Asymmetric Induction in C-Alkylation of Tropane-Derived Enamines: Congruence Between Computation and Experiment

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Supporting Information

ABSTRACT: Quantum chemical studies of C-ethylation of 1-methyl- and 1,4,4-trimethyl-tropane-derived enamines predict good (89:11 er, B3LYP) and high (98:2 er, B3LYP) levels, respectively, of asymmetric induction in the resulting α-alkylated aldehydes. The nonracemic tropanes were synthesized using Mannich cyclization strategies (Robinson-Schöpf and by way of a Davis-type N-sulfonyl amino bisketal, respectively), and ethylation of the derived enamines was found to support the predicted sense and magnitude of asymmetric induction (81:19 er and 95:5 er, respectively). A comparison of several computational methods highlights the robustness of predicted trends in enantioselectivity, enabling theory to guide synthesis.  

INTRODUCTION

Chiral α-alkyl-substituted aldehydes are important building blocks for organic synthesis. Several methods to make them involve a chiral auxiliary alkylation strategy and have proven effective for asymmetric induction, but each approach is not without specific drawbacks. The primary method for generation of enantioenriched α-alkyl-substituted aldehydes through alkylation by nucleophilic substitution with S_N2 reactive electrophiles involves the use of Enders’ lithiated SAMP/RAMP hydrazones, although the requirement for low temperature (usually −80 to −120 °C) and the need for subsequent ozonolysis in cleavage of the auxiliary can cause problems. Alkylation are well-known with Evans’ oxazolidinone or Myers’ pseudoephedrine auxiliaries, but once again further manipulation to the aldehyde is required by the removal of these auxiliaries through reduction. Catalytic α-alkylation of aldehydes by way of transient enamines has attracted much attention in recent years, with the process being described as the “Holy Grail” of organocatalysis. This task with S_N2 reactive electrophiles has proven to be challenging, particularly due to undesired side-reactions such as self-aldolization of the aldehydes, and N- or O-alkylation of the catalysts. Work by MacMillan on asymmetric one-electron-mediated organic transformations using photoredox-organocatalysis constitutes an elegant strategy for performing such catalysis, however this method with organohalides requires a radical capto-stabilizing group on the alkylation partner, reducing the scope of this technique.

While organocatalytic α-alkyl-substituted aldehyde generation through intermolecular nucleophilic substitution remains problematic, we have been investigating alkylation of preformed chiral aldenamines as an expedient route to α-alkylated aldehydes. Steric shielding around N is required in such systems to provide bias for C-alkylation. Our early studies with α,α,α’-trialkylsubstituted piperidine-based auxiliaries provided a promising start (88:12 to 94:6 er for ethylation). Issues with conformational flexibility and inactive ground state conformers (lacking N lone pair—π* overlap) led us to then examine rigidified systems: tropane-derived enamine 1 and homotropane-derived enamine 2 (Scheme 1). On ethylation, these latter systems gave 2-ethylhexanal (3) in 45:55 and 72:28 ers, respectively, with the low er from tropane 1 being accompanied by an initially unexpected reversal in the sense of asymmetric induction. These observations were rationalized through computational investigations of the competing alkylation transition structures (TSs). The (slight) bias for ethylation of tropane-derived enamine 1 from the S- rather than the 6-membered side of the bicycle, even though the 5-membered side possesses ostensibly the greatest steric hindrance, was particularly intriguing. In contrast to this earlier study, where DFT calculations were used to rationalize empirical results, the present work describes the use of computation as a predictive tool. The computational prediction and design of catalysts and reactions is still far from routine, and few examples of stereoselective catalysts or reactions synthesized according to computational designs have been published.

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In the current study, we show computed trends in enantioselectivity that are relatively robust across different theoretical methods, allowing confident, qualitative, predictions to be made. Initial investigation of the intrinsic bias of tropane-derived enamine alkylation proved the model’s accuracy experimentally. These results were then used to inform the design of a new tropane auxiliary with sufficient hindrance on the 6-membered side to induce a significantly improved level of asymmetric alkylation.

**RESULTS AND DISCUSSION**

The stereoselective ethylation of enamines 1 and 2 was modeled by us previously with the B3LYP density functional. A large body of work (most notably from Houk) using this level of theory has successfully rationalized the stereochemical outcome of enamine reactions. Despite the shortcomings of the B3LYP functional, it remains a cost-effective method for geometry optimization in the face of multiple conformations and organic reaction pathways. In our case, TS conformers were systematically optimized and the levels of stereoselectivity computed from the B3LYP Boltzmann populations. Qualitatively, the reversal in facial selectivity between 1 and 2 was reproduced, and the quantitative magnitudes of stereoselectivity were also described reasonably well. The use of quasi-rigid rotor harmonic oscillator (qRRHO) corrected Gibb’s energies lessens the influence of erroneously large vibrational entropies associated with low frequency normal modes on the computed selectivities. As in our earlier studies,

The calculations indicated that tropane-derived enamine 1 preferentially adopts a conformation in which the rotor harmonic oscillator (qRRHO) corrected Gibbs energies reproduces, and the quantitative magnitudes of stereoselectivity associated with low frequency normal modes on the computed geometry optimization in the face of multiple conformations makes the computational study feasible, the experimentally examined enamines was truncated to a level of theory has successfully rationalized the stereochemical outcome of enamine reactions. Despite the shortcomings of the B3LYP functional, it remains a cost-effective method for geometry optimization in the face of multiple conformations and organic reaction pathways.

