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Organocatalytic Enantioselective Michael Addition of 4-Hydroxycoumarin to α,β-Unsaturated Ketones: A Simple Synthesis of Warfarin

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A type of C_2-symmetric secondary amine amide catalysts were developed for the asymmetric Michael addition of 4-hydroxycoumarin to α,β-unsaturated ketones. A series of important biologically and pharmaceutically active compounds were obtained in excellent yields (up to 99%) with high enantioselectivities (up to 89% *ee*) under mild conditions. In addition, enantiopure product could be obtained by a single recrystallization.

Introduction

As one of the most effective anticoagulants, warfarin has been introduced for clinical use as a racemate for more than half a century. Further investigation showed that (*S*)-warfarin had higher anticoagulant activity than the *R* enantiomer (about 5–8 times).[1] However, both racemic and (*S*)-warfarin are associated with a series of syndromes, and weakened patients were only treated with mild (*R*)-warfarin.[2] As a result, achieving the optically pure *R* or *S* enantiomer of warfarin would be of great importance.

Several asymmetric methods have been developed for the synthesis of chiral warfarin, which include a chiral auxiliary strategy,[3a] asymmetric hydrogenation,[3b,3c] and enantioselective hetero-Diels–Alder cycloaddition reaction.[3d] However, lengthy synthesis leads to low yields, or the substrates are difficult to prepare. In 2003, the Jørgensen group reported the first one-step synthesis of enantiomerically pure warfarin from simple materials.[4a] They presented the enantioselective Michael addition of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated ketones catalyzed by secondary amine catalysts.[5–7] Recently, the groups of Chen[4b] and Chin[4c] used the same strategy for the synthesis of pure warfarin catalyzed by a primary amine[8] and diamine, respectively. Good yields and high enantiomeric excess values were obtained, but long reaction times (4–6 d) were required. Hence, an effective method for the synthesis of warfarin is still a challenge.

C_2-symmetric secondary amine amide catalysts,[9] as ligands or organocatalysts, have been shown to be highly efficient in many asymmetric procedures. In previous reports of our group, the catalysts were successfully used for the asymmetric cyanosilylation of aldehydes[9c] and ketones,[9d] aldol reaction,[9f,9g] Henry reaction,[9h] and asymmetric Michael addition of nitroolefins.[9e] We considered that the catalysts could activate the α,β-unsaturated ketones via an iminium ion intermediate in the Michael reaction. Therefore, we developed an enantioselective Michael reaction of 4-hydroxycoumarin and α,β-unsaturated ketones catalyzed by this kind of secondary amine amide organocatalyst to give (*R*)-warfarin and analogues in high yields (up to 99%) and enantioselectivities (up to 89% *ee*) under mild conditions within 12 h.

Results and Discussion

By using 4-hydroxycoumarin (**2**) and benzylideneacetone (**3a**) as the model compounds, a series of amine amide catalysts prepared from amino acids and diamines (**1a**–**g**; Figure 1) were screened at room temperature in CH_2Cl_2, and the results are summarized in Table 1. Initial examination indicated that the diamine backbone moiety was of great importance. (L)-Proline derivative **1d** with a 1,2-diaminobenzene backbone was superior to catalyst **1a** containing an (*S*,*S*)-1,2-diphenylethylenediamine backbone, catalyst **1b** with an ethylenediamine backbone, and catalyst **1c** with an (*S*,*S*)-1,2-diaminocyclohexane backbone (Table 1, Entries 1–4). Catalyst **1e** with a 1,4-diaminobenzene backbone gave poor results too (Table 1, Entry 5). Furthermore, neither (L)-piperidine-2-carboxylic acid derivative **1f** nor (L)-phenylglycine derivative **1g** provided good results (Table 1, Entries 6 and 7). Of all the catalysts examined, catalyst **1d**

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exhibited the highest yield and enantioselectivity in 24 h and gave warfarin with the absolute configuration of *R* (Table 1, Entry 3; 70% yield, 67%*ee*).

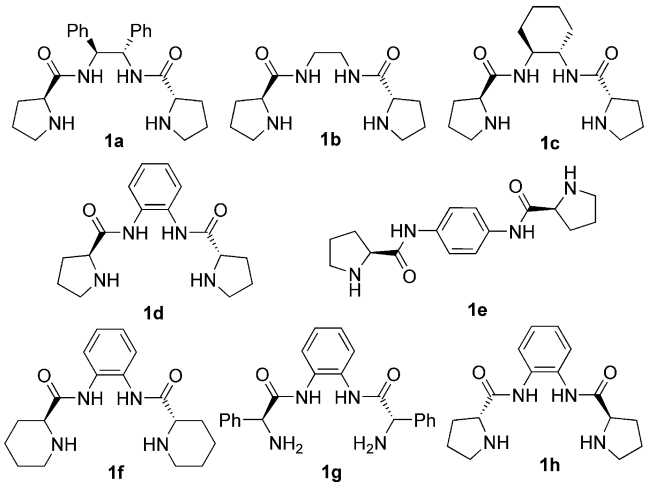
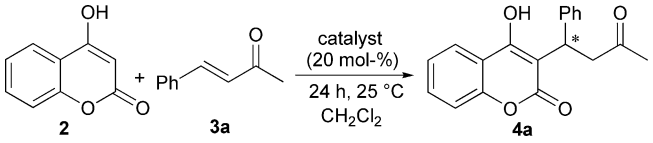


Figure 1. Catalysts screened for the Michael reactions.

