JOC The Journal of Organic Chemistry

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N-Heterocyclic Carbene-Catalyzed [4 + 2] Cyclization of Saturated Carboxylic Acid with *o*-Quinone Methides through in Situ Activation: Enantioselective Synthesis of Dihydrocoumarins

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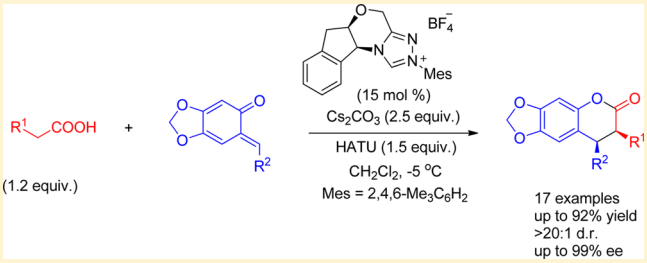
Supporting Information

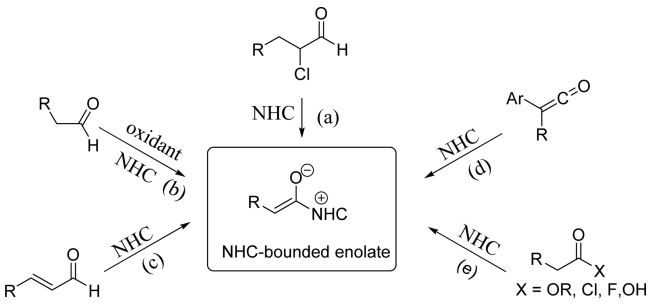
ABSTRACT: An *N*-heterocyclic carbene (NHC)-catalyzed formal [4 + 2] synthesis of dihydrocoumarins was realized from saturated carboxylic acids and *o*-quinone methides via an in situ activation strategy. This protocol results in excellent diastereoselectivity and enantioselectivity and good yields and uses readily available and inexpensive starting materials.



3,4-Dihydrocoumarin derivatives have been illustrated to possess a wide range of biological activities as natural products and pharmaceuticals.[1,2] Therefore, much attention has been paid to the development of efficient assemblies of the 3,4-dihydrocoumarin scaffold. Metal-based catalysts, e.g., Yb(OTf)$_3$, Zn(II)/ bis(hydroxyamide) and PdI$_2$ could promote the synthesis of dihydrocoumarins successfully.[3,4] However, harsh reaction conditions, expensive catalysts, and the complexity of starting materials made it desirable to achieve a facile, rapid, and "green" chemical procedure for the construction and modification of the 3,4-dihydrocoumarin scaffold.

Over the past few decades, *N*-heterocyclic carbenes (NHCs) have been confirmed to be able to act as nucleophiles,[5−7] Brønsted bases,[8] and Lewis bases[9] to promote the asymmetric transformations effectively. Recently, Ye's group and Wang et al. also disclosed the NHC-catalyzed formation of 3,4-dihydrocoumarins.[10] As an important intermediate in NHC catalysis, NHC-bounded enolates **A** could be generated from *α*-chloro aldehydes,[11] aliphatic aldehydes,[12] enals,[13] ketenes,[14] esters,[15] and saturated carboxylic acids (Scheme 1).[16] Then, intermediate **A** could be trapped by other reactive species to assemble the heterocyclic skeletons readily. Compared with other carbonyl compounds, carboxylic acids are more stable, more available, and less enolizable so that they could bypass many side reactions, e.g., aldol condensation. In 2014, Scheidt's group found a smooth method for the synthesis of dihydroquinolones via NHC-bounded enolates generated in situ from saturated carboxylic acids in the presence of carbonyldiimidazole (CDI).[17] Later, our group presented the *β*-functionalization of saturated carboxylic acids in the presence of NHC and 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) to establish spirocyclic oxindolo-*γ*-butyrolactones.[18] Because these activation reagents could promote the creation of homoenolates effectively, we envisioned that the NHC-catalyzed [4 + 2] cyclization of saturated carboxylic acids with *o*-quinone methides through NHC-bounded enolate via in situ activation could provide a new access to 3,4-dihydrocoumarins (Scheme 2).

Scheme 1. Generation of NHC-Bounded Enolates



4-Bromophenylacetic acid **1a** and *o*-quinone methide **2a** were selected as the model substrates to optimize the reaction conditions, and the key results are summarized in Table 1. Initially, several peptide coupling reagents were investigated (Table 1, entries 1−4) and only HATU was found to give the desired product in good yield and excellent enantioselectivity. Subsequently, catalyst **4c** was used prior to other counterparts during an assessment of the NHC precursors (Table 1, entries 5−8). A careful examination of the bases indicated that 3,4-

Received: October 6, 2016
Published: January 11, 2017

DOI: 10.1021/acs.joc.6b02444
J. Org. Chem. 2017, 82, 1790−1795

Scheme 2. New Access to NHC-Bounded Enolates through the in Situ Activation of Carboxylic Acids Facilitated by Peptide Coupling Reagents