As in our earlier studies, the n-butyl group of the experimentally examined enamines was truncated to a methyl group for computational work. The 27-fold reduction in conformational space makes the computational study feasible, while retaining the important steric effects.

Computations for the bicyclic amine-derived enamines showed that the presence of the bridgehead methyl group leads, due to minimization of allylic strain, to only one relevant rotamer about the exocyclic C–N bond (the anti form, referring to the relationship between the double bond and the N–C bond bearing the bridgehead methyl). Furthermore, the calculations indicated that tropane-derived enamine 1 preferentially adopts a conformation in which the five-membered ring is oriented further away from the enamine than the six-membered ring. As a result, the exo-methyl of the gem-dimethyl group is unable to exert a steric influence in the alkylation transition states, and the modest preference for alkylation on the side of the five-membered ring is directed by an axial exo-hydrogen of the six-membered ring (Figure 1).

There is no such conformational bias in homotropane-derived enamine 2, where the exo-methyl lies closer to the site of reactivity and modestly influences alkylation to occur on the side of the unsubstituted six-membered ring. Observing that a difference in ring size influences enamine conformation led us to hypothesize that enamine 4, lacking the biasing element of the gem-dimethyl group, should also undergo stereoselective alkylation (compared with enamine 1, the lack of an endo-methyl group in enamine 4 does not result in axial exo-H being any less close to the C that undergoes alkylation: the H···C distances being 2.85 Å in 1 and 2.86 Å in 4). The level of asymmetric induction with this system would be intriguing as, aside from the bridgehead methyl necessary to confer chirality and restrict the enamine to one rotamer, facial bias on alkylation would simply be dependent on the influence of different ring sizes (5 versus 6) in the otherwise unsubstituted N-bridged bicyclic system 4. The global minimum energy conformation of this enamine illustrates this design element, the N atom being pyramidalized and the C=C bond sitting closer to the six-membered ring. Moreover, models of enamine 5 showed that the incorporation of the gem-dimethyl group in the six-membered ring should, in combination with the conformational bias already described, effectively shield approach to the enamine from the side of the six-membered ring (modeling was performed for the same enantiomeric series as 4, although in subsequent experimental work the “opposite” enantiomer was synthesized). The introduction of this additional biasing element results in two ground state conformations of similar stability. We turned to computations of the competing TSs to predict the sense and levels of stereoinduction resulting from the proposed structural changes.

Alkylation of 4 was predicted to occur preferentially on the same side as the five-membered ring (Figure 2). This reflects the ground-state conformational bias of the enamine (Figure 1).

**Figure 1.** Examine conformations with B3LYP/6-31G(d) relative energies in kJ/mol.

**Figure 2.** Predicted stereoselectivity for ethylation of enamine 4. Most stable (R)- and (S)- B3LYP/6-31G(d)+LANL2DZ transition structures, with forming/breaking distances (Å). NCI isosurfaces highlight noncovalent interactions (blue = attractive; green = weakly interacting; red = repulsive). The proximity of an Hexo atom with the electrophile in the less favorable (S)-TS gives rise to nonbonding interactions in the less favored TS.
The absolute conformation of the TFA salt from deprotection of Boc-protected 1-methyltropane suggested that application of enamine-forming condensation conditions (K₂CO₃, Et₂O, rt, 16 h) for modestly hindered secondary amines and aliphatic aldehydes might be viable, however, when attempted, condensation conditions only returned unreacted 2-methylnortropane together with the α,β-unsaturated aldehyde from self-aldol condensation of hexanal. In contrast, the two-step procedure used successfully to access enamines 1 and 2 gave the desired, hydrolytically unstable, E-enamine (1S,5S)-4. This chemistry involves Grignard addition to the derived formamide (1S,5R)-12 (0.5 g, 92:8 er by HPLC analysis) under Hansson and Wickberg’s nonaqueous workup modification of the classical Bouveault aldoldehyde synthesis. Pleasingly, enamine (1S,5R)-4 underwent alkylation with EtI to give aldehyde (R)-3 in similar er (81:19) to that predicted earlier by computational analysis (89:11 with B3LYP). The modest yield in this reaction (38%), compared with alkylation of trope 1 (78%, Scheme 1), may in part at least stem from significant competing N-alkylation. While the quaternary ammonium salt S2–3 was not isolated, its presence (1:6:1, C1-N ethylation) was tentatively assigned on the basis of direct 1H NMR analysis of the reaction (following heating at 65 °C for 16 h) before hydrolysis; prolonged heating, for a further 48 h, did not alter the ratio of C1-N ethylation. Computational analysis indicated that, for this comparatively less-hindered enamine, N-ethylation would also be kinetically favored on the side of the 5-membered ring (by ~13 kJ/mol, Figure S3).

