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Asymmetric Redox-Annulation of Cyclic Amines

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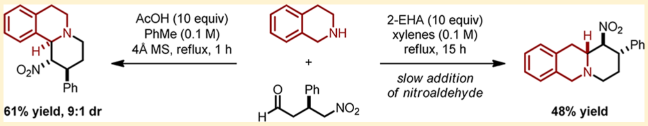
S *Supporting Information*

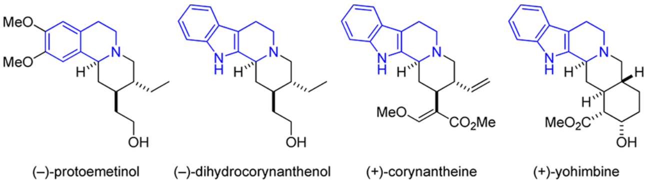
ABSTRACT: Cyclic amines such as 1,2,3,4-tetrahydroisoquinoline undergo regiodivergent annulation reactions with 4-nitrobutyraldehydes. These redox-neutral transformations enable the asymmetric synthesis of highly substituted polycyclic ring systems in just two steps from commercial materials. The utility of this process is illustrated in a rapid synthesis of (−)-protoemetinol. Computational studies provide mechanistic insights and implicate the elimination of acetic acid from an ammonium nitronate intermediate as the rate-determining step.



INTRODUCTION

Tryptoline (tetrahydro-β-carboline) and 1,2,3,4-tetrahydroisoquinoline (THIQ) are substructures of numerous bioactive natural products that contain additional fused rings (Scheme 1).[1]

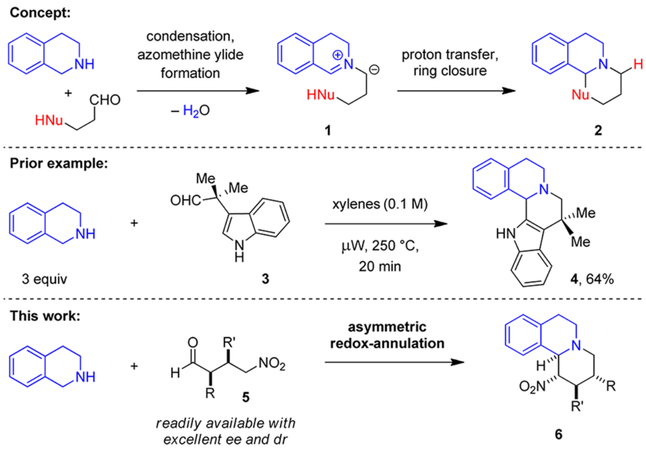
Scheme 1. Selected Natural Products with THIQ and Tryptoline Substructures



The desire to build such highly substituted polycyclic compounds with complete stereocontrol has inspired the development of numerous synthetic methods.[2] Here, we report a redox-neutral annulation strategy that enables the asymmetric synthesis of relevant core structures from simple THIQ or tryptoline and readily available, highly enantioenriched 4-nitrobutyraldehydes.

As part of our ongoing efforts to develop practical methods for the C−H functionalization of amines,[3,4] we recently reported the first examples of what may be termed a redox-annulation of amines (Scheme 2).[3b] Conceptually, an amine such as THIQ engages an aldehyde with a pendent carbon nucleophile to form product **2** via reductive *N*-alkylation/oxidative C−C bond formation in an overall redox-neutral process.[5] Condensation of the two components initially forms an azomethine ylide intermediate **1** that, following proton transfer and ring closure, provides product **2**.[6−9] For instance, THIQ and indole aldehyde **3** form annulation product **4** in 64% yield.[3b] While this is a clear demonstration of the utility of this approach for the facile preparation of polycyclic ring systems, the method requires relatively high reaction temperatures. More serious limitations are the need for using nonenolizable aldehydes and electron-rich aromatic nucleophiles (e.g., indole, β-naphthol).

Scheme 2. Redox-Annulation



In order to be applicable to the synthesis of structures related to those shown in Scheme 1, the redox-annulation would have to proceed with enolizable aldehydes capable of installing a fully saturated ring bearing variable substituents. These considerations, coupled with our goal to perform amine redox-annulations in asymmetric fashion, led to the identification of 4-nitrobutyraldehydes **5** as ideal reaction partners. These precursors are easily prepared in a single step and nearly enantiopure form from aldehydes and nitroalkenes by means of well-established organocatalytic methods.[10] The corresponding annulation products **6** are equipped with substituents in relevant positions and, due to the presence of a nitro group, offer numerous opportunities for further product manipulation.[11]

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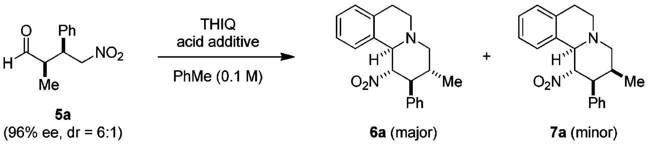
■ EXPERIMENTAL RESULTS AND DISCUSSION

We began our investigation into the feasibility of the proposed annulation process by employing **5a** and THIQ as model substrates (Table 1). The original annulation conditions developed for product **4** failed to provide any desired product (entry 1). Addition of acetic acid (1 equiv), an additive previously shown to be an excellent promoter for amine α-oxygenation[3h] and α-sulfenylation,[3j] did not provide any improvements (entry 2). Gratifyingly, the use of 5 equiv of acetic acid under otherwise identical conditions allowed for the isolation of the desired product as a 1.8:1 mixture of diastereomers **6a** and **7a** in 45% overall yield. The formation of **7a** is readily rationalized by the intermediacy of enamines, causing epimerization of the stereogenic center in α-position of the aldehyde prior to the annulation step. Excess acetic acid apparently reduces the concentration of enamine intermediates, facilitating the redox-isomerization and minimizing undesired side reactions. Indeed, further increase of the amount of acetic acid to 10 equiv led to an increase in yield to 65% (entry 4). With 2-ethylhexanoic acid (2-EHA), the product yield was only 30% (entry 5). Remarkably, with benzoic acid, previously shown to be an excellent catalyst for amine α-functionalizations, no desired product was formed; only epimerization of the starting material was observed (entry 6). Addition of molecular sieves had a beneficial effect, and the amount of THIQ could be lowered to 2 equiv (entry 7). A reduction in temperature from 150 to 120 °C, while reducing the reaction time from 15 to 2 min, led to a further increase in yield to 71% (entry 8). A reaction performed under simple reflux conditions was completed in only 1 h and gave rise to nearly identical results (entry 9). Even at a temperature of only 60 °C, the reaction progressed in an efficient manner (entry 10). For the sake of convenience and to keep reaction times brief, subsequent experiments were performed under reflux in toluene.

Table 1. Evaluation of Reaction Conditions[a]

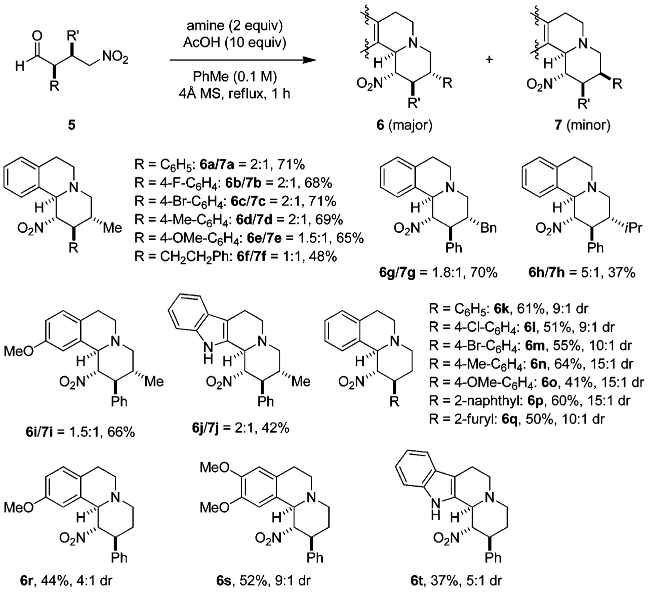


entry	acid (equiv)	temp (°C)	time (min)	yield (%)	ratio **6a**:**7a**
1		150 (μW)	15	complex	ND
2	AcOH (1)	150 (μW)	15	complex	ND
3	AcOH (5)	150 (μW)	15	45	1.8:1
4	AcOH (10)	150 (μW)	15	65	2:1
5	2-EHA (10)	150 (μW)	15	30	1:1
6	$PhCO_2H$ (10)	150 (μW)	15	NR[b]	
7[c]	AcOH (10)	150 (μW)	15	65	1.8:1
8[c]	AcOH (10)	120 (μW)	2	71	1.8:1
9[c]	AcOH (10)	reflux	1 h	71	2:1[d]
10[c]	AcOH (10)	60	15 h	62	2:1

[a] Reactions were performed with **5a** (0.2 mmol) and THIQ (4 equiv). Product ratios were determined by ^1H NMR analysis of the crude reaction mixture. Yields correspond to combined, isolated yields of both diastereomers. ND: not determined. NR: no reaction. [b] Partially epimerized starting material was recovered (dr = 1:1). [c] Performed with **5a** (0.6 mmol) and 2 equiv of THIQ in the presence of 4 Å MS. [d] Both **6a** and **7a** were obtained with 95% ee.

The scope of the asymmetric redox-annulation of THIQ was explored with a range of 4-nitrobutyraldehydes (Scheme 3). α,β-Disubstituted 4-nitrobutyraldehydes **5** with various substitution patterns readily underwent the title reaction, providing products **6**/**7** in moderate to good yields and with diastereoselectivities of up to 5:1. Notably, in all cases, separation of the two diastereomeric products was readily accomplished by standard column chromatography. 4-Nitrobutyraldehydes without α-substituents gave rise to products **6** with good to excellent levels of diastereoselectivity.[12] Importantly, the reaction of mono- and disubstituted 4-nitrobutyraldehydes was also applicable to substituted THIQs and tryptoline.

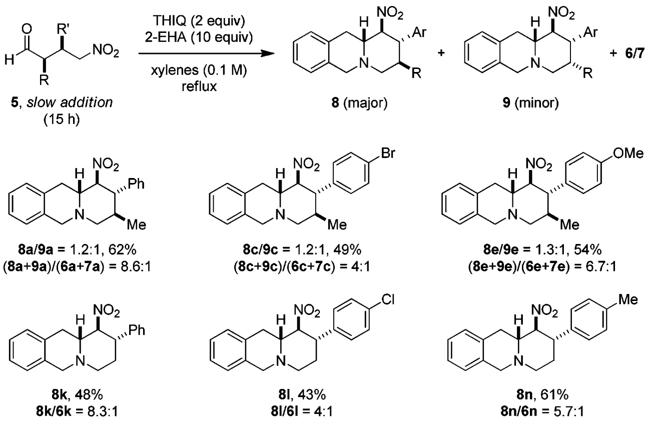
Scheme 3. Scope of the Asymmetric Redox-Annulation[a]



[a] Reactions were performed on a 0.6 mmol scale. For products **6a**/**7a**–**6j**/**7j**, yields correspond to combined, isolated yields of both diastereomers. For products **6k**–**t**, yields correspond to isolated yields of the major diastereomer.

During the development of the title reaction, we occasionally observed small amounts of the regioisomeric annulation products **8** and **9** (Scheme 4). Following extensive experimentation, conditions were identified that provided **8** and **9** as the major products with regioselectivities of up to nearly 9:1.[13] Diastereoselectivities were similar to those observed in redox-annulations that involve the benzylic position, with β-

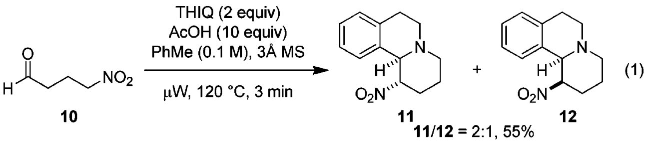
Scheme 4. Divergent Regioselectivity in the Asymmetric Redox-Annulation[a]

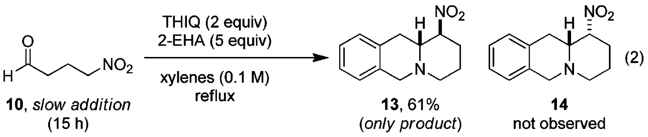


[a] Reactions were performed on a 0.6 mmol scale.

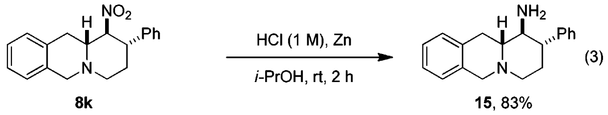
monosubstituted 4-nitrobutyraldehydes providing products **8** in highly diastereoselective fashion. Key to accomplishing redox-annulations at the less reactive α-C−H bond is performing the reaction at higher temperature (reflux in xylenes) and to maintain a low concentration of **5**. This was achieved by syringe pump addition of the corresponding 4-nitrobutyraldehyde. Best results were obtained in the absence of molecular sieves.[14]

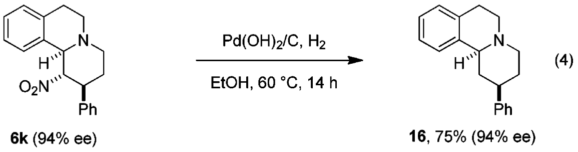
Redox-annulations of THIQ were also performed with parent 4-nitrobutyraldehyde **10** eqs 1 and 2. Regioselective annulation was accomplished at either position through judicious choice of reaction conditions. Diastereomeric products **11** and **12** were obtained in a 2:1 ratio and 55% overall yield (eq 1). This appears to correspond to the thermodynamic equilibrium ratio of these two products.[15] Notably, product **13** was obtained as a single diastereo- and regioisomer in 61% yield (eq 2).

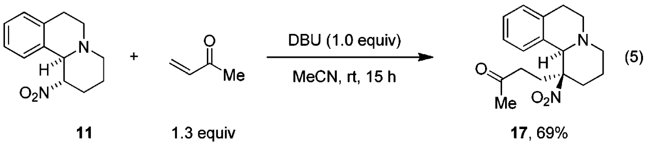




Products derived from the redox-annulation could be readily modified. For instance, reduction of **8k** with Zn/HCl provided amine **15** in 83% yield (eq 3). Removal of the nitro group in **6k** via hydrogenolysis provided heterocycle **16** in 75% yield (eq 4. Importantly, the enantiomeric purity of the material was not affected by this transformation. Finally, compound **11** was alkylated with methyl vinyl ketone in the presence of DBU to yield product **17** as a single diastereomer in 69% yield (eq 5).

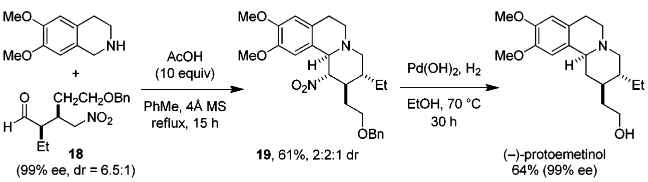






The asymmetric redox-annulation was applied to a short synthesis of the natural product (−)-protoemetinol (Scheme 5).

