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PAPER

Highly enantioselective synthesis of Warfarin and its analogs catalysed by primary amine–phosphinamide bifunctional catalysts†‡

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An efficient enantioselective Michael addition of 4-hydroxycoumarin to α,β-unsaturated ketones catalysed by primary amine–phosphinamide bifunctional catalysts has been developed. This reaction afforded Warfarin and its analogs in moderate to excellent yields (up to 99%) and good to excellent enantioselectivities (up to 99% ee).

Introduction

The past decade has witnessed the rise and continuous prosperity of asymmetric organocatalysis.[1] In particular, the development of chiral primary amines to promote asymmetric reactions has become a rapidly growing area in synthetic organic chemistry, attaining a new level of catalysts beyond secondary amines. Recently, chiral primary amines have been shown to be efficient organocatalysts in a variety of asymmetric transformations: such as Diels–Alder reaction,[2] Friedel–Crafts reaction,[3] Michael reaction,[4] and aldol reaction.[5] To our knowledge, of all the classes of routinely used chiral primary amine catalysts, cinchona alkaloids derivatives,[6] primary amine thioureas,[7] primary–secondary diamines[8] are frequently used in asymmetric catalysis.[9] However, the development of new primary amine–phosphinamide bifunctional catalysts and the expansion of their application to other useful asymmetric organic transformations is rarely reported.[4b,10] On the other hand, our group have reported a highly efficient enantioselective Michael addition of malonates to enones catalysed by simple chiral sulfonamide–primary amine **1** (Fig. 1) with excellent yields and enantioselectivities (up to 99% yield, up to 99% ee).[11] We envisioned that chiral primary amine–phosphinamide catalysts, which have similar structure to primary amine–sulfonamides, can be used as efficient hydrogen bonding bifunctional organocatalysts since phosphinamides are also good units for hydrogen bond formation.

Warfarin is a Vitamin K antagonist, inhibiting Vitamin K epoxide reductase. The sodium salt of Warfarin is one of the most widely prescribed anticoagulants. Warfarin is prescribed as the racemate, but the two enantiomers demonstrate different activity and metabolism. Although several methods using organocatalysis for the preparation of enantiomerically enriched Warfarin have been reported in recent years,[12] the development of cheap catalysts and efficient catalytic procedures for asymmetric synthesis of Warfarin and its analogs is still of great interest for chemists.

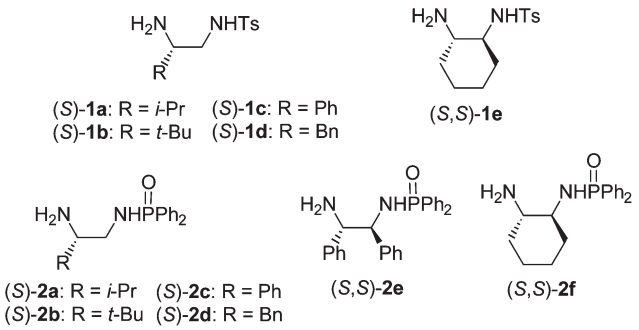

Fig. 1 Sulfonamide and phosphinamide organocatalysts.

With the objective of developing new organocatalysts and applications to asymmetric catalysis, we are interested in the synthesis and application of primary amine–phosphinamide catalysts **2**. In this paper, the catalytic efficiency of chiral phosphamide catalysts **2** and corresponding analogs **1** were evaluated in the Michael addition of 4-hydroxycoumarin to α,β-unsaturated ketones, the desired Warfarin and its analogs were obtained in good to excellent enantioselectivities (up to 99% ee).

Results and discussion

The chiral phosphinamide catalysts **2a–f** (**2e** and **2f** have been previously reported in literature[4b,10]) originating from chiral primary amino alcohols or 1,2-diamines have been synthesized conveniently according to a similar procedure for synthesis of

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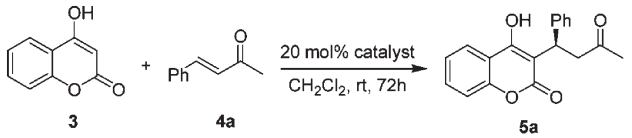
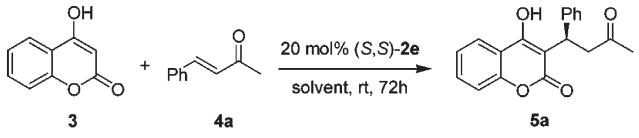
Table 1 Catalyst screening[a]



Entry	Catalyst	Yield[b] (%)	ee[c] (%)
1	(*S*)-**1a**	86	41
2	(*S*)-**1b**	87	57
3	(*S*)-**1c**	80	45
4	(*S*)-**1d**	95	25
5	(*S*,*S*)-**1e**	48	32
6	(*S*)-**2a**	4	—
7	(*S*)-**2b**	45	47
8	(*S*)-**2c**	99	68
9	(*S*)-**2d**	21	25
10	(*S*,*S*)-**2e**	72	88
11	(*S*,*S*)-**2f**	3	—

[a] Unless noted otherwise, the reactions were carried out with **3** (0.20 mmol) and **4a** (0.24 mmol) in the presence of the catalyst (20 mol%) in CH_2Cl_2 (1.5 mL) at room temperature for 72 h. [b] Isolated yield. [c] Determined by chiral HPLC using Daicel Chiralpak IA column, the configuration was assigned according to literature.[12d]

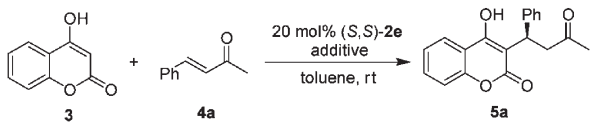
Table 2 Influence of solvents[a]



Entry	Solvent	Yield[b] (%)	ee[c] (%)
1	$CHCl_3$	99	91
2	EtOAc	91	87
3	Et_2O	99	89
4	Toluene	99	93
5	THF	99	86
6	CH_3CN	92	74
7	$ClCH_2CH_2Cl$	76	88

[a] Unless noted otherwise, the reactions were carried out with **3** (0.20 mmol) and **4a** (0.24 mmol) in the presence of the catalyst **2e** (20 mol%) in solvent (1.5 mL) at room temperature for 72 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis, the configuration was assigned according to literature.[12d]

Table 3 Effect of acid additives on Warfarin synthesis[a]



Entry	Additive	Additive loading (mol%)	Yield[b] (%)	ee[c] (%)
1	CH_3CO_2H	20	96	93
2	$PhCO_2H$	20	98	91
3	$4\text{-}O_2NC_6H_4OH$	20	99	89
4	$4\text{-}CH_3C_6H_4CO_2H$	20	97	95
5	$2\text{-}O_2NC_6H_4CO_2H$	20	91	95
6[d,e]	$4\text{-}CH_3C_6H_4CO_2H$	20	99	94
7[d,e]	$4\text{-}CH_3C_6H_4CO_2H$	10	96	93
8[d]	$4\text{-}CH_3C_6H_4CO_2H$	20	94	93
9[d,e,f]	$4\text{-}CH_3C_6H_4CO_2H$	20	39	96