Table 1. Catalyst screening.[a]

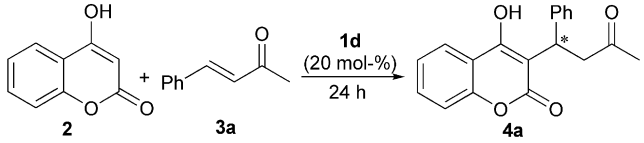


Entry	Catalyst	Yield [%][b]	*ee* [%][c]
1	**1a**	75	13 (*R*)[d]
2	**1b**	78	61 (*R*)
3	**1c**	85	53 (*R*)
4	**1d**	70	67 (*R*)
5	**1e**	42	37 (*R*)
6	**1f**	20	0
7	**1g**	86	13 (*S*)

[a] Unless noted otherwise, the reactions were carried out with **2** (0.10 mmol) and **3a** (0.15 mmol) in the presence of the catalyst (20 mol-%) in CH_2Cl_2 (1.0 mL) at 25 °C for 24 h. [b] Isolated yield after column chromatography. [c] Enantiomeric excess was determined by HPLC analysis on a Chiralpak ADH column. [d] The absolute configuration was determined by comparing with the literature (see ref.[10]).

With the best chiral catalyst **1d** being identified, we next carried out the Michael reaction of **2** with **3a** in different solvents. The results indicated that the solvents had a significant effect on the rate and enantioselectivity of this reaction (Table 2, Entries 1–9). The reaction carried out in Et_2O produced only a trace amount of product (Table 2, Entry 4). Solvents such as $ClCH_2CH_2Cl$, THF, H_2O, MeOH, EtOH, and 2-propanol are not suitable for this reaction, providing **4a** in lower enantioselectivity or yield. When using $CHCl_3$ as solvent, the highest enantioselectivity was observed (up to 73%*ee*; Table 2, Entry 1) with a moderate yield. Remarkably, with the use of *n*-butyl alcohol as solvent, the reaction proceeded quickly and afforded a moderate *ee* value (69%*ee*; Table 2, Entry 9). The reaction temperature showed a noticeable impact on the enantioselectivity. Surprisingly, the *ee* value dropped to 63% when the temperature was lowered to 0 °C (Table 2, Entry 10). Increasing the reaction temperature to 40 °C resulted in a slight improvement in the *ee* value and a 99% yield was achieved in only 12 h (71%*ee*; Table 2, Entry 11). So we chose *n*-butyl alcohol as the standard solvent for the optimization of the reaction conditions.

Table 2. Influence of solvent and temperature.[a]



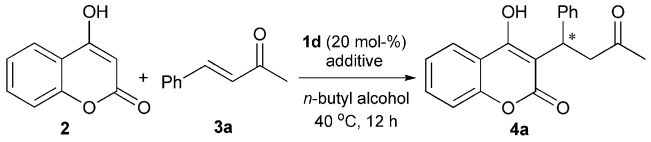
Entry	*T* [°C]	Solvent	Yield [%][b]	*ee* [%][c]
1	25	$CHCl_3$	69	73
2	25	$ClCH_2CH_2Cl$	70	65
3	25	THF	99	41
4	25	Et_2O	7	51
5	25	H_2O	76	29
6	25	MeOH	65	67
7	25	EtOH	44	51
8	25	2-propanol	37	69
9	25	*n*-butyl alcohol	99	69
10	0	*n*-butyl alcohol	99	63
11[d]	40	*n*-butyl alcohol	99	71

[a] Unless noted otherwise, the reactions were carried out with **2** (0.10 mmol) and **3a** (0.15 mmol) in the presence of catalyst **1d** (20 mol-%) in solvent (1.0 mL) for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis; (*R*) products were obtained. [d] At 40 °C for 12 h.

To further improve the enantioselectivity, the effect of additives was investigated. As summarized in Table 3, PhCOOH had no effect on the Michael addition (Table 3, Entry 1). Noticeably, the enantioselectivity showed an obvious increase when 1,2-phthalic acid (20 mol-%) was added (Table 3, Entry 2). A series of diacids screened showed that aliphatic diacids had a slightly higher *ee* value, and succinic acid was the best additive with 78%*ee* (Table 3, Entries 3 and 4). The loading of additive was tested and 10 mol-% loading of succinic acid was found to be suitable (Table 3, Entry 5).

To obtain even higher enantioselectivity, other aspects of this reaction were investigated. To our delight, a small quantity of H_2O had a positive effect on the enantioselectivity. When 50 μL of H_2O was added, the enantioselectivity increased to 83%*ee* (Table 3, Entry 6). However, when the dosage of H_2O was increased further, the yield and enantioselectivity decreased remarkably (Table 3, Entry 7). Interestingly, by using catalyst **1h** prepared from (D)-proline, the reaction achieved absolute opposite configuration with no loss of yield and enantioselectivity (Table 3, Entry 8). Extensive screening showed that the optimal reaction conditions were 20 mol-% of catalyst **1d**, 0.10 mmol of

Table 3. Screening additives for the reaction.[a]



Entry	Additive (mol-%)	Yield [%][b]	*ee* [%][c]
1	PhCOOH (20)	99	73 (*R*)
2	phthalic acid (20)	99	75 (*R*)
3	malonic acid (20)	99	77 (*R*)
4	succinic acid (20)	99	78 (*R*)
5	succinic acid (10)	99	79 (*R*)
6[d]	succinic acid (10)	99	83 (*R*)
7[e]	succinic acid (10)	85	81 (*R*)
8[d,f]	succinic acid (10)	99	83 (*S*)

[a] Unless noted otherwise, the reactions were carried out with **2** (0.10 mmol) and **3a** (0.15 mmol) in the presence of **1d** (20 mol-%) and additive in *n*-butyl alcohol (1.0 mL) at 40 °C for 12 h. [b] Isolated yield after column chromatography. [c] Enantiomeric excess was determined by HPLC analysis on a Chiralpak ADH column. [d] 50 μL H_2O was added. [e] 100 μL H_2O was added. [f] Catalyst **1h** was used.

