Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 2093–2106

TETRAHEDRON:
ASYMMETRY

2-Lithio-*N*-BOC-thiazolidines as chiral acyl anion synthons: evaluation of facial stereoselectivity in the addition of chiral organolithiums to aldehydes

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Received 23 February 2000; accepted 6 April 2000

Abstract

Deprotonation of *N*-BOC-thiazolidines having an isopropyl group in the 4- or 5-position affords chiral organolithiums that add to aldehydes in excellent yields. The relative and absolute configurations at both new stereocenters of the major and minor isomers were deduced. Mechanistic considerations suggest that each organolithium adds with a high degree of diastereoselectivity. We also demonstrated, as proof of principle, that further elaboration of the addition products into α-hydroxyaldehydes and glycols can be achieved. © 2000 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Nearly 50 years ago, several investigators began to probe the reasons for stereoselectivity in the addition of achiral nucleophiles such as organomagnesium and organolithium reagents to the diastereotopic faces of carbonyls having a proximal stereocenter.[1–3] The theory that evolved out of these early efforts, now known generically as 'Cram's rule', has undergone nearly continuous refinement ever since. But what about the opposite possibility for creating diastereomeric transition states: the addition of an organometallic having a stereogenic metal-bearing carbon to enantiotopic carbonyl faces? The past 20 years has seen a surging interest in the chemistry of functionalized organometallics such as α-aminoorganolithiums and -organomagnesiums, and the stereoselectivity (or more commonly with lithium, the lack thereof) in additions of such compounds to carbonyls has recently been reviewed.[4,5] This report details the initial phase of an investigation into the selectivity of functionalized organolithiums to prochiral carbonyls, and is based on the Corey–Seebach reaction.

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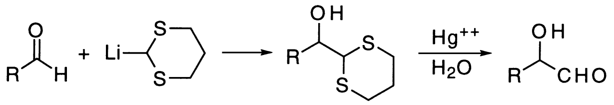
PII: S0957-4166(00)00154-3

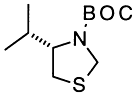
The conversion of an aldehyde to a homologated α-hydroxyaldehyde became possible by the two-step sequence of lithiodithiane addition and hydrolysis (Eq. (1)), the Corey–Seebach reaction, developed in the 1960s and first reviewed over 30 years ago.[6,7] This sequence creates a stereocenter, and we have undertaken an investigation into the possibility of rendering the reaction stereoselective by substitution of a chiral 'acyl anion' for the 2-lithiodithiane.



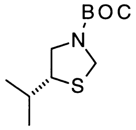
(1)

The addition of chiral organolithiums to enantiotopic carbonyl faces is usually not very selective,[4] so a major reason for undertaking this study was to try to determine the extent to which steric bulk in a chiral organolithium could be used to influence selectivity. In fact, although his purpose was not the same as ours, Eliel showed that lithiation of chiral oxathianes, and *N*-acyloxazines could be added to prochiral aldehydes many years ago, but the enantiofacial selectivity was zero.[8–13] Our thought was to replace one of the dithiane sulfurs with a nitrogen, whose trivalency allows placement of a bulky substituent adjacent to the carbanionic carbon. Also, Beak has shown that *tert*-butoxycarbonyl (BOC) group activates the position α to nitrogen in heterocycles toward deprotonation,[14] providing a configurationally stable, 'dipole-stabilized anion', which reacts with carbonyls to afford addition products in good yields.[14,15] The second sulfur was retained for its ability to constrain the C–Li bond stereoelectronically,[16] and also to help stabilize the carbanion. A stereocenter in the ring would render the heterocycle chiral, and would hopefully constrain the carbanion to a single configuration due to a diastereomeric bias. Finally we knew that, although lithiated piperidines show little diastereoselectivity in additions to aldehydes,[15] there was reason to hope that five-membered heterocycles might be better, since Meyers, Seebach, and Sanner had reported variable, but sometimes high selectivity in additions of lithiated pyrrolidine formamidines and *N*-BOC-imidazolidines to benzaldehyde.[17–21]

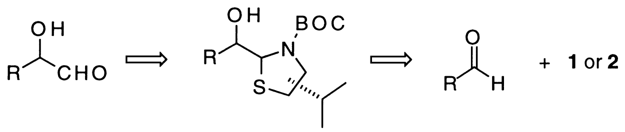
As chiral acyl anion synthons, we therefore chose to examine *N*-BOC-thiazolidines **1** and **2**, as their 2-lithio derivatives, via the strategy shown in Scheme 1. Based on the stereoelectronic considerations discovered in the Corey–Seebach reaction,[16,22–24] and the ability of the BOC group to activate nitrogen heterocycles toward deprotonation as well as offer rigidity via chelation,[14] we hoped that after lithiation, thiazolidines **1** and **2** would provide a chiral nucleophile that could distinguish enantiotopic faces of simple aldehydes well enough to be synthetically useful. In a related strategy, Dondoni used thiazoles in a carbohydrate homologation, through the sequence shown in Eq. (2) (R* is the carbohydrate moiety), which is stereoselective by virtue of Cram's



1

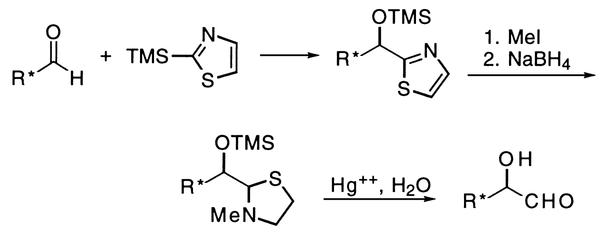


2

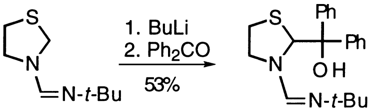


Scheme 1.

rule.[25] Note that in this protocol, the thiazole is reduced to a thiazolidine that serves as a latent carbonyl via the *S*,*N*-acetal functional group. Also relevant is an early report from Meyers that achiral thiazolidine formamidines can be metalated at the 2-position and added to benzophenone (Eq. (3)).[18]

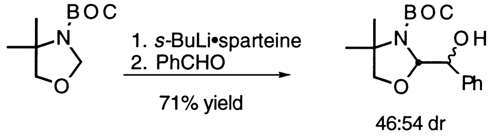


(2)

