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Catalytic Asymmetric Friedel–Crafts/Protonation of Nitroalkenes and *N*-Heteroaromatics

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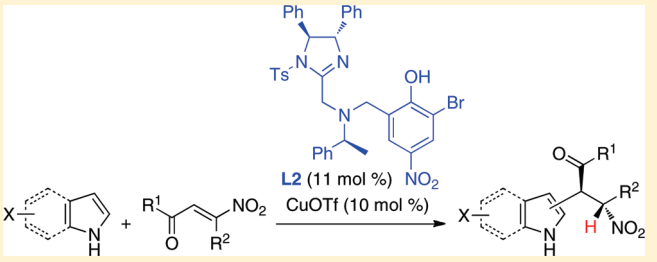
Supporting Information

ABSTRACT: The catalytic asymmetric Friedel–Crafts/protonation of indoles and pyrroles with α-substituted nitroalkenes to give the corresponding adducts in a highly *anti*-selective manner was achieved by an imidazoline–aminophenol (**L2**)–Cu complex. The *anti*-adducts could be successfully transformed to biochemically important α-substituted *β*-heteroarylalkylamines.



Optically active indoles and pyrroles, which are common core structures in natural alkaloids, exhibit significant biological activities.[1] For example, α-methyl tryptamines (AMTs) are agonists of serotonin 5-HT receptors,[2] and AJ-9677 is a clinical candidate of *β*-adrenergic receptor (*β*-AR) agonists to treat obesity, a metabolic syndrome that is often associated with noninsulin dependent (Type II) diabetes.[3] A common structure observed in these compounds is the chiral α-substituted *β*-indolylalkylamine, as shown in red in Figure 1. Yohambine, isolated from the root of the *Rauwolfia serpentina* Benth (N. O. Apocyanaciae) and utilized in the treatment of high blood pressure, also has a methyl substituent at the α-position of the amine.[4] Because biological activities are strongly linked with stereochemistry, much effort has been invested to construct α-substituted *β*-indolylalkylamines in a stereoselective manner.[5] One straightforward approach for the synthesis of chiral α-substituted tryptamines would be the Friedel–Crafts reaction of indoles and nitroalkenes. However, the catalytic asymmetric Friedel–Crafts reaction of indoles with α-substituted nitroalkenes is currently unexplored.[6–9]

In our program for exploring new asymmetric catalysts and their application to the synthesis of nitrogen-containing chiral molecules, we have succeeded in the development of a chiral imidazoline–aminophenol–Cu complex for the catalytic asymmetric Friedel–Crafts reaction of nitroalkenes with indoles and pyrroles.[10] Moreover, the imidazoline–aminophenol–Cu complex was successfully applied to the tandem Friedel–Crafts/Henry (FCH) reaction.[11] In the FCH reaction, the intermediate Cu-nitronate is trapped with an aldehyde for constructing multiple contiguous stereogenic centers. Here, the chiral imidazoline–aminophenol–-Cu catalyst was applied to the tandem Friedel–Crafts reaction/protonation using α-substituted nitroalkenes to give the chiral α-substituted *β*-heteroarylnitroalkanes (Scheme 1).

When the original conditions were applied to the reaction of indole with α-methylnitrostyrene, the reaction using **L1**–CuOTf resulted in only a trace amount of product (Table 1, entry 1).

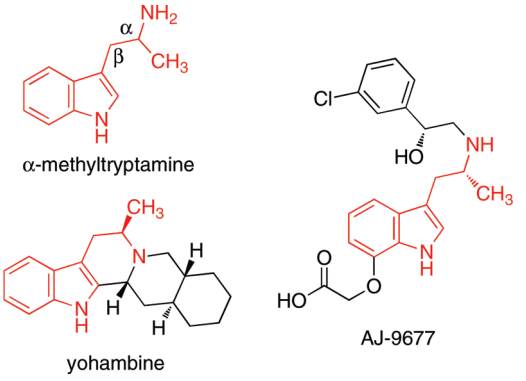


Figure 1. Examples of biologically active chiral α-substituted *β*-indolylalkylamines.

Even when the more Lewis-acidic **L2**–CuOTf catalyst was used, the product was obtained in only 20% yield (entry 2). In contrast, the **L2**–CuOTf smoothly catalyzed the reaction using *β*-nitroacrylate to give the adduct in 93% yield with 89:11 diastereoselectivity.[12] The enantiomeric excess of the major diastereomer was 79% ee. Although the catalyst structure has not been fully elucidated, the existence of Cu-phenoxide in the catalyst formation is suggested by UV spectroscopy. This explains the release of the strong Brønsted acid TfOH into the reaction media. In order to study the effects of the proton source on the diastereoselectivity, the reaction was examined without HFIP (entries 5–6). When the catalyst solution was treated with base to scavenge the acids before the catalysis, the diastereoselectivity was improved to 82:18, and the enantiomeric excess of the major diastereomer increased to 85% ee (entry 6) (see the detailed experimental

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Scheme 1. Working Hypothesis of Cu-Catalyzed Asymmetric Friedel–Crafts/Protonation

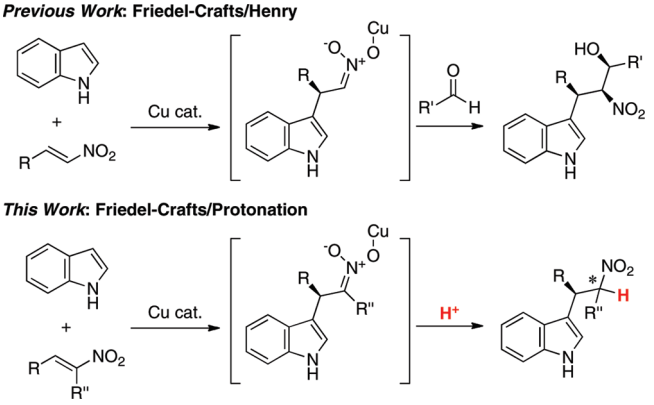
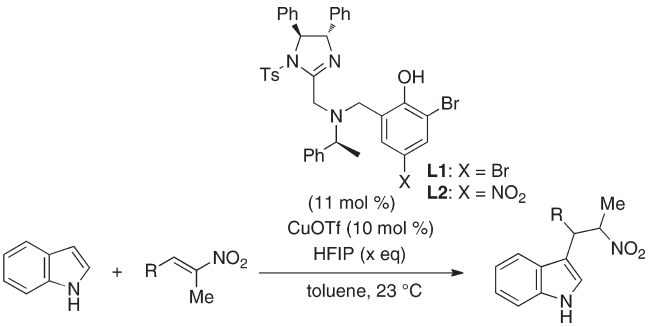


Table 1. Catalytic Asymmetric Friedel–Crafts/Protonation of Indole with α-Methyl Nitroalkenes



entry	R	cat	HFIP (equiv)	time (h)	yield (%)	dr	ee (%) (major/minor)
1	Ph	**L1**	2	23	trace		
2	Ph	**L2**	2	46	20	65/35	ND
3	CO_2Et	**L1**	2	19	74	81/19	64/32
4	CO_2Et	**L2**	2	19	93	89/11	79/50
5	CO_2Et	**L2**		44	91	79/21	84/73
6[a]	CO_2Et	**L2**		44	94	82/18	85/73

[a] Catalyst was treated with K_2CO_3 prior to use.

procedure in the Supporting Information). Although the effects of the additional proton source were reexamined by adding the reaction mixture after the treatment of catalyst with K_2CO_3, the external proton sources examined gave no positive influence on the diastereoselectivities.

