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$(DHQ)_2AQN$-Catalyzed Asymmetric Substitution of Isatin-Derived Hydrazones with O-Boc-Protected Morita–Baylis–Hillman Adducts: A Strategy for Synthesizing Enantioenriched Azo Compounds Incorporating an Oxindole Scaffold

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Supporting Information

ABSTRACT: The first example for the preparation of enantioenriched azo compounds from hydrazones and Morita–Baylis–Hillman adducts has been developed, affording azo compounds incorporating an oxindole scaffold in up to 91% yield along with a 93% ee value under the catalysis of $(DHQ)_2AQN$.

INTRODUCTION

The oxindole framework bearing a tetrasubstituted carbon stereocenter at the 3-position is a privileged heterocyclic motif that constructs the core of a large family of bioactive natural products and a series of pharmaceutically active compounds.[1] Inspired by these important scaffolds, a variety of synthetic methods for producing oxindoles bearing a tetrasubstituted carbon stereocenter at the 3-position and for applications to natural product synthesis have been investigated over the past decade.[1b,c,2]

Azo compounds constitute an important family of compounds with traditional uses in organic chemistry. For example, the application of azodicarboxylates in organic synthesis as nitrogen-atom-containing electrophiles/dienophiles and the use of aromatic azo compounds in the industrial field as pigments and dyes are well-established.[3] The importance of N=N bonds in biologically active molecules and the need for the development of new antibiotics have stimulated the synthesis of new azo prodrugs of the general structure Ar–N=N–R (R = aryl or alkyl) that release therapeutically active amine drugs upon site-specific reduction by bacterial extracellular azoreductase enzymes in the human colon (Scheme 1).[4] However, the synthesis of aliphatic azo compounds is less developed and still remains challenging, presumably due to their inherent instability.[5] Thus far, only a few examples of the enantioselective synthesis of azo compounds are known. These include the radical carboamination/biocatalytic resolution procedure,[6] the enantioselective conjugate addition of hydrazones to electron-deficient alkenes with aminocatalysis or H-bonding catalysis,[7] and the formally heterocarbonyl–ene reaction of hydrazones to ketones with H-bonding catalysis (Scheme 2).[8] Recently, chiral Lewis bases were used to catalyze asymmetric allylic alkylation using Morita–Baylis–Hillman (MBH) adducts as electrophiles, through a S_N2'/S_N2' cascade, and this synthetic method has emerged as a powerful strategy for the construction of multifunctional compounds.[9] To the best of our knowledge, hydrazone has not yet been employed as a nucleophile in the asymmetric S_N2'/S_N2' substitution of MBH adducts. Inspired by these results, and also in conjunction with our efforts on catalytic asymmetric synthesis of oxindoles bearing a tetrasubstituted stereocenter at the C-3 position, we decided to apply the asymmetric S_N2'/S_N2' substitution of MBH adducts to synthesize enantioenriched azo compounds incorporating an oxindole scaffold (Scheme 2).[10]

According to our assumption, *t*-butoxide ion generated in situ from the nucleophilic addition of Lewis base to MBH adduct could abstract a proton of hydrazone to give a nucleophile that could undergo an S_N2' substitution to give azo compounds (Scheme 3).[9,11] Thus, we employed isatin-derived hydrazones as the target molecules to realize this hypothesis.

RESULTS AND DISCUSSION

We first used hydrazone **1a** (1.0 equiv) and MBH adduct **2a** (3.0 equiv) as the substrates to determine the reaction outcome and subsequently optimized the reaction conditions in the presence of 1,4-diazabicyclo[2,2,2]octane (DABCO) (20 mol %) or various chiral Lewis bases (20 mol %) derived from cinchona alkaloids. The results are summarized in Table 1. The treatment of hydrazone **1a** with MBH adduct **2a** in the presence of DABCO gave the desired product **3a** in 51% isolated yield (Table 1, entry 1). Its asymmetric version could be achieved under the catalysis of Q (quinine) and QD (quinidine) in THF at room temperature, affording **3a** in 74% yield along with a 40% ee value and in 74% yield along with −39% ee, respectively (Table 1, entries 2 and 3). A brief survey of the other cinchona alkaloids derived chiral Lewis bases indicated that $(DHQ)_2AQN$ [$(DHQ)_2AQN$ is hydroquinine (anthraquinone-1,4-diyl)-diether] was the best catalyst for this reaction, giving **3a** in

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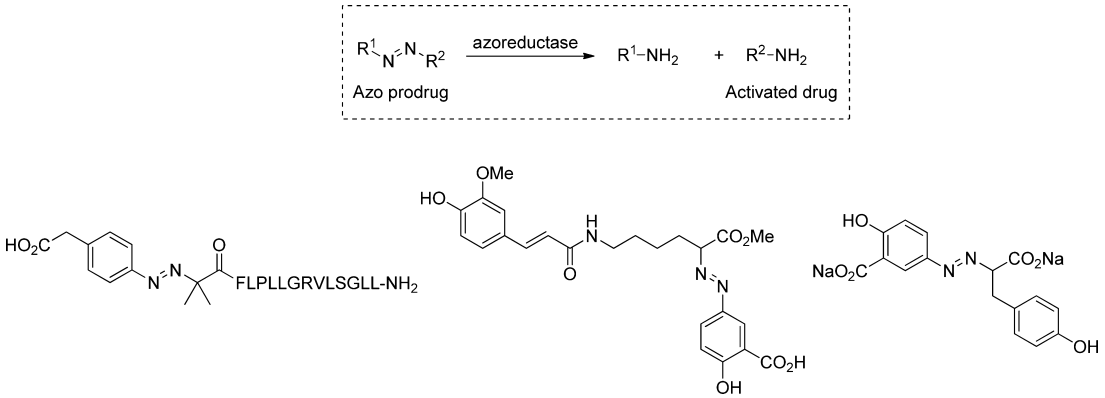
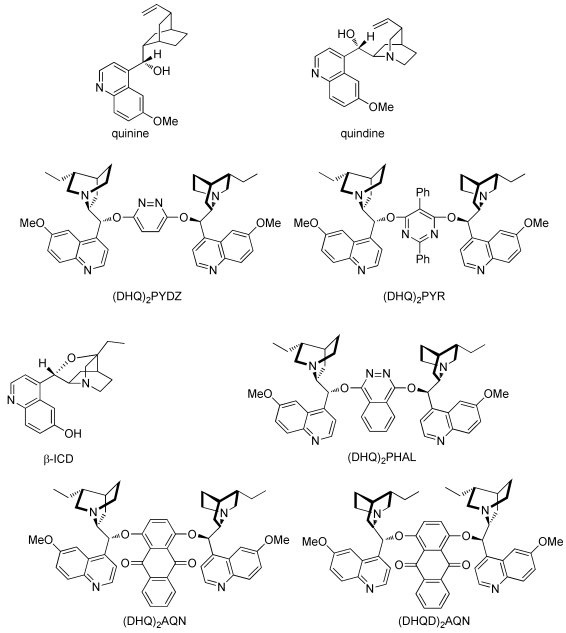
Scheme 1. Design of Prodrug Based on Azoreductase



80% yield and 75% ee value (Table 1, entries 4−9). The examination of solvent effects using **1a** (1.0 equiv) and **2a** (3.0 equiv) revealed that EtOAc (ethyl acetate) was the solvent of choice, giving the desired product **3a** in 80% yield along with a 76% ee value (Table 1, entries 10−14). Carrying out the reaction at 0 °C gave the desired product **3a** in 82% yield along with 80% ee value (Table 1, entry 15). Increasing the concentration of substrate **1a** to 0.1 M and reducing the catalyst loading to 10 mol % had no influence on the reaction outcome (Table 1, entry 16). However, when we reduced the catalyst loading to 5 mol %, the yield of **3a** decreased to 75% (Table 1, entry 17). Thus, we established the optimal reaction conditions for this reaction: hydrazone **1a** (0.1 mmol), MBH adduct **2a** (0.3 mmol), and $(DHQ)_2AQN$ (0.01 mmol) were stirred in 1 mL of EtOAc at 0 °C.



With these optimal conditions in hand, we next examined a variety of isatin-derived hydrazones **1** in this reaction, and the results of these experiments are shown in Table 2. For MBH adducts **2a**−**2c** (R^4 = H), whether R^5 was an ethyl, benzyl, or neopentyl group, the corresponding products **3b**−**3d** could be obtained in good yields along with good ee values (Table 2, entries 1−3, where PMP indicates a *p*-methoxyphenyl group). However, for MBH adduct **2d** (R^4 = *p*-nitrophenyl group and R^5 = ethyl group), the reaction was sluggish to afford the corresponding product **3e** in a 93% ee value and a 11:1 dr value but with 31% yield along with incomplete conversion of hydrazone **1b**, perhaps due to the steric effect (Table 2, entry 4). As for MBH adduct **2c**, whether PG (where PG indicates protecting group) was a *p*-bromobenzyl, allyl, or naphthyl group, the corresponding products **3f**−**3h** could be also obtained in good yields along with good ee values, and this investigation disclosed that the enantioselectivity of **3** could be enhanced if the PG is bearing an aryl moiety (Table 2, entries 5−7). The presence of an electron-donating group (Me or MeO) at C5, C6, or C7 position of isatin-derived hydrazones afforded the desired products **3** in better ee values, demonstrating that the electronic effect had great influence on the control of enantioselectivity, presumably due to the $\pi-\pi$ stacking interaction between the oxindole ring of hydrazone and the quinoline motif of $(DHQ)_2AQN$ (Table 2, entries 8−15). When the aryl group (Ar) of hydrazone was changed to a 3,4-dimethoxyphenyl or 3,4,5-trimethoxyphenyl group, the reaction also proceeded smoothly to afford the corresponding products **3q** and **3r** with good ee values, albeit with lower yields (Table 2, entries 16 and 17). It should be also noted that, when the aryl group (Ar) of hydrazone was changed to a 3,5-dimethylphenyl group, no reaction occurred under the standard conditions, suggesting that it is essential for this asymmetric allylic alkylation of hydrazones using a strongly electron-donating group as the nitrogen substituent to enhance the stability of the key intermediate shown in Scheme 3 (Table 2, entry18).

