JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

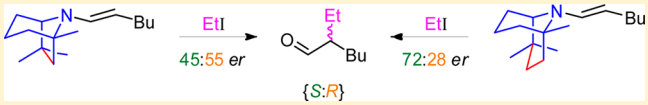
C-Alkylation of Chiral Tropane- and Homotropane-Derived Enamines

David M. Hodgson,* Andrew Charlton, Robert S. Paton,* and Amber L. Thompson

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, U.K.

Supporting Information

ABSTRACT: The synthesis and alkylation of chiral, nonracemic tropane- and homotropane-derived enamines is examined as an approach to enantioenriched α-alkylated aldehydes. The two bicyclic N auxiliaries, which differ by a single methylene group, give opposite senses of asymmetric induction on alkylation with EtI and provide modestly enantioenriched 2-ethylhexanal (following hydrolysis of the alkylated iminium). The observed stereoselectivity is supported by density functional studies of ethylation for both enamines.

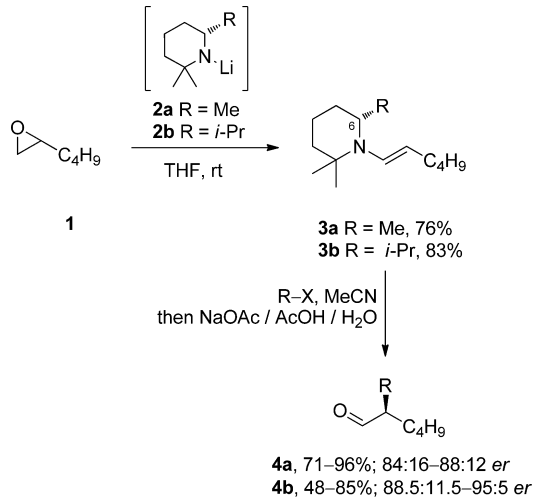


INTRODUCTION

Chiral α-alkyl-substituted aldehydes are widely recognized as valuable materials for synthesis. The aldehyde functional group provides a variety of attractive possibilities for introduction of asymmetry into more complex molecular scaffolds. Chiral α-alkyl-substituted aldehydes have also found direct application in the fragrance industry.[1] Despite longstanding interest by the synthetic community in the development of methodology to access such species directly,[2] success has so far been limited.[3] Currently, one of the most commonly used strategies to generate enantioenriched α-alkyl-substituted aldehydes employs Enders' lithiated SAMP/RAMP hydrazone chemistry.[4] Also effective are alkylations carried out at a higher oxidation level, typically involving Evans' oxazolidinone[5] or Myers' pseudoephedrine auxiliaries.[6] While these methods are robust and normally provide high levels of asymmetric induction, they are not without limitations: Enders' chemistry usually involves very low temperatures (−80 to −120 °C), and all three methods require further manipulation, e.g., ozonolysis (Enders) or reduction (Evans/Myers), to cleave the auxiliary and obtain the aldehyde. Recent years have seen the development of a variety of organocatalytic approaches to achieve direct, asymmetric α-alkylation of aldehydes.[7] Despite this, alkylation involving simple alkyl halides via intermolecular nucleophilic substitution has yet to be achieved organocatalytically. Difficulties with the organocatalytic approach include direct reaction of the amine catalyst with the alkyl halide and/or irreversible *N*-alkylation of the enamine intermediate.[8,9] In the case of MacMillan's elegant combination of photoredox and organocatalysis, a radical stabilizing group is required on the electrophile.[10]

Curphey et al. originally showed that aldenamines which are sterically crowded about N undergo preferential *C*-alkylation with simple alkyl halides.[11] This led us to investigate the possibility of chiral, nonracemic, hindered enamines for asymmetric intermolecular S_N2 alkylation. We previously reported a direct synthesis of enantioenriched mono-α-alkyl-substituted aldehydes **4a,b** by way of *C*-alkylation of chiral piperidine-derived enamines **3a,b** (Scheme 1).[12] These hindered about N enamines were prepared by reaction of the hindered lithium amides **2a,b** with terminal epoxides **1**.[13] The preparation of such enamines by classical condensation techniques is not possible.

Scheme 1. Synthesis and Asymmetric Alkylation of Trialkyl-Substituted Piperidine Enamines 3a,b



In our earlier work, 2,2,6-trimethylpiperidine-derived enamine **3a** gave high yields and significant levels of enantioenrichment on alkylation.[12] Diastereocontrol of enamine alkylation was enhanced by moving to a sterically more demanding substituent on the piperidine (Me → *i*-Pr, Scheme 1, **3b** → **4b**), albeit at the expense of lower alkylation yields. These experimental observations were rationalized through a computational study,[14] which indicates that in enamine **3a** the C-6 Me substituent resides axial in the ground-state conformation (Figure 1; **3(ax)**, R = Me) so as to minimize $A^{1,3}$ strain (Figure 1, **3(eq)**). In contrast, the C-6 *i*-Pr substituent in enamine **3b** is equatorial in the ground state (Figure 1; **3(eq)**, R = *i*-Pr), with the reactive axial conformation (where N lone

Received: November 28, 2012
Published: January 29, 2013

   dx.doi.org/10.1021/jo3025972 | J. Org. Chem. 2013, 78, 1508−1518

pair–π^* overlap becomes possible) only being attainable at elevated temperatures; in this case 1,3-diaxial interactions, exacerbated by the larger isopropyl substituent, outweigh allylic strain present in the conformer with the C-6 *i*-Pr group equatorial. When the C-6 substituent is equatorial, the olefinic component of the enamine twists orthogonal to the nitrogen lone pair, rendering the enamine inactive to *C*-alkylation.[15] The reactive conformation (C-6 substituent axial) which is achieved in the transition state for enamine **3b** alkylation, despite the ground-state preference, is expected to be less accessible for enamines derived from piperidines with larger C-6 substituents.

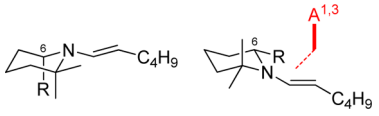


Figure 1. Enamine **3** conformers.

The above findings led to the present study concerning the development of a new class of chiral amine auxiliaries, hopefully capable of attaining elevated er levels while also retaining a high degree of reactivity.

RESULTS AND DISCUSSION

As a starting point in the exploration of more reactive enamines, the design of a new auxiliary centered around modification to the scaffold of the precursor to lithium amide **2b**, piperidine **5** (Figure 2). Tropane **6**, which is conformationally locked, thus alleviating the problems associated with unfavorable conformers, could generate enamines with enhanced reactivity. At the outset, it was considered that the *gem*-dimethyl substitution in tropane **6** (Figure 2) would mimic the isopropyl steric encumberment of enamine **3b** (albeit without the ability to splay outward[14]), thereby providing effective facial discrimination. While a single *exo*-methyl substituent would also potentially suffice (i.e., tropane **6** (Me_{endo} = H); Figure 2), this was not considered further due to the potential greater synthetic complexity associated with inclusion of an additional stereocenter.

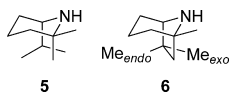
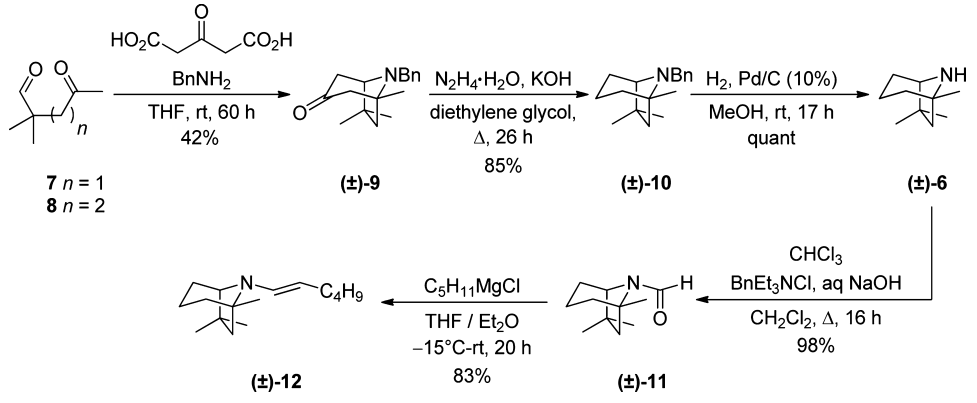


Figure 2. Piperidine **5** and tropane **6**.

We first examined the synthesis and alkylating ability of an enamine derived from racemic tropane (±)-**6**. While there are several methods for the synthesis of tropanes and their typically parent tropinones,[16] there are limited examples[17] of tropanes/tropinones containing the desired substitution pattern (bridgehead alkyl and *gem*-dialkyl α to a CH bridgehead). We envisaged a synthetic sequence using a classical Robinson–Schöpf reaction to construct the azabicyclic core (Scheme 2). Sterner et al. have demonstrated that impressive yields can be obtained by performing Robinson–Schöpf reactions of dialdehydes in THF.[18] Following Sterner's protocol, but using benzylamine (chosen for its greater nucleophilicity compared with ammonia[19] and projected reduction to access the free amine), gave tropinone (±)-**9** in satisfactory yield from readily available (one to two steps) ketoaldehyde **7**.[20] A subsequent Wolff–Kishner reaction to *N*-benzyltropane (±)-**10**[21] and then hydrogenolysis[22] gave the desired tropane (±)-**6** in excellent yield (85% from (±)-**9**).

With tropane (±)-**6** in hand, we examined the feasibility of synthesizing enamine (±)-**12** using the lithium amide–epoxide methodology (cf., **1** → **3**, Scheme 1).[13a] Previous studies in our laboratory indicated that enamine formation from lithium 2,2,5,5-tetramethylpyrrolidide and 1,2-epoxyoctadecane was slow at room temperature and generated unsatisfactory yields at higher temperatures, the latter being due to instability of the intermediate lithiated epoxide in refluxing THF.[23] In the event, attempted formation of enamine (±)-**12** from *N*-lithiotropane **6** and epoxide **1** led to a complex mixture of products from which the enamine could not be isolated by distillation or, due to its hydrolytic sensitivity, by chromatography. Attention turned to alternative methods of hindered aldenamine preparation. We have previously prepared trialkylpiperidine enamines using the unusual reaction of Grignard addition–elimination with formamides reported by Hansson and Wickberg,[24] albeit in low yield and with prolonged reaction time (e.g., reaction between *N*-formyl-2,2,6,6-tetramethylpiperidine and *n*-BuMgCl proceeded in only 32% yield after 7 days).[13b] To examine this strategy in the current work, formamide (±)-**11** was synthesized from tropane (±)-**6** using the method of Blum and Nyberg (Scheme 2).[25] The original Hansson and Wickberg enamine work prescribes excess formamide relative to Grignard reagent; however, we found this inevitably resulted in some inseparable formamide contaminating the product enamine. Modification, using a slight excess

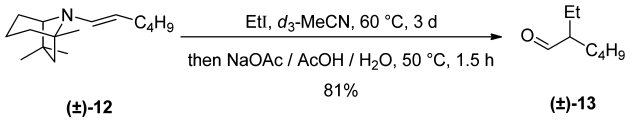
Scheme 2. Synthesis of Tropane-Derived Enamine (±)-12



dx.doi.org/10.1021/jo3025972 | J. Org. Chem. 2013, 78, 1508–1518

(1.25 equiv) of pentylmagnesium chloride, generated the desired enamine (±)-**12** in excellent yield (Scheme 2). The ^{1}H NMR spectrum of enamine (±)-**12** showed separation between the olefinic signals of 1.67 ppm, indicative of alignment of the N lone pair and alkene π orbital, and suggesting a strong *C*-alkylation profile.[15] Indeed, *C*-ethylation of enamine (±)-**12** with EtI gave, after hydrolysis of the resulting iminium, 2-ethylhexanal (±)-**13** in excellent yield (Scheme 3). By comparison, enamine **3b** generated the same aldehyde in only 58% yield under similar conditions.

Scheme 3. Ethylation of Enamine (±)-12



To examine asymmetric alkylation, tropane (±)-**6** was resolved by coupling with *N*-Boc-L-phenylalanine to give Boc-protected α-amino amides **14**, followed by deprotection and chromatographic separation of the diastereomeric α-amino amides **15** and then Edman degradation (Scheme 4).[26] The absolute configuration of tropane (+)-**6** was determined to be 1*R*,5*S* by X-ray crystallographic analysis of the precursor α-amino amide (**S**,**1R**,**5S**)-**15**. Surprisingly, the enamine derived from tropane (−)-(**1S**,**5R**)-**6** underwent alkylation with EtI to give aldehyde (**R**)-**13** in low er (55:45; Scheme 4) with a preference for the opposite sense of asymmetric induction (i.e. the opposite enantiomer) to that seen with piperidine-derived enamines **3a**,**b** (Scheme 1); similarly, enantiopure enamine (**1R**,**5S**)-**12** gave aldehyde (**S**)-**13** in 58:42 er).

