Stereoselectivities of Nucleophilic Additions to Cycloheptanones. Experimental and Theoretical Studies and General Purpose Force Field for the Prediction of Nucleophilic Addition Stereoselectivities

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Received September 3, 1997

The selectivities of nucleophilic additions of ethyl, vinyl, and ethynyllithium and Grignard reagents to a 2-(3′-phenylpropyl)cycloheptanone were investigated experimentally. In all cases, *cis*-cycloheptanol was formed preferentially (40:1−6:1). Theoretical studies were performed on the stereoselectivities of nucleophilic additions of hydride and ethynyllithium reagents to cycloheptanones. An empirical force field for transition states of hydride and ethynyl reagents was used for transition-state geometries and conformational searches. Quantum mechanical calculations on HLi addition to cycloheptanones were compared to the corresponding cyclohexanone calculations. These results show that the formation of 2-alkyl-substituted *cis*-cycloheptanols is preferred for all nucleophiles studied as a result of torsional and steric effects in the transition states of these reactions.

Introduction

The stereoselectivities of nucleophilic additions to cyclohexanones have been extensively studied both experimentally[2,3] and computationally,[4,5] and the origin of these selectivities has been the subject of recent intensive debate.[4−9] By contrast, the stereoselectivities of nucleophilic additions to cycloheptanones and larger cyclic ketones have not been studied systematically. We wish to report both experiments and calculations on nucleophilic additions to 2-substituted cycloheptanones that reveal a general pattern of stereoselectivity for such molecules. We also describe a transition-state force field, developed from studies described in a number of previous papers.[10−13] This force field has been incorporated into the MM2* force field in Macromodel and is now generally available for the prediction of the stereoselectivities of lithium aluminum hydride reductions and organometallic additions to ketones.

Background

We previously studied the stereochemistries of nucleophilic additions to carbonyl compounds computationally and reported quantitative support for the Felkin model for both acyclic and cyclic carbonyl compounds.[11−14] The stereoselectivity of nucleophilic additions to cyclohexanones substituted by relatively nonpolar substituents is influenced by two factors: (1) the steric interaction of the incoming group with 3,5-axial substituents and (2) the torsional strain of the incoming group with respect to all α-bonds.

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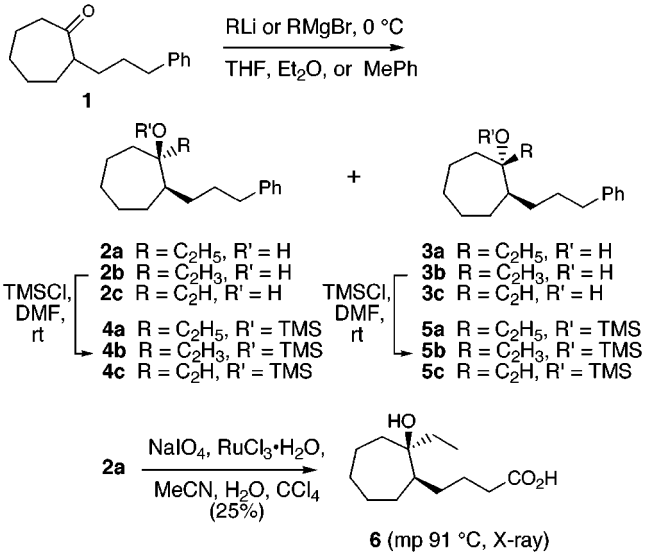
S0022-3263(97)01627-7 CCC: $15.00
Published on Web 04/30/1998

Scheme 1



Fewer studies have been reported for cycloheptanones. In an early application of ^{13}C NMR chemical shifts to the elucidation of stereochemistry, Christl and Roberts reported that the sole product produced (81% yield) from addition of MeLi to 2-methylcycloheptanone in refluxing ether was *cis*-1,2-dimethylcycloheptanol.[15a] The addition of vinylmagnesium bromide to 2-allylcycloheptanone has been reported to give a 98:2 mixture of two isomers; the major isomer was assumed to be the *cis*-alcohol.[15b] Addition of (*E*)-butadienyllithium to 2-butadienylcycloheptanone afforded a single stereoisomeric product, which was also assumed to be the *cis*-alcohol.[15c] Reductions of 2-methylcycloheptanone with $LiAlH_4$ (ds = 73:27), BH_3 (ds = 74:26), disiamylborane (ds = 64:26), dicyclohexylborane (ds = 97:3), di-3-pinanylborane (ds = 98:2), Na (ds = 56:44), and $Al(O\text{-}i\text{-}Pr)_3$ (ds = 65:35) afford predominantly *cis*-2-methylcycloheptanol.[16] Because of the conformational flexibility of cycloheptanones, it is not clear which factor controls these stereochemistries. In a benzocycloheptanone system, Mukherjee et al. predicted that equatorial attack will be preferred, and subsequent experimental studies confirmed this prediction.[17] The prediction was made with a force field described in this paper, and the results were rationalized by torsional effects.

It occurred to both of our groups that the stereoselective formation of *cis*-cycloheptanols might be a general phenomenon. This paper reports experimental and theoretical results that show that this is true.

Results and Discussion

Experimental Studies. The addition of five nucleophiles (ethyllithium, ethylmagnesium bromide, vinyllithium, vinylmagnesium bromide, and ethynyllithium) to 2-(3′-phenylpropyl)cycloheptanone (**1**) at 0 °C was studied in three solvents; THF, Et_2O, and toluene. Product ratios were determined by capillary GLC analysis after silylation of the alcohol products **2** and **3** with trimethylsilyl chloride (Table 1). In all cases, *cis*-cycloheptanol **2** was formed preferentially. The highest stereoselectivities (40:1) were observed for vinylmagnesium bromide (entries 7−9) and the lowest for ethynyllithium (entries 13−15). Stereoselection in general was highest in THF and lowest in toluene.