Because of the important biological meaning of CF_3, ethyl trifluoropyruvate-derived hydrazone was investigated in this asymmetric allylic alkylation of hydrazone, and the result of this experiment is shown in Scheme 4.[12] When ethyl trifluoropyruvate-derived hydrazone was subjected to the standard conditions, the reaction proceeded smoothly, furnishing the desired product **3s** in 82% yield along with a 68% ee value (Scheme 4).

Furthermore, the chiral product **3i** could be smoothly transformed into compound **4a** incorporating a biologically interesting isoxazole scaffold in 60% yield along with 2:1 diastereoselectivity via a 1,3-dipolar cycloaddition (The dr value was determined by ^1H NMR spectroscopic data of the crude product) (Scheme 5).

In summary, we have established a moderately efficient process for the asymmetric allylic alkylation of hydrazones under the catalysis of $(DHQ)_2AQN$. Azo compounds incorporating an oxindole scaffold could be synthesized in good yields with good enantioselectivities under mild conditions. As for future studies, we plan to expand the scope of the substrate and to investigate the biological activity of these obtained azo compounds incorporating an oxindole scaffold.

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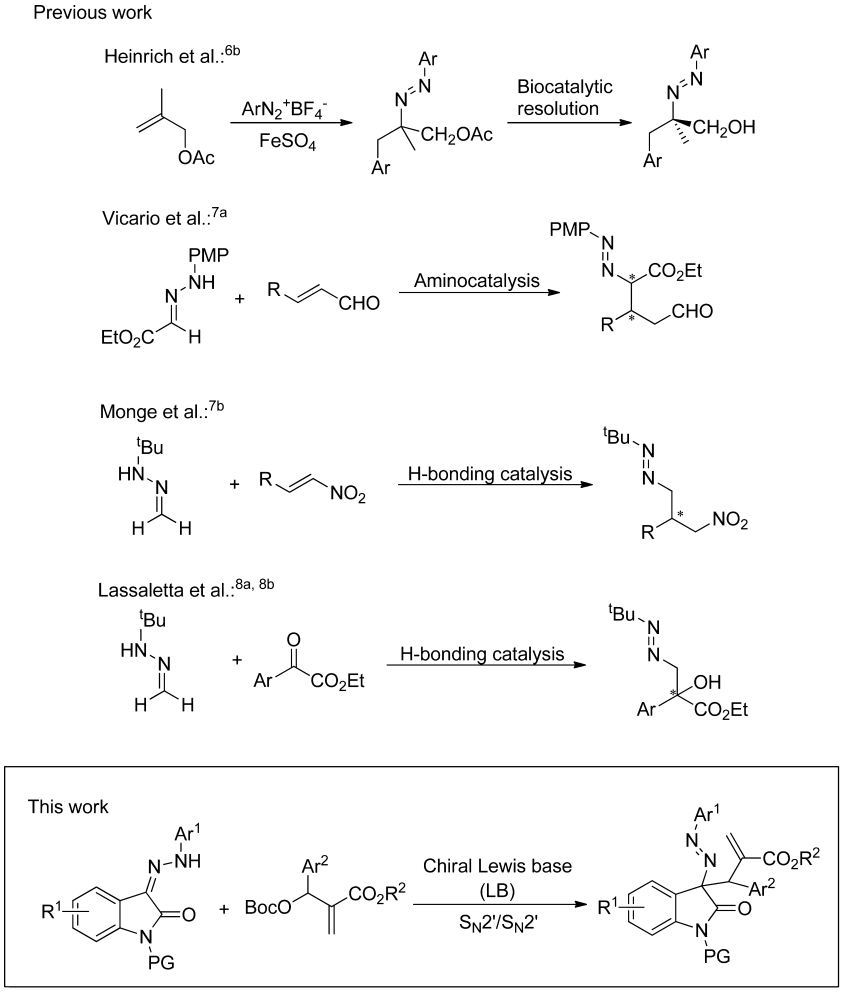
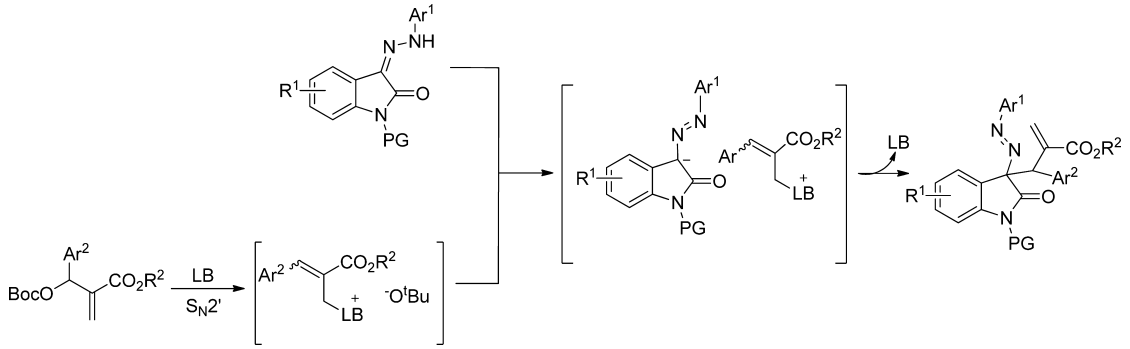
Scheme 2. Previous Investigations on the Enantioselective Preparation of Azo Compounds and Our Work



Scheme 3. Our Strategies for the Asymmetric Synthesis of Azo Compounds



EXPERIMENTAL SECTION

General Remarks. ^{1}H and ^{13}C NMR spectra were recorded at 400 (or 300) MHz, respectively. HRMS spectra were recorded by electrospray ionization (ESI-TOF). The employed solvents were dried by standard methods when necessary. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with silica-gel-coated plates. Flash column chromatography was carried out using 300−400 mesh silica gel at increased pressure. The (*Z*)-configuration of hydrazone substrates **1** has been determined by X-ray crystal data of compound **1i** (see the Supporting Information).

Procedure for the Synthesis of Hydrazones 1a−1n and 1p. Compounds **1a−1n** and **1p** were prepared by a previously reported procedure.[13] A mixture of isatin (1 equiv), arylhydrazine hydrochloride (1.1 equiv), and sodium acetate (2 equiv) in absolute ethanol was heated under reflux for 16 h. The reaction mixture was allowed to cool, and the resulting precipitates were filtered from the solution. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography using an ethyl acetate/petroleum ether gradient mixture to give the corresponding products **1**. The (*Z*)-configuration of hydrazone substrates **1** has been determined by X-ray crystal data of compound **1i** (see below).

Procedure for the Synthesis of Hydrazone 1o. Compound **1o** was prepared by a previously reported procedure.[14] 3,4,5-Trimethoxyaniline (410 mg, 2.26 mmol) was dissolved in the mixture of water (2.40 mL), THF (0.57 mL), and conc. hydrochloric acid (0.76 mL), and

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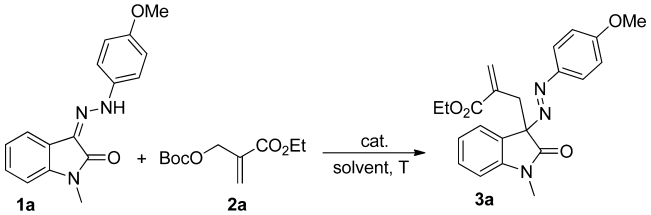
Table 1. Optimization of the Asymmetric Allylic Alkylation of Hydrazones



entry[a]	cat.	solvent	T (°C)	yield (%)[b]	ee (%)[c]
1	DABCO	toluene	rt	51	
2	Q	THF	rt	74	40
3	QD	THF	rt	74	−39
4	β-lCD	THF	rt	79	−34
5	$(DHQ)_2PHAL$	THF	rt	53	48
6	$(DHQ)_2PYDZ$	THF	rt	74	40
7	$(DHQ)_2PYR$	THF	rt	76	17
8	$(DHQ)_2AQN$	THF	rt	80	75
9	$(DHQD)_2AQN$	THF	rt	76	−30
10	$(DHQ)_2AQN$	CH_2Cl_2	rt	81	57
11	$(DHQ)_2AQN$	acetone	rt	85	60
12	$(DHQ)_2AQN$	$PhCF_3$	rt	66	57
13	$(DHQ)_2AQN$	Et_2O	rt	80	69
14	$(DHQ)_2AQN$	EtOAc	rt	80	76
15	$(DHQ)_2AQN$	EtOAc	0	82	80
16[d]	$(DHQ)_2AQN$	EtOAc	0	84	80
17[e]	$(DHQ)_2AQN$	EtOAc	0	75	80

[a]Hydrazone **1** (0.1 mmol), MBH adduct **2a** (0.3 mmol), and catalyst (0.02 mmol) were stirred in 2 mL of solvents for 2 days. [b]Yield of isolated product. [c]Determined by HPLC analysis on a chiral stationary phase. [d]$[\mathbf{1a}]_0$ = 0.1 M and 10 mol % of the catalyst loading. [e]$[\mathbf{1a}]_0$ = 0.1 M and 5 mol % of the catalyst loading, and the reaction time is 1 week.

the solution was cooled to 0 °C. Then, a solution of sodium nitrite (156 mg, 2.26 mmol) in water (0.67 mL) was slowly added with stirring so that the temperature was maintained between 0 and 5 °C. The solution of aryldiazonium salt was stirred at 0 °C for a further 2 h.

The solution of aryldiazonium salt was added dropwise to an ethanolic (10 mL) suspension of 1-benzylindolin-2-one (536 mg, 2.26 mmol) and sodium hydroxide (678 mg in 2.7 mL of water) at 0 °C. Then, the reaction mixture was allowed to stand at 0 °C until the reaction was complete. The mixture was diluted with CH_2Cl_2 and washed with water. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, ethyl acetate:petroleum ether = 1:2) to give the corresponding product **1o** (273 mg, 30%).