The origin of the low er and unanticipated reversal of asymmetric induction was examined using quantum mechanical calculations. Density functional studies of enamine **12*** (Figure 3) at the B3LYP/6-31G(d) level determined that in the ground state the lowest energy conformation **GS1** (Figure 3) has the exocyclic C−N bond pseudoaxial with respect to the six-membered ring.

Computed transition states **TS1**−**TS4** originating from **GS1**, for the reaction of enamine **12*** with EtI in MeCN at 65 °C (Figure 4), suggest a preference for *Re*-face attack (with (**1S**,**5R**)-**12**). The methylene group α to the CH bridgehead influences the facial selectivity of the approaching electrophile

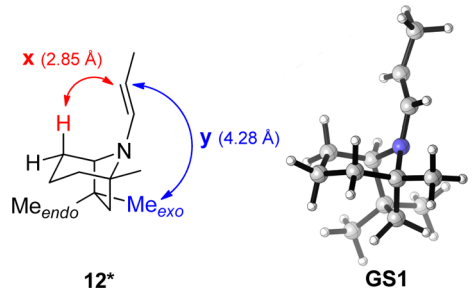


Figure 3. Computed ground-state conformation for enamine **12***.

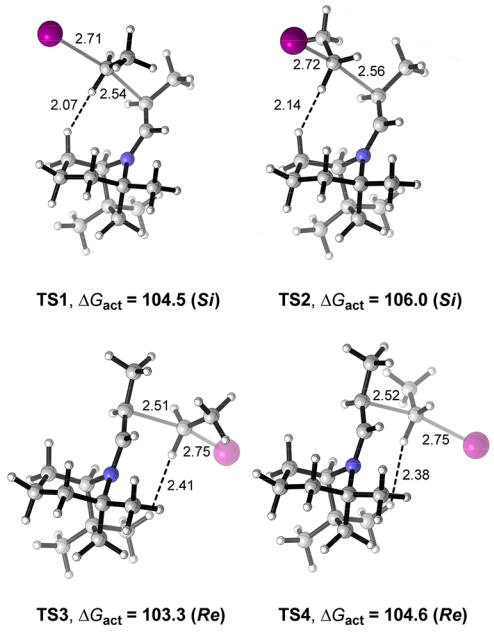
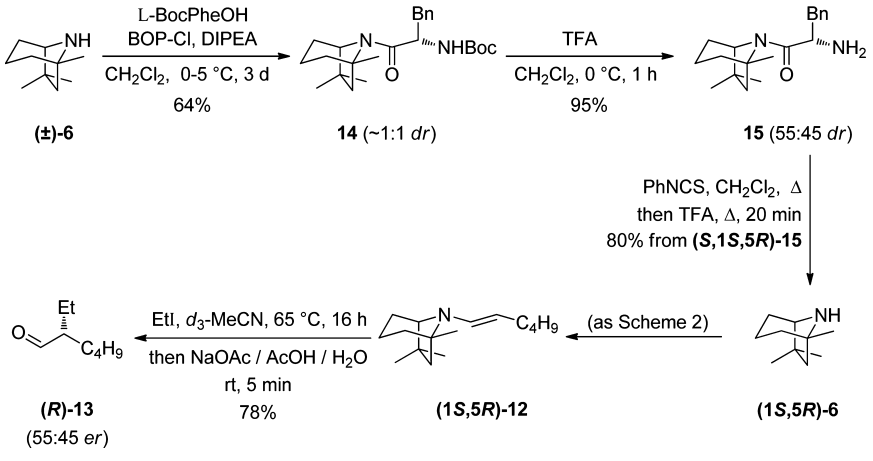


Figure 4. Computed TS geometries for reaction of enamine **12*** with EtI. B3LYP/6-31G(d) free energies in kJ/mol; selected distances shown in Å.

slightly more than that of the *exo*-methyl substituent ($x < y$, Figure 3; and similarly in the transition states **TS1**−**TS4**[35]). Transition states **TS1** and **TS2**, which differ only in the approach orientation of EtI to the *Si* face, lie 1.2 and 2.7 kJ mol^{-1} higher in energy than **TS3**, respectively. The computa-

Scheme 4. Synthesis and Ethylation of Enamine (1S,5R)-12



dx.doi.org/10.1021/jo3025972 | J. Org. Chem. 2013, 78, 1508−1518

tionally determined face selectivity and calculated 62:38 er are in good agreement with the experimental findings.

From Figures 3 and 4 it is clear that the presence of the embedded pyrrolidine places an undesired bias on the orientation of the exocyclic double bond. In response to this, we considered that formal expansion of the two-carbon bridge of the tropane scaffold by a methylene group to generate two rings of equal size (homotropane {6,6}, cf. tropane {6,5}), could give an improved er, since facial discrimination should now be solely dependent on the presence of the *gem*-dimethyl group on one ring. Comparison of the computed ground-state conformations for tropane-derived (**GS1**) and homotropane-derived (**GS2**) enamines shows similar orientations of the common *N*-propenyl group (similar values of *x* and *y*, Figures 3 and 5). However, in contrast to **TS3** and **TS4** (Figure 4), the

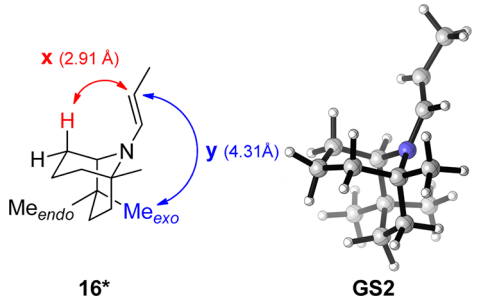


Figure 5. Computed ground-state conformation for enamine **16***.

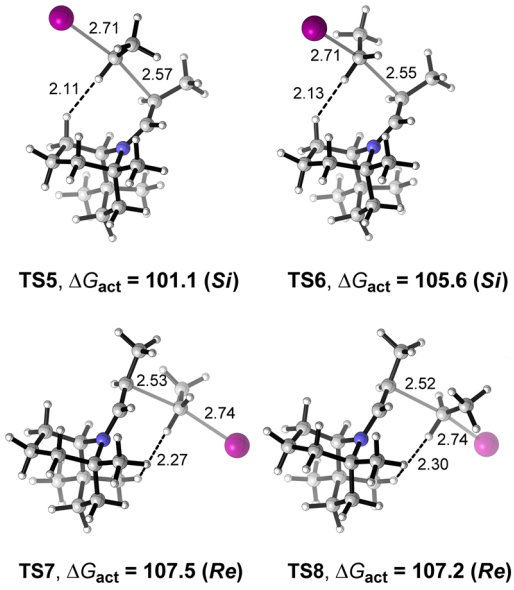


Figure 6. Computed TS geometries for reaction of enamine **16*** with EtI. B3LYP/6-31G(d) free energies in kJ/mol; selected distances shown in Å.

computed transition structures **TS5** and **TS6** for alkylation of homotropane-derived enamine **16*** with EtI (Figure 6) show that the exocyclic C–N bond moves to being essentially equidistant from each piperidine ring of the homotropane ($x \approx y$).[35] Furthermore, the calculated energies of transition states **TS5**–**TS8** predicted significant improvement in er (85:15), with *Si*-face selectivity (with enamine (**1***S*,**5***R*)-**16**).

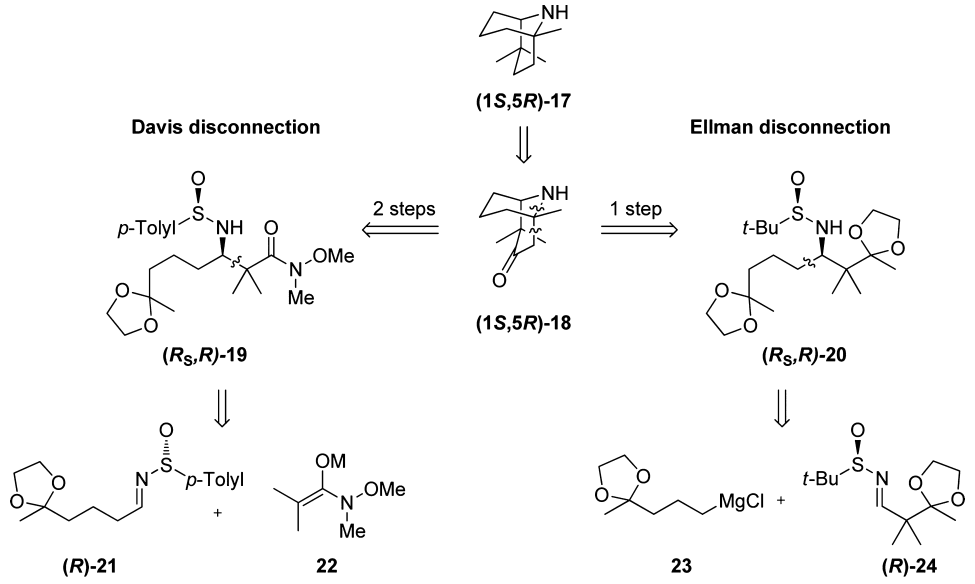
For preparation of the required homotropane **17**, we initially investigated a Robinson–Schöpf strategy similar to that used for preparing tropane **6**. However, the propensity for intramolecular aldol condensation of the required ketoaldehyde **8** led to poor yields in the early stages of the synthetic sequence and consequently generated insufficient quantities of homotropane **17** for subsequent enamine studies. Therefore, it was decided to examine an asymmetric synthesis of homotropane **17**. We were attracted to the elegant chemistry of Davis et al.,[27] which involves enolate addition to chiral ketal sulfinimines followed by Mannich cyclization to construct chiral homotropinones in excellent yields and ers. However, and despite significant experimentation, the envisaged Davis approach (Scheme 5) was hampered by an inability to form the requisite novel Weinreb enolate **21** (M = Li). We therefore investigated constructing a Mannich cyclization substrate by addition of an organometallic rather than an enolate to a sulfinimine (Scheme 5). As sulfinimines prepared from Davis' auxiliary are known to undergo competing *S*- and 1,2-addition using Grignard reagents,[28] we switched to Ellman's *tert*-butyl sulfur analogue.[29] Although the revised strategy relied heavily on addition of an organometallic **23** to a severely hindered sulfinimine **24**, literature precedent suggested that promising yields and diastereoselectivity could be achieved.[30]

Aldehyde **25** (Scheme 6), prepared in four steps from ethyl α-methylacetoacetate (78% overall yield),[31] underwent NaOH-mediated[32] condensation with sulfinamide (***R***)-**26** to give sulfinimine (***R***)-**24** in excellent yield. Addition of Grignard reagent **23** to racemic sulfinimine **24** generated the crude bis-ketal sulfinamide **20** in moderate dr (73:27).[33] Due to the low yield and dr from Grignard approach, we examined addition of organolithium **27** to sulfinimine (***R***)-**24**, which gave the bis-ketal sulfinamide (***R***$_S$,***R***)-**20** in excellent yield (91%) and dr (98:2), with the configuration later being determined by correlation with homotropinone (**1***S*,**5***R*)-**18**. The diastereoselectivity observed using organolithium **27** (opposite to that seen with Grignard reagent **23**) is consistent with that found for reactions of other organolithiums and *tert*-butanesulfinyl aldimines, which are suggested as proceeding through an open transition state.[34] Treatment of bis-ketal sulfinamide (***R***$_S$,***R***)-**20** under the same conditions used by Davis[27] to promote cascade through to the homotropinone (NH_4OAc (25 equiv), AcOH:EtOH (1:1), 36 h, 75 °C) led to deprotection of both ketals but left the sulfinamide group intact. It was considered that stronger acidic conditions would be required for removal of the *tert*-butyl sulfinyl group. Indeed, heating (***R***$_S$,***R***)-**20** in a methanolic–ethereal solution of HCl gave the desired homotropinone (***R***$_S$,***R***)-**18** as a single enantiomer (by chiral HPLC analysis), whose absolute configuration was established by X-ray crystallographic analysis.[35] Wolff–Kishner reaction (and other common deoxygenation strategies) proved unsuccessful for reduction of homotropinone (**1***S*,**5***R*)-**18**, but conversion to homotropane (**1***S*,**5***R*)-**17** was eventually achieved by reduction to the homotropinol (**1***S*,**3***R*,**5***R*)-**28** and deoxygenation of the derived xanthate (**1***S*,**3***R*,**5***R*)-**29** under Barton–McCombie conditions.[36] NOE studies[35] on xanthate (**1***S*,**3***R*,**5***R*)-**29** indicated that reduction of homotropinol (**1***S*,**3***R*,**5***R*)-**28** had proceeded with *exo*-face hydride delivery.

