Articles

A Convenient Synthesis of 3,3-Dichloroazetidines, a New Class of Azetidines

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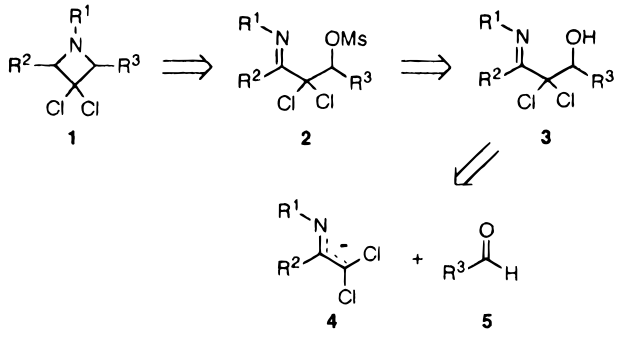
A short synthesis of appropriately substituted 3,3-dichloroazetidines, a virtually unknown class of azetidines, is described. The reaction of 3,3-dichloro-1-azaallylic carbanions, generated from *N*-(1-aryl-2,2-dichloroethylidene)amines, with aromatic aldehydes produced α,α-dichloro-*β*-hydroxy imines that, upon treatment with mesyl chloride, were converted into the corresponding *β*-(mesyloxy) imines. Reaction of these α,α-dichloro-*β*-(mesyloxy) ketimines with potassium cyanide or sodium borohydride in methanol furnished a variety of 2-cyano- and 2-methoxy-3,3-dichloroazetidines in a stereoselective manner. Reduction of *β*-(mesyloxy) imines with sodium cyanoborohydride followed by cyclization with potassium carbonate in DMSO yielded 3,3-dichloroazetidines as well.

Introduction

Azetidines are an important class of azaheterocyclic compounds with remarkable biological activities, which make it an interesting synthetic topic.[1−4] 3,3-Dichloroazetidines **1** constitute a nearly unknown class of four-membered heterocycles. The isolation of only two 3,3-dichloroazetidines has been reported in the literature. A first example was obtained as a byproduct during the synthesis of α-amino acids.[5] The other example concerned the reduction of a strained 3,3-dichloro-1-azetine in 37% yield.[6]

Several general procedures exist for the preparation of azetidines.[1−4] Previously, we have reported a method for the synthesis of azetidines that is based on the reaction of *β*-chloro imines with nucleophiles, such as hydride and cyanide,[7−11] or bases (leading to 2-methyleneazetidines).[12] In this paper, a novel approach based on the reaction of *β*-(mesyloxy) imines **2** with nucleophiles was used to synthesize 3,3-dichloroazetidines **1** (Scheme 1). To our knowledge, only one cyclization of a *β*-(tosyloxy) aldimine leading to an azetidine in very low yield (20%) has been described.[13] *β*-(Mesyloxy) imines **2** can be obtained by reaction of the corresponding *β*-hydroxy imines **3** with mesyl chloride. Here, we describe a new type of directed aldol condensation of 3,3-dichloro-1-azaallylic anions **4** with aldehydes, giving access to α,α-dichloro-*β*-hydroxy ketimines **3**. This aldol-type condensation holds a pivotal position in the construction of 3,3-dichloroazetidines **1** from 1-azaallylic anions **4** and aldehydes **5** (Scheme 1).

Scheme 1



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Scheme 2

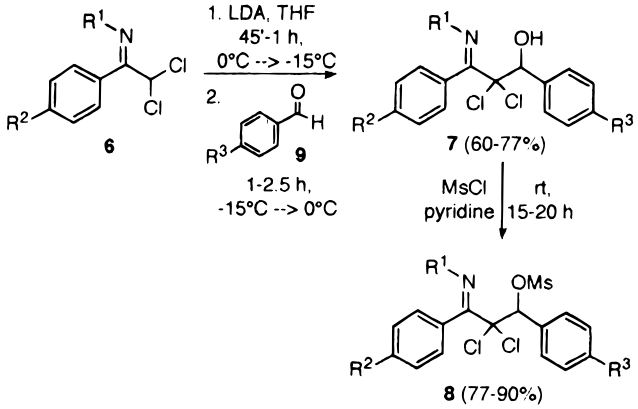


Table 1. Synthesis of α,α-Dichloro-β-hydroxy Imines 7, β-(Mesyloxy)-α,α-dichloro Imines 8, and *N*-Alkyl-*N*-[1,3-diaryl-2,2-dichloro-3-(mesyloxy)propyl]amines 12