Procedure for the Synthesis of Hydrazone 1q. Compound **1q** was prepared by a previously reported procedure with slight modification.[15] To a stirred solution of pyridine (119 mg, 1.5 mmol) in 2 mL of CH_2Cl_2 was added arylhydrazine hydrochloride (262 mg, 1.5 mmol). After the mixture was stirred for a further 30 min, ethyl-3,3,3-trifluoropyruvate (255 mg, 1.5 mmol) was added. The reaction was stirred for 18 h at room temperature before $POCl_3$ (299 mg, 1.95 mmol) and pyridine (154 mL, 1.95 mmol) were added dropwise sequentially. The solution was stirred at room temperature for 18 h, before being diluted with brine, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, CH_2Cl_2:petroleum ether = 2:1) to give the corresponding product **1q** (216 mg, 50%).

Compound ***1a***. Yield: 370 mg, 74%. A yellow solid. m.p.: 120−122 °C. IR (neat) ν 3061, 2996, 2831, 1668, 1611, 1565, 1515, 1468, 1375, 1215, 1176, 1093, 1034, 824, 780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.31 (s, 3H), 3.82 (s, 3H), 6.88 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 9.2 Hz, 2H), 7.11 (t, J = 7.6 Hz, 1H), 7.27 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 9.2 Hz, 2H), 7.63 (d, J = 7.2 Hz, 1H), 12.81 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 25.3, 55.5, 108.2, 114.7, 115.4, 118.4, 121.3, 122.3, 125.7, 127.4, 136.4, 140.5, 155.9, 162.1; HRMS (ESI) Calcd for $C_{16}H_{15}N_3O_2$ requires (M^+ + H): 282.1237, Found: 282.1240.

Compound ***1b***. Yield: 280 mg, 78%. A yellow solid. m.p.: 141−142 °C. IR (neat) ν 3026, 2960, 2931, 2835, 1661, 1609, 1594, 1557, 1518, 1495, 1464, 1362, 1237, 1160, 1101, 1035, 821, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.81 (s, 3H), 4.99 (s, 2H), 6.78 (d, J = 7.6 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 7.07 (td, J = 7.6 Hz, 0.8 Hz, 1H), 7.15 (td, J = 7.6 Hz, 1.2, Hz, 1H), 7.26−7.34 (m, 7H), 7.64 (d, J = 7.2 Hz, 1H), 12.85 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 43.1, 55.6, 109.2, 114.8, 115.6, 118.5, 121.5, 122.5, 125.5, 127.2, 127.4, 127.6, 128.8, 135.9, 136.3, 139.7, 156.1, 162.2; HRMS (ESI) Calcd for $C_{22}H_{19}N_3O_2$ requires (M^+ + H): 358.1550, Found: 358.1554.

Compound ***1c***. Yield: 240 mg, 46%. A yellow solid. m.p.: 178−180 °C. IR (neat) ν 3231, 3042, 2964, 2920, 2838, 1654, 1608, 1592, 1560, 1516, 1357, 1231, 1160, 1098, 1037, 1009, 825, 791, 781 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.81 (s, 3H), 4.93 (s, 2H), 6.74 (d, J = 7.6 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 7.09 (t, J = 7.6 Hz, 1H), 7.14−7.19 (m, 3H), 7.32 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.64 (d, 1H), 12.82 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 42.5, 55.6, 109.0, 114.8, 115.6, 118.6, 121.5, 121.6, 122.6, 125.3, 127.4, 128.9, 131.9, 134.9, 136.2, 139.3, 156.2, 162.1; HRMS (ESI) Calcd for $C_{22}H_{18}BrN_3O_2$ requires (M^+ + H): 436.0655, Found: 436.0660.

Compound ***1d***. Yield: 244 mg, 79%. A yellow solid. m.p.: 122−123 °C. IR (neat) ν 3197, 3049, 2834, 1655, 1609, 1557, 1516, 1464, 1356, 1229, 1171, 1047, 940, 821, 782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.81 (s, 3H), 4.43 (d, J = 5.2 Hz, 2H), 5.21−5.25 (m, 2H), 5.84−5.94 (m, 1H), 6.87 (d, J = 7.6 Hz, 1H), 6.92 (d, J = 9.2 Hz, 2H), 7.10 (t, J = 7.2 Hz, 1H), 7.22 (t, J = 7.2 Hz, 1H), 7.31 (d, J = 9.2 Hz, 2H), 7.64 (d, J = 7.6 Hz, 1H), 12.81 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 41.6, 55.6, 109.1, 114.7, 115.5, 117.5, 118.5, 121.4, 122.4, 125.5, 127.3, 131.4, 136.3, 139.7, 156.0, 161.9; HRMS (ESI) Calcd for $C_{18}H_{17}N_3O_2$ requires (M^+ + H): 308.1394, Found: 308.1394.

Compound ***1e***. Yield: 319 mg, 78%. A yellow solid. m.p.: 186−188 °C. IR (neat) ν 3000, 2926, 2834, 1652, 1607, 1549, 1362, 1231, 1165, 1039, 1011, 826, 812,781 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.82 (s, 3H), 5.16 (s, 2H), 6.82 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 7.07 (t, J = 7.2 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.34 (t, J = 9.2 Hz, 2H), 7.41−7.48 (m, 3H), 7.65 (d, J = 7.2 Hz, 1H), 7.74−7.81 (m, 4H), 12.88 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 43.4, 55.6, 109.3, 114.8, 115.6, 118.5, 121.6, 122.5, 125.1, 125.6, 125.97, 126.02, 126.3, 127.4, 127.7, 127.8, 128.8, 132.8, 133.28, 133.34, 136.4, 139.7, 156.1, 162.3; HRMS (ESI) Calcd for $C_{26}H_{21}N_3O_2$ requires (M^+ + H): 408.1707, Found: 408.1706.

Compound ***1f***. Yield: 250 mg, 67%. A yellow solid. m.p.: 164−165 °C. IR (neat) ν 3007, 2914, 2838, 1663, 1616, 1594, 1561, 1520, 1483, 1435, 1349, 1230, 1183, 1125, 1110, 1039, 875, 826, 797 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 2.35 (s, 3H), 3.81 (s, 3H), 4.97 (s, 2H), 6.67 (d, J = 8.0 Hz, 1H), 6.91−6.97 (m, 3H), 7.25−7.33 (m, 7H), 7.47 (s, 1H), 12.83 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.1, 43.1, 55.6, 109.0, 114.8, 115.5, 119.1, 121.5, 125.7, 127.2, 127.6, 128.0, 128.8, 132.0, 136.0, 136.4, 137.6, 156.0, 162.3; HRMS (ESI) Calcd for $C_{23}H_{21}N_3O_2$ requires (M^+ + H): 372.1707, Found: 372.1704.

Compound ***1g***. Yield: 105 mg, 27%. A yellow solid. m.p.: 180−182 °C. IR (neat) ν 3170, 3065, 2919, 2840, 1652, 1557, 1518, 1348, 1233, 1162, 1035, 829, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.81 (s, 3H), 4.96 (s, 2H), 6.66 (d, J = 8.8 Hz, 1H), 6.92 (d, J = 6.8 Hz, 2H), 7.07 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.25−7.34 (m, 7H), 7.58 (d, J = 1.6 Hz, 1H), 12.87 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 43.2, 55.5, 110.1, 114.8, 115.8, 118.5, 122.9, 124.3, 126.8, 127.2, 127.8, 128.0, 128.9, 135.5, 135.9, 137.8, 156.5, 162.0; HRMS (ESI) Calcd for $C_{22}H_{18}ClN_3O_2$ requires (M^+ + H): 392.1160, Found: 392.1156.

Compound ***1h***. Yield: 263 mg, 68%. A yellow solid. m.p.: 169−172 °C. IR (neat) ν 3001, 2944, 2827, 1654, 1560, 1480, 1232, 1160, 1034, 859, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.80 (s, 3H), 3.81 (s, 3H), 4.95 (s, 2H), 6.65 (d, J = 8.8 Hz, 1H), 6.70 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 2.4 Hz, 1H), 7.24−7.33 (m, 7H), 12.88 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 43.1, 55.5, 55.8, 104.0, 109.8, 113.6, 114.7, 115.6, 122.4, 125.8, 127.2, 127.6,

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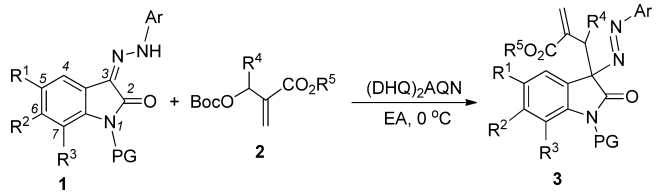
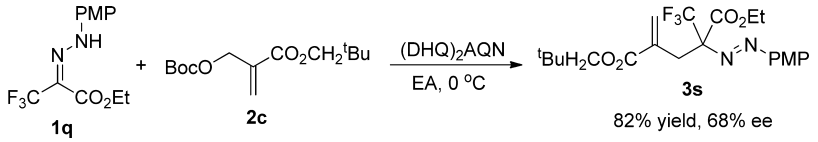
Table 2. Substrate Scope of the Asymmetric Allylic Alkylation of Hydrazones