Scheme 5. Synthesis of (−)-Protoemetinol



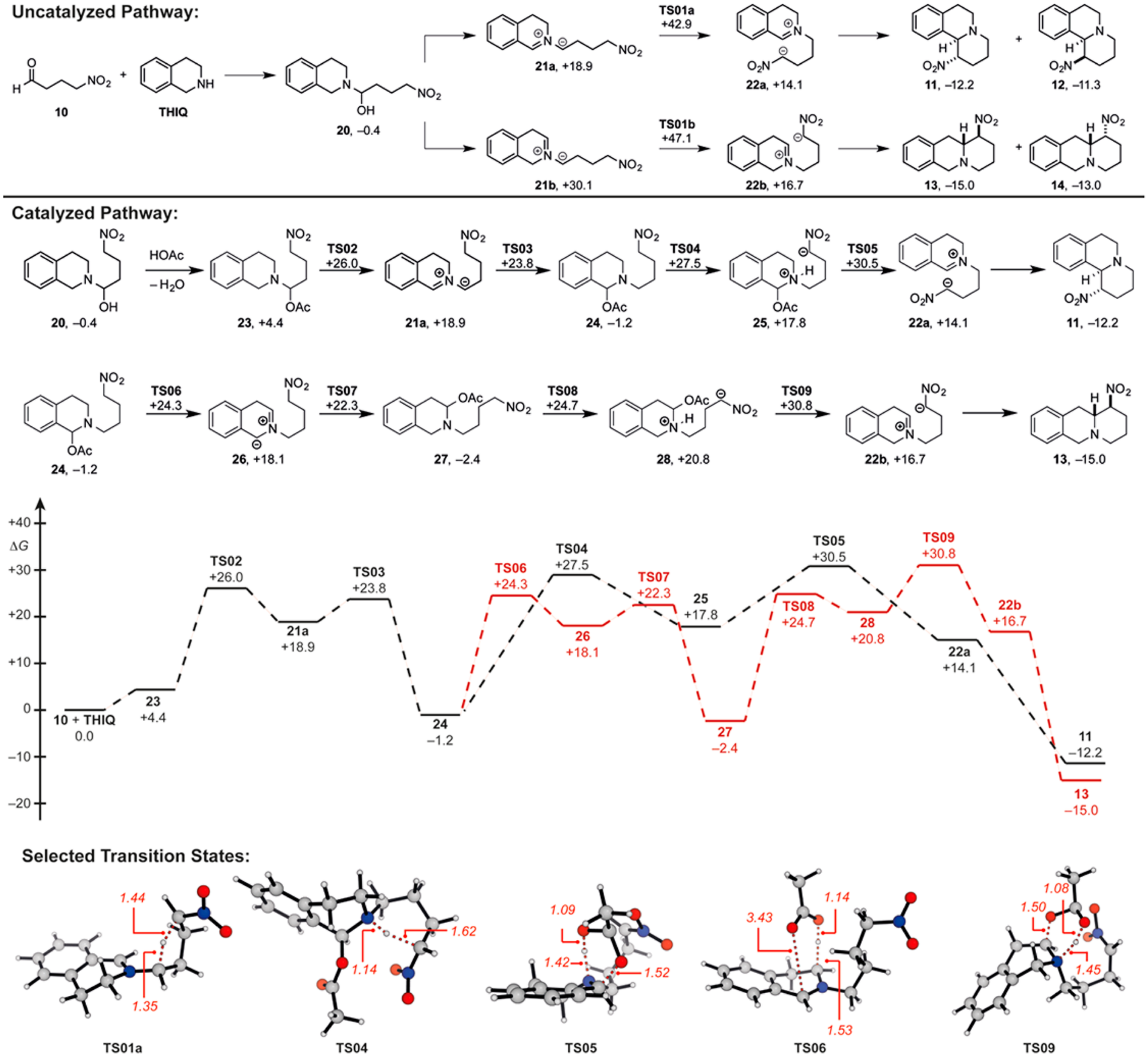
Condensation of 6,7-dimethoxy-THIQ and **18** resulted in the formation of **19** and two of its diastereomers in 61% overall yield. The major diastereomer was converted to (−)-protoemetinol in a single operation that served to remove both the nitro and benzyl groups.

■ COMPUTATIONAL RESULTS AND DISCUSSION

To shed light on the mechanism of the redox-annulations discussed above and to rationalize the high regioselectivities of eqs 1 and 2, we carefully analyzed the reaction between THIQ and 4-nitrobutyraldehyde (**10**) by DFT calculations [M06-2X-D3/def2-QZVP/IEFPCM//M06-L-D3/6-31+G(d,p)/IEFPCM]. Although the uncatalyzed reaction of THIQ and **10** results in complex mixtures, knowledge of this pathway is important to understand any potential background reaction (Scheme 6). Consequently, the uncatalyzed pathway was evaluated first. In the first step of this transformation, THIQ and **10** form the hemiaminal **20** in an almost thermoneutral reaction. Water can be eliminated from **20** in two different orientations yielding the azomethine ylides **21a** and **21b** in highly endergonic transformations (ΔG = +18.9 and +30.1 kcal mol^{-1}). Due to the direct conjugation of the azomethine ylide with the benzene ring, ylide **21a** is significantly more stable than its isomer **21b**. We were unable to locate any transition states for this elimination, and all attempts starting from different transition state guesses resulted in a barrierless addition of water to the corresponding azomethine ylides. Therefore, it was concluded that this reaction occurs without a significant barrier which can be rationalized with the high reactivities of the formed azomethine ylides. In principle, the hemiaminal **20** could also form the corresponding enamine (not shown in Scheme 6) through another elimination of water. This transformation is thermoneutral (ΔG = −0.1 kcal mol^{-1}) and can account for the epimerization of α-substituted aldehydes (Table1). Next, an intramolecular proton transfer takes place between the nitroalkane moiety and the ylide. In both transition states **TS01a** and **TS01b**, the proton transfers occur through five-membered transition states and are very high in energy ($\Delta G^{\ddagger}$ = +42.9 and +47.1 kcal mol^{-1}). In an alternative pathway, the zwitterions **22** could also be formed via a zwitterionic intermediate with an exocyclic double bond (not shown in Scheme 6). As this isomer is formed in a highly endergonic step (ΔG = +25 kcal mol^{-1}) and requires a highly unfavorable 1,3-proton shift, this pathway seems less likely. The zwitterions **22a** and **22b** subsequently undergo intramolecular cyclization reactions to either form the diastereomeric products **11** and **12** or the regioisomers **13** and **14**. These reactions occur without a significant barrier, which can be explained by the high reactivities of nitronate anions and iminium cations.[16] Our calculations predict a small thermodynamic preference ($\Delta\Delta G$ = 0.9 kcal mol^{-1}) for the *cis*-product **11** over the *trans*-product **12**, which is in good agreement with the experimental 2:1 ratio. A much stronger preference ($\Delta\Delta G$ = 2.0 kcal mol^{-1}) for the *cis*-isomer was calculated for **13** compared to **14** in line with the exclusive isolation of **13**.

As the intramolecular proton transfers yielding the zwitterions **22** are very high in energy, we were wondering whether acetic acid could act as a proton shuttle to bypass **TS1a** and **TS1b** as seen in related oxygenation and sulfenylation reactions.[3h,j] However, starting from many different transition-state guesses, we were unable to locate any transition states for such mechanisms. Instead, these structures relaxed to hydrogen-bonded adducts between acetic acid and different polar groups of the azomethine ylides. Furthermore, acetic acid could also

Scheme 6. Calculated Free Energies for the Uncatalyzed and Acetic-Acid-Catalyzed Annulation Reactions and Selected Transition-State Structures [kcal mol^{-1}, M06-2X-D3/def2-QZVP/IEFPCM//M06-L-D3/6-31+G(d,p)/IEFPCM]



facilitate the formation of iminium ions as intermediates in these transformations, but based on our calculations, iminium ions are very high in energy ($\Delta G^{\ddagger} > 47$ kcal mol^{-1}; see the Supporting Information for more details) and were thus ruled out. Instead, we considered a concerted elimination of acetic acid from acetylated hemiaminals (*N*,*O*-acetals) as an alternative mechanism (e.g., **23**, **24**, and **27**), as previously suggested by Yu and coworkers in the formation of pyrroles from pyrroline and aldehydes.[17]

According to the calculated free energy profile in Scheme 6, the combination of THIQ, **10**, and AcOH results in the formation of the *N*,*O*-acetal **23** in a slightly endergonic reaction. Subsequently, acetic acid is eliminated in a concerted yet highly asynchronous transition state (**TS02**, see the Supporting Information) yielding the azomethine ylide **21a**. Next, acetic acid adds across the other terminus of the ylide (**TS03**), resulting in the formation of the more stable isomeric *N*,*O*-acetal **24**. This intermediate can now react via two pathways to form either the product **11** (or **12**) or the regioisomer **13**. For the formation of **11**, the next step involves an intramolecular deprotonation of an acidic proton in *α*-position of the nitro group. This reaction proceeds through a six-membered transition state (**TS04**) and yields the ammonium nitronate **25**. This endergonic step is also reflected in a very late transition state with a short N−H bond (1.14 Å). Next, acetic acid is eliminated through **TS05** ($\Delta G^{\ddagger} =$ 30.5 kcal mol^{-1}), which is also the rate-determining step for the formation of **11**. This reaction proceeds in a concerted yet highly asynchronous fashion in which the cleavage of the C−O bond lacks behind the proton transfer. After cyclization of the generated zwitterion **22a**, the annulation product **11** is formed in an overall exergonic reaction.

The alternate regioisomer **13** could also be obtained from *N*,*O*-acetal intermediate **23**. This pathway is identical to the one discussed for the formation of **11** for the transformation of **23** to

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24. However, from there it continues with an almost isoenergetic isomerization of the *N*,*O*-acetal **24** to the *N*,*O*-acetal **27**. This two-step process consists of elimination and subsequent addition of acetic acid through transition states **TS06** and **TS07**.[18] In principle, **27** could also be obtained in a sequence of elimination and addition of AcOH (**23** → **21b** → **27**, not shown in Scheme 6), and we have calculated the transition states ($\Delta G^{\ddagger}$ = 30.8 and 29.9 kcal mol^{-1}, respectively, Supporting Information) for these transformations as well. As they are significantly higher in energy than the barriers for the pathway involving **26** (Scheme 6), we have to conclude that the azomethine ylide **21b** does not lie on the reaction coordinate for the formation of either **11** or **13**.

Next, the ammonium nitronate **28** is formed through **TS08** before the rate-determining elimination of acetic acid takes place (**TS09**, $\Delta G^{\ddagger}$ = +30.8 kcal mol^{-1}). Alternatively, zwitterions **22** could also be obtained directly from the azomethine ylide **26** through an intramolecular proton transfer. However, these reactions would occur with significantly higher barriers ($\Delta G^{\ddagger}$ = +40.4 kcal mol^{-1} for **26** → **22a** and $\Delta G^{\ddagger}$ = +37.6 kcal mol^{-1} for **26** → **22b**) and thus appear to play no role in this transformation. Finally, the thermodynamic product **13** is formed via cyclization of the zwitterion **22b**.

The calculated energy profile is in good qualitative agreement with the experimental findings. The calculated barriers might be slightly overestimated as in the experimental studies both acetic acid and THIQ are used in excess. The results of eqs 1 and 2 can also be rationalized using the computational data in Scheme 6. Although the energetic difference between both rate-determining steps **TS05** and **TS09** is rather small, the formation of **11** and **12** is kinetically preferred. The conditions of eq 1 favor the formation of the kinetically preferred products **11** and **12**, while the thermodynamically more stable product **13** is obtained exclusively at higher temperatures and longer reaction times.

■ CONCLUSIONS

We have reported the first examples of asymmetric redox-annulations of tetrahydroisoquinolines and tryptoline with readily available, highly enantioenriched 4-nitrobutyraldehydes. Reactions proceed under operationally convenient conditions and do not require the use of expensive catalysts. This strategy enabled the asymmetric preparation of polycyclic amines that contain the core structure of various bioactive compounds in just two steps from commercial materials. Simply by changing the reaction conditions, regioselective redox-annulations can be achieved at the nonbenzylic position of THIQ, enabling the rapid exploration of new chemical space.

■ COMPUTATIONAL METHODS

For the computational investigations, the conformational space for each structure was explored using the OPLS-2005 force field[19] and a modified Monte Carlo search algorithm implemented in MacroModel 10.6.[20] An energy cutoff of 20 kcal mol^{-1} was employed for the conformational analysis, and structures with heavy-atom root-mean-square deviations (RMSD) less than 2 Å after the initial force field optimizations were considered to be the same conformer. The remaining structures were subsequently optimized with the dispersion-corrected M06-L functional[21] with Grimme's dispersion-correction D3[22] and the double-ζ basis set 6-31+G(d,p). Solvation by toluene was taken into account by using the integral equation formalism polarizable continuum model (IEFPCM)[23] for all calculations. Vibrational analysis verified that each structure was a minimum or transition state. Following the intrinsic reaction coordinates (IRC) confirmed that all transition states connected the corresponding reactants and products on the potential energy surface. Thermal corrections were obtained from unscaled harmonic vibrational frequencies at the same level of theory for a standard state of 1 mol L^{-1} and 298.15 K. Entropic contributions to the reported free energies were derived from partition functions evaluated with the quasiharmonic approximation by Truhlar and co-workers.[24] Electronic energies were subsequently obtained from single-point calculations of the M06-L-D3 geometries employing the meta-hybrid M06-2X functional,[25] Grimme's dispersion-correction D3 (zero-damping), the large quadruple-ζ basis set def2-QZVP,[26] and IEFPCM for toluene, a level expected to give accurate energies.[27] An ultrafine grid was used throughout this study for numerical integration of the density. All density functional theory calculations were performed with Gaussian 09.[28]

■ EXPERIMENTAL SECTION

General Information. Starting materials, reagents, and solvents were purchased from commercial sources and used as received unless stated otherwise. Propionaldehyde, isovaleraldehyde, hydrocinnamaldehyde, and *trans*-cinnamaldehyde were purified by distillation prior to use. 1,2,3,4-Tetrahydroisoquinoline was distilled prior to use. Powdered molecular sieves (4 Å) were activated before use by heating in a furnace to 300 °C for 2 h and were stored in a desiccator. Nitroalkenes were prepared according to previously reported procedures.[29] Microwave reactions were carried out in a CEM Discover reactor. Silicon carbide (SiC) passive heating elements were purchased from Anton Paar. Analytical thin-layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished with UV light, potassium permanganate, and Dragendorff−Munier stains followed by heating. Purification of reaction products was carried out by flash column chromatography using Sorbent Technologies Standard grade silica gel (60 Å, 230−400 mesh). Chemical shifts in proton nuclear magnetic resonance spectra (^{1}H NMR) are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 7.26 ppm, CD_2Cl_2 at 5.30 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 hertz. Chemical shifts in proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 77.0 ppm, CD_2Cl_2 at 54.0 ppm). HRMS spectrometry data were recorded on a spectrometer operating on ESI-FTICR (MeCN as solvent). Optical rotations were measured using a 1 mL cell with a 1 dm path length at 589 nm and at 25 °C. (*S*)-Diphenylprolinol trimethylsilyl ether was prepared according to a literature procedure.[30]

General Procedures for the Synthesis of Starting Materials.[10] *General Procedure A.* To a stirred solution of nitroalkene (3 mmol, 1 equiv), (*S*)-diphenylprolinol trimethylsilyl ether (0.15 mmol, 5 mol %), and *p*-nitrophenol (0.15 mmol, 5 mol %) in toluene (3 mL) was added aldehyde (4.5 mmol, 1.5 equiv) at room temperature. The reaction progress was monitored by TLC. After completion, the reaction was quenched by the addition of 1 M HCl (10 mL) and the resulting mixture extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the residue purified by silica gel chromatography.

General Procedure B. To a stirred solution of *trans*-cinnamaldehyde (3 mmol, 1 equiv), (*S*)-diphenylprolinol trimethylsilyl ether (0.3 mmol, 10 mol %), and benzoic acid (0.6 mmol, 20 mol %) in MeOH (6 mL) was added nitromethane (9 mmol, 3 equiv) at room temperature. The reaction progress was monitored by TLC. After completion, the reaction was quenched by the addition of saturated $NaHCO_3$ (10 mL) and the resulting mixture extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the residue purified by silica gel chromatography.

General Procedure C. To a stirred solution of nitroalkene (3 mmol, 1 equiv) and (*S*)-diphenylprolinol trimethylsilyl ether (0.3 mmol, 10 mol %) in dioxane (0.6 mL) was added acetaldehyde (30 mmol, 10 equiv) at 0 °C. The reaction mixture was stirred at room temperature, and the reaction progress was monitored by TLC. After completion, the reaction was quenched by the addition of 1 M HCl (10 mL) and the resulting mixture extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the residue purified by silica gel chromatography.

(2R,3S)-2-Methyl-4-nitro-3-phenylbutanal. The title compound was synthesized following general procedure A.[10j] The product was obtained as a yellow oil in 78% yield (mixture of two diastereomers). Compound **5a** was previously reported, and its published characterization data matched our own in all respects.[10j] The enantiomeric excess was determined by HPLC with Daicel Chiralcel OD-H: *n*-hexane/*i*-PrOH = 90/10, flow rate = 1 mL/min, UV = 210 nm, t_R = 22.4 min (minor) and t_R = 32.9 min (major), 96% ee.