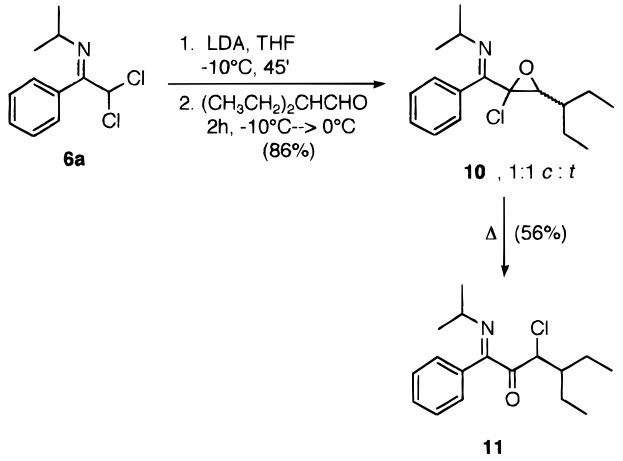
entry	R^1	R^2	R^3	reaction time (h)	product (yield, %)
1	*i*-Pr	H	H	1[a]	**7a** (60)[b]
2	Et	Cl	H	2.5[a]	**7b** (77)[b]
3	*i*-Pr	H	Me	2[a]	**7c** (68)[b]
4	*i*-Pr	H	H	15[c]	**8a** (77)[d]
5	Et	Cl	H	17[c]	**8b** (81)[d]
6	*i*-Pr	H	Me	20[c]	**8c** (90)[d]
7	*i*-Pr	H	H	24[e]	**12a** (88)[f]
8	Et	Cl	H	48[e]	**12b** (77)[f]
9	*i*-Pr	H	Me	48[e]	**12c** (71)[f]

[a] The deprotonations were performed with 1.2 equiv of LDA in THF at 0 °C during 45 min; 10 min before the addition of the aldehyde **9** the reaction mixture was cooled to −15 °C. All reactions were run with 1 equiv of aldehyde **9** in THF; the reaction mixture was allowed to warm from −15 to 0 °C during the condensation. [b] Yield after recrystallization. [c] 10% w/v solutions of compound **7** in pyridine were treated with 1.5 equiv of MsCl at room temperature. [d] Yields after workup and washing with pentane/ether 4:1; purity >99% (^{1}H NMR). [e] Solutions of imines **8** in methanol were treated with 2−3 equiv of sodium cyanoborohydride and 1−1.2 equiv of acetic acid at room temperature. [f] Yields after washing the crude amines **12** with pentane/ether (9/1); purity >99% (^{1}H-NMR); diastereomeric ratio *anti*/*syn* > 99/1 (^{1}H- and ^{13}C-NMR).