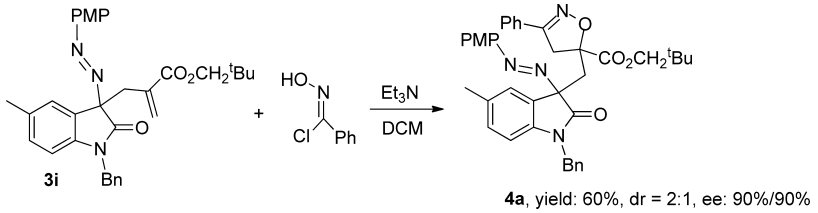
entry[a]	$R^1/R^2/R^3$, PG, Ar	R^4/R^5	yield (%)[b]	ee (%)[c]
1	**1b**, H/H/H, Bn, PMP	**2a**, H/Et	**3b**, 83	85
2	**1b**, H/H/H, Bn, PMP	**2b**, H/Bn	**3c**, 70	87
3	**1b**, H/H/H, Bn, PMP	**2c**, H/neopentyl	**3d**, 82	89
4[d]	**1b**, H/H/H, Bn, PMP	**2d**, *p*-nitrophenyl/Et	**3e**, 31	93
5	**1c**, H/H/H, *p*-bromobenzyl, PMP	**2c**, H/neopentyl	**3f**, 85	90
6	**1d**, H/H/H, allyl, PMP	**2c**, H/neopentyl	**3g**, 82	86
7	**1e**, H/H/H, naphthyl, PMP	**2c**, H/neopentyl	**3h**, 75	91
8	**1f**, Me/H/H, Bn, PMP	**2c**, H/neopentyl	**3i**, 80	90
9	**1g**, Cl/H/H, Bn, PMP	**2c**, H/neopentyl	**3j**, 84	77
10	**1h**, MeO/H/H, Bn, PMP	**2c**, H/neopentyl	**3k**, 91	90
11	**1i**, H/Me/H, Bn, PMP	**2c**, H/neopentyl	**3l**, 82	92
12	**1j**, H/Br/H, Bn, PMP	**2c**, H/neopentyl	**3m**, 64	80
13	**1k**, H/Br/H, Bn, PMP	**2c**, H/neopentyl	**3n**, 71	90
14	**1l**, Me/H/Me, Bn, PMP	**2c**, H/neopentyl	**3o**, 75	68
15	**1m**, H/H/F, Bn, PMP	**2c**, H/neopentyl	**3p**, 81	72
16	**1n**, H/H/H, Bn, 3,4-dimethoxyphenyl	**2c**, H/neopentyl	**3q**, 50	86
17	**1o**, H/H/H, Bn, trimethoxyphenyl	**2c**, H/neopentyl	**3r**, 50	87
18	**1p**, H/H/H, Me, dimethoxyphenyl	**2a**, H/Et		

[a]Hydrazone **1** (0.1 mmol), MBH adduct **2a** (0.3 mmol), and catalyst (0.01 mmol) were stirred in 1 mL of EtOAc at 0 °C for 2 days. [b]Yield of isolated product. [c]Determined by HPLC analysis on a chiral stationary phase. [d]The dr value was determined by ^{1}H NMR spectroscopic data of the crude product.

Scheme 4. Asymmetric Allylic Alkylation of Ethyl Trifluoropyruvate-Derived Hydrazone



Scheme 5. Transformation of Chiral Azo Compounds Incorporating an Oxindole Scaffold



128.8, 133.6, 135.9, 136.3, 155.9, 156.1, 162.3; HRMS (ESI) Calcd for $C_{23}H_{21}N_3O_3$ requires (M^+ + H): 388.1656, Found: 388.1649.

Compound ***1i***. Yield: 222 mg, 60%. A yellow solid. m.p.: 168–171 °C. IR (neat) ν 3004, 2931, 2836, 1667, 1615, 1564, 1517, 1439, 1383, 1236, 1143, 1080, 1024, 828, 809, 765 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.33 (s, 3H), 3.81 (s, 3H), 4.98 (s, 2H), 6.61 (s, 1H), 6.88–6.93 (m, 3H), 7.25–7.35 (m, 7H), 7.52 (d, J = 7.6 Hz, 1H), 12.76 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 22.1, 43.0, 55.6, 109.9, 114.7, 115.4, 118.4, 118.9, 123.3, 125.8, 127.1, 127.6, 128.8, 136.0, 136.5, 137.9, 140.0, 155.9, 162.5; HRMS (ESI) Calcd for $C_{23}H_{21}N_3O_2$ requires (M^+ + H): 372.1707, Found: 372.1704.

Compound ***1j***. Yield: 316 mg, 72%. A yellow solid. m.p.: 196–198 °C. IR (neat) ν 3004, 1673, 1599, 1581, 1557, 1515, 1225, 1150, 1105, 1022, 824, 813, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.82 (s, 3H), 4.96 (s, 2H), 6.91–6.93 (m, 3H), 7.20 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.26–7.36 (m, 7H), 7.48 (d, J = 8.0 Hz, 1H), 12.85 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 43.2, 55.6, 112.4, 114.8, 115.8, 119.6, 120.5, 120.6, 124.5, 125.4, 127.2, 127.9, 128.9, 135.4, 136.1, 140.5, 156.4, 162.1; HRMS (ESI) Calcd for $C_{22}H_{18}BrN_3O_2$ requires (M^+ + H): 436.0655, Found: 436.0651.

Compound ***1k***. Yield: 317 mg, 82%. A yellow solid. m.p.: 183–184 °C. IR (neat) ν 3030, 2936, 2833, 1665, 1559, 1519, 1489, 1439, 1351, 1230, 1149, 1115, 1103, 1033, 1015, 824 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.23 (s, 3H), 2.31 (s, 3H), 3.79 (s, 3H), 5.22 (s, 2H), 6.72 (s, 1H), 6.90 (d, J = 8.8 Hz, 2H), 7.13–7.15 (m, 2H), 7.20–7.24 (m, 1H), 7.27–7.31 (m, 4H), 7.37 (s, 1H), 12.85 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 18.5, 20.8, 44.3, 55.5, 114.7, 115.5, 117.0, 119.8, 122.3, 125.60, 125.65, 127.2, 128.8, 132.0, 132.1, 135.6, 136.4, 137.7, 156.0, 162.9; HRMS (ESI) Calcd for $C_{24}H_{23}N_3O_2$ requires (M^+ + H): 386.1863, Found: 386.1857.

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Compound ***1l***. Yield: 221 mg, 51%. A yellow solid. m.p.: 177−178 °C. IR (neat) ν 3007, 2935, 2830, 1720, 1660, 1591, 1552, 1519, 1495, 1462, 1454, 1442, 1231, 1149, 1090, 1028, 1000 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.82 (s, 3H), 5.51 (s, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.96 (t, J = 7.6 Hz, 1H), 7.22−7.26 (m, 3H), 7.29−7.33 (m, 5H), 7.63 (d, J = 7.6 Hz, 1H), 12.93 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 43.8, 55.6, 102.9, 114.8, 115.9, 117.4, 123.6, 124.1, 124.8, 126.3, 127.2, 128.6, 132.8, 135.9, 136.5, 137.5, 156.5, 162.7; HRMS (ESI) Calcd for $C_{22}H_{18}BrN_3O_2$ requires (M^+ + H): 436.0655, Found: 436.0651.

Compound ***1m***. Yield: 231 mg, 62%. A yellow solid. m.p.: 160−163 °C. IR (neat) ν 3032, 3001, 2935, 1659, 1552, 1519, 1494, 1463, 1454, 1231, 1168, 1149, 1090, 1000, 826, 789, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.82 (s, 3H), 5.14 (s, 2H), 6.89−6.93 (m, 3H), 6.97−7.02 (m, 1H), 7.24−7.38 (m, 7H), 7.42 (d, J = 7.6 Hz, 1H), 12.93 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 44.9 (d, J = 4.4 Hz), 55.6, 114.3 (d, J = 3.0 Hz), 114.8, 115.0 (d, J = 19.4 Hz), 115.8, 123.0 (d, J = 6.8 Hz), 124.6 (d, J = 4.4 Hz), 124.9 (d, J = 4.3 Hz), 125.9 (d, J = 9.7 Hz), 127.5, 127.6, 128.6, 136.0, 137.0, 147.8 (d, J = 241.9 Hz), 156.4, 162.0; ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$) δ −134.6 (dd, J = 11.6 Hz, 4.5 Hz); HRMS (ESI) Calcd for $C_{22}H_{18}FN_3O_2$ requires (M^+ + H): 376.1456, Found: 376.1453.

Compound ***1n***. Yield: 357 mg, 92%. A yellow solid. m.p.: 156−157 °C. IR (neat) ν 3231, 3059, 3000, 2903, 2833, 1664, 1602, 1553, 1465, 1231, 1197, 1165, 1041, 1028, 843, 780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.89 (s, 3H), 3.96 (s, 3H), 5.01 (s, 2H), 6.80−6.88 (m, 3H), 7.07−7.11 (m, 2H), 7.17 (dt, J = 7.6 Hz, 0.8 Hz, 1H), 7.26−7.33 (m, 5H), 7.67 (d, J = 7.2 Hz, 1H), 12.88 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 43.1, 55.9, 56.2, 98.6, 106.2, 109.2, 111.9, 118.6, 121.4, 122.5, 125.7, 127.2, 127.5, 127.7, 128.8, 135.9, 136.7, 139.7, 145.5, 150.0, 162.2; HRMS (ESI) Calcd for $C_{23}H_{21}N_3O_3$ requires (M^+ + H): 388.1656, Found: 388.1655.

Compound ***1o***. Yield: 273 mg, 30%. A yellow solid. m.p.: 177−179 °C. IR (neat) ν 3000, 2935, 1768, 1595, 1571, 1514, 1498, 1466, 1415, 1164, 1129, 996 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.84 (s, 3H), 3.91 (s, 6H), 5.01 (s, 2H), 6.62 (s, 2H), 6.82 (d, J = 7.6 Hz, 1H), 7.09 (t, J = 7.2 Hz, 1H), 7.19 (dt, J = 7.6 Hz, 1.2 Hz, 1H), 7.26−7.36 (m, 5H), 7.68 (d, J = 7.2 Hz, 1H), 12.85 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 43.2, 56.1, 61.1, 91.7, 109.3, 118.9, 121.3, 122.6, 126.4, 127.3, 127.8, 127.9, 128.9, 134.1, 135.7, 138.8, 140.0, 154.1, 162.3; HRMS (ESI) Calcd for $C_{24}H_{23}N_3O_4$ requires (M^+ + H): 418.1761, Found: 418.1765.