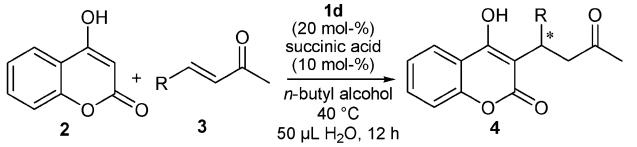
4-hydroxycoumarin (**2**), 0.15 mmol of benzylideneacetone (**3a**) in 1.0 mL of *n*-butyl alcohol, 50 μL of H_2O, and 10 mol-% succinic acid as additive at 40 °C for 12 h.[11]

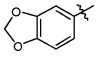
Under the optimized reaction conditions, a wide range of α,β-unsaturated ketones were investigated. As shown in Table 4, the Michael reactions proceeded rapidly to generate warfarin in high yields (up to 99%) and high enantioselectivities (up to 89%*ee*). In general, aromatic α,β-unsaturated ketones with electron-donating substituents afforded warfarin in higher enantioselectivities (Table 4, Entries 2–8) than electron-withdrawing substituents (Table 4, Entries 9–13). Additionally, substrates with *meta* substituents gave products in slightly lower enantioselectivities compared with substrates with substituents in the *ortho* and *para* positions (Table 4, Entry 3 vs. Entries 2 and 4; Entry 10 vs. Entries 9 and 11). Moreover, a 2-naphthyl substrate also achieved high yield and enantioselectivity (Table 4, Entry 14). Alkyl enones were applied too; unfortunately, the enantioselectivities were lower with good yields (Table 4, Entries 15 and 16).

In addition, when the reaction was scaled up to 1 g with 20 mol-% catalyst at 40 °C in an open vessel, good results (99% yield and 83%*ee*) were still obtained in 12 h (Scheme 1). A single recrystallization gave optically pure product **4a** in 54% yield.

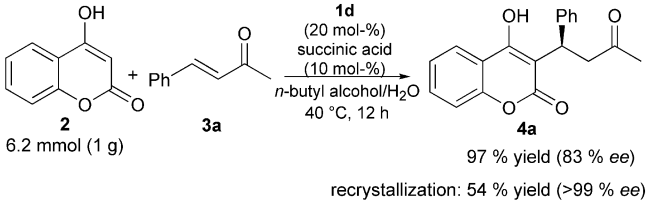
The mechanism of addition of 4-hydroxycoumarins to benzylideneacetone has been well established by previous reports.[4] On the basis of the absolute configuration of warfarin (**4a**), a possible transition state has been proposed (Figure 2). We propose that the mechanism of synthesis of warfarin involves the formation of the iminium ion intermediate from the α,β-unsaturated ketone, and 4-hydroxycoumarin was introduced by H-bond activation. Desired (*R*)-warfarin could be obtained through attack of the iminium ion to the *Re* face.

Table 4. Scope of the enantioselective Michael addition of 4-hydroxycoumarin to α,β-unsaturated ketones **4**.[a]



Entry	R	4	Yield [%][b]	*ee* [%][c]
1	Ph	**4a**	99	83
2	2-MeOC$_6$H$_4$	**4b**	91	89
3	3-MeOC$_6$H$_4$	**4c**	98	81
4	4-MeOC$_6$H$_4$	**4d**	90	87
5	3-MeC$_6$H$_4$	**4e**	84	87
6	4-MeC$_6$H$_4$	**4f**	80	89
7		**4g**	97	85
8	3-OHC$_6$H$_4$	**4h**	95	88
9	2-ClC$_6$H$_4$	**4i**	90	79
10	3-ClC$_6$H$_4$	**4j**	97	75
11	4-ClC$_6$H$_4$	**4k**	92	79
12	4-FC$_6$H$_4$	**4l**	90	80
13	3-CF$_3$C$_6$H$_4$	**4m**	89	78
14	2-naphthyl	**4n**	99	83
15	*n*Pr	**4o**	96	55
16	*i*Pr	**4p**	88	57

[a] The reaction mixture of **2** (0.10 mmol) with **3** (0.15 mmol), **1d** (0.02 mmol), succinic acid (0.01 mmol), and 50 μL H_2O was stirred in *n*-butyl alcohol (1.0 mL) at 40 °C for 12 h. [b] Isolated yield. [c] Determined by HPLC analysis.



Scheme 1. Asymmetric Michael reaction on a gram scale.

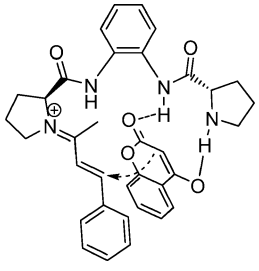


Figure 2. Proposed transition state.