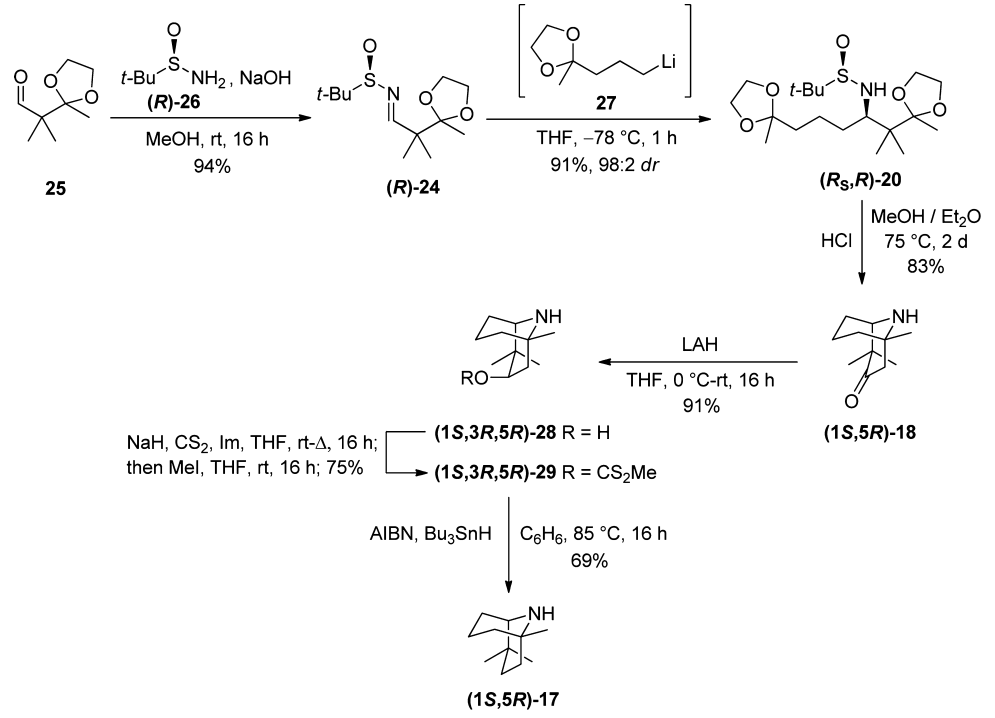
Ethylation of enamine (**1***S*,**5***R*)-**16**, prepared similarly to tropane enamine **12**, proceeded in reasonable yield (Scheme 7), showed a significant improvement in er compared with tropane enamine (**1***R*,**5***S*)-**12**, and gave the same sense of asymmetric induction seen with piperidine derived enamines **3a**,**b** (Scheme 1).

dx.doi.org/10.1021/jo3025972 | *J. Org. Chem.* 2013, 78, 1508–1518

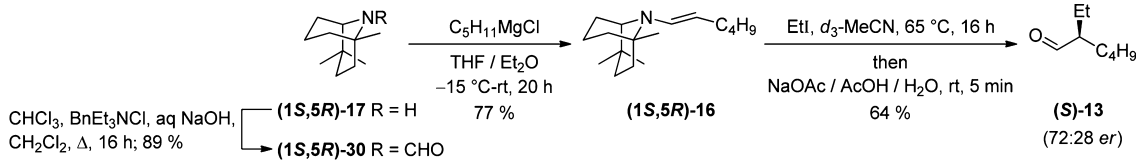
Scheme 5. Retrosynthetic Analyses for Homotropane (1*S*,5*R*)-17



Scheme 6. Synthesis of Homotropane (1*S*,5*R*)-17



Scheme 7. Synthesis and Ethylation of Enamine (1*S*,5*R*)-16



In contrast with tropane enamine (1*R*,5*S*)-12, the sense of asymmetric induction seen with homotropane enamine (1*S*,5*R*)-16 is as originally envisaged, with the *gem*-dimethyl group providing effective steric encumbrance to electrophile approach of the enamine. This is illustrated in Figure 7, where the most important competing diastereomeric TS geometries have been superimposed. Approach of the electrophile toward the *Re* face of enamine **16*** is hindered by the *gem*-dimethyl group, and as a result, the enamine is appreciably nonplanar in the TS and thus less nucleophilic. Later TS geometries with greater C−I distances are found for this minor pathway, lending further support to this interpretation. In contrast, approach

dx.doi.org/10.1021/jo3025972 | J. Org. Chem. 2013, 78, 1508−1518

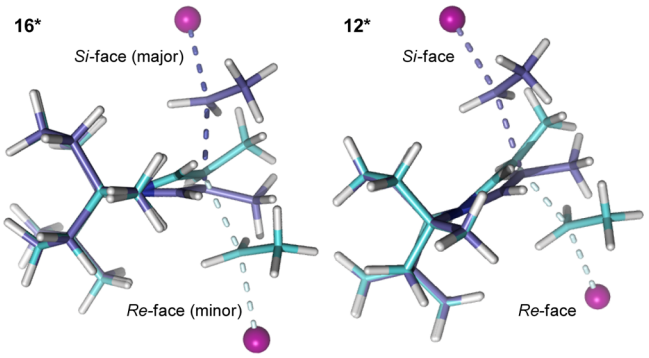


Figure 7. Superimposed TS geometries for homotropane-derived (**16***) and tropane-derived (**12***) enamine alkylation.

toward the *Si* face of enamine **16*** is unhindered and the TS displays a planar enamine geometry and is thus energetically preferred. However, there is a significant reduction in the er for alkylation with enamine (**1*S*,5*R*)-16** in comparison with superficially analogous enamine **3b**. The lower er may be a consequence of the rigidity the cyclohexyl ring imposes on the carbon bearing *gem*-dimethyl substitution. For enamine **3b**, the corresponding axial isopropyl group is able to slightly splay away from the idealized chair, thus relieving 1,3-diaxial interactions and providing increased steric shielding of the enamine *Re* face.[14] Comparison of TS geometries for attack of enamine **12*** (Figures 4 and 7) highlights the fact that the *gem*-dimethyl substituent is now more remote from the *Re* face; the combination of these effects leads to a modest inversion in the sense of facial selectivity.

■ CONCLUSION

The synthesis and asymmetric alkylation profile of enamines derived from chiral tropane **6** and homotropane **17** have been examined. Tropane-derived enamines (**1*S*,5*R***)- and (**1*R*,5*S***)-**12** showed low but reverse diastereofacial selectivity to that initially envisaged. In contrast, homotropane-derived enamine (**1*S*,5*R***)-**16** alkylated with the anticipated sense of (and with significantly improved) diastereoselectivity. The experimental findings are in good agreement with DFT studies for both enamines, where the latter provide insight into the origins of asymmetric induction. While tropane-derived enamine **12** gave a significantly improved yield of ethylation in comparison with enamine **3b**, both auxiliaries failed to provide high levels of asymmetric induction. However, despite the modest ers, the congruence between theory and practical experiment coupled with an ability to modify and, importantly, improve the er through computational studies should assist the future design of chiral auxiliaries and other asymmetric targets. Additionally, the described synthesis of α,α-disubstituted homotropinone (**1*S*,5*R*)-18** demonstrates an efficient strategy to this biologically significant class of chiral compounds that are otherwise difficult to access. Investigations are ongoing to improve on the ers obtained.

■ EXPERIMENTAL SECTION[35]

Tropane (±)-6 Synthesis. *(±)-8-Benzyl-1,6,6-trimethyl-8-azabicyclo[3.2.1]octan-3-one ((±)-9).* Benzylamine (18.0 g, 0.17 mol) was added to a solution of ketoaldehyde 7[20] (19.4 g, 0.15 mol) in THF (500 mL) at room temperature, followed by portionwise addition of acetone-1,3-dicarboxylic acid (24.4 g, 0.17 mol), which resulted in immediate gas evolution (CO_2). (*Caution!* Ensure suitable exhaust!) After stirring for 60 h at room temperature, the mixture was evaporated under reduced pressure. Purification of the residue by column chromatography (deactivated SiO_2, gradient elution 0−4% EtOAc in petroleum ether, with 2% Et_3N also in the eluent) gave tropinone (±)-**9** as a yellow oil (16.3 g, 42%): R_f = 0.37 (4% EtOAc in petroleum ether); IR (film) (cm^{-1}) 2958 m, 1708 s (C═O), 1495 w, 1455 m, 1267 m, 1225 m, 1177 m; ^{1}H NMR (400 MHz) δ 7.44 (d, 2H, J = 7 Hz, Ar (*ortho*)), 7.34 (t, 2H, J = 7 Hz, Ar (*meta*)), 7.30−7.23 (m, 1H, Ar (*para*)), 4.04 and 3.66 (AB, 2H, J_{AB} = 14 Hz, PhCH_2N), 2.85 (d, 1H, J = 4 Hz, COCH$_2$CH), 2.54 and 2.27 (AB, 2H, J_{AB} = 16 Hz, J = 4 Hz, COCH_2CH), 2.50 and 2.16 (AB, 2H, J_{AB} = 16 Hz, COCH_2CCH$_3$), 1.61 and 1.49 (AB, 2H, J_{AB} = 13 Hz, J = 2 Hz, C(CH$_3$)$_2$CH_2) 1.28 (s, 3H, CH$_3$), 1.16 (s, 3H, CH$_3$), 0.93 (s, 3H, CH$_3$); ^{13}C NMR (101 MHz) δ 210.4 (C═O), 139.8 (Ar (*ipso*)), 128.3 (Ar), 128.2 (Ar), 126.9 (Ar (*para*)), 66.1 (C(CH$_3$)$_3$CH), 62.6 (NCCH$_3$), 52.9 (CH$_2$C(CH$_3$)$_2$), 49.6 (NC(Me)CH$_2$CO), 47.3 (PhCH$_2$N), 39.0 (C(CH$_3$)$_2$), 37.4 (CHCH$_2$CO), 32.4 (CH$_3$), 25.5 (CH$_3$), 24.9 (CH$_3$); MS m/z (ESI$^+$) 258.2 (M + H$^+$, 100); HRMS m/z (M + H$^+$) found 258.1851, calcd for $C_{17}H_{24}NO$ 258.1852.

(±)-8-Benzyl-1,6,6-trimethyl-8-azabicyclo[3.2.1]octane ((±)-10). A mixture of tropinone (±)-**9** (4.54 g, 17.6 mmol), hydrazine monohydrate (4.60 g, 0.09 mol), and KOH (14.99 g, 0.27 mol) in diethylene glycol (36 mL) was heated to 190 °C (oil bath) for 24 h. The volatile components were then removed by distillation for 2 h at 200 °C. The reaction mixture was cooled to room temperature and combined with the distillate. The mixture was diluted with water (300 mL) and the aqueous layer extracted with Et_2O (3 × 200 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution 0−2% EtOAc in petroleum ether) gave *N*-benzyltropane (±)-**10** as a clear oil (3.66 g, 85%): R_f = 0.50 (2% EtOAc in petroleum ether); IR (film) (cm^{-1}) 3064 w, 3027 m, 2933 s, 2867 s, 1494 m, 1451 s, 1360 m, 1279 m, 1131 m; ^{1}H NMR (400 MHz) δ 7.54 (d, 2H, J = 7 Hz, Ar (*ortho*)), 7.40 (t, 2H, J = 7 Hz, Ar (*meta*)), 7.35−7.28 (m, 1H, J = 7 Hz, Ar), 3.91 and 3.86 (AB, 2H, J_{AB} = 14 Hz, PhCH_2N), 2.49 (br s, 1H, NCH), 1.96−1.69 (m, 6H, 3 × CH$_2$), 1.72 and 1.60 (AB, 2H, J_{AB} = 13 Hz, CH_2C(CH$_3$)$_2$), 1.29 (s, 3H, CH$_3$), 1.24 (s, 3H, CH$_3$), 1.17 (s, 3H, CH$_3$); ^{13}C NMR (101 MHz) δ 141.6 (Ar (*ipso*)), 128.4 (Ar (*ortho*)), 127.9 (Ar (*meta*)), 126.3 (Ar (*para*)), 64.6 (CHN), 60.0 (NC(CH$_3$)), 51.9 (CH$_2$C(CH$_3$)$_2$), 46.7 (PhCH$_2$N), 37.8 (C(CH$_3$)$_2$), 33.2 (CH$_3$), 28.9 (CH$_2$), 26.8 (CH$_3$), 23.7 (CH$_3$), 18.6 (CH$_2$), 16.6 (CH$_2$); MS m/z (ESI$^+$) 244.2 (M + H$^+$, 71); HRMS m/z (M + H$^+$) found 244.2067, calcd for $C_{17}H_{26}N$ 244.2060.

