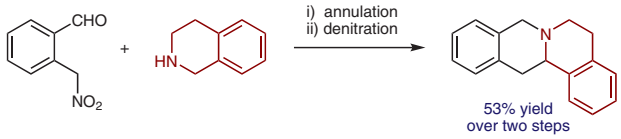
Traceless Redox-Annulations of Alicyclic Amines

Dillon R. L. Rickertsen[◊a]
Longle Ma[◊b]
Anirudra Paul[a]
Khalil A. Abboud[c]
Daniel Seidel*[a]

[a] Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611, USA
seidel@chem.ufl.edu
[b] Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854, USA
[c] Center for X-ray Crystallography, Department of Chemistry, University of Florida, Gainesville, Florida 32611, USA

[◊] These authors contributed equally

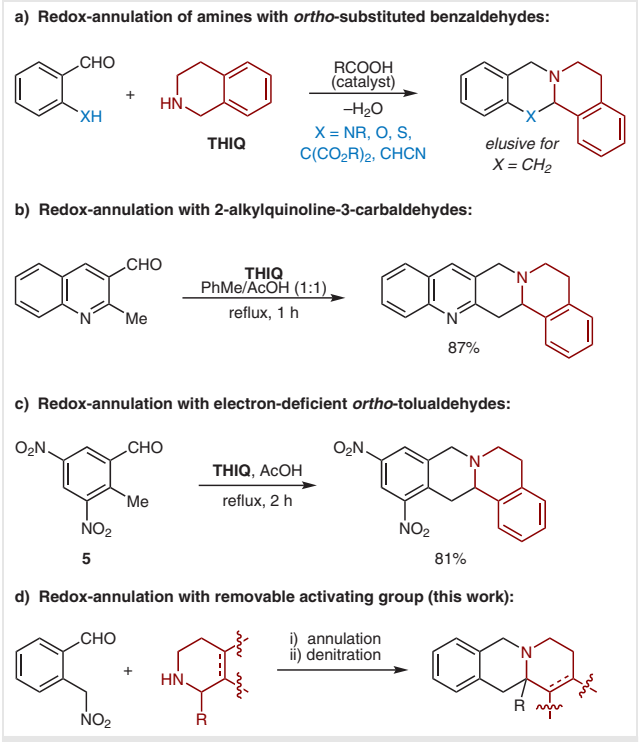


Received: 12.11.2020
Accepted after revision: 04.12.2020
Published online: 16.12.2020
DOI: 10.1055/s-0040-1706004; Art ID: so-2020-d0042-op

Abstract Amines such as 1,2,3,4-tetrahydroisoquinoline undergo redox-neutral annulations with *ortho*-(nitromethyl)benzaldehyde. Benzoic acid acts as a promoter in these reactions, which involve concurrent amine α-C–H bond and N–H bond functionalization. Subsequent removal of the nitro group provides access to tetrahydroprotoberberines not accessible via typical redox-annulations. Also reported are decarboxylative annulations of *ortho*-(nitromethyl)benzaldehyde with proline and pipecolic acid.

Key words C–H bond functionalization, redox-neutral, redox-annulation, denitration, decarboxylative annulation

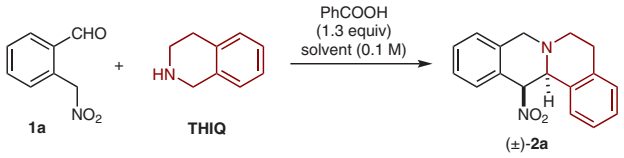
New methods for the C–H bond functionalization of amines and their derivatives continue to be developed at a rapid pace.[1,2] However, few approaches have emerged that are compatible with unprotected secondary amines while at the same time enabling α-C–H bond functionalization with concurrent C–N bond formation.[1m,o] Particularly attractive in this regard are redox-annulations of cyclic amines, which allow for the rapid formation of polycyclic amines from simple starting materials (Scheme 1). Water is the only byproduct in these reactions. Examples of this type of transformation include condensations of amines with *ortho*-aminobenzaldehydes to provide aminals (Scheme 1a, X = NR),[3] and related, carboxylic-acid-catalyzed transformations involving α-C–O and α-C–S bond formation.[4] Redox-annulations that achieve α-C–C bond formation with *ortho*-tolualdehyde derivatives require the presence of at least one electron-withdrawing group on the *ortho*-methyl group.[5] In addition, activation of an *ortho*-methyl group has been achieved with heteroaryl substrates (Scheme 1b)[6] and highly electron-deficient *o*-tolualdehydes (Scheme 1c).[7–10] Here, we report the first redox-annulations of amines with *ortho*-(nitromethyl)benzaldehydes (Scheme 1d). In these reactions, the nitro group acts as a traceless activator as it can be removed in a subsequent step. The overall strategy represents an attractive new pathway to members and analogues of the tetrahydroprotoberberine family of natural products.[11]



Scheme 1 Examples of amine redox-annulations and present work

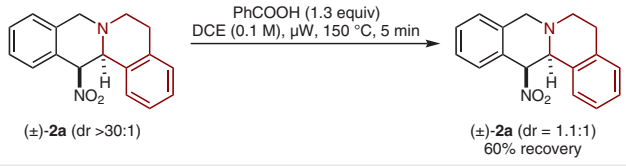
ortho-(Nitromethyl)benzaldehyde (**1a**)[12] and 1,2,3,4-tetrahydroisoquinoline (THIQ) were selected as the model substrates in the initial evaluation of the proposed redox-annulation. Key optimization experiments are summarized in Table 1. While conditions used in other redox-annulations (reflux in toluene with benzoic acid as a promoter) provided the target product **2a** in substantial amounts, improved results were obtained under microwave conditions. The maximum yield of 76% was achieved in a reaction that was performed in dichloroethane solvent at 150 °C for 5 min (entry 4). The reactions exhibited low but variable diastereoselectivities. We suspected that the two diastereomers of **2a** may interconvert under the reaction conditions by means of a retro-nitro-Mannich/nitro-Mannich sequence with little thermodynamic preference for either diastereomer. Indeed, while accompanied by some decomposition, exposure of diastereomerically pure **2a** to the reaction conditions led to the recovery of **2a** as a nearly 1:1 mixture of diastereomers (Scheme 2).

Table 1 Reaction Development[a]



Entry	THIQ (equiv)	Solvent	T (°C)	Time (min)	Yield (%)	dr
1	1.3	PhMe	reflux	60	56	1:1
2	1.3	DCE	reflux	60	58	1.3:1
3[b]	1.3	PhMe	150	5	61	1.1:1
4[b]	1.3	DCE	150	5	76	1:1
5[b]	2.0	DCE	150	5	61	1.1:1
6[b]	1.3	DCE	100	5	71	1.4:1
7[b]	1.3	DCE	100	15	75	1.2:1

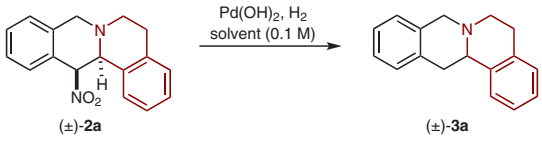
[a] Reactions were performed on a 0.25 mmol scale. All yields correspond to isolated yields. The dr was determined by ^{1}H NMR analysis after purification.
[b] Performed under microwave irradiation.



Scheme 2 Equilibration experiment

We then turned our attention to the denitration step (Table 2). Following some optimization, conditions similar to those developed by Carreira and co-workers were found to be efficient in removing the nitro group,[13] providing product **3a** in up to 70% yield (entry 6).

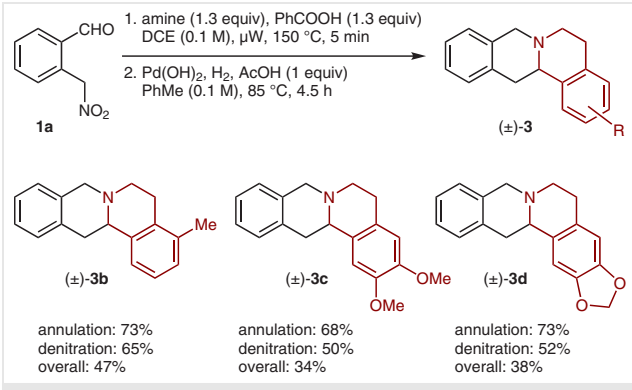
Table 2 Optimization of the Denitration Step[a]



Entry	Solvent	H_2 (atm)	Additive (equiv)	T (°C)	Time (h)	Yield (%)
1	EtOH	10.2	–	85	4.5 h	57
2	EtOH	10.2	–	rt	4.5 h	trace
3[b]	EtOH	1	–	85	4.5 h	trace
4[b]	EtOH	10.2	–	85	24 h	54
5	PhMe	10.2	–	85	4.5 h	54
6	PhMe	10.2	AcOH (1.0)	85	4.5 h	70
7	PhMe	10.2	AcOH (2.0)	85	4.5 h	26

[a] Reactions were performed on a 0.25 mmol scale. All yields correspond to isolated yields.
[b] Reaction was performed on a 0.15 mmol scale.