(2R,3S)-3-(4-Fluorophenyl)-2-methyl-4-nitrobutanal. The title compound was synthesized following general procedure A.[10j] The product was obtained as a yellow oil in 78% yield (mixture of two diastereomers). Compound **5b** was previously reported, and its published characterization data matched our own in all respects.[10i]

(2R,3S)-3-(4-Bromophenyl)-2-methyl-4-nitrobutanal. The title compound was synthesized following general procedure A.[10j] The product was obtained as a yellow solid in 70% yield (mixture of two diastereomers). Compound **5c** was previously reported, and its published characterization data matched our own in all respects.[10j]

(2R,3S)-2-Methyl-4-nitro-3-(p-tolyl)butanal. The title compound was synthesized following general procedure A.[10j] The product was obtained as a yellow oil in 70% yield (mixture of two diastereomers). Compound **5d** was previously reported, and its published characterization data matched our own in all respects.[10c]

(2R,3S)-3-(4-Methoxyphenyl)-2-methyl-4-nitrobutanal. The title compound was synthesized following general procedure A.[10j] The product was obtained as a yellow oil in 68% yield (mixture of two diastereomers). Compound **5e** was previously reported, and its published characterization data matched our own in all respects.[10j]

(2R,3R)-2-Methyl-3-(nitromethyl)-5-phenylpentanal. The title compound was synthesized following general procedure A.[10j] The product was obtained as a yellow oil in 57% yield (mixture of two diastereomers). Compound **5f** was previously reported, and its published characterization data matched our own in all respects.[10j]

(2R,3S)-2-Benzyl-4-nitro-3-phenylbutanal. The title compound was synthesized following general procedure A.[10j] The product was obtained as a yellow oil in 66% yield (mixture of two diastereomers). Compound **5g** was previously reported, and its published characterization data matched our own in all respects.[10j]

(2R,3S)-2-Isopropyl-4-nitro-3-phenylbutanal. The title compound was synthesized following general procedure A.[10j] The product was obtained as a white solid in 57% yield (mixture of two diastereomers). Compound **5h** was previously reported, and its published characterization data matched our own in all respects.[10j]

(S)-4-Nitro-3-phenylbutanal. The title compound was synthesized following general procedure B.[10f] The product was obtained as a yellow oil in 74% yield. Compound **5k** was previously reported, and its published characterization data matched our own in all respects.[10f] The product was reduced to the corresponding alcohol using $NaBH_4$ for HPLC analysis:[31] Daicel Chiralcel OD-H, *n*-hexane/*i*-PrOH = 90/10, flow rate = 1 mL/min, UV = 230 nm, t_R = 17.2 min (minor) and t_R = 21.9 min (major), 95% ee.

(S)-3-(4-Chlorophenyl)-4-nitrobutanal. The title compound was synthesized following general procedure C.[10h] The product was obtained as a yellow oil in 44% yield. Compound **5l** was previously reported, and its published characterization data matched our own in all respects.[10h]

(S)-3-(4-Bromophenyl)-4-nitrobutanal. The title compound was synthesized following general procedure C.[10h] The product was obtained as a yellow oil in 34% yield. Compound **5m** was previously reported, and its published characterization data matched our own in all respects.[10h]

(S)-4-Nitro-3-(p-tolyl)butanal. The title compound was synthesized following general procedure C.[10h] The product was obtained as a yellow solid in 72% yield. Compound **5n** was previously reported, and its published characterization data matched our own in all respects.[10h]

(S)-3-(4-Methoxyphenyl)-4-nitrobutanal. The title compound was synthesized following general procedure C.[10h] The product was obtained as a yellow oil in 56% yield. Compound **5o** was previously reported, and its published characterization data matched our own in all respects.[10h]

(S)-3-(Naphthalen-2-yl)-4-nitrobutanal. The title compound was synthesized following general procedure C.[10h] The product was obtained as a yellow solid in 69% yield. Compound **5p** was previously reported, and its published characterization data matched our own in all respects.[10h]

(R)-3-(Furan-2-yl)-4-nitrobutanal. The title compound was synthesized following general procedure C.[10h] The product was obtained as a yellow oil in 42% yield. Compound **5q** was previously reported, and its published characterization data matched our own in all respects.[10h]

General Procedures for the Asymmetric Redox-Annulation.

General Procedure A. To a mixture of aldehyde (0.6 mmol, 1 equiv), 4 Å MS (0.2 g) and AcOH (6 mmol, 10 equiv) in toluene (6 mL) was added the amine (1.2 mmol, 2 equiv) at room temperature. The mixture was heated under reflux for 1 h. Subsequently, the reaction mixture was allowed to cool to room temperature, diluted with EtOAc (20 mL), and washed with saturated aqueous $NaHCO_3$ (3 × 10 mL). The combined aqueous layers were extracted with EtOAc (2 × 10 mL) and the combined organic layers dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the residue purified by silica gel chromatography.

General Procedure B. A solution of amine (1.2 mmol, 2 equiv) and 2-EHA (6 mmol, 10 equiv) in xylenes (6 mL) was heated under reflux. The aldehyde (0.6 mmol, 0.12 M solution in xylenes) was delivered through the top of the reflux condenser over 15 h via syringe pump. The reaction was then kept under reflux for a further 0.5−1 h at which time the aldehyde was consumed as judged by TLC analysis. Subsequently, the reaction mixture was allowed to cool to room temperature, diluted with EtOAc (20 mL), and washed with saturated aqueous $NaHCO_3$ (3 × 20 mL). The combined aqueous layers were extracted with EtOAc (2 × 10 mL) and the combined organic layers dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the residue purified by silica gel chromatography.

General Procedure C. A 10 mL microwave reaction tube was charged with a 10 × 8 mm SiC passive heating element, aldehyde (0.6 mmol, 1 equiv), toluene (6 mL), amine (1.2 mmol, 2 equiv), 3 Å MS (0.2 g), and AcOH (6 mmol, 10 equiv). The reaction tube was sealed with a Teflon-lined snap cap and heated in a microwave reactor at 120 °C (0−15 psi) for 3 min. After being cooled with compressed air flow, the reaction mixture was diluted with EtOAc (20 mL) and washed with saturated aqueous $NaHCO_3$ (3 × 20 mL). The combined aqueous layers were extracted with EtOAc (2 × 10 mL) and the combined organic layers dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the residue purified by silica gel chromatography.

*Products **6a** and **7a**.* Following general procedure A, products **6a** and **7a** were obtained in a 2:1 ratio (71% combined yield). The relative stereochemistry was determined by GCOSY and NOESY NMR.

*Characterization data for **6a**:* yellowish oil; R_f = 0.32 in 20% EtOAc/Hex; $[\alpha]_D^{25}$ − 31.9 (*c* 0.5, $CHCl_3$); IR (KBr) 3063, 3028, 2959, 2927, 2828, 1539, 1492, 1452, 1311, 1264, 1153, 1094, 750, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.28 (comp, 2H), 7.27−7.25 (m, 1H), 7.19−7.15 (comp, 4H), 7.07 (app t, J = 7.5 Hz, 1H), 6.87 (app d, J = 7.8 Hz, 1H), 4.97 (dd, J = 11.2, 9.8 Hz, 1H), 4.39 (d, J = 9.8 Hz, 1H), 3.34 (ddd, J = 11.4, 9.8, 4.9 Hz, 1H), 3.19 (dd, J = 13.7, 4.1 Hz, 1H), 3.11 (app t, J = 11.4 Hz, 1H), 3.05 (dd, J = 9.6, 6.7 Hz, 1H), 3.00−2.98 (m, 1H), 2.96−2.92 (comp, 2H), 2.30−2.23 (m, 1H), 0.73 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2(2), 134.2(1), 132.9, 129.5, 129.1, 128.1, 128.0, 127.0, 126.3, 91.7, 77.6, 77.3, 77.1, 63.0, 62.1, 56.0, 46.5, 31.2, 29.9, 16.7; HRMS (ESI) m/z calcd for $C_{20}H_{23}N_2O_2$ $[M + H]^+$ 323.1754, found 323.1765; HPLC Daicel Chiralcel OD-H, *n*-hexane/*i*-PrOH = 90/10, flow rate = 1 mL/min; UV = 230 nm, t_R = 7.1 min (major) and t_R = 8.0 min (minor), 95% ee.

*Characterization data for **7a**.* yellowish solid; mp 180−182 °C; R_f = 0.46 in 20% EtOAc/Hex; $[\alpha]_D^{25}$ −130.8 (*c* 0.5, $CHCl_3$); IR (KBr) 3061, 3031, 2957, 2957, 2927, 2893, 2811, 2767, 1546, 1489, 1452, 1351, 1299, 1146, 1111, 738, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32−7.29 (comp, 2H), 7.27−7.20 (comp, 2H), 7.20−7.14 (comp, 3H), 7.11 (app t, J = 7.6 Hz, 1H), 6.90 (app d, J = 7.9 Hz, 1H), 5.09 (dd, J = 11.7, 9.0 Hz, 1H), 4.20 (d, J = 9.0 Hz, 1H), 3.82 (dd, J = 11.7, 5.0 Hz, 1H), 3.25 (dd, J = 12.2, 3.5 Hz, 1H), 3.12 (ddd, J = 14.8, 9.4, 5.0 Hz, 1H), 3.05 (app dt, J = 10.9, 4.4 Hz, 1H), 2.98 (dd, J = 12.2, 1.8 Hz, 1H), 2.86 (ddd, J = 11.1, 9.4, 3.5 Hz, 1H), 2.76 (app dt, J = 15.4, 3.5 Hz, 1H), 2.18−2.09 (m, 1H), 0.95 (d, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 138.5, 136.0, 133.0, 129.5, 128.7, 128.2, 127.6, 127.5, 126.5, 126.3, 88.3, 66.0, 62.0, 52.7, 50.8, 35.8, 31.2, 15.2; m/z (ESI-MS) 323.2 [M + H]$^+$; HPLC Daicel Chiralcel OD-H, n-hexane/i-PrOH = 90/10, flow rate = 1 mL/min; UV = 230 nm, t_R = 6.3 min (minor) and t_R = 6.9 min (major), 95% ee.

*Products **6b** and **7b**.* Following general procedure A, products **6b** and **7b** were obtained in a 2:1 ratio (68% combined yield).

*Characterization data for **6b**:* yellowish oil; R_f = 0.32 in 20% EtOAc/Hex; $[\alpha]_D^{25}$ −32.6 (c 0.5, CHCl$_3$); IR (KBr) 3066, 3033, 2959, 2920, 2843, 1608, 1543, 1509, 1457, 1363, 1311, 1225, 1161, 1096, 733 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.23−7.18 (m, 1H), 7.16−7.13 (comp, 3H), 7.07 (app t, J = 7.5 Hz, 1H), 7.01−6.98 (comp, 2H), 6.85 (app d, J = 7.8 Hz, 1H), 4.90 (dd, J = 11.2, 9.8 Hz, 1H), 4.37 (d, J = 9.8 Hz, 1H), 3.32 (ddd, J = 11.2, 9.4, 4.9 Hz, 1H), 3.18 (dd, J = 13.7, 4.1 Hz, 1H), 3.10 (app t, J = 11.2 Hz, 1H), 3.03 (dd, J = 9.8, 6.7 Hz, 1H), 2.99−2.90 (comp, 3H), 2.25−2.17 (m, 1H), 0.72 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 162.4 (d, J = 246.2 Hz), 134.2, 134.0 (d, J = 3.3 Hz), 132.8, 129.6, 128.2, 126.9, 126.4(0), 126.3(6), 116.1 (d, J = 21.5 Hz), 91.8, 63.0, 62.0, 55.3, 46.5, 31.3, 29.9, 16.6; m/z (ESI-MS) 341.1 [M + H]$^+$.

*Characterization data for **7b**.* Yellowish solid; mp 100−103 °C; (R_f = 0.47 in 20% EtOAc/Hex); $[\alpha]_D^{25}$ −126.5 (c 0.5, CHCl$_3$); IR (KBr) 3063, 2969, 2935, 2910, 2814, 2769, 1608, 1546, 1506, 1427, 1348, 1299, 1222, 1161, 1109, 842, 812, 753, 696 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.21 (app t, J = 7.3 Hz, 1H), 7.18−7.09 (comp, 4H), 7.01−6.98 (comp, 2H), 6.88 (app d, J = 7.9 Hz, 1H), 5.02 (dd, J = 11.7, 9.0 Hz, 1H), 4.17 (d, J = 9.0 Hz, 1H), 3.80 (dd, J = 11.7, 4.9 Hz, 1H), 3.22 (dd, J = 12.2, 3.2 Hz, 1H), 3.12 (ddd, J = 14.6, 9.3, 4.6 Hz, 1H), 3.02 (app dt, J = 10.9, 4.6 Hz, 1H), 2.96 (dd, J = 12.2, 1.7 Hz, 1H), 2.84 (app td, J = 10.9, 3.2 Hz, 1H), 2.74 (app dt, J = 15.5, 3.2 Hz, 1H), 2.15−2.05 (m, 1H), 0.94 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 162.2 (d, J = 245.9 Hz), 136.1, 134.2(9), 134.2(6), 133.0, 129.7 (d, J = 8.0 Hz), 129.5, 127.6, 126.5, 126.2, 115.7 (d, J = 21.4 Hz), 88.6, 66.0, 61.9, 52.1, 50.8, 35.8, 31.2, 15.0; m/z (ESI-MS) 341.1 [M + H]$^+$.

*Products **6c** and **7c**.* Following general procedure A, products **6c** and **7c** were obtained in a 2:1 ratio (71% combined yield).

*Characterization data for **6c**:* yellowish solid; mp 130−132 °C; R_f = 0.37 in 20% EtOAc/Hex; $[\alpha]_D^{25}$ −38.6 (c 0.5, CHCl$_3$); IR (KBr) 3058, 3024, 2954, 2920, 2831, 1731, 1546, 1484, 1452, 1371, 1304, 1245, 1143, 1099, 1074, 1012, 958, 889, 817, 738, 674 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.45−7.40 (comp, 2H), 7.20 (app t, J = 7.4 Hz, 1H), 7.17−7.13 (m, 1H), 7.09−7.05 (comp, 3H), 6.85 (app d, J = 7.9 Hz, 1H), 4.90 (app t, J = 9.7 Hz, 1H), 4.36 (d, J = 9.7 Hz, 1H), 3.31 (ddd, J = 11.6, 10.9, 4.5 Hz, 1H), 3.18 (dd, J = 13.7, 3.9 Hz, 1H), 3.09 (app t, J = 11.6 Hz, 1H), 3.05−3.01 (m, 1H), 2.99−2.89 (comp, 3H), 2.25−2.16 (m, 1H), 0.72 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 137.3, 134.2, 132.7, 132.3, 129.6, 128.2, 126.9, 126.4, 121.9, 91.5, 63.0, 62.0, 55.5, 46.5, 31.2, 29.9, 16.6; m/z (ESI-MS) (^{79}Br) 401.1 [M + H]$^+$, (^{81}Br) 403.1 [M + H]$^+$.

*Characterization data for **7c**:* yellowish solid; mp 185−190 °C; R_f = 0.48 in 20% EtOAc/Hex; $[\alpha]_D^{25}$ −134.9 (c 0.5, CHCl$_3$); IR (KBr) 3061, 3026, 2964, 2927, 2895, 2809, 2764, 1541, 1492, 1447, 1425, 1351, 1291, 1148, 1109, 1072, 1037, 1007, 837, 807, 731 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.45−7.41(comp, 2H), 7.21 (app t, J = 7.4 Hz, 1H), 7.17−7.14 (m, 1H), 7.11 (app t, J = 7.6 Hz, 1H), 7.07−7.03 (comp, 2H), 6.87 (app d, J = 7.9 Hz, 1H), 5.02 (dd, J = 11.6, 9.0 Hz, 1H), 4.18 (d, J = 9.0 Hz, 1H), 3.78 (dd, J = 11.6, 4.9 Hz, 1H), 3.22 (dd, J = 12.2, 3.2 Hz, 1H), 3.11 (ddd, J = 14.8, 9.3, 4.7 Hz, 1H), 3.07−3.00 (m, 1H), 2.98−2.94 (m, 1H), 2.89−2.81 (m, 1H), 2.78−2.70 (m, 1H), 2.14−2.06 (m, 1H), 0.94 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 137.6, 136.1, 132.9(0), 131.9(2), 129.9, 129.6, 127.7, 126.5, 126.2, 121.5, 88.3, 66.0, 61.9, 52.3, 50.8, 35.7, 31.2, 15.0; m/z (ESI-MS) (^{79}Br) 401.1 [M + H]$^+$, (^{81}Br) 403.1 [M + H]$^+$.

*Products **6d** and **7d**.* Following general procedure A, products **6d** and **7d** were obtained in a 2:1 ratio (69% combined yield).