Compound ***1p***. Yield: 640 mg, 76%. A yellow solid. m.p.: 215−218 °C. IR (neat) ν 2962, 2916, 2858, 1674, 1610, 1597, 1557, 1470, 1374, 1275, 1222, 1098, 1051, 799, 783, 764, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 2.34 (s, 6H), 3.30 (s, 3H), 6.70 (s, 1H), 6.87 (d, J = 7.6 Hz, 1H), 7.00 (s, 2H), 7.11 (t, J = 7.6 Hz, 1H), 7.27 (t, J = 7.6 Hz, 1H), 7.66 (d, J = 7.2 Hz, 1H), 12.71 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.4, 25.4, 108.3, 112.1, 118.7, 121.3, 122.4, 125.1, 126.5, 127.7, 139.2, 140.8, 142.5, 162.2; HRMS (ESI) Calcd for $C_{17}H_{17}N_3O$ requires (M^+ + H): 280.1444, Found: 280.1447.

Compound ***1q***. Yield: 216 mg, 50%. A yellow solid. m.p.: 46−48 °C. IR (neat) ν 3190, 2953, 2913, 2832, 1677, 1541, 1509, 1298, 1209, 1185, 1105, 1037, 1012, 834, 788 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.37 (t, J = 7.2 Hz, 3H), 3.80 (s, 3H), 4.35 (q, J = 7.2 Hz, 2H), 6.90 (d, J = 9.2 Hz, 2H), 7.23 (d, J = 9.2 Hz, 2H), 12.64 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 13.9, 55.3, 61.3, 114.6, 114.9 (q, J = 35.8 Hz), 116.4, 121.6 (q, J = 269.1 Hz), 135.2, 156.9, 161.8; ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$) δ −64.5; HRMS (ESI) Calcd for $C_{12}H_{13}F_3N_2O_3$ requires (M^+ + H): 291.0951, Found: 291.0952.

Procedure for the Synthesis of MBH Adducts. Compounds **2a**, **2d**, and **5b** are known compounds.[16] Compounds **2b** and **2c** were prepared by a previously reported procedure.[16a] Acrylate (3 equiv), 30% of aqueous formaldehyde (1 equiv), and 1,4-diazabicyclo[2.2.2]octane (1 equiv) were stirred in water and 1,4-dioxane at room temperature for about 1 week. The mixture was extracted with ethyl ether. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, ethyl acetate:petroleum ether = 1:2) to give the corresponding products **5**. To compound **5** (1.0 equiv) in CH_2Cl_2 was added dropwise di-*tert*-butyl dicarbonate (1.0 equiv) and 4-dimethylaminopyridine (0.05 equiv) in CH_2Cl_2 at 0 °C. The reaction naturally returned to rt and was stirred overnight. The mixture was washed with saturated aqueous $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, ethyl acetate:petroleum ether = 1:20) to give the corresponding products **2**.

Compound ***2b***. Yield: 710 mg, 69%. A colorless liquid. IR (neat) ν 2981, 2945, 1743, 1456, 1395, 1369, 1302, 1278, 1256, 1154, 1099, 950, 859 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.48 (s, 9H), 4.82 (s, 2H), 5.22 (s, 2H), 5.91 (s, 1H), 6.42 (s, 1H), 7.26−7.37 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 27.5, 64.5, 66.5, 82.2, 127.7, 127.9, 128.1, 128.4, 134.9, 135.4, 152.9, 164.6; HRMS (ESI) Calcd for $C_{16}H_{20}O_5$ requires (M^+ + NH_4): 310.1649, Found: 310.1643.

Compound ***5c***. Yield: 1.80 g, 86%. A colorless liquid. IR (neat) ν 3433, 2959, 2871, 1712, 1634, 1466, 1390, 1367, 1304, 1263, 1155, 1052, 944, 817 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 0.98 (s, 9H), 2.33 (brs, 1H), 3.88 (s, 2H), 4.36 (d, J = 6.4 Hz, 2H), 5.85 (s, 1H), 6.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.4, 31.4, 62.5, 74.1, 125.4, 139.5, 166.3; HRMS (ESI) Calcd for $C_9H_{16}O_3$ requires (M^+ + Na): 195.0992, Found:195.0999.

Compound ***2c***. Yield: 1.58 g, 56%. A colorless liquid. IR (neat) ν 2960, 1744, 1277, 1255, 1155, 1099, 949, 857, 792 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 0.97 (s, 9H), 1.50 (s, 9H), 3.87 (s, 2H), 4.82 (s, 2H), 5.88 (s, 1H), 6.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.5, 27.7, 31.4, 64.8, 74.2, 82.5, 127.4, 135.3, 153.0, 165.1; HRMS (ESI) Calcd for $C_{14}H_{24}O_5$ requires (M^+ + NH_4): 290.1962, Found: 290.1968.

General Procedure for the Asymmetric Allylic Alkylation of Hydrazones. Hydrazone **1** (0.1 mmol), MBH adduct **2a** (0.3 mmol), and $(DHQ)_2AQN$ (0.01 mmol) were stirred in 1 mL of EtOAc at 0 °C for 2 days until TLC showed that hydrazone **1** disappeared completely. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography using a CH_2Cl_2/petroleum ether gradient mixture to give the corresponding products **3**.

Compound ***3a***. Yield: 35 mg, 84%. A deep yellow oil. IR (neat) ν 2978, 2936, 2838, 1714, 1602, 1508, 1492, 1469, 1250, 1145, 1024, 839, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.12 (t, J = 7.2 Hz, 3H), 3.248 (s, 3H), 3.252 (d, J = 13.6 Hz, 1H), 3.69 (d, J = 13.6 Hz, 1H), 3.83 (s, 3H), 3.88−4.01 (m, 2H), 5.58 (s, 1H), 6.07 (s, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 9.2 Hz, 2H), 7.00 (t, J = 7.6 Hz, 1H), 7.28 (t, J = 7.2 Hz, 2H), 7.71 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 14.0, 26.3, 35.0, 55.5, 60.7, 81.1, 108.1, 113.8, 122.2, 124.6, 126.3, 126.8, 128.4, 129.3, 135.4, 143.9, 145.8, 162.1, 166.9, 174.5; HRMS (ESI) Calcd for $C_{24}H_{21}N_3O_4$ requires (M^+ + H): 416.1605, Found: 416.1587. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column [λ = 230 nm; eluent: hexane/isopropanol = 70/30; flow rate: 0.50 mL/min; t_{minor} = 12.26 min, t_{major} = 16.47 min; ee% = 80%; $[\alpha]_D^{20}$ = 63.0 (c 0.50, CH_2Cl_2)].

Compound ***3b***. Yield: 39 mg, 83%. A deep yellow oil. IR (neat) ν 3061, 2932, 2839, 1716, 1602, 1585, 1507, 1487, 1466, 1360, 1251, 1177, 1145, 1027, 838, 751, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.09 (t, J = 7.2 Hz, 3H), 3.35 (d, J = 13.2 Hz, 1H), 3.80 (d, J = 13.2 Hz, 1H), 3.84 (s, 3H), 3.88−4.01 (m, 2H), 4.95 (d, J = 16.0 Hz, 1H), 4.99 (d, J = 16.0 Hz, 1H), 5.63 (s, 1H), 6.08 (s, 1H), 6.64 (d, J = 7.6 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.96 (t, J = 7.6 Hz, 1H), 7.13 (td, J = 7.6 Hz, 0.8 Hz, 1H), 7.25−7.34 (m, 6H), 7.72 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 14.0, 34.9, 43.7, 55.5, 60.7, 81.2, 109.2, 113.9, 122.2, 124.6, 126.3, 127.1, 127.2, 127.4, 128.6, 128.8, 129.2, 135.3, 135.4, 143.1, 145.7, 162.1, 167.0, 174.7; HRMS (ESI) Calcd for $C_{28}H_{27}N_3O_4$ requires (M^+ + Na): 492.1894, Found: 492.1903. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column [λ = 230 nm; eluent: hexane/isopropanol = 90/10; flow rate: 0.50 mL/min; t_{minor} = 57.89 min, t_{major} = 79.73 min; ee% = 85%; $[\alpha]_D^{20}$ = 62.6 (c 0.50, CH_2Cl_2)].

Compound ***3c***. Yield: 37 mg, 70%. A deep yellow oil. IR (neat) ν 3063, 2961, 2918, 1716, 1602, 1585, 1507, 1466, 1360, 1257, 1174, 1145, 1028, 750, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.38 (d, J = 13.6 Hz, 1H), 3.83 (s, 3H), 3.84 (d, J = 13.6 Hz, 1H), 4.89−4.97

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(m, 4H), 5.67 (s, 1H), 6.13 (s, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.89−6.93 (m, 3H), 7.12 (td, J = 7.6 Hz, 0.8 Hz, 1H), 7.16−7.31 (m, 11H), 7.71 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 34.9, 43.8, 55.5, 66.4, 81.2, 109.2, 113.9, 122.2, 124.6, 126.3, 127.0, 127.1, 127.4, 127.96, 128.01, 128.4, 128.6, 129.2, 129.4, 135.0, 135.4, 135.7, 143.1, 145.7, 162.2, 166.8, 174.7; HRMS (ESI) Calcd for $C_{33}H_{29}N_3O_4$ requires (M^+ + H): 532.2231, Found: 532.2236. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column [λ = 230 nm; eluent: hexane/isopropanol = 70/30; flow rate: 0.50 mL/min; t_{minor} = 43.86 min, t_{major} = 53.45 min; ee% = 87%; $[\alpha]_D^{20}$ = 57.4 (c 0.50, CH_2Cl_2)].

Compound ***3d***. Yield: 42 mg, 82%. A deep yellow oil. IR (neat) ν 2957, 2869, 1716, 1602, 1585, 1508, 1487, 1466, 1364, 1251, 1176, 1145, 838, 750, 730, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.80 (s, 9H), 3.33 (d, J = 13.6 Hz, 1H), 3.55 (d, J = 10.4 Hz, 1H), 3.59 (d, J = 10.4 Hz, 1H), 3.83 (s, 3H), 3.84 (d, J = 13.6 Hz, 1H), 4.93 (d, J = 16.0 Hz, 1H), 5.01 (d, J = 16.0 Hz, 1H), 5.65 (s, 1H), 6.09 (s, 1H), 6.65 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 9.2 Hz, 2H), 6.95 (t, J = 7.2 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.23−7.34 (m, 6H), 7.72 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.3, 31.1, 34.8, 43.8, 55.5, 74.0, 81.2, 109.1, 113.9, 122.2, 124.6, 126.3, 127.0, 127.2, 127.4, 128.4, 128.6, 129.2, 135.4, 135.5, 143.1, 145.7, 162.1, 167.1, 174.8; HRMS (ESI) Calcd for $C_{31}H_{33}N_3O_4$ requires (M^+ + H): 512.2544, Found: 512.2548. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column [λ = 230 nm; eluent: hexane/isopropanol = 70/30; flow rate: 0.50 mL/min; t_{minor} = 23.78 min, t_{major} = 16.45 min; ee% = 89%; $[\alpha]_D^{20}$ = 56.2 (c 0.50, CH_2Cl_2)].