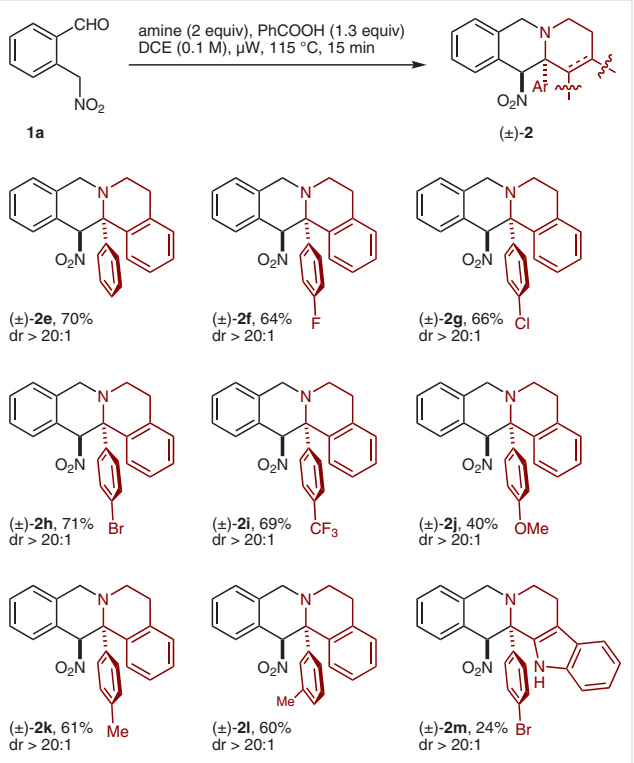
The annulation/denitration sequence was applied to a number of substituted tetrahydroisoquinolines (Scheme 3). Moderate to good yields were achieved in the individual steps with acceptable overall yields. Gratifyingly, 1-aryl tetrahydroisoquinolines with electronically diverse substituents also readily participated in redox-annulations to provide the corresponding sterically congested products as essentially single diastereomers in reasonable yields (Scheme 4). A related tetrahydro-β-carboline also participated in the reaction but provided the annulation product in significantly lower yield.



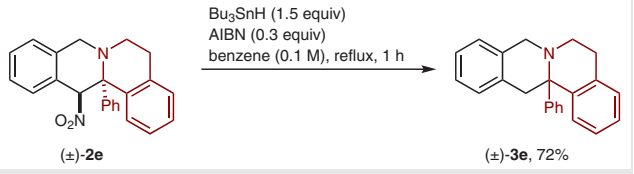
Scheme 3 Evaluation of substituted tetrahydroisoquinolines

Unfortunately, the products shown in Scheme 4 were not amenable to denitration under the reaction conditions employed above. However, removal of the nitro group was readily achieved with tributyltin hydride (Scheme 5).[14]

Despite significant experimentation, less activated amines such as pyrrolidine and piperidine did not participate in redox-annulations with *ortho*-(nitromethyl)benzaldehyde (**1a**). However, as has been shown in a number of



Scheme 4 Formation of sterically congested tetrahydroprotoberberine analogues

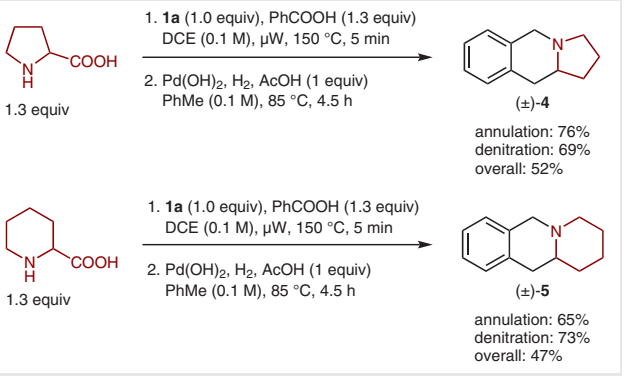


Scheme 5 Denitration of a sterically congested annulation product

related reactions,[15,16] the corresponding decarboxylative reactions in which proline and pipecolic acid are used in place of pyrrolidine and piperidine provided annulation products in good yields (Scheme 6). Denitration under Carreira conditions was also successful.

In conclusion, we have achieved the first traceless redox-annulations of amines using a substrate with an activating nitro group that can be subsequently removed. This strategy provides access to products that are not readily available by using conventional synthetic approaches.

Starting materials, reagents, and solvents were purchased from commercial sources and used as received unless stated otherwise. 1,2,3,4-Tetrahydroisoquinoline was freshly distilled prior to use. L-Proline, L/D-pipecolic acid, 2,2′-(diazene-1,2-diyl)bis(2-methylpropanenitrile), and tributyltin hydride were used as received. HPLC grade 1,2-dichloroethane (DCE) was purchased from Sigma–Aldrich and was used without further purification. Purification of reaction products was carried out by flash column chromatography using Sorbent Technologies Standard Grade silica gel (60 Å, 230–400 mesh). Analytical thin-layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F254 plates. Visualization was accomplished with UV light and Dragendorff–Munier stains, followed by heating. ^{1}H NMR spectra were recorded with a Bruker 400 MHz or Bruker 600 MHz instrument and chemical shifts are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex, br = broad; coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C NMR) spectra were recorded with a Bruker 400 MHz or Bruker 600 MHz instrument and chemical shifts are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 77.16 ppm). Diastereomeric ratios of the products were determined by ^{1}H NMR analysis of the purified products. Accurate mass data (ESI) was obtained with Agilent 1260 Infinity II LC/MSD using MassWorks 5.0 from CERNO bioscience.[17] Reactions under microwave irradiation were conducted with a Biotage Initiator+, SW version: 4.1.4 build 11991.



Scheme 6 Decarboxylative annulation/denitration

1-Phenyl-1,2,3,4-tetrahydroisoquinoline,[18a] 1-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline,[18b] 1-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline,[18b] 1-(4-bromophenyl)-1,2,3,4-tetrahydroisoquinoline,[18c] 1-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline,[18d] 1-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline,[18b] 1-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinoline,[18b] 1-(*m*-tolyl)-1,2,3,4-tetrahydroisoquinoline,[18e] 1-(4-bromophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole,[18f] 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline,[18g] 5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline,[18h] 5-methyl-1,2,3,4-tetrahydroisoquinoline,[18i] and 2-(nitromethyl)benzaldehyde[18j] were prepared according to reported procedures and their published characterization data matched our own in all respects.

13-Nitro-5,8,13,13a-tetrahydro-6*H*-isoquinolino[3,2-*a*]isoquinoline (2a)

2-(Nitromethyl)benzaldehyde (**1a**) (41.3 mg, 0.25 mmol, 1 equiv), 1,2,3,4-tetrahydroisoquinoline (41.5 μL, 0.33 mmol, 1.3 equiv), and benzoic acid (40.3 mg, 0.33 mmol, 1.3 equiv) were added to a microwave vial charged with a stir bar. Dichloroethane (2.5 mL) was added and the microwave vial was sealed. The vial was stirred until complete dissolution of the solids and then placed in the microwave, followed by heating for 5 minutes at 150 °C with the instrument set to low absorption. The reaction mixture was neutralized with sat. $NaHCO_3$ (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed

under reduced pressure and the crude residue was purified by silica gel chromatography using hexanes containing EtOAc (0–15%), yielding **2a** as a mixture of diastereomers with a dr of 1:1.