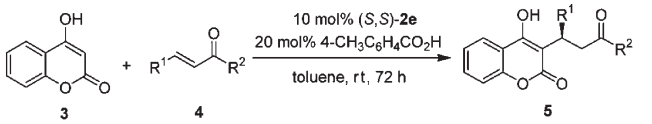
[a] Unless noted otherwise, the reactions were carried out with **3** (0.20 mmol), **4a** (0.24 mmol), catalyst **2e** (20 mol%), additive in toluene (1.5 mL) at room temperature for 48 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. The configuration was assigned according to literature.[12d] [d] The catalyst loading was 10 mol%. [e] The reaction was performed for 72 h. [f] The reaction temperature was 0 °C.

sulfonamides reported by our group.[13] Initially, the model Michael addition reaction of 4-hydroxycoumarin **3** to α,β-unsaturated ketone **4a** was investigated using a series of primary amine organocatalysts **1** and **2** (20 mol%) at room temperature; the results are summarized in Table 1. Catalysts **2a** and **2f** gave <5% yields, and the enantioselectivities were not detected (Table 1, entries 6 and 11). Catalysts **1d** and **2c** performed with excellent yield >95% (Table 1, entries 4 and 8). The reaction catalysed by primary amine–sulfonamides **1a–e** gave poor to moderate enantioselectivities (Table 1, entries 1–5). Among these primary amine–sulfonamide catalysts, **1b** with a bulky *tert*-butyl group worked well and resulted in 57% ee (Table 1, entry 2). **1d** afforded the product with excellent yield (95%) but with low enantioselectivity (Table 1, entry 4). However, among the chiral phosphinamide catalysts, **2e** generated from 1,2-diphenylethane-1,2-diamine performed best with 88% ee (Table 1, entry 10).

After catalyst **2e** was identified as effective, we then evaluated the solvent effect on the enantioselective synthesis of chiral Warfarin. Most of the commonly used solvents such as $CHCl_3$, EtOAc, Et_2O, toluene, and THF could provide Warfarin **5a** in good to excellent yields and enantioselectivities (Table 2, entries 1–5). When the reaction was carried out in $ClCH_2CH_2Cl$ (Table 2, entry 7), Warfarin **5a** was obtained in moderate enantioselectivity and yield. The enantioselectivity decreased to 74% ee with maintenance of yield when using CH_3CN as the solvent (Table 2, entry 6). After screening, toluene was chosen as the best solvent, in which excellent yield and good enantioselectivity were obtained (Table 2, entry 4).

To further improve the enantioselectivity, the effect of acid additives, temperature and catalyst loading were investigated. As summarized in Table 3, variation of acid additives has some effect on the reaction. Comparable yields and a slight decrease in enantioselectivities were obtained when using acetic acid, benzoic acid or 4-nitrobenzoic acid as additives (Table 3, entries 1–3). When using 4-methylbenzoic acid or 2-nitrobenzoic acid as additives, the enantioselectivity was enhanced to 95% ee (Table 3, entries 4 and 5). We then tried to reduce the loading of catalyst **2e** to 10 mol%, to our delight, the reaction afforded Warfarin with maintained yield and enantioselectivity (Table 3, entry 6). We also tried to change the loading of 4-methylbenzoic acid to 10 mol%, however, both the yield and the enantioselectivity were slightly decreased (Table 3, entry 7). Reducing the reaction time to 48 h was not beneficial for enantioselectivity (Table 3, entry 8). When the reaction temperature was reduced to 0 °C, excellent enantioselectivity was obtained, but the reactivity was decreased (Table 3, entry 9). Thus, the reaction was best performed using 4-methylbenzoic acid (20 mol%) and **2e**

Table 4 Enantioselective synthesis of Warfarin and analogs *via* Michael addition[a]



Entry	R^1	R^2	Product	Yield[b] (%)	ee[c] (%)
1	Ph	CH_3	**5a**	99	94
2	3-$O_2NC_6H_4$	CH_3	**5b**	88	92
3	4-$(CH_3)_2NC_6H_4$	CH_3	**5c**	65	86
4	2-$MeOC_6H_4$	CH_3	**5d**	82	91
5	4-$MeOC_6H_4$	CH_3	**5e**	91	94
6	4-$CH_3C_6H_4$	CH_3	**5f**	58	96
7	4-BrC_6H_4	CH_3	**5g**	97	96
8	2-BrC_6H_4	CH_3	**5h**	97	93
9	4-ClC_6H_4	CH_3	**5i**	99	94
10	4-$O_2NC_6H_4$	CH_3	**5j**	98	91
11	2-Furyl	CH_3	**5k**	14	99
12	1-Naphthyl	CH_3	**5l**	86	95
13	Ph	Cyclohexyl	**5m**	12	83
14	Ph	Ph	—	—	—
15	*t*-Bu	Ph	—	—	—
16	Cyclohexyl	Ph	—	—	—

[a] Unless noted otherwise, the reactions were carried out with **3** (0.20 mmol), **4** (0.24 mmol), catalyst **2e** (10 mol%), 4-methylbenzoic acid (20 mol%) in toluene (1.5 mL) at room temperature for 72 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis, the configuration was assigned according to literature.[12d]

(10 mol%) to provide the desired product with 99% yield and 94% ee (Table 3, entry 6).

Under the optimized reaction conditions, the scope of the present organocatalytic asymmetric Michael reaction using catalyst **2e** was extended to various α,β-unsaturated enones and the results are given in Table 4. The Michael reactions proceeded smoothly to generate Warfarin and its analogs in moderate to excellent yields (up to 99%) and good to excellent enantioselectivities (up to 99% ee). For enones with substituted benzene rings, electron-donating substituents led to comparable selectivity but moderate yields relative to the unsubstituted substrate (Table 4, entries 3–6). Electron-withdrawing substituted substrates led to good enantioselectivities and yields (Table 4, entries 2, 7–10). Bromo or chloro-substituted enones worked well for this reaction (Table 4, entries 7–9). Moreover, 1-naphthyl substrate also achieved 86% yield with 95% ee (Table 4, entry 12). Unfortunately, a sharp decrease in yield was observed for the 2-furyl substrate owing to the very low reactivity (no by-product was observed by TLC), and decomposition of the product was also observed after standing at room temperature as can be seen from HPLC chromatograph in the ESI† (Table 4, entry 11). The cyclohexyl substrate only afforded the corresponding product in 12% yield with 85% ee (Table 4, entry 13). When the R^2 group was changed to phenyl, the catalyst **2e** could not promote the reaction at all (Table 4, entries 14–16), this phenomenon indicates that both the steric and electronic effects around carbonyl are important for Michael addition to take place.