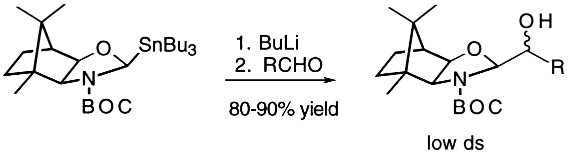


(3)

Recent efforts toward a similar goal utilized *N*-BOC-oxazolidines, lithiated by either deprotonation[26] or tin–lithium exchange.[27,28] In the first case (Eq. (4)), sparteine effected enantioselective deprotonation, but no diastereoselectivity was observed in the addition. After separation, it was shown that each diastereomer was enantiomerically enriched (88–90% ee). Some improvement in diastereoselection was obtained after transmetalation with $MgBr_2$, albeit with some loss of enantioselectivity.[26] Transmetalation from lithium to magnesium to improve diastereoselectivity was used by Seebach in the mid 1980s,[29,30] and subsequently by us,[5,31–35] for similar purposes. In the second case, transmetalation produced a single diastereomer of the organolithium, but a low diastereoselectivity was observed (Eq. (5)).[28] In this case, the authors showed that a strategy employed some time ago by Eliel[36] could be used to advantage: oxidize the carbinol epimers to a ketone, then effect a highly selective hydride reduction via Cram's rule selectivity.



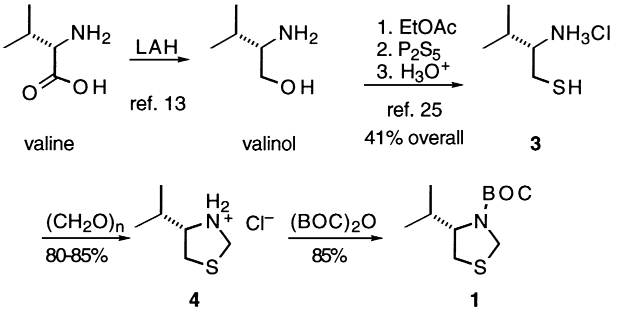
(4)



(5)

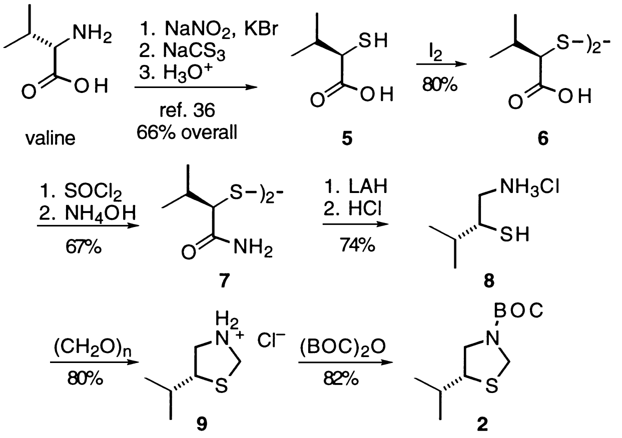
2. Thiazolidine synthesis

The synthesis of **1** is outlined in Scheme 2. Valinol[37] was converted to (*S*)-2-amino-3-methyl-1-butanethiol by the method of Handrick;[38] condensation with formaldehyde gave thiazolidine **4**, and addition of the BOC group afforded **1** in better than 60% yield for the two steps.



Scheme 2.

For the synthesis of **2** (Scheme 3), valine was converted to (*R*)-2-mercapto-3-methylbutanoic acid **5** by the method of Kurth.[39] Oxidation to the disulfide **6** was followed by conversion to the amide, **7**, and reduction to give (*R*)-1-amino-3-methyl-2-butanethiol, **8**, isolated as the hydrochloride salt. Condensation with formaldehyde and acylation as above afforded **2**.



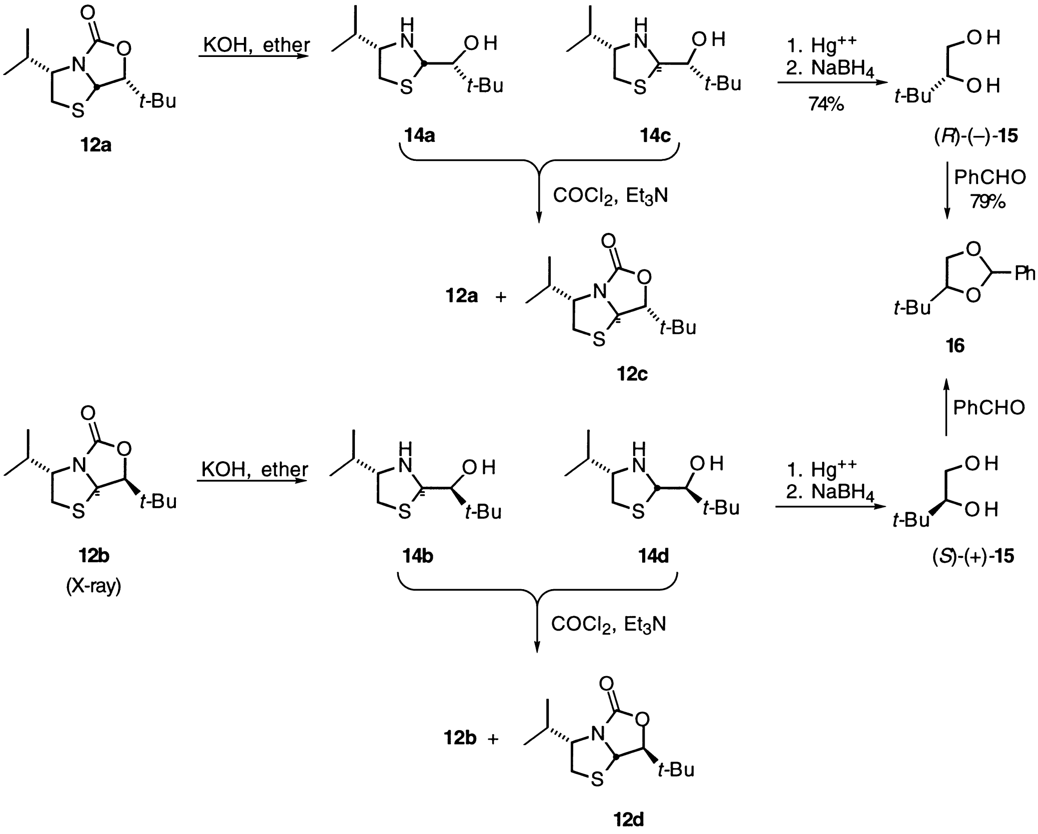
Scheme 3.