Yield: 76% (53.3 mg); brown oil; R_f = 0.16 (hexanes/EtOAc 90:10 v/v).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.47 (dd, *J* = 7.7, 1.3 Hz, 0.5 H), 7.43–7.35 (comp, 1 H), 7.34–7.10 (comp, 6 H), 7.04–6.96 (m, 0.5 H), 6.17 (d, *J* = 3.3 Hz, 0.5 H), 5.90 (d, *J* = 8.6 Hz, 0.5 H), 4.76 (d, *J* = 8.6 Hz, 0.5 H), 4.38 (dd, *J* = 15.8, 1.3 Hz, 0.5 H), 4.26 (d, *J* = 15.3 Hz, 0.5 H), 4.20 (d, *J* = 3.3 Hz, 0.5 H), 3.96 (d, *J* = 15.8 Hz, 0.5 H), 3.79 (d, *J* = 15.3 Hz, 0.5 H), 3.33–3.19 (comp, 1 H), 3.08–2.96 (comp, 2 H), 2.92–2.85 (m, 0.5 H), 2.77–2.69 (m, 0.5 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 136.4, 136.4, 134.7, 134.7, 134.1, 130.0, 129.6, 129.6, 129.5, 129.3, 128.6, 127.8, 127.7, 127.4, 127.3, 127.2, 127.0, 127.0, 126.9, 126.6, 126.3, 126.0, 125.7, 90.1, 87.0, 63.3, 62.1, 57.8, 56.7, 50.8, 48.0, 29.3, 29.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}N_2O_2$: 281.1285; found: 281.1655. Spectral Accuracy: 98.8%.

General Procedure A

2-(Nitromethyl)benzaldehyde (**1a**) (82.6 mg, 0.5 mmol, 1 equiv), amine (0.65 mmol, 1.3 equiv), and benzoic acid (79.4 mg, 0.65 mmol, 1.3 equiv) were added to a microwave vial charged with a stir bar. Dichloroethane (5.0 mL) was added and the microwave vial was sealed. The vial was stirred until complete dissolution of the solids and placed in the microwave, followed by heating for 5 minutes at 150 °C with the instrument set to low absorption. The reaction mixture was neutralized with sat. $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude residue was purified by silica gel chromatography. The product was used directly in the next step.

General Procedure B

The annulation product obtained according to General Procedure A was added to a reaction vial charged with acetic acid (1.0 equiv) and a stir bar. Toluene (5.0 mL) was added followed by 20% wt. $Pd(OH)_2/C$ (66.7 mg). The reaction vial was placed in a bomb and back filled with H_2 (5×). H_2 was added to the bomb until the internal pressure reached 150 PSI. The reaction mixture was heated at 85 °C for 4.5 hours. The reaction mixture was then allowed to cool to r.t., followed by removal of the solvent under reduced pressure. The crude mixture was purified by silica gel chromatography followed by treatment with sat. $NaHCO_3$ (15 mL) and extraction with EtOAc (3 × 15 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure yielding the final product.

General Procedure C

2-(Nitromethyl)benzaldehyde (**1a**) (41.3 mg, 0.25 mmol, 1 equiv), amine (0.50 mmol, 2.0 equiv), and benzoic acid (40.3 mg, 0.33 mmol, 1.3 equiv) were added to a microwave vial charged with a stir bar. Dichloroethane (2.5 mL) was added and the microwave vial was sealed. The vial was stirred until complete dissolution of the solids and placed in the microwave, followed by heating for 15 minutes at 115 °C with the microwave set to low absorption. The reaction mixture was neutralized with sat. $NaHCO_3$ (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude residue was purified by silica gel chromatography.

13-Nitro-13a-phenyl-5,8,13,13a-tetrahydro-6*H*-isoquinolino-[3,2-*a*]isoquinoline (2e)

By following General Procedure C, compound (±)-**2e** was obtained from aldehyde **1a** (41.3 mg, 0.25 mmol, 1equiv) and 1-phenyl-1,2,3,4-tetrahydroisoquinoline (104.g mg, 0.5 mmol, 2.0 equiv). Hexanes containing EtOAc (0–10%) was used as the eluent for silica gel chromatography.

Yield: 70% (62.4 mg) and a > 20:1 diastereomeric ratio; white solid; R_f = 0.13 (hexanes/EtOAc 95:5 v/v).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.58 (dd, *J* = 7.6, 1.5 Hz, 1 H), 7.39–7.34 (comp, 2 H), 7.25–7.16 (comp, 3 H), 7.15–7.09 (comp, 4 H), 7.03 (dd, *J* = 8.0, 1.2 Hz, 1 H), 6.83–6.78 (comp, 2 H), 6.59 (s, 1 H), 3.93 (d, *J* = 16.3 Hz, 1 H), 3.39–3.26 (comp, 3 H), 3.07–3.00 (m, 1 H), 2.91–2.84 (m, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.6, 136.9, 136.8, 136.0, 129.6, 129.2, 128.9, 128.5, 128.4, 128.3, 127.8, 127.6, 127.5, 127.3, 126.8, 126.2, 91.5, 65.8, 52.3, 45.6, 29.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{21}N_2O_2$: 357.1598; found: 357.1589. Spectral Accuracy: 97.3%.

13a-(4-Fluorophenyl)-13-nitro-5,8,13,13a-tetrahydro-6*H*-isoquinolino[3,2-*a*]isoquinoline (2f)

By following General Procedure C, compound (±)-**2f** was obtained from aldehyde **1a** (41.3 mg, 0.25 mmol, 1 equiv) and 1-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (113.g mg, 0.5 mmol, 2.0 equiv). Hexanes containing EtOAc (0–10%) was used as the eluent for silica gel chromatography.

Yield: 64% (59.9 mg) and a > 20:1 diastereomeric ratio; off-white solid; R_f = 0.30 (hexanes/EtOAc 90:10 v/v).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.56 (dd, *J* = 7.7, 1.4 Hz, 1 H), 7.38 (app td, *J* = 7.5, 1.5 Hz, 1 H), 7.34 (app td, *J* = 7.5, 1.4 Hz, 1 H), 7.23–7.11 (comp, 4 H), 7.00 (dd, *J* = 7.9, 1.3 Hz, 1 H), 6.82 (app t, *J* = 8.7 Hz, 2 H), 6.79–6.74 (comp, 2 H), 6.53 (s, 1 H), 3.94 (d, *J* = 16.3 Hz, 1 H), 3.37–3.27 (comp, 2 H), 3.21 (app td, *J* = 11.6, 3.3 Hz, 1 H), 3.03 (ddd, *J* = 11.8, 6.0, 1.9 Hz, 1 H), 2.85 (app dt, *J* = 15.6, 2.7 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.8 (d, $J_{C–F}$ = 247.8 Hz), 136.7, 136.0, 135.4 (d, $J_{C–F}$ = 3.2 Hz), 130.2 (d, $J_{C–F}$ = 7.8 Hz), 129.8, 129.0, 128.9, 128.4, 128.2, 127.6, 127.5, 126.9, 126.3, 114.7 (d, $J_{C–F}$ = 21.0 Hz), 91.5, 65.4, 52.2, 45.5, 29.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{20}FN_2O_2$: 375.1503; found: 375.1379. Spectral Accuracy: 97.4%.

13a-(4-Chlorophenyl)-13-nitro-5,8,13,13a-tetrahydro-6*H*-isoquinolino[3,2-*a*]isoquinoline (2g)

By following General Procedure C, compound (±)-**2g** was obtained from aldehyde **1a** (41.3 mg, 0.25 mmol, 1 equiv) and 1-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline (121.9 mg, 0.5 mmol, 2.0 equiv). Hexanes containing EtOAc (0–15%) was used as the eluent for silica gel chromatography.

Yield: 66% (64.5 mg) and > 20:1 diastereomeric ratio; off-white solid; R_f = 0.52 (hexanes/EtOAc 80:20 v/v).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.56 (dd, *J* = 7.6, 1.4 Hz, 1 H), 7.39–7.33 (comp, 2 H), 7.29–7.11 (comp, 6 H), 7.06–6.96 (m, 1 H), 6.76–6.71 (comp, 2 H), 6.52 (s, 1 H), 3.95 (d, *J* = 16.3 Hz, 1 H), 3.38–3.27 (comp, 2 H), 3.22 (app td, *J* = 11.6, 3.2 Hz, 1 H), 3.05 (dd, *J* = 12.0, 5.8 Hz, 1 H), 2.85 (d, *J* = 15.5 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 138.1, 136.6, 136.4, 136.0, 133.6, 129.8, 129.8, 129.0, 128.8, 128.4, 128.2, 128.0, 127.6, 127.6, 126.8, 126.3, 91.3, 65.5, 52.2, 45.6, 29.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{20}ClN_2O_2$: 391.1208; found: 391.1429. Spectral Accuracy: 97.2%.