Table 1. Addition of Ethyl, Vinyl and Ethynyl Organometallics to Cycloheptanone 1

entry	organometallic[a]	solvent	yield,[b] %	*cis*:*trans*[c]
1	EtMgBr[d]	THF	76	24:1
2	EtMgBr[d]	Et_2O	63	13:1
3	EtMgBr[d]	MePh[e]	81	9:1
4	EtLi[d]	THF[e]	71	24:1
5	EtLi[d]	Et_2O	82	23:1
6	EtLi[d]	MePh[e]	72	14:1
7	CH_2=CHMgBr[f]	THF	78	39:1
8	CH_2=CHMgBr[f]	Et_2O[g]	85	41:1
9	CH_2=CHMgBr[f]	MePh[g]	84	31:1
10	CH_2=CHLi[f]	THF[e]	83	27:1
11	CH_2=CHLi[f]	Et_2O	87	19:1
12	CH_2=CHLi[f]	MePh[e]	80	15:1
13	HC≡CLi[h]	THF	77	8:1
14	HC≡CLi[h]	Et_2O	72	7:1
15	HC≡CLi[h]	MePh	76	6:1

[a] Organometallic nucleophiles were added dropwise to a 0.20−0.23 M solution of **1** at 0 °C. [b] Isolated yield of the mixture of stereoisomeric alcohols **2** and **3**. [c] Capillary GLC analysis of silyl ether derivatives **4** and **5**. FID detector response was assumed to be identical for isomer pairs. [d] 2 equiv of organometallic reagent was used. [e] Solution contains 8−10% of Et_2O. [f] 1 equiv of organometallic reagent was used. [g] Solution contains 8−10% of THF. [h] 5 equiv of the ethylenediamine complex was employed.

The ethynyl silyl ether stereoisomers **4c** and **5c** were separated by column chromatography and desilylated to provide pure samples of the corresponding alcohols **2c** and **3c**. These propargylic alcohols were chemically correlated, respectively, with **2b** and **3b** by reduction with $LiAlH_4$ and with **2a** and **3a** by catalytic hydrogenation. Stereochemical assignments were secured by single-crystal X-ray analysis of hydroxy acid **6**,[18] which was obtained by RuO_4 oxidation of **2a**.[19]

Theoretical Studies. Because seven-membered rings enjoy more conformational flexibility than their six-membered counterparts, cycloheptanone was optimized by employing a Monte Carlo conformational search[20] available in Still's Macromodel program.[21] A total of 1000 conformations were generated and subsequently minimized using the MM2* force field. The five unique conformers located in this search (**7**−**11**) are illustrated in Figure 1. The relative energies are given next to the structures. Conformer **10**, a chair with the carbonyl on the two-carbon stern fragment, was found to be the global

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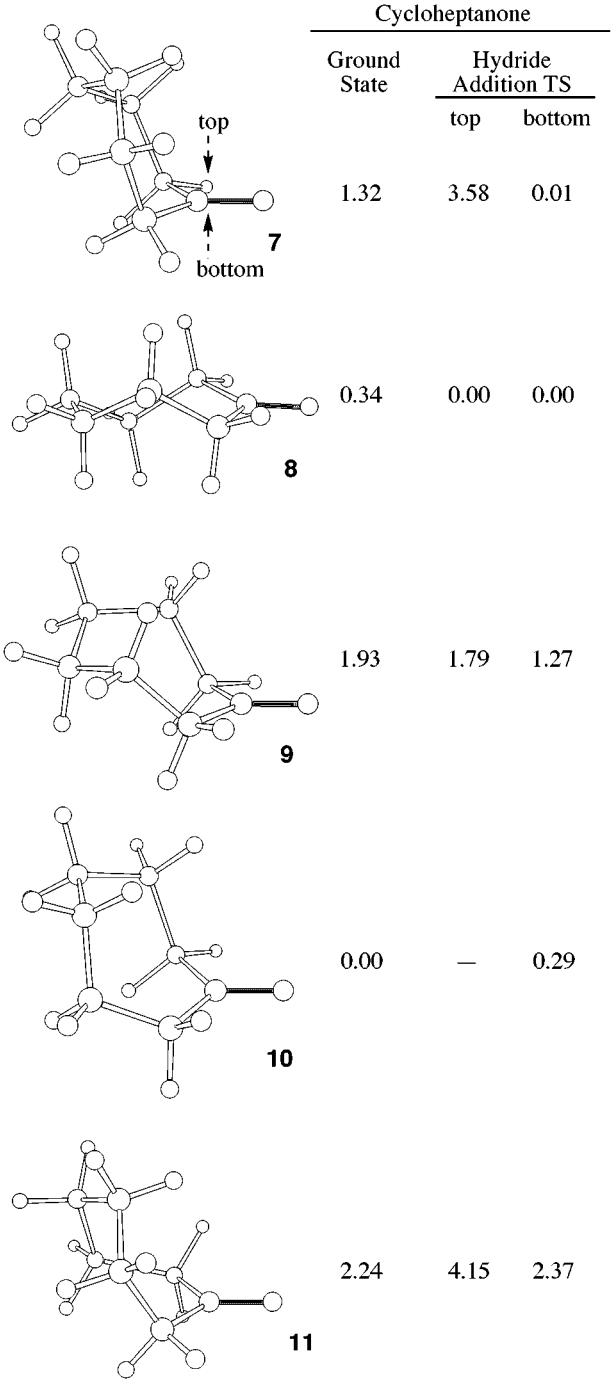

Figure 1. MM2* relative energies of cycloheptanone conformers and the MM2* relative energies of transition states for axial and equatorial attack by hydride on each of these conformers.

minimum. Conformer **8**, a twist conformer, is only 0.34 kcal/mol higher in energy. All of the other structures were higher in energy than **10** by more than 1.3 kcal/mol.