Results and Discussion

Aromatic aldehydes **9** were reacted with the lithium azaenolates derived from α,α-dichloro ketimines **6**, prepared by condensation of α,α-dichloro ketones with primary amines in the presence of titanium(IV) chloride[14] and subsequent deprotonation with lithium diisopropylamide, to give α,α-dichloro-β-hydroxy ketimines **7** in 60−77% yield after recrystallization (Scheme 2). The relative stability of the intermediate 3(,3-di-)chloro-1-azaallylic anions has already been proved by their reaction with other electrophiles.[15,16] The new type of directed-aldol condensation was performed by adding the aldehydes **9** to solutions of the heteroallylic anions derived from imines **6** in THF at −15 °C and quenching with water at 0 °C after a reaction time of 1−2.5 h (Table 1). When the reaction mixture was allowed to warm to room temperature, up to 30% of the starting ketimine **6** and aldehyde **9** were observed in the reaction mixture. This can be explained as originating from a retro-aldol-type cleavage of the initially formed β-hydroxy imine **7**.[17] Surprisingly, when the condensation was performed with aliphatic aldehydes, such as 2-ethylbutanal, instead of aromatic aldehydes **9**, a mixture of *cis*- and *trans*-2-chloro-2-imidoyloxiranes **10** was obtained via a Darzens-type reaction (Scheme 3). A novel Darzens-type condensation of α-monochlorinated ketimines with carbonyl compounds producing α,β-epoxy ketimines has already been reported by us.[18] It has also been described that the anion of 2-(dichloromethyl)-4,4-dimethyl-2-oxazoline reacts with carbonyl compounds to give 2,2-dichloro-3-hydroxy- or 2-chloro-2,3-epoxy-2-oxazolines depending on the reaction conditions.[19] Upon distillation of the α-chloro-α,β-epoxy imine **10**, a thermal rearrangement[20] with formation of α-imino ketone **11** took place (Scheme 3).

Scheme 3



In the next step (Scheme 2), β-(mesyloxy) ketimines **8** were prepared by treatment of the corresponding β-hydroxy imines **7** with mesyl chloride in pyridine (Table 1). When dichloromethane was used as solvent and the imines **7** were reacted at room temperature with mesyl chloride in the presence of 1−5 equiv of pyridine or triethylamine, the starting materials **7** were completely recovered. At higher temperatures conversions into unidentified reaction products occurred.

Next, the β-(mesyloxy) ketimines **8** were converted into 3,3-dichloroazetidines **13** either by a nucleophile-induced one-step cyclization or in a two-step sequence consisting of a reduction followed by a ring closure under basic conditions (Scheme 4).

In the first approach, the α,α-dichloro-β-(mesyloxy) imines **8** were smoothly reduced in good yields (70−88%) by acid-catalyzed reaction with sodium cyanoborohydride in methanol in the presence of acetic acid (1−1.2 equiv) at room temperature (Table 1). As evidenced by ^{1}H and ^{13}C NMR spectroscopy, only one pair of diastereomers of the γ-(mesyloxy)amines **12** was obtained after recrystallization. There was no proof that, before purification, the other diastereomeric pair was present in the reaction mixture (vide infra).