Calculated levels of selectivity for 5* were noticeably higher (B3LYP predicted 98:2, Figure 3) than for any of those enamines studied previously. The most stable TS conformer was the same as for 4*, with the electrophile CH interacting with the enamine N atom. Nonbonding interactions between the axial methyl group and electrophile are visible from the NCI isosurface, giving greater levels of stereoinduction than 4*.

The above computational studies indicated that significant asymmetric induction would be provided by methyl substitution in the 6-membered ring at the 4-position. To study this experimentally, 1,4,4-trimethylnortropane (1R,5R)-20 was synthesized (Scheme 3) following a strategy related to that used to construct homonortropane-derived enamine 2, involving Mannich cyclization chemistry developed by Davis. The Mannich cyclization substrate was prepared by addition of organolithium 14 to sulfinimine (R)-13 (prepared in five steps from ethyl α-methylacetocacetate), which gave bisketal sulfinamide (R,R)-15 in excellent yield (89%, 90:10).
enantiopure (by HPLC analysis) formamide prepared (similarly to enamine 5) in this case, no evidence of competing predetermined computational value (i.e., 98:2 with B3LYP). In Scheme 3); once again providing a close match with the g), proceeded in reasonable yield (63%) and high er (95:5, Scheme 3), which was deoxygenated to 1,4,4-trimethyltrimethylnortropinone (15) in an ethanolic-ethereal solution of HCl gave the desired nortropane (15). Ethylation of enamine (1R,SR)-5 prepared (similarly to enamine (1S,SR)-4) by way of the enantiopure (by HPLC analysis) formamide (1R,SR)-21 (0.4 g), proceeded in reasonable yield (63%) and high er (95:5, Scheme 3); once again providing a close match with the predetermined computational value (i.e., 98:2 with B3LYP). In this case, no evidence of competing N-ethylation was observed by direct 1H NMR analysis of the reaction (following heating at 65 °C for 16 h) before hydrolysis.

Throughout this work the B3LYP functional performed well in describing, and importantly predicting, levels of enantioselectivity and trends between the four synthesized enamines. Relatively small energetic differences between competing TSs can be influenced by noncovalent interactions, notably dispersion forces, and the performance of B3LYP, which lacks long-range correlation effects (as do all semilocal functionals), is perhaps surprisingly good. In this respect, intermolecular basis-set superposition error can mimic the effects of dispersion, albeit in an unphysical way, and equally, dispersion corrections in combination with small basis sets should be approached carefully.29 We repeated our computational analysis with different density functionals, optimizing all competing TSs for each enamine with the implicit (M06-2X) and explicit (B3LYP-D3, wB97XD) inclusion of dispersion effects (Figure 4).30

The increase in enantioselectivity progressing from enamines 1, 2, 4, and 5 obtained experimentally is captured by all four functionals tested (using 1*, 2*, 4*, and 5*). Dispersion is evidently not a decisive element of stereocontrol for these reactions. The experimentally and computationally observed differences in facial selectivity between enamines 1(*) and 4(*) indicate that the presence of the 6-exo Me in 1(*) does slightly work against the inherent bias for alkylation on the side of the five-membered ring. These computational studies suggest a contributory factor to this: the favored transition state for 4* with a favorable N–H interaction is not seen analogously for 1*, as this would result in nonbonded steric interactions between the 6-exo Me and the electrophile. While B3LYP-D3, M06-2X, and wB97XD gave quantitative values of enantioselectivity closer to experiment for 2, B3LYP predictions were actually closer to the final experimental selectivities of 4 and 5. For each diastereomeric pair of TSs, differences in forming and breaking bond distances vary only slightly across different levels of theory (ca. 0.01–0.03 Å). Energy differences between major and minor pathways are therefore relatively insensitive, leading

Figure 3. Predicted stereoselectivity for ethylation of enamine 5*. Most stable (R)- and (S)- B3LYP/6-31G(2d)+LANL2DZ TSs shown, with forming/breaking distances (Å). NCI isosurfaces highlight the proximity of the Me exo group with the electrophile in the less favorable (S)-TS.
to a broad consensus in the levels of selectivity. Tighter transition structures were found with the dispersion-corrected methods vs B3LYP, in some cases with forming/breaking distances shorter by more than 0.1 Å. More pronounced nonbonding interactions arise, and consequently, higher computed levels of selectivity.

**CONCLUSION**

The first tropane-type derived enamines computationally predicted to show high levels of asymmetric induction on alkylation have been synthesized, and the experimentally observed ee% are in good agreement with the DFT studies. The monomethyltropane derived enamine 4 illustrates the use of differing ring size (piperidine versus pyrrolidine in the N-bridged bicycle) as an unusual design element to bias π-facial selectivity with an electrophile. While undesired N-alkylation became competitive with this system, the presence of an additional exo-methyl group in the six-membered ring (enamine 5) was sufficient to restore a synthetically useful yield (63%) and provide the highest level of asymmetric induction for ethylation observed so far (95:5 ee%). This chemistry demonstrates the potential of the tropane scaffold as a useful chiral auxiliary for the synthesis of α-alkylated aldehydes by nucleophilic substitution. Predictions of trends in enantioselectivity, which can be used synthetically to optimize levels of stereoisolation, are in this case relatively insensitive to the level of theory chosen. However, accurate predictions of the precise magnitude of enantioselectivity remain a continuing challenge.