(±)-1,6,6-Trimethyl-8-azabicyclo[3.2.1]octane ((±)-6). A vigorously stirred solution of *N*-benzyltropane (±)-**10** (2.44 g, 10.0 mmol) in MeOH was hydrogenated at 1 atm in the presence of 10% palladium on activated carbon (1.06 g, 10 mol %) for 17 h. After this time, the catalyst was removed by filtration through Celite. To the filtrate was added 1 M HCl in Et_2O (ca. 25 mL). The mixture was evaporated under reduced pressure to give the crude hydrochloride salt, which was recrystallized from EtOAc to give the tropane hydrochloride as a white crystalline solid (1.9 g, quant) (mp 201−203 °C). This salt (1.90 g, 10.0 mmol) was suspended in Et_2O (20 mL) and washed with 3 M aqueous NaOH (20 mL). The ethereal layer was separated and the aqueous phase back-extracted with Et_2O (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated by careful evaporation (228 mm, 35 °C). Purification of the residue by bulb-to-bulb distillation gave tropane (±)-**6** as a clear oil (1.54 g, quant): bp 50−60 °C (14 mm); IR (neat) (cm^{-1}) 3267 w (N−H stretch), 2929 s, 2868 s, 1730 m, 1641 w, 1599 w, 1453 s, 1374 s, 1277 s, 1183 m, 822 s, 739 s; ^{1}H NMR (400 MHz) δ 2.71−2.63 (m, 1H, NCH), 1.83 (br s, 1H, NH), 1.77−1.35 (m, 7H, 3 × CH$_2$ and 1 × CH_AH$_B$), 1.23 (d, 1H, J_{AB} = 13 Hz, CH$_A$$H_B$), 1.15 (s, 3H, NC(CH$_3$)), 1.12 (s, 3H, C(CH$_3$)$_2$), 1.07 (s, 3H, C(CH$_3$)$_2$); ^{13}C NMR (101 MHz) δ 65.6 (NCH), 60.3 (NC(CH$_3$)), 50.6 (CH$_2$), 42.9 (C(CH$_3$)$_2$), 39.1 (CH$_2$), 33.0 (CH$_3$), 28.7 (CH$_3$), 27.4 (CH$_2$), 23.0 (CH$_3$), 19.0 (CH$_2$); MS m/z (ESI$^+$) 154.1 (M + H$^+$, 100); HRMS m/z (M + H$^+$) found 154.1590, calcd for $C_{10}H_{20}N$ 154.1590.

General Procedure for Formamide Synthesis. *(±)-1,6,6-Trimethyl-8-azabicyclo[3.2.1]octane-8-carbaldehyde ((±)-11).* A

dx.doi.org/10.1021/jo3025972 | J. Org. Chem. 2013, 78, 1508−1518

mixture of tropane (±)-**6** (1.54 g, 10.0 mmol), $BnEt_3NCl$ (1.03 g, 4.5 mmol), $CHCl_3$ (7 mL, 0.09 mol), CH_2Cl_2 (32 mL), and 12.5 M aqueous NaOH (25 mL) was stirred under reflux for 16 h, then diluted with water (300 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (150 mL), then 10% aqueous HCl (100 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Purification of the residue by bulb-to-bulb distillation gave formamide (±)-**11** as a clear oil (1.78 g, 98%): bp 140−150 °C (7.6 mm); IR (film) (cm^{-1}) 3054 m, 2962 m, 2875 w, 1649 s (C═O), 1426 m, 1393 m, 1375 m, 1266 s, 740 s; ^{1}H NMR (400 MHz, 293 K) two rotamers (~13:1) δ 8.15 (s, 1H, NCHO (*min*)), 8.14 (s, 1H, NCHO (*maj*)), 3.96 (br s, 1H, NCH (*maj*)), 3.24 (br s, 1H, NCH (*min*)), 1.85−1.40 (m, 8H, 4 × CH_2), 1.38 (s, 3H, CH_3 (*maj*)), 1.12 (s, 3H, CH_3 (*maj*)), 1.10 (s, 3H, CH_3 (*min*)), 1.05 (s, 3H, CH_3 (*min*)), 0.96 (s, 3H, CH_3 (*maj*)); ^{13}C NMR (101 MHz, 293K) two rotamers {~ 13:1} δ 159.2 (C═O (*min*)), 156.7 (C═O (*maj*)), 67.5 (NCH (*min*)), 62.6 (NC(CH_3) (*min*)), 61.3 (NCH (*maj*)), 61.1 (NC(CH_3) (*maj*)), 52.1 (CH_2 (*min*)), 50.6 (CH_2 (*maj*)), 40.8 (CH_2 (*maj*)), 38.7 (NCHC(CH_3)$_2$ (*maj*)), 38.3 (NCHC(CH_3)$_2$ (*min*)), 36.6 (CH_2 (*min*)), 32.1 (CH_3 (*maj*)), 31.8 (CH_3 (*min*)), 29.2 (CH_2 (*min*)), 25.8 (CH_3 (*min*)), 25.5 (CH_2 (*maj*)), 24.4 (CH_3 (*maj*)), 22.4 (CH_3 (*min*)), 22.1 (CH_3 (*maj*)), 18.5 (CH_2 (*min*)), 18.4 (CH_2 (*maj*)); MS *m*/*z* (ESI^+) 204.1 (M + Na^+, 31); HRMS *m*/*z* (M + H^+) found 182.1537, calcd for $C_{11}H_{20}NO$ 182.1539.

General Procedure for Enamine Synthesis. *(±)-8-((E)-Hex-1-en-1-yl)-1,6,6-trimethyl-8-azabicyclo[3.2.1]octane ((±)-12).* Pentylmagnesium chloride (2.0 M in THF, 690 μL, 1.38 mmol) was added dropwise to a stirred solution of tropamide (±)-**11** (200 mg, 1.10 mmol) in Et_2O (1 mL) while the temperature was maintained between −15 and −20 °C. The mixture was kept within this temperature range for 15 min and then warmed to room temperature. After 16 h, the mixture was evaporated under reduced pressure and the crude product purified by bulb-to-bulb distillation to give enamine (±)-**12** as a clear oil (214 mg, 83%): bp 125−135 °C (0.1 mm); IR (neat) (cm^{-1}) 2932 s, 2870 s, 1649 s (C═CNR^{1}R^2), 1332 s, 1247 s, 1139 m, 936 s; ^{1}H NMR (400 MHz, C_6D_6) δ 6.06 (d, 1H, *J* = 14 Hz, NC*H*=CH), 4.38 (dt, 1H, J_1 = 14 Hz, J_2 = 7 Hz, NCH═C*H*), 3.09 (br s, 1H, NC*H*C(CH_3)$_2$), 2.29−2.10 (m, 3H, NCH═CHCH_2 and CH_AH$_B$), 1.69−1.36 (m, 8H, 3 × CH_2 and 2 × CH_AH$_B$), 1.31 (d, 1H, J_{AB} = 13 Hz, CH_AH_B), 1.14 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.04−0.92 (m, 2H, 2 × CH_AH_B), 1.01 (s, 3H, CH_3), 0.95 (t, 3H, *J* = 7 Hz, CH_2CH_3); ^{13}C NMR (101 MHz, C_6D_6) δ 131.1 (NCH═CH), 102.3 (NCH=CH), 65.2 (NCHC(CH_3)$_2$), 61.3 (NC(CH_3)), 51.7 (CH_2), 38.6 (C(CH_3)$_2$), 35.5 (CH_2), 34.9 (CH_2), 33.6 (CH_3), 32.0 (NCH═CHCH_2), 26.1 (CH_3), 23.5 (CH_3), 23.0 (CH_2), 20.1 (CH_2), 18.1 (CH_2), 14.7 (CH_2CH_3); MS *m*/*z* (ESI^+) 236.2 (M + H^+, 100); HRMS *m*/*z* (M + H^+) found 236.2374, calcd for $C_{16}H_{30}N$ 236.2373.

General Procedure for Enamine Alkylation. *(±)-2-Ethylhexanal ((±)-13).* Enamine (±)-**12** (211 mg, 0.90 mmol), d_3-MeCN (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 60 °C for 3 days with occasional shaking until consumption of the enamine was complete by ^{1}H NMR spectroscopy. Buffer solution (AcOH (0.5 g), AcONa (0.5 g), and H_2O (1 mL); 0.5 mL) was then added and the mixture heated at 50 °C. After 1.5 h, the mixture was partitioned between Et_2O (20 mL) and H_2O (10 mL). The organic layer was separated and the aqueous layer back-extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and carefully reduced under vacuum (152 mm, 0 °C). Purification of the residue by column chromatography (SiO_2, 5% Et_2O in petroleum ether) gave 2-ethylhexanal ((±)-**13**)[13] as a clear oil (93 mg, 81%): R_f = 0.41 (5% Et_2O in petroleum ether); IR (neat) (cm^{-1}) 2961 m, 2930 m, 2861 m, 2694 w, 1725 s (C═O), 1461 m, 1381 w, 1154 w, 899 w; ^{1}H NMR (400 MHz) δ 9.56 (d, 1H, *J* = 3 Hz, CHO), 2.23−2.10 (m, 1H, C*H*CHO), 1.71−1.20 (m, 8H, 4 × CH_2), 0.91 (t, 3H, *J* = 7 Hz, CH_3), 0.88 (t, 3H, *J* = 7 Hz, CH_3); ^{13}C NMR (101 MHz) δ 205.7 (C═O), 53.4 (CHCHO), 29.2 (CH_2), 28.1 (CH_2), 22.7 (CH_2), 21.8 (CH_2), 13.9 (CH_3), 11.4 (CH_3).

Resolution of Tropane (±)-6. *tert-Butyl((S)-1-oxo-3-phenyl-1-((1R,5S)-1,6,6-trimethyl-8-azabicyclo[3.2.1]octan-8-yl)propan-2-yl)-carbamate ((S,1R,5S)-14) and tert-Butyl((S)-1-oxo-3-phenyl-1-((1S,5R)-1,6,6-trimethyl-8-azabicyclo[3.2.1]octan-8-yl)propan-2-yl)-carbamate ((S,1S,5R)-14).* To a stirred solution of tropane (±)-**6** (1.50 g, 9.8 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added DIPEA (2.78 g, 21.5 mmol), *N*-Boc-L-PheOH (2.86 g, 10.8 mmol), and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (2.74 g, 10.8 mmol). The reaction mixture was kept in a refrigerator at 0−4 °C for 3 days (TLC monitoring (50% EtOAc in petroleum ether)). After this time, the reaction mixture was diluted with ice-cold EtOAc (750 mL), washed with ice-cold 5% aqueous HCl (500 mL) and 5% aqueous $NaHCO_3$ (500 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution 0−10% EtOAc in petroleum ether) gave an inseparable mixture of Boc-protected α-amino amides (**S,1R,5S**)-**14** and (**S,1S,5R**)-**14** as a white foam (~1:1 dr, 2.50 g, 64%): R_f = 0.29 (10% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 3429 w, 3294 w, 3055 m, 3030 w, 2962 s, 2873 m, 1707 s (C═O), 1635 s (C═O), 1495 s, 1444 s, 1266 s, 1170 s, 1044 m, 739 s; ^{1}H NMR (400 MHz) two diastereomers (~1:1) δ 7.32−7.14 (m, 10H, 2 × Ph), 5.28 (5.22) (d, 2H, *J* = 9 (10) Hz, 2 × N*H*), 4.72−4.59 (m, 2H, 2 × NHC*H*), 3.67 (3.62) (br s, 2H, 2 × NC*H*), 3.24−3.06 (m, 2H, 2 × PhCH_AH$_B$), 2.93−2.75 (m, 2H, 2 × PhCH_AH$_B$), 2.14−2.02 (m, 1H, CH_AH$_B$), 1.95−1.19 (m, 14H, 6 × CH_2 and 2 × CH_AH_B), 1.63 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.40 (s, 9H, *t*-Bu), 1.38 (s, 9H, *t*-Bu), 1.07 (s, 3H, CH_3), 1.012 (s, 3H, CH_3), 1.006 (s, 3H, CH_3), 0.79 (s, 3H, CH_3), 0.49−0.30 (m, 1H, CH_AH$_B$); ^{13}C NMR (101 MHz) two diastereomers (~1:1) δ 170.9 (169.8) (NHCHC═O), 155.0 (154.8) (NHC═O), 137.4 (136.8) (Ar (*ipso*)), 129.9 (129.5) (Ar (*ortho*)), 128.3 (128.2) (Ar (*meta*)), 126.6 (126.5) (Ar (*para*)), 79.5 (79.4) (C(CH_3)$_3$), 68.7 (67.6) (NCHC(CH_3)$_2$), 64.6 (64.3) (NC(CH_3)), 53.5 (53.4) (NHCH), 51.6 (2 × CH_2C(CH_3)$_2$), 39.8 (39.3) (PhCH_2), 38.0 (37.9) (C(CH_3)$_2$), 36.7 (CH_2), 35.0 (CH_2), 32.0 (CH_3), 31.8 (CH_3), 28.29 (CH_2), 28.27 (C(CH_3)$_3$), 28.23 (C(CH_3)$_3$), 27.4 (CH_3), 27.1 (CH_2), 27.0 (CH_3), 22.6 (CH_3), 22.4 (CH_3), 18.4 (2 × CH_2); MS *m*/*z* (ESI^+) 401.3 (M + H^+, 79); HRMS *m*/*z* (M + H^+) found 401.2799, calcd for $C_{24}H_{37}N_2O_3$ 401.2799.