In Chin's previous report, chiral vicinal diamines have been used to catalyze the stereoselective synthesis of Warfarin with up

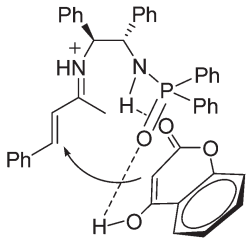


Fig. 2 Proposed transition state model.

to 92% ee using 10 mol% catalyst and 10 equivalents AcOH as additive.[12b] Chen and co-workers reported that 9-amino-9-deoxy-epiquinine was an excellent organocatalyst for the enantioselective Michael addition of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated ketones.[12c] The substrate scopes were broad, and good to excellent enantioselectivities (89–99% ee) were achieved for a number of cyclic 1,3-dicarbonyl compounds and α,β-unsaturated ketones. (*S*)-Warfarin was obtained in 96% ee with 88% yield. But in Chen's report, 20 mol% catalyst and 40 mol% TFA were used, the catalyst amount is larger and more expensive. Feng and co-workers developed C_2-symmetric secondary amine–amide catalysts for the asymmetric Michael addition of 4-hydroxycoumarin to α,β-unsaturated ketones.[12d] The corresponding products were obtained in excellent yields (up to 99%) with high enantioselectivities (up to 89% ee). As comparison with these reported organocatalysts, in our above catalytic system, only 10 mol% phosphinamide catalyst and 20 mol% 4-methylbenzoic acid were used, making our methodology more economic and attractive.

It was reported that triphenylphosphine oxide could form strong hydrogen bonds between the phosphoryl oxygen and the proton donor groups.[14] The chiral phosphinamide has also been widely used as a catalyst in asymmetric borane reductions of ketones.[15] The N–P═O structural unit, like a carbonyl amide, exists partially in the dipolar form in which the lone pair on nitrogen donates electron density to the P═O bond.[15b] The N–P═O group works as a Lewis base to interact with borane in the asymmetric reduction.[15] Structures of N–P═O type and related phosphine oxide are known to be good electron donors and can coordinate to metal ions and other ions through the oxygen atom.[16] According to the absolute configuration of Warfarin **5a**, a possible transition state model was proposed (Fig. 2). We propose that the mechanism of enantioselective synthesis of Warfarin involves the formation of the iminium ion intermediate from the primary amine of the catalyst and the unsaturated enone, and 4-hydroxycoumarin was activated through hydrogen bonding interaction with the P═O group. The P═O group may also work as a Lewis base for deprotonation of acidic hydrogen, and this can enhance the nucleophilic ability of 4-hydroxycoumarin. (*R*)-Warfarin could be obtained through the attack of 4-hydroxycoumarin to the *Re* face of iminium ion just as in the well established mechanism in previous reports.[12]

Conclusions

In summary, a series of primary amine–phosphinamide bifunctional catalysts, easily prepared from chiral amino alcohols or

1,2-diamines, were successfully applied to catalyze the Michael reaction of 4-hydroxycoumarin to α,β-unsaturated ketones. The corresponding Warfarin and its analogs could be obtained in moderate to excellent yields (up to 99%) and good to excellent enantioselectivities (up to 99% ee) under mild conditions. The phosphinamide catalyst expands primary amine catalytic systems in asymmetric catalysis, and further investigations on the application of these catalysts are under way in our laboratory.

Experimental sections

All reagents and solvents were used directly without purification. Flash column chromatography was performed over silica (200–300 mesh). Melting points were measured with a XT-4 melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on Varian Mercury-plus 400 MHz spectrometer. Infrared spectra were obtained with a Perkin Elmer Spectrum One spectrometer. The ESI-HRMS spectra were obtained with a Bruker APEX IV mass spectrometer. Optical rotations were measured with WZZ-3 polarimeter at the indicated concentration with units g/100 mL. The enantiomeric excesses (ee values) of the products were determined by chiral HPLC analysis using an Agilent HP 1200 instrument.

The synthesis of catalysts 2a–f

(*S*)-*N*-Diphenylphosphinyl-3-methylbutane-1,2-diamine (2a). To a round bottom flask containing the (2*S*)-2-*tert*-butoxycarbonylamino-3-methylbutylamine[13a] (1.34 g, 6.6 mmol) were added diphenylphosphinylchloride (1.66 g, 7.0 mmol), Et_3N (3 mL), and CH_2Cl_2 (30 mL). The mixture was stirred at room temperature for 24 h. The mixture was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by silica gel flash chromatography to give corresponding Boc-protected phosphinamide 1.14 g (43% yield). The Boc-protected phosphinamide (0.80 g, 2.0 mmol) was added to a round bottom flask in CH_2Cl_2 (15 mL). Then trifluoroacetic acid (4 mL) was added at 0 °C. After the reaction reached completion, $NaHCO_3$ (aq.) was added at 0 °C. The organic phase was separated, and the water phase was extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was dried and concentrated under vacuum, and the crude residue was purified by silica gel flash chromatography affording **2a** as a white solid (0.42 g, 69% yield); mp 74–76 °C. IR (KBr): *ν* 3416, 2970, 1682, 1542, 1439, 1204, 1126, 835, 799, 728, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 1.90 (br s, 1H, CH), 3.12 (br s, 3H, CH and CH_2), 5.37 (s, 1H, NH), 7.37–7.78 (m, 12H, ArH and NH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.0, 131.8, 131.7, 131.6, 130.9 (d, $^1J_{CP}$ = 128.7 Hz), 130.7 (d, $^1J_{CP}$ = 128.9 Hz), 128.5 (d, $^2J_{CP}$ = 12.7 Hz), 128.5 (d, $^2J_{CP}$ = 12.4 Hz), 58.8 (d, $^2J_{CNP}$ = 3.7 Hz), 41.2, 29.1, 18.4, 17.8 ppm. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{24}N_2OP$ $[M + H]^+$: 303.16208, found: 303.16181.

(*S*)-*N*-Diphenylphosphinyl-3,3-dimethylbutane-1,2-diamine (2b). According to the procedure outlined for **2a**, the Boc-protected phosphinamide intermediate was prepared from (2*S*)-2-*tert*-butoxycarbonylamino-3,3-dimethylbutylamine[13a] (1.08 g, 5.0 mmol) and obtained as solid (1.16 g, 55% yield). This Boc-protected phosphinamide intermediate (0.83 g, 2.0 mmol) was transformed to the desired product **2b** as white solid (0.49 g, 77% yield); mp 64–66 °C. IR (KBr): *ν* 3359, 3161, 3060, 2943, 2896, 2868, 1674, 1438, 1365, 1168, 1127, 1111, 1056, 836, 753, 730, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 0.84 (s, 9H, CH_3), 2.83–2.95 (m, 2H, CH_2), 3.10–3.18 (m, 1H, CH), 4.94–4.99 (m, 1H, NH), 5.66 (s, 2H, NH_2), 7.39–7.50 (m, 6H, ArH), 7.79–7.87 (m, 4H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.7 (d, $^1J_{CP}$ = 127.5 Hz),, 132.5 (d, $^1J_{CP}$ = 127.7 Hz), 132.1, 132.0, 131.8, 131.7, 131.4, 128.4 (d, $^2J_{CP}$ = 12.4 Hz), 61.7 (d, $^2J_{CNP}$ = 6.5 Hz), 42.0, 33.6, 25.9 ppm. HRMS (ESI): *m*/*z* calcd for $C_{18}H_{26}N_2OP$ $[M + H]^+$: 317.17773, found: 317.17752.