3. Additions and stereochemical analysis

Lithiation of **1** occured smoothly at –78°C, and quenching of the anion with deuteriomethanol or trimethylsilyl chloride afforded single diastereomers of **1**-*d* and **10** (Table 1). Quenching of the anion with benzaldehyde, pivaldehyde, and cyclohexanecarboxaldehyde afforded addition products **11**–**13** in excellent yields, as summarized in Table 1. In the aldehyde additions, only two of the four possible stereoisomers were formed in each case with 70% diastereoselectivity for the major isomer. The products from addition of pivaldehyde and cyclohexanecarboxaldehyde cyclized to form oxazolidinones **12** and **13**, respectively, while the benzaldehyde adduct (**11**) did not.

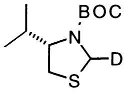
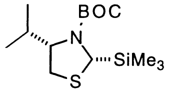
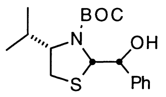
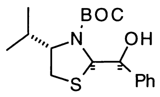
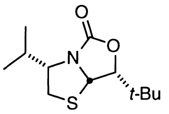
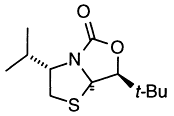
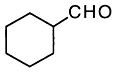
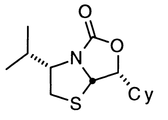
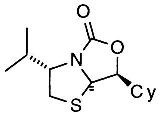
The relative and absolute configurations of the two obtained diastereomers of pivaldehyde adduct **12** (among the four possible) were established as outlined in Scheme 4. The oxazolidinones

12a and **12b** were separated, and although **12a** was an oil, **12b** was crystalline and its structure was established by X-ray crystallography. The two oxazolidinones were then hydrolyzed to aminoalcohols **14a**,**b**.[40] In both cases, approximately 30% of additional stereoisomers were obtained, **14c**,**d**, whose configurations were deduced from the following evidence. Cyclization of the **14a**,**c** mixture with phosgene afforded **12a** and a third oxazolidinone, **12c**. Similarly, the **14b**,**d** mixture provided **12b** and the fourth oxazolidinone, **12d**. Mercuric ion assisted hydrolysis[41] of the thiazolidinone rings of the **14a**,**c** and **14b**,**d** mixtures afforded 3,3-dimethyl-2-hydroxybutanal, which was reduced to the glycol with sodium borohydride for comparison with specific rotations in the literature (the *R* enantiomer is levorotatory[42]). In this way, it was established that (*R*)-(–)-**15** ($[\alpha]_D$ –24.4, *c* 0.75, CHCl$_3$) was obtained from the **14a**,**c** mixture whereas (*S*)-(+)-**15** ($[\alpha]_D$ +25.3, *c* 1.34, CHCl$_3$) was produced from the **14b**,**d** mixture. Enantiomeric purities were determined accurately by cyclization to dioxolanes **16** with benzaldehyde (obtained as a mixture of *cis* and *trans* diastereomers) and NMR analysis using the chiral shift reagent Eu(hfc)$_3$, as reported by Eliel.[43] This analysis indicated that the dioxolanes were enantiomerically pure (er≥95:5), which meant that the **14a**,**c** and **14b**,**d** pairs were epimeric at C-2 of the thiazolidine ring. Note that this epimerization, caused by the unsolvated KOH in ether during the oxazolidinone hydrolysis, does not affect the enantiomer ratio of the ultimate products, e.g. **15**. The relative and absolute configurations of **11** and **13** (Table 1) are assigned by analogy.



Scheme 4.

Table 1
Lithiation/electrophilic substitution of **1** (all reactions in THF)

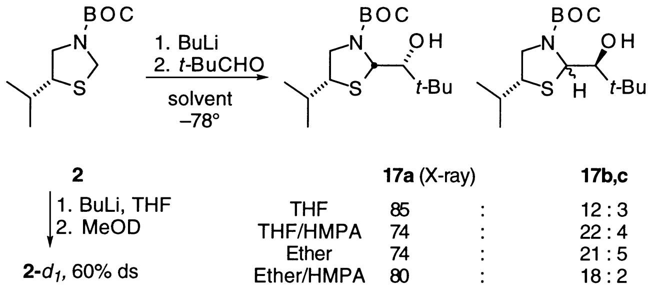
E^+	% Yield[a]	Product(s)[b]	
MeOD	95	 single diastereomer **1**-*d*	
Me_3SiCl	71	 single diastereomer configuration tentative **10**	
PhCHO	87	 **11a**	 **11b**
		70 : 30[c]	
tert-BuCHO	83	 **12a**	 **12b**
		70 : 30	
	83	 **13a**	 **13b**
		70 : 30	

a Yield of analytically pure products

b Ratio determined by NMR, unless otherwise noted

c Ratio determined by capillary GC

The lithiation of thiazolidine **2**, and its addition to pivaldehyde were studied for comparison to the results obtained with **1**, and are summarized in Scheme 5. In short, the selectivity for the major isomer went up a little, but now three diastereomers were observed. The relative and absolute configuration of the major isomer, **17a**, was established by X-ray crystallography. The relative configurations of the two minor diastereomers were not determined, but the absolute configuration at the carbinol carbons was established as follows. Hydrolysis of the thiazolidine alcohols **17a**–**c**, reduction, and dioxolane formation as outlined in Scheme 4 indicated that the glycols had an er of 82:18, within experimental error of the 85:15 ratio observed for the carbinol epimers in **17a**:**17b**,**c**. Thus, both of the minor diastereomers had to have come from diastereomers that were epimeric at the carbinol carbon, and which produced the enantiomeric glycol, as illustrated in **17b**,**c**. Changing solvent or adding HMPA did not improve the stereoselectivity of the addition.



Solvent	17a (X-ray)		17b,c
THF	85	:	12 : 3
THF/HMPA	74	:	22 : 4
Ether	74	:	21 : 5
Ether/HMPA	80	:	18 : 2

Scheme 5.