Transition structures for hydride addition to cycloheptanone were calculated with an MM2* version of the MM2 transition structure force field, which has been successfully applied to stereoselectivities of reductions of cyclohexanones,[11] 2-cyclohexenones,[12] cyclopentanones,[11] and benzocycloheptenones,[17] as well as Grignard and organolithium additions to highly sterically hindered cyclohexanones.[10] In the present study, this force field model was modified and adapted to be included as a special substructure within the MM2* force field present in Macromodel. The parameters are listed in the Appendix. Extensive testing verified that the MM2* implementation of the force field afforded reliable energies that closely paralleled those obtained using the original implementation using Allinger's MM2 program and force field.[11,12] The MM2* force field provides energies in close agreement with experimental data from the literature for a wide range of carbonyl compounds, including mono- and polycyclic cyclohexanones and cyclohexenones, cyclopentanones, and heterocyclic ketones.[12]

A Monte Carlo conformational search was performed as described above to locate the lower energy conformers available for hydride addition to the flexible cycloheptanone system. This search yielded nine unique conformers that lie within 4.2 kcal/mol of the global minimum. Because the axial and equatorial nature of the attack is not always apparent, we describe attack as "top" and "bottom" in the discussion. The two lowest energy conformers are virtually identical in energy; these are bottom hydride addition to **7**, and bottom (equivalent to top addition in this case by C_2 symmetry) hydride addition to **8**. Bottom approach of hydride to **10** also lies close in energy, only 0.3 kcal/mol above the global minimum. Finally, bottom addition to **9** is 1.3 kcal/mol higher in energy than the global minimum. Note that attempts to model top addition to **10** resulted in a conformational change to give conformer **8**; this is likely due to steric interactions with the methylene groups which shield **10** from top attack.

A methyl substituent at the C2 position of cycloheptanone significantly increases the number of conformations available to this substrate. In this case, Monte Carlo conformational searches were employed separately for hydride additions leading to *trans*- and *cis*-2-methylcycloheptanol products. The low-energy conformers are essentially derived from placing a methyl group at the carbonyl α positions on the conformers **7**−**11**. The six transition structures shown in Figure 2 represent the four lowest energy structures leading to cis products (**12**, **15**, **16**, and **17**), along with the two lowest energy structures leading to trans products (**13** and **14**). The enantiomeric pairs are depicted by a single enantiomer for the purpose of clarity. In all cases, the methyl takes the pseudoequatorial position. Structures **12** and **13** are derived from attack of hydride on opposite faces of conformer **8**, and they result in two of the most favorable transition structures leading to the cis and trans products, respectively. The energies of **12** and **16** are essentially equal, since the main difference between them is the position of the remote C4. The low-energy structure **12** has a Felkin-type arrangement[3,11] with *inside* methyl and anti methylene on the front side and *outside* methylene on the rear. Structure **13** has a less favorable *inside* methyl and *outside* methylene on the front side and nearly eclipsing conformation on the rear side. The source for this energy difference is due to both the torsional strain with C7−H and the steric hindrance from a pseudoaxial hydrogen introduced by the 2-methyl group in **13**.

Structures **14** and **15** correspond to top and bottom hydride attack, respectively, on conformer **9**. Structure **15** is more stable than **14** by 1.2 kcal/mol. Structure **9** is similar to benzocycloheptenone; both possess a ring that is more puckered than cyclohexanone. The calculated preference for pseudoequatorial (bottom of **9**) attack

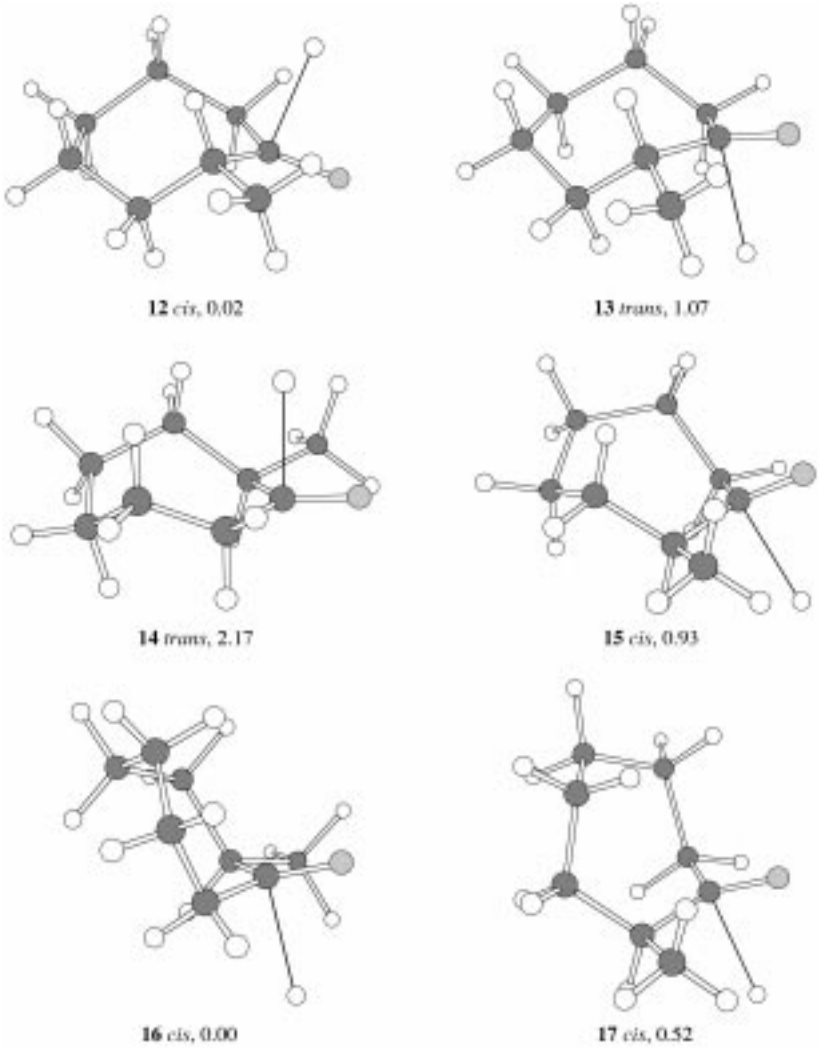

Figure 2. Favored transition structures for nucleophilic additions to 2-methylcycloheptanone. Structures **13** and **14** lead to trans product; structures **12**, **15**, **16**, and **17** lead to cis product.