Under the optimized conditions, the generality of the Friedel–Crafts/protonation of indoles and nitroacrylates was examined, and the results are shown in Table 2.[13]

In addition to β-nitroacrylates, β-nitroenone was also effective in the diastereoselective Friedel–Crafts/protonation and maintained a high enantiomeric excess (entry 3). Various substituted indoles were able to be employed to give the products with good diastereoselectivity, and the major products recorded high enantioselectivities. In particular, the 2-methylindole gave a single diastereomer, though the enantiomeric excess remained at 72% ee (entry 5). A single recrystallization of the product obtained in entry 5 from methanol produced racemic crystal to enrich the enantiomeric

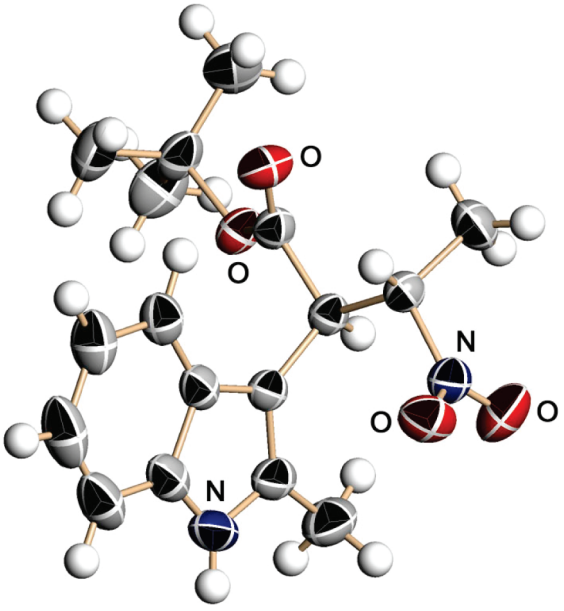


Figure 2. X-ray crystallographic analysis of the Friedel–Crafts/protonation adduct obtained in entry 5 of Table 2.

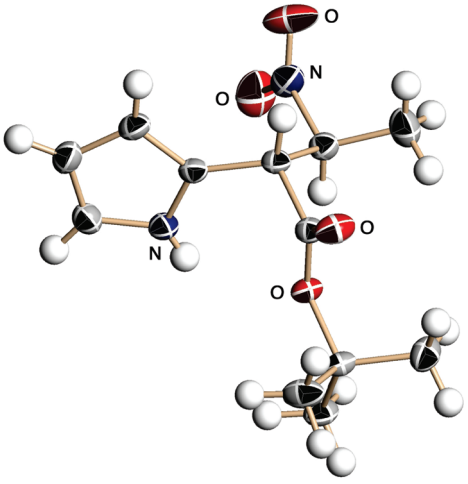


Figure 3. X-ray crystallographic analysis of the Friedel–Crafts/protonation adduct obtained in entry 3 of Table 3.

excess in the solution up to 90% ee. The single X-ray crystallographic analysis of the *rac*-crystal revealed the *anti*-stereochemistry as shown in Figure 2.

Next, we attempted the Friedel–Crafts/protonation using pyrrole.[14−16] The reaction was smoothly catalyzed under similar reaction conditions to give the adducts in a highly enantioselective manner. The scope of the reaction using pyrroles is summarized in Table 3.

Although large R^2 substituents reduced the diastereoselectivity, each diastereomer showed high enantiomeric excess (Table 3, entries 5 and 6). The recrystallization of the product obtained in entry 3 from methanol gave a pure diastereomer. X-ray crystallographic analysis revealed the *anti*-stereochemistry of the major product as shown in Figure 3.

Scheme 2 summarizes why the *anti*-products are preferably obtained.[17] In previous studies on the asymmetric Friedel–Crafts reaction catalyzed by the imidazoline–aminophenol–

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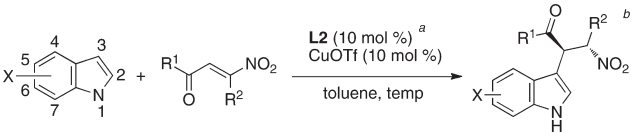
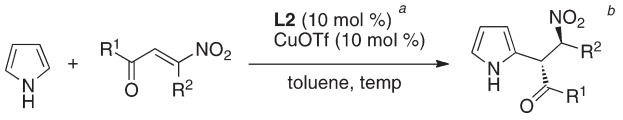
Table 2. L2—CuOTf-Catalyzed Asymmetric Friedel—Crafts/Protonation of Indoles with α-Substituted Nitroalkenes



entry	X	R^1	R^2	temp (°C)	time (h)	yield (%)	dr	ee (%) (major/minor)
1	H	OEt	Me	10	75	90	85/15	80/71
2	H	O-*t*-Bu	Me	10	92	94	90/10	87/62
3	H	Ph	Me	10	67	92	93/7	93/83
4	1-Me	O-*t*-Bu	Me	rt	69	87	89/11	67/64
5	2-Me	O-*t*-Bu	Me	rt	45	90	>99/<1	72/ND
6	4-Me	O-*t*-Bu	Me	rt	94	62	52/48	76/84
7	5-Me	O-*t*-Bu	Me	rt	45	97	89/11	87/78
8	5-OMe	O-*t*-Bu	Me	rt	46	96	90/10	87/65
9	5-Br	O-*t*-Bu	Me	rt	91	84	91/9	90/70
10	7-Me	O-*t*-Bu	Me	rt	88	96	91/9	67/ND
11	H	OEt	Et	rt	120	72	51/49	83/81
12	H	OEt	Ph	0	120	80	77/23	66/75

[a] Catalyst was treated with K_2CO_3 prior to use. [b] The absolute configuration was determined for the product obtained in entry 9. See details in the Supporting Information.

Table 3. L2—CuOTf-Catalyzed Asymmetric Friedel—Crafts/Protonation of Pyrrole with α-Substituted Nitroalkenes



entry	R^1	R^2	temp (°C)	time (h)	yield (%)	dr	ee (%) (major/minor)
1	OEt	Me	0	99	93	84/16	87/84
2	OMe	Me	0	96	98	80/20	87/86
3	O-*t*-Bu	Me	0	98	93	87/13	84/84
4	Ph	Me	0	60	80	93/7	80/15
5	OEt	Et	rt	41	92	66/34	92/86
6	OEt	*n*-C_5H_{11}	rt	94	97	67/33	89/69
7	OEt	Ph	0	41	98	53/47	91/68

[a] Catalyst was treated with K_2CO_3 prior to use. [b] The absolute configuration was determined for the product obtained in entry 3. See the details in the Supporting Information.