(*S*)-*N*-Diphenylphosphinyl-phenylethane-1,2-diamine (2c). According to the procedure outlined for **2a**, the Boc-protected phosphinamide intermediate was prepared from (2*S*)-2-*tert*-butoxycarbonylamino-phenylethylamine[13a] (1.69 g, 7.2 mmol) and obtained as solid (2.98 g, 95% yield). This Boc-protected phosphinamide intermediate (1.31 g, 3.0 mmol) was transformed to the desired product **2c** as white solid (0.90 g, 90% yield); mp 49–51 °C. IR (KBr): *ν* 3408, 2968, 2843, 1622, 1438, 1261, 1176, 1123, 754, 726, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.10–3.25 (m, 2H, CH_2), 4.24 (dd, *J* = 8.6, 4.6 Hz, 1H, CH), 4.90 (br s, 1H, NH), 6.00 (br s, 2H, NH_2), 7.24–7.44 (m, 11H, ArH), 7.66–7.75 (m, 4H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.3, 132.4 (d, $^1J_{CP}$ = 128.5 Hz), 132.1 (d, $^1J_{CP}$ = 128.7 Hz) 132.0, 131.9, 131.8, 131.6, 131.54, 131.51, 128.34, 128.31 (d, $^2J_{CP}$ = 12.4 Hz), 127.2, 126.3, 56.6 (d, $^2J_{CNP}$ = 5.9 Hz), 48.4 ppm. HRMS (ESI): *m*/*z* calcd for $C_{20}H_{22}N_2OP$ $[M + H]^+$: 337.14643, found: 337.14660.

(*S*)-*N*-Diphenylphosphinyl-phenylpropane-1,2-diamine (2d). According to the procedure outlined for **2a**, the Boc-protected phosphinamide intermediate was prepared from (2*S*)-2-*tert*-butoxycarbonylamino-3-phenylpropylamine[13a] (2.54 g, 10.2 mmol) and obtained as solid (3.35 g, 73% yield). The Boc-protected phosphinamide intermediate (0.90 g, 2.0 mmol) was transformed to the desired product **2d** as white solid (0.55 g, 78% yield); mp 78–80 °C. IR (KBr): *ν* 3238, 3060, 2924, 1676, 1497, 1439, 1203, 1174, 1125, 831, 799, 749, 727, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.56–2.77 (m, 2H, CH_2), 2.88 (s, 3H, NH_2 and CH), 3.07–3.23 (m, 2H, CH_2), 4.07 (s, 1H, NH), 7.11–7.24 (m, 5H, ArH), 7.45 (m, 6H, ArH), 7.82–7.87 (m, 4H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.6, 131.9, 131.8, 131.7, 131.6, 131.2 (d, $^1J_{CP}$ = 127.0 Hz), 131.1 (d, $^1J_{CP}$ = 127.2 Hz) 128.52, 128.50 (d, $^2J_{CP}$ = 12.2 Hz), 128.4, 126.6, 54.1 (d, $^2J_{CNP}$ = 4.6 Hz), 43.9, 38.7 ppm. HRMS (ESI): *m*/*z* calcd for $C_{21}H_{24}N_2OP$ $[M + H]^+$: 351.16208, found: 351.16136.

Catalyst **2e** and **2f** were obtained according to the procedure reported in previous literature.[4b,10]

General procedure for enantioselective Michael addition of 4-hydrocoumarin to enones

A mixture of 4-hydrocoumarin **3** (0.2 mmol), enone **4** (0.24 mmol), catalyst **2e** (0.02 mmol), 4-methylbenzoic acid

(0.04 mmol), toluene (1.5 mL) was added to a vial. After stirring at room temperature for 72 h, the reaction mixture was purified by silica gel column chromatography to afford the desired product **5**.

The Michael addition products **5** were found to exist in rapid equilibrium with a pseudodiastereomeric hemiketal form in solution. The exact form is different in various solvents. The equilibrium was very rapid and therefore no pseudodiastereomers were observed during HPLC analysis.

(*R*)-4-Hydroxy-3-(3-oxo-1-phenylbutyl)-chromen-2-one (5a). Compound **5a** was obtained according to the general procedure as a white solid (61.4 mg, 99% yield); mp 169–171 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IA column (*n*-hexane–2-propanol–EtOAc 50 : 20 : 30, flow rate 0.5 mL min^{-1}; detection at 254 nm): minor enantiomer t_R = 8.1, major enantiomer t_R = 10.7 min, 94% ee; $[\alpha]_D^{25}$: +24.0 (*c* 1.0, CH_2Cl_2), Lit.[12d] $[\alpha]_D^{25}$ = +10.3 (*c* 0.6, acetonitrile, 83% ee). ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 1.76 (s, 3H, CH_3 ketal), 2.04–2.06 (m, 2H, CH_2 ketal), 2.45 (s, 1H, CH ketal), 4.13 (s, 1H, OH ketal), 7.16–7.30 (m, 6H, ArH), 7.35 (t, *J* = 7.6 Hz, 1H, ArH), 7.61 (t, *J* = 7.6 Hz, 1H, ArH), 7.87 (dd, *J* = 8.0, 1.2 Hz, 1H, ArH) ppm; ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 162.2, 162.1, 160.8, 160.6, 154.8, 146.0, 133.4, 130.1, 129.7, 129.3, 129.1, 127.8, 125.5, 124.7, 117.9, 101.1, 44.9, 37.6, 28.9, 27.6 ppm.

(*R*)-4-Hydroxy-3-[1-(3-nitrophenyl)-3-oxo-butyl]-chromen-2-one (5b).[17] Compound **5b** was obtained according to the general procedure as a white solid (62.2 mg, 88% yield); mp 191–193 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IA column (*n*-hexane–2-propanol–EtOAc 50 : 10 : 40; flow rate 0.5 mL min^{-1}; detection at 254 nm): minor enantiomer t_R = 11.0, major enantiomer t_R = 13.1 min, 92% ee; $[\alpha]_D^{25}$: +0.8 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 1.80 (s, 3H, CH_3), 2.04–2.08 (m, 2H, CH_2), 2.53 (s, 1H, CH), 4.32 (s, 1H, OH), 7.32–7.40 (m, 2H, ArH), 7.57–7.66 (m, 2H, ArH), 7.78 (d, *J* = 7.6 Hz, 1H, ArH), 7.89 (d, *J* = 7.6 Hz, 1H, ArH), 8.06 (s, 1H, ArH), 8.17 (s, 1H, ArH) ppm; ^{13}C NMR (100 MHz, CD_3SOCD_3): δ = 160.9, 160.3, 159.7, 159.4, 152.3, 147.8, 147.4, 146.3, 134.6, 134.1, 132.2, 132.0, 129.6, 129.1, 124.1, 124.0, 122.8, 122.7, 122.4, 121.8, 121.1, 120.7, 116.3, 116.2, 115.5, 115.3, 109.4, 102.4, 100.9, 100.7, 99.6, 41.9, 34.9, 27.1, 26.6 ppm.