of hydride is also similar to that of benzocycloheptenone; the latter was confirmed by experiments.[17] Structures **16** and **17** both correspond to the bottom hydride attack on conformers **7** and **10**, respectively. These have a Felkin-type arrangement (S (H) *outside*, M (Me) *inside*, L (CH_2) anti) and lead to the cis preference.[11]

To test the MM2* transition-state force field for its applicability to a cycloheptanone system, we performed ab initio calculations for LiH attack on **7**. The energy difference obtained is 3.8 kcal/mol by RHF/3-21G, 2.1 kcal/mol by RHF/6-31G*, and 2.3 kcal/mol by MP2/6-31G*//RHF/3-21G, favoring bottom attack on **7** (Figure 3). These results are comparable to the 3.6 kcal/mol difference from the MM2* force field (Figure 1). Ab initio calculations were also performed on the HLi addition to 2-methylcycloheptanone. We chose the transition structures **12** and **13**, which are the most favorable ones leading to the cis and trans products, respectively. The equatorial entry is favored by 1.1 kcal/mol by RHF/3-21G, 1.0 kcal/mol by RHF/6-31G*//3-21G, 0.7 kcal/mol by MP2/6-31G*//RHF/3-21G. Both the energy differencies and the transition structure conformations are similar to those from the MM2* force field (Figure 4).

The nucleophilic addition of lithium acetylide to **1** gave a mixture of the cis and trans alcohols in a ratio of 89:11−86:14 at 0 °C experimentally (entries 13−15 in Table 1). Recently, the MM2* transition-state force field developed for lithium aluminum hydride reduction was extended to the addition of acetylide anions to carbonyl compounds.[10] This force field was found to give rather accurate predictions for the diastereoselectivity of acetylide anion addition to the substituted cyclohexanones. Monte Carlo conformational searches were performed to locate the lowest energy conformers of **1** for the transition structure leading to **2c** and **3c**. The calculations predict that acetylide anion will prefer to attack in a trans fashion to afford the *cis*-cycloheptanol. The lowest energy transition structures **A** and **B** leading to the cis and the trans products are shown in Figure 5. **A** is favored over **B** by 1.4 kcal/mol. This amounts to a predicted ratio of 93:7 (cis:trans) at 0 °C. The main source for this difference can be seen in the dihedral angles with the vicinal hydrogens (A, 48°; B, 18°). **A** and **B** correspond to **16** and **13**, respectively. The transition structure corresponding to **12** is higher in energy than **A** by 0.13 kcal/mol. Although our calculation predicts the stereoselectivity of **1** with lithium acetylide correctly, the molecule **1** is so flexible that there may be many conformations accessible in the transition state. Consequently, we also performed Monte Carlo conformational searches for the transition structures of 2-methylcycloheptanone, as a model compound, for the reaction of **1**

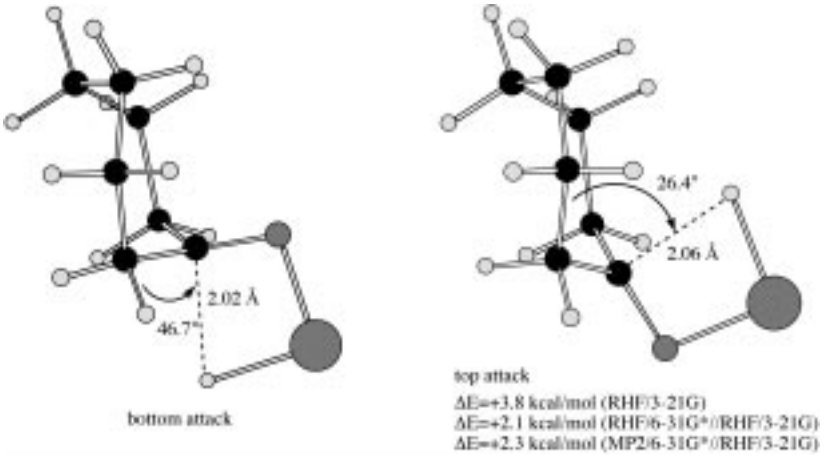

Figure 3. Ab initio transition structures of the LiH addition reaction on **7**.

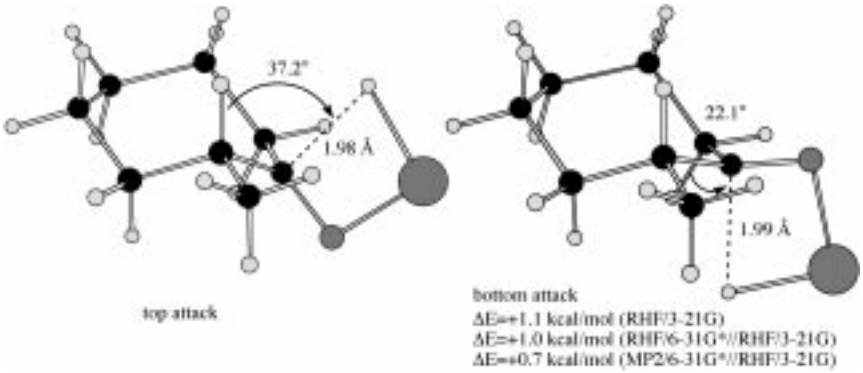

Figure 4. Ab initio transition structures corresponding to **12** and **13**, respectively.

