ORGANIC LETTERS

2008
Vol. 10, No. 11
2239−2242

Aluminum Chloride-Mediated Acylation of Methylenecyclobutanes. A Facile Synthetic Protocol for the Construction of Substituted Cyclopentenes

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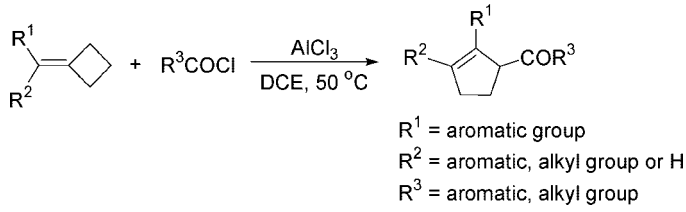
Received March 20, 2008

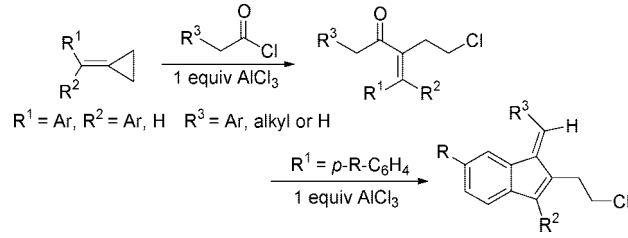
ABSTRACT



Reactions of methylenecyclobutanes (MCBs) with acyl chlorides produce the corresponding substituted cyclopentene derivatives in moderate to high yields via ring enlargement in the presence of aluminum chloride under mild conditions. A plausible mechanism has been proposed on the basis of control and deuterium labeling experiments.

The Lewis acid promoted Friedel−Crafts reaction is a powerful carbon−carbon bond-forming process in organic chemistry.[1] The acylation of an aromatic compound that essentially results in the production of an aromatic ketone by reacting an aromatic substrate with an acyl component is the most common Friedel−Crafts reaction.[2] During the last decades, the chemistry on the acylation of cyclopropanes has been explored with regard to the similarity between the cyclopropane ring and the olefinic double bond.[3] Recently, Huang and co-workers reported that a variety of substituted α,β-unsaturated ketone and benzofulvene derivatives were readily prepared in good to excellent yields via the reaction of methylenecyclopropanes (MCPs), a kind of highly strained but readily accessible molecules, with various acyl chlorides in the presence of aluminum chloride (Scheme 1).[4] As for these closely related analogues, methylenecyclobutanes (MCBs), a class of moderately strained alkenes, it has been known that they could be easily oxidized to the corresponding cyclopentanone or cyclobutylmethanone derivatives in good yields under mild reaction conditions.[5] However, no report on the $AlCl_3$-catalyzed/mediated acylation of MCBs has been disclosed thus far. Therefore, we attempted to examine the reaction of MCBs **1** with a variety of acyl chlorides in the

Scheme 1. Acylation of Methylenecyclopropanes



(1) (a) Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, Chapter 1.8, pp 293−339. (b) Meima, G. R.; Lee, G. S.; Garces, J. M. In *Friedel−Crafts Alkylation*; Sheldon, R. A., Bekkum, H., Eds.; Wiley-VCH: New York, 2001; pp 155−160.

(2) Gore, P. H. In *Aromatic Ketone Synthesis in Friedel−Crafts and Related Reactions*; Olah, G. A., Ed.; John Wiley & Sons Inc.: London, 1964; Vol. III, Part 1, p 1.

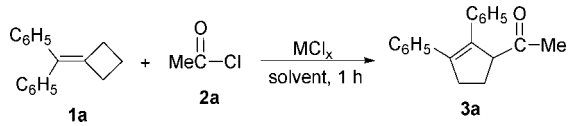
(3) (a) Hart, H.; Curtis, O. E., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 931–934. (b) Hart, H.; Sandri, J. M. *J. Am. Chem. Soc.* **1959**, *81*, 320–326. (c) Hart, H.; Levitt, G. *J. Org. Chem.* **1959**, *24*, 1261–1267. (d) Hart, H.; Schlosberg, R. H. *J. Am. Chem. Soc.* **1966**, *88*, 5030–5033. (e) Hart, H.; Schlosberg, R. H. *J. Am. Chem. Soc.* **1968**, *90*, 5189–5196.