*Characterization data for **6d**:* yellowish oil; R_f = 0.35 in 20% EtOAc/Hex; $[\alpha]_D^{25}$ −34.8 (c 0.5, CHCl$_3$); IR (KBr) 3056, 3021, 2972, 2925, 2905, 2878, 2809, 2767, 1548, 1509, 1492, 1445, 1371, 1346, 1296, 1267, 1254, 1151, 1114, 1037, 951, 832, 802, 733 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.22−7.18 (m, 1H), 7.17−7.14 (m, 1H), 7.13−7.09 (comp, 2H), 7.09−7.04 (comp, 3H), 6.87 (app d, J = 7.9 Hz, 1H), 4.94 (dd, J = 11.2, 9.8 Hz, 1H), 4.38 (d, J = 9.8 Hz, 1H), 3.34 (ddd, J = 11.2, 9.6, 4.9 Hz, 1H), 3.18 (dd, J = 13.7, 4.1 Hz, 1H), 3.11−3.01 (comp, 2H), 3.00−2.91 (comp, 3H), 2.31 (s, 3H), 2.28−2.21 (m, 1H), 0.73 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 137.5, 135.2, 134.2, 133.0, 129.8, 129.5, 128.1, 127.0, 126.3, 105.0, 91.8, 63.0, 62.1, 55.7, 46.4, 31.2, 29.9, 21.3, 16.7; m/z (ESI-MS) 337.2 [M + H]$^+$.

*Characterization data for **7d**:* yellowish oil; R_f = 0.52 in 20% EtOAc/Hex; $[\alpha]_D^{25}$ −157.6 (c 0.5, CHCl$_3$); IR (KBr) 3056, 3024, 2962, 2920, 2895, 2809, 2767, 1546, 1509, 1494, 1450, 1368, 1348, 1294, 1264, 1148, 1114, 1039, 948, 837, 800, 726 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.23−7.19 (m, 1H), 7.17−7.14 (m, 1H), 7.12−7.10 (comp, 3H), 7.09−7.05 (comp, 2H), 6.90 (app d, J = 7.9 Hz, 1H), 5.07 (dd, J = 11.7, 9.0 Hz, 1H), 4.18 (d, J = 9.0 Hz, 1H), 3.78 (dd, J = 11.7, 4.9 Hz, 1H), 3.23 (dd, J = 12.2, 3.3 Hz, 1H), 3.12 (ddd, J = 14.8, 9.3, 4.9 Hz, 1H), 3.04 (app dt, J = 11.1, 4.4 Hz, 1H), 2.97 (dd, J = 12.2, 1.8 Hz, 1H), 2.85 (ddd, J = 11.1, 9.3, 3.5 Hz, 1H), 2.75 (app dt, J = 15.5, 3.5 Hz, 1H), 2.31 (s, 3H), 2.13−2.10 (m, 1H), 0.96 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 137.1, 136.1, 135.5, 133.2, 129.5, 129.4, 128.1, 127.6, 126.5, 126.3, 88.5, 66.0, 62.0, 52.4, 50.8, 35.9, 31.3, 21.3, 15.2; m/z (ESI-MS) 337.2 [M + H]$^+$.

*Products **6e** and **7e**.* Following general procedure A, products **6e** and **7e** were obtained in a 1.5:1 ratio (65% combined yield).

*Characterization data for **6e**:* yellowish solid; mp 110−113 °C; R_f = 0.24 in 20% EtOAc/Hex; $[\alpha]_D^{25}$ −24.5 (c 0.5, CHCl$_3$); IR (KBr) 2954, 2932, 2902, 2833, 2804, 1615, 1546, 1541, 1462, 1380, 1249, 1175, 1116, 1035, 837, 740 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.21−7.17 (m, 1H), 7.16−7.14 (m, 1H), 7.09−7.05 (comp, 3H), 6.86−6.82 (comp, 3H), 4.90 (dd, J = 11.0, 9.8 Hz, 1H), 4.37 (d, J = 9.8 Hz, 1H), 3.77 (s, 3H), 3.33 (ddd, J = 11.3, 9.8, 4.9 Hz, 1H), 3.18 (dd, J = 13.7, 4.1 Hz, 1H), 3.09−3.01 (comp, 2H), 2.99−2.90 (comp, 3H), 2.26−2.17 (m, 1H), 0.73 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 159.2, 134.1, 132.9, 130.2, 129.5, 128.1, 126.9, 126.3, 114.5, 91.9, 62.9, 62.1, 55.4, 55.2, 46.5, 31.3, 29.9, 16.7; m/z (ESI-MS) 353.2 [M + H]$^+$.

*Characterization data for **7e**:* yellowish solid; mp 120−122 °C; R_f = 0.41 in 20% EtOAc/Hex; $[\alpha]_D^{25}$ −178.1 (c 0.5, CHCl$_3$); IR (KBr) 2954, 2927, 2833, 1613, 1543, 1506, 1452, 1361, 1341, 1247, 1180, 1027, 820, 745 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.22−7.18 (m, 1H), 7.16−7.15 (m, 1H), 7.12−7.09 (comp, 3H), 6.89 (app d, J = 7.9 Hz, 1H), 6.85−6.81 (comp, 2H), 5.03 (dd, J = 11.5, 9.2 Hz, 1H), 4.19 (d, J = 9.2 Hz, 1H), 3.78 (s, 3H), 3.76 (dd, J = 8.0, 4.9 Hz, 1H), 3.24−3.22 (m, 1H), 3.11 (ddd, J = 14.6, 9.1, 4.7 Hz, 1H), 3.08−3.02 (m, 1H), 2.98−2.95 (m, 1H), 2.87−2.84 (m, 1H), 2.78−2.75 (m, 1H), 2.15−2.04 (m, 1H), 0.95 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 158.9, 136.0, 133.2, 130.5, 129.5, 129.2, 127.6, 126.5, 126.3, 114.1, 88.6, 65.9, 61.9, 55.4, 52.0, 50.8, 35.9, 31.1, 15.2; m/z (ESI-MS) 353.1 [M + H]$^+$.

*Products **6f** and **7f**.* Following general procedure A, products **6f** and **7f** were obtained in a 1:1 ratio (48% combined yield).

*Characterization data for **6f**:* yellowish oil; R_f = 0.28 in 10% EtOAc/Hex; $[\alpha]_D^{25}$ −37.4 (c 0.5, CHCl$_3$); IR (KBr) 3061, 3024, 2952, 2920, 2870, 1598, 1541, 1497, 1452, 1371, 1314, 1272, 1143, 1096, 941, 750, 698 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.30−7.26 (comp, 2H), 7.24−7.17 (comp, 2H), 7.18−7.12 (comp, 3H), 7.10 (app td, J = 7.6, 1.5 Hz, 1H), 6.89 (app d, J = 7.8 Hz, 1H), 4.82 (dd, J = 11.2, 9.9 Hz, 1H), 4.30 (d, J = 9.9 Hz, 1H), 3.17 (ddd, J = 11.4, 9.9, 4.6 Hz, 1H), 3.09−2.99 (comp, 2H), 2.92 (app dt, J = 16.3, 3.9 Hz, 1H), 2.88−2.81 (comp, 2H), 2.64−2.50 (comp, 2H), 2.21−2.15 (m, 1H), 2.06−1.96 (m, 1H), 1.94−1.85 (m, 1H), 1.62−1.55 (m, 1H), 1.01 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 141.7, 134.2, 133.2, 129.6, 128.7, 128.5, 128.1, 126.9, 126.3, 89.5, 62.8, 62.0, 47.4, 46.2, 30.9, 30.8, 29.8, 27.5, 16.3; m/z (ESI-MS) 351.2 [M + H]$^+$.

*Characterization data for **7f**:* yellowish oil; R_f = 0.42 in 10% EtOAc/Hex; $[\alpha]_D^{25}$ −91.8 (c 0.5, CHCl$_3$); IR (KBr) 3063, 3031, 2930, 2891, 2809, 2767, 1605, 1536, 1498, 1455, 1356, 1299, 1245, 1146, 1104, 736, 694 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.29−7.32 (comp, 2H), 7.23−7.20 (m, 1H), 7.19−7.17 (comp, 3H), 7.13−7.09 (comp, 2H), 6.91 (app d, J = 7.9 Hz, 1H), 4.41 (dd, J = 11.0, 9.2 Hz, 1H), 4.05 (d, J = 9.2 Hz, 1H), 3.09−3.03 (m, 1H), 3.00 (dd, J = 12.2, 3.4 Hz, 1H), 2.98−2.94 (m, 1H), 2.90 (dd, J = 12.2, 2.3 Hz, 1H), 2.81−2.74 (comp, 2H), 2.74−2.67 (m, 1H), 2.54−2.48 (m, 1H), 2.48−2.40 (m, 1H), 2.21−2.15 (m, 1H), 1.71−1.62 (m, 1H), 1.60−1.53 (m, 1H), 1.12 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 141.4, 136.1, 133.6, 129.5, 128.7, 128.5, 127.5, 126.5, 126.3, 125.9, 91.5, 77.5, 77.3, 77.0, 65.2, 61.8, 50.9, 44.7, 32.3, 31.1, 30.4, 29.9, 13.8; m/z (ESI-MS) 351.2 [M + H]$^+$.

*Products **6g** and **7g**.* Following general procedure A, products **6g** and **7g** were obtained in a 1.8:1 ratio (70% combined yield).

*Characterization data for **6g**:* yellowish solid; mp 64−66 °C; R_f = 0.27 in 10% EtOAc/Hex; $[\alpha]_D^{25}$ −61.4 (c 0.5, CHCl$_3$); IR (KBr) 3063, 3026, 2917, 2851, 2754, 1600, 1543, 1492, 1452, 1368, 1311, 1257, 1143, 1099, 738, 696 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.38−7.35 (comp, 2H), 7.31−7.23 (comp, 5H), 7.20−7.17 (comp, 2H), 7.14−7.11 (m, 1H), 7.07 (app t, J = 7.5 Hz, 1H), 7.01−6.99 (comp, 2H), 6.86 (app d, J = 7.8 Hz, 1H), 4.94 (app t, J = 10.4 Hz, 1H), 4.36 (d, J = 9.7 Hz, 1H), 3.29 (app t, J = 11.4 Hz, 1H), 3.21−3.16 (m, 1H), 3.09 (dd, J = 13.7, 4.0 Hz, 1H), 2.98−2.87 (comp, 3H), 2.75 (app dt, J = 10.6, 5.0 Hz, 1H), 2.60 (dd, J = 13.7, 2.8 Hz, 1H), 2.50−2.38 (m, 1H), 2.16 (dd, J = 13.7, 10.5 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 139.4, 138.0, 134.4, 132.8, 129.5, 129.3, 129.0, 128.7, 128.3, 128.0, 126.8, 126.5, 126.4, 92.5, 63.1, 59.4, 54.7, 46.7, 38.3, 37.8, 29.9; m/z (ESI-MS) 399.2 [M + H]$^+$.

*Characterization data for **7g**:* yellowish oil; R_f = 0.48 in 10% EtOAc/Hex; $[\alpha]_D^{25}$ −156.6 (c 0.5, CHCl$_3$); IR (KBr) 3061, 3024, 2952, 2927, 2902, 2804, 2754, 1600, 1546, 1492, 1452, 1356, 1299, 1252, 1143, 760, 701 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37−7.34 (comp, 2H), 7.31−7.21 (comp, 6H), 7.21−7.17 (comp, 2H), 7.17−7.11 (m, 1H), 6.97−6.95 (comp, 2H), 6.91 (d, J = 7.9 Hz, 1H), 5.16 (dd, J = 11.7, 8.9 Hz, 1H), 4.21 (d, J = 8.9 Hz, 1H), 3.97 (dd, J = 11.7, 4.9 Hz, 1H), 3.26 (ddd, J = 14.7, 10.7, 4.9 Hz, 1H), 2.87 (dd, J = 7.9, 3.0 Hz, 1H), 2.84 (dd, J = 6.9, 2.5 Hz, 1H), 2.83−2.79 (comp, 2H), 2.78−2.70 (comp, 2H), 2.46 (dd, J = 13.0, 3.5 Hz, 1H), 2.23−2.17 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 140.9, 138.1, 136.3, 133.2, 129.6, 129.2, 128.9, 128.6, 128.3, 127.7, 127.6, 126.6, 126.3, 126.1, 89.2, 66.5, 57.1, 52.9, 50.8, 43.3, 33.2, 31.6; m/z (ESI-MS) 399.2 [M + H]$^+$.

*Products **6h** and **7h**.* Following general procedure A, products **6h** and **7h** were obtained in a 5:1 ratio (37% combined yield).

*Characterization data for **6h**:* yellowish solid; mp 180−184 °C; R_f = 0.45 in 20% EtOAc/Hex; $[\alpha]_D^{25}$ −23.0 (c 0.5, CHCl$_3$); IR (KBr) 3063, 3026, 2952, 2922, 2868, 2823, 1546, 1497, 1450, 1368, 1306, 1141, 1099, 1005, 750, 726, 696 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.32−7.29 (comp, 2H), 7.25−7.23 (m, 1H), 7.21−7.14 (comp, 4H), 7.07 (app t, J = 7.5 Hz, 1H), 6.85 (app d, J = 7.9 Hz, 1H), 4.92 (app t, J = 9.8 Hz, 1H), 4.35 (d, J = 9.8 Hz, 1H), 3.42 (app t, J = 11.6 Hz, 1H), 3.38−3.29 (m, 1H), 3.19 (dd, J = 13.4, 3.7 Hz, 1H), 3.13−2.96 (comp, 3H), 2.94−2.87 (m, 1H), 2.24−2.15 (m, 1H), 1.50−1.44 (m, 1H), 0.90 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 138.0, 134.2, 132.9, 129.5, 129.2, 128.1, 128.0, 126.9, 126.4, 93.0, 62.9, 54.1, 52.2, 46.7, 40.3, 29.9, 26.6, 21.5, 15.6; m/z (ESI-MS) 351.2 [M + H]$^+$.

*Products **6i** and **7i**.* Following general procedure A, products **6i** and **7i** were obtained in a 1.5:1 ratio (66% combined yield).

*Characterization data for **6i**:* yellowish solid; mp 145−148 °C; R_f = 0.35 in 30% EtOAc/Hex; $[\alpha]_D^{25}$ −11.9 (c 0.5, CHCl$_3$); IR (KBr) 3063, 3026, 3001, 2957, 2922, 2902, 2828, 1610, 1539, 1504, 1452, 1378, 1309, 1252, 1146, 1035, 859, 817, 760, 743, 701 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.31−7.28 (comp, 2H), 7.27−7.21 (m, 1H), 7.17−7.16 (comp, 2H), 6.78 (app d, J = 8.6 Hz, 1H), 6.68−6.65 (m, 1H), 6.62 (dd, J = 8.6, 2.5 Hz, 1H), 4.92 (dd, J = 11.2, 9.8 Hz, 1H), 4.32 (d, J = 9.7 Hz, 1H), 3.75 (s, 3H), 3.35−3.26 (m, 1H), 3.17 (dd, J = 13.7, 4.1 Hz, 1H), 3.08 (app t, J = 11.4 Hz, 1H), 3.05−2.98 (m, 1H), 2.97−2.87 (comp, 3H), 2.30−2.18 (m, 1H), 0.71 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 159.2, 138.2, 135.7, 129.1, 128.0, 128.0, 125.3, 114.4, 112.2, 91.9, 62.6, 62.1, 55.9, 55.4, 46.4, 31.2, 30.2, 16.7; m/z (ESI-MS) 353.1 [M + H]$^+$.

*Characterization data for **7i**:* yellowish solid; mp 130−133; R_f = 0.45 in 30% EtOAc/Hex; $[\alpha]_D^{25}$ −102.0 (c 0.5, CHCl$_3$); IR (KBr) 3061, 3028, 2959, 2932, 2907, 2863, 2806, 2767, 1613, 1546, 1494, 1455, 1356, 1269, 1151, 1116, 1039, 827, 743, 698 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.31−7.28 (comp, 2H), 7.27−7.21 (m, 1H), 7.18−7.15 (comp, 2H), 6.81 (app d, J = 8.2 Hz, 1H), 6.68−6.66 (comp, 2H), 5.05 (dd, J = 11.6, 9.0 Hz, 1H), 4.13 (d, J = 9.0 Hz, 1H), 3.80 (dd, J = 10.2, 5.0 Hz. 1H), 3.78 (s, 3H), 3.22 (dd, J = 12.2, 3.0 Hz, 1H), 3.09 (ddd, J = 14.8, 9.2, 4.5 Hz, 1H), 3.05−2.99 (m, 1H), 2.96 (app d, J = 12.2 Hz, 1H), 2.83 (ddd, J = 12.2, 10.2, 3.3 Hz, 1H), 2.74−2.66 (m, 1H), 2.16−2.07 (m, 1H) 0.94 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 158.8, 138.6, 137.6, 128.7, 128.2, 127.5, 127.4, 125.4, 114.4, 112.2, 88.5, 65.8, 62.0, 55.4, 52.6, 50.7, 35.9, 31.5, 15.1; m/z (ESI-MS) 353.1 [M + H]$^+$.