(*R*)-4-Hydroxy-3-[1-(4-dimethylaminophenyl)-3-oxo-butyl]-chromen-2-one (5c).[18] Compound **5c** was obtained according to the general procedure as a yellow solid (45.9 mg, 65% yield); mp 92–94 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IA column (*n*-hexane–2-propanol–EtOAc 50 : 10 : 40; flow rate 0.5 mL min^{-1}; detection at 254 nm): minor enantiomer t_R = 10.7, major enantiomer t_R = 15.4 min, 86% ee; $[\alpha]_D^{25}$: +7.6 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (s, 1.55H, CH_3 ketal), 1.69 (s, 1.03H, CH_3 ketal), 2.02 (t, *J* = 10.8 Hz, 0.41H, CH_2 keto), 2.26 (s, 0.42H, CH_3 keto), 2.34 (dd, *J* = 6.4, 14.0 Hz, 0.63H, CH_2 ketal), 2.44 (dd, *J* = 6.8, 13.6 Hz, 0.39H, CH_2 ketal), 2.55 (dd, *J* = 14.2, 2.6 Hz, 0.62H, CH_2 ketal), 2.90 (s, 6H, NCH_3), 3.60 (br s, 0.70H, OH ketal), 4.08 (dd, *J* = 10.6, 7.0 Hz, 0. 33H, CH ketal), 4.24 (dd, *J* = 2.4, 6.0 Hz, 0.48H, CH ketal), 4.30 (t, *J* = 10.8 Hz, 0.12H, CH keto), 4.63 (br s, 0.20H, OH ketal), 5.29 (s, 0.12H, OH keto), 6.68 (d, *J* = 8.4 Hz, 2H, ArH), 7.07–7.36 (m, 4H, ArH), 7.46–7.57 (m, 1H, ArH), 7.79–7.91 (m, 1H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$)): δ = 162.2, 161.5, 159.5, 158.7, 152.6, 149.5, 149.1, 144.9, 131.7, 131.1, 130.8, 130.0, 128.7, 128.3, 127.6, 127.4, 123.7, 123.4, 122.9, 122.7, 116.3, 116.1, 115.5, 113.4, 113.1, 111.7, 104.3, 101.5, 100.7, 99.3, 65.5, 42.7, 40.7, 40.5, 39.8, 34.2, 33.0, 27.7, 27.3 ppm.

(*R*)-4-Hydroxy-3-[1-(2-methoxyphenyl)-3-oxo-butyl]-chromen-2-one (5d). Compound **5d** was obtained according to the general procedure as a white solid (55.8 mg, 82% yield); mp 198–199 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IA column (*n*-hexane–2-propanol–EtOAc 50 : 20 : 30; flow rate 0.5 mL min^{-1}; detection at 254 nm): minor enantiomer t_R = 8.1, major enantiomer t_R = 9.6 min, 91% ee; $[\alpha]_D^{25}$: +6.2 (*c* 1.0, CH_2Cl_2), Lit.[12d] $[\alpha]_D^{25}$ = +52.0 (*c* 0.2, acetonitrile, 89% ee). ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 1.73 (s, 3H, CH_3 ketal), 2.04–2.09 (m, 2H, CH_2 ketal), 2.44 (br s, 1H, CH ketal), 3.85 (s, 3H, OCH_3), 4.57 (br s, 1H, OH ketal), 6.82–6.97 (m, 2H, ArH), 7.05–7.17 (m, 2H, ArH), 7.28–7.37 (m, 2H, ArH), 7.60 (t, *J* = 7.6 Hz, 1H, ArH), 7.86 (d, *J* = 7.6 Hz, 1H, ArH) ppm; ^{13}C NMR (100 MHz, CD_3SOCD_3): δ = 160.6, 160.1, 159.2, 158.7, 156.5, 156.3, 152.1, 131.8, 131.6, 131.4, 130.7, 127.9, 126.9, 126.7, 123.9, 123.8, 122.5, 120.4, 119.6, 116.1, 116.0, 115.7, 115.5, 110.8, 110.4, 103.5, 101.9, 100.9, 99.6, 55.4, 40.4, 38.2, 27.2, 26.6 ppm.

(*R*)-4-Hydroxy-3-[1-(4-methoxyphenyl)-3-oxo-butyl]-chromen-2-one (5e). Compound **5e** was obtained according to the general procedure as a white solid (61.7 mg, 91% yield); mp 164–166 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IA column (*n*-hexane–2-propanol–EtOAc 40 : 30 : 30; flow rate 0.5 mL min^{-1}; detection at 254 nm): minor enantiomer t_R = 7.7, major enantiomer t_R = 10.0 min, 94% ee; $[\alpha]_D^{25}$: +1.2 (*c* 1.0, CH_2Cl_2), Lit.[12d] $[\alpha]_D^{25}$ = −8.7 (*c* 0.368, actonitrile, 87% ee). ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 1.74 (s, 3H, CH_3 ketal), 2.04–2.07 (m, 2H, CH_2 ketal), 2.40 (s, 1H, CH ketal), 3.75 (s, 3H, OCH_3), 4.06 (s, 1H, OH ketal), 6.82 (d, *J* = 7.2 Hz, 2H, ArH), 7.17 (d, *J* = 7.6 Hz, 2H, ArH), 7.26–7.36 (m, 2H, ArH), 7.59 (s, 1H, ArH), 7.86 (d, *J* = 7.2 Hz, 1H, ArH) ppm; ^{13}C NMR (100 MHz, CD_3SOCD_3): δ = 160.5, 160.1, 159.1, 158.5, 157.4, 157.2, 152.2, 135.6, 131.8, 131.7, 128.2, 128.0, 123.9, 123.8, 122.6, 122.5, 116.1, 116.0, 115.6, 115.4, 113.5, 113.2, 103.6, 102.2, 101.3, 99.6, 54.8, 42.8, 35.3, 34.3, 27.2, 25.7 ppm.