(+)-(S)-2-Amino-3-phenyl-1-((1R,5S)-1,6,6-trimethyl-8-azabicyclo[3.2.1]octan-8-yl)propan-1-one ((+)-(S,1R,5S)-15) and (+)-(S)-2-Amino-3-phenyl-1-((1S,5R)-1,6,6-trimethyl-8-azabicyclo-[3.2.1]octan-8-yl)propan-1-one ((+)-(S,1S,5R)-15). Anhydrous TFA (62 mL) was added to a stirred solution of Boc-protected α-amino amides (**S,1R,5S**)-**14** and (**S,1S,5R**)-**14** (9.35 g, 23.3 mmol) in CH_2Cl_2 (280 mL) at room temperature. After 1 h, the mixture was evaporated under reduced pressure and the residue dissolved in $CHCl_3$ (300 mL). The resulting solution was washed with 10% aqueous Na_2CO_3 (500 mL). The aqueous layer was separated and back-extracted with $CHCl_3$ (2 × 300 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by column chromatography (SiO_2, gradient elution 5−10% MeOH in EtOAc). The α-amino amide (**S,1R,5S**)-**15** eluted first (*minor diastereomer*, 2.96 g), followed by a mixed fraction (747 mg); the α-amino amide (**S,1S,5R**)-**15** eluted last (*major diastereomer*, 2.94 g), all white solids (55:45 dr, 6.65 g total product, 95%);

Data for minor diastereomer (**S,1R,5S**)-**15**: mp 69−71 °C; R_f = 0.52 (10% MeOH in EtOAc); $[\alpha]_D^{25}$ = +23.4° (*c* = 0.5, MeOH); IR (KBr) (cm^{-1}) 3390 w, 2999 m, 2940 s, 1631 s (C═O), 1493 m, 1442 s, 1341 m, 928 m, 750 s, 704 s; ^{1}H NMR (400 MHz) δ 7.33−7.10 (m, 5H, Ar), 3.68 (t, 1H, *J* = 7 Hz, NH_2CH), 3.49 (br s, 1H, CONC*H*), 3.09 and 2.72 (AB, 2H, J_{AB} = 13 Hz, *J* = 7 Hz, PhCH_2), 1.89 (td, 1H, J_{AB} = 13 Hz, *J* = 6 Hz, CH_AH$_B$), 1.77−1.21 (m, 8H, NH_2, 2 × CH_2, 1 × CH_AH_B and 1 × CH_AH$_B$), 1.64 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 0.77−0.58 (m, 1H, CH_AH_B); ^{13}C NMR (101 MHz) δ 173.4 (C═O), 138.5 (Ar (*ipso*)), 129.6 (Ar), 128.4 (Ar), 126.4 (Ar), 67.5 (CONCH), 64.2 (NC(CH_3)), 55.2 (NH_2CH), 51.3 (CH_2), 41.5 (PhCH_2), 38.1 (NCHC(CH_3)$_2$), 36.1 (CH_2), 32.2 (CH_3), 27.4 (CH_3), 27.4 (CH_2), 22.5 (CH_3), 18.5 (CH_2); MS *m*/*z* (ESI^+) 301.2 (M + H^+, 72); HRMS *m*/*z* (M + H^+) found 301.2277, calcd for $C_{19}H_{29}N_2O$ 301.2274.

dx.doi.org/10.1021/jo3025972 | J. Org. Chem. 2013, 78, 1508−1518

Data for major diastereomer (**S,1S,5R**)-**15**: mp 33−35 °C, R_f = 0.45 (10% MeOH in EtOAc); $[\alpha]_D^{25}$ = +66.0° (*c* = 0.5, MeOH); IR (KBr) (cm^{-1}) 3347 br m (NH_2), 2927 s, 1638 s (C═O), 1560 m, 1443 s, 1367 m, 1288 m, 1120 m, 927 m, 744 s, 703 s; ^{1}H NMR (400 MHz) δ 7.35−7.13 (m, 5H, Ar), 3.75 (br s, 1H, NH_2CH), 3.57 (br s, 1H, $NCHC(CH_3)_2$), 3.07 and 2.72 (AB, 2H, J_{AB} = 13 Hz, J_1 = 8 Hz, J_2 = 5 Hz, $PhCH_2$), 2.12 (td, 1H, J_{AB} = 13 Hz, *J* = 6 Hz, CH_AH_B), 2.00 (br s, 2H, NH_2), 1.90−1.55 (m, 5H, 2 × CH_2 and 1 × CH_AH_B), 1.62 (s, 3H, CH_3), 1.46 (d, 1H, J_{AB} = 13 Hz, CH_AH_B), 1.32 (dd, 1H, J_{AB} = 13 Hz, *J* = 6 Hz, CH_AH_B), 1.12 (s, 3H, CH_3), 0.94 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 174.1 (C═O), 137.9 (Ar (*ipso*)), 129.3 (Ar), 128.5 (Ar), 126.6 (Ar), 68.3 ($NCHC(CH_3)_2$), 64.4 ($NC(CH_3)$), 54.9 (NH_2CH), 51.6 (CH_2), 42.9 ($PhCH_2$), 38.0 ($C(CH_3)_2$), 35.1 (CH_2), 32.3 (CH_3), 28.4 (CH_2), 27.4 (CH_3), 22.6 (CH_3), 18.5 (CH_2); MS *m*/*z* (ESI$^+$) 301.2 (M + H$^+$, 75); HRMS *m*/*z* (M + H$^+$) found 301.2277, calcd for $C_{19}H_{29}N_2O$ 301.2274.

(+)-(1R,5S)-1,6,6-Trimethyl-8-azabicyclo[3.2.1]octane ((+)-(1R,5S)-6) and (−)-(1S,5R)-1,6,6-trimethyl-8-azabicyclo[3.2.1]-octane ((−)-(1S,5R)-6). PhNCS (340 mg, 2.51 mmol) was added to a stirred solution of α-amino amide (**S,1R,5S**)-**15** (686 mg, 2.28 mmol) in CH_2Cl_2 (40 mL) at room temperature. A distillation head, condenser, and receiver flask were connected to the reaction vessel, and CH_2Cl_2 was removed over an oil bath (100 °C). The distillate was recombined with the contents of the reaction vessel, and the distillation procedure was repeated until α-amino amide (**S,1R,5S**)-**15** 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 $CHCl_3$ (100 mL). This solution was partitioned with H_2O (100 mL), and the aqueous layer was separated and basified with 3 M aqueous NaOH. The resulting suspension was washed with Et_2O (5 × 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by bulb-to-bulb distillation (bp 50−60 °C (14 mm)) to give tropane (**1R,5S**)-**6** as a clear oil (316 mg, 90%): $[\alpha]_D^{25}$ = +85.7° (*c* = 1.4, $CHCl_3$); other data as above.

Following the same procedure, reaction of the α-amino amide (**S,1S,5R**)-**15** (3.27 g, 10.9 mmol) with PhNCS (1.62 g, 12.0 mmol) in CH_2Cl_2 (170 mL) gave, after treatment with TFA (85 mL), tropane (**1S,5R**)-**6** (1.34 g, 80%): $[\alpha]_D^{25}$ = −89.6° (*c* = 1.4, $CHCl_3$); other data as above.

Synthesis of Chiral Formamides (1*R*,5*S*)-11 and (1*S*,5*R*)-11. *(+)-(1R,5S)-1,6,6-Trimethyl-8-azabicyclo[3.2.1]octane-8-carbaldehyde ((+)-(1R,5S)-11).* According to the general procedure for formamide synthesis, reaction of tropane (**1R,5S**)-**6** (597 mg, 3.90 mmol), $BnEt_3NCl$ (399 mg, 1.75 mmol), $CHCl_3$ (2.9 mL, 0.04 mol), and 12.5 M aqueous NaOH (9.7 mL) in CH_2Cl_2 (12.7 mL) at reflux for 17 h gave formamide (**1R,5S**)-**11** as a clear oil (656 mg, 93%): $[\alpha]_D^{25}$ = +88.0° (*c* = 1.0, MeOH); other data as above.

(−)-(1S,5R)-1,6,6-Trimethyl-8-azabicyclo[3.2.1]octane-8-carbaldehyde ((−)-(1S,5R)-11). According to the general procedure for formamide synthesis, reaction of tropane (**1S,5R**)-**6** (1.28 g, 8.4 mmol), $BnEt_3NCl$ (856 mg, 3.8 mmol), $CHCl_3$ (6.2 mL, 0.08 mol), and 12.5 M aqueous NaOH (20.7 mL) in CH_2Cl_2 (27 mL) at reflux for 17 h gave formamide (**1S,5R**)-**11** as a clear oil (1.25 g, 82%): $[\alpha]_D^{25}$ = −69.0° (*c* = 0.9, MeOH); other data as above.

Synthesis of Chiral Enamines (1*R*,5*S*)-12 and (1*S*,5*R*)-12. *(1R,5S)-8-((E)-Hex-1-en-1-yl)-1,6,6-trimethyl-8-azabicyclo[3.2.1]-octane ((1R,5S)-12).* According to the general procedure for enamine synthesis, reaction of formamide (**1R,5S**)-**11** (621 mg, 3.43 mmol) with pentylmagnesium chloride (2.0 M in THF, 2.14 mL, 4.28 mmol) in Et_2O (2.5 mL) at room temperature for 17 h gave, after distillation, enamine (**1R,5S**)-**12** (676 mg, 84%):[37] other data as above.

(1S,5R)-8-((E)-Hex-1-en-1-yl)-1,6,6-trimethyl-8-azabicyclo[3.2.1]-octane ((1S,5R)-12). According to the general procedure for enamine synthesis, reaction of formamide (**1S,5R**)-**11** (684 mg, 3.77 mmol) with pentylmagnesium chloride (2.0 M in THF, 2.42 mL, 4.84 mmol) in Et_2O (5 mL) at room temperature for 17 h gave, after distillation, enamine (**1S,5R**)-**12** (504 mg, 57%):[37] other data as above.

Asymmetric Alkylation of Enamines (1*R*,5*S*)-12 and (1*S*,5*R*)-12 with EtI. According to the general procedure for enamine alkylation, reaction of enamine (**1R,5S**)-**12** (151 mg, 0.64 mmol) with EtI (200 mg, 1.28 mmol) in d_3-MeCN (690 μL) at 65 °C for 16 h gave, following hydrolysis with acidic buffer (0.5 mL) at room temperature for 5 min, aldehyde (**S**)-**13**[12] (58:42 *er*,[12,38] 60 mg, 73%).