4. Discussion

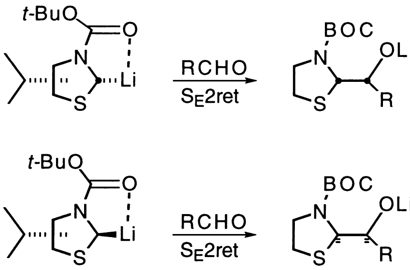
From a synthetic standpoint, the addition of a lithiated thiazolidine to an aldehyde is a viable alternative to lithiated dithianes as a homologation strategy, for addition to both enolizable and non-enolizable aldehydes. Furthermore, unmasking the thiazolidine is readily achieved.

In analyzing the steric course of the process, one critical question is the configuration of the carbanionic carbon in the lithiated thiazolidines, and the configurational stability of same. Although there are examples of inversion of configuration of chiral organolithiums adding to some electrophiles,[44–46] previously recorded examples are in acyclic, benzylic systems. The stereoelectronic requirement of the dipole-stabilization by the BOC group is severe: the Li–C–N–C=O atoms are coplanar, making the lithium pseudo equatorial in a heterocycle, and invertive alkylation impossible. Therefore, in cyclic systems such as pyrrolidines, electrophilic quench occurs with retention when a polar mechanism is operative.[47–49] On the basis of these precedents, we assume that the electrophilic substitution at C-2 of the thiazolidine takes place with retention of configuration ($S_E2$ret).[50]

We have only evaluated configurational stability indirectly. Deprotonation of **1** and electrophilic substitution by protonation or silylation affords only one diastereomer, indicating that only one diastereomer of organolithium Li-**1** is present, and that it is configurationally stable on the timescale of that reaction. In contrast, there are two diastereomers found when Li-**2** is protonated. Since there are two potentially stereoselective reactions (deprotonation and electrophilic quench), these data are uninformative about the configurational stability of Li-**2**. Reaction of either Li-**1** or Li-**2** with aldehydes, which would be a slower reaction, gives products of addition to pivaldehyde by both organolithium diastereomers of Li-**1** and Li-**2** (Table 1 and Scheme 5), indicating epimerization of the organolithium on this timescale. Conceivably, the epimerization of the organolithium could be catalyzed by the electrophile, but this is speculative at this point.

Nevertheless, it appears that the reactions described herein are highly stereoselective, as illustrated in Scheme 6. Specifically, it appears that each epimer of each organolithium, Li-**1** and Li-**2**, adds predominantly or exclusively to give a single relative configuration.

With the assumption of retentive substitution at the lithium-bearing carbon, we can propose likely transition structures, illustrated in Fig. 1, that explain the relative and absolute configurations of the major products from both lithiated thiazolidines. First note that chelation of the lithium by the BOC group produces a [3.3.0] bicyclic system, in which the least hindered (convex) face is the



Scheme 6.

location of the hydrogen at C-2. In the structure on the left, having the *S* configuration at C-2 of the thiazolidine, approach of the electrophile toward the convex face leads to the correct absolute configuration (at C-2 of the thiazolidine) for the major isomers in additions of both Li-**1** and Li-**2**. If the alkyl group of the aldehyde is oriented *anti* to the bulky BOC group and *syn* to the sulfur (as illustrated), the correct relative configuration (about the newly formed bond) is achieved. The structure on the right accounts for the minor product, arising from approach to the convex face of the *R* organolithium. Note that the tilt of the electrophile away from R^1 and R^2 on the thiazolidine results in practically no interaction between the electrophile and the isopropyl of either **1** or **2**. Again, if the aldehyde alkyl group is oriented *anti* to the BOC group, the correct relative configuration about the newly formed bond is achieved. Indeed, these two transition structures account for both the products in the addition of Li-**1** and two of the three addition products of Li-**2**. In the latter case, the third product is produced by reversing the aldehyde face in the structure on the left.

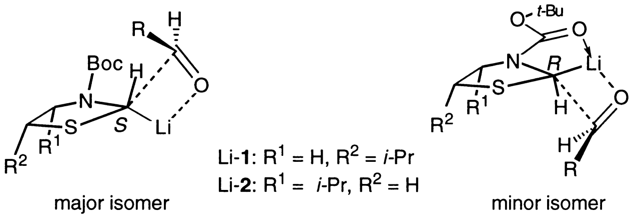


Figure 1.

This analysis assumes that the organolithium is monomeric, and that the addition proceeds through a four-membered ring transition state similar to that calculated for the addition of methyllithium to formaldehyde.[51] Addition via an open dimer or mixed aggregate cannot be discounted, however.[52] Rather subtle effects must govern the relative stability of these transition structures, including interplay of stereoelectronic forces similar to the anomeric effects observed in lithiodithianes,[16,22–24] $A^{1,3}$-strain around the amide, and torsional strain in the five-membered ring.

These results are very encouraging when viewed in the light of the precedents cited in the introduction. In the case of Li-**1**, it appears likely that both *R* and *S* organolithium isomers are present, and that each adds to the aldehyde with near 100% stereoselectivity. The other ring system, **2**, is nearly as selective. When these observations are combined with the methods outlined in Eqs. (4) and (5) for stereoselective lithiation, it seems a highly selective organolithium nucleophile could be in hand after further study.

5. Summary

Substituted, 2-lithio-*N*-BOC-thiazolidines add to both enolizable and non-enolizable aldehydes in excellent yield and good stereoselectivity. The steric course of the addition can be rationalized on steric grounds for the major products. This report also establishes proof of principle that the addition products can be hydrolyzed to α-hydroxy aldehydes and glycols in good yield, providing a foundation for further refinement of a chiral acyl anion synthon based on thiazolidine chemistry and a more selective lithiation methodology.

6. Experimental

All reactions were done under an atmosphere of nitrogen; ethereal solvents were distilled under a nitrogen atmosphere from sodium benzophenone ketyl. NMR spectra were recorded at 400 MHz for protons and 100 MHz for carbon, in $CDCl_3$ unless otherwise noted. Mass spectra were obtained in DCI or FAB mode on a single-stage quadropole instrument. Melting points are uncorrected. X-Ray data have been deposited with the Cambridge Crystallographic Database.