Conclusions

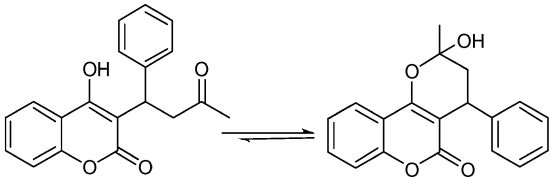
We have developed a highly enantioselective Michael reaction of 4-hydroxycoumarins and α,β-unsaturated ketones by using (L)-proline-derived catalyst **1d**. A series of warfarins was synthesized with high enantioselectivities (up to 89%*ee*), and an enantiopure product could be obtained after a single recrystallization. Moreover, in contrast to pre-

vious reports, the reaction was complete in 12 h with high yields (up to 99%) under mild conditions.

Experimental Section

General Experimental Procedure: Michael reaction was carried out in a test tube with magnetic stirring and no special precautions were taken to exclude water or air from the reaction vessel. A mixture of catalyst **1d** (6.0 mg, 0.02 mmol), succinic acid (1.2 mg, 0.01 mmol), 4-hydroxycoumarin (16.2 mg, 0.10 mmol), and enone **3** (0.15 mmol) in *n*-butyl alcohol (1.0 mL) with H_2O (50 μL) was added to a test tube. The resulting mixture was stirred at 40 °C for 12 h and purified directly by column chromatography (ethyl acetate/petroleum ether, 1:10 to 1:3) to afford products **4**.

α,β-Unsaturated ketones were prepared according to literature procedures.[4a] Catalysts **1a**–**h** were prepared according to literature procedures.[9d] **1d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.77 (m, 4 H), 2.05 (s, 2 H), 2.23 (m, 4 H), 3.02 (m, 4 H), 3.89 (m, 2 H), 7.16 (m, 2 H), 7.68 (m, 2 H), 9.72 (s, 2 H) ppm.



The Michael addition product was found to exist in rapid equilibrium with a pseudodiastereomeric hemiketal form in solution. However, the equilibrium was very rapid and therefore no pseudodiastereomers were observed during HPLC analysis. The equilibrium was also slow enough that they show up as a mixture of ketone and hemiketal by ^{1}H NMR spectroscopy, such as **4a**.

4a: White solid (30.7 mg, 99% isolated yield, 83% *ee*). $[\alpha]_D^{25}$ = +10.3 (*c* = 0.6, acetonitrile). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68 (s, 1.59 H, CH_3 ketal), 1.73 (s, 1.52 H, CH_3 ketal), 1.98–2.05 (m, 0.57 H, CH_2 ketal), 2.30 (s, 0.3 H, CH_3 keto), 2.40–2.58 (m, 1.49 H, CH_2 ketal), 3.20 (br. s, 0.99 H, OH ketal), 3.30 (dd, 0.10 H, CH_2 keto), 3.86 (dd, *J* = 10.4, 19.6 Hz, 0.1 H, CH_2 keto), 4.16 (dd, *J* = 6.8, 11.2 Hz, 0.5 H, CH ketal), 4.29 (dd, *J* = 3.2, 6.8 Hz, 0.5 H, CH ketal), 4.69 (dd, *J* = 2.4, 10.0 Hz, 0.1 H, CH keto), 7.22–7.37 (m, 7 H, ArH), 7.49 (m, 0.6 H, ArH), 7.55 (dt, *J* = 1.6, 8.4 Hz, 0.33 H, ArH), 7.81 (dd, *J* = 1.2, 7.6 Hz, 0.5 H, ArH), 7.90 (dd, *J* = 1.2, 7.6 Hz, 0.5 H, ArH), 7.95 (dd, *J* = 1.6, 8.0 Hz, 0.1 H, ArH), 9.48 (br. s, 0.1 H, OH keto) ppm. HPLC (Daicel Chiralcel AD-H; 2-propanol/*n*-hexane, 20:80; flow rate = 1.0 mL min^{-1}; λ = 254 nm): t_R = 5.65 (major), 8.64 (minor) min.

4b: White solid (30.7 mg, 91% isolated yield, 89% *ee*). $[\alpha]_D^{25}$ = +52.0 (*c* = 0.2, acetonitrile). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67 (s, 2.10 H), 1.69 (s, 1.0 H), 2.04 (dd, *J* = 11.0, 13.2 Hz, 0.67 H), 2.19 (s, 3.0 H), 2.30 (dd, *J* = 7.1, 14.4 Hz, 0.72 H), 2.48 (dd, *J* = 6.9, 13.8 Hz, 0.33 H), 2.64 (dd, *J* = 2.2, 14.5 Hz, 0.69 H), 3.29 (s, 0.30 H), 3.49 (s, 0.65 H), 3.84 (s, 1.1 H), 3.97 (s, 2.1 H), 3.94 (s, 2.4 H), 4.53 (dd, *J* = 2.1, 7.1 Hz, 0.68 H), 4.58 (dd, *J* = 7.3, 10.2 Hz, 0.23 H), 4.96 (dd, *J* = 5.4, 8.5 Hz, 0.1 H), 6.82–7.08 (m, 3.7 H), 7.16–7.36 (m, 4.7 H), 7.44–7.49 (m, 1.4 H), 7.55 (dt, *J* = 4.6, 5.6 Hz, 2.0 H), 7.69 (dd, *J* = 1.6, 7.6 Hz, 1.0 H), 7.81 (dd, *J* = 1.6, 7.9 Hz, 1.0 H), 7.90 (dt, *J* = 1.6, 7.8 Hz, 2.9 H), 9.14 (s, 0.95 H) ppm. HPLC (Daicel Chiralcel AD-H; 2-propanol/*n*-hexane, 20:80; flow rate = 1.0 mL min^{-1}; λ = 254 nm): t_R = 6.39 (major), 11.05 (minor) min.