(*R*)-4-Hydroxy-3-[1-(4-methylphenyl)-3-oxo-butyl]-chromen-2-one (5f). Compound **5f** was obtained according to the general procedure as a white solid (37.7 mg, 58% yield); mp 187–189 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IA column (*n*-hexane–2-propanol–EtOAc 45 : 25 : 30; flow rate 0.5 mL min^{-1}; detection at 254 nm): minor enantiomer t_R = 7.5, major enantiomer t_R = 9.8 min, 96% ee; $[\alpha]_D^{25}$: +16.6 (*c* 1.0, CH_2Cl_2), Lit.[12d] $[\alpha]_{405}^{26}$ = +23.6 (*c* 0.11, actonitrile, 89% ee). ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 1.74 (s, 3H, CH_3 ketal), 2.04–2.06 (m, 2H, CH_2 ketal), 2.27 (s, 3H, CH_3), 2.43 (s, 1H, CH ketal), 4.09 (s, 1H, OH ketal), 7.06 (d, *J* = 7.6 Hz, 2H, ArH), 7.14 (d, *J* = 8.0 Hz, 2H, ArH), 7.28

(d, J = 8.0 Hz, 1H, ArH), 7.35 (t, J = 7.6 Hz, 1H, ArH), 7.60 (t, J = 7.6 Hz, 1H, ArH), 7.86 (dd, J = 7.8, 1.0 Hz, 1H, ArH) ppm; ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 154.8, 143.0, 137.0, 133.4, 130.7, 130.4, 129.2, 129.0, 125.4, 124.7, 117.9, 44.9, 37.2, 28.9, 22.0 ppm.

(*R*)-3-[1-(4-Bromophenyl)-3-oxo-butyl]-4-hydroxychromen-2-one (5g).[17] Compound **5g** was obtained according to the general procedure as a white solid (75.5 mg, 97% yield); mp 184–185 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralcel IA column (*n*-hexane–2-propanol–EtOAc 50 : 20 : 30; flow rate 0.5 mL min^{-1}; detection at 254 nm): minor enantiomer t_R = 8.4, major enantiomer t_R = 12.5 min, 96% ee; $[\alpha]_D^{25}$: +1.4 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 1.76 (s, 3H, CH_3 ketal), 2.04–2.07 (m, 2H, CH_2 ketal), 2.44 (s, 1H, CH ketal), 4.12 (s, 1H, OH ketal), 7.23–7.43 (m, 6H, ArH), 7.62 (t, J = 7.6 Hz, 1H, ArH), 7.86 (d, J = 8.0 Hz, 1H, ArH) ppm; ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 162.1, 160.8, 154.8, 145.6, 133.5, 133.0, 132.5, 131.7, 131.3, 125.5, 124.7, 120.9, 117.9, 105.6, 101.1, 44.5, 42.4, 37.1, 28.9 ppm.

(*R*)-3-[1-(2-Bromophenyl)-3-oxo-butyl]-4-hydroxychromen-2-one (5h). Compound **5h** was obtained according to the general procedure as a white solid (75.5 mg, 97% yield); mp 167–169 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IA column (*n*-hexane–2-propanol–EtOAc 50 : 20 : 30; flow rate 0.5 mL min^{-1}; detection at 254 nm): minor enantiomer t_R = 7.7, major enantiomer t_R = 8.4 min, 93% ee; $[\alpha]_D^{25}$: +9.0 (*c* 1.0, CH_2Cl_2). IR (KBr): ν 3786, 3696, 3453, 3050, 2989, 1689, 1624, 1575, 1393, 1189, 1176, 1070, 764, 750 cm^{-1}; ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 1.79 (s, 3H, CH_3 ketal), 1.98–2.05 (m, 2H, CH_2 ketal), 2.51 (br s, 1H, CH ketal), 4.66 (br s, 1H, OH ketal), 7.11–7.39 (m, 5H, ArH), 7.57–7.63 (m, 2H, ArH), 7.88 (d, J = 7.2 Hz, 1H, ArH) ppm; ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 161.9, 161.0, 154.8, 134.4, 133.5, 129.7, 129.6, 125.5, 124.6, 118.0, 105.6, 101.2, 42.4, 39.9, 36.8, 28.9 ppm. HRMS (ESI): *m/z* calcd for $C_{19}H_{16}BrO_4$ $[M + H]^+$: 387.02265, found: 387.02342.

(*R*)-3-[1-(4-Chlorophenyl)-3-oxo-butyl]-4-hydroxychromen-2-one (5i). Compound **5i** was obtained according to the general procedure as a white solid (67.6 mg, 99% yield); mp 174–176 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralcel IA column (*n*-hexane–2-propanol–EtOAc 50 : 20 : 30; flow rate 0.5 mL min^{-1}; detection at 254 nm): minor enantiomer t_R = 8.2, major enantiomer t_R = 12.1 min, 94% ee; $[\alpha]_D^{25}$: 2.0 (*c* 1.0, CH_2Cl_2), Lit.[12d] $[\alpha]_D^{25}$ = −8.8 (*c* 0.274, acetonitrile, 79% ee). ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 1.77 (s, 3H, CH_3 ketal), 2.04–2.07 (m, 2H, CH_2 ketal), 2.47 (br s, 1H, CH ketal), 4.14 (s, 1H, OH ketal), 7.30–7.38 (m, 6H, ArH), 7.62 (t, J = 7.6 Hz, 1H, ArH), 7.88 (dd, J = 8.0, 1.2 Hz, 1H, ArH) ppm; ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 162.1, 160.8, 154.8, 145.1, 133.5, 132.9, 131.3, 130.9, 130.0, 129.6, 125.5, 124.7, 117.9, 101.2, 44.5, 37.0, 28.9 ppm.

(*R*)-4-Hydroxy-3-[1-(4-nitrophenyl)-3-oxo-butyl]-chromen-2-one (5j).[12a] Compound **5j** was obtained according to the general procedure as a white solid (69.5 mg, 98% yield); mp 191–193 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralcel IA column (*n*-hexane–2-propanol–EtOAc 50 : 20 : 30; flow rate 0.4 mL min^{-1}; detection at 254 nm): minor enantiomer t_R = 13.2, major enantiomer t_R = 18.9 min, 91% ee; $[\alpha]_D^{25}$: +1.8 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, CD_3SOCD_3): δ = 1.61 (s, 1.07H, CH_3 ketal), 1.68 (s, 1.67H, CH_3 ketal), 1.91 (t, J = 4.8 Hz, 0.65H, CH_2), 2.14 (s, 0.28H, CH_3 keto), 2.21–2.26 (m, 0.42H, CH_2), 2.34–2.39 (m, 0.93H, CH_2), 3.35 (s, 1H, CH), 4.17 (s, 1H ,OH), 7.38–7.67 (m, 5H, ArH), 7.85 (d, J = 6.8 Hz, 1H, ArH), 8.11 (t, J = 8.8 Hz, 2H, ArH) ppm; ^{13}C NMR (100 MHz, CD_3SOCD_3): δ = 160.9, 160.3, 159.6, 159.3, 152.4, 152.33, 152.28, 145.8, 145.5, 132.2, 132.1, 128.8, 128.5, 124.1, 124.0, 123.4, 122.9, 122.7, 122.6, 116.3, 116.2, 115.4, 115.3, 102.3, 100.9, 100.8, 99.5, 41.8, 39.9, 35.2, 35.1, 27.1, 26.4 ppm.