Cu complex, (*S*,*S*,*S*)-**L2**—CuOTf, both indole and/or pyrrole nucleophiles attack from the *Re* face of the activated nitroalkenes to give the Cu-nitronate intermediates. The acidic proton adjacent to the nitrogen atom then reacts with the nitronate to give the *anti*-adduct. The reduction of diastereoselectivity in the substrates having bulky R^2 groups is also reasonably explained by considering the steric hindrance between R^2 and CO_2R^1.

The synthetic application of the Friedel—Crafts/protonation product was examined as shown in Scheme 3. After the reduc tion of the nitro functionality using nickel boride, the Pictet—Spengler reaction proceeded smoothly to give the bicyclic compound with good diastereoselectivity. The epimerization of the product was negligible. The NOE experiments revealed the stereochemistry of the major Pictet—Spengler adduct as shown in Scheme 3.

In conclusion, the imidazoline—aminophenol (**L2**)—Cu complex furnished the catalytic asymmetric Friedel—Crafts/protonation to give the α-substituted β-heteroaryl—nitro adducts in a highly *anti*-selective manner. *This is the first report on the diastereoselective construction of the chiral acyclic α-substituted β-indolylalkylamines.*[18] Because the stereochemically diverse indole and pyrrole derivatives are fascinating scaffolds for promoting pharmaceutical research, further application of the products and studies on the detailed mechanism of the Friedel—Crafts/protonation reaction are in progress.

EXPERIMENTAL SECTION

Friedel—Crafts/Protonation (Entry 6, Table 1). Imidazoline—aminophenol ligand (0.016 mmol) in CH_2Cl_2 (0.74 mL) was added to $(CuOTf)_2 \cdot C_6H_6$ (3.7 mg, 0.007 mol) under Ar, and the mixture was stirred for 2 h at room temperature. To the resulting green solution was added K_2CO_3 (3.0 mg, 0.022 mmol) and the mixture stirred for 5 min. After removal of K_2CO_3 by filtration, the solution was concentrated and

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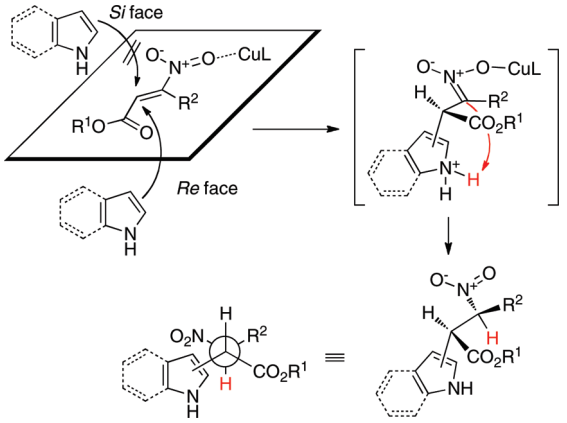
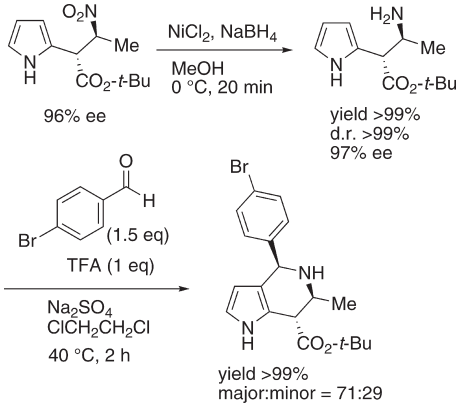
Scheme 2. Proposed Mechanism for the *Anti*-Selective Formation of the Friedel−Crafts/Protonation Adduct



Scheme 3. Chemical Transformations of the Friedel−Crafts/Protonation Adduct



dried under reduced pressure. To the resulting green amorphous solid were subsequently added PhMe (0.37 mL) and nitroalkene (0.147 mmol), and then indole (0.294 mmol) was added. After being stirred for indicated time, the reaction mixture was quenched by water. The organic layer was extracted with AcOEt, and the organic layer was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the diastereomeric ratio was determined by crude ^{1}H NMR. The resulting crude mixture was purified by silica gel column chromatography (hexane/AcOEt = 5:1) to afford adducts: ^{1}H NMR (500 MHz, $CDCl_3$) major δ 8.18 (br, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.25−7.14 (m, 3H), 5.36−5.28 (m, 1H), 4.89 (d, J = 9.7 Hz, 1H), 4.25−4.10 (m, 2H), 1.72 (d, J = 6.9 Hz, 3H),1.22 (t, J = 7.5 Hz, 3H); minor δ 8.25 (br, 1H), 7.69 (d, J = 7.5 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.25−7.14 (m, 3H), 5.36−5.28 (m, 1H), 4.47 (d, J = 11.2 Hz, 1H), 4.25−4.10 (m, 2H), 1.42 (d, J = 6.9 Hz, 3H), 1.18 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) major δ 170.5, 136,1, 126.1, 123.7,122.7, 120.5, 118.9, 111.6, 108.4, 84.9, 61.8, 47.8, 18.2, 14.1; minor δ 170.5, 136,4, 126.1, 123.7, 122.9, 120.4, 119.0, 111.7, 107.9, 83.5, 61.8, 47.2, 18.4, 14.1; HRMS calcd for $C_{14}H_{16}O_4N_2Na$ $(M + Na)^+$ 299.1002, found m/z 299.0997. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane/2-propanol, 1.0 mL/min, 254 nm); major: minor enantiomer t_R = 14.4 min, major enantiomer t_R = 17.7 min; 85% ee; minor: minor enantiomer t_R = 13.0 min, major enantiomer t_R = 21.5 min; 73% ee; $[\alpha]^{24.4}{}_D$ = +129.5 (c = 1.0, $CHCl_3$, dr = 82/18, 85% ee/73% ee); IR (neat) 3418, 1731, 1555, 1457, 1362 cm^{-1}.