6.1. (S)-(+)-4-Isopropylthiazolidine hydrochloride, ***4***

A solution of **3**[38] (3.75g, 22.6 mmol) and paraformaldehyde (0.678, 22.6 mmol) in benzene were refluxed with a Dean–Stark trap for 6 h. The mixture was cooled to room temperature and the solid product was collected by filtration. The product was purified by recrystallization from acetonitrile (80–85% yield). $[\alpha]_D$ +47, (*c* 0.6, EtOH). ^1H NMR $CDCl_3$) 1.05 (3H, d), 1.06 (3H, d), 1.90 (1H, m), 3.17 (1H, t), 3.24 (1H, dd), 3.49 (1H, dd), 4.21 (2H, dd). ^{13}C NMR ($CDCl_3$) 20.6, 21.2, 31.6, 37.0, 49.2, 71.3. Anal. calcd for $C_6H_{14}ClNS$: C 42.99, H 8.36. Found: C 42.87, H 8.43. MS (for $C_6H_{13}NS$, MH^+): 132.

6.2. (S)-(+)-4-Isopropylthiazolidine-3-carboxylic acid tert*-butyl ester,* ***1***

4-Isopropylthiazolidine hydrochloride **4** (16.55 g, 100 mmol) and triethylamine (20.4 g, 200 mmol) were added to a flask containing 200 mL methylene chloride and 100 mL water. Di-*t*-butyl dicarbonate (20.8 g, 100 mmol) in methylene chloride (50 mL) was added to this solution. The mixture was stirred at room temperature for 4–6 h. When the reaction was over, as indicated by TLC, the two layers were separated. The organic layer was washed with water (10 mL) and brine (10 mL), then dried over magnesium sulfate and concentrated. The colorless liquid product was purified by flash chromatography (hexane/ethyl acetate, 20/1). $[\alpha]_D$ +128.6, (*c* 1, CH_2Cl_2). ^1H NMR ($CDCl_3$) 0.88 (3H, d), 0.94 (3H, d), 1.45 (9H, s), 1.98 (1H, m), 2.87 (1H, dd), 3.01 (1H, dd), 4.04 (1H, d), 4.15 (1H, br), 4.83 (1H, br). ^{13}C NMR ($CDCl_3$) 18.9, 19.1, 27.2, 28.1, 30.2, 47.7, 65.0, 80.1, 154.0. IR: (neat) 2940, 2900, 2840, 1690, 1450, 1300–1400 (br), 1260, 1150, 1100, 870, 750 cm^{-1}. MS (M^+): 231. Anal. calcd for $C_{11}H_{21}NO_2S$: C 57.14, H 9.09. Found: C 57.33, H 9.11.

6.3. (R)-(+)-2-((R)-1-Carboxy-2-methyl-propyldisulfanyl)-3-methylbutyric acid, **6**

To 14.82 g (0.11 mol) of sulfide **5**[39] in ether was added iodine (16.65 g, 0.13 mol). The mixture was stirred overnight at room temperature. Saturated sodium thiosulfate solution was added dropwise to the reaction until the brown color disappeared. The aqueous layer was extracted with ether (2×50 mL). The combined organic layers were washed with brine (20 mL), dried over magnesium sulfate and concentrated in vacuo to give a yellow liquid product, which solidified on standing. Recrystallization from hexane gave 12.5 g (80% yield). $[\alpha]_D$ +7.78 (*c* 0.45, CH_2Cl_2). ^1H NMR ($CDCl_3$) 1.08 (12H, m), 2.19 (2H, m), 3.45 (2H, d). ^{13}C NMR ($CDCl_3$) 19.7 (2C), 30.5, 62.8, 178.5. Anal. calcd for $C_{10}H_{18}O_4S_2$: C 45.11, H 6.77. Found: C 44.89, H 6.77. M^+: 266. IR (CH_2Cl_2) 1700 cm^{-1}.

6.4. (R)-(+)-2-((R)-1-Carbamoyl-2-methylpropyl-propyldisulfanyl)-3-methylbutyramide, 7

Thionyl chloride (17.4 mL, (239 mmol) and disulfide acid **6** (15 g, 56.39 mmol) were stirred overnight at room temperature. The unreacted thionyl chloride was removed under aspirator pressure, then the liquid acid chloride remaining in the flask was dissolved in 30 mL THF and treated slowly with 200 mL of ammonium hydroxide solution (28–30%) at 0–5°C. The mixture was kept at 0–5°C for 30 min. The white solid amide product was collected by filtration and purified by recrystallization from ethanol–water solution (10.0 g, 67%). $[\alpha]_D$ +339 (*c* 0.1, DMSO). Mp: 202.0–203.0°C. ^1H NMR ($CDCl_3$/DMSO) 0.92 (6H, d, J = 6.0), 0.97 (6H, d, J = 6.0), 1.94 (2H, m), 3.20 (2H, d, J = 8.4), 7.10 (2H, br), 7.42 (2H, br). ^{13}C NMR 20.3 (2C), 30.0, 61.7, 173.0. Anal. calcd for $C_{10}H_{20}N_2O_2S_2$: C 45.50, H 7.6. Found: C 45.53, H 7.57. MH^+: 265.

6.5. (R)-(+)-1-Amino-3-methylbutane-2-thiol hydrochloride, **8**

Lithium aluminum hydride (1.979 g, 52 mmol) was suspended in THF (100 mL) at 0°C and amide **7** (5.500 g, 21 mmol) was slowly added to it, portionwise. The mixture was then refluxed overnight. After cooling the mixture to 0°C, the mixture was diluted with 100 mL of ether and then slowly quenched with water (10 mL). The mixture was acidified with dilute sulfuric acid (5%) and then adjusted to pH = 8 with powdered sodium carbonate, followed by the addition of 50 mL of 25% potassium sodium tartrate solution. The organic layer was separated. The aqueous layer was continuously extracted with ether over 24 h. The organic layers were combined and dried over anhydrous sodium carbonate. After filtration, the organic solution was treated with a stream of HCl gas. The white solid product was collected by filtration (1.85 g, 74% yield). $[\alpha]_D$ +6.75 (*c* 0.8, H_2O). Mp: 214°C (d). ^1H NMR (D_2O) 0.76 (3H, d, J = 6.8), 0.82 (3H, d, J = 6.8), 1.78 (1H, m), 2.80 (1H, m), 2.81 (1H, m), 3.64 (1H, d, J = 9.6). ^{13}C NMR (DMSO) 17.2, 21.0, 30.7, 44.5, 44.6. Anal. calcd for $C_5H_{14}ClNS$: C 38.60, H 9.00. Found: C 38.68, H 9.06. MS (for $C_5H_{13}NS$, MH^+) 120.