According to the general procedure for enamine alkylation, reaction of enamine (**1S,5R**)-**12** (214 mg, 0.91 mmol) with EtI (284 mg, 1.82 mmol) in d_3-MeCN (1 mL) at 65 °C for 16 h gave, following hydrolysis with acidic buffer (0.5 mL) at room temperature for 5 min, aldehyde (**R**)-**13**[12] (55:45 er,[12,38] 91 mg, 78%).

Homotropane (1*S*,5*R*)-17 Synthesis. *2-Methyl-2-(2-methyl-1,3-dioxolan-2-yl)propanal (25).* 2-Methyl-2-(2-methyl-1,3-dioxolan-2-yl)propan-1-ol[31] (7.2 g, 44.9 mmol) was dissolved in CH_2Cl_2 (40 mL) at room temperature. The resulting solution was added rapidly to a suspension of PCC (14.5 g, 67.3 mmol) in CH_2Cl_2 (70 mL) at room temperature with stirring. The mixture immediately turned black on addition of the alcohol. After stirring overnight at room temperature, the mixture was diluted with anhydrous Et_2O (200 mL), the solvent decanted, and the residual black solid washed with Et_2O (3 × 100 mL). The combined organic layers were passed through a small pad of Florisil, and the filtrate was concentrated under reduced pressure. Purification of the residue by bulb-to-bulb distillation gave aldehyde **25**[39] as a clear oil (6.6 g, 93%): bp 75−80 °C (11 mm) (lit.[39] bp 90−95 °C (7 mm)); R_f = 0.44 (10% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2984 m, 2888 m, 1725 s (C═O), 1471 w, 1376 m, 1215 m, 1163 m, 1099 m, 1045 s (O−C−O), 755 s; ^{1}H NMR (400 MHz) δ 9.69 (s, 1H, CHO), 4.07−3.86 (m, 4H, C_2H_4), 1.23 (s, 3H, CH_3CO), 1.10 (s, 6H, $C(CH_3)_2$); ^{13}C NMR (101 MHz) δ 205.3 (C═O), 111.8 (O−C−O), 64.9 (C_2H_4), 53.7 ($C(CH_3)_2$), 20.2 ($CH_3C\{OC_2H_4O\}$), 17.8 ($C(CH_3)_2$); MS *m*/*z* (ESI$^+$) 181.1 (M + Na$^+$, 6); HRMS *m*/*z* (M + Na$^+$) found 181.0831, calcd for $C_8H_{14}NaO_3$ 181.0835.

(−)-(R,E)-2-Methyl-N-(2-methyl-2-(2-methyl-1,3-dioxolan-2-yl)-propylidene)propane-2-sulfinamide ((−)-(R)-24). Finely ground NaOH (28 mg, 0.70 mmol) was added to a stirred solution of sulfinamide (**R**)-**26** (86 mg, 0.71 mmol) in MeOH (3.5 mL) at room temperature. After 15 min, aldehyde **25** (112 mg, 0.71 mmol) was added. After 16 h, the reaction mixture was evaporated under reduced pressure and the residue dissolved in Et_2O (2 mL) and washed with saturated aqueous NH_4Cl (2 mL). The aqueous layer was separated and back-extracted with Et_2O (4 × 2 mL), and the organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure, to give chiral sulfinimine (**R**)-**24** as a clear oil (175 mg, 94%): R_f = 0.10 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$ = −246.5° (*c* = 0.3, $CHCl_3$); IR (neat) (cm^{-1}) 2981 m, 2885 m, 1620 m (C═N), 1474 m, 1459 m, 1363 m, 1163 m, 1143 m, 1084 s and 1042 s (S═O and O−C−O), 949 m, 886 m; ^{1}H NMR (400 MHz) δ 8.14 (s, 1H, HC═N), 4.05−3.85 (m, 4H, C_2H_4), 1.27 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.19 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (101 MHz) δ 173.4 (C═N), 112.2 (O−C−O), 65.1 (OCH_2CH_2O), 65.0 (OCH_2CH_2O), 56.8 ($C(CH_3)_3$), 49.5 ($C(CH_3)_2$), 22.3 ($C(CH_3)_3$), 20.7 (CH_3), 20.6 (CH_3), 20.1 (CH_3); MS *m*/*z* (ESI$^+$) 284.1 (M + Na$^+$, 100); HRMS *m*/*z* (M + Na$^+$) found 284.1288, calcd for $C_{12}H_{23}NNaO_3S$ 284.1291.

Grignard Addition to Sulfinimine (±)-24. (±)-2-Methyl-N-(2-methyl-2,6-bis(2-methyl-1,3-dioxolan-2-yl)hexan-3-yl)propane-2-sulfinamides ((±)-(S_S,R)-20 and (±)-(R_S,S)-20). Magnesium turnings were stirred vigorously under argon overnight,[40] resulting in a color change from gray to black. THF (1.3 mL) was added, followed by 1,2-dibromoethane (2−3 drops), at which point the mixture started to bubble. With close monitoring of the reaction mixture, 2-(3-chloropropyl)-2-methyl-1,3-dioxolane[41] (1.05 g, 6.4 mmol) was added dropwise, ensuring the temperature did not exceed 50 °C (ice bath). After addition, the mixture was stirred for 2 h at room temperature and then diluted with THF (1.9 mL). A portion of the freshly prepared solution of Grignard reagent **23** (190 μL) was added to a stirred solution of sulfinimine (±)-**24** (50 mg, 0.19 mmol) in THF (1.7 mL) at −78 °C and the resultant mixture warmed to room temperature after 30 min. After 16 h the reaction mixture was quenched with saturated aqueous NH_4Cl (2 mL), diluted with H_2O (2 mL), and extracted with Et_2O (3 × 5 mL). The combined organic

dx.doi.org/10.1021/jo3025972 | J. Org. Chem. 2013, 78, 1508−1518

layers were dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution 10−100% Et_2O in petroleum ether) gave inseparable diastereomers of bis-ketal sulfinamide (±)-**20** (73:27 dr) and an unknown, inseparable impurity. From this mixture it was possible, by precipitation with petroleum ether, to partially extract the racemic major diastereomers (±)-(**S_S,R**)-**20** and (±)-(**R_S,S**)-**20** as a white solid (34 mg, 45%); the rest of the material was obtained as a crude mixture (39 mg): mp 75−79 °C; R_f = 0.12 (50% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 3444 w, 3297 w (N−H stretch), 2981 m, 2880 m, 1707 w, 1650 w, 1474 m, 1373 m, 1128 m, 1045 s (S═O and O−C−O), 876 m; ^{1}H NMR (400 MHz) δ 4.05−3.82 (m, 8H, 2 × OC_2H_4O), 3.61 (d, 1H, J = 6 Hz, NH), 3.15−3.00 (m, 1H, J = 6 Hz, NHC*H*), 2.10−1.98 (m, 1H, NHCHCH_AH_B), 1.88−1.78 (m, 1H, CHCH$_2$CH_AH_B), 1.77−1.66 (m, 1H, J_{AB} = 14 Hz, CH-(CH$_2$)$_2$CH_AH_B), 1.65−1.54 (m, 1H, J_{AB} = 14 Hz, CH(CH$_2$)$_2$CH$_A$H$_B$), 1.50−1.36 (m, 2H, NHCHCH$_A$H$_B$ and CHCH$_2$CH$_A$H$_B$), 1.34 (s, 3H, CH_3), 1.243 (s, 9H, C(CH_3)$_3$), 1.235 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 0.92 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 113.8 (O−C−O), 110.2 (O−C−O), 64.7 (OCH_2), 64.6 (OCH_2), 64.5 (OCH_2), 64.2 (OCH_2), 63.6 (NHCH), 56.5 (C(CH_3)$_3$), 46.6 (C(CH_3)$_2$), 39.1 (CHCH$_2$CH$_2$), 32.3 (NHCHCH$_2$), 23.9 (CH_3), 23.1 (C(CH_3)$_3$), 22.0 (CH-(CH$_2$)$_2$CH$_2$), 21.7 (CH_3), 19.9 (CH_3), 19.6 (CH_3); MS m/z (ESI$^+$) 414.2 (M + Na$^+$, 100); HRMS m/z (M + H$^+$) found 392.2470, calcd for $C_{19}H_{38}NO_5S$ 392.2465.

Organolithium ***27*** *Addition to Sulfinimine* ***(R)-24****. (−)-(R)-2-Methyl-N-((R)-2-methyl-2,6-bis(2-methyl-1,3-dioxolan-2-yl)hexan-3-yl)propane-2-sulfinamide (*(−)-(**R_S,R**)-**20***).* 2-(3-Iodopropyl)-2-methyl-1,3-dioxolane[42] (5.88 g, 23.0 mmol) was dissolved in pentane/Et_2O (3:2, 225 mL) at room temperature with stirring. The resulting solution was cooled to −78 °C, and *t*-BuLi (1.7 M in pentane, 28.4 mL, 48.3 mmol) was added dropwise. The mixture was stirred at −78 °C for 5 min and then warmed to room temperature, which resulted in formation of a white slurry. The mixture was stirred at room temperature for 1 h and then recooled to −78 °C. The freshly prepared organolithium **27** was transferred, dropwise via cannula, to a solution of sulfinimine (**R**)-**24** (3.00 g, 11.5 mmol) in THF (57 mL) at −78 °C. After 16 h at −78 °C the mixture was quenched with MeOH (100 mL), warmed to room temperature, and then diluted with H_2O (400 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (4 × 250 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution 50−80% EtOAc in petroleum ether) gave bis-ketal sulfinamide (**R_S,R**)-**20** (98:2 dr, 4.09 g, 91%): R_f = 0.12 (50% EtOAc in petroleum ether); $[\alpha]_D^{25}$ = −78.8° (c = 2.2, $CHCl_3$); IR (neat) (cm^{-1}) 3275 w (N−H stretch), 2979 m, 2881 m, 1474 m, 1377 m, 1217 m, 1157 m, 1062 s and 1041 s (S═O and O−C−O), 949 m, 874 m; ^{1}H NMR (400 MHz) δ 5.25 (br s, 1H, NH), 4.07−3.84 (m, 8H, 2 × OC_2H_4O), 3.24 (br s, 1H, NHC*H*), 1.77−1.55 (m, 4H, 1 × CH_2 and 2 × CH_AH_B), 1.50−1.36 (m, 2H, 2 × CH$_A$H$_B$), 1.32 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.21 (s, 9H, C(CH_3)$_3$), 1.05 (s, 3H, CH_3), 0.92 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 114.6 (O−C−O), 109.9 (O−C−O), 65.2 (OCH_2), 64.6 (2 × OCH_2), 63.6 (OCH_2), 58.7 (NHCH), 55.4 (C(CH_3)$_3$), 45.3 (C(CH_3)$_2$), 39.4 (CH_2), 33.1 (NHCHCH$_2$), 23.8 (CH_3), 23.2 (CH_3), 22.9 (C(CH_3)$_3$), 22.8 (CH_2), 19.3 (CH_3), 16.8 (CH_3); MS m/z (ESI$^+$) 392.2 (M + H$^+$, 100); HRMS m/z (M + Na$^+$) found 414.2275, calcd for $C_{19}H_{37}NNaO_5S$ 414.2285.

(−)-(1S,5R)-1,4,4-Trimethyl-9-azabicyclo[3.3.1]nonan-3-one ((−)-(**1S,5R**)-**18***).* HCl (2 M in Et_2O, 86 mL) was added to a stirred solution of bis-ketal sulfinamide (**R_S,R**)-**20** (2.69 g, 6.9 mmol) in MeOH (250 mL) at room temperature. The resulting mixture was heated at 75 °C for 2 days. After this time, the mixture was cooled to room temperature, and the volatiles were removed by evaporation under reduced pressure. Aqueous NaOH (3 M, 100 mL) was added to the residue and the resulting suspension stirred for 15 min and then washed with CH_2Cl_2 (5 × 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution 0−10% MeOH in EtOAc) gave homotropinone (**1S,5R**)-**18** as a clear crystalline solid (1.04 g, 83%); mp 40−42 °C; R_f = 0.36 (10% MeOH in EtOAc); $[\alpha]_D^{25}$ = −94.4° (c = 0.3, $CHCl_3$); IR (neat) (cm^{-1}) 3310 w (N−H stretch), 2953 m, 2930 m, 1699 s (C═O), 1655 w, 1457 m, 1380 m, 1201 m, 909 m, 730 s; ^{1}H NMR (400 MHz) δ 2.93 (br s, 1H NCH), 2.35 and 2.17 (AB, 2H, J_{AB} = 16 Hz, CH_2C═O), 1.88 (br s, 1H, NH), 1.82 (d, 1H, J_{AB} = 13 Hz, NCHCH_AH_B), 1.57−1.32 (m, 4H, CH_2, CH_AH_B and CH$_A$H$_B$), 1.31−1.15 (m, 1H, CH$_A$H$_B$), 1.22 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.02 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 216.2 (C═O), 60.8 (NCH), 53.7 (NCCH$_3$), 50.0 (*C*H$_2$C═O), 46.8 (C(CH_3)$_2$), 38.6 (CH(CH$_2$)$_2$CH$_2$), 31.5 (CH_3), 27.7 (CH_3), 27.2 (NCHCH$_2$), 21.3 (CH_3), 17.9 (CH$_2$CH$_2$CH$_2$); MS m/z (ESI$^+$) 182.1 (M + H$^+$, 52); HRMS m/z (M + H$^+$) found 182.1534, calcd for $C_{11}H_{20}NO$ 182.1539.

