1,5-Asymmetric Induction in Squarate Cascades. Conformational Control of Helicity by Chiral Amino Substituents during Conrotatory Octatetraene Cyclization Prior to β-Elimination

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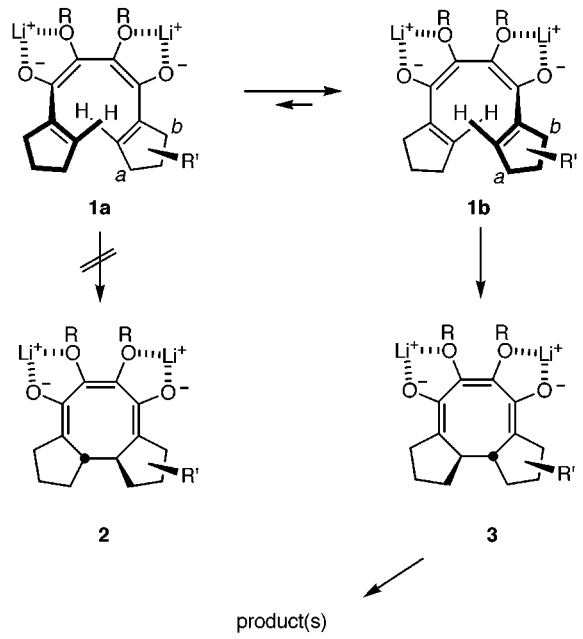
Both the sigmatropic and electrocyclic rearrangement pathways that can arise when a pair of alkenyl anions are added to a squarate ester have high stereochemical demands. The distinction is nontrivial. When cis addition occurs initially, the stereoinduction that materializes at this point is fully transmitted into the product(s). The more commonly observed trans addition exhibits fleeting stereochemical consequences because of rapid equilibration of the octatetraenyl intermediates. In this instance, product distribution is governed by the relative rates of conrotatory cyclization at this advanced stage. Herein reported is a complete dissection of a squarate cascade when a stereogenic center attached to an amino substituent effects 1,5-asymmetric induction prior to β-elimination of the entire fragment. Deuterium labeling permits a direct measure of the contrasting kinetic imbalances associated with the two possible modes of alkenyl anion addition. Furthermore, quantitative analysis of the partitioning experienced by the two helical octatetraenes is readily accomplished. This work constitutes the first example where a complete dynamic profile for these complex processes has been possible. The fact that long-range asymmetric induction has been instrumental in solving the mechanistic puzzle is noteworthy.

Squarate ester cascades are now well-recognized to be powerful synthetic transforms for the rapid construction of complex polycyclic molecules.[1] Two variants are known, both having the formidable potential for generating new C−C bonds and up to five new stereogenic centers in a single step. As an added benefit, the highly functionalized products are amenable to further chemical change,[2] thereby providing very convenient access to additional structurally intricate substances.

When the two alkenyllithium reagents add in cis fashion to the squarate, a pathway not generally observed unless chelation control operates,[3−6] product stereochemistry is set at this very early step. This is because the ensuing dianionic oxy-Cope rearrangement very reliably transmits the original stereoselectivity into the structural scaffolding of the final product(s).

Trans introduction of the alkenyl anions, the customarily dominant reaction channel because of its associated steric and electrostatic advantages, is quickly followed by conrotatory 4π ring opening of the cyclobutene dialkoxide to a doubly charged octatetraenyl intermediate.[1] The stereochemical information resident within the first-formed dialkoxides is subsequently lost because of the remarkable ability of these helical (and therefore chiral) polyolefinic intermediates to experience mutual equilibration. The stereochemically determining step is linked to the rates of 8π conrotatory closure of these helices, with that coil experiencing the minimal steric impedance to cyclization giving rise to the major (or exclusive) product.

There are at least two interesting ways of potentially controlling the outcome of the latter mechanistic pathway in systematic fashion. The first is to position a stereodifferentiating R′ group proximal to the octatetraene bonding sites as in **1**. For **1a**, the R′ group finds itself intercalated inside the spiral instead of being positioned on the exterior as in **1b**. The steric congestion present



in **1a** deters formation of **2**. Since **1b** is not similarly

(1) (a) Negri, J. T.; Morwick, T.; Doyon, J.; Wilson, P. D.; Hickey, E. R.; Paquette, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 12189. (b) Paquette, L. A.; Morwick, T. *J. Am. Chem. Soc.* **1995**, *117*, 1451. (c) Paquette, L. A.; Doyon, J. *J. Am. Chem. Soc.* **1995**, *117*, 6799. (d) Paquette, L. A.; Morwick, T. *J. Am. Chem. Soc.* **1997**, *119*, 1230. (e) Paquette, L. A.; Doyon, J. *J. Org. Chem.* **1997**, *62*, 1723.

(2) Morwick, T. M.; Paquette, L. A. *J. Org. Chem.* **1996**, *61*, 146.

(3) Paquette, L. A.; Morwick, T. M.; Negri, J. T.; Rogers, R. D. *Tetrahedron* **1996**, *52*, 3075.

(4) Paquette, L. A.; Kuo, L. H.; Doyon, J. *Tetrahedron* **1996**, *52*, 11625.

(5) Paquette, L. A.; Kuo, L. H.; Doyon, J. *J. Am. Chem. Soc.* **1997**, *119*, 3038.

(6) Paquette, L. A.; Kuo, L. H.; Tae, J. *J. Org. Chem.* **1998**, *63*, 2010 (preceding paper in this issue).

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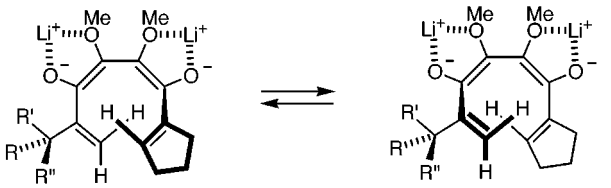
crowded, closure to give **3** operates exclusively in many cases.[7,8] In the final analysis, it is the stereogenic center substituted by R′ that is controlling all the others that materialize in the eventual polycyclic product(s). When the R′ group resides at position *a* in **1**, 1,2-asymmetric induction has been found to operate at a very high level. The alternative bonding of R′ to site *b* (now an example of 1,3-stereoinduction) has understandably proven to be less effective in exhibiting chirality transfer since the substituent finds itself in a more distal relationship to the trigonal centers undergoing bonding.

