Novel Diethylaluminum Chloride Promoted Reactions of the Azetidine Ring: Efficient and Stereocontrolled Entry to Functionalized Olefins, Pyrrolidines, and Pyrroles

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The first examples of Lewis acid promoted fragmentation or rearrangement of the azetidine ring are reported. Azetidine precursors, *cis*-*β*-lactams, were easily available as single *cis*-diastereoisomers by the Staudinger reaction. Both *cis*- and *trans*-4-formyl-*β*-lactams react with the appropriate diol or dithiol under acid catalysis to yield dioxolanes or dithiolanes, while reaction with trimethyl orthoformate or benzenethiol gave 4-acetal or thioacetal *β*-lactams, respectively. Azetidines were smoothly obtained by reduction of easily available *β*-lactams with monochloroalane (AlH_2Cl), generated in situ from $LiAlH_4/AlCl_3$. The chemical reactivity of azetidines with $AlEt_2Cl$ was further investigated. Different substituted azetidines showed varied behavior on product formation during diethylaluminum chloride promoted reactions. Azetidines having 4-methoxyphenyl or 2-furyl groups at C2 and a benzyl or allyl substituent at nitrogen efficiently reacted with $AlEt_2Cl$ to give olefins stereoselectively through a fragmentation process, while acetal or thioacetal azetidines under the standard reaction conditions afforded in a stereocontrolled manner pyrrolidines as the sole product. Furthermore, thioacetal azetidines bearing a substituent at C3 on the azetidine ring that can promote aromatization (phenoxy or exocyclic double bond) gave pyrroles by reaction with $AlEt_2Cl$.

Introduction

Since the discovery of the *β*-lactam ring as the essential feature of the *β*-lactam antibiotics,[1] much has been learned about the chemical reactivity of this four-membered heterocycle. Thus, processes of ring opening, fragmentation, and rearrangement involving any of the four bonds of the 2-azetidinone ring have been reported,[2] and developed to a synthetically useful level to prepare different kinds of compounds.[3] However, the chemistry of azetidines has been much less investigated. While much of the effort involving the azetidine nucleus has been directed toward its synthesis,[4] as it is a component of many biologically active drugs and natural products,[5] few examples of rearrangements or fragmentations of the azetidine ring are known. It has been shown that 1,2,2′-trisubstituted azetidines, on heating, form alkenes through a Hoffmann-type elimination.[6] Some activated 3-iminoazetidines undergo a slow ring opening to give 2-aza-1,3-dienes.[7] Ring opening of 3-substituted 4-arylazetidines to give the corresponding amino alcohols takes place upon catalytic hydrogenation on palladium or Raney nickel.[8] The Beckmann rearrangement of 3-(mesyloxyimino)azetidines over alumina gives 4-imidazolidinones,[9] and 2-pyrrolidinones are obtained both by cobalt carbonyl catalyzed carbonylation of azetidines[10] and through intramolecular acylation in (3-azetidinyl)-acetic acids.[11] Finally, photolysis of 3-acylazetidines results in the formation of pyrroles.[12] During the course of our ongoing project directed toward developing efficient routes to prepare bi- and polycyclic *β*-lactam systems,[13]

(1) For some reviews on *β*-lactam antibiotics, see: (a) Dürckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180. (b) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vols. 1−3. (c) Soughgate, R.; Branch, C.; Coulton, S.; Hunt, E. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukacs, G., Ed.; Springer: Berlin, 1993; Vol. 2, p 621. (d) Soughgate, R. *Contemp. Org. Synth.* **1994**, *1*, 417. (e) *The Chemistry of β-Lactams*; Page, M. I., Ed.; Chapman and Hall: London, 1992.

(2) For reviews, see: (a) *The Organic Chemistry of β-Lactams*, Georg, G. I., Ed.; VCH: New York, 1993. (b) Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* **1988**, *27*, 1755.(c) Ojima, I. *Adv. Asymm. Synth.* **1995**, *1*, 95.

(3) See, for example: (a) Alcaide, B.; Martín-Cantalejo, Y.; Pérez-Castells, J.; Sierra, M. A.; Monje, A. *J. Org. Chem.* **1996**, *61*, 9156. (b) Alcaide, B.; Pérez-Castells, J.; Polanco, C.; Sierra, M. A. *J. Org. Chem.* **1995**, *60*, 6012. (b) Alcaide, B.; Martín-Cantalejo, Y.; Rodríguez-López, J.; Sierra, M. A. *J. Org. Chem.* **1993**, *58*, 4767 and references therein.

(4) For reviews on the synthesis and chemistry of azetidines, see: (a) De Kimpe, N. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Eds; Elsevier: Oxford, 1996; Vol. 1B, Chapter 1.18, pp 507−589. (b) Moore, J. A.; Ayers, R. S. In *Chemistry of Heterocyclic Compounds-Small Ring Heterocycles*; Hassner, A., Ed.; Wiley: New York, 1983; Part 3, pp 1−217. (c) Cromwell, N. H.; Phillips, B. *Chem. Rev.* **1979**, *79*, 331.

(5) Selected examples: (a) Kobayashi, J.; Ishibashi, M. *Heterocycles* **1996**, *42*, 943. (b) Shuman, R. T.; Rothenberger, R. B.; Campbell, C. S.; Smith, G. F.; Gifford-Moore, D. S. *J. Med. Chem.* **1995**, *38*, 4446. (c) Frigola, J.; Torrens, A.; Castrillo, J. A.; Mas, J.; Vañó, D.; Berrocal, J. M.; Calvet, C.; Salgado, L.; Redondo, J.; García-Granda, S.; Valentí, E.; Quintana, J. R. *J. Med. Chem.* **1994**, *37*, 4195. (d) Frigola, J.; Pares, J.; Corbera, J.; Vano, D.; Merce, R. *J. Med. Chem.* **1993**, *36*, 801. (e) Duréault, A.; Portal, M.; Carreaux, F.; Depezay, J. C. *Tetrahedron* **1993**, *49*, 4201. (f) Kobayashi, J.; Cheng, J. F.; Isibashi, M.; Wälchli, M. R.; Yamamura, S.; Ohizumi, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1135. (g) Kozikowski, A. P.; Tueckmantel, W.; Reynolds, I. J.; Wroblewski, J. T. *J. Med. Chem.* **1990**, *33*, 801, 1561. (h) Isono, K. *J. Antibiot.* **1988**, *41*, 1711. (i) Isono, K.; Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.* **1969**, *91*, 7490.

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(8) (a) Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K.; Yamashita, M.; Abe, R. *J. Org. Chem.* **1991**, *56*, 5263. (b) Yamashita, M.; Ojima, I. *J. Am. Chem. Soc.* **1991**, *105*, 6339.

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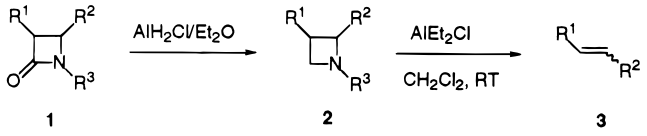
Table 1. Diethylaluminum Chloride Mediated Fragmentation of Azetidines 2



1 **2** **3**

β-lactam	R^1	R^2	R^3	azetidine	yield[a] (%)	olefin	*E*/*Z*[b]	yield[a] (%)
cis-**1a**	PhO	4-$MeOC_6H_4$	Bn	*cis*-**2a**	91	3a	0:100	57
cis-**1b**	PhO	Ph	Bn	*cis*-**2b**	91	NR[c]		
cis-**1c**	PhO	4-$NO_2C_6H_4$	Bn	*cis*-**2c**	91	NR[c]		
cis-**1d**	PhO	2-furyl	allyl	*cis*-**2d**	97	3b	0:100	58
trans-**1d**	PhO	2-furyl	allyl	*trans*-**2d**	85	3b	67:33	61
cis-**1e**	PhO	2-furyl	Bn	*cis*-**2e**	85	3b	0:100	53
cis-**1f**	PhO	2-furyl	4-$MeOC_6H_4$	*cis*-**2f**	57	NR[c]		
trans-**1g**	Ph	4-$MeOC_6H_4$	Bn	*trans*-**2g**	54	3c	100:0	68
trans-**1h**	vinyl	4-$MeOC_6H_4$	Bn	*trans*-**2h**	91	3d	100:0	76
cis-**1i**	PhO	styryl	Bn	*cis*-**2i**	73	3e	0:100	72

[a] Yield of pure, isolated product with correct analytical and spectral data. [b] The ratio based on the ^1H NMR spectra of the crude reaction mixtures before purification. [c] NR = no reaction was observed. Unreacted starting azetidine **2** was recovered.

we undertook a parallel study on the azetidine nucleus[14] to check the electronic and/or steric effects involved in the cyclization processes, because the planarity of the amide nitrogen imposed by the amide resonance is excluded in azetidines.[15] We now report full details of two new, hitherto unprecedented diethylaluminum chloride promoted reactions of the azetidine ring, namely, its fragmentation to form olefins and its rearrangement to form pyrrolidines, fused pyrrolidines, and pyrroles.