**EXPERIMENTAL SECTION**

**General Details.** Where anhydrous conditions were required, reactions were performed using flame-dried glassware under an atmosphere of nitrogen. C6H6, CH2Cl2, Et2O, MeOH, EtOH, pentane, and THF were dried over 4 Å molecular sieves, then degassed and dried over activated alumina under nitrogen. CD3CN was purchased in THF were dried over 4 Å molecular sieves, then degassed and dried over activated alumina under nitrogen. C6H6, CH2Cl2, Et2O, MeOH, EtOH, pentane, and THF were dried over 4 Å molecular sieves, then degassed and dried over activated alumina under nitrogen. CD3CN was purchased in glass ampules (0.75 mL), and C6D6 was purchased as a bottled reagent at an atmosphere of nitrogen. C6H6, CH2Cl2, Et2O, MeOH, EtOH, pentane, and THF were dried over 4 Å molecular sieves, then degassed and dried over activated alumina under nitrogen. CD3CN was purchased in glass ampules (0.75 mL), and C6D6 was purchased as a bottled reagent at an atmosphere of nitrogen. C6H6, CH2Cl2, Et2O, MeOH, EtOH, pentane, and THF were dried over 4 Å molecular sieves, then degassed and dried over activated alumina under nitrogen. CD3CN was purchased in glass ampules (0.75 mL), and C6D6 was purchased as a bottled reagent at an atmosphere of nitrogen. C6H6, CH2Cl2, Et2O, MeOH, EtOH, pentane, and THF were dried over 4 Å molecular sieves, then degassed and dried over activated alumina under nitrogen. CD3CN was purchased in glass ampules (0.75 mL), and C6D6 was purchased as a bottled reagent at an atmosphere of nitrogen. C6H6, CH2Cl2, Et2O, MeOH, EtOH, pentane, and THF were dried over 4 Å molecular sieves, then degassed and dried over activated alumina under nitrogen. CD3CN was purchased in glass ampules (0.75 mL), and C6D6 was purchased as a bottled reagent at an atmosphere of nitrogen. C6H6, CH2Cl2, Et2O, MeOH, EtOH, pentane, and THF were dried over 4 Å molecular sieves, then degassed and dried over activated alumina under nitrogen. CD3CN was purchased in glass ampules (0.75 mL), and C6D6 was purchased as a bottled reagent at an atmosphere of nitrogen. C6H6, CH2Cl2, Et2O, MeOH, EtOH, pentane, and THF were dried over 4 Å molecular sieves, then degassed and dried over activated alumina under nitrogen.