13a-(4-Bromophenyl)-13-nitro-5,8,13,13a-tetrahydro-6*H*-isoquinolino[3,2-*a*]isoquinoline (2h)

By following General Procedure C, compound (±)-**2h** was obtained from aldehyde **1a** (41.3 mg, 0.25 mmol, 1 equiv) and 1-(4-bromophenyl)-1,2,3,4-tetrahydroisoquinoline (144.1 mg, 0.5 mmol, 2.0 equiv). Hexanes containing EtOAc (0–10%) was used as the eluent for silica gel chromatography.

Yield: 71% (77.3 mg) and > 20:1 diastereomeric ratio; off-white solid; R_f = 0.27 (hexanes/EtOAc 90:10 v/v).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.58 (dd, *J* = 7.7, 1.4 Hz, 1 H), 7.42–7.35 (comp, 2 H), 7.33–7.25 (comp, 2 H), 7.25–7.08 (comp, 4 H), 7.08–7.00 (m, 1 H), 6.72–6.67 (comp, 2 H), 6.54 (s, 1 H), 3.97 (d, *J* = 16.3 Hz, 1 H), 3.41–3.29 (comp, 2 H), 3.25 (app td, *J* = 11.6, 3.2 Hz, 1 H), 3.07 (ddd, *J* = 12.0, 6.0, 2.0 Hz, 1 H), 2.87 (app dt, *J* = 15.4, 2.6 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 138.6, 136.6, 136.3, 136.0, 131.0, 130.1, 129.8, 129.0, 128.8, 128.4, 128.2, 127.6, 127.6, 126.8, 126.3, 121.8, 91.2, 65.5, 52.2, 45.5, 29.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{20}BrN_2O_2$: 435.0703; found: 435.0610. Spectral Accuracy: 98.1%.

13-Nitro-13a-(4-(trifluoromethyl)phenyl)-5,8,13,13a-tetrahydro-6*H*-isoquinolino[3,2-*a*]isoquinoline (2i)

By following General Procedure C, compound (±)-**2i** was obtained from aldehyde **1a** (41.3 mg, 0.25 mmol, 1 equiv) and 1-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (138.6 mg, 0.5 mmol, 2.0 equiv). Hexanes containing EtOAc (0–10%) was used as the eluent for silica gel chromatography.

Yield: 69% (73.2 mg) and > 20:1 diastereomeric ratio; off-white solid; R_f = 0.30 (hexanes/EtOAc 90:10 v/v).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.58 (dd, *J* = 7.6, 1.5 Hz, 1 H), 7.43–7.32 (comp, 4 H), 7.24–7.17 (comp, 2 H), 7.14 (app ddt, *J* = 6.5, 4.6, 2.1 Hz, 2 H), 6.99 (dd, *J* = 7.9, 1.2 Hz, 1 H), 6.94 (d, *J* = 8.3 Hz, 2 H), 6.57 (s, 1 H), 3.97 (d, *J* = 16.4 Hz, 1 H), 3.40–3.30 (comp, 2 H), 3.26 (app td, *J* = 11.5, 3.0 Hz, 1 H), 3.18–3.05 (m, 1 H), 2.89 (dd, *J* = 15.7, 2.9 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 143.7, 136.5, 136.0, 129.9, 129.7 (q, J_{C-F} = 32.6 Hz), 129.2, 128.8, 128.7, 128.5, 128.2, 127.7, 126.9, 126.4, 124.8 (q, J_{C-F} = 3.8 Hz), 123.9 (q, J_{C-F} = 272.4 Hz), 91.1, 65.6, 52.2, 45.6, 29.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{20}F_3N_2O_2$: 425.1471; found: 425.1820. Spectral Accuracy: 97.5%.

13a-(4-Methoxyphenyl)-13-nitro-5,8,13,13a-tetrahydro-6*H*-isoquinolino[3,2-*a*]isoquinoline (2j)

By following General Procedure C, compound (±)-**2j** was obtained from aldehyde **1a** (41.3 mg, 0.25 mmol, 1 equiv) and 1-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (119.7 mg, 0.5 mmol, 2.0 equiv). Hexanes containing EtOAc (0–10%) was used as the eluent for silica gel chromatography.

Yield: 40% (38.6 mg) and > 20:1 diastereomeric ratio; off-white solid; R_f = 0.19 (hexanes/EtOAc 90:10 v/v).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.60–7.54 (m, 1 H), 7.39–7.32 (comp, 2 H), 7.21–7.09 (comp, 4 H), 7.07–6.97 (m, 1 H), 6.73–6.68 (comp, 2 H), 6.68–6.62 (comp, 2 H), 6.54 (s, 1 H), 3.91 (d, *J* = 16.1 Hz, 1 H), 3.71 (s, 3 H), 3.39–3.27 (comp, 2 H), 3.23 (app td, *J* = 11.6, 3.2 Hz, 1 H), 3.00 (ddd, *J* = 11.7, 5.9, 1.9 Hz, 1 H), 2.84 (app dt, *J* = 15.4, 2.6 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 158.7, 137.2, 136.9, 136.0, 131.6, 129.8, 129.6, 129.2, 128.9, 128.4, 128.3, 127.5, 127.3, 126.8, 126.1, 113.0, 91.7, 65.5, 55.2, 52.3, 45.5, 29.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{23}N_2O_3$: 387.1703; found: 387.1899. Spectral Accuracy: 98.8%.

13-Nitro-13a-(*p*-tolyl)-5,8,13,13a-tetrahydro-6*H*-isoquinolino-[3,2-*a*]isoquinoline (2k)

By following General Procedure C, compound (±)-**2k** was obtained from aldehyde **1a** (41.3 mg, 0.25 mmol, 1 equiv) and 1-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinoline (111.7 mg, 0.5 mmol, 2.0 equiv). Hexanes containing EtOAc (0–10%) was used as the eluent for silica gel chromatography.

Yield: 61% (56.5 mg) and > 20:1 diastereomeric ratio; off-white solid; R_f = 0.32 (hexanes/EtOAc 90:10 v/v).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 7.9, 1.2 Hz, 1 H), 7.40–7.31 (comp, 2 H), 7.24–7.15 (comp, 2 H), 7.12 (ddd, *J* = 9.5, 7.1, 1.9 Hz, 2 H), 7.03 (d, *J* = 7.9, 1.2 Hz, 1 H), 6.94 (d, *J* = 8.2 Hz, 2 H), 6.70–6.65 (comp, 2 H), 6.57 (s, 1 H), 3.91 (d, *J* = 16.2 Hz, 1 H), 3.39–3.24 (comp, 3 H), 3.05–2.99 (m, 1 H), 2.85 (dd, *J* = 15.3, 3.0 Hz, 1 H), 2.24 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 137.3, 137.1, 136.9, 136.5, 136.0, 129.5, 129.3, 128.9, 128.5, 128.5, 128.4, 128.3, 127.4, 127.2, 126.8, 126.1, 91.62, 65.7, 52.3, 45.56, 29.6, 21.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{23}N_2O_2$: 371.1759; found: 371.1935. Spectral Accuracy: 97.5%.

13-Nitro-13a-(*m*-tolyl)-5,8,13,13a-tetrahydro-6*H*-isoquinolino-[3,2-*a*]isoquinoline (2l)

By following General Procedure C, compound (±)-**2l** was obtained from aldehyde **1a** (41.3 mg, 0.25 mmol, 1 equiv) and 1-(*m*-tolyl)-1,2,3,4-tetrahydroisoquinoline (111.7 mg, 0.5 mmol, 2.0 equiv). Hexanes containing EtOAc (0–10%) was used as the eluent for silica gel chromatography.

Yield: 60% (55.6 mg) and > 20:1 diastereomeric ratio; off-white solid; R_f = 0.28 (hexanes/EtOAc 90:10 v/v).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.57 (dd, *J* = 7.6, 1.5 Hz, 1 H), 7.38–7.32 (comp, 2 H), 7.23–7.16 (comp, 2 H), 7.12 (app ddt, *J* = 6.4, 4.5, 2.2 Hz, 2 H), 7.07–6.96 (comp, 3 H), 6.66–6.54 (comp, 3 H), 3.92 (d, *J* = 16.2 Hz, 1 H), 3.39 (d, *J* = 16.2 Hz, 1 H), 3.35–3.27 (comp, 2 H), 3.09–3.01 (m, 1 H), 2.92–2.83 (m, 1 H), 2.15 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.6, 137.3, 136.9, 136.8, 135.9, 129.4, 129.4, 129.2, 128.8, 128.5, 128.3, 128.3, 127.5, 127.3, 127.2, 126.7, 126.0, 125.3, 91.5, 65.7, 52.3, 45.5, 29.5, 21.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{23}N_2O_2$: 371.1754; found: 371.2009. Spectral Accuracy: 98.2%.