Results and Discussion

To test the behavior of the azetidine nucleus under the influence of diethylaluminum chloride, we prepared a set of different substituted azetidines. Azetidines **2** were smoothly obtained by reduction of easily available β-lactams **1**[2a,16] with monochloroalane (AlH_2Cl), generated in situ from $LiAlH_4/AlCl_3$, following the procedure reported by Ojima.[8a] The reaction was instantaneous at room temperature, and the stereochemistry of the starting monolactams remained unaltered during the process. Azetidines **2** were further reacted with $AlEt_2Cl$ (1 M solution in hexanes) in dichloromethane at room temperature to give olefins **3**, including vinyl ethers and conjugated dienes. Pure compounds **3** were isolated in fair to good yields (53−76%) by flash chromatography, but some decomposition was observed for the sensitive vinyl ethers **3a**,**b** during purification. The stereochemistry of the azetidine was transferred unaltered to the olefin in the tested cases, except for *trans*-azetidine **2d**, which gave an *E*/*Z* mixture of olefins. The *E*/*Z* geometry of the double bonds in these compounds was consistent with vinylic coupling constants of ca. 7.0 and 14.0 Hz for the *Z*- and *E*-isomers, respectively, in their ^1H NMR spectra (Table 1).

These examples show that azetidines **2a**,**d**,**e**,**g**−**i** having 4-methoxyphenyl, 2-furyl, or styryl groups at C2 and benzyl or allyl substituents at nitrogen efficiently reacted with $AlEt_2Cl$, while azetidines **2b**,**c**,**f** bearing phenyl or 4-nitrophenyl groups at C2 and 4-methoxyphenyl substituents at nitrogen were unreactive. The above results strongly suggest that an electron donor group able to stabilize a positive charge at the C2 position and a basic azetidine nitrogen are necessary for the fragmentation to occur.

Next, acetal and thioacetal azetidines **6** were selected as suitable substrates to react with diethylaluminum chloride. Starting substrates, *cis*- and *trans*-acetal azetidines **6**, were prepared from the corresponding 4-formyl-β-lactams **4** in two steps using standard methodology. *cis*-4-Formyl-β-lactams, *cis*-**4**,[17] suffered regiospecific C4-epimerization to yield *trans*-4-formyl-β-lactams, *trans*-**4**, through a dimethylamine promoted heterogeneous process recently developed in our group.[18] Reaction of aldehydes **4** with the appropriate diol or dithiol under acidic catalysis gave the corresponding cyclic acetals **5a**−**e** or dithioacetals **5f**−**k** in good to excellent yields (42−99%) (Table 2). Treatment of aldehydes **4** with trimethyl orthoformate or benzenethiol, in the presence of an acidic catalyst, yielded 4-acetal β-lactams **7a**−**c** (43−88%) or 4-dithioacetal β-lactams **7d**−**h** (31−89%), respectively (Table 3). Reaction of compounds **5** and **7** with AlH_2Cl formed the required acetal azetidines **6** and **8**, respectively (Tables 2 and 3).

Reaction of azetidines **6** with $AlEt_2Cl$ using different experimental conditions, particularly by variation of the amount of $AlEt_2Cl$ and the temperature, proceeded selectively to afford fused pyrrolidines **9** as the sole

(13) See, among others: (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Commun.* **1999**, 1913. (b) Alcaide, B.; Alonso, J. M.; Aly, M. A.; Sáez, E.; Martínez-Alcázar, M. P.; Hernández-Cano, F. *Tetrahedron Lett.* **1999**, *40*, 5391. (c) Alcaide, B.; Almendros, P. *Tetrahedron Lett.* **1999**, *40*, 1015. (d) Alcaide, B.; Polanco, C.; Sierra, M. A. *J. Org. Chem.* **1998**, *63*, 6786. (e) Alcaide, B.; Rodríguez-Vicente, A. *Tetrahedron Lett.* **1998**, *39*, 6589. (f) Alcaide, B.; Polanco, C.; Sáez, E.; Sierra, M. A. *J. Org. Chem.* **1996**, *61*, 7125.

(14) For a preliminary communication of a part of this work, see: Alcaide, B.; Salgado, N. R.; Sierra, M. A. *Tetrahedron Lett.* **1998**, *39*, 467.

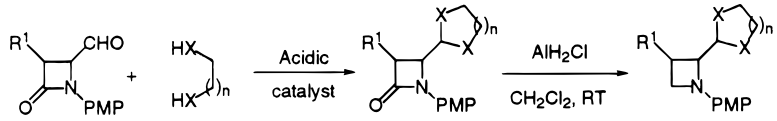
(15) For some selected examples reporting the bizarre effects caused by the inhibition of NC=O resonance in amides, especially in the so-called anti-Bredt amides, see: (a) Alcaide, B.; Casarrubios, L.; Domínguez, G.; Sierra, M. A.; Monge, A. *J. Am. Chem. Soc.* **1995**, *117*, 5604. (b) Brouillette, W. J.; Einspahr, H. M. *J. Org. Chem.* **1984**, *49*, 5113. (c) Collins, T. J.; Coots, R. J.; Furutani, T. T.; Keech; J. T.; Peake, G. T.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1986**, *108*, 5333. (d) Somayaji, V.; Brown, R. S. *J. Am. Chem. Soc.* **1987**, *109*, 4738. (e) Somayaji, V.; Skorey, K. I.; Brown, R. S. *J. Org. Chem.* **1986**, *51*, 4866. Slebocka-Tilk, H.; Brown, R. S. *J. Org. Chem.* **1987**, *52*, 805. (f) Williams, R. M.; Lee, B. H.; Miller, M. M.; Anderson, O. P. *J. Am. Chem. Soc.* **1989**, *111*, 1073.

(16) β-Lactams **1** were prepared in multigram quantities by standard acid chloride−imine cyclization, and were used as single *cis*- or *trans*-diastereomers throughout this work.

(17) (a) Alcaide, B.; Martín-Cantalejo, Y.; Plumet, J.; Rodríguez-López, J.; Sierra, M. A. *Tetrahedron Lett.* **1991**, *32*, 803. (b) Alcaide, B.; Martín-Cantalejo, Y.; Pérez-Castells, J.; Rodríguez-López, J.; Sierra, M. A.; Monge, A.; Pérez-García, V. *J. Org. Chem.* **1992**, *57*, 5921.

(18) Alcaide, B.; Aly, M.; Rodríguez-Vicente, A. *Tetrahedron Lett.* **1998**, *39*, 5865.

Table 2. Synthesis of Cyclic Acetal or Thioacetal Azetidines 6

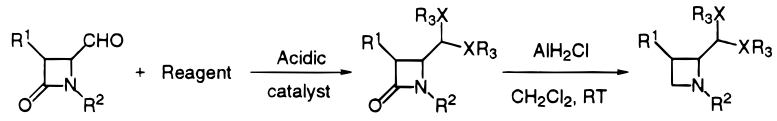


4 5 6

formyl-β-lactam	R^1	acidic catalyst	X	*n*	acetal β-lactam	yield[a] (%)	acetal azetidine	yield[a] (%)
cis-**4a**	Ph	PTSA	O	1	*cis*-**5a**	94	*cis*-**6a**	85
cis-**4b**	Me	PTSA	O	1	*cis*-**5b**	77	*cis*-**6b**	97
cis-**4c**	PhO	PTSA	O	1	*cis*-**5c**	77	*cis*-**6c**	94
trans-**4a**	Ph	PTSA	O	1	*trans*-**5a**	49	*trans*-**6a**	71
4d		PTSA	O	1	**5d**	44	**6d**	69
cis-**4b**	Me	PTSA	O	2	*cis*-**5e**	79	*cis*-**6e**	90
cis-**4a**	Ph	$BF_3(OEt)_2$	S	1	*cis*-**5f**	71	*cis*-**6f**	81
cis-**4b**	Me	$BF_3(OEt)_2$	S	1	*cis*-**5g**	82	*cis*-**6g**	95
cis-**4c**	PhO	$BF_3(OEt)_2$	S	1	*cis*-**5h**	71	*cis*-**6h**	89
cis-**4e**		$BF_3(OEt)_2$	S	1	*cis*-**5i**	99	*cis*-**6i**	73
trans-**4a**	Ph	$BF_3(OEt)_2$	S	1	*trans*-**5f**	85	*trans*-**6f**	97
trans-**4b**	Me	$BF_3(OEt)_2$	S	1	*trans*-**5g**	99	*trans*-**6g**	96
4d		$BF_3(OEt)_2$	S	1	**5j**	42	**6j**	100
cis-**4b**	Me	$BF_3(OEt)_2$	S	2	*cis*-**5k**	84	*cis*-**6k**	100

[a] Yield of pure, isolated product with correct analytical and spectral data. PMP = 4-$MeOC_6H_4$.