10.1021/ol8006502 CCC: $40.75 © 2008 American Chemical Society
Published on Web 05/02/2008

presence of $AlCl_3$. In this paper, we wish to present a novel ring enlargement of MCBs in the $AlCl_3$-mediated reactions with acyl chlorides to produce the corresponding cyclopentene derivatives in good yields.

Initial examinations using diphenylmethylenecyclobutane **1a** (1.0 or 3.0 equiv) as the substrate to react with acetyl chloride **2a** (1.0−1.5 equiv) in the presence of $AlCl_3$ (1.0−1.5 equiv) in dichloromethane were aimed at determining the optimal conditions, and the results of these experiments are summarized in Table 1. 1-(2,3-Diphenylcyclopent-2-enyl)ethanone **3a** was obtained in 32% yield at room temperature (20 °C) within 1 h via a ring enlargement when equal molar amounts of **1a**, **2a**, and $AlCl_3$ were employed (Table 1, entry 1). Increasing the employed amounts of **2a** and $AlCl_3$ as well as decreasing the reaction temperature did not improve the yields of **3a** under otherwise identical conditions (Table 1, entries 2, 3 and 4). When the employed amounts of **2a** and $AlCl_3$ were reduced to 1/3 equiv of **1a**, **3a** was formed in 51% yield at room temperature (Table 1, entry 5). Further examination of the reaction conditions revealed that increasing the reaction temperature to 40 °C afforded **3a** in 60% yield in 1,2-dichloroethane (DCE) when 3.0 equiv of **1a** and 1.0 equiv of **2a** and $AlCl_3$ were employed (Table 1, entry 6). Moreover, at 50 °C, **3a** was obtained in 70% and 72% yields when 3.0 equiv of **1a** and 1.0 equiv of **2a** and $AlCl_3$ as well as 2.0 equiv of **1a** and 1.0 equiv of **2a** and $AlCl_3$ were employed, respectively (Table 1, entries 7 and 8). The examination of the solvent effects indicated that DCE is the best one for this transformation (Table 1, entries 9−11). On the other hand, using other Lewis acids such as $FeCl_3$, $ZnCl_2$, $TiCl_4$, $SnCl_4$, or $HgCl_2$ instead of $AlCl_3$ did not give satisfactory results (Table 1, entries 12−16). Only 32% of **3a** was produced when $ZnCl_2$ was utilized as a Lewis acid under the standard conditions (Table 1, entry 13). Therefore, the best conditions are to carry out the reaction in DCE at 50 °C using 2.0 equiv of **1a** and 1.0 equiv of **2a** and $AlCl_3$.

Table 1. Optimization of the Reaction Conditions

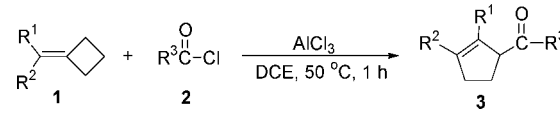


entry	MCl_x	**1a/2a**/MCl_x	solvent	T (°C)	yield[b] (%) of **3a**
1	$AlCl_3$	1/1/1	CH_2Cl_2	rt	32
2	$AlCl_3$	1/1.1/1.1	CH_2Cl_2	rt	27
3	$AlCl_3$	1/1.5/1.5	CH_2Cl_2	rt	17
4	$AlCl_3$	1/1/1	CH_2Cl_2	0	trace
5	$AlCl_3$	3/1/1	CH_2Cl_2	rt	51
6	$AlCl_3$	3/1/1	DCE	40	60
7	$AlCl_3$	3/1/1	DCE	50	70
8[a]	*$AlCl_3$*	*2/1/1*	*DCE*	*50*	*72*
9	$AlCl_3$	2/1/1	Et_2O	30	NR
10	$AlCl_3$	2/1/1	THF	50	NR
11	$AlCl_3$	2/1/1	MeCN	50	NR
12	$FeCl_3$	2/1/1	DCE	50	trace
13	$ZnCl_2$	2/1/1	DCE	50	32
14	$TiCl_4$	2/1/1	DCE	50	NR
15	$SnCl_2$	2/1/1	DCE	50	NR
16	$HgCl_2$	2/1/1	DCE	50	NR

[a] Reaction conditions: **1a** (0.6 mmol), MCl_x (0.3 mmol), MeCOCl (0.3 mmol), solvent (2.0 mL). The reactions were carried out at various temperatures. [b] Isolated yields.