13b-(4-Bromophenyl)-14-nitro-5,7,8,13,13b,14-hexahydroindolo-[2′,3′:3,4]pyrido[1,2-*b*]isoquinoline (2m)

2-(Nitromethyl)benzaldehyde (82.6 mg, 0.5 mmol, 1 equiv), 1-(4-bromophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (327.2 mg, 1.0 mmol, 2.0 equiv), and benzoic acid (79.4 mg, 0.65 mmol, 1.3 equiv) were added to a microwave vial charged with a stir bar. Dichloroethane (5.0 mL) was added and the microwave vial was sealed. The vial was stirred and placed in the microwave, followed by heating for

15 minutes at 115 °C with the microwave set to low absorption. The reaction mixture was neutralized with sat. $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude residue purified by silica gel chromatography using hexanes containing EtOAc (0–15%) as the eluent, yielding **2m**.

Yield: 24% (56.9 mg) and > 20:1 diastereomeric ratio; pale-green solid; R_f = 0.40 (hexanes/EtOAc 80:20 v/v).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.83 (s, 1 H), 7.59 (d, *J* = 7.7 Hz, 1 H), 7.49–7.41 (comp, 2 H), 7.38 (app td, *J* = 7.5, 1.3 Hz, 1 H), 7.32–7.26 (comp, 4 H), 7.24–7.19 (comp, 2 H), 6.73 (d, *J* = 8.3 Hz, 2 H), 6.51 (s, 1 H), 4.08 (d, *J* = 16.3 Hz, 1 H), 3.48 (d, *J* = 16.3 Hz, 1 H), 3.22 (app td, *J* = 12.7, 11.9, 3.9 Hz, 1 H), 3.13 (app ddt, *J* = 16.4, 10.7, 4.4 Hz, 2 H), 2.98–2.91 (m, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 137.0, 131.5, 130.9, 130.0, 129.9, 128.6, 128.1, 127.8, 127.0, 126.4, 122.9, 119.9, 118.9, 113.4, 111.5, 90.0, 63.8, 51.5, 46.7, 21.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{21}BrN_3O_2$: 474.0812; found: 474.0616. Spectral Accuracy: 97.7%.

5,8,13,13a-Tetrahydro-6*H*-isoquinolino[3,2-*a*]isoquinoline (3a)

By following General Procedures A and B, compound (±)-**3a** was obtained from aldehyde **1a** (82.6 mg, 0.5 mmol, 1 equiv) and 1,2,3,4-tetrahydroisoquinoline (81.7 µL, 0.65 mmol, 1.3 equiv). Hexanes containing EtOAc (0–20%) was used as the eluent for silica gel chromatography. Characterization data for **3a** match literature reports in all respects.[19a,19b]

Yield: 53% (62.4 mg) over two steps; yellow solid; R_f = 0.39 (hexanes/EtOAc 70:30 v/v).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 7.0 Hz, 1 H), 7.26–7.14 (comp, 6 H), 7.10 (dd, *J* = 6.5, 2.7 Hz, 1 H), 4.06 (d, *J* = 14.9 Hz, 1 H), 3.85–3.67 (comp, 2 H), 3.48–3.36 (m, 1 H), 3.32–3.15 (comp, 2 H), 2.96 (ddd, *J* = 16.3, 11.3, 1.8 Hz, 1 H), 2.85–2.75 (m, 1 H), 2.72–2.62 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.0, 134.6, 134.6, 134.5, 129.0, 128.9, 126.4, 126.3, 126.3, 126.2, 126.0, 125.6, 60.0, 58.7, 51.3, 36.8, 29.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N$: 236.1434; found: 236.1526. Spectral Accuracy: 98.6%.

4-Methyl-5,8,13,13a-tetrahydro-6*H*-isoquinolino[3,2-*a*]isoquinoline (3b)

By following General Procedures A and B, compound (±)-**3b** was obtained from aldehyde **1a** (82.6 mg, 0.5 mmol, 1 equiv) and 5-methyl-1,2,3,4-tetrahydroisoquinoline (95.7 mg, 0.65 mmol, 1.3 equiv). Hexanes containing EtOAc (0–10%) was used as the eluent for silica gel chromatography.

Yield: 47% (58.6 mg) over two steps; white solid; R_f = 0.25 (hexanes/EtOAc 90:10 v/v).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.28–7.17 (comp, 5 H), 7.13–7.10 (comp, 2 H), 4.09 (d, *J* = 14.9 Hz, 1 H), 3.87–3.69 (comp, 2 H), 3.42 (dd, *J* = 16.3, 4.1 Hz, 1 H), 3.27 (ddd, *J* = 11.5, 5.8, 2.2 Hz, 1 H), 3.10–2.88 (comp, 2 H), 2.77 (app dt, *J* = 16.5, 2.9 Hz, 1 H), 2.67 (app td, *J* = 11.4, 3.8 Hz, 1 H), 2.31 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 138.0, 136.3, 134.6, 134.4, 133.2, 128.8, 127.6, 126.4, 126.2, 125.9, 125.9, 123.3, 60.1, 58.8, 51.2, 36.9, 27.1, 19.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}N$: 250.1590; found: 250.1705. Spectral Accuracy: 99.0%.

2,3-Dimethoxy-5,8,13,13a-tetrahydro-6*H*-isoquinolino[3,2-*a*]isoquinoline (3c)

By following General Procedures A and B, compound (±)-**3c** was obtained from aldehyde **1a** (82.6 mg, 0.5 mmol, 1 equiv) and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (125.6 mg, 0.65 mmol, 1.3 equiv). Hexanes containing EtOAc (0–40%) was used as the eluent for silica gel chromatography. Characterization data for **3c** match a literature report in all respects.[19c]

Yield: 34% (50.2 mg) over two steps; white solid; R_f = 0.14 (hexanes/EtOAc 75:25 v/v).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.20–7.12 (comp, 3 H), 7.11–7.06 (m, 1 H), 6.75 (s, 1 H), 6.62 (s, 1 H), 4.04 (d, *J* = 14.9 Hz, 1 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.78–3.73 (m, 1 H), 3.70–3.62 (m, 1 H), 3.34 (dd, *J* = 16.2, 3.9 Hz, 1 H), 3.20–3.12 (comp, 2 H), 2.98–2.87 (m, 1 H), 2.73–2.60 (comp, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 147.6, 147.6, 134.4, 129.7, 128.8, 126.7, 126.4, 126.2, 126.0, 111.4, 108.6, 59.6, 58.6, 56.2, 55.9, 51.4, 36.8, 29.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}NO_2$: 296.1645; found: 296.1739. Spectral Accuracy: 98.6%.

5,8,13,13a-Tetrahydro-6*H*-[1,3]dioxolo[4,5-*g*]isoquinolino-[3,2-*a*]isoquinoline (3d)

By following General Procedures A and B, compound (±)-**3d** was obtained from aldehyde **1a** (82.6 mg, 0.5 mmol, 1 equiv) and 5,6,7,8-tetrahydro[1,3]dioxolo[4,5-g]isoquinoline (115.2 mg, 0.65 mmol, 1.3 equiv). Hexanes containing EtOAc (0–20%) was used as the eluent for silica gel chromatography. Characterization data for **3d** match a literature report in all respects.[19b]

Yield: 38% (53.1 mg) over two steps; white solid; R_f = 0.28 (hexanes/EtOAc 75:25 v/v).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.21–7.13 (comp, 3 H), 7.11–7.05 (m, 1 H), 6.76 (s, 1 H), 6.60 (s, 1 H), 5.92–5.91 (comp, 2 H), 4.03 (d, *J* = 14.9 Hz, 1 H), 3.75 (d, *J* = 14.9 Hz, 1 H), 3.62 (dd, *J* = 11.2, 4.0 Hz, 1 H), 3.29 (dd, *J* = 16.2, 4.0 Hz, 1 H), 3.18–3.09 (comp, 2 H), 2.95–2.87 (m, 1 H), 2.71–2.58 (comp, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 146.3, 146.1, 134.4, 134.3, 130.8, 128.8, 127.8, 126.4, 126.2, 126.0, 108.5, 105.6, 100.9, 60.0, 58.6, 51.4, 36.9, 29.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{18}NO_2$: 280.1332; found: 280.1565. Spectral Accuracy: 99.1%.