Table 3. Synthesis of Acyclic Acetal or Thioacetal Azetidines 8



4 7 8

formyl-β-lactam	R^1	R^2	acidic catalyst	reagent	X	R^3	acetal β-lactam	yield[a] (%)	acetal azetidine	yield[a] (%)
cis-**4b**	Me	PMP	amberlite	$HC(OMe)_3$	O	Me	*cis*-**7a**	88	*cis*-**8a**	100
cis-**4c**	PhO	PMP	amberlite	$HC(OMe)_3$	O	Me	*cis*-**7b**	43	*cis*-**8b**	92
cis-**4m**	PhO	Bn	amberlite	$HC(OMe)_3$	O	Me	*cis*-**7c**	55	*cis*-**8c**	93
cis-**4a**	Ph	PMP	$BF_3(OEt)_2$	PhSH	S	Ph	*cis*-**7d**	72	*cis*-**8d**	98
cis-**4b**	Me	PMP	$BF_3(OEt)_2$	PhSH	S	Ph	*cis*-**7e**	89	*cis*-**8e**	100
cis-**4c**	PhO	PMP	$BF_3(OEt)_2$	PhSH	S	Ph	*cis*-**7f**	76	*cis*-**8f**	100
cis-**4m**	PhO	Bn	$BF_3(OEt)_2$	PhSH	S	Ph	*cis*-**7g**	31	*cis*-**8g**	66
trans-**4a**	Ph	PMP	$BF_3(OEt)_2$	PhSH	S	Ph	*trans*-**7d**	64	*trans*-**8d**	97
trans-**4b**	Me	PMP	$BF_3(OEt)_2$	PhSH	S	Ph	*trans*-**7e**	72	*trans*-**8e**	74
4d		PMP	$BF_3(OEt)_2$	PhSH	S	Ph	**7h**	66	**8h**	100

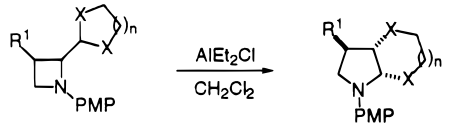
[a] Yield of pure, isolated product with correct analytical and spectral data. PMP = 4-$MeOC_6H_4$.

product (Table 4). This transformation tolerates alkyl, alkenyl, and aryl substituents at C3 on the azetidine ring, for both cyclic acetals and dithioacetals. The only exception was dithianyl azetidine *cis*-**6k**, which under the reaction conditions of method A, after a few minutes, gave a complex reaction mixture of unidentified products. The behavior of 3-phenoxy and 3-isopropylidene derivatives is worthy of note, showing a dramatic change in reactivity due to the acetal moiety. Thus, while 2-dioxolanyl azetidines *cis*-**6c** and **6d** were unreactive under different tested conditions, the corresponding 2-dithiolanyl azetidines *cis*-**6h** and **6j** smoothly gave pyrrole derivatives **19a** and **19b**, respectively (see later in Table 6).

The above results clearly show that diethylaluminum chloride promoted reaction of azetidines **6** bearing a cyclic acetal moiety is a stereoselective process for the preparation of bicyclic pyrrolidines **9**, the reaction being slightly faster when dithiolanyl azetidines **6f**,**g**,**i** are used as starting materials. It should be mentioned that the stereochemistry of the starting azetidine has no influence on the stereochemistry of the final product; e.g., fused pyrrolidine **9e** was obtained with similar yield by the diethylaluminum chloride promoted rearrangement of azetidine *cis*-**6g** or azetidine *trans*-**6g**. Formation of olefins **3** and fused pyrrolidines **9** can be rationalized through initial coordination of the lone electron pair of nitrogen to $AlEt_2Cl$ to give the coordinate species **10**. This coordination should promote C2−N1 bond breakage to form zwitterion **11**.[19] Intermediate **11** may react through two different pathways depending on the nature of the group attached to C2. For electron-donor aryl groups (R^2 = furyl, *p*-anisyl), the C3−C4 bond would break to yield the observed olefin **3**, together with iminium salt **12**. Different behavior of azetidines **2** and **6** may be due to the presence of a cyclic acetal or thioacetal group at C2

(19) 2-Alkoxy azetidines, putative intermediates in the transformation of β-chloroimines to β-(alkylamino)carbonyl compounds, have been postulated to experience a related N1−C2 bond breakage, in basic alkoxide media. Sulmon, P.; De Kimpe, N.; Schamp, N. *Tetrahedron* **1989**, *45*, 2937.

Table 4. Synthesis of Fused Pyrrolidines 9

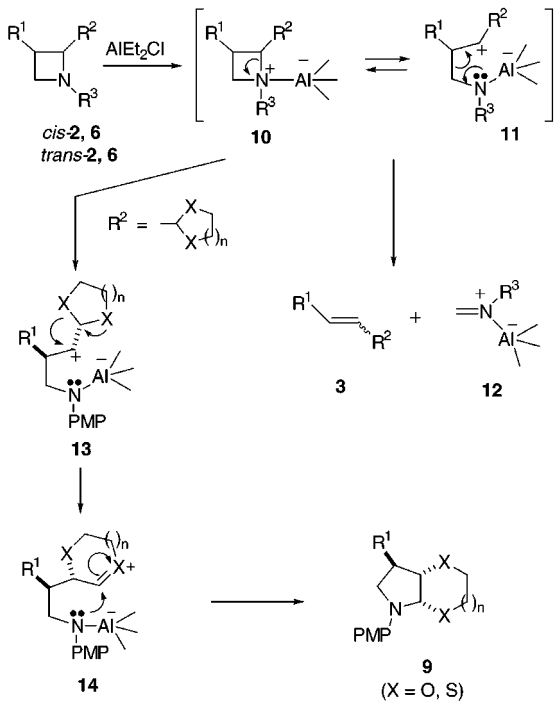


6 **9**

acetal azetidine	R^1	X	*n*	method[a]	time	fused pyrrolidines	yield[b] (%)
cis-**6a**	Ph	O	1	A	2 d	**9a**	35
cis-**6b**	Me	O	1	A	12 d	**9b**	35
cis-**6e**	Me	O	2	B	6 d	**9c**	64
cis-**6f**	Ph	S	1	A	12 h	**9d**	30
cis-**6g**	Me	S	1	A	19 h	**9e**	86
cis-**6g**	Me	S	1	B	5 min	**9e**	82
cis-**6g**	Me	S	1	C	30 min	**9e**	61
cis-**6i**		S	1	A	1 h	**9f**	66
cis-**6i**		S	1	B	3 h	**9f**	64
trans-**6f**	Ph	S	1	A	12 h	**9d**	30
trans-**6g**	Me	S	1	A	19 h	**9e**	71

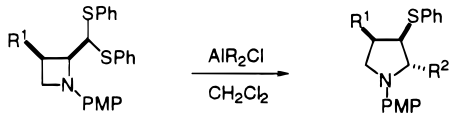
[a] Method A: The reaction was carried out at room temperature with an azetidine:$AlEt_2Cl$ ratio of 1:1. Method B: The reaction was carried out at reflux temperature with an azetidine:$AlEt_2Cl$ ratio of 1:1. Method C: The reaction was carried out at reflux temperature with an azetidine:$AlEt_2Cl$ ratio of 1:2. [b] Yield of pure, isolated product with correct analytical and spectral data. PMP = 4-$MeOC_6H_4$.

Scheme 1



in compounds **6**. This acetal moiety promotes the conversion of intermediate **11** to a new carbocation **14**, which is, in turn, trapped intramolecularly by the nitrogen atom, to yield the double rearranged product **9**. The stereochemical result can be tentatively interpreted through species **13**, a common intermediate for both *cis*- and *trans*-azetidines **2** and **6**, which suffers a rearrangement to give **14**, the nucleophilic moiety being delivered from the less hindered face (Scheme 1). Alternatively, the high selectivity observed in reactions of azetidines **2** or **6** may point to a concerted fragmentation of the aluminum coordinated azetidine **10** to form the reaction

Table 5. Synthesis of Pyrrolidines 15



cis-**8** **15**

acetal azetidine	R^1	R^2	method[a]	time	pyrrolidines	yield[b] (%)
cis-**8d**	Ph	Et	A	24 h	**15a**	67
cis-**8e**	Me	Et	A	12 h	**15b**	31
cis-**8e**	Me	Et	B	10 min	**15b**	72
cis-**8e**	Me	Et	C	12 h	**15b**	63
cis-**8e**	Me	Me	B	10 min	**15c**	38

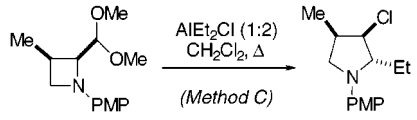
[a] Method A: The reaction was carried out at room temperature with an azetidine:$AlEt_2Cl$ ratio of 1:1. Method B: The reaction was carried out at reflux temperature with an azetidine:$AlEt_2Cl$ ratio of 1:1. Method C: The reaction was carried out at reflux temperature with an azetidine:$AlEt_2Cl$ ratio of 1:2. [b] Yield of pure, isolated product with correct analytical and spectral data.

products without involvement of chelated or unchelated open-chain zwitterions. According to the proposed reaction pathway, electron-donating groups attached at C2 should promote formation of a carbon−carbon double bond to give compounds **3**. The strong preference for the rearrangement of the five-membered ring in compounds **6** may be due to the increased stability of the new carbocation **14** formed.

To examine the rearrangement reaction on acyclic thioacetals, we chose azetidines *cis*-**8d**,**e** as precursors for the reaction with $AlEt_2Cl$ or $AlMe_2Cl$, and the process succeeded in the stereoselective synthesis of pyrrolidines **15** (Table 5).[20] However, when isomeric azetidines *trans*-**8d**,**e** were treated with $AlEt_2Cl$ under standard conditions, complex mixtures of products were obtained (it should be mentioned that azetidines *cis*-**6** and *trans*-**6** gave the same fused bicyclic pyrrolidines; see Table 4).