(−)-(1S,3R,5R)-1,4,4-Trimethyl-9-azabicyclo[3.3.1]nonan-3-ol ((−)-(**1S,3S,5R**)-**28***).* LAH (361 mg, 9.5 mmol) was dissolved in THF (10 mL) with stirring and external cooling (ice bath). Homotropinone (**1S,5R**)-**18** (1.50 g, 8.3 mmol) in THF (10 mL) was added, dropwise, with stirring at 0 °C. The reaction temperature was maintained at 0 °C for 30 min and then warmed to room temperature and stirred overnight. After this time, the mixture was recooled to 0 °C and quenched: H_2O (360 μL), then 15% aqueous NaOH (360 μL), and then H_2O (1.1 mL). (*Caution!*) The resulting suspension was filtered and the filter cake washed with CH_2Cl_2 (100 mL). The filtrate was concentrated under reduced pressure, to give homotropinol (**1S,3R,5R**)-**28** as a white solid (1.38 g, 91%): mp 105−110 °C; R_f = 0.10 (20% MeOH in EtOAc); $[\alpha]_D^{25}$ = −22.4° (c = 1.9, $CHCl_3$); IR (neat) (cm^{-1}) 3130 br m (O−H and N−H), 2898 m, 1459 m, 1418 m, 1287 m, 1106 m, 1047 s, 968 s, 821 s; ^{1}H NMR (500 MHz) δ 3.62 (dd, 1H, J_1 = 6 Hz, J_2 = 3 Hz, C*H*OH), 2.70 (d, 1H, J = 4 Hz, NCH), 2.59−2.41 (m, 1H, CH$_2$CH_AH_BCH$_2$), 2.12 (br s, 2H, NH and OH), 1.84 (dd, 1H, J_{AB} = 14 Hz, J = 6 Hz, CH_AH_BCHOH), 1.77 (dd, 1H, J_{AB} = 14 Hz, J = 6 Hz, NCHCH_AH_B), 1.59−1.45 (m, 3H, CH$_A$H$_B$CHOH, NCHCH$_A$H$_B$ and CH(CH$_2$)$_2$CH_AH_B), 1.43−1.32 (m, 2H, CHCH$_2$CH$_A$H$_B$CH$_A$H$_B$), 1.09 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 0.97 (s, 3H, CH_3); ^{13}C NMR (125 MHz) δ 71.7 (CHOH), 58.2 (NCH), 47.9 (NC(CH_3)), 41.0 (CH_2CHOH), 36.8 (CH(CH$_2$)$_2$CH$_2$), 36.0 (C(CH_3)$_2$), 33.3 (CH_3), 30.4 (CH_3), 25.9 (NCHCH$_2$), 21.8 (CH_3), 17.2 (CH$_2$CH$_2$CH$_2$); MS m/z (ESI$^+$) 184.2 (M + H$^+$, 32); HRMS m/z (M + H$^+$) found 184.1695, calcd for $C_{11}H_{22}NO$ 184.1696.

(−)-S-Methyl O-((1S,3R,5R)-1,4,4-Trimethyl-9-azabicyclo[3.3.1]-nonan-3-yl)carbonodithioate ((−)-(**1S,3R,5R**)-**29***).* Homotropinol (**1S,3R,5R**)-**28** (299 mg, 1.63 mmol) was dissolved in THF (5 mL) with stirring at room temperature. Imidazole (25 mg, 0.36 mmol) and NaH (203 mg, 8.46 mmol) were added, and the resulting mixture was stirred at room temperature for 30 min. CS_2 (647 μL, 10.76 mmol) was added, dropwise, resulting in an orange coloration. The mixture was heated at 70 °C for 16 h, then cooled to room temperature and MeI (203 μL, 3.26 mmol) added, dropwise. The resulting mixture was stirred at room temperature for 16 h, then evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution 0−20% MeOH in EtOAc) gave xanthate (**1S,3R,5R**)-**29** as an orange solid (336 mg, 75%): mp 40−44 °C; $[\alpha]_D^{25}$ = −17.3° (c = 0.8, $CHCl_3$); R_f = 0.21 (20% MeOH in EtOAc); IR (neat) (cm^{-1}) 2920 m, 1704 w, 1592 w, 1424 m, 1374 m, 1226 s (C═S), 1049 s (MeS−CS−O−R), 965 m, 753 m; ^{1}H NMR (500 MHz) δ 5.60 (dd, 1H, J_1 = 6 Hz, J_2 = 2 Hz, C*H*−O−CS$_2$Me), 2.75 (d, 1H, J = 5 Hz, NCH), 2.60 (s, 3H, SCH_3), 2.39−2.25 (m, 1H, CH$_2$CH_AH_BCH$_2$), 2.00−1.86 (m, 2H, O−CHCH_AH_B and NCHCH_AH_B), 1.77 (dd, 1H, J_{AB} = 16 Hz, J = 2 Hz, O−CHCH$_A$H$_B$), 1.71−1.57 (m, 1H, NCHCH$_A$H$_B$), 1.55−1.39 (m, 3H, CHCH$_2$CH$_A$H$_B$CH$_2$), 1.23 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 0.99 (s, 3H, CH_3); ^{13}C NMR (125 MHz) δ 215.7 (C═S), 83.9 (CH−OCS$_2$Me), 57.7 (NCH), 47.4 (NC(CH_3)), 37.8 (O−CHCH$_2$), 36.4 (C(CH_3)$_2$), 35.9 (CH(CH$_2$)$_2$CH$_2$), 33.3 (CH_3), 29.9 (CH_3), 25.5 (NCHCH$_2$), 22.5 (CH_3), 18.9 (SMe), 16.9 (CH$_2$CH$_2$CH$_2$); MS m/z (ESI$^+$) 274.2 (M + H$^+$, 100); HRMS m/z (M + H$^+$) found 274.1286, calcd for $C_{13}H_{24}NOS_2$ 274.1294.

(−)-(1S,5R)-1,4,4-Trimethyl-9-azabicyclo[3.3.1]nonane ((−)-(**1S,5R**)-**17***).* Xanthate (**1S,3R,5R**)-**29** (750 mg, 2.74 mmol) and AIBN (135 mg, 0.82 mmol) were dried under vacuum (0.1 mm) for 1 h. Benzene (degassed under Ar for 1 h, 24 mL) was added, followed by

dx.doi.org/10.1021/jo3025972 | J. Org. Chem. 2013, 78, 1508−1518

Bu_3SnH (740 μL, 2.75 mmol), dropwise with stirring at room temperature. The mixture was heated at 85 °C for 16 h, then cooled to room temperature and diluted with 5% aqueous HCl (20 mL). The aqueous layer was washed with CH_2Cl_2 (20 mL) and the organic layer separated. The aqueous layer was basified with 3 M aqueous NaOH and the resulting suspension extracted with Et_2O (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), and the mixture concentrated by careful evaporation (228 mm, 35 °C). Purification of the residue by bulb-to-bulb distillation gave homotropane **(1*S*,5*R*)-17** as a clear oil (316 mg, 69%): bp 75−85 °C (10 mm); R_f = 0.59 (20% MeOH in EtOAc); $[\alpha]_D^{25}$ = −2.2° (*c* = 1.0, $CHCl_3$); IR (neat) (cm^{-1}) 2949 s, 1486 m, 1450 m, 1361 m, 1196 m, 1061 m, 945 m, 865 m, 753 s; ^{1}H NMR (500 MHz) δ 2.55 (d, 1H, *J* = 5 Hz, NC*H*), 2.02−1.87 (m, 3H, 3 × CH_AH_B), 1.74−1.29 (m, 8H, 3 × CH$_A$*H*$_B$, 2 × CH_2 and NH), 1.08 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 0.93 (s, 3H, CH_3); ^{13}C NMR (125 MHz) δ 58.2 (NCH), 47.7 ($NCCH_3$), 37.6 (CH_2), 35.2 (CH_2), 34.9 (CH_2), 33.3 (CH_3), 32.1 ($C(CH_3)_2$), 28.9 (CH_3), 28.3 (CH_3), 26.6 ($NCHCH_2$), 20.4 ($CH_2CH_2CH_2$); MS *m*/*z* (ESI$^+$) 168.6 (M + H$^+$, 42); HRMS *m*/*z* (M + H$^+$) found 168.1744, calcd for $C_{11}H_{21}N$ 168.1747.

(−)-(1S,5R)-1,4,4-Trimethyl-9-azabicyclo[3.3.1]nonane-9-carbaldehyde ((−)-(1S,5R)-30). According to the general procedure for formamide synthesis, reaction of homotropane **(1*S*,5*R*)-17** (156 mg, 0.93 mmol), $BnEt_3NCl$ (104 mg, 0.46 mmol), $CHCl_3$ (749 μL, 9.36 mmol), and 12.5 M aqueous NaOH (2.5 mL) in CH_2Cl_2 (3.3 mL) at reflux for 16 h gave formamide **(1*S*,5*R*)-30** as a clear oil (178 mg, 98%): bp 130−140 °C (1.5 mm); R_f = 0.33 (Et_2O); $[\alpha]_D^{25}$ = −0.6° (*c* = 1.0, $CDCl_3$); IR (film) (cm^{-1}) 2935 m, 1644 s (C═O), 1450 m, 1391 s, 1358 m, 1280 m, 1139 m, 1110 m, 910 w, 752 w; ^{1}H NMR (400 MHz) δ 8.34 (s, 1H, *J* = 5 Hz, CHO), 4.26 (d, 1H, *J* = 5 Hz, NCH), 2.12−1.86 (m, 3H, 3 × CH_AH_B), 1.83−1.71 (m, 2H, 2 × CH_AH_B), 1.67−1.48 (m, 4H, 4 × CH$_A$*H*$_B$), 1.36 (s, 3H, CH_3), 1.31 (dd, 1H, J_{AB} = 14 Hz, *J* = 6 Hz, CH$_A$*H*$_B$), 0.98 (s, 3H, CH_3), 0.94 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 158.8 (C═O), 53.3 ($NC(CH_3)$), 52.4 (NCH), 39.3 (CH_2), 36.2 (CH_2), 34.5 (CH_2), 33.8 ($C(CH_3)_2$), 28.7 (CH_3), 27.7 (CH_3), 27.1 (CH_3), 25.2 (CH_2), 19.9 (CH_2); MS *m*/*z* (ESI$^+$) 196.2 (M + H$^+$, 7); HRMS *m*/*z* (M + H$^+$) found 196.1697, calcd for $C_{12}H_{22}NO$ 196.1696.