With these optimal conditions in hand, we next carried out this novel acylation using a variety of starting materials **1** and acyl chlorides **2** as shown in Table 2. As for symmetrical MCBs **1a**−**e**, the reactions proceeded smoothly with various aliphatic or aromatic acyl chlorides **2** to afford the corresponding cyclopentenes **3b**−**m** in 51−77% yields (Table 2, entries 1−12). The substituents on the aromatic ring of MCBs **1** and acyl chlorides did not have significant influence on this reaction outcomes. However, as for unsymmetrical aromatic MCBs **1f** and **1g**, the corresponding products **3n** and **3o** were obtained as isomeric mixtures in good yields (Table 2, entries 13 and 14). It should be noted that using aliphatic MCB **1h**, in which both R^1 and R^2 are alkyl groups, as the substrate or using sulfonyl chloride such as p-$BrC_6H_4SO_2Cl$ as acylation reagent under the standard conditions, no reactions occurred (Table 2, entries 15 and 16).

Table 2. Scope and Limitations on the Acylation of MCBs Catalyzed by $AlCl_3$



entry[a]	MCBs (R^1/R^2)	**2** (R^3)	yield[b] (%) of **3**
1	**1a** (C_6H_5/C_6H_5)	**2b** (Et)	**3b**, 70
2	**1a**	**2c** (C_6H_5)	**3c**, 64
3	**1a**	**2d** ($C_6H_5CH_2$)	**3d**, 71
4	**1b** (p-MeC_6H_4/p-MeC_6H_4)	**2a** (Me)	**3e**, 77
5	**1b**	**2b** (Et)	**3f**, 77
6	**1c** (p-ClC_6H_4/p-ClC_6H_4)	**2a** (Me)	**3g**, 67
7	**1c**	**2b** (Et)	**3h**, 68
8	**1c**	**2e** (p-$NO_2C_6H_4$)	**3i**, 53
9	**1c**	**2f** (p-BrC_6H_4)	**3j**, 61
10	**1d** (p-FC_6H_4/p-FC_6H_4)	**2a** (Me)	**3k**, 68
11	**1d**	**2b** (Et)	**3l**, 67
12	**1e** (p-BrC_6H_4/p-BrC_6H_4)	**2f** (p-BrC_6H_4)	**3m**, 51
13	**1f** (m,p-$Me_2C_6H_3$/C_6H_5)	**2a** (Me)	**3n**, 73[c]
14	**1g** (p-ClC_6H_4/C_6H_5)	**2a** (Me)	**3o**, 65[d]
15	**1h** (Bu/Bu)	**2a** (Me)	**3p**, −[e]
16	**1a**	**2g** (p-$BrC_6H_4SO_2Cl$)	**3q**, −[e]

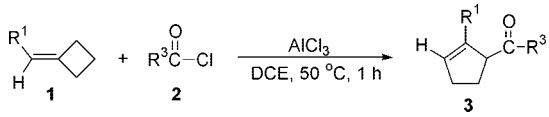
[a] Reaction conditions: **1** (0.6 mmol), $AlCl_3$ (0.3 mmol), R^3COCl (0.3 mmol), DCE (2.0 mL). The reactions were carried out at 50 °C. [b] Isolated yields. [c] Isomeric mixtures (1:1) based on GLC. [d] Isomeric mixtures (1:2) based on ^1H NMR spectrum. [e] No reaction.