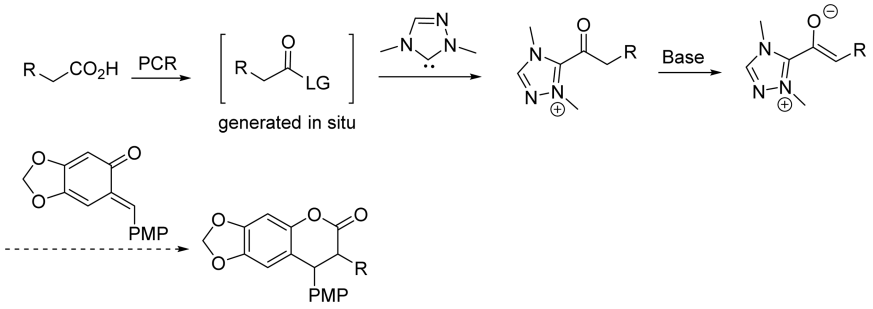
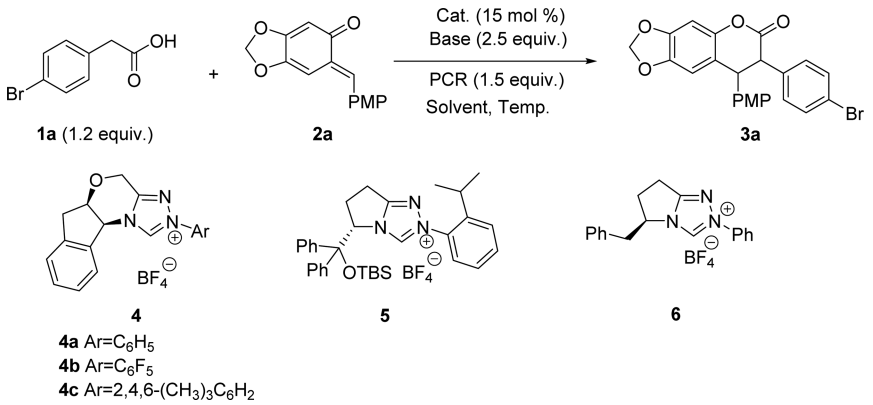


Table 1. Optimization of the Reaction Conditions.[a]



	NHC cat.	base	PCR	solvent	yield (%)[c]	d.r.[d]	ee (%)[e]
1	**4c**	Cs_2CO_3	CDI	CH_2Cl_2			
2	**4c**	Cs_2CO_3	DCC[b]/HOBt[b]	CH_2Cl_2	36	1:5	53
3	**4c**	Cs_2CO_3	DIC[b]/HOBt	CH_2Cl_2	55	1:4	29
4	**4c**	Cs_2CO_3	HATU	CH_2Cl_2	72	12:1	96
5	**4a**	Cs_2CO_3	HATU	CH_2Cl_2	45	1:2	63
6	**4b**	Cs_2CO_3	HATU	CH_2Cl_2	trace		
7	**5**	Cs_2CO_3	HATU	CH_2Cl_2	37	2:1	24
8	**6**	Cs_2CO_3	HATU	CH_2Cl_2	41	8:1	92

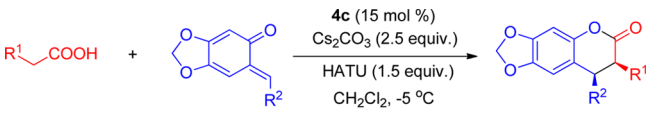
[a]Reaction conditions: **1a** (0.24 mmol), **2a** (0.2 mmol), NHC cat. (0.03 mmol), base (0.5 mmol), PCR (0.3 mmol), solvent (4 mL), −5 °C. [b]DCC = dicyclohexylcarbodiimide. DIC = *N*,*N*-diisopropylcarbodiimide. HOBt = 1-hydroxybenzotriazole. [c]Isolated yields. [d]Diastereomeric ratio determined by ^{1}H NMR spectroscopy. [e]The ee values were determined by HPLC.

dihydrocoumarins could be obtained in 72% yield with 12:1 ratio of cis:trans-isomers and 96% ee using Cs_2CO_3 (Table 1, Supporting Information, entries 9−12). Then CH_2Cl_2, 1,4-dioxane, THF, toluene, and $CHCl_3$ were deployed to explore the scope of the solvents (Table 1, Supporting Information, entries 13−16). The results showed that alkanes and ether solvents had different effects on the d.r. value, and CH_2Cl_2 was best among them. Subsequently, a scrutiny of the amount of catalyst indicated that 15 mol % of **4c** should be optimal (Table 1, Supporting Information, entries 19−20). Gratifyingly, both the reaction diastereo- and enantioselectivity were improved by further lowering the temperature to −5 °C (Table 1, Supporting Information, entries 17−18); thus, the optimal reaction condition was finally established (Table 1, entry 4).

With the optimized reaction conditions in hand, we focused on our attention to evaluate the scope of these formal [4 + 2] annulations (Table 2). These reactions showed that a broad range of acetic acids substituted by aryl or alkyl groups **1** were compatible with the protocol. Both electron-withdrawing (such as F, Cl, Br, I, and CF_3) and electron-rich groups, including Me and OMe, were tolerated at the C-2, C-3, and C-4 positions of the phenyl ring, affording the desired products with high diastereo- and enantioselectivity (Table 2, entries 1−10). To our delight, the acetic acids possessing fused aryl groups, including 2-(naphthalen-1-yl) and 2-(naphthalen-2-yl), or a heteroaryl group, e.g., thiophen-2-yl, could also be employed in this [4 + 2] cyclization to provide the corresponding products in moderate yields (Table 2, entries 12−14). It should be noted that this protocol could be applied to butyric acid, delivering the anticipated cycloadduct diastereoselectively and enantioselectively in moderate yield (Table 2, entry 15). Thus, this methodology showed good tolerance to the alkyl substituents. Furthermore, *o*-quinone methides with a cinnamyl substituent worked also well for the reaction (Table 2, entry 16). In addition, the reaction involving a new *o*-quinone methide **5** substituted by two methoxy groups was carried out, and the expected products was obtained in 63% yield with excellent diastereo- and enantioselectivity (>20:1 dr, 97% ee, see Scheme