Interestingly, reaction of acetal azetidine *cis*-**8a** with diethylaluminum chloride at reflux temperature of dichloromethane, using an azetidine:$AlEt_2Cl$ molar ratio of 1:2, proceeded selectively to give chloropyrrolidine **16** in moderate yield (Scheme 2). However, azetidines *cis*-**8b**,**c** were unreactive under different experimental conditions.

Scheme 2

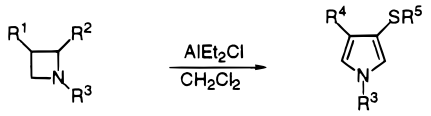


cis-**8a** **16**

The relative stereochemistry of products **9**, **15**, and **16** is different, so the preferred formation of pyrrolidines **15** and **16** is inconsistent with participation of the same suggested transition structures to form bicycles **9** (Scheme 1). Different behavior of azetidines *trans*-**6** and *trans*-**8**

(20) Because of the importance of substituted, stereoisomerically pure pyrrolidines as building blocks for the synthesis of natural products and pharmaceuticals, their stereocontrolled synthesis remains an intensive research area. See, for example: (a) Lown, J. W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, p 653. (b) Pearson, W. H. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: New York, 1988; Vol. 1, Part A, p 323. (c) Kopach, M. E.; Fray, A. H.; Meyers, A. I. *J. Am. Chem. Soc.* **1996**, *118*, 9876. (d) Barluenga, J.; Canteli, R. M.; Florez, J. *J. Org. Chem.* **1996**, *61*, 3753. (e) Karlson, S.; Han, F.; Högberg, H.-E.; Caldirola, P. *Tetrahedron: Asymmetry* **1999**, *10*, 2605.

Table 6. Synthesis of Pyrroles 19

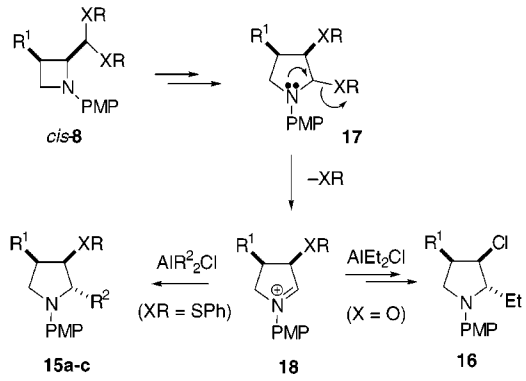


6, 8 **19**

thioacetal azetidine	R^1	R^2	R^3	R^4	R^5	method[a]	pyrrole	yield[b] (%)
cis-**6h**	PhO	Dith[c]	PMP	H		A	**19a**	67
6j		Dith[c]	PMP	^{i}Pr		A	**19b**	38
cis-**8f**	PhO		PMP	H	Ph	B	**19c**	55
cis-**8g**	PhO		Bn	H	Ph	C	**19d**	72

[a] Method A: The reaction was carried out at room temperature with an azetidine:$AlEt_2Cl$ ratio of 1:1. Method B: The reaction was carried out at reflux temperature with an azetidine:$AlEt_2Cl$ ratio of 1:1. Method C: The reaction was carried out at reflux temperature with an azetidine:$AlEt_2Cl$ ratio of 1:2. [b] Yield of pure, isolated product with correct analytical and spectral data. PMP = 4-$MeOC_6H_4$. [c] Dith = 1,3-dithiolan-2-yl.

Scheme 3

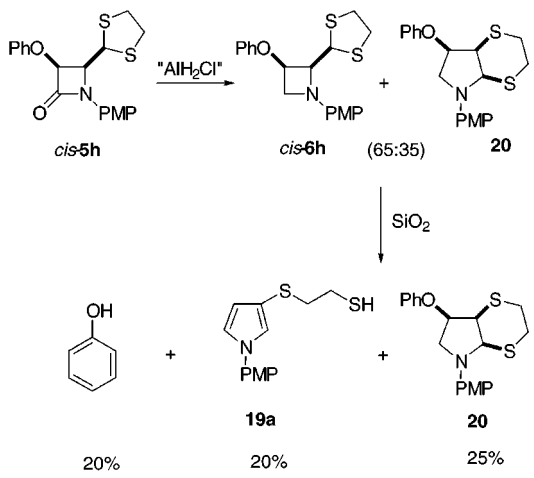


in their reactions with $AlEt_2Cl$ may also point out that formation of bicycles **9** and pyrrolidines **15** should not be similar. We believe that for monocyclic compounds **15** and **16** the XR group at C2 in the former pyrrolidine **17** is eliminated to give an iminium salt **18**, the alkyl moiety being delivered from the organometallic reagent on the less hindered face at the iminium cation (Scheme 3). However, a clear explanation for the stereochemistry at C4 has not yet been found. Azetidine *cis*-**8a** should evolve into an intermediate bearing an oxygenated substituent at C3. This intermediate should be coordinated by another molecule of $AlEt_2Cl$ with further substitution for a chlorine atom, yielding the chloropyrrolidine **16**. As far as we know this behavior of diethylaluminum chloride is unprecedented. The difference in reactivity of dimethylacetal azetidine *cis*-**8a** and diphenylthioacetal azetidines *cis*-**8d**,**e** may be due to the strong oxophilicity of aluminum, allowing a better coordination with the oxygen prior to the sulfur.

3-Phenoxy and 3-isopropylidene thioacetal azetidines *cis*-**6h**, **6j**, and *cis*-**8f**−**g** were treated with $AlEt_2Cl$ under the above conditions to furnish pyrroles **19** in moderate to good yields (38−72%) (Table 6). In this manner a new methodology is available for the preparation of different novel 3-thio-functionalized pyrrole derivatives. The introduction of substituents at the 3-position of pyrroles is of great importance in the synthesis of natural products, while these pyrroles are not easily accessible.[21]

Of special interest in this context was the reaction of acetal β-lactam *cis*-**5h** with monochloroalane (AlH_2Cl),

Scheme 4

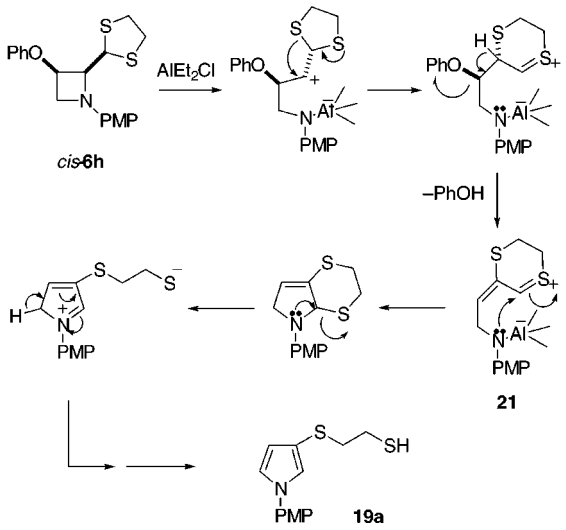


on standing for longer reaction time (45 min). The ^1H NMR spectrum of the crude reaction mixture showed the expected azetidine *cis*-**6h** together with bicycle **20** (ratio *cis*-**6h**:**20** = 65:35). After flash chromatography on silica gel, bicycle **20** (25%), pyrrole **19a** (20%), and phenol (20%) were isolated. From this result it is evident that azetidine *cis*-**6h** and not bicycle **20** was transformed into pyrrole **19a** and phenol under chromatographic conditions. In an independent experiment, when compound **20** was treated with $AlEt_2Cl$ under the usual reaction conditions, unaltered **20** was recovered, confirming that azetidine *cis*-**6h**, and not bicycle **20**, was the pyrrole precursor. The stereochemistry of bicycle **20** and bicyclic pyrrolidines **9** is different at the C9 stereocenter, but it should be mentioned that the origin is totally different (Scheme 4).

Formation of pyrroles **19a**,**c**,**d** can be illustrated following the scheme drawn for compound **19a**. The main difference between this mechanistic proposal and the given explanation for the formation of bicyclic pyrrolidines **9** is the elimination of a molecule of phenol, giving intermediate **21**, which evolves to yield pyrrole **19a**

(21) See, for example: (a) Pavri, N. P.; Trudell, M. L. *J. Org. Chem.* **1997**, *62*, 2649. (b) Tehrani, K. A.; Borremans, D.; De Kimpe, N. *Tetrahedron* **1999**, *55*, 4133. (c) Kesteleyn, B.; Rosas Alonso, E.; Stevens, Ch.; Dejaegher, Y.; Peristeropoulou, M.; Nguyen Van, T.; Kulinkovich, O.; De Kimpe, N. *Tetrahedron* **1999**, *55*, 4153.

Scheme 5



(Scheme 5). Pyrrole **19b** should have a similar origin, but now formation of pyrrole **19b** must arise from the isomerization of the ethylenic bond. A substituent at C3 on the azetidine ring that can promote aromatization seems to be the driving force for pyrrole formation.