*Products **6j** and **7j**.* Following general procedure A, products **6j** and **7j** were obtained in a 2:1 ratio (42% combined yield).

*Characterization data for **6j**:* yellowish oil; R_f = 0.36 in 20% EtOAc/Hex; $[\alpha]_D^{25}$ −17.5 (c 0.5, CHCl$_3$); IR (KBr) 3407, 3058, 3026, 2952, 2905, 2838, 2806, 1724, 1548, 1492, 1450, 1378, 1361, 1267, 1165, 740, 698 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.59 (br s, 1H), 7.50 (app d, J = 7.5 Hz, 1H), 7.35−7.32 (comp, 3H), 7.31−7.27 (m, 1H), 7.19−7.14 (comp, 3H), 7.13−7.07 (m, 1H), 4.91−4.87 (m, 1H), 4.26 (d, J = 9.4 Hz, 1H), 3.23−3.18 (m, 2H), 3.05−2.93 (comp, 2H), 2.90−2.81 (comp, 2H), 2.69−2.61 (m, 1H), 2.35−2.21 (m, 1H), 0.77 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 137.5, 136.8, 129.2, 128.3, 126.7, 122.7, 120.0, 118.5, 111.6, 111.2, 93.2, 62.7, 61.8, 56.5, 51.3, 34.9, 22.1, 16.9; HRMS (ESI) m/z calcd for $C_{22}H_{24}N_3O_2$ [M + H]$^+$ 362.1863, found 362.1875.

*Characterization data for **7j**:* yellowish solid; mp 160−163 °C; R_f = 0.40 in 20% EtOAc/Hex; $[\alpha]_D^{25}$ −25.7 (c 0.5, CHCl$_3$); IR (KBr) 3409, 3061, 3031, 2964, 2898, 2838, 2774, 1697, 1632, 1541, 1452, 1343, 1269, 1170, 1114, 1072, 1007, 968, 736, 696 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.61 (br s, 1H), 7.51 (app d, J = 7.8 Hz, 1H), 7.35−7.32 (comp, 2H), 7.28 (app d, J = 7.3 Hz, 1H), 7.24−7.21 (comp, 2H), 7.20−7.15 (m, 1H), 7.13−7.09 (m, 1H), 5.28 (dd, J = 11.8, 9.4 Hz, 1H), 4.18−4.12 (m, 1H), 3.72 (dd, J = 11.8, 4.5 Hz, 1H), 3.15−3.07 (comp, 2H), 3.06−2.97 (comp, 2H), 2.88−2.74 (comp, 2H), 2.22−2.14 (m, 1H), 1.01 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 136.9, 128.8, 128.4, 127.8, 126.7, 122.7, 120.0, 118.5, 111.6, 87.7, 63.8, 62.1, 52.9, 52.7, 35.9, 22.1, 14.5; m/z (ESI-MS) 362.2 [M + H]$^+$.

*Product **6k**.* Following general procedure A, product **6k** was obtained in 61% yield. The relative stereochemistry was determined by GCOSY and NOESY NMR.

*Characterization data for **6k**:* yellowish solid; mp 150−152 °C; R_f = 0.42 in 30% EtOAc/Hex; $[\alpha]_D^{25}$ −56.3 (c 0.5, CHCl$_3$); IR (KBr) 3059, 3028, 2931, 2862, 2862, 2834, 1714, 1630, 1551, 1489, 1447, 1364, 1036, 1143, 1108, 1081, 752, 700 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.33−7.30 (comp, 2H), 7.29−7.19 (comp, 4H), 7.18−7.14 (m, 1H), 7.08 (app t, J = 7.3 Hz, 1H), 6.87 (app d, J = 7.8 Hz, 1H), 4.97 (dd, J = 11.1, 9.8 Hz, 1H), 4.37 (d, J = 9.8 Hz, 1H), 3.56 (app td, J = 12.7, 4.4 Hz, 1H), 3.38−3.22 (comp, 3H), 3.07 (ddd, J = 15.8, 9.3, 6.3 Hz, 1H), 2.98 (app dt, J = 16.4, 4.1 Hz, 1H), 2.90 (ddd, J = 9.9, 6.1, 3.6 Hz, 1H), 2.17−2.09 (m, 1H), 1.83−1.77 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 139.9, 134.2, 133.0, 129.5, 129.2, 128.1, 128.0, 127.5, 127.0, 126.3, 91.0, 63.1, 54.5, 49.0, 45.9, 29.8, 28.2; m/z (ESI-MS) 309.1 [M + H]$^+$; HPLC Daicel Chiralcel OD-H, n-hexane/i-PrOH = 90/10, flow rate = 1 mL/min, UV = 230 nm, t_R = 11.1 min (major) and t_R = 13.9 min (minor), 94% ee.

*Product **6l**.* Following general procedure A, product **6l** was obtained in 51% yield.

*Characterization data for **6l**:* yellowish solid; mp 150−152 °C; R_f = 0.31 in 30% EtOAc/Hex; $[\alpha]_D^{25}$ −50.1 (c 0.5, CHCl$_3$); IR (KBr) 3021, 2941, 2914, 2845, 2824, 1644, 1541, 1485, 1369, 1309, 1143, 1102, 1067, 1105, 811, 766, 755 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.31−7.27 (comp, 2H), 7.24−7.19 (m, 1H), 7.17−7.15 (comp, 3H), 7.08 (app t, J = 7.2 Hz, 1H), 6.85 (app d, J = 7.8 Hz, 1H) 4.91 (app t, J = 9.6 Hz, 1H), 4.37 (d, J = 9.6 Hz, 1H), 3.54 (app td, J = 12.8, 4.4 Hz, 1H), 3.37−3.22 (comp, 3H), 3.11−3.03 (m, 1H), 3.01−2.97 (m, 1H), 2.91 (ddd, J = 10.1, 5.9, 3.9 Hz, 1H), 2.15−2.05 (m, 1H), 1.83−1.76 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 138.2, 134.1, 133.9, 132.5, 129.6, 129.4, 128.8, 128.3, 126.9, 126.4, 90.9, 63.0, 54.4, 48.3, 46.1, 29.7, 28.1; m/z (ESI-MS) (^{35}Cl) 343.2 [M + H]$^+$, (^{37}Cl) 345.2 [M + H]$^+$.

*Product **6m**.* Following general procedure A, product **6m** was obtained in 55% yield.

Characterization data for ***6m:*** yellowish solid; mp 150−153 °C; R_f = 0.31 in 30% EtOAc/Hex; $[\alpha]_D^{25}$ −48.9 (*c* 0.5, $CHCl_3$); IR (KBr) 3021, 2941, 2914, 2855, 2824, 1644, 1541, 1485, 1451, 1364, 1309, 1143, 1102, 1067, 1105, 811, 766, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46−7.40 (comp, 2H), 7.24−7.18 (m, 1H), 7.16 (d, *J* = 7.1 Hz, 1H), 7.12−7.05 (comp, 3H), 6.84 (app d, *J* = 7.8 Hz, 1H), 4.89 (dd, *J* = 11.2, 9.6 Hz, 1H), 4.34 (d, *J* = 9.6 Hz, 1H), 3.53 (app td, *J* = 12.8, 4.4 Hz, 1H), 3.34−3.18 (comp, 3H), 3.04 (ddd, *J* = 15.5, 9.1, 6.2 Hz, 1H), 2.97 (app dt, *J* = 16.3, 4.2 Hz, 1H), 2.92−2.85 (m, 1H), 2.11−2.02 (m, 1H), 1.79−1.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 134.2, 132.8, 132.3, 129.6, 129.2, 128.2, 126.9, 126.3, 121.9, 90.8, 63.1, 54.4, 48.5, 46.0, 29.8, 28.2; *m*/*z* (ESI-MS) (^{79}Br) 387.1 $[M + H]^+$, (^{81}Br) 389.1 $[M + H]^+$.

Product ***6n****.* Following general procedure A, product **6n** was obtained in 64% yield.

Characterization data for ***6n:*** yellowish solid; mp 154−156 °C; R_f = 0.48 in 30% EtOAc/Hex; $[\alpha]_D^{25}$ −29.6 (*c* 0.5, $CHCl_3$); IR (KBr) 3021, 2948, 2917, 2855, 2824, 1648, 1548, 1510, 1364, 1306, 1140, 1102, 1067, 1036, 942, 804, 752 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23−7.20 (m, 1H), 7.19−7.16 (m, 1H), 7.14−7.11 (comp, 4H), 7.08 (app t, *J* = 7.5 Hz, 1H), 6.88 (app d, *J* = 7.9 Hz, 1H), 4.99−4.89 (m, 1H), 4.37 (d, *J* = 9.6 Hz, 1H), 3.58−3.48 (m, 1H), 3.36−3.30 (m, 1H), 3.28 (dd, *J* = 13.2, 2.1 Hz, 1H), 3.26−3.21 (m, 1H), 3.10−3.04 (m, 1H), 3.02−2.95 (m, 1H), 2.91−2.87 (m, 1H), 2.32 (s, 3H), 2.17−2.06 (m, 1H), 1.83−1.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 137.0, 134.2, 133.1, 129.9, 129.5, 128.1, 127.3, 127.0, 126.3, 91.2, 63.1, 54.5, 48.6, 45.9, 29.9, 28.3, 21.3; *m*/*z* (ESI-MS) 323.1 $[M + H]^+$.

Product ***6o****.* Following general procedure A, product **6o** was obtained in 41% yield.

Characterization data for ***6o:*** yellowish solid; mp 120−124 °C; R_f = 0.26 in 30% EtOAc/Hex; $[\alpha]_D^{25}$ −31.3 (*c* 0.5, $CHCl_3$); IR (KBr) 3063, 3031, 2999, 2927, 2860, 2833, 1610, 1546, 1514, 1452, 1366, 1306, 1249, 1175, 1143, 1101, 1035, 827, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22−7.17 (m, 1H), 7.17−7.10 (comp, 3H), 7.06 (app t, *J* = 7.5 Hz, 1H), 6.89−6.80 (comp, 3H), 4.88 (dd, *J* = 11.2, 9.7 Hz, 1H), 4.34 (d, *J* = 9.7 Hz, 1H), 3.77 (s, 3H), 3.54−3.45 (m, 1H), 3.34−3.18 (comp, 3H), 3.05 (ddd, *J* = 15.7, 9.3, 6.3 Hz, 1H), 2.96 (app dt, *J* = 16.4, 4.1 Hz, 1H), 2.92−2.85 (m, 1H), 2.09 (ddd, *J* = 15.0, 12.8, 4.7 Hz, 1H), 1.80−1.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 134.2, 133.0, 132.0, 129.5, 128.5, 128.1, 127.0, 126.3, 114.5, 91.4, 63.1, 55.4, 54.5, 48.2, 45.9, 29.8, 28.3; *m*/*z* (ESI-MS) 339.2 $[M + H]^+$.

Product ***6p****.* Following general procedure A, product **6p** was obtained in 60% yield.

Characterization data for ***6p:*** Yellowish solid; mp > 190 °C; R_f = 0.45 in 30% EtOAc/Hex; $[\alpha]_D^{25}$ −12.5 (*c* 0.5, $CHCl_3$); IR (KBr) 3055, 3017, 2927, 2855, 2810, 1600, 1537, 1496, 1440, 1357, 1309, 1140, 1102, 1063, 939, 856, 745 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 7.86−7.85 (comp, 3H), 7.71 (s, 1H), 7.56−7.45 (comp, 2H), 7.40 (app d, *J* = 8.4 Hz, 1H), 7.26−7.22 (comp, 2H), 7.09 (app t, *J* = 6.2 Hz, 1H), 6.86 (app d, *J* = 7.8 Hz, 1H), 5.11 (app t, *J* = 9.6 Hz, 1H), 4.43 (d, *J* = 9.6 Hz, 1H), 3.75 (app td, *J* = 12.4, 4.3 Hz, 1H), 3.41 (app td, *J* = 11.2, 4.6 Hz, 1H), 3.38−3.33 (m, 1H), 3.29 (dd, *J* = 13.0, 3.2 Hz, 1H), 3.15−2.99 (comp, 2H), 2.99−2.88 (m, 1H), 2.29−2.21 (m, 1H), 1.87−1.85 (m, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 137.6, 134.8, 133.7, 133.3, 133.0, 129.6, 128.9, 128.0, 127.9, 127.8, 126.9, 126.5(8), 126.5(5), 126.2, 126.0, 125.1, 91.0, 63.1, 54.3, 49.1, 45.7, 29.8, 28.0; *m*/*z* (ESI-MS) 359.2 $[M + H]^+$.

Product ***6q****.* Following general procedure A, product **6q** was obtained in 50% yield.

Characterization data for ***6q:*** yellowish solid; mp 128−130 °C; R_f = 0.35 in 30% EtOAc/Hex; $[\alpha]_D^{25}$ −35.2 (*c* 0.5, $CHCl_3$); IR (KBr) 3118, 3062, 3021, 2952, 2921, 2858, 1548, 1496, 1454, 1361, 1309, 1146, 1102, 1081, 1012, 932, 742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.30 (m, 1H), 7.22−7.17 (m, 1H), 7.16−7.12 (m, 1H), 7.07 (app t, *J* = 7.5 Hz, 1H), 6.84 (app d, *J* = 7.8 Hz, 1H), 6.26 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.11 (app d, *J* = 3.3 Hz, 1H), 4.92 (app t, *J* = 9.8 Hz, 1H), 4.32 (d, *J* = 9.8 Hz, 1H), 3.74 (app td, *J* = 12.6, 4.4 Hz, 1H), 3.36−3.17 (comp, 3H), 3.05 (ddd, *J* = 16.3, 9.9, 6.5 Hz, 1H), 2.93 (app dt, *J* = 16.4, 3.6 Hz, 1H), 2.86 (ddd, *J* = 11.3, 6.4, 2.9 Hz, 1H), 2.22−2.14 (m, 1H), 1.90−1.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 142.5, 134.1, 132.7, 129.5, 128.2, 127.0, 126.2, 110.5, 106.7, 88.9, 62.7, 53.8, 45.4, 41.8, 29.7, 24.8; *m*/*z* (ESI-MS) 299.2 $[M + H]^+$.

Product ***6r****.* Following general procedure A, product **6r** was obtained in 44% yield.

Characterization data for ***6r:*** yellowish solid; mp 150−152 °C; R_f = 0.29 in 30% EtOAc/Hex; $[\alpha]_D^{25}$ −35.1 (*c* 0.5, $CHCl_3$); IR (KBr) 3062, 3024, 2997, 2927, 2858, 2834, 1610, 1541, 1506, 1454, 1364, 1306, 1271, 1250, 1143, 1032, 763, 693 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32−7.29 (comp, 2H), 7.25 (d, *J* = 7.1 Hz, 1H), 7.24−7.20 (comp, 2H), 6.79 (d, *J* = 8.6 Hz, 1H), 6.68 (d, *J* = 2.3 Hz, 1H), 6.63 (dd, *J* = 8.6, 2.6 Hz, 1H), 4.92 (dd, *J* = 11.1, 9.7 Hz, 1H), 4.31 (d, *J* = 9.7 Hz, 1H), 3.76 (s, 3H), 3.54 (app td, *J* = 12.6, 4.3 Hz, 1H), 3.33−3.25 (comp, 2H), 3.23 (ddd, *J* = 13.7, 4.5, 1.8 Hz, 1H), 3.03 (ddd, *J* = 15.7, 9.2, 6.3 Hz, 1H), 2.94 (app dt, *J* = 15.7, 4.0 Hz, 1H), 2.89−2.85 (m, 1H), 2.15−2.06 (m, 1H), 1.84−1.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 140.0, 135.7, 129.2, 128.1, 127.9, 127.5, 125.4, 114.4, 112.1, 91.3, 62.8, 55.4, 54.5, 48.9, 45.9, 30.2, 28.3; *m*/*z* (ESI-MS) 339.1 $[M + H]^+$.