(*R*)-3-(1-Furan-2-yl-3-oxo-butyl)-4-hydroxychromen-2-one (5k).[12a] Compound **5k** was obtained according to the general procedure as a white solid (8.5 mg, 14% yield); mp 120–121 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralcel IA column (*n*-hexane–2-propanol–EtOAc 60 : 10 : 30; flow rate 0.5 mL min^{-1}; detection at 254 nm): minor enantiomer t_R = 13.1, major enantiomer t_R = 13.7 min, 99% ee; $[\alpha]_D^{25}$: +6.5 (*c* 0.4, CH_2Cl_2). ^{1}H NMR (400 MHz, CD_3SOCD_3): δ = 1.56 (s, 1.42H, CH_3 ketal), 1.60 (s, 0.74H, CH_3 ketal), 2.11–2.21 (m, 1.68H, CH_2 ketal + CH_3 keto), 2.30 (dd, J = 6.4, 13.6 Hz, 0.62H, CH_2 ketal), 2.39 (dd, J = 4.8, 14.0 Hz, 0.31H, CH_2 ketal), 3.28 (dd, J = 17.6, 7.6 Hz, 0.34H, CH_2 keto), 3.41 (dd, J = 17.6, 6.8 Hz, 0.37H, CH_2 keto), 4.08 (t, J = 5.6 Hz, 0.23 H, CH ketal), 4.14 (dd, J = 6.8, 9.6 Hz, 0.49H, CH ketal), 4.22 (t, J = 6.4 Hz, 0.14H, CH ketal), 4.97 (t, J = 7.0 Hz, 0.33H, CH keto), 5.97 (d, J = 3.2 Hz, 0.18H, ArH), 6.09 (d, J = 3.2 Hz, 0.25H, CH), 6.16 (d, J = 2.8 Hz, 0.43H, ArH), 6.28–6.35 (m, 0.88H, ArH), 7.11 (s, 0.35H, OH ketal), 7.34–7.47 (m, 3H, ArH), 7.59–7.66 (m, 1H, ArH), 7.80 (d, J = 6.8 Hz, 0.66H, ArH), 8.00 (d, J = 8.0 Hz, 0.27H, ArH), 11.75 (s, 0.33H, OH keto) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.7, 162.7, 162.1, 161.8, 161.6, 159.3, 159.0, 154.4, 154.0, 152.7, 152.6, 141.9, 141.1, 140.7, 132.1, 131.9, 131.5, 123.9, 123.81, 123.77, 123.5, 123.0, 122.7, 116.4, 116.2, 116.0, 115.7, 115.4, 110.7, 110.3, 106.5, 106.2, 106.0, 99.6, 99.5, 99.0, 44.8, 38.1, 35.8, 30.2, 29.7, 29.1, 28.1, 27.8, 27.1 ppm.

(*R*)-4-Hydroxy-3-(1-naphthalen-1-yl-3-oxo-butyl)-chromen-2-one (5l).[17] Compound **5l** was obtained according to the general procedure as a white solid (62.0 mg, 86% yield); mp 98–100 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IA column (*n*-hexane–2-propanol–EtOAc 50 : 20 : 30; flow rate 0.5 mL min^{-1}; detection at 254 nm): minor enantiomer t_R = 8.4, major enantiomer t_R = 10.5 min, 96% ee; $[\alpha]_D^{25}$: +4.8 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59 (s, 0.95H, CH_3 ketal), 1.61 (s, 1.75H, CH_3 ketal), 2.04 (s, 0.41H, CH_2 ketal), 2.29 (s, 0.30H, CH_3 keto), 2.47–2.60 (m, 0.88H, CH_2 ketal), 2.71 (dd, J = 14.4, 2.0 Hz, 0.50H, CH_2 ketal), 3.38 (dd, J = 19.2, 2.4 Hz, 0.14H, CH_2 keto), 3.54 (s, 0.41H, OH), 3.98 (d, J = 10.8 Hz, 0.22H, CH ketal), 4.07 (dd, J = 19.2, 10.4 Hz, 0.15H, CH_2 keto), 5.00 (d, J = 6.8 Hz, 0.77H, CH ketal), 5.32 (dd, J = 10.0, 2.4 Hz, 0.11H, CH keto), 7.21–7.95 (m, 10H, ArH), 8.12 (d, J = 8.4 Hz, 1H, ArH), 9.70 (s, 0.12H, OH keto) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.5, 162.2, 161.6, 160.7, 160.2, 159.8, 152.7, 152.5, 139.4,

137.1, 134.5, 134.0, 133.6, 131.9, 131.6, 131.3, 131.1, 130.7, 129.3, 128.9, 128.1, 127.7, 126.7, 126.3, 125.8, 125.4, 125.3, 125.2, 124.9, 123.9, 123.7, 123.5, 123.0 122.9, 122.8, 122.7, 116.4, 116.1, 115.9, 115.5, 107.5, 103.9, 101.1, 100.3, 99.4, 46.6, 37.7, 31.5, 29.7, 27.8, 27.4 ppm.

(*R*)-4-Hydroxy-3-(4-cyclohexyl-3-oxo-1-phenylbutyl) – chromen-2-one (5m). Compound **5m** was obtained according to the general procedure as a white solid (8.8 mg, 12% yield); mp 149–151 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IA column (*n*-hexane–2-propanol–EtOAc 60 : 10 : 30; flow rate 0.5 mL min^{-1}; detection at 254 nm): minor enantiomer t_R = 13.0, major enantiomer t_R = 17.5 min, 83% ee; $[\alpha]_D^{25}$: 15.6 (*c* 0.45, CH_2Cl_2); IR (KBr): *v* 3384, 3061, 3028, 2924, 2853, 1686, 1613, 1564, 1386, 1250, 1104, 765, 699, 626 cm^{-1}; ^1H NMR (400 MHz, CD_3SOCD_3): δ = 1.08–1.21 (m, 5.09H, CH_2), 1.57–1.99 (m, 5.91H, CH + CH_2), 2.09–2.45 (m, 1.33H, CH_2 ketal), 3.37 (dd, *J* = 5.6, 18.0 Hz, 0.34H, CH_2 keto), 3.58 (dd, *J* = 8.0, 18.0 Hz, 0.33H, CH_2 keto), 3.98–4.02 (m, 0.66H, CH ketal), 4.94 (t, *J* = 6.8 Hz, 0.33H, CH keto), 5.76 (s, 0.16H, OH ketal), 6.98 (s, 0.56H, ArH), 7.18–7.39 (m, 6.50H, ArH), 7.57–8.02 (m, 2.10H, ArH), 11.69 (s, 0.37H, OH keto) ppm; ^{13}C NMR (100 MHz, CD_3SOCD_3): δ = 211.7, 161.6, 160.7, 160.3, 160.1, 159.2, 158.8, 152.3, 152.0, 151.9, 144.1, 143.9, 142.7, 131.8, 128.1, 127.8, 127.7, 127.4, 127.3, 126.9, 125.8, 125.4, 124.0, 123.9, 123.7, 123.3, 122.6, 122.4, 116.2, 116.0, 115.7, 115.4, 107.7, 104.0, 103.4, 102.6, 102.1, 49.6, 46.4, 44.7, 42.4, 38.0, 36.6, 35.0, 34.9, 34.6, 28.0, 27.8, 26.8, 26.7, 26.0, 25.8, 25.6, 25.5, 25.4, 25.04, 24.97 ppm. HRMS (ESI): *m*/*z* calcd for $C_{24}H_{25}O_4$ $[M + H]^+$: 377.17474, found: 377.17470 ppm.