Entry 2, Table 2: yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) major δ 8.16 (br, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.23 (m, 1H), 7.12 (t, J = 8.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 5.26−5.20 (m, 1H), 4.41 (d, J = 9.7 Hz, 1H), 1.71 (d, J = 6.9 Hz, 3H), 1.41 (s, 9H); minor δ 8.22 (br, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.23 (m, 1H), 7.12 (t, J = 8.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 5.26−5.20 (m, 1H), 4.36 (d, J = 10.9 Hz, 1H), 1.40 (d, J = 6.9 Hz, 3H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) major δ 169.6, 136,1, 126.2, 123.5, 122.6, 120.1, 119.0, 111.5, 108.8, 85.0, 82.6, 48.7, 28.0, 18.0; minor δ 169.6, 136.4, 125.9, 123.5, 122.8, 120.3, 119.1, 111.7, 108.8, 83.7, 82.4, 48.3, 27.9, 18.5; HRMS calcd for $C_{16}H_{20}O_4N_2Na$ $(M + Na)^+$ 327.1315, found m/z 327.1305; enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (90:10 hexane/ 2-propanol, 1.0 mL/min, 254 nm); major: major enantiomer t_R = 27.3 min, minor enantiomer t_R = 31.7 min; 87% ee; minor: minor enantiomer t_R = 15.7 min, minor enantiomer t_R = 24.2 min; 62% ee; $[\alpha]^{24.6}{}_D$ = +60.3 (c = 1.0, $CHCl_3$, dr = 90/10, 87% ee/62% ee); IR (neat) 3413, 2981, 1724, 1553, 1457, 1368 cm^{-1}.

Entry 3, Table 2: yellow solid; ^{1}H NMR(500 MHz, $CDCl_3$) major δ 8.16 (br, 1H), 7.98 (m, 2H), 7.78−7.74 (m, 1H), 7.48 (m, 1H), 7.36 (m, 2H), 7.30−7.27 (m, 1H), 7.19−7.17 (m, 2H), 7.15 (m,1H), 5.55−5.47 (m, 1H), 5.41 (d, J = 10.0 Hz, 1H), 1.73 (d, J = 6.3 Hz, 3H); minor δ 8.23 (br, 1H), 7.94 (m, 2H), 7.80−7.79 (m, 1H), 7.48 (m, 1H), 7.36 (m, 2H), 7.30−7.27 (m, 1H), 7.19−7.17 (m, 2H), 7.15 (m, 1H), 5.55−5.47 (m, 1H), 5.41 (d, J = 10.0 Hz, 1H), 1.51 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) major δ 195.7, 136.5, 135.9, 133.7, 128.8, 128.7, 125.8, 124.4, 122.7, 120.7, 118.7, 111.7, 108.6, 86.5, 49.4, 18.9; minor δ 195.7, 136.5, 135.9, 133.7, 128.8, 128.7, 125.6, 124.4, 122.5, 120.8, 118.7, 111.7, 108.6, 86.5, 49.4, 18.9; HRMS calcd for $C_{18}H_{16}O_3N_2Na$ $(M + Na)^+$ 331.1053, found m/z 331.1046; enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (90:10 hexane/2-propanol, 1.0 mL/min, 254 nm); major: major enantiomer t_R = 16.5 min, minor enantiomer t_R = 30.7 min; 93% ee; minor: major enantiomer t_R = 18.4 min, minor enantiomer t_R = 22.3 min; 83% ee; $[\alpha]^{24.9}{}_D$ = +223.4 (c = 1.0, $CHCl_3$, dr = 93/7, 93% ee/83% ee); IR (neat) 3410, 3059, 1676, 1549, 1449, 1360 cm^{-1}.

Entry 4, Table 2: white solid; ^{1}H NMR (500 MHz, $CDCl_3$) major δ 7.68 (d, J = 8.0 Hz, 1H), 7.27 (m, 1H), 7.24−7.21 (m, 1H), 7.15−7.12 (m, 1H), 7.09 (s, 1H), 5.25−5.19 (m, 1H), 4.39 (d, J = 9.5 Hz, 1H), 3.74 (s, 3H), 1.70 (d, J = 6.7 Hz, 3H), 1.42 (s, 9H); minor δ 7.68 (d, J = 8.0 Hz, 1H), 7.32 (m, 1H), 7.28−7.25 (m, 1H), 7.17−7.13 (m, 1H), 7.04 (s, 1H), 5.25−5.19 (m, 1H), 4.33 (d, J = 10.9 Hz, 1H), 3.74 (s, 3H), 1.40 (d, J = 6.7 Hz, 3H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) major δ 169.7, 136.9, 128.0, 126.8, 122.1, 119.7, 119.1, 109.5, 107.1, 85.1, 82.4, 48.6, 33.0, 28.0, 18.0; minor δ 169.7, 136.9, 128.0, 126.8, 122.3, 119.8, 119.3, 109.7, 107.1, 83.8, 82.4, 48.2, 33.0, 27.9, 18.5; HRMS calcd for $C_{17}H_{22}O_4N_2Na$ $(M + Na)^+$ 341.1472, found m/z 341.1465; enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane/2-propanol, 1.0 mL/min, 254 nm); major: major enantiomer t_R = 6.3 min, minor enantiomer t_R = 6.9 min; 67% ee; minor: major enantiomer t_R = 7.4 min, minor enantiomer t_R = 9.3 min; 64% ee; $[\alpha]^{22.1}{}_D$ = +56.7 (c = 1.0, $CHCl_3$, dr = 89/11, 67% ee/64% ee); IR (neat) 2979, 1723, 1550, 1474, 1367 cm^{-1}.

Entry 5, Table 2: yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$); δ 7.85 (br, 1H), 7.71−7.67 (m, 1H), 7.25−7.20 (m, 2H), 7.11−7.04 (m, 1H), 5.49−5.41 (m, 1H), 4.23 (d, J = 10.9 Hz, 1H), 2.40 (s, 3H), 1.76 (d, J = 6.6 Hz, 3H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ169.4, 135.2, 134.1, 126.6, 121.4, 120.0, 119.0, 110.6, 104.3, 83.7, 82.4, 49.1, 28.0, 18.3, 11.7; HRMS calcd for $C_{17}H_{22}O_4N_2Na$ $(M + Na)^+$ 341.1472, found m/z 341.1461; enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane/2-propanol, 0.5 mL/min, 254 nm); major enantiomer t_R = 12.3 min, minor enantiomer t_R = 13.1 min; 72% ee; $[\alpha]^{20.3}{}_D$ = +72.0 (c = 1.0, $CHCl_3$, dr = >99/<1, 72% ee); IR (neat) 3400, 2979, 1721, 1551, 1458, 1367 cm^{-1}.

Entry 6, Table 2: yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) major δ 8.20 (br, 1H), 7.32−6.86(m, 4H), 5.18−5.08 (m, 1H), 4.82 (d, J = 10.0 Hz, 1H),

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2.80 (s, 3H), 1.72 (d, J = 6.6 Hz, 3H), 1.40 (s, 9H); minor δ 8.26 (br, 1H), 7.32−6.86(m, 4H), 5.18−5.08 (m, 1H), 4.82 (d, J = 10.0 Hz, 1H), 2.82 (s, 3H), 1.46 (d, J = 6.6 Hz, 3H), 1.36 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) major δ 170.3, 136.0, 130.5, 125.0, 122.7, 122.5, 122.3, 109.7, 109.5, 86.1, 82.4, 48.4, 27.9, 20.6, 18.2; minor δ 171.2, 136.2, 130.4, 125.0, 122.8, 122.5, 122.2, 110.2, 109.8, 85.5, 82.1, 47.3, 27.8, 21.1, 18.3; HRMS calcd for $C_{17}H_{22}O_4N_2Na$ $(M + Na)^+$ 341.1472, found m/z 341.1467; enantiomeric excess was determined by HPLC with a Chiralcel OD-H + Chiralpak AS-H column (90:10 hexane/2-propanol, 1.0 mL/min, 254 nm); major: minor enantiomer t_R = 14.9 min, major enantiomer t_R = 16.9 min; 76% ee; minor: minor enantiomer t_R = 13.5 min, major enantiomer t_R = 20.5 min; 84% ee; $[\alpha]^{21.8}_D$ = +138.8 (c=1.0, $CHCl_3$, d.r.=52/48, 76% ee/84% ee); IR (neat) 3404, 2978, 1720, 1549, 1455, 1359 cm^{-1}.