Product ***6s****.* Following general procedure A, product **6s** was obtained in 52% yield.

Characterization data for ***6s:*** yellowish solid; mp 148−151 °C; R_f = 0.42 in 50% EtOAc/Hex; $[\alpha]_D^{25}$ −18.9 (*c* 0.5, $CHCl_3$); IR (KBr) 3059, 3028, 2990, 2945, 2921, 2889, 2883, 2855, 2834, 1610, 1544, 1520, 1447, 1354, 1261, 1226, 1143, 1112, 1019, 873, 759, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30−7.28 (comp, 2H), 7.25−7.22 (m, 1H), 7.22−7.18 (comp, 2H), 6.61 (s, 1H), 6.37 (s, 1H), 4.89 (dd, *J* = 11.2, 9.6 Hz, 1H), 4.27 (d, *J* = 9.6 Hz, 1H), 3.83 (s, 3H), 3.72 (s, 3H), 3.51 (app td, *J* = 12.7, 4.3 Hz, 1H), 3.30−3.18 (comp, 3H), 2.99−2.91 (m, 1H), 2.89−2.83 (comp, 2H), 2.10 (ddd, *J* = 15.1, 12.7, 4.8 Hz, 1H), 1.78 (app ddt, *J* = 13.7, 4.3, 2.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7, 147.3, 139.8, 129.1, 128.0, 127.4, 126.6, 125.1, 111.8, 109.8, 91.7, 63.0, 56.0(1), 55.9(9), 54.5, 49.0, 46.2, 29.5, 28.2; *m*/*z* (ESI-MS) 369.1 $[M + H]^+$.

Product ***6t****.* Following general procedure A, product **6t** was obtained in 37% yield.

Characterization data for ***6t:*** yellowish solid; mp 144−146 °C; (R_f = 0.31 in 30% EtOAc/Hex); $[\alpha]_D^{25}$ −38.5 (*c* 0.5, $CHCl_3$); IR (KBr) 3409, 3056, 3031, 2947, 2917, 2846, 2806, 2757, 1729, 1598, 1546, 1492, 1455, 1356, 1311, 1264, 1168, 738, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (br s, 1H), 7.55−7.50 (m, 1H), 7.39−7.33 (comp, 2H), 7.33−7.29 (m, 1H), 7.27−7.21 (comp, 3H), 7.17 (app td, *J* = 7.6, 1.3 Hz, 1H), 7.14−7.10 (m, 1H), 4.88 (dd, *J* = 11.2, 9.5 Hz, 1H), 4.25 (d, *J* = 9.5 Hz, 1H), 3.44−3.33 (m, 1H), 3.25−3.18 (comp, 2H), 3.05−2.93 (comp, 2H), 2.92−2.78 (comp, 2H), 2.21−2.13 (m, 1H), 1.99 (app ddt, *J* = 13.6, 4.7, 2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 136.8, 130.2, 129.3, 128.3, 127.5, 126.7, 122.7, 120.0, 118.5, 111.6, 111.2, 92.8, 61.9, 55.1, 51.3, 49.7, 31.5, 22.1; *m*/*z* (ESI-MS) 348.2 $[M + H]^+$.

Products ***8a*** *and* ***9a****.* Following general procedure B, products **8a** and **9a** were obtained in a 1.2:1 ratio (62% combined yield). The relative stereochemistry was determined by GCOSY and NOESY NMR.

Characterization data for ***8a:*** yellowish oil; R_f = 0.37 in 20% EtOAc/Hex; $[\alpha]_D^{25}$ +24.8 (*c* 0.5, $CHCl_3$); IR (KBr) 3066, 3031, 2977, 2895, 2816, 2776, 2757, 2678, 1546, 1494, 1452, 1375, 1289, 1151, 1119, 1072, 1039, 751, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.30 (comp, 2H), 7.29−7.27 (m, 1H), 7.21−7.12 (comp, 4H), 7.08−7.03 (comp, 2H), 4.66 (dd, *J* = 11.1, 8.2 Hz, 1H), 4.03 (d, *J* = 15.2 Hz, 1H), 3.56 (d, *J* = 15.2 Hz, 1H), 3.19 (dd, *J* = 18.5, 10.4 HZ, 1H), 3.01−2.92 (comp, 2H), 2.93−2.85 (m, 1H), 2.84−2.77 (m, 1H), 2.26−2.13 (comp, 2H), 0.78 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 132.9, 131.3, 129.0, 128.2, 127.9, 126.8, 126.3, 125.8, 96.2, 62.8, 60.6, 57.4, 54.0, 34.3, 32.8, 16.9; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{23}N_2O_2$ $[M + H]^+$ 323.1754, found 323.1765.

Characterization data for ***9a:*** yellowish solid; mp 182−185 °C; R_f = 0.48 in 20% EtOAc/Hex; $[\alpha]_D^{25}$ −31.6 (*c* 0.5, $CHCl_3$); IR (KBr) 3068, 3028, 2975, 2895, 2813, 2778, 2763, 1546, 1494, 1455, 1375, 1364, 1289, 1156, 1115, 1032, 750, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.32 (comp, 2H), 7.28−7.23 (comp, 3H), 7.20−7.13 (comp, 2H), 7.12−7.02 (comp, 2H), 5.09 (dd, *J* = 12.3, 9.1 Hz, 1H), 3.96 (d, *J* = 15.1 Hz, 1H), (dd, *J* = 12.3, 4.5 Hz, 1H), 3.53 (d, *J* = 15.1 Hz, 1H), 3.16−3.02 (comp, 2H), 2.92−2.82 (comp, 2H), 2.70 (dd, *J* = 11.5, 3.2 Hz, 1H), 2.31−2.14 (m, 1H), 1.00 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 138.1, 133.2, 131.5, 128.6, 128.2, 127.7, 127.5, 126.7, 126.2, 125.8, 89.7, 62.0, 61.7, 57.8, 49.8, 35.0, 33.1, 13.3; *m/z* (ESI-MS) 323.2 [M + H]$^+$.

Products ***8c*** *and* ***9c***. Following general procedure B, products **8c** and **9c** were obtained in a 1.2:1 ratio (49% combined yield).

Characterization data for ***8c***: yellow solid; mp 180−182 °C; R_f = 0.31 in 20% EtOAc/Hex; $[\alpha]_D^{25}$ +36.7 (c 0.5, CHCl$_3$); IR (KBr) 3068, 3026, 2962, 2930, 2883, 1971, 1929, 1897, 1714, 1650, 1546, 1489, 1452, 1375, 1262, 1153, 1007, 815, 758, 738 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.49−7.43 (comp, 2H), 7.20−7.12 (comp, 2H), 7.09−7.04 (comp, 4H), 4.59 (dd, J = 11.4, 8.4 Hz, 1H), 4.02 (d, J = 15.1 Hz, 1H), 3.55 (d, J = 15.1 Hz, 1H), 3.21−3.13 (m, 1H), 3.04−2.73 (comp, 4H), 2.24−2.06 (comp, 2H), 0.78 (d, J = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 136.6, 132.7, 132.1, 131.1, 128.2, 126.7, 126.3, 125.8, 121.8, 95.9, 62.6, 60.5, 57.2, 53.4, 34.2, 32.7, 16.7; *m/z* (ESI-MS) (^{79}Br) 401.1 [M + H]$^+$, (^{81}Br) 403.1 [M + H]$^+$.

Characterization data for ***9c***: yellow solid; mp >200 °C; R_f = 0.53 in 20% EtOAc/Hex; $[\alpha]_D^{25}$ −32.2 (c 0.5, CHCl$_3$); IR (KBr) 3066, 3025, 2964, 2928, 2896, 2811, 2762, 1892, 1730, 1652, 1546, 1489, 1456, 1377, 1363, 1306, 1287, 1257, 1153, 1108, 1073, 1009, 825, 800, 749 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51−7.44 (comp, 2H), 7.20−7.14 (comp, 2H), 7.14−7.03 (comp, 4H), 5.02 (dd, J = 12.3, 8.9 Hz, 1H), 3.96 (d, J = 15.1 Hz, 1H), 3.61 (dd, J = 12.3, 4.5 Hz, 1H), 3.52 (d, J = 15.1 Hz, 1H), 3.12−3.01 (comp, 2H), 2.94−2.80 (comp, 2H), 2.68 (dd, J = 11.6, 3.2 Hz, 1H), 2.24−2.13 (m, 1H), 0.98 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 137.1, 133.1, 131.8, 131.4, 129.4, 128.2, 126.7, 126.3, 125.8, 121.5, 89.5, 61.8, 61.6, 57.7, 49.3, 34.8, 33.1, 13.2; *m/z* (ESI-MS) (^{79}Br) 401.2 [M + H]$^+$, (^{81}Br) 403.2 [M + H]$^+$.

Products ***8e*** *and* ***9e***. Following general procedure B, products **8e** and **9e** were obtained in a 1.3:1 ratio (54% combined yield).

Characterization data for ***8e***: yellow solid; mp 115−117 °C; R_f = 0.28 in 20% EtOAc/Hex; $[\alpha]_D^{25}$ +25.1 (c 0.5, CHCl$_3$); IR (KBr) 3024, 2965, 2928, 2894, 2821, 2762, 2680, 1959, 1902, 1796, 1593, 1545, 1495, 1373, 1362, 1255, 1093, 1011, 933, 818, 745 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.18−7.13 (comp, 2H), 7.12−7.07 (comp, 2H), 7.09−7.02 (comp, 2H), 6.88−6.84 (comp, 2H), 4.59 (dd, J = 11.4, 8.7 Hz, 1H), 4.01 (d, J = 15.2 Hz, 1H), 3.78 (s, 3H), 3.54 (d, J = 15.2 Hz, 1H), 3.23−3.13 (m, 1H), 2.99−2.88 (comp, 2H), 2.96−2.80 (comp, 2H), 2.22−2.10 (comp, 2H), 0.78 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 159.3, 133.1, 131.5, 129.7, 128.5, 127.0, 126.5, 126.1, 114.5, 96.7, 63.1, 60.8, 57.6, 55.4, 53.5, 34.6, 33.1, 17.1; *m/z* (ESI-MS) 353.2 [M + H]$^+$.

Characterization data for ***9e***: yellow solid; mp >200 °C; (R_f = 0.45 in 20% EtOAc/Hex); $[\alpha]_D^{25}$ −31.6 (c 0.5, CHCl$_3$); IR (KBr) 3026, 3013, 2992, 2969, 2955, 2899, 2835, 2780, 2761, 1966, 1922, 1884, 1613, 1548, 1512, 1456, 1442, 1399, 1380, 1355, 1310, 1300, 1254, 1178, 1028, 829, 748 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.19−7.13 (comp, 4H), 7.11−7.06 (m, 1H), 7.06−7.02 (m, 1H), 6.89−6.85 (comp 2H), 5.03 (dd, J = 12.3, 9.2 Hz, 1H), 3.95 (d, J = 15.1 Hz, 1H), 3.79 (s, 3H), 3.58 (dd, J = 12.3, 4.5 Hz, 1H), 3.52 (d, J = 15.1 Hz, 1H), 3.12−3.00 (comp, 2H), 2.93−2.79 (comp, 2H), 2.68 (dd, J = 11.5, 3.2 Hz, 1H), 2.21−2.13 (m, 1H), 1.00 (d, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 159.1, 133.4, 131.7, 130.3, 129.0, 128.4, 126.9, 126.4, 126.0, 114.3, 90.2, 62.2, 61.9, 58.0, 55.5, 49.3, 35.3, 33.4, 13.6; *m/z* (ESI-MS) 353.2 [M + H]$^+$.

Product ***8k***. Following general procedure B, product **8k** was obtained in 48% yield. The relative stereochemistry was determined by GCOSY and NOESY NMR.

Characterization data for ***8k***: yellow solid; mp 160−163 °C; R_f = 0.47 in 30% EtOAc/Hex; $[\alpha]_D^{25}$ +27.2 (c 0.5, CHCl$_3$); IR (KBr) 3061, 3026, 2932, 2865, 2799, 2749, 1721, 1650, 1541, 1437, 1366, 1240, 1141, 1141, 738 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37−7.30 (comp, 2H), 7.30−7.27 (m, 1H), 7.25−7.20 (comp, 2H), 7.19−7.13 (comp, 2H), 7.09−7.02 (comp, 2H), 4.62 (dd, J = 11.4, 8.6 Hz, 1H), 4.03 (d, J = 15.1 Hz, 1H), 3.58 (d, J = 15.1 Hz, 1H), 3.30 (app td, J = 11.8, 4.8 Hz, 1H), 3.23 (app dt, J = 11.8, 3.0 Hz, 1H), 3.02−2.91 (comp 2H), 2.89−2.78 (m, 1H), 2.49 (app td, J = 11.8, 3.6 Hz, 1H), 2.16−1.95 (comp, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 139.2, 132.9, 131.3, 129.0, 128.2, 128.0, 127.2, 126.8, 126.3, 125.8, 95.7, 60.6, 57.5, 55.1, 47.2, 32.9, 30.9; *m/z* (ESI-MS) 309.1 [M + H]$^+$.

Product ***8l***. Following general procedure B, product **8l** was obtained in 43% yield.

Characterization data for ***8l***: yellow solid; mp 165−167 °C; R_f = 0.48 in 30% EtOAc/Hex; $[\alpha]_D^{25}$ +18.2 (c 0.5, CHCl$_3$); IR (KBr) 3042, 2965, 2928, 2894, 2821, 2762, 2680, 1959, 1902, 1796, 1593, 1543, 1495, 1373, 1362, 1351, 1255, 1093, 1085, 1011, 933, 818, 745 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.34−7.29 (comp, 2H), 7.18−7.13 (comp, 4H), 7.10−7.04 (comp, 2H), 4.56 (dd, J = 11.3, 8.6 Hz, 1H), 4.03 (d, J = 15.2 Hz, 1H), 3.58 (d, J = 15.2 Hz, 1H), 3.29 (app td, J = 11.4, 5.5 Hz, 1H), 3.25−3.18 (m, 1H), 3.02−2.91 (comp, 2H), 2.87−2.79 (comp, 2H), 2.47 (app td, J = 11.6, 4.4 Hz, 1H), 2.10−1.99 (comp, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 137.6, 133.7, 132.8, 131.1, 129.2, 128.5, 128.1, 126.7, 126.2, 125.7, 95.4, 60.4, 57.3, 54.9, 46.5, 32.8, 30.7; *m/z* (ESI-MS) (^{35}Cl) 343.2 [M + H]$^+$, (^{37}Cl) 345.2 [M + H]$^+$.

Product ***8n***. Following general procedure B, product **8n** was obtained in 61% yield.

Characterization data for ***8n***: yellow solid; mp 175−178 °C; R_f = 0.51 in 30% EtOAc/Hex; $[\alpha]_D^{25}$ +19.4 (c 0.5, CHCl$_3$); IR (KBr) 3021, 2947, 2922, 2894, 2820, 2759, 2687, 2356, 1924, 1897, 1548, 1515, 1496, 1456, 1376, 1351, 1256, 1152, 811, 748 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.21−7.12 (comp, 6H), 7.11−7.05 (comp, 2H), 4.61 (dd, J = 11.4, 8.7 Hz, 1H), 4.04 (d, J = 15.2 Hz, 1H), 3.59 (d, J = 15.2 Hz, 1H), 3.29 (dd, J = 11.8, 4.7 Hz, 1H), 3.23 (app dt, J = 11.8, 3.2 Hz, 1H), 3.04−2.93 (comp, 2H), 2.86 (dd, J = 13.7, 7.0 Hz, 1H), 2.48 (app td, J = 11.8, 3.5 Hz, 1H), 2.34 (s, 3H), 2.15−1.99 (comp, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 137.6, 136.2, 132.9, 131.3, 129.7, 128.2, 127.0, 126.8, 126.3, 125.8, 95.8, 60.6, 57.5, 55.1, 46.8, 32.9, 30.9, 21.1; *m/z* (ESI-MS) 323.1[M + H]$^+$.

Products ***11*** *and* ***12***. Following general procedure C, products **11** and **12** were obtained in a 2:1 ratio (55% combined yield). The relative stereochemistry was determined by GCOSY and NOESY NMR.