Under these optimal conditions, we further investigated the acylation of a variety of unsymmetrical MCBs **1i**−**k**

(4) Huang, X.; Yang, Y.-W. *Org. Lett.* **2007**, *9*, 1667–1670.
(5) (a) Graham, S. H.; William, A. J. S. *J. Chem. Soc.* **1959**, 4066–4072. (b) Farcasiu, D.; Schleyer, P. V. R.; Ledlie, D. *J. Org. Chem.* **1973**, *38*, 3455–3459. (c) Graham, S. H.; William, A. J. S. *J. Chem. Soc. C* **1966**, 655–660. (d) Fitjer, L.; Kanschik, A.; Majewski, M. *Tetrahedron Lett.* **1988**, *29*, 5525–5528. (e) Shen, Y. M.; Wang, B.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 1429–1432. (f) Jiang, M.; Liu, L.-P.; Shi, M. *Tetrahedron* **2007**, *63*, 9599–9604.

where R^1 is an aromatic group and R^2 is a proton, and found these reactions also proceeded smoothly to give the corresponding cyclopentenes **3r**−**y** in 72−87% yields as a single isomer whether they have electron-poor or electron-rich aromatic ring (Table 3, entries 1−8). Their structures were

Table 3. Scope and Limitations on the Acylation of MCBs Catalyzed by $AlCl_3$



entry[a]	MCBs (R^1)	R^3	yield (%)[b] of **3**
1	**1i** (p-ClC_6H_4)	**2a** (Me)	**3r**, 85
2	**1i**	**2b** (Et)	**3s**, 87
3	**1j** (p-BrC_6H_4)	**2a** (Me)	**3t**, 82
4	**1j**	**2b** (Et)	**3u**, 84
5	**1j**	**2e** (p-BrC_6H_4)	**3v**, 82
6	**1j**	**2e** (Me_2CH)	**3w**,72
7	**1k** (p-MeC_6H_4)	**2a** (Me)	**3x**, 80
8	**1k**	**2c** (C_6H_5)	**3y**, 75

[a] Reaction conditions: **1** (0.6 mmol), $AlCl_3$ (0.3 mmol), R^3COCl (0.3 mmol), DCE (2.0 mL). The reactions were carried out at 50 °C. [b] Isolated yields.

determined by spectroscopic data, HRMS and microanalyses (see the Supporting Information). Furthermore, the X-ray crystal structure of **3v** was determined and its CIF data are presented in the Supporting Information (Figure 1).[6]

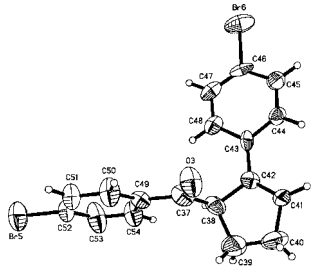
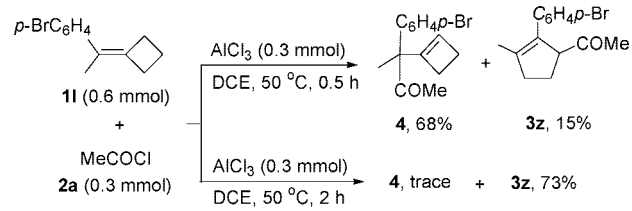


Figure 1. ORTEP drawing of **3v**.

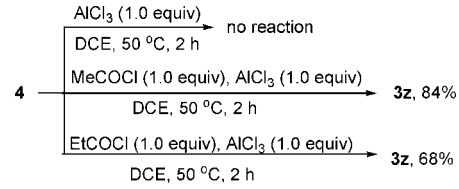
Furthermore, when using MCB **1l** in which R^1 is an aromatic group and R^2 is a methyl group as the substrate, we found that 3-cyclobut-1-enyl-3-methylbutan-2-one derivative **4** was formed in 68% yield along with **3z** in 15% yield within 0.5 h under the standard conditions. However, when the reaction time was prolonged to 2 h, traces of **4** were obtained and the yield of **3z** increased to 73%, indicating that **4** might be the intermediate in this reaction (Scheme 2). As the control experiments shown in Scheme 3, we also confirmed that **4** remained unchanged by treatment with $AlCl_3$ (1.0 equiv) in DCE at 50 °C after 2 h in the absence of acetyl chloride **2a** and adding 1.0 equiv of acyl chloride **2a** or **2b** into the mixture afforded **3z** in 84% yield

Scheme 2. Reaction of MCB **1l** with Acetyl Chloride in the Presence of $AlCl_3$



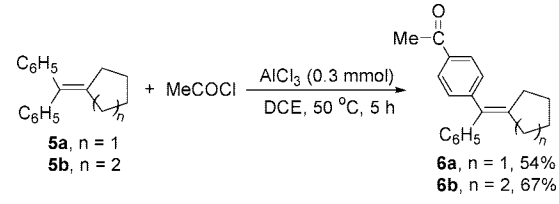
and 68% yield, respectively under the standard conditions. These results suggest that compound **4** itself is not affected by Lewis acid, but could undergo rearrangement to produce **3** in the coexistence of Lewis acid and acyl chloride.