Compound ***3e***. Yield: 18 mg, 31%. A deep yellow oil. IR (neat) ν 3064, 2930, 2840, 1714, 1602, 1519, 1508, 1466, 1345, 1250, 1146, 1026, 839, 728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.16 (t, J = 7.2 Hz, 3H), 3.84 (s, 3H), 3.85 (s, 3H) (minor isomer), 4.00−4.14 (m, 2H), 4.80 (d, J = 15.6 Hz, 1H), 4.85 (d, J = 15.6 Hz, 1H), 5.60 (s, 1H) (minor isomer), 5.65 (s, 1H), 5.68 (s, 1H) (minor isomer), 5.72 (s, 1H), 6.34 (s, 1H) (minor isomer), 6.42 (s, 1H), 6.66 (d, J = 8.4 Hz, 1H) (minor isomer), 6.71 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 8.8 Hz, 2H), 7.01 (t, J = 7.6 Hz, 0.8 Hz, 1H), 7.10−7.12 (m, 2H), 7.18−7.24 (m, 4H), 7.41−7.44 (m, 3H), 7.61 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H) (minor isomer), 7.95 (d, J = 9.2 Hz, 2H) (minor isomer), 8.00 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 14.0, 43.8, 49.8, 55.6, 61.4, 82.7, 109.5, 114.0, 122.5, 123.2, 124.7, 125.9, 127.3, 127.4, 127.6, 128.5, 129.7, 131.1, 135.2, 139.0, 142.8, 145.3, 145.6, 147.0, 162.4, 167.2, 173.8; HRMS (ESI) Calcd for $C_{34}H_{30}N_4O_6$ requires (M^+ + H): 591.2238, Found: 591.2246. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column [λ = 230 nm; eluent: hexane/isopropanol = 80/20; flow rate: 0.50 mL/min; t_{minor} = 36.42 min, t_{major} = 27.0 min; ee% = 93%; $[\alpha]_D^{20}$ = −32.0 (c 0.50, CH_2Cl_2)].

Compound ***3f***. Yield: 50 mg, 85%. A deep yellow oil. IR (neat) ν 2957, 2869, 1717, 1603, 1508, 1488, 1466, 1363, 1296, 1252, 1175, 1146, 1012, 838, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.81 (s, 9H), 3.34 (d, J = 13.2 Hz, 1H), 3.55 (d, J = 10.4 Hz, 1H), 3.59 (d, J = 10.4 Hz, 1H), 3.82 (d, J = 13.2 Hz, 1H), 3.84 (s, 3H), 4.88 (d, J = 16.0 Hz, 1H), 4.93 (d, J = 16.0 Hz, 1H), 5.65 (s, 1H), 6.09 (s, 1H), 6.61 (d, J = 7.6 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.97 (t, J = 7.6 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 6.8 Hz, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.3, 31.1, 34.8, 43.2, 55.5, 74.0, 81.1, 108.9, 113.9, 121.4, 122.4, 124.6, 126.4, 127.0, 128.4, 129.0, 129.2, 131.7, 134.5, 135.4, 142.7, 145.7, 162.2, 167.0, 174.7; HRMS (ESI) Calcd for $C_{31}H_{32}BrN_3O_4$ requires (M^+ + H): 590.1649, Found: 590.1673. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column [λ = 254 nm; eluent: hexane/isopropanol = 70/30; flow rate: 0.70 mL/min; t_{minor} = 11.63 min, t_{major} = 16.49 min; ee% = 90%; $[\alpha]_D^{20}$ = 49.1 (c 0.50, CH_2Cl_2)].

Compound ***3g***. Yield: 38 mg, 82%. A deep yellow oil. IR (neat) ν 2957, 2869, 2839, 1710, 1603, 1585, 1505, 1488, 1466, 1360, 1178, 1029, 989, 838, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.83 (s, 9H), 3.28 (d, J = 13.6 Hz, 1H), 3.55 (d, J = 10.8 Hz, 1H), 3.58 (d, J = 10.8 Hz, 1H), 3.78 (d, J = 13.6 Hz, 1H), 3.83 (s, 3H), 4.28 (dd, J = 17.2 Hz, 4.8 Hz, 1H), 4.50 (dd, J = 17.2 Hz, 4.8 Hz, 1H), 5.19−5.27 (m,2H), 5.64(s, 1H), 5.78−5.87 (m,1H), 6.09 (s, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 9.2 Hz, 2H), 6.98 (t, J = 7.6 Hz, 1H), 7.22 (dt, J = 7.6 Hz, 0.8 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.4, 31.2, 34.9, 42.3, 55.5, 74.0, 81.1, 109.0, 113.8, 117.3, 122.2, 124.6, 126.4, 126.9, 128.3, 129.2, 131.1, 135.4, 143.2, 145.8, 162.1, 167.0, 174.3; HRMS (ESI) Calcd for $C_{27}H_{31}N_3O_4$ requires (M^+ + H): 462.2387, Found: 462.2396. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column [λ = 230 nm; eluent: hexane/isopropanol = 70/30; flow rate: 0.50 mL/min; t_{minor} = 10.26 min, t_{major} = 11.77 min; ee% = 86%; $[\alpha]_D^{20}$ = 50.0 (c 0.50, CH_2Cl_2)].

Compound ***3h***. Yield: 42 mg, 75%. A deep yellow oil. IR (neat) ν 2957, 2869, 1717, 1602, 1508, 1487, 1466, 1029, 994, 838, 812, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.78 (s, 9H), 3.37 (d, J = 13.6 Hz, 1H), 3.55 (d, J = 10.4 Hz, 1H), 3.59 (d, J = 10.4 Hz, 1H), 3.83 (s, 3H), 3.87 (d, J = 13.6 Hz, 1H), 5.07 (d, J = 15.6 Hz, 1H), 5.19 (d, J = 15.6 Hz, 1H), 5.70 (s, 1H), 6.13 (s, 1H), 6.68 (d, J = 7.6 Hz, 1H), 6.91−6.96 (m, 3H), 7.09 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.43−7.47 (m, 3H), 7.73−7.81 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.3, 31.1, 34.8, 44.0, 55.5, 74.0, 81.3, 109.2, 113.9, 122.2, 124.6, 125.3, 125.9, 126.0, 126.2, 126.3, 127.0, 127.6, 127.7, 128.50, 128.53, 129.3, 132.7, 132.9, 133.2, 135.5, 143.1, 145.8, 162.2, 167.1, 174.8; HRMS (ESI) Calcd for $C_{35}H_{35}N_3O_4$ requires (M^+ + H): 562.2700, Found: 562.2710. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column [λ = 230 nm; eluent: hexane/isopropanol = 70/30; flow rate: 0.50 mL/min; t_{minor} = 15.64 min, t_{major} = 20.42 min; ee% = 91%; $[\alpha]_D^{20}$ = 28.8 (c 0.50, CH_2Cl_2)].

Compound ***3i***. Yield: 42 mg, 80%. A deep yellow oil. IR (neat) ν 2956, 2925, 2855, 1721, 1603, 1508, 1497, 1254, 1168, 1146, 838, 808 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.82 (s, 9H), 2.24 (s, 3H), 3.32 (d, J = 13.6 Hz, 1H), 3.54 (d, J = 10.4 Hz, 1H), 3.65 (d, J = 10.4 Hz, 1H), 3.83 (d, J = 13.6 Hz, 1H), 3.84 (s, 3H), 4.93 (d, J = 16.0 Hz, 1H), 4.98 (d, J = 16.0 Hz, 1H), 5.63 (s, 1H), 6.08 (s, 1H), 6.54 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 8.8 Hz, 3H), 7.12 (s, 1H), 7.22−7.33 (m, 5H), 7.72 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.0, 26.4, 31.2, 34.6, 43.8, 55.5, 74.0, 81.3, 108.9, 113.9, 124.6, 126.9, 127.1, 127.2, 127.4, 128.3, 128.5, 129.5, 131.7, 135.5, 135.6, 140.7, 145.8, 162.1, 167.2, 174.7; HRMS (ESI) Calcd for $C_{32}H_{35}N_3O_4$ requires (M^+ + H): 526.2700, Found: 526.2707. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column [λ = 230 nm; eluent: hexane/isopropanol = 90/10; flow rate: 0.50 mL/min; t_{minor} = 17.67 min, t_{major} = 16.66 min; ee% = 90%; $[\alpha]_D^{20}$ = 24.1 (c 0.50, CH_2Cl_2)].

Compound ***3j***. Yield: 48 mg, 84%. A deep yellow oil. IR (neat) ν 2957, 2924, 2854, 1724, 1604, 1508, 1464, 1258, 1175, 1147, 1096, 1029, 804 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.85 (s, 9H), 3.34 (d, J = 14.0 Hz, 1H), 3.56 (d, J = 10.8 Hz, 1H), 3.74 (d, J = 10.8 Hz, 1H), 3.81 (d, J = 14.0 Hz, 1H), 3.85 (s, 3H), 4.93 (d, J = 16.0 Hz, 1H), 4.98 (d, J = 16.0 Hz, 1H), 5.66 (s, 1H), 6.11 (s, 1H), 6.55 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 7.09 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.24−7.34 (m, 6H), 7.73 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.3, 31.2, 34.9, 43.9, 55.5, 74.1, 81.1, 110.1, 114.0, 124.7, 126.8, 127.1, 127.6, 128.6, 128.7, 128.8, 129.2, 135.0, 135.1, 141.6, 145.6, 162.4, 166.9, 174.4; HRMS (ESI) Calcd for $C_{31}H_{32}ClN_3O_4$ requires (M^+ + Na): 568.1974, Found: 568.1983. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column [λ = 230 nm; eluent: hexane/isopropanol = 90/10; flow rate: 0.50 mL/min; t_{minor} = 26.46 min, t_{major} = 29.92 min; ee% = 77%; $[\alpha]_D^{20}$ = −6.7 (c 0.50, CH_2Cl_2)].