Configurational Assignment for Pyrrolidines 9, 15, 16, and 20. The structure and stereochemistry of compounds **9**, **15**, **16**, and **20** have been assigned by NMR techniques. NOE irradiation of H1 on fused pyrrolidine **9d** resulted in 11% enhancement in the signals corresponding to H6 and the phenyl group, while NOE irradiation of H6 resulted in enhancement of the signals corresponding to H1 and the 4-methoxyphenyl group (19% and 23%, respectively). On the basis of these data, a *syn*-H1−H6/*anti*-H1−H9 relative stereochemistry was assigned. Irradiation of H6 in compound **9f** gave a NOE enhancement of 15% on H1 and an enhancement of 20% on the signals corresponding to the 4-methoxyphenyl group, being assigned a *syn* relative disposition between H1 and H6. Furthermore, NOE irradiation of H1 resulted in enhancements of the signals corresponding to H6 and the isopropylidene group (8% and 9%, respectively), being assigned an *anti*-H1−H9 relative stereochemistry (Figure 1).

For compound **20**, NOE enhancements of H1 (8%) and the 4-methoxyphenyl group (12%) on irradiation of H6, NOE enhancements of H6 (6%) and H9 (8%) on irradiation of H1, and NOE enhancements of H1 (9%) and H8 (8%) on irradiation of H9 were consistent with a *syn*-H1−H6/*syn*-H1−H9 relative stereochemistry (Figure 1).

NOE irradiation of H3 on pyrrolidine **15b** resulted in enhancements of the signals corresponding to H4 and the ethyl moiety (13% and 15%, respectively). Furthermore, a 2% enhancement of the C4-methyl group was observed on irradiation of H2, which is in agreement with the proposed stereochemistry (Figure 2). The stereochemistry for chloropyrrolidine **16** was immediately deduced by comparison with the above results. Thus, NOE enhancements of 15%, 12%, and 14% were observed on CH_2CH_3, CH_2CH_3, and H4, respectively, when H3 was irradiated, which is consistent with an *anti*-H2−H3/*syn*-H3−H4 relative stereochemistry (Figure 2).

Conclusions. The present study provides the first insight into the manner in which a variety of different substituted azetidines undergo fragmentation and rearrangement reactions promoted by diethylaluminum chloride. These results show that diethylaluminum chloride promoted reactions on the azetidine nucleus, namely, its fragmentation and its rearrangement, are efficient and stereocontrolled processes which can be used to prepare different types of interesting functionalized compounds, including olefins, monocyclic pyrrolidines, fused bicyclic pyrrolidines, and pyrroles. Furthermore, as far as we know, these are the first examples of Lewis acid promoted fragmentation or rearrangement on the azetidine nucleus. Notwithstanding the mechanistic dichotomy on monocyclic pyrrolidine formation, the different behavior of acetal azetidines reported herein is significant and will have a bearing on their application in organic synthesis. Other aspects of the novel reactivity of the azetidine ring are under investigation.

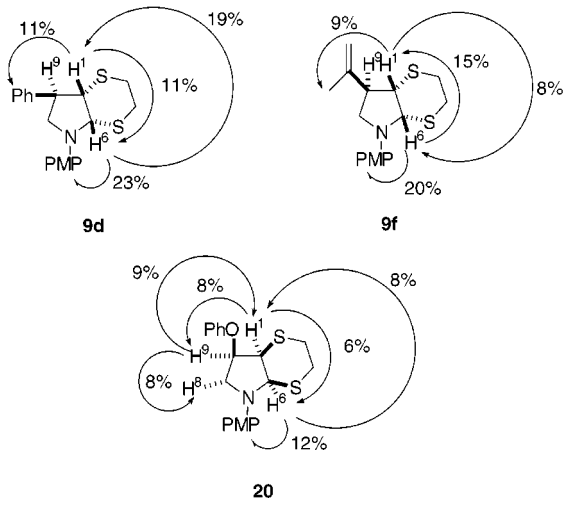


Figure 1. Relative stereochemistry of fused pyrrolidines **9d**, **9f**, and **20**.

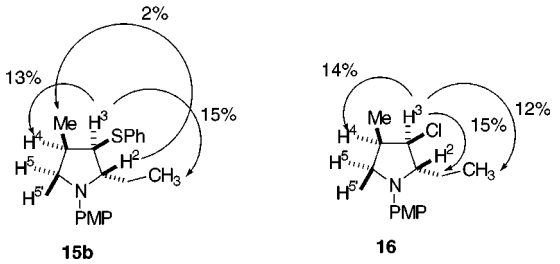


Figure 2. Relative stereochemistry of pyrrolidines **15b** and **16**.

Experimental Section

General Methods. General experimental data and procedures have been previously reported.[13f] All NMR spectra were recorded in $CDCl_3$ solutions with TMS as the internal standard unless otherwise stated. All commercially available compounds were used without further purification. 4-Formyl-*β*-lactams **4** were used in all cases as single *cis*-[17] or *trans*-isomers.[18]

General Method for the Synthesis of Azetidines 2, 6, and 8. A solution of anhydrous $AlCl_3$ (3 mmol) in dry Et_2O (10 mL) was added via syringe to a well-stirred suspension of $LiAlH_4$ (3 mmol) in anhydrous Et_2O (10 mL). The mixture was refluxed for 30 min, cooled to rt, and transferred via cannula to a solution of the corresponding *β*-lactam **1**, **5**, or **7** (1 mmol), in dry Et_2O (5 mL). Inmediately, after the end of the addition, TLC analysis showed the complete transformation of the starting material. The reaction mixture was cooled to 0 °C and then quenched with water (10 mL), diluted with Et_2O (15 mL),

and washed with brine (20 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude products were used without any further purification. Representative examples for the preparation of azetidines follow.[22]

***cis*-2-(1′,3′-Dithiolan-2-yl)-1-(*p*-methoxyphenyl)-3-phenoxyazetidine, *cis*-6h.** From acetal β-lactam *cis*-**5h** (0.35 g, 0.94 mmol), $AlCl_3$ (0.37 g, 2.81 mmol), and $LiAlH_4$ (0.11 g, 2.81 mmol), 0.30 g (89%) of azetidine *cis*-**6h** was obtained as a colorless oil. ^{1}H NMR: δ 3.27 (m, 4 H), 3.75 (s, 3 H), 3.99 (dd, 1 H, J = 8.8, 7.3 Hz), 4.19 (dd, 1 H, J = 9.2, 4.4 Hz), 4.42 (dd, 1 H, J = 8.5, 7.7 Hz), 5.02 (dt, 1 H, J = 7.3, 4.0 Hz), 5.24 (d, 1 H, J = 8.8 Hz), 6.76 (m, 4 H), 6.90 (m, 2 H), 7.19 (m, 3 H). ^{13}C NMR: δ 156.9, 152.7, 144.7, 129.6, 121.6, 116.3, 115.7, 114.9, 73.4, 68.4, 59.9, 55.8, 53.3, 38.5, 38.1. IR ($CHCl_3$): ν 1430, 1220. Anal. Calcd for $C_{19}H_{21}NS_2O_2$: C, 63.48; H, 5.89; N, 3.90; S, 17.84. Found: C, 63.28; H, 5.95; N, 3.50; S, 17.57.

***trans*-2-(1′,3′-Dithiolan-2-yl)-1-(*p*-methoxyphenyl)-3-methylazetidine, *trans*-6g.** From acetal β-lactam *trans*-**5g** (0.11 g, 0.37 mmol), $AlCl_3$ (0.15 g, 1.11 mmol) and $LiAlH_4$ (44 mg, 1.11 mmol), 0.10 g (96%) of azetidine *trans*-**6g** was obtained as a colorless oil. ^{1}H NMR: δ 1.23 (d, 3 H, J = 7.0 Hz), 2.76 (m, 1 H), 3.11 (t, 1 H, J = 6.6 Hz), 3.24 (m, 4 H), 3.67 (s, 3 H), 3.73 (d, 1 H, J = 5.9 Hz), 4.10 (t, 1 H, J = 6.6 Hz), 5.00 (d, 1 H, J = 5.2 Hz), 6.63 (dd, 2 H, J = 8.9 Hz), 6.79 (dd, 2 H, J = 8.8, 2.2 Hz). ^{13}C NMR: δ 152.5, 146.2, 114.5, 113.5, 75.3, 58.1, 57.9, 55.8, 38.6, 38.4, 29.9, 19.8. IR ($CHCl_3$): ν 1520. Anal. Calcd for $C_{14}H_{19}NS_2O$: C, 59.75; H, 6.80; N, 4.98; S, 22.78. Found: C, 59.35; H, 6.40; N, 4.58; S, 23.38.

***cis*-2-Dimethoxymethyl-1-(*p*-methoxyphenyl)-3-methylazetidine, *cis*-8a.** From acetal β-lactam *cis*-**7a** (0.19 g, 0.72 mmol), $AlCl_3$ (0.28 g, 2.15 mmol), and $LiAlH_4$ (86 mg, 2.15 mmol), 0.17 g (100%) of azetidine *cis*-**8a** was obtained as a pale yellow oil. ^{1}H NMR: δ 1.36 (d, 3 H, J = 7.3 Hz), 2.72 (m, 1 H), 3.46 and 3.49 (s, each 3 H), 3.60 (dd, 1 H, J = 7.0, 4.0 Hz), 3.69 (dd, 1 H, J = 8.8, 7.0 Hz), 3.75 (s, 3 H), 3.97 (t, 1 H, J = 8.8 Hz), 4.59 (d, 1 H, J = 7.7 Hz), 6.72 (s, 4 H). ^{13}C NMR: δ 152.5, 146.9, 114.3, 114.2, 106.5, 66.8, 59.1, 57.3, 55.8, 53.8, 26.6, 15.7. IR ($CHCl_3$): ν 1430, 1230. Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 67.31; H, 8.82; N, 5.97.