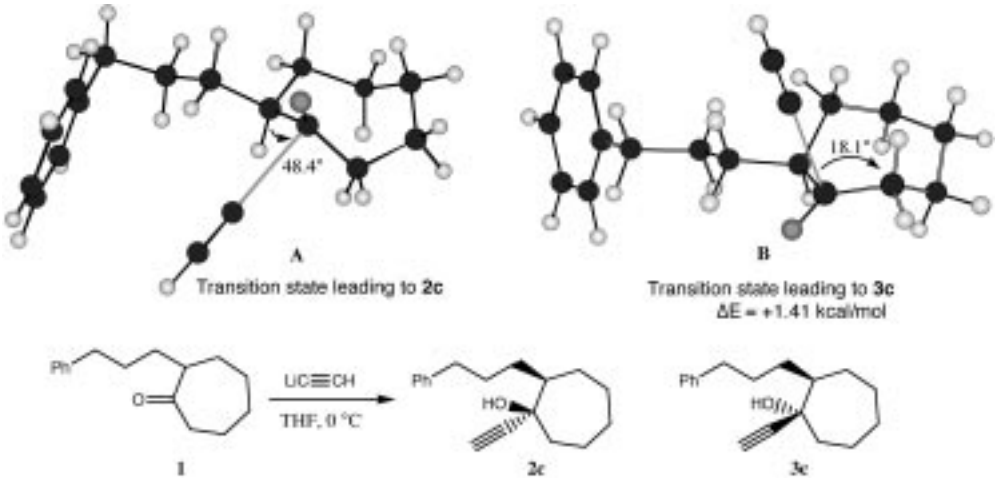

Figure 5. MM2* transition state models for lithium acetylide addition to **1**.

with acetylide anion. The lowest energy transition structures, **C** and **D**, leading to the cis and trans alcohols, **18** and **19**, respectively, are shown in Figure 6. The equatorial transition structure **C** is more stable than **D** by 1.1 kcal/mol, which corresponds to a product ratio **18**:**19** = 88:12 at 0 °C. We found 12 optimized transition structures leading to **18** and eight optimized transition structures leading to **19** within 3.0 kcal/mol of the global minimum transition structure. On the basis of a Boltzmann distribution including all transition structures within 3.0 kcal/mol, the product ratio is predicted to be 93:7. **C** and **D** correspond to **12** and **13**, respectively. **C** has a different cycloheptanone conformation from **A**. The transition structure corresponding to **A** is 0.19 kcal/mol less stable than **C**. In this case, the energy difference between **C** and **D** can be also due to the torsional effect (see Figure 6).

Conclusions

Nucleophilic additions of ethyl-, vinyl-, and ethynyllithium and Grignard reagents to a 2-alkyl-substituted cycloheptanone were performed experimentally. In all cases, *cis*-cycloheptanol was formed preferentially. The MM2* force field was applied to analyze nucleophilic attack of hydride and ethynyllithium on 2-methylcyclo-

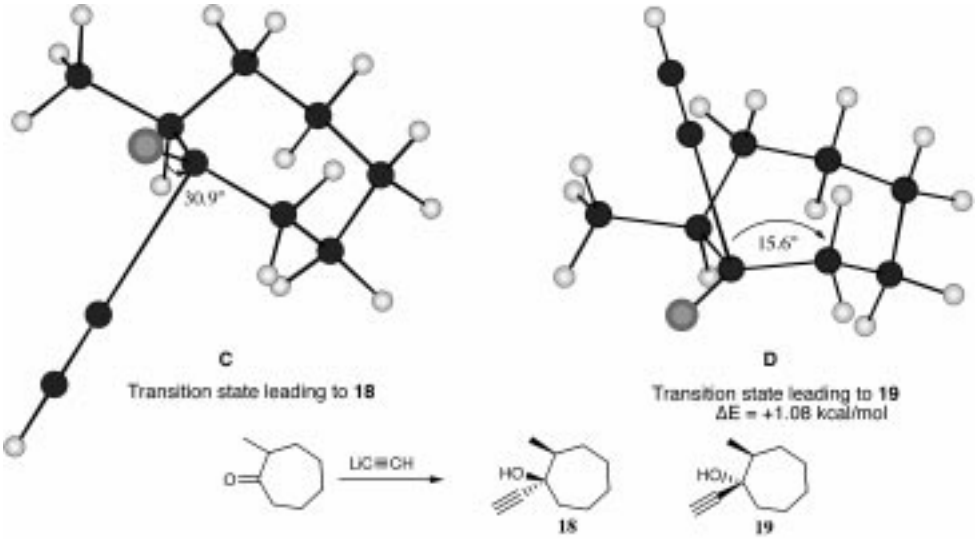

Figure 6. MM2* transition-structure models for lithium acetylide addition to 2-methylcycloheptanone.

heptanone and gave results comparable to those obtained from experiments and ab initio calculations. This success provides support for the proposal that the cis products from the nucleophilic attack on 2-alkyl-substituted cycloheptanones are favored due to torsional effects.

In this study, we observed higher selectivity when the size of the nucleophile is increased. With cyclohexanones this change results in a substantial decrease in the axial preference, with an equatorial approach being typically favored with alkyl and vinyl organometallics. With cycloheptanones, the preference for the cis product is increased as the size of the nucleophile increases. These trends result from a combination of steric repulsions and torsional effects in the transition state.