6.6. (R)-(+)-5-Isopropylthiazolidine hydrochloride, **9**

A mixture of aminothiol hydrochloride **8** (2.27 g, 14.5 mmol) and paraformaldehyde (0.44 g, 14.5 mmol) in benzene (50 mL) were refluxed overnight. The benzene was removed by evaporation to give the crude product which was recrystallized from acetonitrile (1.96 g, 80%). Mp: 145–146°C. $[\alpha]_D$ +78.13 (*c* 0.75, H_2O). ^1H NMR ($CDCl_3$) 1.05 (3H, d, J = 6.8), 1.06 (3H, d, J = 6.0), 1.92 (1H, m), 3.17 (1H, t, J = 12), 3.52 (1H, dd, J_1 = 9.0, J_2 = 7.2), 3.79 (1H, dd, J_1 = 11.6, J_2 = 6.8), 4.16 (2H, dd, J_1 = 18.8, J_2 = 10.0). ^{13}C NMR (DMSO) 21.2, 21.6, 32.8, 47.9, 51.0, 53.9. Anal. calcd for $C_6H_{14}ClNS$: C 42.99, H 8.40. Found: C 42.90, H 8.45. MS (for $C_6H_{14}NS$, M^+) 131.

*6.7. (*R*)-(+)-5-Isopropylthiazolidine-3-carboxylic acid* tert-*butyl ester, **2***

The title compound was prepared from **9** by the same procedure used for the preparation of **1** from **4**. Pure **2** was obtained in 82% yield after flash chromatography (hexane/ethyl acetate, 30/1). $[\alpha]_D$ +7.3 (*c* 0.6, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) 1.00 (3H, d, J = 5.2), 1.02 (3H, d, J = 6.0), 1.47 (9H, s), 1.88 (1H, m), 3.23 (1H, dd, J_1 = 11, J_2 = 6.4), 3.33 (1H, dd, J_1 = 14, J_2 = 7.4), 3.80 (1H, m), 4.42 (2H, d), 4.45 (1H, br). Anal. calcd for $C_{11}H_{21}NO_2S$: C 57.14, H 9.09. Found: C 57.43, H 9.16. MS (MH^+): 232. IR (neat) 2805, 2780, 2720, 1620, 1310, 1080 cm^{-1}.

6.8. General procedure A for the metalation of N-*BOC-thiazolidines **1** and **2***

Under nitrogen, to a stirred solution of *N*-BOC-thiazolidine (0.5 M) in THF at –78°C, was slowly added 1.3 equiv. of *n*-BuLi (1.6 M in hexanes). The yellow solution was stirred at –78°C for 10 min. A slight excess of the electrophile was added dropwise by syringe. The reaction mixture was stirred for 20 min, then warmed to rt and quenched with brine. The aqueous layer was extracted twice with ether. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give the crude product.

*6.9. (2*R*,4*R*)-4-Isopropyl-2-trimethylsilylthiazolidine-3-carboxylic acid* tert-*butyl ester, **10***

The title compound was prepared as a white solid from **1** and trimethylsilyl chloride according to general procedure A. The pure product was obtained in 76% after purification by flash chromatography (hexane/ethyl acetate, 20/1). The absolute configuration at C-2 is tentative. $[\alpha]_D$ +132.3 (*c* 0.35, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) 0.16 (9H, s), 0.87 (3H, d), 0.88 (3H, d), 1.42 (9H, s), 1.90–2.00 (1H, m), 2.83 (1H, dd), 2.91 (1H, dd), 3.82 (1H, s), 4.10 (1H, m). ^{13}C NMR ($CDCl_3$) –0.03, 18.7, 19.2, 28.3, 30.2, 33.4, 53.2, 66.8, 19.9, 153.9. IR (CH_2Cl_2) 1690 cm^{-1}. Anal. calcd for $C_{14}H_{29}NO_2SiS$: C 55.45, H 9.57. Found: C 55.67, H 9.33. MS (M^+): 303.

*6.10. (2*S*,4*S*)-4-Isopropyl-2-((*R*)-1-hydroxy-1-phenylmethyl)-thiazolidine-3-carboxylic acid* tert-*butyl ester, **11a**, and (2*R*,4*S*)-4-isopropyl-2-((*S*)-1-hydroxy-1-phenylmethyl)-thiazolidine-3-carboxylic acid* tert-*butyl ester, **11b***

The title compounds were prepared in 87% yield according to general procedure A from **1** and benzaldehyde. The two diastereomers were obtained in 70:30 ratio and were not separated. The product was purified by flash chromatography (hexane/ethyl acetate, 10/1). The ^{1}H NMR data for each isomer was deduced by analysis of the spectrum of the mixture. Compound **11a**: ^{1}H NMR ($CDCl_3$) 0.77 (3H, d), 0.79 (3H, d), 1.48 (9H, s), 2.20 (1H, m), 3.50 (2H, m), 4.59 (1H, m), 5.15 (1H, d), 5.35 (1H, d), 7.19–7.30 (5H, m). Compound **11b**: ^{1}H NMR ($CDCl_3$) 0.85 (3H, d), 0.87 (3H, d), 1.48 (9H, s), 2.20 (1H, m), 3.50 (2H, dd), 4.59 (1H, m), 5.09 (1H, d), 5.25 (1H, d), 7.19 (5H, m). MS (MH^+): 338. IR: 3480, 3090, 3020, 1720 cm^{-1}. Anal. calcd for $C_{18}H_{27}NO_3S$: C 68.14, H 8.01. Found: C 68.34, H 8.02.