DOI: 10.1021/acs.joc.6b02444
J. Org. Chem. 2017, 82, 1790−1795

Table 2. Scope of Reactions[a]



1 2 3

	R^1	R^2	product	yield (%)[c]	d.r.[d]	ee (%)[e]
1	4-BrC_6H_4	PMP	**3a**	72	12:1	96
2	Ph	PMP	**3b**	80	>20:1	99
3	4-FC_6H_4	PMP	**3c**	68	15:1	98
4	4-IC_6H_4	PMP	**3d**	79	13:1	90
5	4-$CH_3C_6H_4$	PMP	**3e**	86	>20:1	98
6	4-*i*-PrC_6H_4	PMP	**3f**	83	12:1	86
7	3-ClC_6H_4	PMP	**3g**	72	8:1	96
8	3-BrC_6H_4	PMP	**3h**	72	7:1	90
9	3-$CH_3OC_6H_4$	PMP	**3i**	53	12:1	92
10	4-$CF_3C_6H_4$	PMP	**3j**	56	5:1	88
11	2-$CH_3C_6H_4$	PMP	**3k**	78	20:1	97
12	2-(naphthalene-1-yl)	PMP	**3l**	71	>20:1	86
13	2-(naphthalene-2-yl)	PMP	**3m**	54	>20:1	96
14	thiophen-2-yl	PMP	**3n**	60	3:2	79
15	ethyl	PMP	**3o**	65	>20:1	99
16	4-$CH_3OC_6H_4$	cinnamyl	**3p**	71	>20:1	99
17	4-BrC_6H_4	PEP[b]	**3q**	68	15:1	96

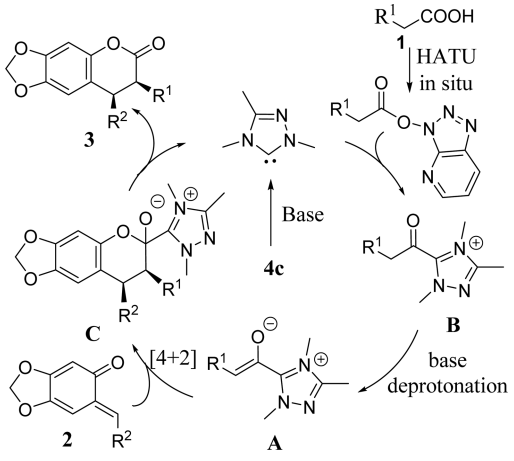
[a]Reaction conditions: **1** (0.24 mmol), **2** (0.2 mmol), **4c** (0.03 mmol), Cs_2CO_3 (0.3 mmol), HATU (0.3 mmol), DCM (4 mL), −5 °C. [b]*p*-Ethoxyphenyl. [c]Isolated yields. [d]Diastereomeric ratio determined by ^1H NMR spectroscopy. [e]The ee values were determined by HPLC.

2, Supporting Information). These results highlighted the wide application scope of the NHC-catalyzed asymmetric construction of 3,4-dihydrocoumarin.

The absolute configuration of **3h** was determined by the X-ray analysis of its crystal. Other product configurations were deduced based on analogy (see the Supporting Information for further details).

A reasonable mechanism for this NHC-catalyzed [4 + 2] cyclization is illustrated in Scheme 3. The addition of catalyst **4c** to the ester substrates which were generated in situ from the saturated carboxylic acids gave intermediate **B**, which underwent a deprotonation to give rise to the NHC-bounded enolate

Scheme 3. Possible Catalytic Mechanism



intermediate **A** in the presence of base. The later formal [4 + 2] annulation of intermediate **A** with *o*-quinone methides **2** provided zwitterionic intermediate **C**, which was transformed into the final cycloadduct product **3** through collapse, and the catalyst was regenerated.

In summary, we developed an NHC-catalyzed [4 + 2] cyclization of saturated carboxylic acids with *o*-quinone methides through in situ activation strategy. With this approach, a diverse set of 3,4-dihydrocoumarin derivatives were generated in moderate to good yields with excellent d.r. and ee values. Aside from the extension of the scope of the protocol developed herein, other NHC-catalyzed conversions of saturated carboxylic acids via in situ activation are underway in our laboratory.

EXPERIMENTAL SECTION

General Procedure for the Preparation of Compounds 3a−r. An oven-dried 10 mL Schlenk tube equipped with a magnetic stir bar was charged with triazolium salt **4c** (12.6 mg, 0.03 mmol), Cs_2CO_3 (162.9 mg, 0.50 mmol), saturated carboxylic acids **1** (0.24 mmol), *o*-quinone methides **2** (0.2 mmol), and HATU (114.0 mg, 0.3 mmol). This tube was closed with a septum, evacuated, and refilled with nitrogen. To this mixture was added freshly distilled CH_2Cl_2 (4 mL) with a syringe. Then, the mixture was stirred at −5 °C until completion (monitored by TLC). After removal of the solvent under reduced pressure, the resulting crude residue was purified by column chromatography (silica gel, mixtures of petroleum ether:ethyl acetate, 7:1, v/v) to afford the desired product **3**.