Compound ***3k***. Yield: 49 mg, 91%. A deep yellow oil. IR (neat) ν 2957, 2837, 1713, 1601, 1507, 1494, 1435, 1252, 1179, 1144, 1026, 838, 810, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.81 (s, 9H), 3.33 (d, J = 13.6 Hz, 1H), 3.57 (d, J = 10.8 Hz, 1H), 3.65 (d, J = 10.8 Hz, 1H), 3.71 (s, 3H), 3.82 (d, J = 13.6 Hz, 1H), 3.84 (s, 3H), 4.92 (d, J = 16.0 Hz, 1H), 4.98 (d, J = 16.0 Hz, 1H), 5.65 (s, 1H), 6.10 (d, J = 0.8 Hz, 1H), 6.54 (d, J = 8.4 Hz, 1H), 6.65 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 6.92 (d, J = 9.2 Hz, 2H), 6.95 (d, J = 2.8 Hz, 1H), 7.24−7.33 (m, 5H), 7.72 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.3, 31.2, 34.7, 43.9, 55.5, 55.7, 74.0, 81.5, 109.5, 113.3, 113.9, 114.0, 124.6, 127.2, 127.4, 128.2, 128.4, 128.6, 135.4, 135.5, 136.4, 145.8, 155.5, 162.2, 167.1, 174.5; HRMS (ESI) Calcd for $C_{32}H_{35}N_3O_5$ requires (M^+ + H): 542.2649, Found: 542.2654. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column [λ = 230 nm; eluent: hexane/isopropanol = 90/10; flow rate: 0.50 mL/min; t_{minor} = 53.77 min, t_{major} = 50.38 min; ee% = 90%; $[\alpha]_D^{20}$ = 18.3 (c 0.50, CH_2Cl_2)].

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Compound ***3l***. Yield: 43 mg, 82%. A deep yellow oil. IR (neat) ν 2957, 2869, 1716, 1620, 1602, 1507, 1374, 1251, 1146, 837, 810, 733, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 0.80 (s, 9H), 2.22 (s, 3H), 3.30 (d, J = 13.6 Hz, 1H), 3.54 (d, J = 10.4 Hz, 1H), 3.62 (d, J = 10.4 Hz, 1H), 3.82 (d, J = 13.6 Hz, 1H), 3.83 (s, 3H), 4.91 (d, J = 15.6 Hz, 1H), 4.99 (d, J = 15.6 Hz, 1H), 5.63 (d, J = 0.8 Hz, 1H), 6.07 (d, J = 0.8 Hz, 1H), 6.48 (s, 1H), 6.76 (d, J = 7.6 Hz, 1H), 6.91 (d, J = 9.2 Hz, 2H), 7.19 (d, J = 7.6 Hz, 1H), 7.24−7.34 (m, 5H), 7.71 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.8, 26.3, 31.1, 34.7, 43.7, 55.5, 74.0, 81.1, 109.9, 113.8, 122.9, 124.0, 124.6, 126.1, 127.1, 127.4, 128.3, 128.6, 135.5, 135.6, 139.5, 143.2, 145.8, 162.1, 167.2, 175.1; HRMS (ESI) Calcd for $C_{32}H_{35}N_3O_4$ requires (M^+ + H): 526.2700, Found: 526.2704. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column [λ = 230 nm; eluent: hexane/isopropanol = 90/10; flow rate: 0.50 mL/min; t_{minor} = 32.91 min, t_{major} = 16.42 min; ee% = 92%; $[\alpha]_D^{20}$ = 79.8 (c 0.50, CH_2Cl_2)].

Compound ***3m***. Yield: 38 mg, 64%. A deep yellow oil. IR (neat) ν 2957, 2869, 1716, 1601, 1507, 1484, 1430, 1370, 1252, 1175, 1145, 1029, 839, 730, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 0.81 (s, 9H), 3.31 (d, J = 13.6 Hz, 1H), 3.55 (d, J = 10.8 Hz, 1H), 3.62 (d, J = 10.8 Hz, 1H), 3.81 (d, J = 13.6 Hz, 1H), 3.85 (s, 3H), 4.88 (d, J = 16.0 Hz, 1H), 4.98 (d, J = 16.0 Hz, 1H), 5.66 (s, 1H), 6.08 (s, 1H), 6.79 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 7.09 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.26−7.36 (m, 5H), 7.70 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.3, 31.2, 34.8, 43.9, 55.5, 74.1, 80.9, 112.4, 114.0, 123.1, 124.7, 125.1, 125.8, 127.2, 127.7, 127.9, 128.7, 128.8, 134.9, 135.1, 144.5, 145.6, 162.3, 167.0, 174.6; HRMS (ESI) Calcd for $C_{31}H_{32}BrN_3O_4$ requires (M^+ + H): 590.1649, Found: 590.1672. Enantiomeric excess was determined by HPLC with a Chiralcel IC column [λ = 230 nm; eluent: hexane/isopropanol = 80/20; flow rate: 0.50 mL/min; t_{minor} = 43.20 min, t_{major} = 20.49 min; ee% = 80%; $[\alpha]_D^{20}$ = 64.4 (c 0.50, CH_2Cl_2)].

Compound ***3n***. Yield: 38 mg, 71%. A deep yellow oil. IR (neat) ν 2957, 2869, 1715, 1601, 1507, 1348, 1252, 1146, 1028, 997, 837, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 0.86 (s, 9H), 2.16 (s, 3H), 2.21 (s, 3H), 3.33 (d, J = 14.0 Hz, 1H), 3.57 (d, J = 10.8 Hz, 1H), 3.68 (d, J = 10.8 Hz, 1H), 3.84 (s, 3H), 3.86 (d, J = 14.0 Hz, 1H), 5.17 (d, J = 16.8 Hz, 1H), 5.27 (d, J = 16.8 Hz, 1H), 5.64 (s, 1H), 6.13 (s, 1H), 6.71 (s, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.98 (s, 1H), 7.22−7.33 (m, 5H), 7.73 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 18.5, 20.7, 26.4, 31.2, 34.6, 45.1, 55.5, 74.0, 80.8, 113.8, 119.4, 124.60, 124.63, 125.8, 127.0, 127.9, 128.3, 128.6, 131.7, 133.8, 135.7, 137.5, 138.7, 145.8, 162.1, 167.3, 175.6; HRMS (ESI) Calcd for $C_{33}H_{37}N_3O_4$ requires (M^+ + H): 540.2857, Found: 540.2857. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column [λ = 230 nm; eluent: hexane/isopropanol = 90/10; flow rate: 0.30 mL/min; t_{minor} = 69.03 min, t_{major} = 59.54 min; ee% = 90%; $[\alpha]_D^{20}$ = 99.8 (c 0.50, CH_2Cl_2)].

Compound ***3o***. Yield: 44 mg, 75%. A deep yellow oil. IR (neat) ν 2957, 2927, 1717, 1601, 1507, 1462, 1449, 1345, 1252, 1166, 1146, 1027, 994, 838, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 0.87 (s, 9H), 3.33 (d, J = 13.6 Hz, 1H), 3.59 (d, J = 10.4 Hz, 1H), 3.63 (d, J = 10.4 Hz, 1H), 3.84 (s, 3H), 3.85 (d, J = 13.6 Hz, 1H), 5.38 (d, J = 16.8 Hz, 1H), 5.51 (d, J = 16.8 Hz, 1H), 5.62 (s, 1H), 6.10 (s, 1H), 6.85 (t, J = 8.0 Hz, 1H), 6.92 (d, J = 9.2 Hz, 2H), 7.24−7.33 (m, 7H), 7.71 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.4, 31.2, 34.8, 44.7, 55.5, 74.1, 80.4, 102.2, 113.9, 123.5, 124.7, 125.6, 126.5, 126.9, 128.3, 129.0, 130.2, 134.9, 135.2, 137.3, 140.8, 145.6, 162.3, 167.0, 175.4; HRMS (ESI) Calcd for $C_{31}H_{32}BrN_3O_4$ requires (M^+ + H): 590.1649, Found: 590.1676. Enantiomeric excess was determined by HPLC with a Chiralcel IC column [λ = 230 nm; eluent: hexane/isopropanol = 80/20; flow rate: 0.50 mL/min; t_{minor} = 47.31 min, t_{major} = 20.34 min; ee% = 67%; $[\alpha]_D^{20}$ = 128.8 (c 0.50, CH_2Cl_2)].

Compound ***3p***. Yield: 43 mg, 81%. A deep yellow oil. IR (neat) ν 2957, 2869, 1717, 1628, 1601, 1507, 1473, 1344, 1249, 1187, 1146, 1029, 838, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 0.82 (s, 9H), 3.32 (d, J = 13.6 Hz, 1H), 3.56 (d, J = 10.4 Hz, 1H), 3.60 (d, J = 10.4 Hz, 1H), 3.82 (d, J = 13.6 Hz, 1H), 3.84 (s, 3H), 5.07 (d, J = 15.2 Hz, 1H), 5.13 (d, J = 15.2 Hz, 1H), 5.60 (s, 1H), 6.04 (s, 1H), 6.90−6.94 (m, 4H), 7.10−7.12 (m, 1H), 7.25−7.33 (m, 3H), 7.37−7.39 (m, 2H), 7.70 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.3, 31.2, 34.9, 45.4 (d, J = 15.0 Hz), 55.5, 74.0, 81.1, 113.9, 117.4 (d, J = 59.4 Hz), 122.30, 122.33, 122.9 (d, J = 18.3 Hz), 124.7, 127.4, 127.5, 128.4, 128.8, 129.9, 134.9, 136.8, 145.6, 147.2 (d, J = 291.5 Hz), 162.3, 167.0, 174.5; ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$) δ −133.8 (t, J = 7.2 Hz); HRMS (ESI) Calcd for $C_{31}H_{32}FN_3O_4$ requires (M^+ + Na): 552.2269, Found: 552.2272. Enantiomeric excess was determined by HPLC with a Chiralcel IC column [λ = 230 nm; eluent: hexane/isopropanol = 80/20; flow rate: 0.50 mL/min; t_{minor} = 39.15 min, t_{major} = 19.21 min; ee% = 72%; $[\alpha]_D^{20}$ = 58.1 (c 0.50, CH_2Cl_2)].