Entry 7, Table 2: yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) major δ 8.08 (br, 1H), 7.48 (s, 1H), 7.27−7.17 (m, 2H), 7.02 (m, 1H), 5.26−5.19 (m, 1H), 4.39 (d, J = 9.5 Hz, 1H), 2.46 (s, 3H), 1.71 (d, J = 6.6 Hz, 3H), 1.42 (s, 9H); minor δ 8.13 (br, 1H), 7.48 (s, 1H), 7.27−7.17 (m, 2H), 7.06 (m, 1H), 5.26−5.19 (m, 1H), 4.33 (d, J = 10.9 Hz, 1H), 2.47 (s, 3H), 1.40 (d, J = 6.6 Hz, 3H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) major δ 169.3, 134.4, 129.3, 126.5, 124.2, 123.5, 118.6, 111.1, 108.3, 85.0, 82.5, 48.7, 28.0, 21.7, 17.9; minor δ 170.5, 134.7, 129.2, 126.5, 124.4, 123.5, 118.7, 111.3, 108.3, 83.8, 82.3, 48.3, 27.9, 21.7, 18.6; HRMS calcd for $C_{17}H_{22}O_4N_2Na$ $(M + Na)^+$ 341.1472, found m/z 341.1466; enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane/2-propanol, 1.0 mL/min, 254 nm); major: minor enantiomer t_R = 8.4 min, major enantiomer t_R = 9.2 min; 87% ee; minor: minor enantiomer t_R = 7.2 min, major enantiomer t_R = 12.5 min; $[\alpha]^{21.5}_D$ = +75.5 (c = 1.0, $CHCl_3$, dr = 89/11, 87% ee/78% ee); IR (neat) 3410, 2979, 1721, 1550, 1455, 1367 cm^{-1}.

Entry 8, Table 2: yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) major δ 8.14 (br, 1H), 7.27−7.11 (m, 3H), 6.84 (dd, J = 8.6, 2.3 Hz, 1H), 5.25−5.19 (m, 1H), 4.39 (d, J = 9.7 Hz, 1H), 3,87 (s, 3H), 1.72 (d, J = 6.6 Hz, 3H), 1.42 (s, 9H); minor δ 8.21 (br, 1H), 7.27−7.11 (m, 3H), 6.88 (dd, J = 8.8, 2.3 Hz, 1H), 5.25−5.19 (m, 1H), 4.32 (d, J = 10.0 Hz, 1H), 3,86 (s, 3H), 1.40(d, J = 7.2 Hz, 3H), 1.39 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) major δ 169.6, 154.4, 131,2, 126.7, 124.0, 112.9, 112.2, 108.5, 100.6, 84.9, 82.5, 55.9, 48.7, 28.0, 18.1; minor δ 169.6, 154.4, 131,2, 126.7, 124.2, 113.2, 112.4, 108.3, 100.6, 84.9, 82.4, 55.9, 48.7, 27.9, 18.5; HRMS calcd for $C_{17}H_{22}O_5N_2Na$ $(M + Na)^+$ 357.1421, found m/z 357.1414; enantiomeric excess was determined by HPLC with a Chiralcel OD-H + Chiralpak AD-H column (90:10 hexane/2-propanol, 0.8 mL/min, 254 nm); major: major enantiomer t_R = 30.7 min, minor enantiomer t_R = 43.1 min; 87% ee; minor: minor enantiomer t_R = 43.1 min, minor enantiomer t_R = 44.8 min; 65% ee; $[\alpha]^{24.9}_D$ = +85.9 (c = 1.0, $CHCl_3$, dr = 90/10, 87% ee/65% ee); IR (neat) 3423, 2986, 1724, 1554, 1457, 1368, 1153 cm^{-1}.

Entry 9, Table 2: yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) major δ 8.20 (br, 1H), 7.86 (d, J = 1.7 Hz, 1H), 7.27 (dd, J = 10.3, 1.7 Hz, 1H), 7.20 (s, 1H), 7.20 (d, J = 10.3 Hz, 1H), 5.25−5.19 (m, 1H), 4.30 (d, J = 9.7 Hz, 1H), 1.71 (d, J = 6.6 Hz, 3H), 1.42 (s, 9H); minor δ 8.25 (br, 1H), 7.85 (d, J = 1.7 Hz, 1H), 7.32 (dd, J = 9.1, 1.7 Hz, 1H), 7.26 (d, J = 9.1 Hz, 1H), 7.20 (m, 1H), 5.24−5.18 (m, 1H), 4.30 (d, J = 10.6 Hz, 1H), 1.40 (d, J = 7.2 Hz, 3H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) major δ 169.2, 134.7, 127.8, 125.5, 124.7, 121.7, 113.5, 113.0, 108.5, 84.8, 82.9, 48.9, 28.0, 18.2; minor δ 170.0, 135.0, 127.8, 125.8, 124.7, 121.8, 113.7, 113.2, 108.2, 83.4, 82.8, 48.2, 27.9, 18.5; HRMS calcd for $C_{16}H_{19}O_4N_2BrNa$ $(M + Na)^+$ 405.0420, found m/z 405.0411; enantiomeric excess was determined by HPLC with a Chiralcel OD-H + OD-H column (90:10 hexane/2-propanol, 1.0 mL/min, 254 nm); major: major enantiomer t_R = 18.4 min, minor enantiomer t_R = 22.0 min; 90% ee; minor: minor enantiomer t_R = 17.3 min, major enantiomer t_R = 19.5 min; 70% ee; major $[\alpha]^{25.0}_D$ = +70.2 (c = 1.0, $CHCl_3$, major only, 90% ee); minor $[\alpha]^{25.0}_D$ = +56.8 (c = 1.0, $CHCl_3$, minor only, 70% ee); IR (neat) 3421, 1717, 1556, 1456, 1362, 1154 cm^{-1}.