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Notes and references

1 (*a*) S. B. Tsogoeva, *Eur. J. Org. Chem.*, 2007, 1701; (*b*) O. M. Berner, L. Tedeschi and D. Enders, *Eur. J. Org. Chem.*, 2002, 1877; (*c*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138; (*d*) H. Li, Y. Wang, T. Tang and L. Deng, *J. Am. Chem. Soc.*, 2004, **126**, 9906; (*e*) P. Li, S. Wen, F. Yu, Q. Liu, W. Li, Y. Wang, S. Liang and J. Ye, *Org. Lett.*, 2009, **11**, 753; (*f*) L. Zu, W. Wang, J. Wang, H. Li and W. H. Duan, *Org. Lett.*, 2005, **7**, 4713; (*g*) J. P. Malerich, K. Hagihara and V. H. Rawal, *J. Am. Chem. Soc.*, 2008, **130**, 14416.
2 (*a*) K. Ishihara and K. Nakano, *J. Am. Chem. Soc.*, 2005, **127**, 10504; (*b*) A. Sakakura, K. Suzuki, K. Nakano and K. Ishihara, *Org. Lett.*, 2006, **8**, 2229.
3 W. Chen, W. Du, L. Yue, R. Li, Y. Wu, L. S. Ding and Y. C. Chen, *Org. Biomol. Chem.*, 2007, **5**, 816.
4 (*a*) Y. M. Xu and A. Córdova, *Chem. Commun.*, 2006, 460; (*b*) D. J. Morris, A. S. Partridge, C. V. Manville, D. T. Racys, G. Woodward, G. Docherty and M. Wills, *Tetrahedron Lett.*, 2010, **51**, 209.
5 (*a*) V. Bisai, A. Bisai and V. K. Singh, *Tetrahedron*, 2012, **68**, 4541; (*b*) P. Zhou, L. Zhang, S. Luo and J.-P. Cheng, *J. Org. Chem.*, 2012, **77**, 2526; (*c*) Z. Chai and G. Zhao, *Catal. Sci. Technol.*, 2012, **2**, 29.
6 (*a*) C. G. Oliva, A. M. S. Silva, D. I. S. P. Resende, F. A. A. Paz and J. A. S. Cavaleiro, *Eur. J. Org. Chem.*, 2010, 3449; (*b*) C. Liu and Y. Lu, *Org. Lett.*, 2010, **12**, 2278; (*c*) L. T. Dong, R. J. Lu, Q. S. Du, J. M. Zhang, S. P. Liu, Y. N. Xuan and M. Yan, *Tetrahedron*, 2009, **65**, 4124; (*d*) Q. Zhu, L. Cheng and Y. Lu, *Chem. Commun.*, 2008, 6315.
7 P. J. Li, Y. C. Wang, X. M. Liang and J. X. Ye, *Chem. Commun.*, 2008, 3302.
8 Y. Q. Yang, X. K. Chen, H. Xiao, W. Liu and G. Zhao, *Chem. Commun.*, 2010, **46**, 4130.
9 (*a*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2001, **40**, 3726; (*b*) J. Seayad and B. List, *Org. Biomol. Chem.*, 2005, **3**, 719; (*c*) A. P. Brogan, T. J. Dickerson and K. D. Janda, *Angew. Chem., Int. Ed.*, 2006, **45**, 8100; (*d*) A. G. Doyle and E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713; (*e*) T. Akiyama, J. Itoh and K. Fuchibe, *Adv. Synth. Catal.*, 2006, **348**, 999.
10 K. L. Tan and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2007, **46**, 1315.
11 C. H. Luo, Y. Jin and D. M. Du, *Org. Biomol. Chem.*, 2012, **10**, 4116.
12 (*a*) N. Halland, T. Hansen and K. A. Jorgensen, *Angew. Chem., Int. Ed.*, 2003, **42**, 4955; (*b*) H. Kim, C. Yen, P. Preston and J. Chin, *Org. Lett.*, 2006, **8**, 5239; (*c*) J. W. Xie, L. Yue, W. Chen, W. Du, J. Zhu, J. G. Deng and Y. C. Chen, *Org. Lett.*, 2007, **9**, 413; (*d*) Z. H. Dong, L. J. Wang, X. H. Chen, X. H. Liu, L. L. Lin and X. M. Feng, *Eur. J. Org. Chem.*, 2009, 5192; (*e*) H. M. Yang, K. Z. Jiang, J. X. Jiang, G. Q. Lai and L. W. Xu, *Tetrahedron*, 2010, **66**, 9708; (*f*) M. Rogozińska, A. Adamkiewicz and J. Mlynarski, *Green Chem.*, 2011, **13**, 1155.
13 (*a*) H. Liu and D. M. Du, *Adv. Synth. Catal.*, 2010, **352**, 1113; (*b*) X. Du, H. Liu and D.-M. Du, *Eur. J. Org. Chem.*, 2011, 786.
14 (*a*) M. C. Etter and P. W. Baures, *J. Am. Chem. Soc.*, 1988, **110**, 639; (*b*) M. C. Etter and S. M. Reutzel, *J. Am. Chem. Soc.*, 1991, **113**, 2586.
15 (*a*) O. Molt and T. Schrader, *Synthesis*, 2002, 2633; (*b*) B. Burns, N. P. King, H. Tye, J. R. Studley, M. Gamble and M. Wills, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1027; (*c*) M. P. Gamble, A. R. C. Smith and M. Wills, *J. Org. Chem.*, 1998, **63**, 6068; (*d*) D. Basavaiah, V. Chandrashekar, U. Das and G. J. Reddy, *Tetrahedron: Asymmetry*, 2005, **16**, 3955.
16 (*a*) M. Benaglia and S. Rossi, *Org. Biomol. Chem.*, 2010, **8**, 3824; (*b*) M. Kanai, Y. Hamashima and M. Shibasaki, *Tetrahedron Lett.*, 2000, **41**, 2405; (*c*) S. S. Kim and J. M. Kwak, *Tetrahedron*, 2006, **62**, 49.
17 R. Q. Mei, X. Y. Xu, Y. C. Li, J. Y. Fu, Q. C. Huang and L. X. Wang, *Tetrahedron Lett.*, 2011, **52**, 1566.
18 E. J. Valente, D. S. Eggleston and V. Schomaker, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1986, **42**, 1809.