***cis*-3-Isopropyliden-1-(*p*-methoxyphenyl)-2-bis(phenylthiomethyl)azetidine, 8h.** From acetal β-lactam **7h** (126 mg, 0.28 mmol), $AlCl_3$ (0.11 g, 0.84 mmol) and $LiAlH_4$ (34 mg, 0.84 mmol), 0.12 g (100%) of azetidine **8h** was obtained as a colorless oil. ^{1}H NMR: δ 1.59 and 1.70 (s, each 3 H), 3.75 (s, 3 H), 4.07 and 4.66 (d, each 1 H, J = 11.0 Hz), 4.79 (s, 1 H), 4.96 (br s, 1 H), 6.47 and 6.75 (d, each 2 H, J = 9.0 Hz), 7.21 (m, 7 H), 7.40 (m, 3 H). ^{13}C NMR: δ 152.3, 144. 7, 135.4, 133.4, 132.3, 129.0, 127.9, 127.5, 126.3, 124.1, 114.5, 113.6, 74.0, 64.4, 59.8, 55.8, 19.9, 19.3. IR ($CHCl_3$): ν 1430, 1220. Anal. Calcd for $C_{26}H_{27}NS_2O_2$: C, 72.02; H, 6.28; N, 3.23; S, 14.79. Found: C, 71.99; H, 6.17; N, 3.35; S, 14.85.

General Method for the Reaction of Azetidines with Diethylaluminum Chloride. Method A. To a solution of the appropriate azetidine **2**, **6**, or **8** (1.0 mmol) in CH_2Cl_2 (5 mL) was added, via syringe, a cooled solution of $AlEt_2Cl$ (0.12 g, 1.0 mmol) in hexane (1.0 mL). The reaction was stirred under argon at room temperature until complete disappearance of the azetidine (TLC). The reaction mixture was cooled (0 °C), and then saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was allowed to warm to room temperature before being diluted with CH_2Cl_2 (15 mL). The organic layer was separated dried ($MgSO_4$) and the solvent removed under reduced pressure. Residues were purified by flash chromatography eluting with EtOAc/hexanes mixtures.

Method B. To a solution of the appropriate azetidine **6** or **8** (1.0 mmol) in CH_2Cl_2 (5 mL) was added, via syringe, a solution of $AlEt_2Cl$ (0.12 g, 1.0 mmol) in hexane (1.0 mL). The reaction was stirred under argon at reflux temperature until complete disappearance of the azetidine (TLC). The reaction mixture was cooled (0 °C), and then saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was allowed to warm to room temperature before being diluted with CH_2Cl_2 (15 mL). The organic layer was separated and dried ($MgSO_4$) and the solvent removed under reduced pressure. Residues were purified by flash chromatography eluting with EtOAc/hexanes mixtures.

Method C. To a solution of the appropriate azetidine **6** or **8** (1.0 mmol) in CH_2Cl_2 (5 mL) was added, via syringe, a solution of $AlEt_2Cl$ (0.24 g, 2.0 mmol) in hexane (2.0 mL). The reaction was stirred under argon at room temperature until complete disappearance of the azetidine (TLC). The reaction mixture was cooled (0 °C), and then saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was allowed to warm to room temperature before being diluted with CH_2Cl_2 (15 mL). The organic layer was separated and dried ($MgSO_4$) and the solvent removed under reduced pressure. Residues were purified by flash chromatography eluting with EtOAc/hexanes mixtures. Representative examples for the preparation of olefins **3**, pyrrolidines **9**, **15**, and **16**, and pyrroles **19** following different methods follow.

(*Z*)-2-(*p*-Methoxyphenyl)-1-phenoxyethene, 3a. Method A. From azetidine *cis*-**2a** (80 mg, 0.20 mmol) and $AlEt_2Cl$ (0.20 mL, 0.20 mmol), 20 mg (57%) of alkene **3a** was obtained as a pale yellow oil after purification by flash chromatography (AcOEt/hexanes, 1:20). ^{1}H NMR: δ 3.81 (s, 3 H), 5.59 (d, 1 H, J = 6.9 Hz), 6.54 (d, 1 H, J = 6.9 Hz), 6.87 (d, 2 H, J = 9.0 Hz), 7.10 (d, 1 H, J = 10.8 Hz), 7.12 (d, 1 H, J = 8.7 Hz), 7.31 (m, 4 H), 7.63 (d, 2 H, J = 8.7 Hz). ^{13}C NMR: δ 140.3, 129.6, 127.7, 123.1, 114.2, 113.7, 113.5, 110.2, 55.3, 29.7. IR ($CHCl_3$): ν 1600, 1510. Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.22; H, 6.64.

(*E*)-1-(*p*-Methoxyphenyl)-2-phenylethene, 3c. Method A. From azetidine *trans*-**2g** (0.15 g, 0.45 mmol) and $AlEt_2Cl$ (0.45 mL, 0.45 mmol), 60 mg (68%) of alkene **3c** was obtained as a colorless solid after purification by flash chromatography (EtOAc/hexanes, 1:10). Mp: 131−134 °C. ^{1}H NMR: δ 3.74 (s, 3 H), 6.83 (t, 2 H, J = 8.8 Hz), 6.97 (d, 2 H, J = 14.3 Hz), 7.15 (m, 2 H), 7.26 (m, 2 H), 7.36 (m, 3 H). ^{13}C NMR: δ 159.2, 137.6, 130.1, 128.6, 128.1, 127.7, 127.2, 126.5, 126.2, 114.1, 55.3, 29.7. IR (KBr): ν 1510, 1250. Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.82; H, 6.85.

(*E*)-1-(*p*-Methoxyphenyl)butadiene, 3d. Method A. From azetidine *trans*-**2h** (0.13 g, 0.46 mmol) and $AlEt_2Cl$ (0.46 mL, 0.46 mmol), 60 mg (76%) of alkene **3d** was obtained as a pale yellow oil after purification by flash chromatography (EtOAc/hexanes, 1:5). ^{1}H NMR: δ 3.73 (s, 3 H), 5.03 (dd, 1 H, J = 9.5, 1.5 Hz), 5.20 (dd, 1 H, J = 16.5, 1.5 Hz), 6.40 (dd, 1 H, J = 16.5, 10.3 Hz), 6.44 (dd, 1 H, J = 16.9, 2.5 Hz), 6.60 (dd, 1 H, J = 14.7, 10.6 Hz), 6.78 and 7.25 (d, each 2 H, J = 9.0 Hz). ^{13}C NMR: δ 159.3, 137.4, 132.4, 129.9, 127.6 (3 C), 116.4, 114.1, 55.3. IR (KBr): ν 1510, 1250. Anal. Calcd for $C_{11}H_{12}O$: C, 91.61; H, 8.39. Found: C, 91.21; H, 8.69.

(1*E*,4*Z*)-1-Phenoxy-4-phenylbutadiene, 3e. Method A. From azetidine *cis*-**2i** (89 mg, 0.26 mmol) and $AlEt_2Cl$ (0.26 mL, 0.26 mmol), 42 mg (72%) of alkene **3e** was obtained as a colorless oil after purification by flash chromatography (EtOAc/hexanes, 1:7). ^{1}H NMR: δ 5.64 (dd, 1 H, J = 11.4, 6.3 Hz), 6.48 (d, 1 H, J = 6.3 Hz), 6.55 (d, 1 H, J = 15.8 Hz), 7.08 (m, 3 H), 7.19 (m, 6 H), 7.45 (m, 2 H). IR ($CHCl_3$): ν 1510, 1250. Anal. Calcd for $C_{11}H_{12}O$: C, 91.61; H, 8.39. Found: C, 91.31; H, 8.49.

(1*R,6*R**,9*R**)-2,5-Dioxa-7-(*p*-methoxyphenyl)-9-phenyl-7-azabycyclo[4,3,0]nonane, 9a. Method A.** From azetidine *cis*-**6a** (34 mg, 0.10 mmol) and $AlEt_2Cl$ (0.10 mL, 0.10 mmol), 12 mg (35%) of compound **9a** was obtained as a colorless oil after purification by flash chromatography (AcOEt/hexanes, 1:8). ^{1}H NMR: δ 3.49 (ddd, 1 H, J = 8.8, 5.7, 2.3 Hz), 3.75 (s, 3H), 3.77 (dd, 1 H, J = 4.8, 1.8 Hz), 3.79 (m, 1 H), 3.82 (d, 1 H, J = 6.2 Hz), 3.90 (ddd, 1 H, J = 9.4, 4.8, 1.8 Hz), 3.96 (m, 2 H), 4.04 (m, 2 H), 4.72 (d, 1 H, J = 4.4 Hz), 6.68 and 6.76 (d, each 2 H, J = 9.0 Hz), 7.29 (m, 5 H). ^{13}C NMR: δ 152.2, 142.2, 138.1, 128.9, 128.4, 127.4, 115.0, 114.9, 104.5, 65.5, 64.8, 57.2, 55.7, 49.0, 45.6. IR ($CHCl_3$): ν 1720. Anal.