*(7R,8S)-7-(4-Bromophenyl)-8-(4-methoxyphenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (**3a**).* White solid. Yield: 0.068 g (72%); mp: 155−156 °C. ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.33 (d, J = 8.4 Hz, 2H), 7.26 (s, 1H), 6.74−6.64 (m, 6H), 6.55 (s, 1H), 5.97 (dd, J_1 = 14.8 Hz, J_2 = 1.2 Hz, 2H), 4.29 (d, J = 6.4 Hz, 1H), 4.09 (d, J = 6.0 Hz, 1H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.6, 159.2, 147.8, 145.5, 144.6, 133.3, 131.8, 131.1, 129.7, 129.3, 121.9, 119.1, 114.0, 107.1, 101.8, 99.1, 55.2, 51.7, 48.8. IR (potassium bromide) (ν, cm^{-1}): 3627, 2921, 2375, 1754, 1514, 1480, 1445, 1253, 1155, 939, 848, 735. HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{23}H_{17}BrNaO_5$: 475.0157; found: 475.0126. $[\alpha]_D^{25}$ = +338 (c = 0.1, $CHCl_3$). HPLC analysis: 96% ee [Daicel Chiralcel OZ-H, *n*-hexane/methanol = 90/10, v = 0.8 mL min^{-1}, λ = 254 nm, t (major) = 17.7 min, t (minor) = 23.8 min].

*(7R,8S)-8-(4-Methoxyphenyl)-7-phenyl-7,8-dihydro-6H-[1,3]-dioxolo[4,5-g]chromen-6-one (**3b**).* White solid. Yield: 0.061 g (80%); mp: 158−160 °C. ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.24−7.17 (m, 3H), 6.81−6.79 (m, 2H), 6.75 (s, 1H), 6.71−6.89 (m, 2H), 6.65−6.63 (m, 2H), 6.55 (s, 1H), 5.97 (dd, J_1 = 13.6 Hz, J_2 = 1.2 Hz, 2H), 4.33 (d, J = 6.0 Hz, 1H), 4.13 (d, J = 6.0 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.0, 159.0, 147.6, 145.7, 144.5, 134.2, 130.1, 129.8, 129.6, 127.9, 127.6, 119.4, 113.9, 107.2, 101.8, 99.1, 55.2, 52.2, 48.9. IR (potassium bromide) (ν, cm^{-1}): 3627, 2903, 1762, 1610, 1511, 1481, 1440, 1252, 1153, 1035, 935, 833, 752. HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{23}H_{18}NaO_5$: 397.1052; found: 397.1052. $[\alpha]_D^{25}$ = +284 (c = 0.1, $CHCl_3$). HPLC analysis: 99% ee [Daicel Chiralcel OZ-H, *n*-hexane/methanol = 90/10, v = 0.8 mL min^{-1}, λ = 254 nm, t (major) = 17.5 min, t (minor) = 23.6 min].

*(7R,8S)-7-(4-Fluorophenyl)-8-(4-methoxyphenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (**3c**).* White solid. Yield: 0.053 g (68%); mp: 146−148 °C. ^1H NMR (400 MHz, $CDCl_3$): δ_H 6.94−6.89 (m, 2H), 6.80−6.77 (m, 3H), 6.75−6.72 (m, 2H), 6.67−6.65 (m, 2H), 6.58 (s, 1H), 6.00 (dd, J_1 = 14.4 Hz, J_2 = 1.2 Hz, 2H), 4.35 (d, J = 6.4 Hz, 1H), 4.11 (d, J = 6.0 Hz, 1H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.9, 162.2 (J_{C-F} = 246.5 Hz), 159.1, 147.7, 145.6, 144.6, 131.7 (J_{C-F} = 8.1 Hz), 130.1 (J_{C-F} = 3.3 Hz), 129.7, 129.4, 114.9 (J_{C-F} = 21.4 Hz), 114.7, 114.0, 107.1, 101.8, 99.1, 55.2, 51.4, 49.0. IR (potassium bromide) (ν, cm^{-1}): 3627, 2921, 1754, 1513, 1479, 1443, 1251, 1155, 1034, 848, 827, 744. HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{23}H_{17}FNaO_5$: 415.0958; found: 415.0959. $[\alpha]_D^{25}$ = +155 (c =

DOI: 10.1021/acs.joc.6b02444
J. Org. Chem. 2017, 82, 1790−1795

0.1, $CHCl_3$). HPLC analysis: 98% ee [Daicel Chiralcel OZ-H, *n*-hexane/methanol = 90/10, v = 0.8 mL min^{-1}, λ = 254 nm, t (major) = 15.4 min, t (minor) = 18.8 min].

*(7R,8S)-7-(4-Iodophenyl)-8-(4-methoxyphenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (**3d**).* White solid. Yield: 0.071 g (79%); mp: 170−171 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.53 (d, J = 8.4 Hz, 2H), 6.74−6.71 (m, 3H), 6.66−6.64 (m, 2H), 6.55−6.52 (m, 3H), 5.97 (dd, J_1 = 14.8 Hz, J_2 = 1.2 Hz, 2H), 4.27 (d, J = 6.4 Hz, 1H), 4.09 (d, J = 6.0 Hz, 1H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.6, 159.2, 147.8, 145.5, 144.6, 137.0, 134.0, 132.0, 129.7, 129.3, 119.1, 114.0, 107.1, 101.8, 99.1, 93.7, 55.2, 51.8, 48.8. IR (potassium bromide) (ν, cm^{-1}): 3627, 2921, 2375, 1753, 1511, 1482, 1250, 1157, 936, 840, 738. HRMS (APCI) m/z: calcd for $[M + H]^+$ $C_{23}H_{18}IO_5$: 501.0199; found: 501.0198. $[\alpha]_D^{25}$ = +129 (c = 0.1, $CHCl_3$). HPLC analysis: 90% ee [Daicel Chiralcel OZ-H, *n*-hexane/methanol = 90/10, v = 0.8 mL min^{-1}, λ = 254 nm, t (major) = 18.6 min, t (minor) = 26.8 min].