Experimental Section[22]

2-(3′-Phenylpropyl)cycloheptanone (1). Following the general procedures of Corey and Enders,[26] a THF solution (40 mL) of cycloheptanone *N*,*N*-dimethylhydrazone (13.9 g, 90.0 mmol) was deprotonated with LDA (1 M in THF, 99 mmol, −78 °C for 1 h and 0 °C for 1 h), a solution of 3-bromo-1-phenylpropane (19.7 g, 99.0 mmol) and THF (60 mL) was added at −78 °C, and the resulting colorless solution was allowed to warm to room temperature. Aqueous workup provided the alkylated hydrazone, which was dissolved in CH_2Cl_2 and cleaved with *m*-chloroperbenzoic acid (81%, 21.1 g, 99.0 mmol) at −78 °C as described to provide crude **1**. Flash column chromatography (silica gel, 5:1 hexanes−EtOAc) gave 10.0 g (40%) of pure **1**: >99% pure by GLC analysis; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25−7.28 (m, 2H), 7.16−7.19 (m, 3H), 2.60 (app dd, J = 12.9, 7.4 Hz, 2H), 2.38−2.52 (m, 3H), 1.82−1.86 (m, 4H), 1.72 (app dt, J = 15.5, 6.7 Hz, 1H), 1.59 (app pentuplet, J = 7.7 Hz, 3H), 1.27−1.41 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.3, 142.2, 128.3, 128.2, 125.6, 52.1, 42.6, 35.9, 31.9, 31.2, 29.4, 29.0, 28.4, 24.4 ppm; IR (film) 1700 cm^{-1}; MS (CI) *m*/*z* 231.1745 (231.1748 calcd for $C_{16}H_{23}O$, MH).

General Procedure for Reaction of Organometallic Reagents with Cycloheptanone 1. Preparation of (1*R,2*R**)-1-Ethynyl-2-(3′-phenylpropyl)-1-(trimethylsiloxy)cycloheptane (4c) and (1*R**,2*S**)-1-Ethynyl-2-(3′-phenylpropyl)-1-(trimethylsiloxy)cycloheptane (5c).** A solution of **1** (0.262 g, 1.11 mmol) and THF (5 mL) was cooled to 0 °C and added dropwise by cannula to a 0 °C solution of lithium acetylene−ethylenediamine complex (0.515 g, 5.54 mmol) and THF (5 mL). The resulting solution was allowed to warm to room temperature over 4 h , and after 12 h was quenched with aqueous NH_4Cl (20 mL). The aqueous phase was extracted with EtOAc (4 × 20 mL), and the combined organic layers were washed with brine (4 × 10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (10:3, hexanes−ether) to give 0.31 g (76%) of an inseparable mixture of **2c** and **3c** (6:1 by ^{1}H NMR analysis) as a colorless oil.

A sample of a comparable mixture of **2c** and **3c** (0.388 g, 1.51 mmol), TMSCl (0.411 g, 3.24 mmol), DMF (15 mL), and imidazole (0.55 g, 8.1 mmol) was maintained at room temperature for 12 h and then cooled in an ice−water bath and quenched with H_2O (20 mL). The resulting mixture was extracted with ether (50 mL), and the extracts were washed with brine (3 × 30 mL), dried ($MgSO_4$), and concentrated to give a yellow oil that GLC analysis showed was a 7:1 mixture of **4c** and **5c**, respectively. Separation by flash column chromatography (100:1 hexane−CH_2Cl_2) gave isomerically pure samples of **4c** (0.37 g, 74%) and **5c** (0.11 g, 22%). **4c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.29 (m, 2H), 7.16−7.71 (m, 3H), 2.66−2.71 (m, 1H), 2.57−2.63 (m, 1H), 2.38 (s, 1H, 2.08), 2.13−2.08 (dd, J = 14.3, 8.8 Hz, 1H), 1.26−1.83 (m, 14H), 0.19 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 143.1, 128.6, 128.4, 125.7, 90.1, 75.0, 72.0, 51.5, 43.7, 36.6, 31.6, 30.4, 28.8, 27.7, 26.1, 21.4, 2.1 ppm; MS (CI) *m*/*z* 329.2310 (329.2301 calcd for $C_{21}H_{33}OSi$, MH). **5c:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.30 (m, 2H), 7.17−7.21 (m, 3H), 2.60−2.65 (m, 2H), 2.49 (s, 1H), 1.93 (app ddd, J = 3.7, 2.8, 1.8 Hz, 2H), 1.22−1.81 (m, 13H), 0.17 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 128.4, 128.2, 125.5, 86.7, 76.5, 74.0, 51.5, 43.8, 36.3, 31.5, 29.9, 27.6, 27.0,

(22) Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium and benzophenone, while toluene was distilled from CaH_2 under reduced pressure. Capillary GC analyses were performed on a Hewlett-Packard Model 5790A gas chromatograph equipped with a flame ionization detector and a dimethylpolysiloxane column. Stereoisomers **4** and **5** were separated under isothermal conditions at 170 °C. Lithium acetylide−ethylenediamine complex, ethylmagnesium bromide (1 M in THF), and vinylmagnesium bromide (1 M in THF) were purchased from Aldrich Chemical Co. and used as received. Ethyllithium (1.2 M in Et_2O) was made from lithium metal and ethyl bromide.[23] Solid vinyllithium was prepared from tetravinyltin.[24] The molarity of solutions of these reagents in THF, toluene, or Et_2O were determined by titration with *sec*-butyl alcohol in xylene and 1,10-phenanthroline.[25a] Vinyllithium was titrated using 1,3-diphenylacetone *p*-tosylhydrazone.[25b] Other general experimental details are described in: Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241−11250.