4c: White solid (33.1 mg, 98% isolated yield, 81% *ee*). $[\alpha]_D^{25}$ = +2.9 (*c* = 0.69, acetonitrile). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.70 (s, 1.7 H), 1.75 (s, 1.5 H), 1.99 (dd, *J* = 1.6, 12.0 Hz, 1.0 H), 2.31 (s, 0.3 H), 2.42 (dd, *J* = 7.4, 14.2 Hz, 0.5 H), 2.50 (dd, *J* = 6.9, 14.0 Hz, 0.5 H), 2.56 (dd, *J* = 3.0, 14.2 Hz, 0.5 H), 3.14 (s, 0.5 H), 3.33 (s, 0.6 H), 3.78 (s, 3.4 H), 3.80–3.95 (m, 0.25 H) 4.15 (dd, *J* = 6.8, 12.6 Hz, 0.8 H) 4.28 (dd, *J* = 2.9, 6.9 Hz, 0.5 H), 4.70 (d, *J* = 7.2 Hz, 0.09 H), 6.76–6.91 (m, 3.4 H), 7.19–7.26 (m, 1.6 H), 7.28–7.38 (m, 2.5 H), 7.49–7.58 (m, 1.2 H), 7.23 (dd, *J* = 1.48, 7.8 Hz, 0.33 H), 7.91 (dd, *J* = 1.52, 7.9 Hz, 0.46 H), 9.43 (s, 0.07 H) ppm. HPLC (Daicel Chiralcel AD-H; 2-propanol/*n*-hexane,20:80; flow rate = 1.0 mL min^{-1}; λ = 254 nm): t_R = 6.67 (major), 17.08 (minor) min.

4d: White solid (30.4 mg, 90% isolated yield, 87% *ee*). $[\alpha]_D^{24}$ = –8.7 (*c* = 0.368, acetonitrile). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67 (s, 1.87 H), 1.70 (s, 1.50 H), 1.95–2.01 (m, 0.54 H), 2.27 (s, 0.35 H), 2.34–2.53 (m, 1.61 H), 3.40 (s, 0.5 H), 3.60 (s, 0.5 H), 3.76 (d, 3.2 H), 3.80 (m, 0.2 H), 4.10 (dd, *J* = 6.9, 11.3 Hz, 0.5 H), 4.22 (dd, *J* = 3.1, 6.7 Hz, 0.5 H), 4.65 (dd, *J* = 2.3, 10.0 Hz, 0.1 H), 6.81–6.86 (m, 2.3 H), 7.11–7.35 (m, 5 H), 7.47 (dt, *J* = 4.6, 8.2 Hz, 0.68 H), 7.55 (dt, *J* = 1.6, 7.4 Hz, 0.27 H), 7.80 (dd, *J* = 1.3, 6.9 Hz, 0.25 H), 7.89 (dd, *J* = 1.5, 7.9 Hz, 0.25 H), 9.44 (br. s, 0.1 H) ppm. HPLC (Daicel Chiralcel AD-H; 2-propanol/*n*-hexane, 20:80; flow rate = 1.0 mL min^{-1}; λ = 254 nm): t_R = 7.73 (major), 18.78 (minor) min.

4e: White solid (30.3 mg, 94% isolated yield, 87% *ee*). $[\alpha]_D^{24}$ = +6.1 (*c* = 0.392, acetonitrile). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69 (s, 1.91 H), 1.74 (s, 1.58 H), 1.98–2.06 (m, 0.58 H), 2.31 (s, 0.3 H), 2.32 (s, 3.2 H), 2.44 (dd, *J* = 6.9, 14.2 Hz, 0.5 H), 2.48 (dd, *J* = 6.9, 14.0 Hz, 0.5 H), 2.55 (dd, *J* = 3.04, 14.2 Hz, 0.5 H), 3.15 (d, *J* = 2.12 Hz, 0.49 H), 3.30 (d, *J* = 2.9 Hz, 0.63 H), 3.84 (m, 0.09 H), 4.13 (dd, *J* = 3.9, 11.4 Hz, 0.54 H), 4.29 (dd, *J* = 2.9, 6.8 Hz, 0.58 H), 4.66–4.70 (m, 0.1 H), 7.03–7.13 (m, 3.8 H), 7.18–7.25 (m, 1.5 H), 7.29–7.39 (m, 2.3 H), 7.49–7.61 (m, 1.3 H), 7.83 (dd, *J* = 1.5, 7.8 Hz, 0.33 H), 7.93 (dd, *J* = 1.6, 7.9 Hz, 0.38 H), 7.95 (dd, *J* = 1.6, 8.0 Hz, 0.10 H), 9.42 (s, 0.09 H) ppm. HPLC (Daicel Chiralcel AD-H; 2-propanol/*n*-hexane, 20:80; flow rate = 1.0 mL min^{-1}; λ = 254 nm): t_R = 4.98 (major), 7.51 (minor) min.