Entry 10, Table 2: yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) major δ 8.13 (br, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 2.6 Hz, 1H), 7.08−7.05 (m, 1H), 6.99 (d, J = 7.2 Hz, 1H), 5.27−5.21 (m, 1H), 4.40 (d, J = 9.7 Hz, 1H), 2.43 (s, 3H), 1.71 (d, J = 6.6 Hz, 3H), 1.42 (s, 9H); minor δ 8.20 (br, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 2.6 Hz, 1H), 7.10−7.03 (m, 1H), 6.99 (d, J = 7.2 Hz, 1H), 5.27−5.21 (m, 1H), 4.35 (d, J = 10.6 Hz, 1H), 2.48 (s, 3H), 1.40 (d, J = 6.9 Hz, 3H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) major δ 169.8, 135.9, 128.5, 126.0, 123.3, 120.9, 120.5, 116.9, 109.4, 85.2, 82.7, 49.1, 28.2, 18.2, 16.7; minor δ 169.8, 136.1, 128.5, 126.0, 123.3, 121.1, 120.7, 117.1, 109.4, 84.0, 82.7, 49.1, 28.1, 18.7, 16.7; HRMS calcd for $C_{17}H_{22}O_4N_2Na$ $(M + Na)^+$ 341.1472, found: m/z 341.1466; enantiomeric excess was determined by HPLC with a Chiralcel OD-H + Chiralpak AS-H column (95:5 hexane/2-propanol, 1.0 mL/min, 254 nm); major: minor enantiomer t_R = 31.8 min, major enantiomer t_R = 34.7 min; 67% ee; $[\alpha]^{22.0}_D$ = +49.8 (c = 1.0, $CHCl_3$, dr = 91/9, 67% ee/ND); IR (neat) 3414, 2979, 1720, 1550, 1455, 1367 cm^{-1}.

Entry 11, Table 2: yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) major δ 8.24 (br, 1H), 7.72 (t, J = 7.45 Hz, 1H), 7.40 (d, J = 8.02 Hz, 1H), 7.26−7.13 (m, 3H), 5.26−5.17 (m, 1H), 4.44 (d, J = 10.9 Hz, 1H), 4.23−4.02 (m, 2H), 2.17−2.00 (m, 1H), 1.82−1.66 (m, 1H), 1.21 (t, J = 6.9 Hz, 3H), 0.87 (t, J = 7.5 Hz, 3H); minor δ 8.16 (br, 1H), 7.72 (t, J = 7.45 Hz, 1H), 7.33 (d, J = 8.02 Hz, 1H), 7.26−7.13 (m, 3H), 5.26−5.17 (m, 1H), 4.53 (d, J = 10.9 Hz, 1H), 4.23−4.02 (m, 2H), 2.17−2.00 (m, 1H), 1.82−1.66 (m,1H), 1.16 (t, J = 7.5 Hz, 3H), 1.04 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, diastereomixture) δ 171.4, 170.7, 136,4, 136,1, 126.0(2C), 123.6(2C), 122.9, 122.7, 120.5, 120.3, 119.1(2C), 111.7, 111.5, 108.5, 108.2, 91.5, 89.3, 61.7(2C), 47.2, 45.8, 31.7, 26.3, 25.1, 22.7, 10.5, 9.6; HRMS calcd for $C_{15}H_{18}O_4N_2Na$ $(M + Na)^+$ 313.1159, found m/z 313.1154; enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (90:10 hexane/2-propanol, 1.0 mL/min, 254 nm); major: major enantiomer t_R = 11.7 min, minor enantiomer t_R = 12.9 min; 87% ee; minor: minor enantiomer t_R = 8.5 min, major enantiomer t_R = 9.4 min; 65% ee; $[\alpha]^{25.1}_D$ = +65.1 (c = 1.0, $CHCl_3$, dr = 51/49, 88% ee/81% ee); IR (neat) 3414, 2979, 1729, 1552, 1458, 1374 cm^{-1}.

Entry 12, Table 2: yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) major δ 8.24 (br, 1H), 7.91−7.07 (m, 10H), 6.27 (d, J = 11.7 Hz, 1H), 5.12 (d, J = 11.7 Hz, 1H), 3.97−3.84 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H); minor δ 8.02 (br, 1H), 7.91−7.07 (m, 10H), 7.27 (d, J = 11.7 Hz, 1H), 4.97 (d, J = 11.5 Hz, 1H), 4.30−4.23 (m, 1H), 4.15−4.09 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) major δ 169.7, 136.2, 132.9, 130.5, 129.1, 128.4, 126.1, 123.6, 122.8, 120.4, 119.3, 111.6, 108.6, 92.5, 61.5, 47.7, 13.8; minor δ 169.7, 136.2, 132.9, 130.5, 128.9, 127.7, 126.1, 124.0, 122.6, 120.3, 119.0, 111.5, 108.6, 90.2, 62.0, 47.6, 14.1; HRMS calcd for $C_{19}H_{18}O_4N_2Na$ $(M + Na)^+$ 361.1159, found m/z 361.1153; enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane/2-propanol, 1.0 mL/min, 254 nm); major: major enantiomer t_R = 33.6 min, minor enantiomer t_R = 37.0 min; 66% ee; minor: minor enantiomer t_R = 20.4 min, major enantiomer t_R = 22.8 min; 75% ee; $[\alpha]^{25.1}_D$ = +114.8 (c = 1.0, $CHCl_3$, dr = 77/23, 66% ee/75% ee); IR (neat) 3412, 3062, 1728, 1554, 1457, 1368 cm^{-1}.

Entry 1, Table 3: yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) major δ 8.70 (br, 1H), 6.75−6.74 (m, 1H), 6.13−6.11 (m, 1H), 6.10−6.08 (m, 1H), 5.08−5.02 (m, 1H), 4.28−4.10 (m, 1H), 1.60 (d, J = 6.6 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H); minor δ8.47 (br, 1H), 6.77−6.76 (m,1H), 6.17−6.15 (m, 1H), 6.13−6.11 (m, 1H), 5.08−5.02 (m, 1H), 4.28−4.10 (m, 3H), 1.43 (d, J= 6.9 Hz, 3H), 1.23 (t, J= 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) major δ 169.9, 122.3, 119.1, 109.1, 108.8, 85.1, 62.2, 49.1, 17.7, 14.1; minor δ 169.9, 121.2, 119.2, 109.2, 108.8, 83.5, 62.2, 49.0, 17.8, 14.0; HRMS calcd for $C_{10}H_{14}O_4N_2Na$ $(M + Na)^+$ 249.0846, found m/z 249.0845; enantiomeric excess was determined by HPLC with a Chiralpak AD-H+ Chiralcel OD-H column (98:2 hexane/2-propanol, 0.8 mL/min, 254 nm); major: minor enantiomer t_R = 55.4 min, major enantiomer t_R = 64.6 min; 87% ee; minor: minor enantiomer t_R = 53.0 min,

major enantiomer t_R = 75.6 min; 84% ee; $[\alpha]^{24.3}_D$ = +52.8 (*c* = 1.0, $CHCl_3$, dr = 84/16, 87% ee/84% ee); IR (neat) 3409, 2989, 1730, 1554, 1361 cm^{-1}.