Characterization data for ***11***: yellowish oil; R_f = 0.40 in 50% EtOAc/Hex; IR (KBr) 3056, 3033, 2932, 2851, 2804, 2754, 1529, 1489, 1452, 1368, 1306, 1143, 740 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.12 (app t, J = 7.4 Hz, 1H), 7.05 (app d, J = 7.5 Hz, 1H), 7.00 (app t, J = 7.5 Hz, 1H), 6.78 (app d, J = 7.5 Hz, 1H), 4.74−4.62 (m, 1H), 4.20 (d, J = 9.3 Hz, 1H), 3.15−3.07 (m, 1H), 3.04−2.93 (comp, 2H), 2.90−2.85 (comp, 2H), 2.75 (app dt, J = 11.1, 5.3 Hz, 1H), 2.30−2.23 (comp, 2H) 1.82−1.72 (m, 1H), 1.63−1.55 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 134.4, 133.3, 129.6, 127.9, 126.6, 126.3, 86.0, 62.6, 53.8, 46.6, 31.1, 29.3, 20.0; *m/z* (ESI-MS) 233.2 [M + H]$^+$.

Characterization data for ***12***: yellowish oil; R_f = 0.50 in 50% EtOAc/Hex; IR (KBr) 3061, 3026, 2932, 2865, 2799, 2749, 1721, 1650, 1541, 1437, 1366, 1240, 1141, 1141, 738 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.22−7.13 (comp, 3H), 7.12−7.09 (m, 1H), 5.18 (app dt, J = 4.5, 2.3 Hz, 1H), 3.68 (s, 1H), 3.16 (ddd, J = 16.9, 12.2, 5.3 Hz, 1H), 3.12−3.07 (m, 1H), 3.00 (ddd, J = 11.1, 5.3, 1.7 Hz, 1H), 2.69−2.60 (comp, 2H), 2.59−2.50 (m, 1H), 2.41 (app td, J = 12.0, 3.0 Hz, 1H), 2.26−2.15 (m, 1H), 1.94 (ddd, J = 18.5, 9.3, 4.9 Hz, 1H), 1.72−1.61 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 135.9, 133.8, 129.4, 126.8, 126.2, 124.4, 82.7, 65.6, 56.5, 52.7, 29.5, 28.9, 21.1; *m/z* (ESI-MS) 233.2 [M + H]$^+$.

Product ***13***. Following general procedure B (5 equiv of 2-EHA was used), product **13** was obtained in 61% yield. The relative stereochemistry was determined by GCOSY and NOESY NMR.

Characterization data for ***13***: yellowish solid; mp 75−77 °C; (R_f = 0.43 in 50% EtOAc/Hex); IR (KBr) 3066, 3028, 2950, 2820, 2754, 2687, 2361, 2329, 1964, 1919, 1842, 1805, 1546, 1496, 1463, 1455, 1357, 1347, 1277, 1237, 1218, 1117, 1105, 744 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.17−7.10 (comp, 2H), 7.08−6.99 (comp, 2H), 4.45−4.40 (m, 1H), 3.95 (d, J = 15.2 Hz, 1H), 3.53 (d, J = 15.2 Hz, 1H), 3.12−3.05 (m, 1H), 2.91−2.80 (comp, 3H), 2.40−2.32 (m, 1H), 2.27 (app td, J = 12.1, 2.8 Hz, 1H), 2.09−1.99 (m, 1H), 1.95−1.87 (m, 1H), 1.78 (ddd, J = 16.3, 8.4, 3.5 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 133.0, 131.5, 128.2, 126.6, 126.2, 125.8, 89.8, 59.9, 57.5, 54.7, 32.7, 30.1, 22.8; *m/z* (ESI-MS) 233.2 [M + H]$^+$.

Product ***15***. Compound **8k** was reduced following an adapted literature procedure.[32] To a stirred solution of **8k** (0.09 mmol, 0.053 g) in *i*-PrOH (2 mL) was added 1 M HCl (1.8 mmol, 1.8 mL) followed by Zn dust (5.45 mmol, 0.356 g). The reaction mixture was stirred at room temperature for 2 h. The reaction was then quenched by addition of saturated $NaHCO_3$ (aq). The resulting mixture was stirred vigorously for 20 min and then filtered through a plug of Celite and washed with EtOAc. The filtrate was extracted with EtOAc, and the combined organic layers were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography to give the title compound as a white solid in 83% yield.

*Characterization data for **15**:* mp 122−125 °C; R_f = 0.25 in 5% MeOH/EtOAc; $[\alpha]_D^{25}$ +66.8 (*c* 0.5, $CHCl_3$); IR (KBr); 3409, 3061, 3024, 2919, 2801, 2755, 1949, 1599, 1588, 1553, 1493, 1453, 1362, 1346, 1120, 1096, 1011, 863, 748 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.32 (comp, 2H), 7.30−7.24 (comp, 3H), 7.17−7.10 (comp, 3H), 7.07−7.02 (m, 1H), 3.95 (d, *J* = 15.2 Hz, 1H), 3.50 (d, *J* = 15.2 Hz, 1H), 3.31 (dd, *J* = 16.5, 4.4 Hz, 1H), 3.19 (app dt, *J* = 11.5, 3.3 Hz, 1H), 2.87−2.77 (comp, 2H), 2.49−2.41 (m, 1H), 2.38 (app td, *J* = 12.2, 2.8 Hz, 1H), 2.23 (app dq, *J* = 10.5 Hz, 4.3 Hz, 1H), 2.05 (app qd, *J* = 12.8, 3.7 Hz, 1H), 1.93−1.86 (m, 1H), 1.24 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 133.6, 133.3, 128.8, 128.3, 127.8, 126.9, 126.4, 125.8, 125.7, 64.8, 59.6, 58.1, 55.8, 51.3, 34.0, 32.2; *m*/*z* (ESI-MS) 279.2 [M + H]$^+$.

*Product **16**.* Compound **6k** was denitrated following an adapted literature procedure.[33] To a stirred solution of **6k** (31 mg, 0.1 mmol, 94% ee) in EtOH (2 mL) was added $Pd(OH)_2/C$ (20 wt %, 75 mg). The reaction mixture was purged twice with hydrogen gas and then placed under 1 bar of hydrogen gas at 60 °C for 14 h. After being cooled to room temperature, the mixture was filtered through a Celite pad and washed with ethyl acetate. The solvent was removed under reduced pressure, and the crude material purified by flash chromatography to give the desired product as an off-white solid in 75% yield.

*Characterization data for **16**:* mp 124−127 °C; R_f = 0.41 in 40% EtOAc/Hex; $[\alpha]_D^{25}$ −27.2 (*c* 0.5, $CHCl_3$); IR (KBr) 3058, 3032, 2942, 2915, 2801, 2742, 1598, 1494, 1450, 1348, 1296, 1151, 1131, 1104, 1064, 1039, 963, 758, 733, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.27 (comp, 4H), 7.25−7.18 (comp, 2H), 7.16−7.09 (comp, 3H), 3.32 (app d, *J* = 11.0 Hz, 1H), 3.23 (ddd, *J* = 17.0, 12.1, 6.1 Hz, 1H), 3.15 (app dt, *J* = 11.4, 3.1 Hz, 1H), 3.06 (dd, *J* = 11.4, 6.0 Hz, 1H), 2.87−2.72 (comp, 2H), 2.60 (app td, *J* = 11.6, 3.9 Hz, 1H), 2.54−2.49 (comp, 2H), 2.03−1.87 (comp, 2H), 1.70 (app q, *J* = 12.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.4, 138.1, 134.7, 129.2, 128.7, 127.2, 126.5, 126.3, 126.0, 125.0, 63.5, 57.1, 52.6, 43.7, 39.2, 33.3, 29.9; *m*/*z* (ESI-MS) 264.3 [M + H]$^+$; HPLC Daicel Chiralcel OD-H, *n*-hexane/*i*-PrOH/diethylamine = 94.95/5/0.05, flow rate = 1 mL/min, UV = 254 nm, t_R = 6.2 min (major) and t_R = 22.1 min (minor), 94% ee.

*Product **17**.* Alkylation of **11** was achieved following an adapted literature procedure.[34] To a stirred solution of **11** (0.1 mmol, 0.023 g) and methyl vinyl ketone (0.13 mmol, 0.01 mL) in MeCN (1 mL) was added DBU (0.1 mmol, 0.015 mL) at room temperature. The reaction mixture was stirred for 15 h at room temperature. Solvent was removed under reduced pressure, and the crude material purified by flash chromatography to give the title compound as a colorless oil in 69% yield.

*Characterization data for **17**.* The relative stereochemistry was determined by GCOSY and NOESY NMR: R_f = 0.32 in 20% EtOAc/Hex; IR (KBr) 3073, 3021, 2962, 2900, 2814, 2759, 1719, 1645, 1521, 1450, 1358, 1299, 1252, 1141, 1106, 1052, 745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19−7.11 (m, 1H), 7.08−7.03 (comp, 2H), 6.69 (app d, *J* = 7.9 Hz, 1H), 4.27 (s, 1H), 3.18−3.06 (m, 1H), 3.03−2.99 (m, 1H), 2.90 (app dd, *J* = 10.8, 3.0 Hz, 1H), 2.79−2.63 (comp, 2H), 2.59−2.45 (comp, 4H), 2.36−2.21 (m, 1H), 2.15−2.02 (comp, 4H), 1.95−1.87 (m, 1H), 1.80−1.61 (comp, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 137.4, 132.1, 129.2, 127.0, 126.2, 125.6, 94.5, 69.7, 55.7, 51.1, 37.8, 34.7, 30.9, 30.0, 22.5, 22.4; *m*/*z* (ESI-MS) 303.2 [M + H]$^+$.

*Product **18**.* To a stirred solution of (*E*)-(((4-nitrobut-3-en-1-yl)oxy)methyl)benzene (0.858 g, 4.14 mmol, 1 equiv), (*S*)-diphenylprolinol trimethylsilyl ether (0.135 g, 0.414 mmol, 10 mol %), and *p*-nitrophenol (0.028 g, 0.207 mmol, 5 mol %) in toluene (4.14 mL) was added *n*-butyraldehyde (1.12 mL, 12.42 mmol, 3 equiv) at room temperature. The reaction mixture was stirred for 14 h and quenched by the addition of 1 M HCl (10 mL), and the resulting mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the residue purified by silica gel chromatography to give the title compound as a colorless oil in 73% yield (dr = 6.5:1).

*Characterization data for **18** (major diastereomer):* colorless oil; R_f = 0.35 in 10% EtOAc/Hex; $[\alpha]_D^{25}$ +3.76 (*c* 0.25, $CHCl_3$); IR (KBr) 3032, 2967, 2876, 2735, 1722, 1555, 1496, 1454, 1382, 1204, 1100, 1027, 739, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.67 (d, *J* = 1.2 Hz, 1H), 7.38−7.28 (m, 5H), 4.62 (dd, *J* = 12.8, 6.6 Hz, 1H), 4.46−4.45 (comp, 2H), 4.42 (dd, *J* = 12.8, 6.5 Hz, 1H), 3.51 (t, *J* = 5.8 Hz, 2H), 2.90−2.84 (m, 1H), 2.49−2.40 (m, 1H), 1.86−1.62 (comp, 3H), 1.54−1.46 (m, 1H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.9, 137.8, 128.4, 127.7(4), 127.6(8), 76.9, 73.1, 67.4, 54.0, 34.5, 29.1, 18.5, 12.1; *m*/*z* (ESI-MS) 280.2 [M + H]$^+$; HPLC Daicel Chiralcel OJ-H, *n*-hexane/*i*-PrOH = 90/10, flow rate =1 mL/min, UV = 230 nm, t_R = 78.2 min (major) and t_R = 96.4 min (minor), 99% ee.

*Product **19**.* A solution of the amine (0.232 g, 1.2 mmol, 2 equiv) and AcOH (0.346 mL, 6 mmol, 10 equiv) in toluene (6 mL) was heated under reflux. 4-Nitrobutyraldehyde **18** (0.167 g, 0.6 mmol, 0.12 M solution in toluene) was delivered through the top of the reflux condenser over 15 h via syringe pump. The reaction was then kept under reflux for a further 0.5−1 h at which time the aldehyde was consumed as judged by TLC analysis. Subsequently, the reaction mixture was allowed to cool to room temperature, diluted with EtOAc (20 mL), and washed with saturated aqueous $NaHCO_3$ (3 × 20 mL). The combined aqueous layers were extracted with EtOAc (2 × 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the residue purified by silica gel chromatography. Products **19**, **19′**, and **19″** were obtained in a 2:2:1 ratio, 61% combined yield.

*Characterization Data for **19** (1S,2R,3R,11bR)-2-(2-(Benzyloxy)-ethyl)-3-ethyl-9,10-dimethoxy-1-nitro-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinoline).* The relative stereochemistry was determined by GCOSY and NOESY NMR: brown oil; R_f = 0.45 in 50% EtOAc/Hex; $[\alpha]_D^{25}$ −16.4 (*c* 0.25, $CHCl_3$); IR (KBr) 3061, 2959, 2865, 2831, 1741, 1682, 1631, 1539, 1519, 1467, 1356, 1262, 1225, 1143, 1111, 740 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.19 (comp, 5H), 6.58 (s, 1H), 6.34 (s, 1H), 4.88−4.77 (m, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.43 (d, *J* = 12.0 Hz, 1H), 4.09 (d, *J* = 9.8 Hz, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 3.48 (t, *J* = 6.6 Hz, 2H), 3.13 (dd, *J* = 13.5, 4.0 Hz, 1H), 3.02−2.97 (m, 1H), 2.92−2.85 (m, 1H), 2.81−2.62 (comp, 3H), 2.25−2.18 (m, 1H), 1.89−1.82 (m, 1H), 1.80−1.58 (comp, 3H), 1.23−1.09 (m, 1H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7, 147.2, 138.4, 128.6, 127.7(7), 127.7(5), 126.4, 125.4, 111.8, 109.8, 91.2, 73.3, 67.0, 62.8, 59.0, 56.1, 56.0, 46.1, 43.6, 33.8, 29.4, 28.2, 23.3, 11.0; *m*/*z* (ESI-MS) 455.1 [M + H]$^+$.

*Characterization Data for **19′** ((1S,2R,3S,11bR)-2-(2-(Benzyloxy)-ethyl)-3-ethyl-9,10-dimethoxy-1-nitro-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinoline).* The relative stereochemistry was determined by GCOSY and NOESY NMR: brown oil; R_f = 0.42 in 20% EtOAc/Hex; $[\alpha]_D^{25}$ −69.9 (*c* 0.25, $CHCl_3$); IR (KBr) 3026, 3009, 2937, 2865, 2806, 1726, 1608, 1551, 1462, 1363, 1269, 1225, 1096,1010, 876, 743, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.26 (comp, 5H), 6.56 (s, 1H), 6.41 (s, 1H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.44 (d, *J* = 11.9 Hz, 1H), 4.39−4.30 (m, 1H), 4.01 (d, *J* = 8.9 Hz, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 3.50−3.43 (comp, 2H), 3.00−2.94 (comp, 2H), 2.88 (ddd, *J* = 11.0, 4.9, 3.0 Hz, 1H), 2.79−2.68 (comp, 2H), 2.59−2,54 (comp, 2H), 1.74−1.53 (comp, 4H), 1.52−1.42 (m, 1H), 1.42−1.31 (m, 1H), 0.88 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 147.4, 138.4, 128.6, 128.4, 127.9(2), 127.8(5), 125.8, 111.8, 108.8, 92.4, 73.1, 67.0, 65.0, 57.0, 56.0, 51.3, 42.7, 37.2, 30.4, 28.2, 18.9, 12.5; *m*/*z* (ESI-MS) 455.1 [M + H]$^+$.

*Characterization data for **19″** (1R,2R,3S,11bS)-2-(2-(benzyloxy)-ethyl)-3-ethyl-9,10-dimethoxy-1-nitro-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinoline):* brown oil; R_f = 0.55 in 50% EtOAc/Hex; $[\alpha]_D^{25}$ +49.4 (*c* 0.25, $CHCl_3$); IR (KBr) 3063, 3033, 2959, 2932, 2860, 2801, 2754, 1734, 1615, 1541, 1519, 1363, 1264, 1104, 740, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.26 (comp, 5H), 6.56 (s, 1H), 6.50 (s, 1H), 5.53 (app t, *J* = 2.1 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 1H), 3.80−3.73 (m, 1H), 3.72−3.67 (m, 1H), 3.55 (s, 3H), 3.20−3.07 (m, 1H), 3.07−2.95 (m, 1H), 2.86 (dd, J = 10.8, 3.0 Hz, 1H), 2.81–2.70 (m, 1H), 2.59–2.46 (comp, 2H), 2.39–2.19 (comp, 2H), 1.92–1.74 (comp, 2H), 1.35–1.23 (comp, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6, 147.2, 137.8, 128.5, 127.9, 127.8, 127.5, 125.5, 111.6, 107.2, 86.0, 73.5, 70.1, 59.8, 56.9, 55.8, 55.7, 52.7, 39.8, 36.3, 28.9, 25.1, 23.1, 11.5; m/z (ESI-MS) 455.1 $[M + H]^+$.