4f: White solid (25.8 mg, 80% isolated yield, 89% *ee*). $[\alpha]_{405}^{26}$ = +23.6 (*c* = 0.11, acetonitrile). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.67 (s, 1.4 H), 1.72 (s, 1.3 H), 2.0 (dd, *J* = 13.9, 26.3 Hz, 0.49 H), 2.29 (s, 0.28 H), 2.30 (d, *J* = 4.7 Hz, 2.9 H), 2.39 (dd, *J* = 6.9, 14.2 Hz, 0.53 H), 2.16 (dd, *J* = 6.9, 14.0 Hz, 0.44 H), 2.53 (dd, *J* = 3.0, 14.1 Hz, 0.5 H), 3.2 (s, 0.39 H), 3.23 (s, 0.5 H), 3.31 (d, *J* = 2.2 Hz, 0.08 H), 3.84 (m, 0.12 H), 4.13 (dd, *J* = 6.9, 11.5 Hz, 0.45 H), 4.26 (dd, *J* = 2.6, 6.7 Hz, 0.45 H), 4.66 (d, *J* = 8.5 Hz, 0.08 H), 7.08–7.19 (m, 4.2 H), 7.21–7.36 (m, 2.5 H), 7.49–7.57 (m, 1.0 H), 7.81 (dd, *J* = 1.14, 6.7 Hz, 0.27 H), 7.90 (dd, *J* = 1.26, 7.92 Hz, 0.29 H), 7.94 (dd, *J* = 1.08, 7.9 Hz, 0.13 H), 9.43 (s, 0.1 H) ppm. HPLC (Daicel Chiralcel AD-H; 2-propanol/*n*-hexane, 10:90; flow rate = 1.0 mL min^{-1}; λ = 254 nm): t_R = 17.25 (major), 22.12 (minor) min.

4g: White solid (34.1 mg, 97% isolated yield, 85% *ee*). $[\alpha]_D^{26}$ = –9.0 (*c* = 0.334, acetonitrile). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67 (s, 1.6 H), 1.72 (s, 1.5 H), 1.93–2.00 (m, 0.5 H), 2.27 (s, 0.27 H), 2.34–2.51 (m, 1.5 H), 3.17 (s, 0.45 H), 0.36 (s, 0.5 H), 3.78 (m, 0.08 H), 4.05–4.11 (m, 0.7 H), 4.19 (dd, *J* = 3.0, 6.8 Hz, 0.5 H), 4.61 (m, 0.08 H), 5.91 (d, *J* = 9.1 Hz, 2.2 H), 6.67–6.79 (m, 3.3 H), 7.20–7.35 (m, 3.0 H), 7.46–7.57 (m, 1.1 H), 7.81 (dd, *J* = 1.48, 7.84 Hz, 0.3 H), 7.89 (dd, *J* = 1.68, 7.92 Hz, 0.3 H), 7.92 (dd, *J* = 1.4, 7.84 Hz, 0.08 H), 9.40 (s, 0.06 H) ppm. HPLC (Daicel Chiralcel

AD-H; 2-propanol/*n*-hexane, 20:80; flow rate = 1.0 mL min^{-1}; λ = 254 nm): t_R = 7.31 (major), 14.03 (minor) min.

4h: White solid (30.8 mg, 95% isolated yield, 88%*ee*). $[\alpha]_{405}^{21}$ = +20.8 (*c* = 0.674, acetonitrile). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (s, 1.5 H), 1.72 (s, 1.4 H), 1.99 (dd, *J* = 11.4, 14.0 Hz, 0.5 H), 2.27 (s, 0.33 H), 2.34–2.54 (m, 1.3 H), 3.17–3.50 (br. m, 0.6 H), 3.75 (m, 0.16 H), 4.11 (m, 1.2 H), 4.21 (dd, *J* = 2.76, 6.52 Hz, 0.5 H), 4.67 (dd, *J* = 2.52, 7.36 Hz, 0.1 H), 6.62–6.82 (m, 3 H), 7.07–7.14 (m, 1 H), 7.21–7.34 (m, 3 H), 7.47–7.58 (m, 1 H), 7.82 (dd, *J* = 1.44, 7.76 Hz, 0.33 H), 7.89 (dd, *J* = 1.4, 7.76 Hz, 0.33 H), 7.92 (dd, *J* = 1.56, 7.92 Hz, 0.08 H), 9.49 (s, 0.06 H) ppm. HPLC (Daicel Chiralcel AD-H; 2-propanol/*n*-hexane, 10:90; flow rate = 1.0 mL min^{-1}; λ = 254 nm): t_R = 34.8 (major), 43.7 (minor) min.