(22) Full spectroscopic and analytical data for compounds not included in the Experimental Section are described in the Supporting Information.

Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.43; H, 6.94; N, 4.64.

(1*R,7*R**,10*R**)-2,6-Dioxa-8-(*p*-methoxyphenyl)-10-methyl-8-azabicyclo[5,3,0]decane, 9c. Method C.** From azetidine *cis*-**6e** (90 mg, 0.32 mmol) and $AlEt_2Cl$ (0.70 mL, 0.70 mmol), 59 mg (64%) of compound **9c** was obtained as a colorless oil after purification by flash chromatography (AcOEt/hexanes, 1:5). ^{1}H NMR: δ 1.03 (d, 3 H, J = 6.8 Hz), 1.23 (m, 1 H), 1.99 (m, 1 H), 2.26 (m, 1 H), 3.40 (dd, 1 H, J = 10.6, 5.9 Hz), 3.56 (m, 3 H), 3.67 (s, 3 H), 3.70 (m, 2 H), 4.05 (td, 2 H, J = 10.7, 5.9 Hz), 4.58 (d, 1 H, J = 2.9 Hz), 6.59 and 6.69 (d, each 2 H, J = 9.0 Hz). ^{13}C NMR: δ 152.2, 142.0, 115.2, 114.9, 101.7, 66.9 (2 C), 57.8, 55.7, 48.8, 36.7, 25.8, 14.2. IR ($CHCl_3$): ν 1730. MS (EI): m/z 263 (M^+, 8), 212 (100). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04, N, 5.32. Found: C, 68.82; H, 8.44; N, 5.72.

(1*R,6*R**,9*R**)-2,5-Dithia-7-(*p*-methoxyphenyl)-9-methyl-7-azabicyclo[4,3,0]nonane, 9e. Method A.** From azetidine *cis*-**6g** (0.18 g, 0.64 mmol) and $AlEt_2Cl$ (0.64 mL, 0.64 mmol), 0.16 g (86%) of compound **9e** was obtained as a colorless oil after purification by flash chromatography (AcOEt/hexanes, 1:8).

Method B. From azetidine *cis*-**6g** (48 mg, 0.17 mmol) and $AlEt_2Cl$ (0.17 mL, 0.17 mmol), 40 mg (82%) of compound **9e** was obtained as a colorless oil after purification by flash chromatography (AcOEt/hexanes, 1:17).

Method C. From azetidine *cis*-**6g** (42 mg, 0.15 mmol) and $AlEt_2Cl$ (0.30 mL, 0.30 mmol), 26 mg (61%) of compound **9e** was obtained as a colorless oil after purification by flash chromatography (AcOEt/hexanes, 1:8).

Method A. From azetidine *trans*-**6g** (185 mg, 0.66 mmol) and $AlEt_2Cl$ (0.66 mL, 0.66 mmol), 132 mg (71%) of compound **9e** was obtained as a colorless oil after purification by flash chromatography (AcOEt/hexanes, 1:8). ^{1}H NMR: δ 1.24 (d, 3 H, J = 7.0 Hz), 2.47 (dd, 1 H, J = 8.3, 2.5 Hz), 2.75 (dd, 1 H, J = 10.7, 4.4 Hz), 2.81 (dd, 1 H, J = 13.6, 4.4 Hz), 2.94 (m, 4 H), 3.52 (m, 1 H), 3.74 (s, 3 H), 5.18 (d, 1 H, J = 4.4 Hz), 6.67 and 6.83 (d, each 2 H, J = 9.0 Hz). ^{13}C NMR: δ 151.9, 138.9, 114.9, 113.1, 61.4, 55.8, 53.8, 47.1, 33.7, 29.9, 23.9, 16.2. IR ($CHCl_3$): ν 1720. MS (EI): m/z 281 (M^+, 62), 174 (100). Anal. Calcd for $C_{14}H_{19}NS_2O$: C, 59.75; H, 6.80; N, 4.98; S, 22.78. Found: C, 59.35; H, 7.20; N, 6.40; S, 22.38.

(2*S,3*R**,4*R**)-2-Ethyl-1-(*p*-methoxyphenyl)-4-phenyl-3-phenylthiopyrrolidine, 15a. Method A.** From azetidine *cis*-**8d** (0.13 g, 0.29 mmol) and $AlEt_2Cl$ (0.29 mL, 0.29 mmol), 76 mg (67%) of compound **15a** was obtained as a colorless oil after purification by flash chromatography (AcOEt/hexanes, 1:9). ^{1}H NMR: δ 0.79 (t, 3 H, J = 7.3 Hz), 1.52 and 1.80 (m, each 1 H), 3.66 (m, 1 H), 3.80 (dd, 2 H, J = 8.8, 4.9 Hz), 3.81 (s, 3 H), 3.90 (dd, 1 H, J = 5.8, 1.9 Hz), 4.03 (m, 1 H), 6.54 and 6.86 (d, each 2 H, J = 9.0 Hz), 7.26 (m, 10 H). ^{13}C NMR: δ 132.9, 129.1, 128.9, 128.7, 128.6, 128.4, 128.2, 127.7, 127.5, 127.1, 115.1, 112.5, 68.1, 57.0, 55.9, 51.4, 45.6, 26.4, 10.3. MS (EI): m/z 389 (M^+, 49), 251 (100). Anal. Calcd for $C_{25}H_{27}NSO$: C, 77.08; H, 6.99; N, 3.60; S, 8.23. Found: C, 77.48; H, 7.39; N, 4.01; S, 8.63.

(2*S,3*R**,4*R**)-2-Ethyl-1-(*p*-methoxyphenyl)-4-methyl-3-phenylthiopyrrolidine, 15b. Method A.** From azetidine *cis*-**8e** (90 mg, 0.22 mmol) and $AlEt_2Cl$ (0.22 mL, 0.22 mmol), 22 mg (31%) of compound **15b** was obtained as a colorless oil after purification by flash chromatography (AcOEt/hexanes, 1:21).

Method B. From azetidine *cis*-**8e** (45 mg, 0.11 mmol) and $AlEt_2Cl$ (0.11 mL, 0.11 mmol), 26 mg (72%) of compound **15b** was obtained as a colorless oil after purification by flash chromatography (AcOEt/hexanes, 1:21).

Method C. From azetidine *cis*-**8e** (78 mg, 0.19 mmol) and $AlEt_2Cl$ (0.38 mL, 0.38 mmol), 39 mg (63%) of compound **15b** was obtained as a colorless oil after purification by flash chromatography (AcOEt/hexanes, 1:17). ^{1}H NMR (C_6D_6): δ 0.39 (t, 3 H, J = 7.4 Hz), 1.41 (d, 3 H, J = 6.8 Hz), 1.09 and 1.51 (m, each 1 H), 2.33 (m, 1 H), 2.83 (dd, 1 H, J = 9.5, 9.0 Hz), 3.07 (m, 1 H), 3.21 (m, 1 H), 3.25 (s, 3 H), 3.44 (d, 1 H J = 7.9 Hz), 6.35 and 7.11 (d, each 2 H, J = 9.0 Hz), 6.76 (m, 5 H). ^{13}C NMR: δ 150.6, 142.2, 135.4, 132.4, 128.9, 126.9, 114.9, 112.1, 68.4, 56.8, 55.5, 54.5, 35.3, 26.2, 14.0, 10.5. MS (EI): m/z 327 (M^+, 63), 189 (100). Anal. Calcd for $C_{20}H_{25}NSO$: C, 73.35; H, 7.69; N, 4.28; S, 9.79. Found: C, 73.75; H, 8.09; N, 4.68; S, 10.19.

(2*S,3*R**,4*R**)-2,4-Dimethyl-1-(*p*-methoxyphenyl)-3-phenylthiopyrrolidine, 15c. Method B.** From azetidine *cis*-**8e** (0.10 g, 0.25 mmol) and $AlMe_2Cl$ (0.25 mL, 0.25 mmol), 30 mg (38%) of compound **15c** was obtained as a colorless oil after purification by flash chromatography (AcOEt/hexanes, 1:19). ^{1}H NMR: δ 1.22 and 1.27 (d, each 3 H, J = 6.8 Hz), 2.82 (m, 1 H), 3.12 (t, 1 H, J = 8.8 Hz), 3.55 (m, 2 H), 3.67 (s, 3 H), 3.75 (m, 1 H), 6.39 and 6.75 (d, each 2 H, J = 9.0 Hz), 7.15 (m, 5 H). MS (EI): m/z 313 (M^+, 98), 189 (100). Anal. Calcd for $C_{19}H_{23}NSO$: C, 72.80; H, 7.40; N, 4.47; S, 10.23. Found: C, 73.20; H, 7.80; N, 4.87; S, 10.63.