Entry 2, Table 3: yellow oil; ^1H NMR (500 MHz, $CDCl_3$) major δ 8.56 (br, 1H), 6.76−6.75 (m, 1H), 6.14−6.11 (m, 1H), 6.10−6.08 (m, 1H), 5.09−5.02 (m, 1H), 4.24 (d, *J* = 8.6 Hz, 1H), 3.76 (s, 3H), 1.60 (d, *J* = 6.9 Hz, 3H); minor δ 8.41 (br, 1H), 6.78−6.76 (m, 1H), 6.14−6.11 (m, 1H), 6.10−6.08 (m, 1H), 5.09−5.02 (m, 1H), 4.26 (d, *J* = 9.7 Hz, 1H), 3.72 (s, 3H), 1.44 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) major δ 170.4, 122.2, 119.2, 109.2, 108.9, 85.0, 53.0, 48.9, 17.8; minor δ 170.4, 122.2, 119.3, 109.3, 109.1, 83.3, 53.0, 48.8, 17.8; HRMS calcd for $C_9H_{12}O_4N_2Na$ $(M + Na)^+$ 235.0689, found *m*/*z* 235.0689; enantiomeric excess was determined by HPLC with a Chiralpak AD-H+ Chiralcel OJ-H column (90:10 hexane/2-propanol, 1.0 mL/min, 254 nm); major: minor enantiomer t_R = 45.9 min, major enantiomer t_R = 52.9 min; 87% ee; minor: minor enantiomer t_R = 25.5 min, major enantiomer t_R = 28.7 min; 86% ee; $[\alpha]^{24.6}_D$ = +72.2 (*c* = 1.0, $CHCl_3$, dr = 80/20, 87% ee/86% ee); IR (neat) 3404, 2956, 1735, 1554, 1360 cm^{-1}.

Entry 3, Table 3: white solid; ^1H NMR (500 MHz, $CDCl_3$) major δ 8.65 (br, 1H), 6.75−6.74 (m, 1H), 6.13−6.11 (m, 1H), 6.08−6.06 (m, 1H), 5.00−4.95 (m, 1H), 4.14 (d, *J* = 8.6 Hz, 1H), 1.59 (d, *J* = 6.9 Hz, 3H), 1.46 (s, 9H); minor δ 8.45 (br, 1H), 6.76−6.75 (m, 1H), 6.17−6.15 (m, 1H), 6.09−6.08 (m, 1H), 5.00−4.95 (m, 1H), 4.11 (d, *J* = 10.3 Hz, 1H), 1.42 (d, *J* = 6.6 Hz, 3H), 1.41 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) major δ 168.9, 122.8, 118.9, 108.9, 108.7, 85.4, 83.3, 49.9, 27.9 17.5; minor δ 169.8, 122.5, 118.9, 109.1, 108.9, 83.7, 83.1, 49.9, 27.8 17.8 HRMS calcd for $C_{12}H_{18}O_4N_2Na$ $(M + Na)^+$ 277.1159, found *m*/*z* 277.1151; enantiomeric excess was determined by HPLC with a Chiralpak AD-H + Chiralcel OD-H column (95:5 hexane/2-propanol, 0.8 mL/min, 254 nm); major: minor enantiomer t_R = 21.4 min, major enantiomer t_R = 22.6 min; 84% ee; minor: minor enantiomer t_R = 20.0 min, major enantiomer t_R = 33.5 min; 84% ee; $[\alpha]^{24.8}_D$ = +31.3 (*c* = 1.0, $CHCl_3$, dr = 87/13, 84% ee/84% ee); IR (neat) 3411, 2981, 1722, 1553, 1369 cm^{-1}.

Entry 4, Table 3: yellow oil; ^1H NMR (500 MHz, $CDCl_3$) major δ 8.33 (br, 1H), 7.98 (m, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 6.72−6.71 (m, 1H), 6.12−6.10 (m, 1H), 6.09− 6.07 (m, 1H), 5.32−5.22 (m, 2H), 1.61 (d, *J* = 6.3 Hz, 3H); minor δ 8.25 (br, 1H), 7.98 (m, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 6.74−6.73 (m, 1H), 6.22−6.20 (m, 1H), 6.15−6.13 (m, 1H), 5.32−5.22 (m, 2H), 1.52 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) major δ 195.9, 135.9, 134.3, 129.1, 128.9, 122.6, 119.8, 109.8, 109.4, 86.5, 50.6, 18.6; minor δ 195.9, 135.9, 134.3, 129.1, 128.9, 122.6, 119.8, 109.8, 109.4, 86.5, 50.6, 18.6; HRMS calcd for $C_{14}H_{14}O_3N_2Na$ $(M + Na)^+$ 281.0897, found *m*/*z* 281.0891; enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (95:5 hexane/2-propanol, 1.0 mL/min, 254 nm); major: minor enantiomer t_R = 48.5 min, major enantiomer t_R = 62.3 min; 80% ee; minor: minor enantiomer t_R = 22.2 min, major enantiomer t_R = 30.2 min; 15% ee; $[\alpha]^{25.7}_D$ = +72.5 (*c* = 0.25, $CHCl_3$, dr = 93/7, 80% ee/15% ee); IR (neat) 3410, 2931, 1675, 1551, 1361 cm^{-1}.

Entry 5, Table 3: yellow oil; ^1H NMR (500 MHz, $CDCl_3$) major δ 8.47 (br, 1H), 6.77−6.76 (m, 1H), 6.17−6.15 (m, 1H), 6.14−6.12 (m, 1H), 4.97−4.87 (m, 1H), 4.30−4.07 (m, 3H), 1.83−1.68 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H); minor δ 8.55 (br, 1H), 6.75−6.73 (m, 1H), 6.12−6.10 (m, 1H), 6.09−6.08 (m, 1H), 4.97−4.87 (m, 1H), 4.30−4.07 (m, 3H), 2.08−1.99 (m, 1H), 1.84−1.71 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) major δ 170.8, 122.0, 119.2, 109.2(2C), 89.4, 62.2, 47.6, 24.9, 14.0, 9.5; minor δ 170.0, 122.3, 119.1, 109.0, 108.9, 91.8, 62.2, 48.4, 25.8, 14.1, 10.4; HRMS calcd for $C_{11}H_{16}O_4N_2Na$ $(M + Na)^+$ 263.1002, found *m*/*z* 263.0998; enantiomeric excess was determined by HPLC with a Chiralcel OJ-H+ Chiralpak AS-H column (90:10 hexane/2-propanol, 1.0 mL/min, 254 nm); major: minor enantiomer t_R = 17.9 min, major enantiomer t_R = 20.1 min; 92% ee; minor: minor enantiomer t_R = 25.6 min, major enantiomer t_R = 28.1 min; 86% ee; $[\alpha]^{25.2}_D$ = +80.9 (*c* = 1.0, $CHCl_3$, dr = 66/34, 92% ee/86% ee); IR (neat) 3393, 2980, 1727, 1553, 1374 cm^{-1}.