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Chart 1

mm2.fld file

```
 C          Van der Waals Interactions                                  Opt. Descriptor
 C          --- --- ----- ------------                                  ---- --
 C        Radius       Eps        Offset      Charge                    Atm1 Lp
 C         (ang)    (kcal/mole)   (ang)
-6
  C1      1.9400      0.0440     0.0000                                 0000    O 1
  C2      1.9400      0.0440     0.0000                                 0200    O 1
  C2      1.9400      0.0440     0.0000                                 0000    O 1
  C3      1.9000      0.0440     0.0000                                 0000    O 1
  C3      2.0000      0.0440     0.0000                                 0000    M 1
  CP      1.9400      0.0440     0.0000     1.0000                      0000    A 2
  CR      1.9000      0.0440     0.0000                                 0000    A 2
  CM      1.9400      0.0440     0.0000    -1.0000                      0000    A 2
  CX      1.9400      0.0440     0.0000                                 0000    A 3

 C                        Special Substructures
 C                        ------- -------------
-3
 C  Hydride Addition to Ketone TS (Wu, Houk, Flores, Trost, JOC(1991))
 9  C2(=O)(.H1)[-C2=C2]
-2
 1   2   1                  1.269      5.36
 1   3   1                  2.035      2.00
 1  C3   1                  1.510      4.40
 1  H1   1                  1.077      4.60
 1   4   5                  1.340      8.00
 1   4   1                  1.490      4.40
 2   3   1   2             96.277      0.250
 2  C3   1  H1            114.28       0.360
 2  C3   1  C3            115.59       0.450
 2   2   1  H1            120.26       0.500
 2   3   1  C3             96.079      0.250
 2   3   1  H1             86.814      0.250
 4   2   1  C3  C3         -0.40       0.500      -0.200
 4   2   1  C3  H1          0.00       0.00        0.180
 4   3   1  C3  C3         -0.2       -0.2         0.4
 4   3   1  C3  H1          0.0        0.0         0.3
 4   3   1  C3  C2         -0.2       -0.2         0.4
 4   2   1  C3  C2         -0.4        0.5        -0.2
 4  C3   1  C3  C3          0.6        0.4         0.7
 4  C3   1  C3  C2          0.6        0.4         0.7
 4  H1   1  C3  C3          0.6        0.4         0.7
 4   2   1   4   5          0.0        1.0         0.0
 4   2   1   4  C3          0.0        0.0         0.0
 4   2   1   4  H1          0.0        0.0         0.0
 4   3   1   4   5          0.0        3.0         0.0
 4   3   1   4  C3          0.0        0.0         0.0
 4   3   1   4  H1          0.0        0.0         0.0
-3
 C Acetylide Addition to Ketone TS (Ando, Houk, 1996)
 9 C2(=O)(.CX)[-C2=C2]
-2
 1   2   1                  1.269      5.36
 1   3   1                  2.66       2.00
 1  C3   1                  1.510      4.40
 1  H1   1                  1.077      4.60
 1   4   5                  1.340      8.00
 1   4   1                  1.490      4.40
 1   3  C1                  1.212     15.60
 2   3   1   2             96.277      0.250
 2  C3   1  H1            114.28       0.360
 2  C3   1  C3            115.59       0.450
 2   2   1  H1            120.26       0.500
 2   3   1  C3             96.079      0.250
 2   3   1  H1             86.814      0.250
 2   1   3  C1            180.000      0.360
 4   2   1  C3  C3         -0.40       0.500      -0.200
 4   2   1  C3  H1          0.00       0.00        0.180
 4   3   1  C3  C3         -0.2       -0.2         0.4
 4   3   1  C3  H1          0.0        0.0         0.3
 4   3   1  C3  C2         -0.2       -0.2         0.4
 4   2   1  C3  C2         -0.4        0.5        -0.2
 4  C3   1  C3  C3          0.6        0.4         0.7
 4  C3   1  C3  C2          0.6        0.4         0.7
 4  H1   1  C3  C3          0.6        0.4         0.7
 4   2   1   4   5          0.0        1.0         0.0
 4   2   1   4  C3          0.0        0.0         0.0
 4   2   1   4  H1          0.0        0.0         0.0
 4   3   1   4   5          0.0        3.0         0.0
 4   3   1   4  C3          0.0        0.0         0.0
 4   3   1   4  H1          0.0        0.0         0.0
 4  C3   1   3  C1          0.0        0.0         0.0
 4  H1   1   3  C1          0.0        0.0         0.0
 4   2   1   3  C1          0.0        0.0         0.0
 4   4   1   3  C1          0.0        0.0         0.0
 4   1   3  C1  00          0.0        0.0         0.0
```

atom.typ

```
# Alkaline earth:
70       20     40.80000    Ca     4     1.73      F      F      !  1.00     F       !
71       56    137.34000    Ba     4     2.08      F      F      !  0.80     F       !
200       6     12.0        CX     2     1.78      T      F      !  2.50     F      C1
```

26.9, 20.9, 2.0 ppm; MS (CI) *m*/*z* 328.2210 (328.2222 calcd for $C_{21}H_{32}OSi$, M).

(1*R,2*S**)-1-Ethenyl-2-(3′-phenylpropyl)cycloheptan-1-ol (3b).** Following the general procedures of Corey and coworkers,[27] a mixture of $LiAlH_4$ (1 M in THF, 0.550 mL), solid $NaOCH_3$ (0.060 g, 1.1 mmol), and THF (2 mL) was stirred at room temperature for 30 min, and a solution of isomerically pure alcohol **3c** (0.050 g, 0.27 mmol) and THF (2 mL) was then added by cannula. The resulting mixture was heated at reflux (oil bath, 80 °C) for 16 h and after being cooled to room temperature was quenched with aqueous NH_4Cl (15 mL). The aqueous layer was extracted with ether (3 × 25 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated to give 0.138 g of a 13:1 mixture (^{1}H NMR analysis) of **3b** and **3c** as a colorless oil. Since these compounds could not be separated, this mixture was dissolved in toluene (0.5 mL) and heated at 100 °C in the presence of Ag_2CO_3 (0.021 g, 0.077 mmol) to fragment **3c** back to cycloheptanone **1**.[28] After 16 h, the reaction was allowed to cool to room temperature and was diluted with ether (20 mL) and filtered through a short column of Celite. The filtrate was concentrated, and the residue was purified by flash chromatography (10:3 hexanes−ether) to give 0.11 g (87%) of pure **3b** as a nearly colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.37 (m, 2H), 7.24−7.76 (m, 3H), 6.01 (dd, J = 17.2, 11.0 Hz, 1H), 5.30 (dd, J = 17.2, 1.1 Hz, 1H), 5.14 (d, J = 11.0 Hz, 1H,), 2.67−2.73 (m, 1H), 2.61−2.64 (m, 1H), 1.89−1.93 (m, 2H), 1.29−1.82 (m, 13H), 1.04−1.07 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 142.8, 128.3, 128.2, 125.6, 111.6, 78.3, 49.1, 42.9, 36.3, 31.9, 30.4, 30.2, 29.9, 28.4, 21.7 ppm; MS (CI) *m*/*z* 259.2063 (259.2061 calcd for $C_{18}H_{27}O$, MH).