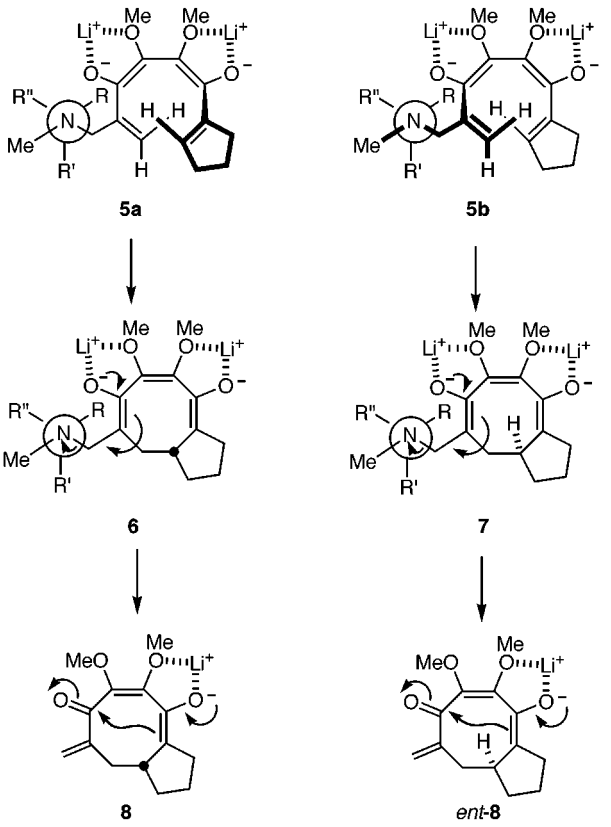
A more subtle tactic is to introduce a stereogenic atom in an equally proximal location to the cyclization termini, as exemplified in **4**. The expectation is that the configuration at the chiral center would impact on the competing rates of closure of **4a** and **4b**. Although the distance



4a **4b**

factor is allylic in its magnitude, many examples of high π-facial stereoselectivity have been reported for compounds of this general type, particularly when highly ordered six-ring transition states are involved.[9]

We now report examples in which the stereogenic center is still further removed from the octatetraenyl framework and bonded to nitrogen as in **5**. Competitive conrotation within either of the diastereomeric coiled conformations labeled as **5a** and **5b** can be expected to proceed at nonidentical rates. The absolute configuration



5a **5b**

6 **7**

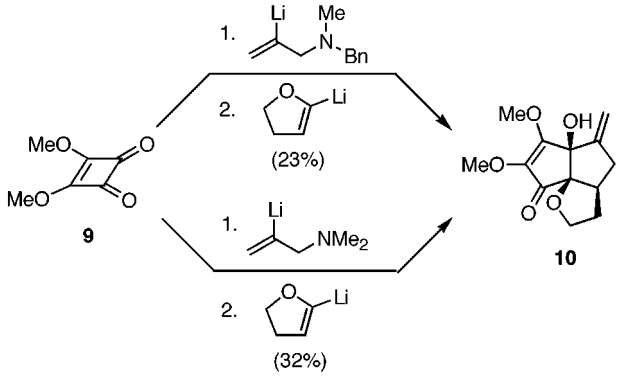
8 *ent*-**8**

of the newly formed methine carbon in **6** and **7** would perforce represent a direct measure of this kinetic imbalance, both in magnitude and in direction. Since the transmission of chirality is necessarily a process involving long-range 1,5-asymmetric induction, moderate stereoselectivity should be forthcoming because of the concertedness of the ring closure and the stereoalignment demanded of these polyolefins in the cyclization transition states.[10]

A notably useful aspect of this particular mechanistic cascade is the expectation that **6** and **7**, once formed, would undergo β-elimination of the chiral amide anion.[6] Such an event would result in the formation of **8** and *ent*-**8**, and culminate in their regiodirected transannular aldolization to give the enantiomers of a single polycyclic ketone. Chiral HPLC analysis for the determination of percent ee and knowledge of absolute configuration would constitute the tools necessary to realize a particularly stringent test of π-facial discrimination during stereocontrolled 8π bonding within octatetraenyl helices.

Results and Discussion

Synthetic Considerations. In studies preliminary to this investigation, observations were made that the β-elimination of amino groups was not universally operative but notably dependent on the nature of the companion alkenyl anion.[6] Particularly relevant was the finding that the use of 5-lithiodihydrofuran as one of the nucleophilic reagents invariably resulted in expulsion of the amide functionality. The conversion of **9** to **10** via two independent (although related) means illustrates the point.



9 **10**

As a consequence, variants of this reaction were targeted for detailed investigation. The requisite optically active amines were selected from various classes, viz. acyclic, cyclic, and heterocyclic, including a C_2-symmetric example. In those cases where the starting amine was primary, a methyl group was introduced prior to reaction with 2,3-dibromopropene, as shown in Scheme 1. The known secondary amines were allylated directly. In those examples where steric hindrance was present, a change in reaction conditions from triethylamine in

(7) Paquette, L. A.; Hamme, A. T., II.; Kuo, L. H.; Doyon, J.; Kreuzholz, R. *J. Am. Chem. Soc.* **1997**, *119*, 1242.

(8) Paquette, L. A., Kuo, L. H.; Hamme, A. T., II.; Kreuzholz, R.; Doyon, J. *J. Org. Chem.* **1997**, *62*, 1730.

(9) Procter, G. Asymmetric Synthesis; Oxford University Press: Oxford, England, 1996.

(10) For an analysis of conformational transmission of chirality in the specific case of a 1,4-asymmetric induction process, consult: Lucero, M. J.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 826.

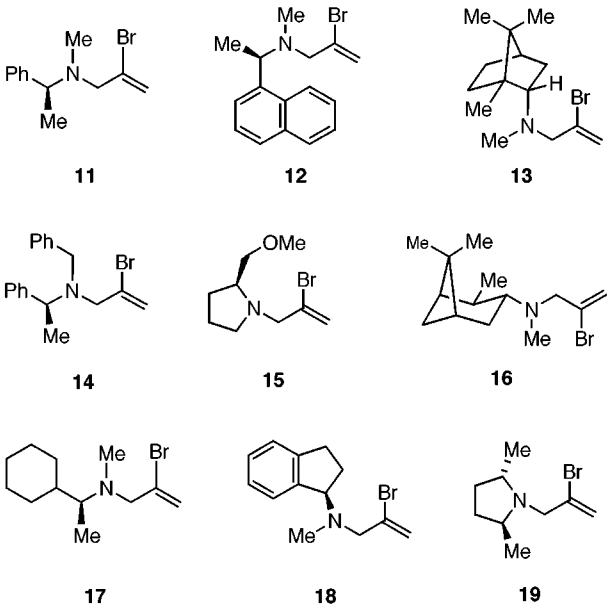
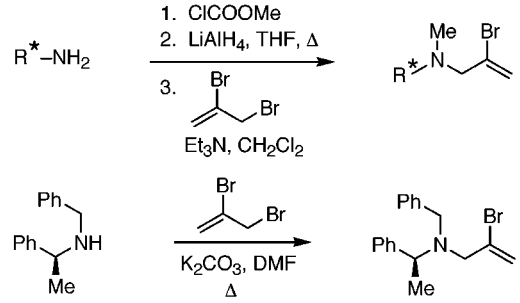


Figure 1. The enantiopure bromo amines utilized in this investigation.

Scheme 1

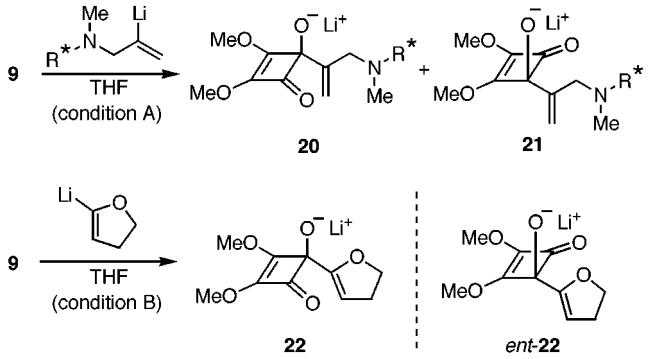


CH_2Cl_2 to the more harsh potassium carbonate in refluxing DMF was mandated.