Scheme 3. Control Experiments



The cyclobutane ring is essential in this transformation because if using diphenylmethylenecyclopentane **5a** and diphenylmethylenecyclohexane **5b** as the substrates under the standard conditions, the corresponding Friedel−Crafts products **6a** and **6b** were obtained in 54% and 67% yields, respectively (Scheme 4).

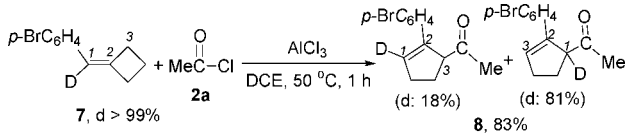
Scheme 4. Acylation of **5a** (0.6 mmol) and **5b** (0.6 mmol) with Acetyl Chloride (0.3 mmol) in the Presence of $AlCl_3$



To confirm the mechanism of this acylation reaction, we performed deuterium labeling studies with deuterated methylenecyclobutane **7** (Scheme 5). Under the standard conditions, reaction of **7** (D > 99%) with acetyl chloride afforded the product mixtures of **8** in 83% yield with 18% and 81% D content at C_1 position, respectively based on the corresponding ^1H NMR spectroscopic data, suggesting that the acylation occurred at two different places (see the Supporting Information).

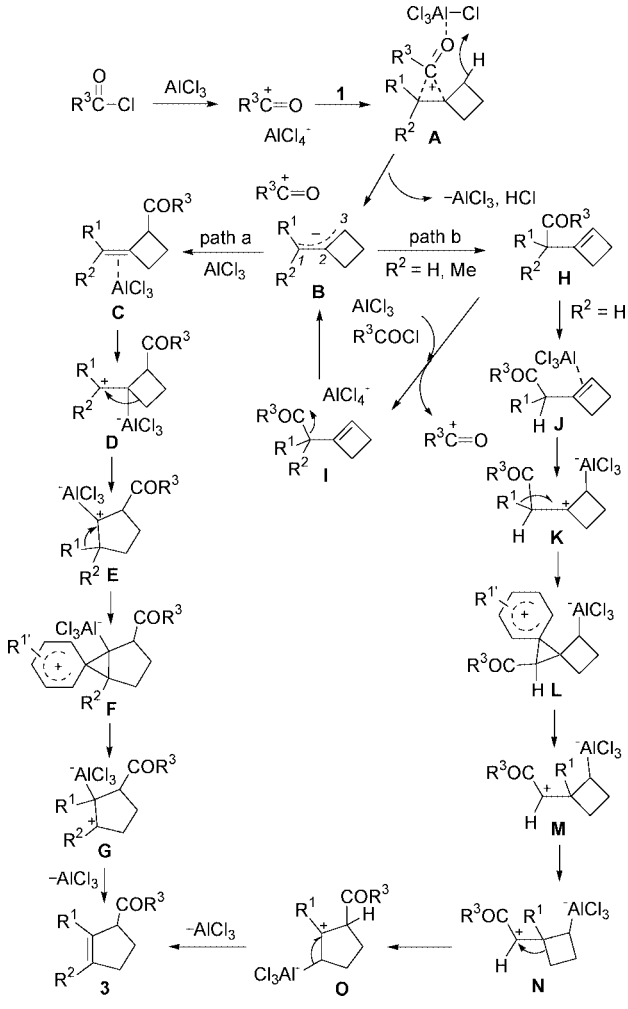
A plausible mechanism for the formation of cyclopentene derivatives **3** is outlined in Scheme 6 based on the above