(−)-Protoemetinol. To a stirred solution of starting material **19** (91 mg, 0.2 mmol) in EtOH (4 mL) was added $Pd(OH)_2/C$ (20 wt %, 112 mg). The reaction mixture was purged twice with hydrogen gas and then placed under 1 bar of hydrogen gas at 70 °C for 30 h. After being cooled to room temperature, the mixture was filtered through a Celite pad and washed with ethyl acetate. The solvent was removed under reduced pressure and the crude material purified by flash chromatography to give the desired product as a yellow oil in 64% yield. (−)-Protoemetinol was previously reported, and its published characterization data matched our own in all respects.[2g,l]

Characterization data for (−)-protoemetinol: yellow oil; R_f = 0.45 in 30% MeOH/EtOAc; $[\alpha]_D^{25}$ −46.5 (c 0.6, $CHCl_3$); IR (KBr) 3422, 2956, 2931, 2874, 2868, 2751, 1610, 1510, 1463, 1365, 1330, 1253, 1230, 1148, 1100, 1040, 1000, 867, 767, 732; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.67 (s, 1H), 6.56 (s, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.79–3.69 (comp, 2H), 3.14–3.00 (comp, 3H), 2.99–2.93 (m, 1H), 2.61 (app d, J = 15.9 Hz, 1H), 2.47 (app td, J = 11.5, 3.9 Hz, 1H), 2.33 (app d, J = 12.8 Hz, 1H), 2.05–1.97 (m, 1H), 1.93 (app dt, J = 11.1, 7.8 Hz, 1H), 1.70–1.63 (m, 1H), 1.49–1.36 (comp, 3H), 1.28–1.18 (m, 1H), 1.16–1.06 (m, 1H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.4, 147.1, 130.0, 126.7, 111.5, 108.3, 62.7, 61.4, 60.6, 56.1, 55.8, 52.5, 41.3, 37.6, 37.3, 35.9, 29.1, 23.5, 11.1; HRMS (ESI) m/z calcd for $C_{19}H_{30}NO_3$ $[M + H]^+$ 320.2220, found 320.2225.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01384.

X-ray crystal structure of compound **6c** (CIF)
X-ray crystal structure of compound **7c** (CIF)
X-ray crystal structure of compound **8** (CIF)
NMR spectra for all reported compounds; 2D-NMR spectra for selected compounds; Cartesian coordinates, energies of all calculated structures, and details of computational methods (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Kutchan, T. M. *Phytochemistry* **1993**, *32*, 493. (b) Cordell, G. A. *Phytochemistry* **2013**, *91*, 29.

(2) For selected recent syntheses of the compounds shown in Scheme 1, see: (a) Ihara, M.; Yasui, K.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1469. (b) Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2006**, *8*, 1533. (c) Mergott, D. J.; Zuend, S. J.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 745. (d) Chang, J.-K.; Chang, B.-R.; Chuang, Y.-H.; Chang, N.-C. *Tetrahedron* **2008**, *64*, 9685. (e) Nuhant, P.; Raikar, S. B.; Wypych, J.-C.; Delpech, B.; Marazano, C. *J. Org. Chem.* **2009**, *74*, 9413. (f) English, B. J.; Williams, R. M. *J. Org. Chem.* **2010**, *75*, 7869. (g) Sun, X.; Ma, D. *Chem. - Asian J.* **2011**, *6*, 2158. (h) Wanner, M. J.; Claveau, E.; van Maarseveen, J. H.; Hiemstra, H. *Chem. - Eur. J.* **2011**, *17*, 13680. (i) Zhang, W.; Bah, J.; Wohlfarth, A.; Franzén, J. *Chem. - Eur. J.* **2011**, *17*, 13814. (j) Herle, B.; Wanner, M. J.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2011**, *76*, 8907. (k) Palframan, M. J.; Parsons, A. F.; Johnson, P. *Tetrahedron Lett.* **2011**, *52*, 1154. (l) Lin, S.; Deiana, L.; Tseggai, A.; Córdova, A. *Eur. J. Org. Chem.* **2012**, *2012*, 398. (m) Lebold, T. P.; Wood, J. L.; Deitch, J.; Lodewyk, M. W.; Tantillo, D. J.; Sarpong, R. *Nat. Chem.* **2012**, *5*, 126. (n) Moon, H.; An, H.; Sim, J.; Kim, K.; Paek, S.-M.; Suh, Y.-G. *Tetrahedron Lett.* **2015**, *56*, 608.

(3) Examples from our laboratory: (a) Zhang, C.; De, C. K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416. (b) Zhang, C.; Das, D.; Seidel, D. *Chem. Sci.* **2011**, *2*, 233. (c) Ma, L.; Chen, W.; Seidel, D. *J. Am. Chem. Soc.* **2012**, *134*, 15305. (d) Das, D.; Sun, A. X.; Seidel, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 3765. (e) Dieckmann, A.; Richers, M. T.; Platonova, A. Y.; Zhang, C.; Seidel, D.; Houk, K. N. *J. Org. Chem.* **2013**, *78*, 4132. (f) Chen, W.; Wilde, R. G.; Seidel, D. *Org. Lett.* **2014**, *16*, 730. (g) Chen, W.; Kang, Y.; Wilde, R. G.; Seidel, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 5179. (h) Richers, M. T.; Breugst, M.; Platonova, A. Y.; Ullrich, A.; Dieckmann, A.; Houk, K. N.; Seidel, D. *J. Am. Chem. Soc.* **2014**, *136*, 6123. (i) Chen, W.; Seidel, D. *Org. Lett.* **2014**, *16*, 3158. (j) Jarvis, C. L.; Richers, M. T.; Breugst, M.; Houk, K. N.; Seidel, D. *Org. Lett.* **2014**, *16*, 3556.

(4) Selected recent reviews on amine α-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) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W. *Chem. - Eur. J.* **2012**, *18*, 10092. (d) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (e) Peng, B.; Maulide, N. *Chem. - Eur. J.* **2013**, *19*, 13274. (f) Wang, L.; Xiao, J. *Adv. Synth. Catal.* **2014**, *356*, 1137. (g) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. (h) Vo, C.-V. T.; Bode, J. W. *J. Org. Chem.* **2014**, *79*, 2809. (i) Haibach, M. C.; Seidel, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 5010. (j) Seidel, D. *Acc. Chem. Res.* **2015**, *48*, 317.

(5) Additional reviews covering various aspects of redox-neutral chemistry Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854. (b) Mahatthananchai, J.; Bode, J. W. *Acc. Chem. Res.* **2014**, *47*, 696. (c) Ketcham, J. M.; Shin, I.; Montgomery, T. P.; Krische, M. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 9142. (d) Huang, H.; Ji, X.; Wu, W.; Jiang, H. *Chem. Soc. Rev.* **2015**, *44*, 1155.

(6) The intermediacy of azomethine ylides has been established in related processes. For instance, see ref 3e,h.

(7) Examples of other recent redox-neutral amine α-C–H functionalizations that likely involve azomethine ylides as intermediates: (a) Zheng, L.; Yang, F.; Dang, Q.; Bai, X. *Org. Lett.* **2008**, *10*, 889. (b) Zheng, Q.-H.; Meng, W.; Jiang, G.-J.; Yu, Z.-X. *Org. Lett.* **2013**, *15*, 5928. (c) Lin, W.; Cao, T.; Fan, W.; Han, Y.; Kuang, J.; Luo, H.; Miao, B.; Tang, X.; Yu, Q.; Yuan, W.; Zhang, J.; Zhu, C.; Ma, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 277. (d) Haldar, S.; Mahato, S.; Jana, C. K. *Asian J. Org. Chem.* **2014**, *3*, 44. (e) Rahman, M.; Bagdi, A. K.; Mishra, S.; Hajra, A. *Chem. Commun.* **2014**, *50*, 2951. (f) Li, J.; Wang, H.; Sun, J.; Yang, Y.; Liu, L. *Org. Biomol. Chem.* **2014**, *12*, 2523.

(8) Selected recent reviews on azomethine ylides: (a) Padwa, A.; Pearson, W. H. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Wiley: Chichester, U. K., 2002; Vol. 59. (b) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765. (c) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484. (d) Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2006**, *2006*, 2873. (e) Najera, C.; Sansano, J. M. *Top. Heterocycl. Chem.* **2008**, *12*, 117. (f) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887. (g) Nyerges, M.; Toth, J.; Groundwater, P. W. *Synlett* **2008**, *2008*, 1269. (h) Burrell, A. J. M.; Coldham, I. *Curr. Org. Synth.* **2010**, *7*, 312. (i) Anac, O.; Gungor, F. S. *Tetrahedron* **2010**, *66*, 5931.

(9) Other recent examples of redox-neutral amine C–H functionalizations: (a) Kang, Y. K.; Kim, S. M.; Kim, D. Y. *J. Am. Chem. Soc.* **2010**, *132*,

11847. (b) Cao, W.; Liu, X.; Wang, W.; Lin, L.; Feng, X. *Org. Lett.* **2011**, *13*, 600. (c) Mori, K.; Ehara, K.; Kurihara, K.; Akiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 6166. (d) Barluenga, J.; Fananas-Mastral, M.; Fernandez, A.; Aznar, F. *Eur. J. Org. Chem.* **2011**, *2011*, 1961. (e) Zhou, G.; Liu, F.; Zhang, J. *Chem. - Eur. J.* **2011**, *17*, 3101. (f) He, Y.-P.; Du, Y.-L.; Luo, S.-W.; Gong, L.-Z. *Tetrahedron Lett.* **2011**, *52*, 7064. (g) Jurberg, I. D.; Peng, B.; Woestefeld, E.; Wasserloos, M.; Maulide, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 1950. (h) Sugiishi, T.; Nakamura, H. *J. Am. Chem. Soc.* **2012**, *134*, 2504. (i) Wang, Y.; Chi, Y.; Zhang, W.-X.; Xi, Z. *J. Am. Chem. Soc.* **2012**, *134*, 2926. (j) Han, Y.-Y.; Han, W.-Y.; Hou, X.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2012**, *14*, 4054. (k) Chen, L.; Zhang, L.; Lv, J.; Cheng, J.-P.; Luo, S. *Chem. - Eur. J.* **2012**, *18*, 8891. (l) He, Y.-P.; Wu, H.; Chen, D.-F.; Yu, J.; Gong, L.-Z. *Chem. - Eur. J.* **2013**, *19*, 5232. (m) Kang, Y. K.; Kim, D. Y. *Chem. Commun.* **2014**, *50*, 222. (n) Mori, K.; Kurihara, K.; Akiyama, T. *Chem. Commun.* **2014**, *50*, 3729. (o) Mori, K.; Kurihara, K.; Yabe, S.; Yamanaka, M.; Akiyama, T. *J. Am. Chem. Soc.* **2014**, *136*, 3744.

(10) Selected reports on the preparation of enantioenriched 4-nitrobutyraldehydes: (a) Betancort, J. M.; Barbas, C. F. *Org. Lett.* **2001**, *3*, 3737. (b) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611. (c) Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147. (d) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (e) Zu, L.; Li, H.; Wang, J.; Yu, X.; Wang, W. *Tetrahedron Lett.* **2006**, *47*, 5131. (f) Gotoh, H.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 5307. (g) García-García, P.; Ladépêche, A.; Halder, R.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 4719. (h) Hayashi, Y.; Itoh, T.; Ohkubo, M.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4722. (i) Husmann, R.; Jörres, M.; Raabe, G.; Bolm, C. *Chem. - Eur. J.* **2010**, *16*, 12549. (j) Patora-Komisarska, K.; Benohoud, M.; Ishikawa, H.; Seebach, D.; Hayashi, Y. *Helv. Chim. Acta* **2011**, *94*, 719. (k) Alza, E.; Sayalero, S.; Kasaplar, P.; Almaşi, D.; Pericàs, M. A. *Chem. - Eur. J.* **2011**, *17*, 11585. For a recent review, see: (l) Scheffler, U.; Mahrwald, R. *Chem. - Eur. J.* **2013**, *19*, 14346.

(11) Ono, N., Ed. *The Nitro Group in Organic Synthesis*; Wiley-VCH: Weinheim, 2001.

(12) For products **6k**−**t**, the minor diastereomer is epimeric at the carbon center bearing the nitro group. A pure sample of the minor diastereomer of **6k** was found to slowly isomerize to the major diastereomer when exposed to the reaction conditions. Partial isomerization to the apparently thermodynamically more stable major isomer may also occur during column-chromatographic purification. The absolute and relative configurations of all compounds were determined by X-ray (compounds **6c**, **7c**, and **8c**), 2D-NMR, and careful analysis of coupling constants and were based on the known absolute configurations of the enantioenriched starting materials.

(13) The regioisomeric products and their respective diastereomers were all readily separable by standard column chromatography.

(14) Product isomerization does not appear to play a major role in this reversal in regioselectivity. Attempts to isomerize products **6a**/**7a** into **8a**/**9a** and vice versa have been unsuccessful under a variety of conditions, including the reaction conditions that allow for the selective formation of either regioisomeric pair.

(15) Exposure of either diastereomerically pure **10** or **11** to DBU in THF solution led to nearly identical ~2:1 mixtures of **10** and **11**.

(16) (a) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66. (b) Bug, T.; Lemek, T.; Mayr, H. *J. Org. Chem.* **2004**, *69*, 7565. (c) Appel, R.; Chelli, S.; Tokuyasu, T.; Troshin, K.; Mayr, H. *J. Am. Chem. Soc.* **2013**, *135*, 6579.

(17) Xue, X.; Yu, A.; Cai, Y.; Cheng, J.-P. *Org. Lett.* **2011**, *13*, 6054.

(18) A direct isomerization of the azomethine ylides (i.e., **21** → **26**), formally a 1,3-hydride shift, is highly unlikely and would proceed with very high barriers ($\Delta G^{\ddagger} > +75$ kcal mol^{-1}); see also: Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781.

(19) Banks, J. L.; Beard, H. S.; Cao, Y.; Cho, A. E.; Damm, W.; Farid, R.; Felts, A. K.; Halgren, T. A.; Mainz, D. T.; Maple, J. R.; Murphy, R.; Philipp, D. M.; Repasky, M. P.; Zhang, L. Y.; Berne, B. J.; Friesner, R. A.; Gallicchio, E.; Levy, R. M. *J. Comput. Chem.* **2005**, *26*, 1752−1780.

(20) *MacroModel, V. 10.6*; Schrödinger, LLC: New York, 2014.

(21) Zhao, Y.; Truhlar, D. G. *J. Chem. Phys.* **2006**, *125*, 194101.

(22) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *J. Chem. Phys.* **2010**, *132*, 154104.

(23) Cancès, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032−3041.

(24) Ribeiro, R. F.; Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2011**, *115*, 14556−14562.

(25) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215−241.

(26) Weigend, F.; Ahlrichs, R. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297−3305.

(27) Goerigk, L.; Grimme, S. *Phys. Chem. Chem. Phys.* **2011**, *13*, 6670−6688.

(28) Gaussian 09, Revision D.01: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr. ; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J.; Gaussian, Inc.: Wallingford, CT, 2009.

(29) Simpson, A. J.; Lam, H. W. *Org. Lett.* **2013**, *15*, 2586.

(30) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794.

(31) Jentzsch, K. I.; Min, T.; Etcheson, J. I.; Fettinger, J. C.; Franz, A. K. *J. Org. Chem.* **2011**, *76*, 7065.

(32) Moreau, B.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 18014.

(33) (a) Fessard, T. C.; Motoyoshi, J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2078. (b) Dobish, M. C.; Johnston, J. N. *Org. Lett.* **2010**, *12*, 5744.

(34) Trost, B. M.; Bringley, D. A.; Seng, P. S. *Org. Lett.* **2012**, *14*, 234.

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