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1-Methylpropane (15,5R)-4 Synthesis. (±)-8-Benzyl-1-methyl-8-azabicyclo[3.2.1]octan-3-one (±)-7. To a stirred solution of NaOAc (7.70 g, 94 mmol) in H₂O (70 mL) was added benzylamine (2.50 mL, 23 mmol) followed immediately by concd HCl (2.00 mL, 24 mmol), maintaining the reaction temperature below 10 °C. After 15 min, acetonitrile-1,3-dicarboxylic acid (3.65 g, 25 mmol) was added to form a homogeneous reaction mixture (pH ~ 5), followed by dropwise addition of 4-oxopentanal (2.10 g, 21 mmol) over 10 min. The reaction mixture was then warmed to 40 °C. After 7 h, the reaction mixture was cooled to 15 °C, the pH adjusted to ~10 with 50% aq NaOH (~5 mL), and the reaction mixture extracted with CH₂Cl₂ (3 × 120 mL). The combined organic layers were dried (Na₂SO₄) and evaporated under reduced pressure. Purification of the residue by column chromatography (Et₂O-Na-deactivated SiO₂, gradient elution 0–4% EtOAc in petroleum ether containing 2% EtN) gave tropone (±)-7 as a yellow oil (2.70 g, 56%). Rf = 0.15 (4% EtOAc in petroleum ether); IR (neat) (cm⁻¹) 1712 s (C=O); ¹H NMR (400 MHz) δ 7.35 (d, 2H, J = 7 Hz, Ar (ortho)), 7.29–7.25 (m, 2H, Ar (meta)), 7.21–7.18 (m, 1H, Ar (para)), 3.84 (d, 2H, J = 13 Hz, CH₂(Ph), 3.67 (d, 1H, J = 13 Hz, CH₂(Ph), 3.38 (dd, 1H, J = 7 Hz, J = 5 Hz, J = 2 Hz, CH₂N), 2.60 (d, 1H, J = 16 Hz, COCH₂CH₂N), 2.46 (d, 1H, J = 16 Hz, COCH₂CH₂N), 1.23 (dd, 2H, J = 16 Hz, 1.67 (m, 2H, 1.41–1.34 (m, 1H, CH₂CH₂N), 1.23 (s, 3H, CH₃); ¹C NMR (101 MHz) δ 210.2 (CO), 139.7 (Ar (ipso)), 128.4 (Ar (ortho), Ar (meta)), 127.0 (Ar (para)), 62.6 (NCC₃H₇), 56.8 (CH₂), 50.8 (COCH₂CH₂N), 48.1 (NCH₂Ph), 42.8 (COCH₂CH₂), 36.6 (CH₂CH₂N), 27.6 (CH₂CH₂), 24.8 (CH₂); HRMS (ESI/TOF) m/z [M+H]⁺ calc'd for C₁₇H₂₅N₂O 273.1967, found 273.1964. (±)-8-Benzyl-1-methyl-8-azabicyclo[3.2.1]octan-3-one (±)-8. Tropone (±)-7 (1.83 g, 8.0 mmol) and hydrazine monohydrate (2.88 g, 57.5 mmol) were added to a stirred solution of powdered KOH (7.06 g, 120 mmol) in diethyl glycol (17 mL) at rt. The mixture was then heated to 220 °C. After 24 h, the reaction mixture was cooled to rt, diluted with H₂O (120 mL), and extracted with EtO (3 × 120 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO₂, gradient elution 0–2% EtOAc in petroleum ether containing 2% EtN) gave tropone (±)-8 as a pale yellow oil (1.52 g, 88%). Rf = 0.24 (4% EtOAc in petroleum ether); ¹H NMR (400 MHz) δ 7.40 (d, 2H, J = 7.5 Hz, Ar (ortho)), 7.33–7.29 (m, 2H, Ar (meta)), 7.24–7.21 (m, 1H, Ar (para)), 3.86 (d, 1H, J = 14 Hz, CH₂(Ph)), 3.59 (d, 1H, J = 14 Hz, CH₂(Ph)), 3.13–3.12 (m, 1H, CH₂N), 1.93–1.50 (m, 8H, 3 × CH₂, 2 × CH₃), 1.19 (dd, 1H, J = 12 Hz, J = 4 Hz, CH₃), 1.16 (s, 3H, CH₃), 1.07–1.01 (m, 1H, CH₂(Ph)), 1.43 (s, 3H, CH₃), 1.41 (s, 3H, CH₃), 1.34 (s, 3H, CH₃), 1.27 (s, 3H, CH₃), 27.5 (CH₃), 24.7 (CH₂), 18.4 (CH₂); HRMS (ESI/TOF) m/z [M+H]⁺ calc'd for C₁₇H₂₅N₂O 273.1967, found 273.1968. (±)-1-Methyl-8-azabicyclo[3.2.1]octan-3-one (±)-9. Pd/C (10 wt %, 766 mg, 0.72 mmol) was added to a stirred solution of tropone (±)-8 (1.54 g, 7.15 mmol) in MeOH (200 mL) at rt. Hydrogen gas was bubbled through the solution for 1 min and the mixture was then vigorously stirred under a hydrogen atmosphere for 24 h. The catalyst was removed by filtration through Celite and 2 M HCl in EtO (19 mL) was added to the filtrate. The filtrate was evaporated under reduced pressure and the residue was washed with CH₂Cl₂ (5 × 20 mL) to give tropone hydrochloride salt as a pale yellow (1.15 g) (mp 220–222 °C). This salt (1.15 g, 7.20 mmol) was suspended in EtO (20 mL) and washed with 3 M aq NaOH (20 mL). The ether layer was separated and the aq phase back-extracted with EtO (3 × 20 mL). The combined organic layers were dried (Na₂SO₄) and concentrated by careful evaporation (228 mm, 35 °C), giving 1-methyltropone (±)-9 as a clear oil (394 mg; quant.); IR (neat) (cm⁻¹) 3658 w (N=H), 1636 w (CO–NH); ¹H NMR (400 MHz) δ 3.45–3.44 (m, 1H, NCH), 1.90–1.33 (m, 11H, 5 × CH₂ and NH), 1.15 (s, 3H, NCH₃), 1.35 (s, 3H, CH₃); ¹C NMR (101 MHz) δ 59.4 (NCH₂CH₃), 55.9 (NCH), 39.1 (CH₂), 35.9 (CH₂), 32.0 (CH₂). 30.7 (CH₂), 27.5 (CH₃), 18.6 (CH₃); HRMS (ESI/TOF) m/z [M+H]⁺ calc'd for C₁₇H₂₅N₂O 273.1967, found 273.1961.
(+)-(1S,5R)-1-Methyl-8-azabicyclo[3.2.1]octan-8-yl-3-phenylpropan-1-one TFA Salt (S,5R,5S)-11-TFA. Anhydrous TFA (7 mL) was added to a stirred solution of Boc-protected α-amine amide (S,5R,5S)-10 (1.0 g, 2.7 mmol) in CH2Cl2 (30 mL) at rt. After 15 min, the mixture was evaporated under reduced pressure and the residue dissolved in CH2Cl2 (3 × 20 mL) to give TFA salt (S,5R,5S)-11. The distillate was recombined with the contents of the reaction vessel, and the distillation procedure was repeated until α-amine amide (S,5R,5S)-11 had been consumed (determined by TLC (10% MeOH in EtOAc)). Upon completion, the mixture was concentrated to dryness and TFA (20 mL) added to the residue. The resulting solution was heated at 50 °C for 20 min. After this time, the reaction mixture was evaporated under reduced pressure and the residue dissolved in CHCl3 (100 mL). This solution was partitioned with H2O (100 mL), and the aq layer was separated and basified with 3 M aq NaOH (100 mL). The resulting suspension was washed with EtO (5 × 100 mL). The combined organic layers were dried (Na2SO4) and carefully evaporated under reduced pressure to give 1-methyltropane (1S,5R)-9 as a clear oil (276 mg, 93%): [α]225 +8.5 (c 0.4, CHCl3); other data as above.