4i: White solid (30.8 mg, 90% isolated yield, 79%*ee*). $[\alpha]_D^{25}$ = +35.1 (*c* = 0.61, acetonitrile). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.72 (s, 1.5 H), 1.77 (s, 1.5 H), 2.06 (d, *J* = 3.04 Hz, 1.0 H), 2.31 (s, 0.3 H), 2.39 (dd, *J* = 7.4, 14.4 Hz, 0.5 H), 2.60 (dd, *J* = 3.04, 14.4 Hz, 0.7 H), 3.07 (s, 0.5 H), 3.20 (d, *J* = 19.4 Hz, 0.1 H), 3.28 (s, 0.5 H), 4.01 (dd, *J* = 11.3, 19.0 Hz, 0.1 H), 4.13 (dd, *J* = 7.2, 14.3 Hz, 0.7 H), 4.56 (dd, *J* = 3.0, 7.4 Hz, 0.5 H), 4.83 (d, *J* = 9.7 Hz, 0.1 H), 7.13–7.21 (m, 3.4 H), 7.27–7.38 (m, 2.7 H), 7.42 (m, 0.5 H), 7.47–7.61 (m, 1.3 H), 7.73 (s, 0.1 H), 7.83 (dd, *J* = 1.44, 7.8 Hz, 0.3 H), 7.90 (dd, *J* = 1.6, 7.9 Hz, 0.3 H), 7.99 (dd, *J* = 1.4, 7.9 Hz, 0.1 H), 9.54 (s, 0.1 H) ppm. HPLC (Daicel Chiralcel AD-H; 2-propanol/*n*-hexane, 20:80; flow rate = 1.0 mL min^{-1}; λ = 254 nm): t_R = 5.48 (major), 8.79 (minor) min.

4j: White solid (33.1 mg, 97% isolated yield, 75%*ee*). $[\alpha]_{405}^{26}$ = +17.8 (*c* = 0.36, acetonitrile). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.71 (s, 1.03 H), 1.76 (s, 1.51 H), 2.00 (m, 0.82 H), 2.31 (s, 0.28 H), 2.42–2.51 (m, 1.19 H), 3.06 (s, 0.33 H), 3.21 (s, 0.47 H), 3.86 (dd, *J* = 10.6, 19.7 Hz, 0.09 H), 4.13 (m, 0.72 H), 4.22 (m, 0.39 H), 4.67 (dd, *J* = 1.8, 10.4 Hz, 0.06 H), 7.13–7.38 (m, 6.66 H), 7.50–7.61 (m, 1.04 H), 7.82 (dd, *J* = 1.44, 8.2 Hz, 0.37 H), 7.88 (dd, *J* = 1.56, 7.92 Hz, 0.25 H), 7.97 (dd, *J* = 1.48, 8.0 Hz, 0.09 H), 9.57 (s, 0.07 H) ppm. HPLC (Daicel Chiralcel AD-H; 2-propanol/*n*-hexane, 20:80; flow rate = 1.0 mL min^{-1}; λ = 254 nm): t_R = 4.88 (major), 6.21 (minor) min.

4k: White solid (31.5 mg, 92% isolated yield, 79%*ee*). $[\alpha]_D^{25}$ = –8.8 (*c* = 0.274, acetonitrile). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.69 (s, 1.06 H), 1.74 (m, 1.50 H), 1.95 (d, *J* = 12.2 Hz, 0.51 H), 2.29 (s, 0.33 H), 2.40 (d, *J* = 7.14 Hz, 0.35 H), 2.45 (m, 0.85 H), 3.09 (s, 0.33 H), 3.26 (d, *J* = 19.3, 21.1 Hz, 0.53 H), 3.84 (dd, *J* = 10.4, 19.4 Hz, 0.09 H), 4.14 (dd, *J* = 6.84, 11.6 Hz, 0.50 H), 4.20 (dd, *J* = 3.5, 6.9 Hz, 0.34 H), 4.64 (dd, *J* = 2.22, 10.4 Hz, 0.09 H), 7.15–7.35 (m, 6.2 H), 7.49–7.58 (m, 0.96 H), 7.81 (d, *J* = 7.92 Hz, 0.36 H), 7.87 (dd, *J* = 0.9, 7.92 Hz, 0.25 H), 7.94 (dd, *J* = 0.72, 7.92 Hz, 0.09 H), 9.57 (s, 0.08 H) ppm. HPLC (Daicel Chiralcel AD-H; 2-propanol/*n*-hexane, 20:80; flow rate = 1.0 mL min^{-1}; λ = 254 nm): t_R = 5.35 (major), 6.98 (minor) min.

4l: White solid (29.3 mg, 90% isolated yield, 80%*ee*). $[\alpha]_D^{26}$ = +7.3 (*c* = 0.386, acetonitrile). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69 (s, 1.2 H), 1.72 (s, 1.7 H), 1.95 (dd, *J* = 11.6, 13.8 Hz, 0.5 H), 2.29 (s, 0.3 H), 2.37 (dd, *J* = 7.0, 14.2 Hz, 0.4 H), 2.46 (m, 0.9 H), 3.25–3.30 (dd, *J* = 2.4, 19.4 Hz, 0.1 H), 3.37 (s, 0.32 H), 3.79 (s, 0.48 H), 3.85 (dd, *J* = 10.3, 19.4 Hz, 0.1 H), 4.16 (dd, *J* = 6.8, 11.5 Hz, 0.6 H), 4.21 (dd, *J* = 3.8, 6.9 Hz, 0.5 H), 4.67 (d, *J* = 8.6 Hz, 0.1 H), 6.94–7.02 (m, 1.9 H), 7.15–7.34 (m, 4.1 H), 7.47–7.59 (m, 1 H), 7.80 (dd, *J* = 1.64, 8.52 Hz, 0.5 H), 7.87 (dd, *J* = 1.52, 7.88 Hz, 0.33 H), 7.95 (dd, *J* = 1.44, 7.96 Hz, 0.1 H), 9.60 (s, 0.07 H) ppm. HPLC (Daicel Chiralcel AD-H; 2-propanol/*n*-hexane, 20:80; flow rate = 1.0 mL min^{-1}; λ = 254 nm): t_R = 4.98 (major), 9.06 (minor) min.