The nine reagents generated in this manner are grouped in Figure 1. All of the starting amines have been previously described in enantiopure condition,[11] thus facilitating access to **11**−**19**.

Execution of the Rearrangement Cascades. It is necessary to realize that two lines of mechanistic inquiry are being investigated simultaneously. If a lithiated amine is added first (condition A), the extent of cis addition of the second alkenyl anion is certain to be different than that observed if the lithiated dihydrofuran is the lead reagent (condition B). No matter how the cis/trans ratio of the cyclobutene dialkoxides might be partitioned, the outcome of the ensuing cascade should be rationalizable in terms of the associated partitioning between the [3,3] sigmatropic and stepwise electrocyclic options. The distinction is nontrivial. For the anionic oxy-Cope alternative, the key asymmetric step is the addition of the homochiral nitrogen-containing vinyl anion to the squarate ester. As depicted in Scheme 2,

Scheme 2



condition A will necessarily generate **20** and **21** in unequal amounts. The overall response requires that this stereoinduction be fully transmitted into the product mixture. Reversal of the addition sequence as under condition B gives rise only to racemic **22**, since nucleophilic attack at either carbonyl group from either direction must occur at equal rates. Once **22** has been generated, there remains no opportunity for the enantiopure allylic amine to exert any stereochemical bias at all during cis addition.

On the other hand, trans 1,2-addition to **20**−**22** carries only fleeting stereochemical consequences, since the asymmetric step materializes only later at the time of conrotatory octatetraene cyclization. Although the latter scenario is of immediate interest here, the relative kinetic ordering associated with the formation of **20** and **21** offers an equally unrivaled opportunity for gaining new perspectives on carbonyl addition processes.

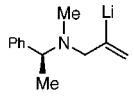
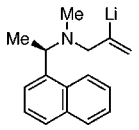
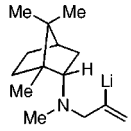
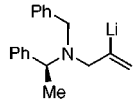
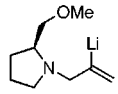
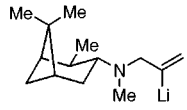
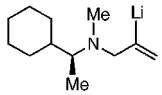
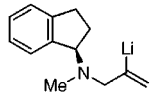
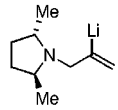
The experimental data are given in Table 1. Entries 3, 4, 7, and 8 are characterized by notably low levels of chirality transmission. Conversely, the most stereochemically responsive chiral auxiliaries are found in entries 1, 5, 6, and 9. It is significant that replacement of the *N*-methyl group in **11** (entry 1) by a more bulky benzyl substituent (entry 4) results in increased reaction efficiency accompanied by a substantial dropoff in enantioselectivity. Replacement of the phenyl group in **11** by an α-naphthyl (entry 2) has a similar, although less dramatic, outcome. The cyclohexyl analogue of **17** (entry 7) is still less suited to our purposes. The *endo*-bornylamine **13** (entry 3) is inferior to its pinanyl counterpart **16** (entry 6). The presence of an added chelation site (entry 5) is beneficial and the C_2-symmetric example **19** (entry 9) exhibits a useful product distribution.

The crossovers in enantioselectivity observed between conditions A and B in entries 3 and 4 are fascinating and warrant explanation. The initial addition of 5-lithiodihydrofuran to generate **22** is predictably recognized to foster a modest level of chelation control as the second alkenyl anion is introduced.[3] Accordingly, the product compositions generated under these circumstances will often contain higher levels of oxy-Cope product. When the tricyclic ketones resulting from the sigmatropic and electrocyclic cascade exhibit optical rotations of different sign, the observable effect will be manifested in this way.

Determination of Absolute Stereochemistry. The absolute stereochemistry of **10** was determined by an

(11) The primary amines required for the preparation of **11**, **12**, **16**, **17**, and **18** as well as the secondary amine precursor to **14** were purchased from the Aldrich Chemical Co. *endo*-Bornylamine was prepared from D-camphor (Forster, M. O. *J. Chem. Soc.* **1898**, *73*, 386), (*S*)-(+)-2-(methoxymethyl)pyrrolidine from (*S*)-proline (Enders, D.; Fey, P.; Kipphardt, H. *Org. Synth.* **1987**, *65*, 173), and (2*S*,5*S*)-2,5-dimethylpyrrolidine from L-alanine (Yamazaki, T.; Gimi, R.; Welch, J. T. *Synlett* **1991**, 573).

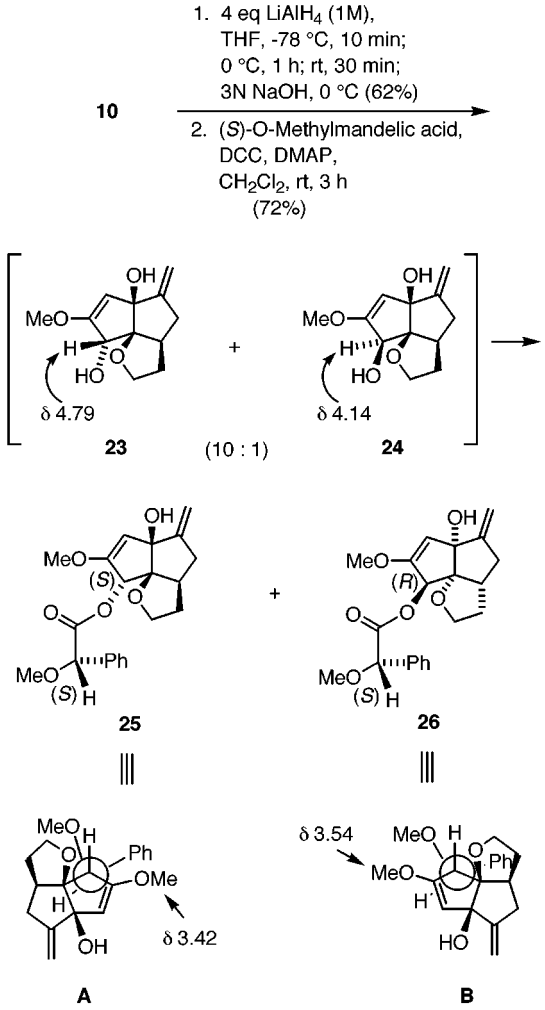
Table 1. Evaluation of Chiral Substituents at Nitrogen on the Enantioselectivity of a Squareate Ester Cascade

entry	amino-substituted anion[a]	reaction conditions[b]	major product enantiomer	Yield, %	percent ee
1		A	**10**	29	35
		B	**10**	24	18
2		A	**10**	27	23
3		A	*ent*-**10**	27	13
		B	**10**	39	13
4		A	*ent*-**10**	52	14
		B	**10**	20	<3
5		A	**10**	18	36
6		A	*ent*-**10**	33	35
		B	*ent*-**10**	27	31
7		A	**10**	25	8
8		A	**10**	28	8
9		A	*ent*-**10**	21	29

[a] Generated from **11-19** by halogen−metal exchange with *tert*-butyllithium in THF at −78 °C. [b] A: addition of the amino-substituted reagent precedes introduction of 5-lithiodihydrofuran. B: the reverse of A.

established NMR method.[12] Initially, its oxygenated ring was reduced with lithium aluminum hydride at low temperature to give principally the demethoxylated α-alcohol **23** (Scheme 3). The appreciable deshielding of the carbinol proton in **23** (δ 4.79) relative to that experienced by the epimeric proton in **24** (δ 4.14), which can be directly attributed to proximity to the ethereal oxygen, defines the relative configuration of the reduction products. Coupling of **23** to (*S*)-O-methylmandelic acid furnished the diastereomeric esters **25** and **26**, which could be separated chromatographically. Structures **A** and **B** illustrate the Mosher models[13] of these esters in

Scheme 3



the form of "extended Newman projections". Comparison of the chemical shifts of the methoxy groups in these derivatives shows those in **A** to be more upfield. This effect can be attributed to shielding experienced as the result of spatial proximity to the phenyl substituent, thereby requiring it to be the *S*,*S* isomer.