(+)-(S)-2-Amino-1-((1R,5S)-1-methyl-8-azabicyclo[3.2.1]octan-8-yl)-3-phenylpropan-1-one TFA Salt (S,5R,5S)-11-TFA. Anhydrous TFA (7 mL) was added to a stirred solution of Boc-protected α-amine amide (S,5R,5S)-10 (1.0 g, 2.7 mmol) in CH2Cl2 (30 mL) at rt. After 15 min, the mixture was evaporated under reduced pressure and the residue dissolved in CH2Cl2 (3 × 20 mL) to give TFA salt (S,5R,5S)-11. The distillate was recombined with the contents of the reaction vessel, and the distillation procedure was repeated until α-amine amide (S,5R,5S)-11 had been consumed (determined by TLC (10% MeOH in EtOAc)). Upon completion, the mixture was concentrated to dryness and TFA (20 mL) added to the residue. The resulting solution was heated at 50 °C for 20 min. After this time, the reaction mixture was evaporated under reduced pressure and the residue dissolved in CHCl3 (100 mL). This solution was partitioned with H2O (100 mL), and the aq layer was separated and basified with 3 M aq NaOH (100 mL). The resulting suspension was washed with EtO (5 × 100 mL). The combined organic layers were dried (Na2SO4) and carefully evaporated under reduced pressure to give 1-methyltropane (1S,5R)-9 as a clear oil (276 mg, 93%): [α]225 +8.5 (c 0.4, CHCl3); other data as above.

General Procedure for Enamine Alkylation. (R)-2-Ethylhexanol (R)-3. Enamine (1S,5R)-4 (188 mg, 0.90 mmol), CD3CN (1 mL), and EtI (281 mg, 1.80 mmol) were placed in an NMR tube fitted with a PTFE valve. This mixture was heated at 65 °C for 16 h with occasional shaking until consumption of the enamine was complete by 1H NMR spectroscopy. Buffer solution (AcOH (0.5 g), NaOAc (0.5 g), and H2O (1 mL); 0.5 mL) was then added and the mixture stirred at rt for 5 min. The mixture was then partitioned between Et2O (20 mL) and H2O (10 mL). The organic layer was separated and the aq layer back-extracted with Et2O (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (MgSO4), and carefully reduced under vacuum (152 mm, 0 °C).

Trimethyltropane (1R,5R)-20 Synthesis. (−)-(R)-2-Methyl-N-(1R)-4-methyl-1,4-bis[2-methyl-1,3-dioxolane-2-yl]penta-3-ylpropan-1-one (1R)-21. (−)-2-Lodovinol (1R)-22 (5.56 g, 23.0 mmol) was dissolved in pentane/Et2O (3:2, 225 mL) at rt with stirring. The resulting solution was cooled to −78 °C, and t-BuLi (1.7 M in pentane, 28 mL, 48.3 mmol) was added dropwise. The mixture was stirred at −78 °C for 5 min, then warmed to rt, which resulted in formation of a white slurry. The mixture was stirred at rt for 1 h, then recooled to −78 °C. The freshly prepared organolithium 14 was transferred, dropwise via cannula, to a solution of sulfimine (R)-13 (2.4 g, 9.2 mmol, 98:2 er) in THF (52 mL) at −78 °C. After 16 h at −78 °C, the mixture was quenched with MeOH (100 mL), warmed to rt, then diluted with H2O (400 mL). The organic layer was separated, and the aq layer extracted with Et2O (4 × 250 mL). The combined organic layers were dried (Na2SO4) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO2, gradient elution 50–80% EtOAc in petroleum ether) gave bisketal sulfimine (R)-15 as a colorless, clear oil (90:10 dr as determined by integration of the 1H NMR resonances at δ 3.21 and 3.03, 3.08, 0.89%): [α]225 −78.8 (c 0.5, CHCl3); IR (neat) (cm−1) 2875 w (N-H); 1059 s (S=O and O-C=O); 1H NMR (400 MHz) δ 5.30 (br s, 1H, NH), 4.06–3.90 (m, 6H, 2 x OC2H5), 3.29–3.27 (m, 2H, NHC), 2.01–1.84 (m, 2H, CH2C2H5), 1.72–1.64 (m, 3H, CH2CH2H5), 1.56–1.46 (m, 1H, CH2CH2H5), 1.34 (s, 3H, CH3), 1.23 (s, 3H, C(CH3), 1.08 (s, 3H, CH3), 0.96 (s, 3H, CH3); 13C NMR (101 MHz) δ 114.6 (O=C=O), 110.0 (O=C=O), 65.2 (OCH3), 64.6 (OCH3), 64.5 (OCH3), 63.6 (OCH3), 58.5 (NHCH3), 55.4 (C(CH3)), 45.4 (C(CH3)), 37.6 (CH2CH2H5), 27.1 (CH2CH2H5), 23.7 (CH3), 23.1 (CH3), 22.9 (C(CH3)), 19.3 (CH3), 16.8 (CH3); HRMS (ESI/TOF) m/z [M+H]+ calcd for C18H36NO5S 378.2309; found 378.2300.