Compound ***3q***. Yield: 27 mg, 50%. A deep yellow oil. IR (neat) ν 2956, 2925, 2854, 1721, 1603, 1508, 1497, 1466, 1364, 1147, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 0.80 (s, 9H), 3.33 (d, J = 13.6 Hz, 1H), 3.55 (d, J = 10.4 Hz, 1H), 3.59 (d, J = 10.4 Hz, 1H), 3.85 (d, J = 13.6 Hz, 1H), 3.91 (s, 3H), 3.93 (s, 3H), 4.93 (d, J = 16.0 Hz, 1H), 5.04 (d, J = 16.0 Hz, 1H), 5.65 (s, 1H), 6.08 (s, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.96 (t, J = 7.2 Hz, 1H), 7.14 (dt, J = 8.0 Hz, 1.2 Hz, 1H), 7.24−7.34 (m, 7H), 7.46 (dd, J = 8.4 Hz, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.3, 31.2, 34.9, 43.9, 55.95, 56.05, 74.0, 81.2, 102.0, 109.2, 110.0, 120.5, 122.3, 126.4, 127.0, 127.3, 127.5, 128.4, 128.6, 129.3, 135.4, 135.5, 143.1, 145.7, 149.3, 152.0, 167.1, 174.8; HRMS (ESI) Calcd for $C_{32}H_{35}N_3O_5$ requires (M^+ + H): 542.2649, Found: 542.2659. Enantiomeric excess was determined by HPLC with a Chiralcel IC column [λ = 230 nm; eluent: hexane/isopropanol = 80/20; flow rate: 0.50 mL/min; t_{minor} = 85.82 min, t_{major} = 52.86 min; ee% = 86%; $[\alpha]_D^{20}$ = 67.8 (c 0.50, CH_2Cl_2)].

Compound ***3r***. Yield: 30 mg, 50%. A deep yellow oil. IR (neat) ν 2957, 2870, 1717, 1599, 1496, 1465, 1364, 1220, 1176, 1126, 1001, 847, 751, 732, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 0.80 (s, 9H), 3.33 (d, J = 13.6 Hz, 1H), 3.55 (d, J = 10.4 Hz, 1H), 3.59 (d, J = 10.4 Hz, 1H), 3.87 (d, J = 13.6 Hz, 1H), 3.88 (s, 3H), 3.91 (s, 6H), 4.92 (d, J = 15.6 Hz, 1H), 5.05 (d, J = 15.6 Hz, 1H), 5.65 (s, 1H), 6.08 (s, 1H), 6.68 (d, J = 8.4 Hz, 1H), 6.98 (t, J = 7.6 Hz, 1H), 7.05 (s, 2H), 7.16 (dd, J = 7.2 Hz, 6.8 Hz, 1H), 7.26−7.34 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 26.3, 31.2, 34.7, 43.9, 56.2, 61.0, 74.0, 81.5, 100.3, 109.2, 122.3, 126.4, 126.7, 127.3, 127.5, 128.5, 128.6, 129.4, 135.3, 135.4, 140.7, 143.2, 147.3, 153.3, 167.1, 174.5; HRMS (ESI) Calcd for $C_{33}H_{37}N_3O_6$ requires (M^+ + Na): 594.2575, Found: 594.2583. Enantiomeric excess was determined by HPLC with a Chiralcel PA-2 column [λ = 230 nm; eluent: hexane/isopropanol = 60/40; flow rate: 0.80 mL/min; t_{minor} = 35.86 min, t_{major} = 24.76 min; ee% = 87%; $[\alpha]_D^{20}$ = 68.8 (c 0.50, CH_2Cl_2)].

Compound ***3s***. Yield: 36 mg, 82%. A deep yellow oil. IR (neat) ν 2960, 2843, 1747, 1719, 1603, 1509, 1253, 1144, 1029, 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 0.91 (s, 9H), 1.26 (t, J = 7.2 Hz, 3H), 3.44 (s, 2H), 3.71 (s, 2H), 3.87 (s, 3H), 4.22−4.30 (m, 2H), 5.67 (d, J = 0.8 Hz, 1H), 6.27 (d, J = 1.2 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 13.9, 26.4, 31.3, 31.6, 55.6, 62.2, 74.3, 81.9 (q, J = 23.5 Hz), 114.1, 123.9 (q, J = 283.7 Hz), 125.1, 129.4, 134.6, 145.4, 163.0, 165.4, 166.9; ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$) δ −70.4; HRMS (ESI) Calcd for $C_{21}H_{27}F_3N_2O_5$ requires (M^+ + H): 445.1945, Found: 445.1949. Enantiomeric excess was determined by HPLC with a Chiralcel PC-2 column [λ = 230 nm; eluent: hexane/isopropanol = 24/1; flow rate: 0.50 mL/min; t_{minor} = 15.05 min, t_{major} = 13.44 min; ee% = 68%; $[\alpha]_D^{20}$ = −56.1 (c 0.50, CH_2Cl_2)].

Procedure for the Conversion of Product 3i. Compound **3i** (115 mg, 0.22 mmol), *N*-hydroxybenzimidoyl chloride (51 mg, 0.33 mmol), and Et_3N (33 mg, 0.33 mmol) were stirred in 2 mL of CH_2Cl_2 at rt. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, ethyl acetate:petroleum ether = 1:5) to give the major diastereoisomer of compound **4a** (56 mg, 40%) and the minor diastereoisomer of compound **4a** (28 mg, 20%).

Major Diastereoisomer of Compound ***4a***. Yield: 56 mg, 40%. A yellow foam. m.p.: 88−90 °C. IR (neat) ν 2957, 2924, 2853, 1717, 1602, 1507, 1496, 1360, 1253, 1172, 1144, 1028, 838, 807, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 0.89 (s, 9H), 2.21 (s, 3H), 3.40 (d, J = 14.4 Hz, 1H), 3.47 (d, J = 14.4 Hz, 1H), 3.50 (d, J = 17.2 Hz, 1H), 3.54 (d, J = 10.8 Hz, 1H), 3.71 (d, J = 10.8 Hz, 1H), 3.80 (d, J = 17.2 Hz, 1H), 3.83 (s, 3H), 4.76 (d, J = 16.0 Hz, 1H), 5.20 (d, J = 16.0 Hz, 1H), 6.57 (d, J = 7.6 Hz, 1H), 6.87−6.90 (m, 3H), 7.09 (s, 1H), 7.27−7.37 (m, 6H), 7.43 (d, J = 7.2 Hz, 2H), 7.47−7.49 (m, 2H), 7.65 (d, J = 8.8 Hz, 2H);

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^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.0, 26.3, 31.4, 39.1, 41.9, 44.0, 55.5, 74.8, 78.8, 87.4, 109.3, 113.9, 124.6, 125.9, 126.7, 127.4, 127.5, 128.1, 128.5, 128.6, 128.9, 129.8, 130.1, 131.9, 135.6, 140.9, 145.5, 157.1, 162.3, 170.3, 174.7; HRMS (ESI) Calcd for $C_{39}H_{40}N_4O_5$ requires (M^+ + Na): 667.2891, Found: 667.2891. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column [λ = 230 nm; eluent: hexane/isopropanol = 80/20; flow rate: 0.60 mL/min; t_{minor} = 35.22 min, t_{major} = 30.00 min; ee% = 90%; $[\alpha]_D^{20}$ = 40.0 (*c* 1.00, CH_2Cl_2)].

Minor Diastereoisomer of Compound ***4a***. Yield: 28 mg, 20%. A yellow foam. m.p.: 82−85 °C. IR (neat) ν 2958, 2923, 2853, 1724, 1602, 1585, 1507, 1497, 1360, 1254, 1174, 1146, 1028, 908, 806, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.86 (s, 9H), 2.27 (s, 3H), 3.26 (d, *J* = 14.4 Hz, 1H), 3.51 (d, *J* = 10.0 Hz, 1H), 3.58 (d, *J* = 14.4 Hz, 1H), 3.66 (d, *J* = 17.2 Hz, 1H), 3.71 (d, *J* = 17.2 Hz, 1H), 3.74 (d, *J* = 10.0 Hz, 1H), 3.84 (s, 3H), 4.73 (d, *J* = 16.0 Hz, 1H), 5.14 (d, *J* = 16.0 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 6.90−6.94 (m, 3H), 7.18 (s, 1H), 7.24−7.43 (m, 8H), 7.58−7.60 (m, 2H), 7.66 (d, *J* = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 21.0, 26.3, 31.3, 40.1, 44.0, 45.6, 55.5, 75.1, 78.9, 87.1, 109.3, 113.9, 124.8, 126.7, 126.8, 127.27, 127.28, 127.7, 128.57, 128.61, 128.9, 129.8, 130.2, 131.6, 135.7, 141.2, 145.6, 155.9, 162.2, 171.6, 175.2; HRMS (ESI) Calcd for $C_{39}H_{40}N_4O_5$ requires (M^+ + Na): 667.2891, Found: 667.2895. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column [λ = 230 nm; eluent: hexane/isopropanol = 80/20; flow rate: 0.50 mL/min; t_{minor} = 17.49 min, t_{major} = 19.72 min; ee% = 90%; $[\alpha]_D^{20}$ = 31.3 (*c* 1.00, CH_2Cl_2)].

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectroscopic and analytic data of the compounds **1a**−**1q**, **3a**−**3s**, **2b**−**2c**, and **4a** as well as X-ray crystal data of **1i** are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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