Determination of the percent ee values was facilitated by the fact that **10** and *ent*-**10** exhibit widely divergent retention times on a CHIRALPAK AD column in a solvent system constituted of isopropyl alcohol and hexanes (1:2). The values reported in Table 1 were arrived at by chiral HPLC analysis in this fashion.

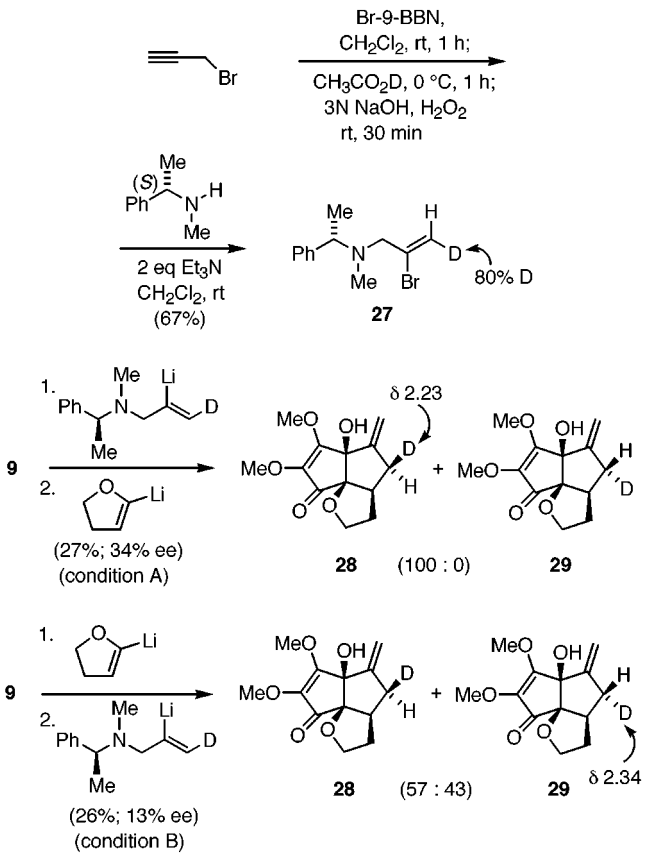
Deuterium Labeling Studies. Distinction between the operation of either the oxy-Cope or the electrocyclic cascade requires that the lithiated allylamine carry an appropriate stereochemical marker. Since the smallest structural change that can be implemented is to substitute deuterium for hydrogen, our attention was turned to the preparation of **27** (Scheme 4). To this end, propargyl bromide was subjected to bromoboration with *B*-bromo-9-borabicyclo[3.3.1]nonane in anticipation of sterically directed Markovnikov addition.[14] Deuteriolysis of the vinylborane so formed with acetic acid-*O*-*d* afforded regio- and stereoselectively labeled 2,3-dibromopropene-*1-d*, from which **27** was generated by conventional displacement. While ^{1}H NMR analysis showed the level

(12) (a) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 4929. (b) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

(13) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(14) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731.

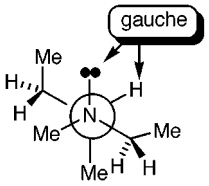
Scheme 4



of deuterium incorporation to be 80%, ^{2}D NMR revealed the double bond geometry to be exclusively *Z*. The lithiated form of **27** was subsequently utilized in a matched pair of experiments.

In the first cascade, the aminated nucleophile **27** was the lead reagent, to be followed by 5-lithiodihydrofuran. The second set of conditions involved reversal of this order. As expected, the yields and percent ee values compare closely to those earlier realized in the unlabeled examples (Table 1). The stereochemical assignments to **28** and **29** rest reliably on the distinctive chemical shifts of the exo (δ 2.23) and endo deuterium substituents (δ 2.34) in $CHCl_3$ solution. These methylene positions had earlier been defined by detailed analysis of the high-field ^{1}H NMR spectrum of **10**.

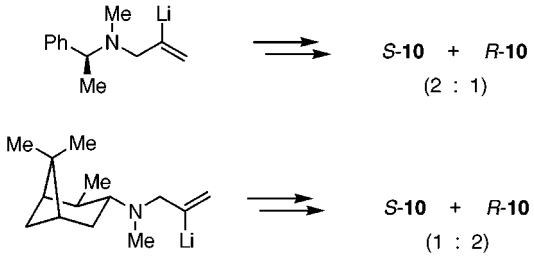
What now has become clear is the extremely high level of adherence to the electrocyclic pathway under condition A. In the absence of any measurable cis attack during the second-stage addition, a feature that is directly related to the absence of detectable levels of **29**, the percent ee therefore represents the asymmetric partitioning associated with the competitive ring closures of **30** and **31** (Scheme 5). The faster rate of cyclization of **30** can be understood by according proper consideration to the conformation preferentially adopted by tertiary amines which carry a stereogenic center at their α-position. The detailed NMR and molecular mechanics study of the stereodynamics of *N*-ethyl-*N*-methyl-2-aminobutane (**32**) performed by Danehey and co-workers[15] is representative. The D NMR behavior of **32** is consistent with that model in which diastereomeric interconversion via nitrogen inversion is impeded by a relatively high barrier ($\Delta G^{\ddagger}$ = 7.3 kcal/mol). Conformational interconversion is slightly less demanding ($\Delta G^{\ddagger}$ = 6.4 kcal/mol), with the most stable spatial arrangement exhibiting a gauche relationship between the nitrogen lone pair and the α-hydrogen at the stereogenic center. As seen in the Newman projection, the large groups are positioned anti



32

to each other. Should the same requirements logically apply to **30** and **31**, the helical orientation in **30** is seen to be quite free of nonbonded steric compression. In contrast, the state of affairs in **31** is such that the dihydrofuran moiety must recognize an added modicum of interaction with the α-methylbenzyl substituent, with the result that conrotatory cyclization in this instance is bridled to some degree.

Product partitioning can now be comparably appreciated for the other cascades reported herein. The data for entries 1 and 6, for example, are internally consistent if the pinanyl substituent destabilizes the pro-*S* conformation relative to the pro-*R* option. While the effects are certainly subtle, they do point up the reality of effective 1,5-asymmetric transmission in these systems.