*(7R,8S)-8-(4-Methoxyphenyl)-7-(p-tolyl)-7,8-dihydro-6H-[1,3]-dioxolo[4,5-g]chromen-6-one (**3e**).* White solid. Yield: 0.067 g (86%); mp: 75−77 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.98 (d, J = 8.0 Hz, 2H), 6.94 (s, 1H), 6.79−6.75 (m, 3H), 6.70 (d, J = 7.6 Hz, 2H), 6.65 (d, J = 8.4 Hz, 2H), 6.02 (d, J = 16.8 Hz, 2H), 4.69 (d, J = 6.0 Hz, 1H), 4.23 (d, J = 6.4 Hz, 1H), 3.68 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.3, 159.0, 147.6, 145.7, 144.5, 137.3, 131.1, 130.0, 129.8, 128.7, 119.6, 113.8, 107.2, 101.7, 99.1, 55.2, 51.9, 48.8, 21.1. IR (potassium bromide) (ν, cm^{-1}): 3627, 2921, 2380, 1755, 1611, 1512, 1480, 1440, 1251, 1154, 1033, 936, 848, 746. HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{24}H_{20}NaO_5$: 411.1208; found: 411.1208. $[\alpha]_D^{25}$ = +95 (c = 0.1, $CHCl_3$). HPLC analysis: 98% ee [Daicel Chiralcel OZ-H, *n*-hexane/methanol = 90/10, v = 0.8 mL min^{-1}, λ = 254 nm, t (major) = 14.8 min, t (minor) = 19.5 min].

*(7R,8S)-7-(4-Isopropylphenyl)-8-(4-methoxyphenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (**3f**).* White solid. Yield: 0.069 g (83%); mp: 191−192 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.04 (d, J = 8.0 Hz, 2H), 6.74 (s, 1H), 6.72−6.64 (m, 6H), 6.54 (s, 1H), 5.96 (dd, J_1 = 13.6 Hz, J_2 = 1.2 Hz, 2H), 4.29 (d, J = 6.4 Hz, 1H), 4.12 (d, J = 6.4 Hz, 1H), 3.76 (s, 3H), 2.88−2.81 (m, 1H), 1.21 (dd, J_1 = 6.8 Hz, J_2 = 2.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.3, 159.0, 148.2, 147.6, 145.7, 144.4, 131.4, 129.9, 129.8, 126.0, 119.6, 113.8, 107.2, 101.7, 99.1, 55.2, 51.9, 48.8, 33.7, 24.0, 23.9. IR (potassium bromide) (ν, cm^{-1}): 3627, 2921, 2380, 1761, 1610, 1512, 1481, 1439, 1252, 1153, 1034, 936, 822, 741. HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{26}H_{24}NaO_5$: 439.1521; found: 439.1521. $[\alpha]_D^{25}$ = +97 (c = 0.1, $CHCl_3$). HPLC analysis: 86% ee [Daicel Chiralcel OZ-H, *n*-hexane/methanol = 90/10, v = 0.8 mL min^{-1}, λ = 254 nm, t (major) = 12.1 min, t (minor) = 17.8 min].

*(7R,8S)-7-(3-Chlorophenyl)-8-(4-methoxyphenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (**3g**).* White solid. Yield: 0.059 g (72%); mp: 147−148 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.29 (d, J = 8.4 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 6.97 (s, 1H), 6.82−6.78 (m, 5H), 6.64 (d, J = 8.4 Hz, 2H), 6.04 (d, J = 16.8 Hz, 2H), 4.86 (d, J = 6.4 Hz, 1H), 4.29 (d, J = 6.4 Hz, 1H), 3.68 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.4, 159.2, 147.8, 145.6, 144.6, 130.3, 129.65, 129.7, 129.1, 128.3, 119.0, 114.5, 114.0, 107.1, 101.8, 99.1, 55.3, 51.9, 48.9. IR (potassium bromide) (ν, cm^{-1}): 3627, 2921, 2375, 1754, 1514, 1480, 1443, 1251, 1134, 1035, 939, 848, 745. HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{23}H_{17}ClO_5$: 431.0662; found: 431.0644. $[\alpha]_D^{25}$ = +174 (c = 0.1, $CHCl_3$). HPLC analysis: 96% ee [Daicel Chiralcel OZ-H, *n*-hexane/methanol = 90/10, v = 0.8 mL min^{-1}, λ = 254 nm, t (major) = 16.5 min, t (minor) = 21.6 min].

*(7R,8S)-7-(3-Bromophenyl)-8-(4-methoxyphenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (**3h**).* White solid. Yield: 0.065 g (72%); mp: 150−151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.40−7.38 (m, 1H), 7.06 (t, J = 8.0 Hz, 1H), 6.97−6.95 (m, 1H), 6.76−6.69 (m, 4H), 6.65−6.63 (m, 2H), 6.56 (s, 1H), 5.99 (dd, J_1 = 14.4 Hz, J_2 = 1.2 Hz, 2H), 4.30 (d, J = 6.4 Hz, 1H), 4.10 (d, J = 6.4 Hz, 1H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.4, 159.2, 147.8, 145.5, 144.6, 136.5, 133.2, 130.8, 129.7, 129.4, 128.8, 121.8, 119.0, 114.0, 107.1, 101.8, 99.1, 55.3, 51.9, 48.9. IR (potassium bromide) (ν, cm^{-1}): 3627, 2921, 2375, 1754, 1513, 1480, 1447, 1255, 1144, 1033, 937, 846, 747. HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{23}H_{17}BrNaO_5$: 475.0157; found: 475.0125. $[\alpha]_D^{25}$ = +185 (c = 0.1, $CHCl_3$). HPLC analysis: 90% ee [Daicel Chiralcel OZ-H, *n*-hexane/methanol = 90/10, v = 0.8 mL min^{-1}, λ = 254 nm, t (major) = 14.7 min, t (minor) = 17.0 min].