Scheme 5. Deuterium Labeling Experiment



deuterium labeling and control experiments. The in situ generated acyl cation in the presence of $AlCl_3$ reacts with MCB **1** to produce intermediate **A**, which eliminates an allylic proton to give intermediate **B**.[7] When both R^1 and R^2 are aromatic groups, intermediate **C** is produced via intermediate **B** in the presence of $AlCl_3$ and subsequently gives intermediate **D** (path a). Ring enlargement of cyclobutane affords intermediate **E** along with the fromation of intermediate **F** which is a phenonium ion intermediate.[8] Aryl transfer through intermediate **F** furnishes intermediate **G**, which produces the corresponding product **3** via the elimination of $AlCl_3$. On the other hand, when R^1 is an aromatic group and R^2 is a H atom or a methyl group, intermediate **H** (compound **4** in Scheme 2) is probably first formed via intermediate **B** (path b). Intermediate **H** (R^2 = Me or H) can afford intermediate **C** via intermediates **I** and **B** through intramolecular rearrangements to furnish the corresponding product **3**. In the mean time, intermediate **H** (R^2 = H, not Me) can also produce intermediate **K** from intermediate **J** in the presence of $AlCl_3$. Aryl transfer gives intermediate **L** which is also a phenonium ion intermediate.[8] Then, the corresponding product **3** is produced similarly via intermediates **M**, **N**, and **O** successively. When both R^1 and R^2 are aromatic groups, the reaction exclusively proceeds through path a, presumably due to that the two sterically bulky aromatic groups block out the acylation at C_1 position. When R^1 is an aromatic group and R^2 is a H atom, the rearrangement can proceed mainly through path b and partially through path a to afford the corresponding product **3** which are consistent with the deuterium labeling experiment shown in Scheme 4. When R^1 is an aromatic group and R^2 is a methyl group, intermediate **H** is fairly stable, which can be isolated from the reaction mixtures. Moreover, a control experiment using intermediate **C** as the substrate indeed afforded the corresponding product **3** in moderate yield under the standard reaction conditions, indicating that intermediate **C** should be the reaction intermediate (Supporting Information).

Scheme 6. Proposed Reaction Mechanism



In summary, we have developed an efficient acylation reaction of methylenecyclobutanes using $AlCl_3$ as a Lewis acid to produce cyclopentene derivatives **3** in moderate to good yields via ring enlargement with easily available reagents under mild conditions. These functionalized cyclopentenes are a common structural motif found in many natural products and bioactive compounds. A plausible mechanism has been proposed on the basis of control and deuterium labeling experiments. Clarification of the reaction mechanism and further application of this transformation are in progress.

Acknowledgment. We thank the Shanghai Municipal Committee of Science and Technology (04JC14083, 06XD14005) and the National Natural Science Foundation of China for financial support (20472096, 20672127, and 20732008).

Supporting Information Available: Detailed description of experimental procedures, full characterization of new compounds shown in Tables 1–3, X-ray crystal analysis data of **3v**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) The crystal data of **3v** have been deposited in CCDC with no. 671857. Empirical formula: $C_{18}H_{14}Br_2O$; formula weight: 406.11; crystal color, habit: colorless, prismatic; crystal dimensions: 0.431 × 0.365 × 0.227 mm; crystal system: monoclinic; lattice type: primitive; lattice parameters: a = 11.323(2) Å, b = 31.150(6) Å, c = 13.860(3) Å, α = 90°, β = 96.603(3)°, γ = 90°, V = 4856.2(16) Å^3; space group: $P2(1)/c$; Z = 12; D_{calc} = 1.666 g/cm^3; F_{000} = 2400; diffractometer: Rigaku AFC7R; residuals: R; Rw: 0.0413, 0.0613.

(7) (a) The examples for the similar allylic addition reaction: Chou, P. K.; Dahlke, G. D.; Kass, S. R. *J. Am. Chem. Soc.* **1993**, *115*, 315–324. (b) Glasovac, Z.; Eckert, M. M.; Dacres, J. E.; Kass, S. R. *J. Chem. Soc., Perkin Trans. 2* **2002**, 410–415.

(8) (a) Selected papers on the aryl transfer through phenonium ion: Jackson, E. L.; Pastiut, L. *J. Am. Chem. Soc.* **1928**, *50*, 2249–2260. (b) Cram, D. J. *J. Am. Chem. Soc.* **1949**, *71*, 3863–3870. (c) Cram, D. J. *J. Am. Chem. Soc.* **1952**, *74*, 2129–2137.