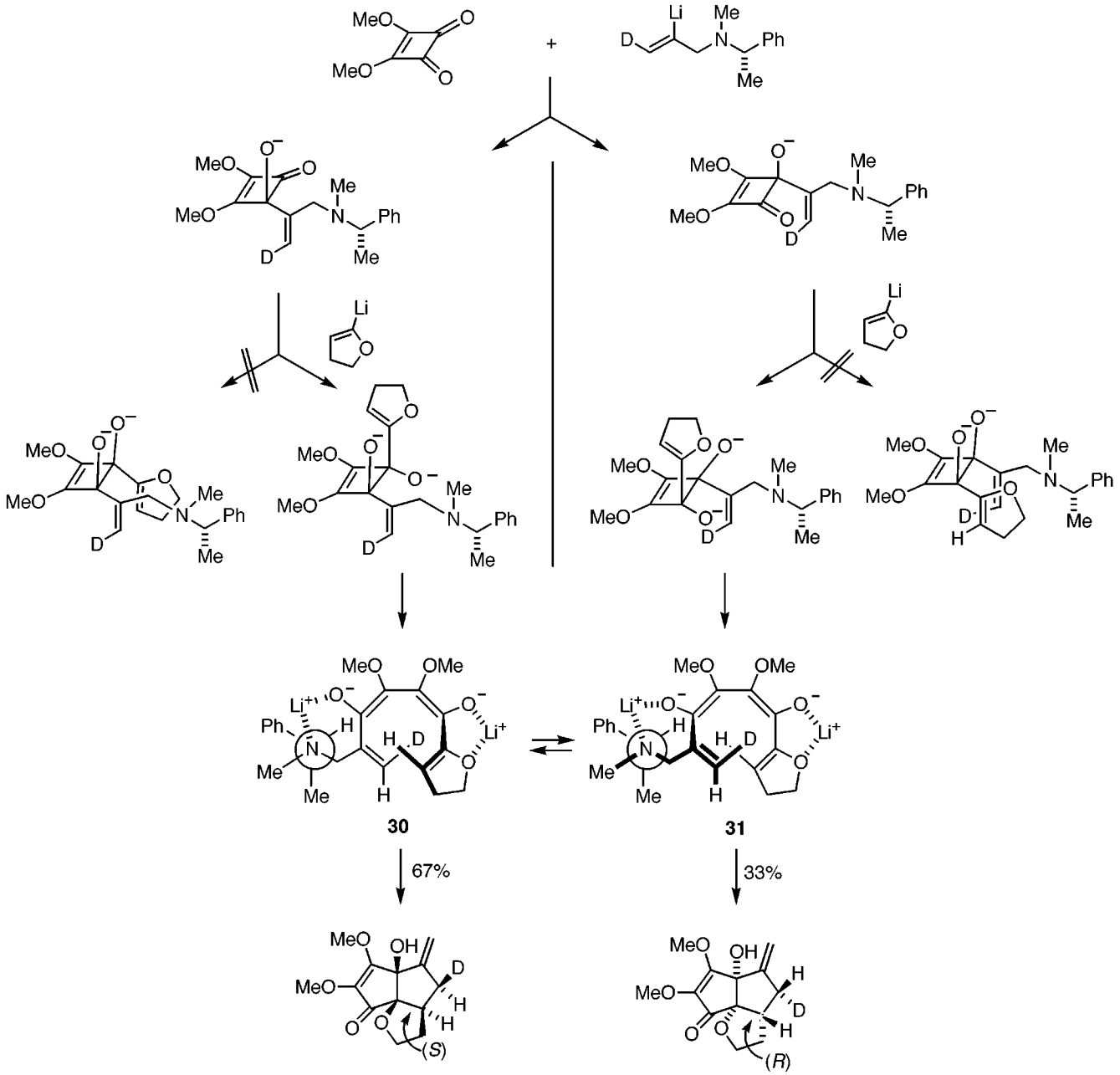


Complete dissection of the mechanistic details associated with condition A (Scheme 5) allows for equally insightful analysis of the more intricate features set in motion under condition B. Involvement of the dihydrofuranyl anion as the lead nucleophile gives rise to monoalkoxides **22** and *ent*-**22**, as stated before. The early introduction of an ethereal oxygen center in this manner provides a sufficiently good binding site for lithium ions so that a certain percentage of the lithioallylamine subsequently introduced is enticed into cis addition (Scheme 6). This event leads necessarily to the formation of **33** and **34**, respectively, and results in rapid [3,3] sigmatropic shifting via a boatlike transition state[16] with complete transmission of stereochemistry. Thus, **33** proceeds strictly via **35** to (*R*)-**10**-*endo*-*d*, while **34** gives rise to (*S*)-**10**-*endo*-*d*, following initial conversion to **36**. A necessary requirement of the olefin geometry in the labeled lithiated allylamine is the ultimate placement of the deuterium in a relationship anti to the tetrahydrofuran ring in **10**. This stereochemical feature is opposite

(15) Danehey, C. T., Jr.; Grady, G. L.; Bonneau, P. R.; Bushweller, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 7269.

(16) (a) Berson, J. A.; Dervan, P. B. *J. Am. Chem. Soc.* **1972**, *94*, 7597. (b) Paquette, L. A.; Colapret, J. A.; Andrews, D. R. *J. Org. Chem.* **1985**, *50*, 201.

Scheme 5



to that demanded of the electrocyclic alternative arising from initial trans addition.

From the four equations given below,

$$(R)\text{-}\mathbf{10}\text{-}exo\text{-}d = 0.57 \times 0.33 \times 100 = 19\%$$

$$(S)\text{-}\mathbf{10}\text{-}exo\text{-}d = 0.57 \times 0.67 \times 100 = 38\%$$