*(7R,8S)-7-(3-Methoxyphenyl)-8-(4-methoxyphenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (**3i**).* White solid. Yield: 0.043 g (53%); mp: 170−171 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.16−7.12 (t, J = 8.0 Hz, 1H), 6.82−6.69 (m, 6H), 6.58 (s, 1H), 6.48 (d, J = 7.6 Hz, 1H), 6.28 (s, 1H), 5.99 (d, J = 14.0 Hz, 2H), 4.32 (d, J = 6.0 Hz, 1H), 4.15 (d, J = 6.0 Hz, 1H), 3.77 (s, 3H), 3.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.9, 159.1, 158.9, 147.7, 145.6, 144.5, 135.6, 129.8, 129.8, 128.9, 122.4, 119.4, 115.2, 113.9, 107.2, 101.8, 99.1, 55.3, 55.0, 52.1, 48.9. IR (potassium bromide) (ν, cm^{-1}): 3627, 2960, 1760, 1610, 1511, 1484, 1441, 1247, 1155, 1034, 942, 866, 755. HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{24}H_{20}NaO_6$: 427.1158 found: 427.1156. $[\alpha]_D^{25}$ = +100 (c = 0.2, $CHCl_3$). HPLC analysis: 92% ee [Daicel Chiralcel OZ-H, *n*-hexane/methanol = 90/10, v = 0.8 mL min^{-1}, λ = 254 nm, t (major) = 19.2 min, t (minor) = 25.0 min].

*(7R,8S)-8-(4-Methoxyphenyl)-7-(o-tolyl)-7,8-dihydro-6H-[1,3]-dioxolo[4,5-g]chromen-6-one (**3j**).* White solid. Yield: 0.061 g (78%); mp: 62−63 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.18 (d, J = 7.6 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 6.96 (s, 1H), 6.84 (t, J = 7.6 Hz, 1H), 6.78 (s, 1H), 6.72 (d, J = 8.4 Hz, 2H), 6.58 (d, J = 8.4 Hz, 2H), 6.31 (d, J = 7.6 Hz, 1H), 6.03 (d, J = 14.0 Hz, 2H), 4.79 (d, J = 6.0 Hz, 1H), 4.31 (d, J = 6.0 Hz, 1H), 3.67 (s, 3H), 2.31 (s, 3H) . ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.2, 159.0, 147.7, 145.7, 144.5, 135.9, 132.2, 130.7, 130.1, 129.9, 129.6, 127.5, 125.3, 119.3, 113.8, 107.2, 101.8, 99.1, 55.2, 47.5, 47.0, 19.6. IR (potassium bromide) (ν, cm^{-1}): 3627, 2921, 2380, 1745, 1615, 1519, 1475, 1446, 1244, 1155, 1032, 939, 846, 743. HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{24}H_{20}NaO_5$: 411.1208; found: 411.1208. $[\alpha]_D^{25}$ = +132 (c = 0.1, $CHCl_3$). HPLC analysis: 97% ee [Daicel Chiralcel OZ-H, *n*-hexane/methanol = 90/10, v = 0.8 mL min^{-1}, λ = 254 nm, t (major) = 11.2 min, t (minor) = 13.7 min].

*(7S,8R)-8-(4-Methoxyphenyl)-7-(4-(trifluoromethyl)phenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (**3k**).* White solid. Yield: 0.050 g (56%); mp: 85−86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.46 (d, J = 8.0 Hz, 2H), 6.92 (d, J = 8.0 Hz, 2H), 6.76 (s, 1H), 6.71 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 8.8 Hz, 2H), 6.56 (s, 1H), 5.98 (d, J = 15.6 Hz, 2H), 4.40 (d, J = 6.0 Hz, 1H), 4.12 (d, J = 6.4 Hz, 1H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.4, 159.2, 147.8, 145.5, 144.7, 138.3, 130.6, 129.6, 129.1 (J_{C-F} = 1.5 Hz), 128.8, 124.8 (J_{C-F} = 3.8 Hz), 119.0, 114.1, 107.1, 101.8, 99.1, 55.2, 52.0, 48.8. IR (potassium bromide) (ν, cm^{-1}): 3620, 2951, 1723, 1529, 1479, 1442, 1326, 1252, 1153, 1044, 858, 829, 734. HRMS (APCI) m/z: calcd for $[M + H]^+$ $C_{24}H_{18}F_3O_5$: 443.1106; found: 443.1083. $[\alpha]_D^{25}$ = +96 (c = 0.1, $CHCl_3$). HPLC analysis: 88% ee [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 92/8, v = 0.8 mL min^{-1}, λ = 254 nm, t (major) = 19.4 min, t (minor) = 18.4 min].