(−)-(15R)-1,4,4-Trimethyl-8-azabicyclo[3.2.1]octan-3-one ((1S,5R)-16). HCl (2 M in EtOH, 100 mL) was added to a stirred solution of bisketal sulfimine (R)-15 (3.02 g, 8.0 mmol) in EtOAc (200 mL) at rt. The reaction mixture was then heated at 75 °C for 3 days, then cooled to rt, and evaporated under reduced pressure. Aq NaOH (3 M, 120 mL) was added to the residue and the resulting suspension stirred for 15 min, then washed with CHCl3 (5 × 100 mL). The combined organic layers were dried (Na2SO4) and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO2, gradient elution 0–25% MeOH in EtOAc) gave tropinine (1S,5R)-16 as a white solid (896 mg, 67%), recrystallization from 30% EtOAc in petroleum ether gave tropinine 2-hydroxy-2-methyl-3-cyclohexene crystals (682 mg, 51%): mp 35–37 °C; Rf = 0.16 (10% MeOH in EtOAc); [α]225 = −56.5 (c 0.5, CHCl3); IR (neat) (cm−1) 3302 w (N-H), 1703 s (C=O); 1H NMR (400 MHz) δ 3.21 (d, 1H, NCH), 2.53 (dd, 1H, J = 15.5 Hz, 2.5 Hz, 14H2CH2=C=O), 2.26 (br s, 1H, NH),...
(1S,3R)-18-Trimethyl-8-azabicyclo[3.2.1]octane-8-carbodithioate ([1R,5R]-19). Xanthate ([1S,3R,5R]-18 (100 mg, 0.286 mmol) and AIBN (28 mg, 0.17 mmol) were dried under vacuum (0.1 mmHg) for 1 h. Benzene (degassed under N₂ for 1 h, 2.5 mL) was added, followed by Bu₃SnH (155 μL, 0.58 mmol), dropwise with stirring at rt. The mixture was heated at 85 °C for 16 h, then cooled to rt and the volatiles removed by evaporation under reduced pressure. Purification of the residue by column chromatography (SiO₂, gradient elution 0–2% Et₂O in petroleum ether) gave carbodithioate ([1R,5R]-19 as a yellow oil (50 mg, 72%): Rf = 0.45 (2% Et₂O in petroleum ether); [α]³⁰° +183.3 (c = 0.3, CHCl₃); 1H NMR (400 MHz) δ 0.05 (br s, 1H, NCH), 2.60 (s, 3H, SCH₃), 2.30–2.23 (m, 1H, NCH₂CH₂CH₃), 1.91–1.80 (m, 4H, CH₂CH₂CH₂CH₃), 1.85 (s, 3H, CH₃), 1.64–1.56 (m, 1H, CHCH₂CH₂CH₃), 1.33–1.23 (m, 2H, NCH₂CH₂CH₃, CHCH₂CH₂CH₃), 1.08 (s, 3H, CH₃), 0.93 (s, 3H, CH₃); 13C NMR (101 MHz) ð 194.8 (C(S)=O), 72.9 (NCH₃), 68.9 (N(CH₃)₃), 38.0 (CH₂CH₃), 34.3 (NCH₂CH₃), 32.4 (CH₂CH₂), 27.6 (CH₂), 27.2 (CH₂), 24.6 (CH₂), 21.9 (CH₃), 19.5 (SCH₃); HRMS (ESI/TOF) m/z [M+H⁺] calcd for C₁₁H₂₀N₂O 182.1539; found 182.1538.

(1S,3R,5R)-1,4,4-Trimethyl-8-azabicyclo[3.2.1]octane ([1R,5R]-20). Aq HCl (6 M, 10 mL) was added to a stirred solution of carbodithioate ([1R,5R]-19 (100 mg, 0.41 mmol) at rt. The resulting mixture was heated at 130 °C for 3 days. After this time, the mixture was cooled to rt, basified with 3 M aq NaOH (30 mL), and the resulting suspension extracted with Et₂O (3 × 50 mL). The combined organic layers were dried (Na₂SO₄), and the mixture concentrated by careful evaporation (228 mm, 35 °C) to give tropane ([1R,5R]-20 as a clear oil (53 mg, 84%): [α]³⁰° +76.1 (c = 0.3, CHCl₃); 1H NMR (400 MHz) δ 2.82 (d, 1H, J = 6.5 Hz, NHC), 1.84–1.68 (m, 1H, NCH₂CH₂CH₃), 1.56–1.18 (m, 8H, 3 x CH₂, NHCH₂CH₂CH₃), 1.15 (s, 3H, CH₃), 1.00 (s, 3H, CH₃), 0.80 (s, 3H, CH₃); 13C NMR (101 MHz) δ 65.8 (NCH₃), 58.6 (NC(CH₃)₃), 36.0 (CH₂CH₃), 34.8 (NCH₂CH₃), 32.7 (C(CH₃)₂), 32.0 (C(CH₃)₂), 28.1 (CH₂CH₂), 27.3 (CH₂), 27.1 (CH₃), 25.3 (CH₃); HRMS (ESI/TOF) m/z [M+H⁺] calcd for C₁₃H₂₃N₂O 254.1590; found 254.1598.