Entry 6, Table 3: yellow oil; ^1H NMR (500 MHz, $CDCl_3$) major δ 8.46 (br, 1H), 6.77−6.76 (m, 1H), 6.17−6.15 (m, 1H), 6.13−6.10 (m, 1H), 5.00−4.93 (m, 1H), 4.27−4.07 (m, 3H), 1.76−1.63 (m, 2H), 1.42−1.09 (m, 9H), 0.82 (t, *J* = 6.9 Hz, 3H); minor δ 8.54 (br, 1H), 6.74−6.73 (m, 1H), 6.13−6.10 (m, 1H), 6.09−6.07 (m, 1H), 5.00−4.93 (m, 1H), 4.27−4.07 (m, 3H), 2.05−1.98 (m, 2H), 1.42−1.09 (m, 9H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) major δ 170.8, 122.1, 119.2, 109.2 (2C), 88.3, 62.2, 48.3, 32.2, 30.9, 24.7, 22.3, 14.0, 13.9; minor δ 170.0, 122.3, 119.1, 109.0, 108.9, 90.5, 62.2, 48.7, 31.5, 29.8, 25.5, 22.3, 14.2, 14.1; HRMS calcd for $C_{14}H_{22}O_4N_2Na$ $(M + Na)^+$ 305.1472, found *m*/*z* 305.1466; enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (90:10 hexane/2-propanol, 1.0 mL/min, 254 nm); major: minor enantiomer t_R = 8.6 min, major enantiomer t_R = 11.2 min; 89% ee; minor: major enantiomer t_R = 7.1 min, minor enantiomer t_R = 7.8 min; 69% ee; $[\alpha]^{22.2}_D$ = +58.5 (*c* = 1.0, $CHCl_3$, dr = 67/33, 89% ee/69% ee); IR (neat) 3395, 2928, 1723, 1550, 1372 cm^{-1}.

Entry 7, Table 3: yellow oil; ^1H NMR (500 MHz, $CDCl_3$) major δ 7.97 (br, 1H), 7.57 (m, 1H), 7.45−7.23 (m, 4H), 6.58−6.56 (m, 1H), 5.99−5.97 (m, 1H), 5.93 (d, *J* = 11.5 Hz, 1H), 5.84−5.82 (m, 1H), 4.71 (d, *J* = 11.5 Hz, 1H), 4.32−4.14 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H); minor δ 8.58 (br, 1H), 7.57 (m, 1H), 7.45−7.23 (m, 4H), 6.78−6.77 (m, 1H), 6.22−6.21 (m, 1H), 6.16−6.14 (m, 1H), 5.91 (d, *J* = 11.7 Hz, 1H), 4.84 (d, *J* = 11.5 Hz, 1H), 3.98−3.86 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) major δ 169.1, 132.1, 130.1, 129.1, 127.7, 121.1, 118.8, 109.1, 108.9, 90.9, 62.3, 49.3, 14.0; minor δ 170.6, 132.6, 130.6, 129.1, 128.3, 122.6, 119.3, 109.2, 109.0, 93.1, 61.9, 49.3, 13.7; HRMS calcd for $C_{15}H_{16}O_4N_2Na$ $(M + Na)^+$ 311.1002, found *m*/*z* 311.0996; enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (90:10 hexane/2-propanol, 0.5 mL/min, 254 nm); major: minor enantiomer t_R = 33.6 min, major enantiomer t_R = 53.6 min; 91% ee; minor: major enantiomer t_R = 22.1 min, minor enantiomer t_R = 23.7 min; 68% ee; $[\alpha]^{25.6}_D$ = +149.8 (*c* = 1.0, $CHCl_3$, dr = 53/47, 91% ee/68% ee); IR (neat) 3401, 3037, 1727, 1554, 1370 cm^{-1}.

Chemical Transformation of the Friedel−Crafts/Protonation Adduct (Scheme 3). Reduction of the Friedel−Crafts/protonation adduct: see the procedure in ref 10b. The product obtained in entry 3 of Table 3 was recrystallized from MeOH to give pure *anti* isomer with 96% ee: ^1H NMR (500 MHz, $CDCl_3$) δ 9.23 (br, 1H), 6.73 (m, 1H), 6.13−6.11 (m, 1H), 6.03 (m, 1H), 3.35−3.27 (m, 2H), 1.44 (s, 9H), 1.11 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 126.4, 117.7, 108.2, 107.9, 81.5, 54.1, 50.2, 28.1, 21.5; HRMS calcd for $C_{12}H_{21}O_2N_2$ $(M + H)^+$ 225.1598, found *m*/*z* 225.1593; enantiomeric excess was determined by HPLC with a Chiralpak AD-H + AS-H column (100:1 hexane/2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_R = 72.9 min, minor enantiomer t_R = 97.3 min; $[\alpha]^{22.2}_D$ = +12.9 (*c* = 0.167, $CHCl_3$, 97% ee); IR (neat) 3385, 3186, 2977, 1719 cm^{-1}.

Pictet−Spengler reaction: see the procedure in ref 10b. Major product: ^1H NMR (500 MHz, $CDCl_3$) δ 8.25 (br, 1H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 6.62−6.61 (m, 1H), 5.63−5.62 (m, 1H), 4.97 (s, 1H), 3.48−3.42 (m, 2H), 1.52 (s, 9H), 1.32 (d, *J* = 5.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 131.7, 131.6, 130.2, 130.1, 123.0, 121.3, 117.1, 106.1, 82.1, 58.5, 52.1, 49.1, 28.3, 21.1; HRMS calcd for $C_{19}H_{24}O_2N_2Br$ $(M + H)^+$ 391.1016, found *m*/*z* 391.1006; $[\alpha]^{21.9}_D$ = −14.0 (*c* = 0.5, $CHCl_3$); IR (neat) 2972, 2929, 1718, 1156 cm^{-1}. Minor product: ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (br, 1H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.71−6.70 (m, 1H), 5.84−5.83 (m, 1H), 4.98 (s, 1H), 3.46−3.41 (m, 1H), 3.31 (d, *J* = 6.3 Hz, 1H), 1.47 (s, 9H), 1.21 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 131.4 (2C), 130.2 (2C), 123.2, 121.1, 117.7, 106.3, 81.9, 54.3, 48.0, 47.0, 28.3, 20.0; HRMS calcd for $C_{19}H_{24}O_2N_2Br$ $(M + H)^+$ 391.1016, found *m*/*z* 391.1006; $[\alpha]^{21.9}_D$ = −13.9 (*c* = 0.5, $CHCl_3$); IR (neat) 2971, 2925, 1716, 1152 cm^{-1}.

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■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra of products in the Friedel−Crafts/protonation and in the derivatization in Scheme 3. Structural determination of the Pictet−Spengler product obtained in Scheme 3. CIF files of Figures 2 and 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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