*(7R,8S)-8-(4-Methoxyphenyl)-7-(naphthalen-1-yl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (**3l**).* White solid. Yield: 0.060 g (71%); mp: 134−135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.96−7.90 (m, 2H), 7.77 (d, J = 8.4 Hz, 1H), 7.55−7.506 (m, 2H), 7.23 (t, J = 7.6 Hz, 1H), 6.83−6.80 (m, 2H), 6.63−6.60 (m, 3H), 6.48−6.44 (m, 2H), 6.01 (dd, J_1 = 16.0 Hz, J_2 = 1.2 Hz, 2H), 5.24 (d, J = 6.0 Hz, 1H), 4.27 (d, J = 6.0 Hz, 1H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.9, 159.0, 147.8, 145.8, 144.6, 133.7, 131.3, 129.9, 129.6, 129.5, 129.3, 129.1, 128.1, 126.6, 125.4, 124.8, 121.3, 119.5, 113.7, 107.3, 101.8, 99.2, 55.2, 47.3, 46.6. IR (potassium bromide) (ν, cm^{-1}): 3627, 2921, 2360, 1770, 1610, 1512, 1481, 1440, 1251, 1152, 1120, 1035, 935, 831, 746. HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{27}H_{20}NaO_5$: 447.1208; found: 447.1206. $[\alpha]_D^{25}$ = +320 (c = 0.1, $CHCl_3$). HPLC analysis: 86% ee [Daicel Chiralcel OZ-H, *n*-hexane/methanol = 90/10, v = 0.8 mL min^{-1}, λ = 254 nm, t (major) = 15.7 min, t (minor) = 23.1 min].

*(7R,8S)-8-(4-Methoxyphenyl)-7-(naphthalen-2-yl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (**3m**).* White solid. Yield: 0.046 g (54%); mp: 104−105 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.80−7.75 (m, 1H), 7.71−7.66 (m, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.48−7.41 (m, 3H), 6.78 (s, 1H), 6.75 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 6.84−

DOI: 10.1021/acs.joc.6b02444
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6.63 (m, 4H), 6.57 (s, 1H), 5.98 (dd, J_1 = 15.6 Hz, J_2 = 1.2 Hz, 2H), 4.50 (d, J = 6.4 Hz, 1H), 4.21 (d, J = 6.0 Hz, 1H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.1, 159.1, 147.7, 145.7, 144.6, 133.0, 132.7, 131.9, 129.8, 129.6, 129.4, 127.9, 127.8, 127.6, 127.2, 126.1, 125.9, 119.4, 113.9, 107.2, 101.8, 99.2, 55.3, 52.4, 49.1. IR (potassium bromide) (ν, cm^{-1}): 3627, 2902, 1759, 1608, 1509, 1439, 1399, 1244, 1150, 1036, 940, 853, 776. HRMS (ESI) m/z: calcd for $[M + Na]^+$ $C_{27}H_{20}NaO_5$: 447.1208; found: 447.1208. $[\alpha]_D^{25}$ = +664 (c = 0.1, $CHCl_3$). HPLC analysis: 96% ee [Daicel Chiralcel OZ-H, n-hexane/methanol = 90/10, v = 0.8 mL min^{-1}, λ = 254 nm, t (major) = 27.2 min, t (minor) = 35.6 min].

*(7S,8S)-8-(4-Methoxyphenyl)-7-(thiophen-2-yl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (**3n**).* White solid. Yield: 0.046 g (60%); mp: 55−56 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.21 (d, J = 5.2 Hz, 1H), 7.05 (d, J = 7.2 Hz, 1H), 6.80−6.74 (m, 6H), 6.58 (s, 1H), 6.01−5.99 (m, 2H), 4.68 (d, J = 5.6 Hz, 1H), 4.28 (d, J = 6.0 Hz, 1H), 3.77 (d, J = 1.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.3, 159.2, 147.8, 145.5, 144.6, 135.4, 129.5, 128.6, 126.3, 125.5, 118.9, 114.0, 107.2, 101.8, 99.1, 55.2, 48.9, 47.3. IR (potassium bromide) (ν, cm^{-1}): 3432, 2904, 1766, 1610, 1512, 1481, 1439, 1252, 1153, 1111, 1034, 934, 858, 703. HRMS (ESI) m/z: calcd for $[M + NH_4]^+$ $C_{21}H_{20}NO_5S$: 398.1062; found: 398.1057. $[\alpha]_D^{25}$ = +287 (c = 0.1, $CHCl_3$). HPLC analysis: 79% ee [Daicel Chiralcel OZ-H, n-hexane/methanol = 90/10, v = 0.8 mL min^{-1}, λ = 254 nm, t (major) = 22.7 min, t (minor) = 28.7 min].

*(7S,8S)-7-Ethyl-8-(4-methoxyphenyl)-7,8-dihydro-6H-[1,3]-dioxolo[4,5-g]chromen-6-one (**3o**).* Yellow oil. Yield: 0.042 g (65%). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.97 (d, J = 8.4 Hz, 2H), 6.86−6.82 (m, 4H), 6.00 (d, J = 19.2 Hz, 2H), 4.23 (d, J = 6.4 Hz, 1H), 3.70 (s, 3H), 3.07−3.03 (m, 1H), 1.65−1.58 (m, 1H), 1.20−1.11 (m, 1H) 0.97 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 170.2, 158.9, 147.4, 145.4, 144.2, 130.6, 128.8, 119.7, 114.3, 107.2, 101.6, 99.0, 55.2, 46.3, 44.5, 20.2, 12.03. IR (potassium bromide) (ν, cm^{-1}): 3432, 2965, 1762, 1610, 1513, 1482, 1440, 1252, 1154, 1118, 1035, 945, 834, 799. HRMS (APCI) m/z: calcd for $[M + H]^+$ $C_{19}H_{19}O_5$: 327.1232; found: 327.1232. $[\alpha]_D^{25}$ = −20 (c = 0.1, (reported: −36.0976[19]) $CHCl_3$). HPLC analysis: 99% ee [Daicel Chiralcel OZ-H, n-hexane/methanol = 90/10, v = 0.8 mL min^{-1}, λ = 254 nm, t (major) = 22.4 min, t (minor) = 24.1 min].