6.11. *(3*S*,6*R*,6a*S*)-6-*tert*-Butyl-3-isopropyl-tetrahydro-5-oxa-1-thia-3a-aza-pentalen-4-one,* ***12a****, and (3*S*,6*S*,6a*R*)-6-*tert*-butyl-3-isopropyl-tetrahydro-5-oxa-1-thia-3a-aza-pentalen-4-one,* ***12b***

The title compounds were prepared in 83% yield according to general procedure A from **1** and pivaldehyde. The two diastereomers were obtained in a 2.5:1 ratio and separated by flash chromatography (hexane/ethyl acetate, 20/1). Compound **12a**: (4*S*,5*R*,8*S*): $[\alpha]_D$ +204.3 (*c* 0.4, CH_2Cl_2). ^1H NMR ($CDCl_3$) 0.95–1.05 (16H, m), 3.00 (1H, dd), 3.18 (1H, dd), 4.06 (1H, m), 4.18 (1H, d, J = 2.0), 4.77 (1H, d, J = 2.0). ^{13}C NMR ($CDCl_3$) 19.0, 19.4, 24.4, 30.7, 34.1, 35.1, 64.5, 67.0, 88.1, 159.8. MS (MH^+): 244. IR (neat) 2920, 2830, 1740 cm^{-1}. Anal. calcd for $C_{12}H_{21}NO_2S$: C 59.26, H 8.64. Found: C 59.55, H 8.87. Compound **12b**: (4*R*,5*S*,8*S*): $[\alpha]_D$ +211.05 (*c* 0.4, CH_2Cl_2). ^1H NMR ($CDCl_3$) 0.99 (3H, d, J = 6.8), 1.00 (3H, d, J = 7.0), 1.15 (9H, s), 2.50 (1H, m), 2.90 (1H, m), 3.20 (1H, m), 3.95 (1H, m), 4.49(1H, d, J = 5.2), 4.92 (1H, d, J = 5.2). ^{13}C NMR ($CDCl_3$) 19.3, 19.5, 26.3, 32.0, 33.3, 36.4, 66.2, 68.7, 83.0, 160.8. MS (MH^+): 244. IR (CH_2Cl_2) 3015, 2968, 2942, 1746. Anal. calcd for $C_{12}H_{21}NO_2S$: C 59.26, H 8.64. Found: C 59.45, H 8.63. X-Ray crystallography data have been deposited with the Cambridge Crystallographic Database.

6.12. *(3*S*,6*R*,6a*S*)-6-Cyclohexyl-3-isopropyl-tetrahydro-5-oxa-1-thia-3a-aza-pentalen-4-one,* ***13a****, and (3*S*,6*S*,6a*R*)-6-cyclohexyl-3-isopropyl-tetrahydro-5-oxa-1-thia-3a-aza-pentalen-4-one,* ***13b***

The title compounds were synthesized from **1** and cyclohexane carboxyaldehyde according to general procedure A in 83% yield. The crude product was purified by flash chromatography (hexane/ethyl acetate, 35/1). The two diastereomers **13a** and **13b** were not separated. The ^1H NMR data for each isomer was deduced by analysis of the spectrum of the mixture. ^1H NMR ($CDCl_3$) **13a**: 0.95–1.90 (18H, m), 2.95 (2H, m), 4.05 (1H, m), 4.37, 4.95 (1H, dd). Compound **13b**: 0.95–1.90 (18H, m), 3.08 (1H, dd), 3.15 (1H, dd), 4.05 (1H, m), 4.29 (1H, dd), 4.76 (1H, dd). MS (M^+): 269. Anal. calcd for $C_{14}H_{23}NO_2S$: C 62.45, H 8.55. Found: C 62.29, H 8.87.

6.13. *(2*S*,5*R*)-2-((*S*)-1-Hydroxy-2,2-dimethylpropyl)-5-isopropyl-thiazolidine-3-carboxylic acid* tert*-butyl ester,* ***17a***

The title compound was prepared from **2** and pivaldehyde according to general procedure A and separated from diastereomers **17b,c** by flash chromatography (hexane/ethyl acetate, 30/1) and recrystallization (hexane/ethyl acetate, 30/1). ^1H NMR ($CDCl_3$) 0.93 (9H, s), 1.00 (3H, d, J = 6.8), 1.05 (3H, d, J = 6.8), 1.48 (9H, s), 1.77 (1H, m), 3.11 (2H, m), 3.49 (1H, m), 4.39 (1H, br), 5.43 (1H, br). ^{13}C NMR ($CDCl_3$) 21.3, 22.5, 26.4, 28.5, 33.1, 25.1, 52.1, 55.8, 65.4, 80.8, 146.6. Anal. calcd for $C_{16}H_{31}NO_3S$: C 60.57, H 9.78. Found: C 60.32, H 9.88. MS (MH^+): 318. X-Ray crystallographic data have been deposited with the Cambridge Crystallographic Database.

6.14. *General procedure B for the hydrolysis of oxazolidinones* ***12*****/*****13***

This procedure is based on Gassman's for the hydrolysis of tertiary amides.[40] The addition product (**12** or **13**) was dissolved in ether (0.5 g/mL). Under nitrogen, to this solution was added excess powdered KO*t*-Bu (6 equiv.) and H_2O (2 equiv.). The mixture was stirred at room temperature overnight then was poured on to ice water. The two layers were separated and the aqueous layer was warmed to 40°C and acidified with concentrated HCl. The acidic solution was extracted with ether three times to remove any neutral compounds. Then the aqueous layer was carefully neutralized with powdered sodium carbonate, and extracted with ether three times. The combined organic layer was dried over magnesium sulfate and concentrated.

*6.15. General procedure C for the synthesis of glycols from the aminoalcohols **14***

The first step in this procedure is based on Corey's procedure for the hydrolysis of dithianes.[41] To the solution of the aminoalcohol in 80% CH_3CN/H_2O was added mercuric(II) chloride (1.13 equiv.) in 80% CH_3CN/H_2O. A white precipitate formed. The mixture was stirred at room temperature for 6 h, then diluted with water. The precipitate was removed by filtration and the liquid was extracted with pentane/ether (1/1). The combined organic layers were treated with excess sodium borohydride and stirred for 2 h at rt. The reaction was quenched with water and the aqueous layer was extracted with chloroform. The combined organic layers were dried over magnesium sulfate. The solvent was evaporated in vacuo. The glycols were purified by flash chromatography (hexane/ethyl acetate, 3/7).