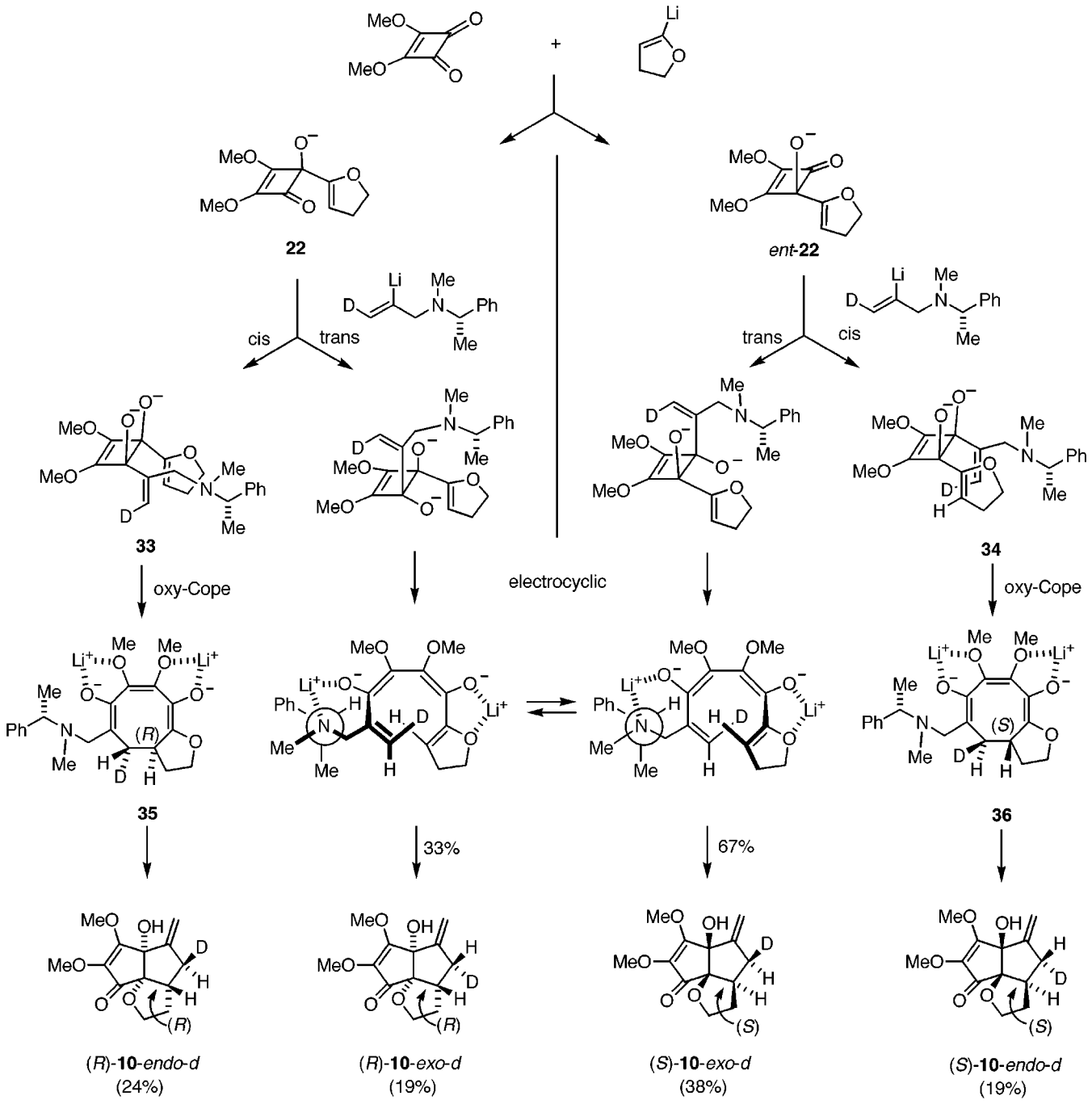
$$(R)\text{-}\mathbf{10}\text{-}endo\text{-}d = 0.43 - (R)\text{-}\mathbf{10}\text{-}exo\text{-}d \times 100 = 24\%$$

$$(S)\text{-}\mathbf{10}\text{-}endo\text{-}d = 0.57 - (S)\text{-}\mathbf{10}\text{-}exo\text{-}d \times 100 = 19\%$$

it is possible to derive the percent composition of the four possible products formed in Scheme 6. If it be assumed that partitioning of the helical intermediates is unchanged relative to that determined for condition A (Scheme 5), then the limits for the two *exo-d* ketones are governed by the multiplication products of the extent to which the *exo-d* isomer is formed (57%, Scheme 4) and the relative manner in which **30** and **31** advance to the respective tricyclic ketones (33% or 67%, Scheme 5). To arrive at the levels of the *endo-d* isomers, it becomes necessary only to subtract from the product composition determined in Scheme 4 the relative amounts of their *exo-d* counterparts generated by the electrocyclic route. In this final analysis, the enantiomeric *endo-d* isomers in combination represent 43% of the total, and the *exo-d* products the remaining 57%. Also, the two *R* antipodes make up 43% of the mixture and the *S* enantiomers 57%.

Overview. A complete dissection of an asymmetric squarate ester cascade has been accomplished. The analysis has been made possible by the self-immolative manner in which a chiral amino substituent induces long-range 1,5-asymmetric induction prior to being ejected from an advanced intermediate. Despite the substantive intramolecular distances that materialize between the developing stereogenic center and the chiral nitrogen substituent during conrotatory cyclization of the helical octatetraene dialkoxides, stereochemical transmission

Scheme 6



levels up to 35% ee were observed in several examples. We believe the highly ordered nature of these stereoelectronically demanding transition states to be responsible. If this is correct, variants of these tandem reactions may prove more generally applicable than heretofore appreciated for the impressively abbreviated enantiocontrolled construction of complex polycyclic systems.

Experimental Section

The general experimental protocols followed in this study parallel those described earlier in ref 6.

General Procedure for Converting Primary Amines to 2-Bromoallylamines. A solution of the primary amine (23.3 mmol) in CH_2Cl_2 (20 mL) was admixed with potassium carbonate (6.43 g, 46.5 mmol) in water (20 mL) and with tetra-*n*-butylammonium iodide (50 mg). This mixture was cooled to 0 °C, treated dropwise with methyl chloroformate (2.64 g, 2.80 mmol), warmed to room temperature, and stirred for 5 h. The separated aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic layers were dried and concentrated to leave a colorless oil.

This oily carbamate was dissolved in dry THF (10 mL), added dropwise to a cold (0 °C), stirred slurry of lithium aluminum hydride (1.32 g, 34.9 mmol) in dry THF (70 mL), and refluxed overnight. After being cooled, the reaction mixture was treated with 2 N NaOH (2 mL) solution, and the resultant precipitate was filtered off and rinsed thoroughly with ether. The filtrate was freed of solvent and used directly.

The unpurified *N*-methylamine was dissolved in CH_2Cl_2 (50 mL) and treated with triethylamine (4.9 mL, 34.9 mmol) and then 2,3-dibromopropene (3.0 mL, 23.3 mmol). The reaction mixture was stirred overnight, washed with water (50 mL), dried, and concentrated in vacuo. Chromatography of the

residue on silica gel (elution with 10:1 hexanes/ethyl acetate) gave the desired bromoamine.

(*S*)-*N*-(2-Bromoallyl)-*N*,α-dimethylbenzylamine (11): 77% yield; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.23 (m, 5 H), 5.90 (s, 1 H), 5.57 (s, 1 H), 3.71 (q, J = 6.8 Hz, 1 H), 3.28 (d, J = 14.9 Hz, 1 H), 3.07 (d, J = 14.9 Hz, 1 H), 2.23 (s, 3 H), 1.40 (d, J = 6.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 143.3, 132.6, 128.1 (2 C), 127.6 (2 C), 126.9, 117.8, 62.6, 40.1, 38.0, 18.0 ppm; MS m/z (M^+) calcd 253.0466, obsd 253.0486; [α] −12.3° (*c* 0.21, $CHCl_3$).

(*R*)-*N*-(2-Bromoallyl)-*N*,α-dimethyl-1-naphthalenemethylamine (12): 69% overall yield; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, J = 7.7 Hz, 1 H), 7.87 (m, 1 H), 7.78 (d, J = 8.2 Hz, 1 H), 7.63 (d, J = 7.0 Hz, 1 H), 7.56−7.44 (m, 3 H), 5.88 (s, 1 H), 5.54 (s, 1 H), 4.44 (q, J = 6.7 Hz, 1 H), 3.37 (d, J = 15.0 Hz, 1 H), 3.22 (d, J = 15.0 Hz, 1 H), 2.31 (s, 3 H), 1.53 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 139.8, 134.0, 132.4, 131.7, 128.6, 127.6, 125.5, 125.3, 125.2, 124.5, 124.4, 117.6, 63.0, 60.1, 38.1, 16.9 ppm; MS m/z (M^+) calcd 303.0622, obsd 303.0620; [α] −34.1° (*c* 0.22, $CHCl_3$).