13a-Phenyl-5,8,13,13a-tetrahydro-6*H*-isoquinolino[3,2-*a*]isoquinoline (3e)

Compound (±)-**2e** (71.3 mg, 0.20 mmol. 1.0 equiv), and AIBN (9.9 mg, 0.06 mmol, 0.3 equiv) was added to benzene (2.0 mL) and stirred until complete dissolution. Tributyltin hydride (80.9 µL, 0.3 mmol, 1.5 equiv) was then added and the reaction mixture was heated under reflux for 1 hour. The reaction mixture was extracted with 1 M HCl (3 × 10 mL) and the combined aqueous layers were basified with 1 M NaOH. The aqueous layer was back extracted with EtOAc (3 × 15 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude residue was purified by silica gel chromatography using hexanes containing EtOAc (0–5%) as the eluent yielding **3e**.

Yield: 72% (44.8 mg); white solid; R_f = 0.33 (hexanes/EtOAc 95:5 v/v).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.25–7.13 (comp, 10 H), 7.06 (app td, *J* = 7.4, 1.7 Hz, 1 H), 6.98 (d, *J* = 7.5 Hz, 1 H), 6.78 (dd, *J* = 7.9, 1.3 Hz, 1 H), 3.71–3.55 (comp, 3 H), 3.44 (d, *J* = 17.5 Hz, 1 H), 3.28–3.23 (m, 1 H), 3.17 (ddd, *J* = 11.8, 8.3, 4.7 Hz, 1 H), 3.09 (app dt, *J* = 11.9, 5.3 Hz, 1 H), 3.02 (app dt, *J* = 15.8, 4.8 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 134.5, 134.2, 133.4, 129.8, 128.9, 128.9, 128.4, 128.2, 127.9, 127.8, 126.9, 126.5, 126.4, 126.0, 126.0, 126.0, 62.5, 53.5, 46.5, 36.2, 29.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{22}N$: 312.1747; found: 312.1787. Spectral Accuracy: 97.4%.

1,2,3,5,10,10a-Hexahydropyrrolo[1,2-*b*]isoquinoline (4)

By following General Procedures A and B, compound (±)-**4** was obtained from aldehyde **1a** (82.6 mg, 0.5 mmol, 1 equiv) and L-proline (74.8 mg, 0.65 mmol, 1.3 equiv). Dichloromethane containing MeOH (0–10%) was used as the eluent for silica gel chromatography. Characterization data for **4** match a literature report in all respects.[19e]

Yield: 52% (45.0 mg) over two steps; colorless oil; R_f = 0.13 (CH_2Cl_2/MeOH 96:4 v/v).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.13–7.10 (comp, 3 H), 7.11–7.05 (m, 1 H), 4.16 (d, *J* = 14.6 Hz, 1 H), 3.47 (d, *J* = 14.6 Hz, 1 H), 3.30 (app td, *J* = 8.7, 2.5 Hz, 1 H), 3.01 (dd, *J* = 15.9, 3.9 Hz, 1 H), 2.78–2.71 (m, 1 H), 2.42–2.36 (m, 1 H), 2.31 (app q, *J* = 8.8 Hz, 1 H), 2.12 (dddd, *J* = 12.3, 9.8, 6.8, 4.2 Hz, 1 H), 1.95 (app ddtd, *J* = 12.7, 11.2, 8.6, 4.2 Hz, 1 H), 1.89–1.79 (m, 1 H), 1.58 (dddd, *J* = 12.3, 11.3, 9.8, 6.8 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 135.0, 134.9, 129.1, 126.7, 126.3, 125.8, 60.8, 55.9, 54.8, 36.0, 31.1, 21.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}N$: 174.1277; found: 174.1276. Spectral Accuracy: 99.4%.

1,3,4,6,11,11a-Hexahydro-2*H*-pyrido[1,2-*b*]isoquinoline (5)

By following General Procedures A and B, compound (±)-**5** was obtained from aldehyde **1a** (82.6 mg, 0.5 mmol, 1 equiv) and L/D-pipecolic acid (84.0 mg, 0.65 mmol, 1.3 equiv). Dichloromethane containing MeOH (0–4%) was used as the eluent for silica gel chromatography. Characterization data for **5** match a literature report in all respects.[19d]

Yield: 47% (44.0 mg) over two steps; white solid; R_f = 0.18 in EtOAc.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.12–7.08 (comp, 2 H), 7.06–7.03 (m, 1 H), 7.02–6.98 (m, 1 H), 3.86 (d, *J* = 15.1 Hz, 1 H), 3.39 (d, *J* = 15.1 Hz, 1 H), 3.12–3.05 (m, 1 H), 2.90–2.62 (comp, 2 H), 2.25 (app tt, *J* = 10.2, 4.2 Hz, 1 H), 2.12 (app td, *J* = 11.4, 4.2 Hz, 1 H), 1.88–1.76 (comp, 2 H), 1.76–1.67 (comp, 2 H), 1.42–1.32 (comp, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 134.3, 134.0, 128.1, 126.2, 126.0, 125.6, 58.4, 58.4, 56.2, 36.8, 33.7, 25.9, 24.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{18}N$: 188.1434; found: 188.1383. Spectral Accuracy: 99.2%.

Funding Information

Financial support from the NIH–NIGMS (Grant R01GM101389) is gratefully acknowledged. We further acknowledge the National Science Foundation (grant # 1828064 to K.A.A.) and the University of Florida for funding the purchase of the X-ray equipment.

Acknowledgment

We thank Dr. Ion Ghiviriga (University of Florida) for assistance with NMR experiments.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706004.

References

(1) Selected recent reviews on amine C–H functionalization, including redox-neutral approaches: (a) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069. (b) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem. Eur. J.* **2010**, *16*, 2654. (c) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (d) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W. *Chem. Eur. J.* **2012**, *18*, 10092. (e) Jones, K. M.; Klussmann, M. *Synlett* **2012**, *23*, 159. (f) Peng, B.; Maulide, N. *Chem. Eur. J.* **2013**, *19*, 13274. (g) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem. Int. Ed.* **2014**, *53*, 74. (h) Haibach, M. C.; Seidel, D. *Angew. Chem. Int. Ed.* **2014**, *53*, 5010. (i) Wang, L.; Xiao, J. *Adv. Synth. Catal.* **2014**, *356*, 1137. (j) Vo, C.-V. T.; Bode, J. W. *J. Org. Chem.* **2014**, *79*, 2809. (k) Seidel, D. *Org. Chem. Front.* **2014**, *1*, 426. (l) Qin, Y.; Lv, J.; Luo, S. *Tetrahedron Lett.* **2014**, *55*, 551. (m) Seidel, D. *Acc. Chem. Res.* **2015**, *48*, 317. (n) Beatty, J. W.; Stephenson, C. R. J. *Acc. Chem. Res.* **2015**, *48*, 1474. (o) Mahato, S.; Jana, C. K. *Chem. Rec.* **2016**, *16*, 1477. (p) Qin, Y.; Zhu, L.; Luo, S. *Chem. Rev.* **2017**, *117*, 9433. (q) Cheng, M.-X.; Yang, S.-D. *Synlett* **2017**, *28*, 159. (r) Chu, J. C. K.; Rovis, T. *Angew. Chem. Int. Ed.* **2018**, *57*, 62. (s) Gonnard, L.; Guérinot, A.; Cossy, J. *Tetrahedron* **2019**, *75*, 145. (t) Liu, S.; Zhao, Z.; Wang, Y. *Chem. Eur. J.* **2019**, *25*, 2423. (u) Antermite, D.; Bull, J. A. *Synthesis* **2019**, *51*, 3171. (v) Trowbridge, A.; Walton, S. M.; Gaunt, M. J. *Chem. Rev.* **2020**, *120*, 2613.