(1S,5R)-9-((E)-Hex-1-en-1-yl)-1,4,4-trimethyl-9-azabicyclo[3.3.1]nonane ((1S,5R)-16). According to the general procedure for enamine synthesis, reaction of formamide **(1*S*,5*R*)-30** (174 mg, 0.89 mmol) with pentylmagnesium chloride (2.0 M in THF, 557 μL, 1.11 mmol) in Et_2O (810 μL) at room temperature for 16 h gave, after distillation, enamine **(1*S*,5*R*)-16** (170 mg, 77%): bp 125−130 °C (0.1 mm); IR (neat) (cm^{-1}) 3059 w, 2952 s, 2918 s, 2871 m, 1640 s (C═CNR^{1}R^2), 1451 m, 1258 s, 1108 s, 936 s, 903 s, 768 m; ^{1}H NMR (400 MHz, C_6D_6) δ 6.36 (d, *J* = 14 Hz, NC*H*═CH), 4.40 (dt, 1H, J_1 = 14 Hz, J_2 = 7 Hz, NCH═C*H*), 3.13 (d, 1H, *J* = 5 Hz, NC*H*CH_2), 2.21 (dt, 2H, J_1 = J_2 = 7 Hz, CH═CHCH_2), 2.05−1.64 (m, 4H, 4 × CH_AH_B), 1.53−1.16 (m, 10H, 4 × CH$_A$*H*$_B$ and 3 × CH_2), 1.15 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 0.96 (t, 3H, CH_2CH_3), 0.87 (s, 3H, CH_3); ^{13}C NMR (101 MHz, C_6D_6) δ 133.9 (NCH═CH), 98.5 (NCH═CH), 58.0 (NCH), 53.3 ($NC(CH_3)$), 37.1 (CH_2), 36.4 (CH_2), 35.8 (CH_2), 35.0 (CH_2), 34.7 ($C(CH_3)_2$), 32.0 (CH═CHCH_2), 30.4 (CH_3), 29.2 (CH_3), 28.8 (CH_3), 23.0 (CH_2), 21.7 (CH_2), 19.5 (CH_2), 14.7 (CH_2CH_3); MS *m*/*z* (ESI$^+$) 250.3 (M + H$^+$, 100); HRMS *m*/*z* (M + H$^+$) found 250.2528, calcd for $C_{17}H_{32}N$ 250.2529.[37]

Asymmetric Alkylation of Enamine (1*S*,5*R*)-16 with EtI. According to the general procedure for enamine alkylation, reaction of enamine **(1*S*,5*R*)-16** (125 mg, 0.50 mmol) with EtI (156 mg, 1.00 mmol) in d_3-MeCN (536 μL) at 65 °C for 16 h gave, following hydrolysis with acidic buffer (0.5 mL) at room temperature for 5 min, aldehyde **(*S*)-13**[12] (72:28 er,[12,38] 41 mg, 64%).

Computational Methodology. Density functional theory (DFT) calculations were performed using the Gaussian 09 package.[43] Optimizations of the enamine ground-state structures and of transition-state structures for alkylation were performed with the B3LYP density functional[44] using the default (fine) grid density for numerical integration. 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. This level of DFT calculation has been shown in previous studies to compute relative TS energies in quantitative accord with experimental selectivities.[14] The Pople 6-31G(d) basis set was used for all elements except I, which was described with the LANL2DZ effective core potential and associated valence basis of Hay and Wadt.[45] Effects of solvation due to acetonitrile were implicitly included in all geometry optimizations and in the evaluation of energies using a conductor-like polarizable continuum model (CPCM).[46] Free energies were evaluated at the reaction temperature of 65 °C employing the so-called quasi-harmonic approximation, where all vibrational frequencies lower than 100 cm^{-1} were raised to 100 cm^{-1} as a way to correct for the well-known breakdown of the harmonic oscillator model for the free energies of low-frequency vibrational modes.[47] All possible conformational isomers of the diastereomeric transition structures arising from rotation about the incipient C−C bond were considered and optimized for each enamine: in each case there are two TS geometries for attack from either enamine diastereoface lying within 10 kJ/mol of the global minimum energy structure and thus are the major contributors to the selectivity.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, figures, tables, and CIF files giving ^{1}H and ^{13}C NMR spectra for all new compounds, ^{77}Se NMR for determination of er, NOEs of xanthate **(1*S*,3*R*,5*R*)-29** for assignment of stereochemistry, HPLC traces showing enantiopurity, X-ray diffraction data for determination of absolute configuration, Cartesian coordinates, imaginary frequencies, computed energies, and *x*,*y* distances for **TS1**−**TS8**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: david.hodgson@chem.ox.ac.uk (D.M.H.); robert.paton@chem.ox.ac.uk (R.S.P.; computational studies).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the EPSRC and GlaxoSmithKline for an Organic Synthesis Studentship (A.C.), Oxford University Press John Fell Fund (R.S.P.), and the Royal Society (RG 110617; R.S.P.). Additionally, we wish to thank Dr. Arne Dieckmann (UCLA) for helpful discussions and for sharing computer code, Dr. Barbara Odell for NOE 1D NMR analysis, and Dr. Andrew J. Whitehead for helpful discussions.

■ REFERENCES

(1) For example, see: Enders, D.; Backes, M. *Tetrahedron: Asymmetry* **2004**, *15*, 1813−1817.

(2) Göttlich, R. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Brückner, R., Ed.; Thieme: Stuttgart, Germany, 2006; Vol. *25*, pp 355−366.

(3) Košmrlj, J.; Weigel, L. O.; Evans, D. A.; Downey, C. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 3208−3209.

(4) (a) Enders, D.; Wortmann, L.; Peters, R. *Acc. Chem. Res.* **2000**, *33*, 157−169. (b) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253−2329.

(5) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: London, 1983; Vol. *3*, pp 1−110.

(6) Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496−6511.

(7) Vesely, J.; Rios, R. *ChemCatChem* **2012**, *4*, 942−953.

(8) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450−451.

(9) (a) Ibrahem, I.; Córdova, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1952−1956. (b) Afewerki, S.; Ibrahem, I.; Rydfjord, J.; Breistein, P.; Córdova, A. *Chem. Eur. J.* **2012**, *18*, 2972−2977.
(10) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77−80.
(11) (a) Curphey, T. J.; Hung, J. C. Y. *Chem. Commun.* **1967**, 510. (b) Curphey, T. J.; Hung, J. C. Y.; Chu, C. C. C. *J. Org. Chem.* **1975**, *40*, 607−614.
(12) Hodgson, D. M.; Kaka, N. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 9958−9960.
(13) (a) Hodgson, D. M.; Bray, C. D.; Kindon, N. D. *J. Am. Chem. Soc.* **2004**, *126*, 6870−6871. (b) Hodgson, D. M.; Bray, C. D.; Kindon, N. D.; Reynolds, N. J.; Coote, S. J.; Um, J. M.; Houk, K. N. *J. Org. Chem.* **2009**, *74*, 1019−1028.
(14) Um, J. M.; Kaka, N. S.; Hodgson, D. M.; Houk, K. N. *Chem. Eur. J.* **2010**, *16*, 6310−6316.
(15) (a) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207−222. For reviews of enamine chemistry, see: (b) Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975−2050. (c) *Enamines: Synthesis, Structure, and Reactions*, 2nd ed.; Cook, A. G., Ed.; Marcel Dekker: New York, 1987. (d) *The Chemistry of Enamines*; Rappoport, Z., Ed.; Wiley: Chichester, U.K., 1994. (e) Sammakia, T.; Abramite, J. A.; Sammons, M. F. In *Science of Synthesis*; Trost, B. M., Molander, G. A., Ed.; Thieme: Stuttgart, Germany, 2006; Vol. 33, pp 405−441.
(16) (a) For a review, see: Pollini, G. P.; Benetti, S.; De Risi, C.; Zanirato, V. *Chem. Rev.* **2006**, *106*, 2434−2454. (b) For a recent asymmetric synthesis of tropinones, see: Davis, F. A.; Theddu, N.; Gaspari, P. M. *Org. Lett.* **2009**, *11*, 1647−1650.
(17) (a) Bapat, J. B.; St. Black, D. C.; Brown, R. F. C.; Ichlov, C. *Aust. J. Chem.* **1972**, *25*, 2445−2450. (b) Ikeda, M.; Kugo, Y.; Sat, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1819−1824. (c) Zhang, W.; Pugh, G. *Tetrahedron* **2003**, *59*, 3009−3018.
(18) Jarevång, T.; Anke, H.; Amke, T.; Erkel, G.; Sterner, O. *Acta Chem. Scand.* **1998**, *52*, 1350−1352.
(19) For an amine nucleophilicity scale, see: Brotzel, F.; Chu, Y. C.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 3679−3688.
(20) (a) Salomon, R. G.; Ghosh, S. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. 7, pp177−181. (b) Magnus, P. D.; Nobbs, M. S. *Synth. Commun.* **1980**, *10*, 273−278. (c) Pauley, D.; Anderson, F.; Hudlicky, T. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. 8, pp 208−210.
(21) Harrison, J. R.; O'Brien, P.; Porter, D. W.; Smith, N. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3623−3631.
(22) Naylor, A.; Howarth, N.; Malpass, J. R. *Tetrahedron* **1993**, *49*, 451−468.
(23) Bray, C. D. Ph.D. Dissertation, University of Oxford, 2005.
(24) Hansson, C.; Wickberg, B. *J. Org. Chem.* **1973**, *38*, 3074−3076.
(25) Blum, Z.; Nyberg, K. *Acta Chem. Scand.* **1981**, *35b*, 743−745.
(26) Thompson, W. J.; Anderson, P. S.; Britcher, S. F.; Lyle, T. A.; Thies, J. E.; Magill, C. A.; Varga, S. L.; Schwering, J. E.; Lyle, P. A.; Christy, M. E.; Evans, B. E.; Colton, C. D.; Holloway, M. K.; Springer, J. P.; Hirshfield, J. M.; Ball, R. G.; Amato, J. S.; Larsen, R. D.; Wong, E. H. F.; Kemp, J. A.; Tricklebank, M. D.; Singh, L.; Oles, R.; Priestly, T.; Marshall, G. R.; Knight, A. R.; Middlemiss, D. N.; Woodruff, G. N.; Iversen, L. L. *J. Med. Chem.* **1990**, *33*, 789−808.
(27) (a) Davis, F. A.; Edupuganti, R. *Org. Lett.* **2010**, *12*, 848−851. (b) For a recent review, see: Edupuganti, R.; Davis, F. A. *Org. Biomol. Chem.* **2012**, *10*, 5021−5031.
(28) Moreau, P.; Essiz, M.; Mérour, J.-Y.; Bouzard, D. *Tetrahedron: Asymmetry* **1997**, *8*, 591−598.
(29) (a) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913−9914. (b) Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883−8904.
(30) For example, see: (a) Senanayake, C. H.; Rubin, P. D.; Jerussi, T. P. WO0246138A2, **2002**; *Chem. Abstr.* **2002**, *137*, 20209. (b) Lu, B. Z.; Senanayake, C.; Li, N.; Han, Z.; Bakale, R. P.; Wald, S. A. *Org. Lett.* **2005**, *7*, 2599−2602. (c) Plobeck, N.; Powell, D. *Tetrahedron: Asymmetry* **2002**, *13*, 303−310.
(31) (a) Hodgson, P. K. G.; Warren, S. *J. Chem. Soc., Perkin Trans. 2.* **1975**, 372−380. (b) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539−1546. (c) For improved reduction conditions, see: Saito, K.; Onizawa, Y.; Kusama, H.; Iwasaw, N. *Chem. Eur. J.* **2010**, *16*, 4716−4720.
(32) Ardej-Jakubisiak, M.; Kawęcki, R.; Świetlińska, A. *Tetrahedron: Asymmetry* **2007**, *18*, 2507−2509.
(33) See the Experimental Section for details.
(34) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600−3740.
(35) See the Supporting Information for details, including general experimental conditions.
(36) Desmaële, D.; Mekouar, K.; d'Angelo, J. *J. Org. Chem.* **1997**, *62*, 3890−3901.
(37) $[\alpha]_D^{25}$ not recorded owing to the hydrolytic instability of the enamine.
(38) Silks, L. A.; Peng, J.; Odom, J. D.; Dunlap, R. B. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2495−2498.
(39) Vig, O. P.; Singh, G.; Chugh, O. P.; Matta, K. L. *J. Indian Chem. Soc.* **1969**, *46*, 363−366.
(40) Baker, K. V.; Brown, J. M.; Hughes, N.; Jerome Skarnulis, A.; Sexton, A. *J. Org. Chem.* **1991**, *56*, 698−703.
(41) Gutiérrez, M. C.; Sleegers, A.; Simpson, H. D.; Alphand, V.; Furstoss, R. *Org. Biomol. Chem.* **2003**, *1*, 3500−3506.
(42) (a) Chiarello, J.; Joullié, M. M. *Tetrahedron* **1988**, *44*, 41−48. (b) Olszewski, T. K.; Bomont, C.; Coutrot, P.; Grison, C. *J. Organomet. Chem.* **2010**, *695*, 2354−2358.
(43) Frisch, M. J.; et al. *Gaussian 09, revision A.02*; Gaussian, Inc., Wallingford, CT, 2009.
(44) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789. (c) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200−1211. (d) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623−11627.
(45) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299−310.
(46) (a) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995−2001. (b) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669−681.
(47) Ribeiro, R. F.; Marenich, A. V.; Cramer, C. J.; Tuhlar, D. G. *J. Phys. Chem. B* **2011**, *115*, 14556−14562.