−7.48 (m, 1H), 7.45−7.37 (m, 2H), 7.36−7.25 (m, 3H), 7.17−7.03 (m, 2H), 6.28 (d, J = 7.2 Hz, 1H), 5.34 (t, J = 7.2 Hz, 1H), 4.72 (d, J = 7.2 Hz, 1H), 2.88 (t, J = 6.0 Hz, 2H), 2.68 (t, J = 6.4 Hz, 2H), 2.12−1.81 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 198.5 (C═O), 167.1 (═C), 166.8 (C═O), 165.5 (C═O), 135.4 (ArC), 133.3 (ArC), 132.1 (ArC), 129.2 (ArC), 128.7 (ArC), 128.3 (ArC), 128.1 (ArC), 128.1(ArC), 127.1 (ArC), 126.0 (ArC), 120.8 (═C), 52.2(CH), 41.9 (CH_2), 41.5 (CH), 31.1 (CH_2), 23.8 (CH_2), 21.0 (CH_2); IR (KBr): 3752, 3676, 3650, 3422, 2919, 2850, 1782, 1655, 1580, 1517, 1487, 1452, 1262, 1129, 1016, 931, 803, 699, 547 cm^{-1}; ESI FTMS exact mass calcd for $(C_{23}H_{21}NO_4 + Na)^+$ requires m/z 398.1369, found m/z 398.1377; enantiomeric ratio (er) value: 90:10, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 11.117 min (major), t_R = 15.553 min (minor).

***N*-(5-Acetyl-6-methyl-2-oxo-4-phenyl-3,4-dihydro-2*H*-pyran-3-yl)benzamide (3ae).** Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 48 h; >95:5 dr; yield: 32% (11.2 mg); white solid; mp 125.8−127.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.75−7.63 (m, 2H), 7.53 (t, J = 7.6 Hz, 1H), 7.47−7.39 (m, 2H), 7.36−7.28 (m, 3H), 7.15−6.92 (m, 2H), 6.48 (d, J = 6.0 Hz, 1H), 5.28 (t, J = 6.8 Hz, 1H), 4.61 (d, J = 7.2 Hz, 1H), 2.50 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 197.3 (C═O), 167.3 (═C), 166.2 (C═O), 159.5 (C═O), 134.5 (ArC), 133.1 (ArC), 132.3 (ArC), 129.4 (ArC), 128.8 (ArC), 128.7 (ArC), 128.2 (ArC), 127.1 (ArC), 117.3 (═C), 53.0 (CH), 42.9 (CH), 29.6 (CH_3), 18.7 (CH_3); IR (KBr): 3421, 2962, 2923, 2850, 1654, 1521, 1457, 1262, 1096, 1024, 803, 701, 664 cm^{-1}; ESI FTMS exact mass calcd for $(C_{21}H_{19}NO_4 + Na)^+$ requires m/z 372.1212, found m/z 372.1219; enantiomeric ratio (er) value: 51:49, determined

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by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 7.063 min, t_R = 13.063 min.

Experimental Procedure for the Synthesis of Product 5. Methanol (1 mL) was added to compound *ent*-**3aa** (0.2 mmol), which was stirred at 50 °C for 12 h. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated under reduced pressure to give the residue, which was purified through flash column chromatography on silica gel to afford pure product **5**.

Methyl (2*S*,3*S*)-2-Benzamido-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-3-phenylpropanoate (5). Flash column chromatography eluent, dichloromethane/carbinol = 30/1; reaction time = 24 h; >95:5 dr; yield: 99% (83.4 mg); white solid; mp 136.8−137.9 °C; $[\alpha]_D^{20}$ = −186.0 (*c* 0.4, acetone); ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 7.80−7.70 (m, 2H), 7.56−7.47 (m, 1H), 7.46−7.36 (m, 2H), 7.33−7.17 (m, 4H), 7.15−7.06 (m, 1H), 5.40 (d, J = 6.0 Hz, 1H), 5.09 (d, J = 6.4 Hz, 1H), 3.64 (s, 3H), 2.38 (s, 4H), 1.07 (s, 6H); ^{13}C NMR (100 MHz, methanol-d_4) δ (ppm): 192.4 (C═O), 172.2 (C═O), 168.2 (C═O), 139.7 (ArC), 133.5 (ArC), 131.4 (ArC), 128.2 (ArC), 127.7 (ArC), 127.0 (ArC), 126.8 (ArC), 125.8 (ArC), 112.6 (═C), 55.5 (CH), 51.2 (CH_3), 39.5 (CH_2), 37.7 (CH), 31.4 (C), 29.2 (CH_3), 27.0 (CH_3); IR (KBr): 3567, 3147, 2959, 2925, 2852, 2716, 2341, 1889, 1750, 1559, 1540, 1457, 1089, 1026, 668, 617 cm^{-1}; ESI FTMS exact mass calcd for ($C_{25}H_{27}NO_5$ −H) $^-$ requires m/z 420.1811, found m/z 420.1830; enantiomeric ratio (er) value: 93:7, determined by HPLC (Daicel Chiralpak IC, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 6.947 min (minor), t_R = 25.960 min (major).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00603.

Screening of catalysts and optimization of reaction conditions, ^{1}H NMR spectra of the control experiments, characterization data (including ^{1}H and ^{13}C NMR spectra and HPLC traces) of products **3** and **5**, and single crystal data of product **3ka** (PDF)

Single crystal data of product **3ka** (CIF)

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Notes

The authors declare no competing financial interest.

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