(2) Recent examples of mechanistically diverse amine C–H bond functionalization reactions: (a) Zhao, Z.; Luo, Y.; Liu, S.; Zhang, L.; Feng, L.; Wang, Y. *Angew. Chem. Int. Ed.* **2018**, *57*, 3792. (b) Wang, F.; Rafiee, M.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2018**, *57*, 6686. (c) Greßies, S.; Klauck, F. J. R.; Kim, J. H.; Daniliuc, C. G.; Glorius, F. *Angew. Chem. Int. Ed.* **2018**, *57*, 9950. (d) Griffiths, R. J.; Kong, W. C.; Richards, S. A.; Burley, G. A.; Willis, M. C.; Talbot, E. P. A. *Chem. Sci.* **2018**, *9*, 2295. (e) Idiris, F. I. M.; Majeste, C. E.; Craven, G. B.; Jones, C. R. *Chem. Sci.* **2018**, *9*, 2873. (f) Li, S.-S.; Lv, X.; Ren, D.; Shao, C.-L.; Liu, Q.; Xiao, J. *Chem. Sci.* **2018**, *9*, 8253. (g) Maier, A. F. G.; Tussing, S.; Zhu, H.; Wicker, G.; Tzvetkova, P.; Flörke, U.; Daniliuc, C. G.; Grimme, S.; Paradies, J. *Chem. Eur. J.* **2018**, *24*, 16287. (h) Mori, K.; Isogai, R.; Kamei, Y.; Yamanaka, M.; Akiyama, T. *J. Am. Chem. Soc.* **2018**, *140*, 6203. (i) Shang, M.; Chan, J. Z.; Cao, M.; Chang, Y.; Wang, Q.; Cook, B.; Torker, S.; Wasa, M. *J. Am. Chem. Soc.* **2018**, *140*, 10593. (j) Lennox, A. J. J.; Goes, S. L.; Webster, M. P.; Koolman, H. F.; Djuric, S. W.; Stahl, S. S. *J. Am. Chem. Soc.* **2018**, *140*, 11227. (k) Zhang, J.; Park, S.; Chang, S. *J. Am. Chem. Soc.* **2018**, *140*, 13209. (l) Nauth, A. M.; Schechtel, E.; Dören, R.; Tremel, W.; Opatz, T. *J. Am. Chem. Soc.* **2018**, *140*, 14169. (m) Jiang, H.-J.; Zhong, X.-M.; Yu, J.; Zhang, Y.; Zhang, X.; Wu, Y.-D.; Gong, L.-Z. *Angew. Chem. Int. Ed.* **2019**, *58*, 1803. (n) Ashley, M. A.; Yamauchi, C.; Chu, J. C. K.; Otsuka, S.; Yorimitsu, H.; Rovis, T. *Angew. Chem. Int. Ed.* **2019**, *58*, 4002. (o) Guin, S.; Dolui, P.; Zhang, X.; Paul, S.; Singh, V. K.; Pradhan,

S.; Chandrashekar, H. B.; Anjana, S. S.; Paton, R. S.; Maiti, D. *Angew. Chem. Int. Ed.* **2019**, *58*, 5633. (p) Whitehurst, W. G.; Blackwell, J. H.; Hermann, G. N.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2019**, *58*, 9054. (q) Ma, Y.; Yao, X.; Zhang, L.; Ni, P.; Cheng, R.; Ye, J. *Angew. Chem. Int. Ed.* **2019**, *58*, 16548. (r) Grainger, R.; Heightman, T. D.; Ley, S. V.; Lima, F.; Johnson, C. N. *Chem. Sci.* **2019**, *10*, 2264. (s) Vasu, D.; Fuentes de Arriba, A. L.; Leitch, J. A.; de Gombert, A.; Dixon, D. J. *Chem. Sci.* **2019**, *10*, 3401. (t) Asako, S.; Ishihara, S.; Hirata, K.; Takai, K. *J. Am. Chem. Soc.* **2019**, *141*, 9832. (u) Lin, W.; Zhang, K.-F.; Baudoin, O. *Nat. Catal.* **2019**, *2*, 882. (v) Chan, J. Z.; Chang, Y.; Wasa, M. *Org. Lett.* **2019**, *21*, 984. (w) Zhou, L.; Shen, Y.-B.; An, X.-D.; Li, X.-J.; Li, S.-S.; Liu, Q.; Xiao, J. *Org. Lett.* **2019**, *21*, 8543. (x) Kataoka, M.; Otawa, Y.; Ido, N.; Mori, K. *Org. Lett.* **2019**, *21*, 9334. (y) Lee, M.; Adams, A.; Cox, P. B.; Sanford, M. S. *Synlett* **2019**, *30*, 417. (z) Kapoor, M.; Chand-Thakuri, P.; Maxwell, J. M.; Liu, D.; Zhou, H.; Young, M. C. *Synlett* **2019**, *30*, 519. (aa) Ohmatsu, K.; Suzuki, R.; Furukawa, Y.; Sato, M.; Ooi, T. *ACS Catal.* **2020**, *10*, 2627. (ab) Roque, J. B.; Kuroda, Y.; Jurczyk, J.; Xu, L.-P.; Ham, J. S.; Göttemann, L. T.; Roberts, C. A.; Adpressa, D.; Saurí, J.; Joyce, L. A.; Musaev, D. G.; Yeung, C. S.; Sarpong, R. *ACS Catal.* **2020**, *10*, 2929. (ac) Rand, A. W.; Yin, H.; Xu, L.; Giacoboni, J.; Martin-Montero, R.; Romano, C.; Montgomery, J.; Martin, R. *ACS Catal.* **2020**, *10*, 4671. (ad) Liu, W.; Babl, T.; Röther, A.; Reiser, O.; Davies, H. M. L. *Chem. Eur. J.* **2020**, *26*, 4236. (ae) Verma, P.; Richter, J. M.; Chekshin, N.; Qiao, J. X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2020**, *142*, 5117. (af) Walker, M. M.; Koronkiewicz, B.; Chen, S.; Houk, K. N.; Mayer, J. M.; Ellman, J. A. *J. Am. Chem. Soc.* **2020**, *142*, 8194. (ag) Feng, K.; Quevedo, R. E.; Kohrt, J. T.; Oderinde, M. S.; Reilly, U.; White, M. C. *Nature* **2020**, *580*, 621. (ah) Sarver, P. J.; Bacauanu, V.; Schultz, D. M.; DiRocco, D. A.; Lam, Y.-h.; Sherer, E. C.; MacMillan, D. W. C. *Nat. Chem.* **2020**, *12*, 459. (ai) McManus, J. B.; Onuska, N. P. R.; Jeffreys, M. S.; Goodwin, N. C.; Nicewicz, D. A. *Org. Lett.* **2020**, *22*, 679. (aj) Oeschger, R.; Su, B.; Yu, I.; Ehinger, C.; Romero, E.; He, S.; Hartwig, J. *Science* **2020**, *368*, 736. (ak) Short, M. A.; Blackburn, J. M.; Roizen, J. L. *Synlett* **2020**, *31*, 102.

(3) (a) Zhang, C.; De C, K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416. (b) Zheng, L.; Yang, F.; Dang, Q.; Bai, X. *Org. Lett.* **2008**, *10*, 889. (c) Dieckmann, A.; Richers, M. T.; Platonova, A. Y.; Zhang, C.; Seidel, D.; Houk, K. N. *J. Org. Chem.* **2013**, *78*, 4132. (d) Richers, M. T.; Deb, I.; Platonova, A. Y.; Zhang, C.; Seidel, D. *Synthesis* **2013**, *45*, 1730.

(4) (a) Richers, M. T.; Breugst, M.; Platonova, A. Y.; Ullrich, A.; Dieckmann, A.; Houk, K. N.; Seidel, D. *J. Am. Chem. Soc.* **2014**, *136*, 6123. (b) Jarvis, C. L.; Richers, M. T.; Breugst, M.; Houk, K. N.; Seidel, D. *Org. Lett.* **2014**, *16*, 3556. (c) Mahato, S.; Haque, M. A.; Dwari, S.; Jana, C. K. *RSC Adv.* **2014**, *4*, 46214.

(5) (a) Ma, L.; Seidel, D. *Chem. Eur. J.* **2015**, *21*, 12908. (b) Paul, A.; Chandak, H. S.; Ma, L.; Seidel, D. *Org. Lett.* **2020**, *22*, 976.

(6) (a) Li, J.; Qin, C.; Yu, Y.; Fan, H.; Fu, Y.; Li, H.; Wang, W. *Adv. Synth. Catal.* **2017**, *359*, 2191. (b) Li, J.; Fu, Y.; Qin, C.; Yu, Y.; Li, H.; Wang, W. *Org. Biomol. Chem.* **2017**, *15*, 6474. (c) Zhu, Z.; Seidel, D. *Org. Lett.* **2017**, *19*, 2841.