(1*R,2*R**)-1-Ethenyl-2-(3′-phenylpropyl)cycloheptan-1-ol (2b)** was prepared from pure **2c** in an identical fashion: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25−7.29 (m, 2H), 7.16−7.18 (m, 3H), 5.93 (dd, J = 17.2, 10.6 Hz, 1H), 5.18 (dd, J = 17.2, 1.47 Hz, 1H), 5.03 (dd, J = 10.6, 1.2 Hz, 1H), 2.60−2.63 (m, 1H), 2.51−2.55 (m 1H), 1.26−1.87 (m, 15H), 1.03−1.09 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.4, 142.7, 128.3, 128.2, 125.6, 110.6, 77.7, 47.6, 41.8, 36.2, 30.3, 30.3, 29.4, 29.0, 26.7, 21.5 ppm; MS (CI) *m*/*z* 259.2053 (259.2061 calcd for $C_{18}H_{27}O$, MH).

(1*R,2*S**)-1-ethyl-2-(3′-phenylpropyl)cycloheptan-1-ol (3a).** A mixture of isomerically pure **3c** (0.038 g, 0.15 mmol), EtOAc (10 mL), and 10% palladium on carbon (0.023 g) was maintained at room temperature under an atmosphere of H_2 until **3c** was no longer detected by GLC analysis. After being purged with N_2, the mixture was filtered through a short column of Celite and the filtrate was concentrated to give 0.0392 g (∼100%) of **3a** as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.30 (m, 2H), 7.16−7.20 (m, 3H), 2.66−2.68 (m, 1H), 2.57−2.61 (m, 1H), 1.12−1.80 (m, 18H), 0.87−0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 128.4, 128.3, 125.6, 77.1, 49.9, 39.7, 36.4, 30.6, 30.3, 29.5, 29.3, 28.6, 27.6, 21.2, 7.4 ppm; MS (CI) *m*/*z* 260.2127 (260.2140 calcd for $C_{18}H_{28}O$, M).

(1*R,2*R**)-1-Ethyl-2-(3′-phenylpropyl)cycloheptan-1-ol (2a)** was prepared from pure **2c** in an identical fashion: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.29 (m, 2H,) 7.16−7.22 (m, 3H), 2.67−2.69 (m, 1H), 2.58−2.66 (m, 1H), 1.88 (t, J = 14.1, 8.0 Hz, 1H), 1.36−1.85 (m, 14H), 1.22−1.30 (q, J = 8.8 Hz, 2H), 0.92−1.12 (q, J = 9.8 Hz, 1H), 0.87−0.90 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 128.2, 128.1, 125.5, 76.6, 47.4, 38.2, 36.3, 32.4, 30.4, 29.9, 29.5, 28.4, 27.1, 22.0, 7.8 ppm; MS (CI) *m*/*z* 260.2131 (260.2140 calcd for $C_{18}H_{28}O$, M).

3-[(1′*R,2′*R**)-2-ethyl-2-hydroxycycloheptyl]butanoic Acid (6).** Following the general procedure of Sharpless,[19] a mixture of isomerically pure **2a** (0.328 g, 1.26 mmol), $NaIO_4$ (4.9 g, 23 mmol), $RuCl_3 \cdot H_2O$ (0.0057 g, 0.028 mmol), H_2O (20 mL), CCl_4 (10 mL), and MeCN (10 mL) was stirred for 48 h at room temperature and then quenched with CH_2Cl_2 (20 mL) and H_2O (30 mL). The organic and the aqueous layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and EtOAc (3 × 20 mL), and the combined organic layers were washed with aqueous HCl (2 mL, 1 M), dried ($MgSO_4$), and filtered. After concentration, the resulting yellow oil was triturated with ether (50 mL), and the ether solution was filtered through a short column of Celite. This filtrate was concentrated, and the residue was purified by flash chromatography (1:1 hexanes−EtOAc, containing 1% HOAc) to give 0.0703 g (25%) of **6** as a colorless solid. Recrystallization from (hexanes−EtOAc) gave single crystals: mp 90−91 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25−6.25 (s, 1H), 2.31−2.41 (m, 2H), 1.78−1.90(m, 3H), 1.09−1.69 (m, 15H), 0.86−0.89 (t, J = 7.5 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 179.2, 77.1, 47.4, 38.2, 34.3, 32.4, 29.8, 29.5, 28.4, 27.1, 23.6, 22.1, 7.9 ppm; IR (film) 3448, 2807, 1709, 1686 cm^{-1}.

Acknowledgment. We are grateful to the National Institute of General Medical Sciences, National Institutes of Health for financial support (K.N.H. and L.E.O.) and to Fujisawa Foundation for a scholarship to K.A.

Appendix

Chart 1 lists the parameters used for the MM2* force field in Macromodel.

Supporting Information Available: Copies of ^{13}C NMR spectra (125 MHz, $CDCl_3$) for compounds **1**, **2a**, **2b**, **3a**, **3b**, **4c** and **5c** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO971627B

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