(1*R*,2*S*,4*R*)-*N*-(2-Bromoallyl)-*N*-methyl-2-bornanamine (13): 72% overall yield; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 (s, 1 H), 5.54 (s, 1 H), 3.29 (d, J = 15.6 Hz, 1 H), 3.06 (d, J = 15.6 Hz, 1 H), 2.51 (m, 1 H), 2.22 (s, 3 H), 2.10−1.95 (m, 2 H), 1.71 (m, 1 H), 1.57 (t, J = 4.6 Hz, 1 H), 1.30−1.15 (m, 2 H), 1.10 (dd, J = 12.4, 4.0 Hz, 1 H), 0.95 (s, 3 H), 0.87 (s, 3 H), 0.83 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 132.9, 117.0, 69.7, 65.1, 50.0, 48.9, 44.3, 41.9, 36.5, 28.7, 27.0, 20.1, 18.7, 16.6 ppm; MS m/z (M^+) calcd 285.1092, obsd 285.1094; [α] 23.7° (*c* 0.20, $CHCl_3$). Anal. Calcd for $C_{14}H_{24}$BrN: C, 58.74; H, 8.45. Found: C, 58.61; H, 8.41.

(1*R*,2*R*,3*R*,5*S*)-*N*-(2-Bromoallyl)-*N*-methyl-3-pinanamine (16): 70% overall yield; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (s, 1 H), 5.53 (s, 1 H), 3.33 (d, J = 14.9 Hz, 1 H), 3.18 (d, J = 14.9 Hz, 1 H), 3.11 (m, 1 H), 2.31 (s, 3 H), 2.26 (m, 1 H), 2.10−1.90 (s, 3 H), 1.80−1.70 (m, 2 H), 1.19 (s, 3 H), 1.10 (d, J = 7.1 Hz, 3 H), 0.98 (s, 3 H), 0.86 (d, J = 9.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 133.2, 117.2, 63.2, 61.9, 48.0, 41.5, 39.9, 39.0, 37.9, 33.3, 28.0, 27.1, 23.3, 21.7 ppm; MS m/z (M^+) calcd 285.1092, obsd 285.1088; [α] −60.5° (*c* 0.63, $CHCl_3$). Anal. Calcd for $C_{14}H_{24}$BrN: C, 58.74; H, 8.45. Found: C, 58.74; H, 8.44.

(*S*)-*N*-(2-Bromoallyl)-*N*,α-dimethylcyclohexanemethylamine (17): 80% overall yield; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (s, 1 H), 5.50 (s, 1 H), 3.23 (d, J = 15.3 Hz, 1 H), 3.10 (d, J = 15.3 Hz, 1 H), 2.30 (m, 1 H), 2.20−2.10 (m, 1 H), 2.15 (s, 3 H), 1.75−1.60 (m, 4 H), 1.30−1.10 (m, 4 H), 0.95−0.75 (m, 2 H), 0.88 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 133.4, 116.7, 63.2, 62.6, 41.5, 36.2, 30.9, 30.5, 26.7, 26.5, 26.3, 10.0 ppm; MS m/z (M^+) calcd 259.0935, obsd 259.0933; [α] −30.7° (*c* 0.61, $CHCl_3$). Anal. Calcd for $C_{12}H_{22}$BrN: C, 55.39; H, 8.52. Found: C, 55.44; H, 8.49.

(*R*)-*N*-(2-Bromoallyl)-*N*-methyl-1-indanamine (18): 75% overall yield; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (m, 1 H), 7.30−7.20 (m, 3 H), 6.00 (s, 1 H), 5.61 (s, 1 H), 4.52 (t, J = 7.5 Hz, 1 H), 3.29 (d, J = 14.9 Hz, 1 H), 3.19 (d, J = 14.9 Hz, 1 H), 3.05−2.80 (m, 2 H), 2.32 (s, 3 H), 2.25−2.10 (m, 1 H), 2.10−1.95 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 143.3, 143.2, 132.7, 127.4, 126.2, 125.0, 124.5, 117.4, 69.0, 61.3, 37.8, 30.4, 24.3 ppm; MS m/z (M^+) calcd 265.0466, obsd 265.0457; [α] −32.1° (*c* 0.85, $CHCl_3$). Anal. Calcd for $C_{13}H_{16}$BrN: C, 58.66; H, 6.06. Found: C, 58.58; H, 6.06.

General Procedure for Converting Secondary Amines to 2-Bromoallylamines. A. Mild Conditions. The amine (28.0 mmol) was dissolved in CH_2Cl_2 (70 mL) and treated sequentially with triethylamine (8.61 mL, 56.0 mmol) and 2,3-dibromopropene (3.97 mL, 28.0 mmol). The reaction mixture was stirred overnight and processed in the previously described manner.

(*S*)-1-(2-Bromoallyl)-2-(methoxymethyl)pyrrolidine (15): 92% yield; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (s, 1 H), 5.47 (s, 1 H), 3.68 (d, J = 15.0 Hz, 1 H), 3.40−3.20 (m, 2 H), 3.31 (s, 3 H), 3.18 (d, J = 15.0 Hz, 1 H), 3.08 (m, 1 H), 2.73 (m, 1 H), 2.25 (m, 1 H), 1.95−1.53 (series of m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) 132.4, 117.3, 76.5, 63.5, 62.6, 59.0, 54.2, 28.5, 23.1 ppm; MS m/z (M^+) calcd 233.0415, obsd 233.0396; [α] −64.6° (*c* 0.35, $CHCl_3$). Anal. Calcd for C_9H_{16}BrNO: C, 46.17; H, 6.89. Found: C, 46.26; H, 6.84.

(2*S*,5*S*)-1-(2-Bromoallyl)-2,5-dimethylpyrrolidine (19): 84% yield; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (m, 1H), 5.48 (s, 1 H), 3.33 (s, 2 H), 3.15−3.00 (m, 2 H), 2.10−1.90 (m, 2 H), 1.45−1.30 (m, 2 H), 0.94 (d, J = 6.2 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) 133.5, 116.4, 55.7, 55.1, 31.0, 17.3 ppm; MS m/z (M^+) calcd 217.0466, obsd 217.0451; [α] 83.5° (*c* 0.22, $CHCl_3$). Anal. Calcd for C_9H_{16}BrN: C, 49.56; H, 7.39. Found: C, 49.27; H, 7.36.

B. More Forcing Conditions. (*S*)-*N*-(2-Bromoallyl)-α-methyldibenzylamine (14). A mixture of the secondary amine (3.0 mL, 14.3 mmol), K_2CO_3 (5.95 g, 42.9 mmol), *n*-Bu_4NI (50 mg), and 2,3-dibromopropene (1.85 mL, 14.3 mmol) in DMF (35 mL) was refluxed for 2.5 h. The reaction mixture was cooled to room temperature, filtered off, and diluted with brine (50 mL) and ether (100 mL). The separated organic layer was washed with brine (50 mL), dried, and concentrated to give 4.4 g (93%) of colorless liquid **14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62−7.38 (m, 10 H), 6.11 (s, 1 H), 5.74 (s, 1 H), 4.19 (q, J = 6.9 Hz, 1 H), 3.81 (d, J = 14.0 Hz, 1 H), 3.72 (d, J = 14.0 Hz, 1 H), 3.54 (d, J = 15.2 Hz, 1 H), 3.33 (d, J = 15.2 Hz, 1 H), 1.58 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 142.1, 139.5, 133.1, 128.6, 128.2, 128.0, 127.8, 126.8, 118.0, 57.6, 56.5, 53.4, 14.4 ppm; MS m/z (M^+) calcd 329.0779, obsd 329.0787; [α] −33.6° (*c* 0.35 $CHCl_3$). Anal. Calcd for $C_{18}H_{20}$BrN: C, 65.46; H, 6.10. Found: C, 65.39; H, 6.06.