4m: White solid (33.5 mg, 89% isolated yield, 78%*ee*). $[\alpha]_{405}^{26}$ = +13.1 (*c* = 0.321, acetonitrile). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.71 (s, 1.1 H), 1.75 (s, 1.8 H), 1.93–2.04 (m, 0.7 H), 2.31 (s, 0.3 H), 2.39–2.49 (m, 1.4 H), 3.02 (s, 0.3 H), 3.32 (d, 0.7 H), 3.90 (dd, *J* = 10.7, 19.3 Hz, 0.09 H), 4.21–4.26 (m, 1 H), 4.70 (d, *J* = 9.96 Hz, 0.1 H), 7.21–7.58 (m, 8.3 H), 7.82 (d, *J* = 7.86 Hz, 0.4 H), 7.87 (d, *J* = 7.86 Hz, 0.3 H), 7.96 (d, *J* = 7.86 Hz, 0.1 H), 9.63 (s, 0.1 H) ppm. HPLC (Daicel Chiralcel AD-H; 2-propanol/*n*-hexane, 20:80; flow rate = 1.0 mL min^{-1}; λ = 254 nm): t_R = 4.03 (major), 5.68 (minor) min.

4n: White solid (35.4 mg, 99% isolated yield, 83%*ee*). $[\alpha]_D^{26}$ = –9.8 (*c* = 0.614, acetonitrile). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68 (s, 1.5 H), 1.72 (s, 1.5 H), 2.04–2.12 (m, 0.5 H), 2.33 (s, 0.03 H), 2.44–2.54 (m, 1 H), 2.64 (dd, *J* = 3.12, 14.2 Hz, 0.5 H), 3.20 (s, 0.5 H), 3.29 (s, 0.5 H), 3.43 (dd, *J* = 2.48, 19.3 Hz, 0.1 H), 3.96 (dd, *J* = 9.96, 19.3 Hz, 0.1 H), 4.33 (dd, *J* = 6.88, 11.4 Hz, 0.5 H), 4.44 (dd, *J* = 3.04, 7.0 Hz, 0.5 H), 4.84 (d, 0.1 H), 7.25–7.80 (m, 11 H), 7.84 (d, *J* = 8.32 Hz, 0.65 H), 7.92 (dd, *J* = 1.56, 7.84 Hz, 0.4 H), 7.96 (d, *J* = 1.52 Hz, 0.05 H), 9.52 (s, 0.1 H) ppm. HPLC (Daicel Chiralcel AD-H; 2-propanol/*n*-hexane, 20:80; flow rate = 1.0 mL min^{-1}; λ = 254 nm): t_R = 7.127 (major), 13.613 (minor) min.

4o: White solid (26.3 mg, 96% isolated yield, 55%*ee*). $[\alpha]_D^{20}$ = +39.3 (*c* = 0.468, acetonitrile). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83–0.90 (m, 4 H), 0.92–0.98 (m, 2 H), 1.14–1.29 (m, 3 H), 1.29–1.41 (m, 1.5 H), 1.51–1.64 (m, 1.5 H), 1.70–1.85 (m, 4 H), 1.92–2.04 (m, 1 H), 2.10–2.20 (m, 4 H), 2.24–2.36 (m, 1 H), 2.74 (s, 0.5 H), 2.79–2.86 (m, 1 H), 2.96–3.02 (m, 0.5 H), 3.20–3.26 (m, 1 H), 3.34–3.41 (m, 1 H), 7.19–7.30 (m, 4 H), 7.44–7.51 (m, 2 H), 7.76 (m, 1 H), 7.91 (m, 1 H), 9.61 (s, 1 H) ppm. HPLC (Daicel Chiralcel AD-H; 2-propanol/*n*-hexane, 10:90, flow rate = 1.0 mL min^{-1}; λ = 254 nm): t_R = 8.45 (major), 13.14 (minor) min.

4p: White solid (24.1 mg, 88% isolated yield, 57%*ee*). $[\alpha]_D^{21}$ = +48.7 (*c* = 0.496, acetonitrile). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.67 (dd, *J* = 1.76, 6.88 Hz, 1.03 H), 0.77 (dd, *J* = 1.68, 6.52 Hz, 4 H), 0.86 (m, 2 H), 1.00 (m, 4.54 H), 1.51–1.65 (m, 1.24 H), 1.77–1.83 (m, 1.80 H), 2.05 (m, 0.42 H), 2.15 (dd, *J* = 7.12, 13.8 Hz, 0.45 H), 2.21 (s, 3 H), 2.57 (m, 1 H), 2.76 (t, *J* = 10.2, 20.4 Hz, 1 H), 2.95 (d, *J* = 20.0 Hz, 1 H), 3.05 (dd, *J* = 5.1, 8.6 Hz, 0.45 H), 3.27–3.36 (m, 1.3 H), 7.20–7.33 (m, 4 H), 7.45–7.54 (m, 2 H), 7.74–7.80 (m, 1 H), 7.91–7.94 (m, 1 H), 9.48 (s, 1 H) ppm. HPLC (Daicel Chiralcel AD-H; 2-propanol/*n*-hexane, 10:90; flow rate = 1.0 mL min^{-1}; λ = 254 nm): t_R = 7.73 (major), 13.34 (minor) min.

Supporting Information (see footnote on the first page of this article): ^{1}H NMR and ^{13}C NMR spectra and HPLC chromatograms.

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