Acknowledgements

We thank Professor Mark Kurth for supplying the experimental details for the synthesis of **5**. Financial support by the National Institutes of Health and the Petroleum Research Fund is also gratefully acknowledged.

References

1. Curtin, D. Y.; Harris, E. E.; Meislich, E. K. *J. Am. Chem. Soc.* **1952**, *74*, 2901–2904.
2. Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 828–5835.
3. Prelog, V. *Helv. Chim. Acta* **1953**, *36*, 308–319.
4. Gawley, R. E. In *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI: Greenwich, CT, 1998; Vol. 3; pp. 77–111.
5. Gawley, R. E. In *Grignard Reagents: New Developments;* Richey, H. G., Ed.; Wiley & Sons: New York, 2000; pp. 139–164.
6. Seebach, D. *Synthesis* **1969**, 17–36.
7. Kolb, M. In *Encylopedia of Reagents for Organic Synthesis*; Paquette, L., Ed. 2-Lithio-1,3-dithiane. Wiley & Sons: Chichester, 1995; Vol. 5; pp. 2983–2989.
8. Ko, K.-Y.; Eliel, E. L. *J. Org. Chem.* **1986**, *51*, 5353–5362.
9. He, X.-C.; Eliel, E. L. *Tetrahedron* **1987**, *43*, 4979–4987.
10. He, X.-C.; Eliel, E. L. *J. Org. Chem.* **1990**, *55*, 2114–2119.
11. Ohwa, M.; Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1986**, *51*, 2599–2601.
12. Frye, S. V.; Eliel, E. L. *Tetrahedron Lett.* **1985**, *26*, 3907–3910.
13. Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1984**, *49*, 576–578.
14. Beak, P.; Lee, W.-K. *Tetrahedron Lett.* **1989**, *30*, 1197–1200.
15. Beak, P.; Lee, W. K. *J. Org. Chem.* **1990**, *55*, 2578–2580.
16. Abatjoglou, A. G.; Eliel, E. L.; Kuyper, L. F. *J. Am. Chem. Soc.* **1977**, *99*, 8262–8269.
17. Meyers, A. I.; Hoeve, W. T. *J. Am. Chem. Soc.* **1980**, *102*, 7125–7126.
18. Meyers, A. I.; Edwards, P. D.; Rieker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270–3276.
19. Sanner, M. A. *Tetrahedron Lett.* **1989**, *30*, 1909–1912.
20. Meyers, A. I.; Hellring, S. *Tetrahedron Lett.* **1981**, *22*, 5119–5122.
21. Pfammatter, E.; Seebach, D. *Liebigs Ann. Chem.* **1991**, 1323–1336.
22. Bernardi, F.; Csizmadia, I. G.; Mangini, A.; Schlegel, H. B.; Whangbo, M.-H.; Wolfe, S. *J. Am. Chem. Soc.* **1975**, *97*, 2209–2218.

23. Lehn, J.-M.; Wipff, G. *J. Am. Chem. Soc.* **1976**, *98*, 7498–7505.
24. Epiotis, N. D.; Yates, R. L.; Bernardi, F.; Wolfe, S. *J. Am. Chem. Soc.* **1976**, *98*, 5435–5439.
25. Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1989**, *54*, 693–702.
26. Kise, N.; Urai, T.; Yoshida, J. *Tetrahedron: Asymmetry* **1998**, *9*, 3125–3128.
27. Colombo, L.; Di Giacomo, M.; Brusotti, G.; Delogu, G. *Tetrahedron Lett.* **1994**, *35*, 2063–2066.
28. Colombo, L.; Di Giacomo, M.; Brusotti, G.; Milano, E. *Tetrahedron Lett.* **1995**, *36*, 2863–2866.
29. Seebach, D.; Syfrig, M. A. *Angew. Chem., Int. Ed. Engl.* **1984**, *3*, 248–249.
30. Seebach, D.; Hansen, J.; Seiler, P.; Gromek, J. M. *J. Organomet. Chem.* **1985**, *285*, 1–13.
31. Rein, K. S.; Chen, Z.-H.; Perumal, P. T.; Echegoyen, L.; Gawley, R. E. *Tetrahedron Lett.* **1991**, *32*, 1941–1944.
32. Rein, K. S.; Gawley, R. E. *Tetrahedron Lett.* **1990**, *31*, 3711–3714.
33. Rein, K. S.; Gawley, R. E. *J. Org. Chem.* **1991**, *56*, 1564–1569.
34. Zhang, P.; Gawley, R. E. *Tetrahedron Lett.* **1992**, *33*, 2945–2948.
35. Gawley, R. E.; Zhang, P. *J. Org. Chem.* **1996**, *61*, 8103–8112.
36. Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: Orlando, 1983; Vol. 2; pp. 125–155.
37. Dickman, D. A.; Meyers, A. I.; Smith, G. A.; Gawley, R. E. *Org. Synth.* **1990**, *Coll. Vol. VII*, 530–533.
38. Handrick, G. R.; Atkinson, E. R.; Granchelli, F. E.; Bruni, R. *J. Med. Chem.* **1965**, *8*, 762–766.
39. Kurth, M. J.; Tahir, S. H.; Olmstead, M. M. *J. Org. Chem.* **1990**, *55*, 2286–2288.
40. Gassman, P. G.; Hodgson, P. K. G.; Balchunis, R. J. *J. Am. Chem. Soc.* **1976**, *98*, 1275–1276.
41. Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553–3560.
42. Guette, J.-P.; Spassky, N. *Bull. Soc. Chim. Fr.* **1972**, 4217–4224.
43. Ko, K.-K.; Frazee, W. J.; Eliel, E. L. *Tetrahedron* **1984**, *40*, 1333–1343.
44. Hoppe, D.; Carstens, A.; Krämer, T. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1424–1425.
45. Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097–6108.
46. Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561–11570.
47. Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708–9710.
48. Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231–3239.
49. Bertini Gross, K. M.; Jun, Y. M.; Beak, P. *J. Org. Chem.* **1997**, *62*, 7679–7689.
50. Gawley, R. E. *Tetrahedron Lett.* **1999**, *40*, 4297–4300.
51. Kaufmann, E.; Schleyer, P. v. R.; Houk, K. N.; Wu, Y.-D. *J. Am. Chem. Soc.* **1985**, *107*, 5560–5562.
52. Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1993**, *115*, 11016–11017.