(1S,3R,5R)-1,4,4-Trimethyl-8-azabicyclo[3.2.1]octane-8-carbaldehyde ([1R,5R]-21). According to the general procedure for formamide synthesis, reaction of tropane ([1R,5R]-20 (356 mg, 2.32 mmol), Bu₄NCl (262 mg, 1.15 mmol), CHCl₃ (1.87 mL, 23.40 mmol), and 12.5 M aq NaOH (6.40 mL) in CH₂Cl₂ (10.0 mL) at reflux for 16 h gave formamide ([1R,5R]-21 as colorless crystals (400 mg, 95%): mp 173–174 °C); IR (neat) (cm⁻¹) 3438, 1564 (C=O); 1H NMR (400 MHz) δ 4.17 (s, 1H, CHO), 4.23 (d, 1H, J = 7 Hz, NCH), 1.85–1.42 (m, 4H, CH₂CH₂CH₂CH₃, 3 x CH₂), 1.44 (s, 3H, NC(CH₃)₃), 1.27–1.22 (m, 1H, CH₂CH₃), 0.97 (s, 3H, CH₃), 0.92 (s, 3H, CH₃); 13C NMR (101 MHz) δ 156.4 (C(C)=O), 60.2 (NCH₃), 60.0 (NC(CH₃)₃), 37.4 (CH₂), 35.4 (CH₂), 35.0 (C(CH₃)₂), 31.7 (CH₃), 27.0 (CH₂), 24.5 (CH₂), 23.7 (CH₃), 23.0 (CH₃); HRMS (ESI/TOF) m/z [M+Na⁺] calcd for C₁₄H₂₄N₂O₂Na 298.1519; found 298.1516.
Asymmetric Alkylation of Enamine (1R,5R)-5 with EtI (S)-2-Ethoxyhexan-1-ol (S)-3. According to the general procedure for enamine alkylation, reaction of enamine (1R,5R)-5 (235 mg, 1.0 mmol) with EtI (312 mg, 2.0 mmol) in CD2CN (1 mL) at 65 °C for 16 h gave, following hydrolysis with acidic buffer (0.5 mL) at rt for 5 min, aldehyde (S)-312 as a clear oil (95:5 cr; 228, 90 mg, 63%).

Computational Methodology. Density functional theory (DFT) calculations were performed using the Gaussian 09 package.31 Optimizations of the enamine ground state structures and of transition state structures for alkylation were performed using the default (fine) grid density for numerical integration with the B3LYP, wB97XD, and M06-2X functionals.32 Optimizations were also performed with an atom-pairwise density independent Becke-Johnson damped D3-dispersion correction (s0 = 1.0; a1 = 0.3981; s2 = 1.9889; a3 = 4.4211).33 Harmonic vibrational frequencies were computed for all optimized structures to verify that they were either minima or transition states, possessing zero imaginary frequencies and one imaginary frequency, respectively. The Pople 6-31G(d) basis set was used for all elements except I, which was described with the effective core potential and associated valence basis of Hay and Wadt.34 Gibbs energies were evaluated at the reaction evaluation of energies using a conductor-like polarizable continuum model (CPCM).35 Gibbs energies were evaluated at the reaction temperature of 65 °C. A quasi-rigid rotor harmonic oscillator approximation was applied, switching to a free rotor description of vibrational entropy below 100 cm−1. This mitigates spuriously large entropic terms from low frequencies, reducing the sensitivity of the computed selectivities to the choice of numerical convergence criteria or grid size.36 Conformers of the diastereometric transition structures arising from rotation about the incipient C–C bond were systematically generated and optimized for each enamine: in each case there are three TS geometries for attack from either enamine diastereoface. Stereoselectivities were computed from a summation of competing Boltzmann populations.37 Noncovalent interaction (NCI) isosurfaces were generated from the B3LYP densities using NCIplot using default density (0.2) and reduced density gradient (1.0) cutoffs.38 Molecular graphics were produced by Pymol, including Bondi Atomic van der Waals radii where appropriate.39

■ ASSOCIATED CONTENT

1 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01954.

H and 13C NMR spectra, 77Se NMR spectra for determination of ee, and HPLC traces of formamides showing enantio purity (PDF)

Determination of absolute configuration, Cartesian coordinates, imaginary frequencies, and computed energies (ZIP)

X-ray crystallographic data for compound (S,1S,1R,5S)-11·THF (CIF)

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Notes

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