(7) Paul, A.; Adili, A.; Seidel, D. *Org. Lett.* **2019**, *21*, 1845.

(8) Additional examples of amine redox-annulations: (a) Zhang, C.; Das, D.; Seidel, D. *Chem. Sci.* **2011**, *2*, 233. (b) Kang, Y.; Chen, W.; Breugst, M.; Seidel, D. *J. Org. Chem.* **2015**, *80*, 9628. (c) Chen, W.; Seidel, D. *Org. Lett.* **2016**, *18*, 1024. (d) Zhu, Z.; Lv, X.; Anesini, J. E.; Seidel, D. *Org. Lett.* **2017**, *19*, 6424. (e) Zhu, Z.; Chandak, H. S.; Seidel, D. *Org. Lett.* **2018**, *20*, 4090. (f) Liu, Y.; Wu, J.; Jin, Z.; Jiang, H. *Synlett* **2018**, *29*, 1061.

(9) For detailed discussions on the mechanisms of these transformations, see references: (a) Xue, X.; Yu, A.; Cai, Y.; Cheng, J.-P. *Org. Lett.* **2011**, *13*, 6054. (b) Ma, L.; Paul, A.; Breugst, M.; Seidel, D. *Chem. Eur. J.* **2016**, *22*, 18179; see also refs 1m, 3c, 4a, 4b, and 8b.

(10) Examples of redox-neutral α-C–H bond annulations of secondary amines that likely involve a pericyclic step: (a) Grigg, R.; Nimal Gunaratne, H. Q.; Henderson, D.; Sridharan, V. *Tetrahedron* **1990**, *46*, 1599. (b) Soeder, R. W.; Bowers, K.; Pegram, L. D.; Cartaya-Marin, C. P. *Synth. Commun.* **1992**, *22*, 2737. (c) Grigg, R.; Kennewell, P.; Savic, V.; Sridharan, V. *Tetrahedron* **1992**, *48*, 10423. (d) Deb, I.; Seidel, D. *Tetrahedron Lett.* **2010**, *51*, 2945. (e) Kang, Y.; Richers, M. T.; Sawicki, C. H.; Seidel, D. *Chem. Commun.* **2015**, *51*, 10648. (f) Cheng, Y.-F.; Rong, H.-J.; Yi, C.-B.; Yao, J.-J.; Qu, J. *Org. Lett.* **2015**, *17*, 4758. (g) Yang, Z.; Lu, N.; Wei, Z.; Cao, J.; Liang, D.; Duan, H.; Lin, Y. *J. Org. Chem.* **2016**, *81*, 11950. (h) Rong, H.-J.; Cheng, Y.-F.; Liu, F.-F.; Ren, S.-J.; Qu, J. *J. Org. Chem.* **2017**, *82*, 532. (i) Purkait, A.; Roy, S. K.; Srivastava, H. K.; Jana, C. K. *Org. Lett.* **2017**, *19*, 2540.

(11) (a) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341. (b) Grycova, L.; Dostal, J.; Marek, R. *Phytochemistry* **2007**, *68*, 150. (c) Bhadra, K.; Kumar, G. S. *Med. Res. Rev.* **2011**, *31*, 821. (d) Yu, J.; Zhang, Z.; Zhou, S.; Zhang, W.; Tong, R. *Org. Chem. Front.* **2018**, *5*, 242.

(12) (a) Enders, D.; Wang, C.; Bats, J. W. *Synlett* **2009**, 1777. (b) Enders, D.; Hahn, R.; Atodiresei, I. *Adv. Synth. Catal.* **2013**, *355*, 1126. (c) Hahn, R.; Jafari, E.; Raabe, G.; Enders, D. *Synthesis* **2015**, *47*, 472.

(13) Fessard, T. C.; Motoyoshi, H.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 2078.

(14) Ono, N.; Miyake, H.; Kamimura, A.; Hamamoto, I.; Tamura, R.; Kaji, A. *Tetrahedron* **1985**, *41*, 4013.

(15) Decarboxylative annulations: (a) Cohen, N.; Blount, J. F.; Lopresti, R. J.; Trullinger, D. P. *J. Org. Chem.* **1979**, *44*, 4005. (b) Tang, M.; Tong, L.; Ju, L.; Zhai, W.; Hu, Y.; Yu, X. *Org. Lett.* **2015**, *17*, 5180. (c) Kang, Y.; Seidel, D. *Org. Lett.* **2016**, *18*, 4277. (d) Wu, J.-s.; Jiang, H.-j.; Yang, J.-g.; Jin, Z.-n.; Chen, D.-b. *Tetrahedron Lett.* **2017**, *58*, 546. (e) Paul, A.; Thimmegowda, N. R.; Galani Cruz, T.; Seidel, D. *Org. Lett.* **2018**, *20*, 602; see also references 3a, 3b, 3d, 5b, 6c, 8a, 8e, and 14..

(16) Selected reviews on decarboxylative coupling reactions not limited to amino acids: (a) Rodriguez, N.; Goossen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030. (b) Xuan, J.; Zhang, Z.-G.; Xiao, W.-J. *Angew. Chem. Int. Ed.* **2015**, *54*, 15632. (c) Patra, T.; Maiti, D. *Chem. Eur. J.* **2017**, *23*, 7382. (d) Wei, Y.; Hu, P.; Zhang, M.; Su, W. *Chem. Rev.* **2017**, *117*, 8864. (e) Rahman, M.; Mukherjee, A.; Kovalev, I. S.; Kopchuk, D. S.; Zyryanov, G. V.; Tsurkan, M. V.; Majee, A.; Ranu, B. C.; Charushin, V. N.; Chupakhin, O. N.; Santra, S. *Adv. Synth. Catal.* **2019**, *361*, 2161.

(17) (a) Kind, T.; Fiehn, O. *BMC Bioinformatics* **2007**, *8*, 105. (b) Wang, Y.; Gu, M. *Anal. Chem.* **2010**, *82*, 7055.

(18) Starting material synthesis: (a) Ghislieri, D.; Green, A. P.; Pontini, M.; Willies, S. C.; Rowles, I.; Frank, A.; Grogan, G.; Turner, N. J. *J. Am. Chem. Soc.* **2013**, *135*, 10863. (b) Gray, N. M.; Cheng, B. K.; Mick, S. J.; Lair, C. M.; Contreras, P. C. *J. Med. Chem.* **1989**, *32*, 1242. (c) Ji, Y.; Wang, J.; Chen, M.; Shi, L.; Zhou, Y. *Chin. J. Chem.* **2018**, *36*, 139. (d) Tamayo, N. A.; Bo, Y.; Gore, V.; Ma, V.; Nishimura, N.; Tang, P.; Deng, H.; Klionsky, L.; Lehto, S. G.; Wang, W.; Youngblood, B.; Chen, J.; Correll, T. L.; Bartberger, M. D.; Gavva, N. R.; Norman, M. H. *J. Med. Chem.* **2012**, *55*, 1593. (e) Ji, Y.; Shi, L.; Chen, M.-W.; Feng, G.-S.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2015**, *137*, 10496. (f) Zhao, Z.; Sun, Y.; Wang, L.; Chen, X.; Sun, Y.; Lin, L.; Tang, Y.; Li, F.; Chen, D. *Tetrahedron*

Lett. **2019**, *60*, 800. (g) Schönbauer, D.; Sambiagio, C.; Noël, T.; Schnürch, M. *Beilstein J. Org. Chem.* **2020**, *16*, 809. (h) Cutter, P. S.; Miller, R.; Schore, N. E. *Tetrahedron* **2002**, *58*, 1471. (i) Bailey, D. M.; Degrazia, C. G.; Lape, H. E.; Frering, R.; Fort, D.; Skulan, T. *J. Med. Chem.* **1973**, *16*, 151. (j) See also ref 12b.

(19) (a) Kraus, G. A.; Wu, T. A. *Tetrahedron* **2010**, *66*, 569. (b) Dai-Ho, G.; Mariano, P. S. *J. Org. Chem.* **1988**, *53*, 5113. (c) Orito, K.; Satoh, Y.; Nishizawa, H.; Harada, R.; Tokuda, M. *Org. Lett.* **2000**, *2*, 2535. (d) Azzena, U. *J. Chem. Soc., Perkin Trans. 1* **2002**, 360. (e) Lahm, G.; Stoye, A.; Opatz, T. *J. Org. Chem.* **2012**, *77*, 6620.