(2*S,3*R**,4*R**)-3-Chloro-2-ethyl-1-(*p*-methoxyphenyl)-4-methylpyrrolidine, 16. Method C.** From azetidine *cis*-**8a** (0.10 g, 0.39 mmol) and $AlEt_2Cl$ (0.78 mL, 0.78 mmol), 30 mg (36%) of compound **16** was obtained as a colorless oil after purification by flash chromatography (AcOEt/hexanes, 1:14). ^{1}H NMR (C_6D_6): δ 0.68 (t, 3 H, J = 7.5 Hz), 0.72 (d, 3 H, J = 7.8 Hz), 1.57 (m, 1 H), 1.62 (m, 1 H), 2.22 (m, 1 H), 2.88 (dd, 1 H, J = 10.7, 8.5 Hz), 3.13 (dd, 1 H, J = 8.5, 7.1 Hz), 3.43 (s, 3 H), 3.72 (dd, 1 H, J = 10.0, 3.7 Hz), 3.82 (d, 1 H, J = 4.4 Hz), 6.53 and 6.87 (d, each 2 H, J = 9.4 Hz). ^{13}C NMR: δ 119.4, 115.2 (4 C), 112.3, 67.9, 61.9, 56.0, 36.3, 29.7, 26.8, 13.2, 10.9. MS (CI): m/z 255 ($M^+ + 2$, 39), 253 (M^+, 100). Anal. Calcd for $C_{14}H_{20}NClO$: C, 66.26; H, 7.94; N, 5.52; Cl, 13.97. Found: C, 65.86; H, 7.54; N, 5.12; Cl, 13.57.

3-(1′,4′-Dithiabutyl)-1-(*p*-methoxyphenyl)pyrrole, 19a. Method A. From azetidine *cis*-**6h** (70 mg, 0.18 mmol) and $AlEt_2Cl$ (0.18 mL, 0.18 mmol), 30 mg (67%) of compound **19a** was obtained as a colorless oil after purification by flash chromatography (AcOEt/hexanes, 1:2). ^{1}H NMR: δ 1.73 (dd, J = 8.1, 7.7 Hz), 2.72 (m, 2 H), 2.88 (m, 2 H), 3.84 (s, 3 H), 6.34 (m, 1 H), 6.95 (m, 3 H), 7.06 (ddd, 1 H, J = 4.0, 2.2, 1.8 Hz), 7.27 (dd, 2 H, J = 9.0, 2.0 Hz). ^{13}C NMR: δ 158.0, 133.7, 124.1, 123.8, 122.1, 120.7, 115.1, 114.7, 112.6, 55.6, 40.8, 24.5. MS (EI): m/z 265 (M^+, 83), 205 (100). Anal. Calcd for $C_{13}H_{15}NS_2O$: C, 58.84; H, 5.70; N, 5.28; S, 24.16. Found: C, 59.24; H, 5.30; N, 5.68; S, 24.56.

3-(1′,4′-Dithiabutyl)-4-isopropyl-1-(*p*-methoxyphenyl)-pyrrole, 19b. Method A. From azetidine **6j** (0.11 g, 0.37 mmol) and $AlEt_2Cl$ (0.37 mL, 0.37 mmol), 40 mg (38%) of compound **19b** was obtained as a colorless oil after purification by flash chromatography (AcOEt/hexanes, 1:6). ^{1}H NMR: δ 1.16 (d, 6 H, J = 7.9 Hz), 1.71 (dd, 1 H, J = 8.0, 7.7 Hz), 2.70 (m, 2 H), 2.81 (m, 2 H), 3.03 (m, 1 H), 3.76 (s, 3 H), 6.77 (d, 1 H, J = 2.6 Hz), 6.92 (dd, 2 H, J = 8.8, 2.2 Hz), 7.03 (d, 1 H, J = 2.6 Hz), 7.27 (dd, 2 H, J = 8.8, 2.2 Hz). ^{13}C NMR: δ 157.7, 135.9, 134.0, 124.4, 121.7, 116.0, 114.6, 111.3, 55.6, 40.8, 25.4, 24.5, 24.1. MS (EI): m/z 307 (M^+, 94), 232 (100). Anal. Calcd for $C_{16}H_{21}NS_2O$: C, 62.50; H, 6.88; N, 4.56; S, 20.85. Found: C, 62.90; H, 7.12; N, 4.96; S, 21.25.

1-(*p*-Methoxyphenyl)-3-phenylthiopyrrole, 19c. Method B. From azetidine *cis*-**8f** (80 mg, 0.18 mmol) and $AlEt_2Cl$ (0.18 mL, 0.18 mmol), 20 mg (55%) of compound **17c** was obtained as a colorless oil after purification by flash chromatography (AcOEt/hexanes, 1:6). ^{1}H NMR: δ 3.75 (s, 3 H), 6.42 (dd, 1 H, J = 2.9, 1.8 Hz), 6.97 (dd, 2 H, J = 8.8, 2.1 Hz), 7.08 (m, 2 H), 7.22 (m, 4 H), 7.32 (dd, 2 H, J = 8.8, 2.2 Hz). ^{13}C NMR: δ 158.1, 140.2, 133.7, 128.7, 126.0, 125.4, 124.8, 122.1, 121.2, 115.9, 114.8, 110.6, 55.6. MS (EI): m/z 281 (M^+, 100). Anal. Calcd for $C_{17}H_{15}NSO$: C, 72.57; H, 5.37; N, 4.98; S, 11.39. Found: C, 72.17; H, 5.77; N, 4.48; S, 11.79.

1-Benzyl-3-phenylthiopyrrole, 19d. Method C. From azetidine *cis*-**8g** (40 mg, 0.09 mmol) and $AlEt_2Cl$ (0.18 mL, 0.18 mmol), 17 mg (72%) of compound **19d** was obtained as an oil after purification by flash chromatography (AcOEt/hexanes, 1:16). ^{1}H NMR: δ 5.08 (s, 2 H), 6.29 (dd, 1 H, J = 2.7, 1.7 Hz), 6.76 (dd, 1 H, J = 2.6, 2.2 Hz), 6.90 (t, 1 H, J = 2.0 Hz), 7.07 (m, 7 H), 7.28 (m, 3 H). ^{13}C NMR: δ 140.7, 137.2, 128.8, 128.6, 128.0, 127.2 (3 C), 125.7, 124.6, 122.7, 115.1, 53.8, 30.9. MS (EI): m/z 265 (M^+, 87), 91 (100). Anal. Calcd for $C_{17}H_{15}NS$:

C, 76.94; H, 5.70; N, 5.28; S, 12.08. Found: C, 77.34; H, 5.30; N, 5.14; S, 12.25.

Monochloroalane Promoted Reaction of *β*-Lactam *cis*-5h. A solution of anhydrous $AlCl_3$ (0.35 g, 2.65 mmol) in anhydrous Et_2O (8 mL) was added via syringe to a well stirred suspension of $LiAlH_4$ (0.11 mg, 2.65 mmol) in anhydrous Et_2O (8 mL). The mixture was refluxed for 30 min, cooled to rt, and transferred via cannula to a solution of acetal *β*-lactam *cis*-**5h** (0.33 g, 0.88 mmol) in dry Et_2O (4 mL). The reaction was stirred under argon at room temperature for 45 min, cooled to 0 °C, and then quenched with water (8 mL), diluted with Et_2O (13 mL), and washed with brine (2 × 5 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure, and after purification by flash chromatography (AcOEt/hexanes, 1:12), 47 mg (20%) of the less polar compound **19a** (identical to that obtained from azetidine *cis*-**6h**), 17 mg (20%) of phenol, and 79 mg (25%) of the more polar product **20** were obtained.

(1*R,6*R**,9*S**)-2,5-Dithia-7-(*p*-methoxyphenyl)-9-phenoxy-7-azabicyclo[4,3,0]nonane, 20.** ^{1}H NMR: *δ* 3.76 (s, 3 H), 3.96 (m, 4 H), 4.10 (dd, 1 H, *J* = 6.2, 3.7 Hz), 4.15 (dd, 1 H, *J* = 8.8, 3.3 Hz), 4.24 (dd, 1 H, *J* = 6.3, 6.6 Hz), 5.07 (td, 1 H, *J* = 7.0, 2.9 Hz), 5.53 (d, 1 H, *J* = 5.1 Hz), 6.74 (d, 2 H, *J* = 9.0 Hz), 6.83 (m, 4 H), 6.91 (td, 1 H, *J* = 7.2, 1.1 Hz), 7.21 (d, 2 H, *J* = 9.0 Hz). ^{13}C NMR: *δ* 157.2, 152.6, 114.8, 129.5, 121.4, 115.2, 114.5, 113.7, 102.8, 69.6, 67.9, 65.4, 65.1, 59.2, 55.8. IR ($CHCl_3$): *ν* 1730. MS (EI): *m*/*z* 359 (M^+, 2), 254 (100). Anal. Calcd for $C_{19}H_{21}NO_2S_2$: C, 63.48; H, 5.89; N, 3.90; S, 17.84. Found: C, 63.88; H, 6.29; N, 4.30; S, 18.24.

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Supporting Information Available: Spectroscopic and analytical data for isomerically pure compounds **1a**−**i**, **2a**−**i**, **3b**, **5a**−**k**, **6a**−**g**, **6i**−**k**, **7a**−**h**, **8b**−**g**, **9b**, **9d**, and **9f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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