*(7S,8S)-7-(4-Methoxyphenyl)-8-((E)-styryl)-7,8-dihydro-6H-[1,3]-dioxolo[4,5-g]chromen-6-one (**3p**).* White solid. Yield: 0.057 g (71%); mp: 172−173 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.31−7.21 (m, 5H), 7.15 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 7.70 (s, 1H), 6.62 (s, 1H), 6.28 (d, J = 15.6 Hz, 1H), 6.06−5.99 (m, 3H), 4.16 (d, J = 5.6 Hz, 1H), 3.85 (dd, J_1 = 8 Hz, J_2 = 5.6 Hz, 1H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.6, 159.1, 147.7, 145.6, 144.5, 136.3, 133.8, 130.9, 128.6, 127.9, 126.5, 126.0, 125.6, 118.0, 113.9, 107.0, 101.8, 99.2, 55.3, 50.3, 45.9. IR (potassium bromide) (ν, cm^{-1}): 3627, 2837, 1766, 1615, 1517, 1480, 1438, 1253, 1151, 1119, 1037, 967, 826, 758. HRMS (APCI) m/z: calcd for $[M + H]^+$ $C_{25}H_{21}O_5$: 401.1389; found: 401.1369. $[\alpha]_D^{25}$ = +123 (c = 0.1, $CHCl_3$). HPLC analysis: 99% ee [Daicel Chiralcel OZ-H, n-hexane/methanol = 90/10, v = 0.8 mL min^{-1}, λ = 254 nm, t (major) = 14.4 min, t (minor) = 13.3 min].

*(7R,8S)-7-(4-Bromophenyl)-8-(4-ethoxyphenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (**3q**).* White solid. Yield: 0.064 g (68%); mp: 83−84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.33−7.30 (m, 2H), 6.73−6.61 (m, 7H), 6.54 (s, 1H), 5.96 (dd, J_1 = 14.4 Hz, J_2 = 1.2 Hz, 2H), 4.28 (d, J = 6.4 Hz, 1H), 4.07 (d, J = 6.4 Hz, 1H), 3.96(q, J = 7.0 Hz, 2H), 1.38 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.6, 158.6, 147.7, 145.5, 144.6, 133.4, 131.8, 131.1, 129.7, 129.1, 121.9, 119.2, 114.6, 107.2, 101.8, 99.1, 63.4, 51.7, 48.8, 14.8. IR (potassium bromide) (ν, cm^{-1}): 2979, 2898, 2360, 2342, 1769, 1610, 1510, 1481, 1440, 1250, 1153, 1127, 1074, 1037, 1011, 924, 863, 824, 795, 730. HRMS (APCI) m/z: calcd for $[M + H]^+$ $C_{24}H_{20}BrO_5$: 467.0494; found: 467.0490. $[\alpha]_D^{25}$ = +172 (c = 0.1, $CHCl_3$). HPLC analysis: 96% ee [Daicel Chiralpak IC, n-hexane/i-PrOH = 92/8, v = 0.8 mL min^{-1}, λ = 254 nm, t (major) = 27.6 min, t (minor) = 35.4 min].

*(3R,4S)-3-(4-Bromophenyl)-6,7-dimethoxy-4-(4-methoxyphenyl)-chroman-2-one (**3r**).* White solid. Yield: 0.059 g (63%); mp: 86−87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.33 (d, J = 8.4 Hz, 2H), 6.77 (s, 1H), 6.72 (d, J = 8.8 Hz, 2H), 6.68−6.64 (m, 4H), 6.59 (s, 1H), 4.32 (d, J = 6.4 Hz, 1H), 4.13 (d, J = 6.4 Hz, 1H), 3.92 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.8, 159.2, 149.3, 146.1, 144.9, 133.5, 131.8, 131.1, 129.7, 129.4, 121.9, 117.7, 114.0, 110.2, 101.1, 56.2, 56.2, 55.2, 52.1, 48.7. IR (potassium bromide) (ν, cm^{-1}): 3000, 2933, 2835, 2360, 2342, 1769, 1609, 1511, 1464, 1409, 1253, 1231, 1192, 1124, 1072, 1030, 1011, 928, 856, 804, 765, 732. HRMS (APCI) m/z: calcd for $[M + H]^+$ $C_{24}H_{22}BrO_5$: 469.0651; found: 469.0656. $[\alpha]_D^{25}$ = +110 (c = 0.1, $CHCl_3$). HPLC analysis: 97% ee [Daicel Chiralpak IC, n-hexane/i-PrOH = 92/8, v = 0.8 mL min^{-1}, λ = 254 nm, t (major) = 75.0 min, t (minor) = 84.5 min].

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02444.

^{1}H and ^{13}C NMR spectra for all pure products (PDF)

X-ray crystal data for **3h** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support by the National Natural Science Foundation of China (Grants 21242014 and 21372101), a project funded by the Priority Academic Program Development of Jiangsu Higher Education Institution (TAPP).

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DOI: 10.1021/acs.joc.6b02444
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