Prototypical Squarate Ester Cascade. I. Condition A. To a cold (−78 °C), magnetically stirred solution of **11** (687 mg, 2.70 mmol) in dry THF (5 mL) was added *tert*-butyllithium (3.20 mL of 1.7 M in pentane, 5.40 mmol) dropwise. After 20 min at this temperature, a solution of dimethyl squarate (256 mg, 1.80 mmol) in THF (5 mL) was slowly introduced, to be followed 30 min later with 5-lithio-2,3-dihydrofuran [prepared from dihydrofuran (0.27 mL, 3.60 mmol) and *tert*-butyllithium (2.12 mL of 1.7 M in pentane, 3.60 mmol)] as rapidly as possible. The reaction mixture was continuously agitated for 2 h at −78 °C, allowed to warm to room temperature overnight (13 h), and diluted at 0 °C with deoxygenated NH_4Cl solution (10 mL). After 1.5 h at 20 °C, saturated $NaHCO_3$ solution (20 mL) was introduced, the separated aqueous layer was extracted with ether (2 × 30 mL), and the combined organic layers were dried and evaporated. Chromatography of the residue on silica gel (elution with 2:1 hexanes/ethyl acetate) gave 133 mg (29%, 35% ee) of **10** as a colorless liquid. This product was spectroscopically identical to known racemic material.[6]

II. Condition B. A cold (−78 °C) solution of 2,3-dihydrofuran (0.15 mL, 1.98 mol) in dry THF (5 mL) was treated dropwise with *tert*-butyllithium (1.17 mL of 1.7 M in pentane, 1.98 mmol). After 10 min at −78 °C, 30 min at 0 °C, and an additional 10 min at −78 °C, a solution of dimethyl squarate (256 mg, 1.80 mmol) in THF (5 mL) was slowly introduced followed 30 min later by the lithiated amine [prepared from **11** (916 mg, 3.60 mmol) and *tert*-butyllithium (2.12 mL of 1.7 M in pentane, 7.20 mmol) in THF (5 mL) at −78 °C]. The reaction mixture was stirred at −78 °C for 2 h and at room temperature for 13 h prior to being returned to 0 °C and treated with deoxygenated saturated NH_4Cl solution (10 mL). The preceding workup was next followed to provide 111 mg (24% of **10** (18% ee).

Preparation of the (*S*)-Mandelate Esters in 25 and 26. A solution of **10** (355 mg, 1.41 mmol, 35% ee) in dry THF (10 mL) was treated with a solution of lithium aluminum hydride in THF (5.6 mL of 1.0 M, 5.6 mmol) at −78 °C. After 10 min, the reaction mixture was warmed to 0 °C for 1 h, at room temperature for 30 min, and quenched with 3 N sodium hydroxide solution. After filtration to remove solids, the filtrate was concentrated and the residue was chromatographed on silica gel. Elution with 1:1 hexanes/ethyl acetate gave pure **23** (195 mg, 62%) as a white solid.

This alcohol was dissolved in CH_2Cl_2 (20 mL) and treated sequentially with dicyclohexylcarbodiimide (269 mg, 1.31

mmol), (*S*)-*O*-methylmandelic acid (159 mg, 0.96 mmol), and 4-(dimethylamino)pyridine (10 mg). After 3 h at room temperature, the solid precipitate was filtered off, the filtrate was concentrated, and the residue was chromatographed on silica gel (elution with 8:1 hexanes/ethyl acetate) to give 233 mg (72%) of **25** and **26** (ratio 2:1) that proved to be partially separable under these conditions.

For **25**: IR (film, cm^{-1}) 3590, 1756, 1651; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50−7.40 (m, 2 H), 7.40−7.25 (m, 3 H), 5.89 (s, 1 H), 5.15 (s, 1 H), 4.84 (s, 1 H), 4.81 (s, 1 H), 4.55 (s, 1 H), 3.70−3.60 (m, 1 H), 3.55−3.45 (m, 1 H), 3.42 (s, 3 H), 3.40 (s, 3 H), 2.80 (s, 1 H), 2.75−2.65 (m, 1 H), 2.50−2.35 (m, 1 H), 2.04 (d, J = 15.2 Hz, 1 H), 1.75−1.65 (m, 1 H), 1.45−1.35 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 169.9, 158.3, 154.1, 136.1, 128.5, 128.4, 126.8, 107.1, 101.5, 95.1, 83.9, 82.9, 79.0, 69.3, 57.5, 56.6, 39.3, 35.4, 33.6 ppm; MS m/z (M^+) calcd 372.1573, obsd 372.1530.

For **26**: IR (film, cm^{-1}) 3590, 1756, 1651; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.35 (m, 2 H), 7.35−7.20 (m, 3 H), 5.90 (s, 1 H), 5.12 (s, 1 H), 4.79 (s, 2 H), 4.56 (s, 1 H), 3.60−3.45 (m, 1 H), 3.54 (s, 3 H), 3.36 (s, 3 H), 3.25−3.15 (m, 1 H), 2.78 (s, 1 H), 2.30−2.20 (m, 2 H), 1.83 (d, J = 13.6 Hz, 1 H), 1.35−1.10 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) 169.3, 157.8, 153.7, 136.2, 128.6, 128.4, 127.2, 106.8, 101.5, 94.8, 83.5, 81.9, 78.6, 68.9, 57.0, 56.5, 38.8, 35.0, 33.1 ppm; MS m/z (M^+) calcd 372.1573, obsd 372.1570.

(*S*)-*N*-[(*Z*)-2-Bromoallyl-*3*-*d*])-*N*,α-dimethylbenzylamine (27). A cold (0 °C) solution of bromo-9-BBN (52 mL of 1.0 M in CH_2Cl_2, 52 mmol) was treated dropwise with propargyl bromide (3.0 mL of 80% in toluene, 32 mmol), stirred at room temperature for 1 h, and returned to 0 °C prior to the introduction of CH_3CO_2D (10 mL). After 1 h at this temperature, 3 N sodium hydroxide solution (160 mL) and 30% hydrogen peroxide were added. The reaction mixture was stirred at 20 °C for 30 min prior to separation of the aqueous phase and extraction of the latter with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried and concentrated to leave the labeled 2,3-dibromopropene, which was immediately reacted with freshly prepared *N*-methylamine (5.24 g, 38 mmol) in CH_2Cl_2 (220 mL) containing triethylamine (42.2 mL, 158 mmol). After a 5 h reaction time, the predescribed workup was applied and 5.45 g (61%) of **27** was obtained as a colorless oil; ^2H NMR (76.8 MHz, $CHCl_3$) δ 5.53 (80% d_1; 100% *Z*).

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