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Scheme 4

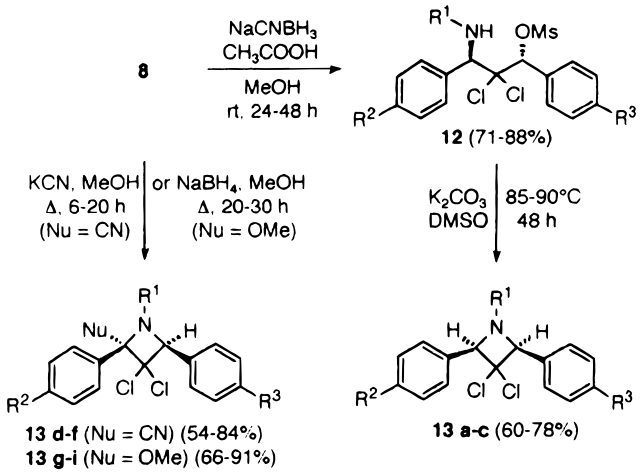


Table 2. Synthesis of *cis*-3,3-Dichloroazetidines 13

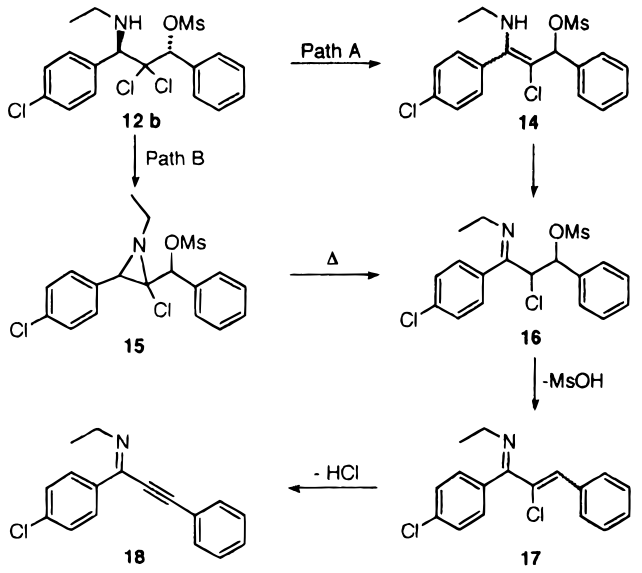
entry	R^1	R^2	R^3	method[a]	reaction condns	azetidine **13** (yield, %)[b]
1	*i*-Pr	H	H	A	90 °C, 48 h	**13a** (63)
2	Et	Cl	H	A	85 °C, 48 h	**13b** (60)[c]
3	*i*-Pr	H	Me	A	85 °C, 48 h	**13c** (78)
4	*i*-Pr	H	H	B	Δ, 6 h	**13d** (54)
5	Et	Cl	H	B	Δ, 20 h	**13e** (57)
6	*i*-Pr	H	Me	B	Δ, 6 h	**13f** (84)
7	*i*-Pr	H	H	C	Δ, 30 h	**13g** (66)
8	Et	Cl	H	C	Δ, 30 h	**13h** (91)[d]
9	*i*-Pr	H	Me	C	Δ, 20 h	**13i** (88)

[a] Method A: amines **12** were reacted with 3 equiv of K_2CO_3 in DMSO at 85−90 °C. Method B: imines **8** were treated with 2 equiv of KCN in methanol under reflux. Method C: imines **8** were treated with 2 equiv of $NaBH_4$ in methanol under reflux. [b] Yields after purification by recrystallization (pentane/ether) or flash chromatography (hexane/ethyl acetate) (see the Experimental Section). [c] The imine **13** was isolated as a byproduct in 22% yield (Scheme 5). [d] Crude product (purity >95%).

In the next stage, cyclization of the 3-(mesyloxy) amines **12** with potassium carbonate in DMSO at 85−90 °C afforded 2,4-diaryl-3,3-dichloroazetidines **13a**−**c** (Table 2). After purification by recrystallization or flash chromatography, these azetidines (one stereoisomer) were obtained as crystalline products in yields ranging from 60 to 78% (Table 1). No long-range couplings were observed between the protons at C-2 and C-4 of the azetidines **13**. The relative stereochemistry at C-2 and C-4 of the azetidines **13a**−**c** was undoubtedly assigned by X-ray crystallographic analysis,[21] showing that compound **13c** had the cis stereochemistry. The fact that only *cis*-2,4-diarylazetidines were obtained also implies that in the previous step *anti*-(*RR*,*SS*)-3-(mesyloxy) amines **12** were formed exclusively.

Only *N*-ethylamine **12b** did not cyclize without side reactions when treated with potassium carbonate in DMSO at 85 °C. Functionalized azetidine **13b** was the major product in the reaction mixture, but it was contaminated with the imidoyl-substituted alkyne **18**, which was isolated in 22% yield after flash chromatography. It seemed likely that the reaction occurred via an intermediate α-chloro imine **16**, which can be formed

Scheme 5



via two plausible pathways as presented in Scheme 5. The first possibility concerns a 1,2-dehydrochlorination of **12b** leading to the β-chloro enamine **14**, which isomerizes into α-chloro ketimine **16** (path A). Alternatively, an intramolecular nucleophilic substitution can give rise to the 2-chloroaziridine **15**, which thermally rearranges to the same intermediate **16** (path B). Under the basic conditions, two 1,2-elimination reactions finally lead to the formation of the alkyne **18** (Scheme 5). Both mechanistic pathways are plausible, but the route via the aziridine **15** (path B) better answers the question why the side reaction is only observed starting from a sterically less hindered *N*-ethyl derivative **12b**.

In a second approach, the synthesis of 2,4-diaryl-3,3-dichloroazetidines **13** from β-(mesyloxy) imines **8** was accomplished conveniently in one step by a nucleophile-induced ring closure (Scheme 4). Treatment of β-(mesyloxy)-α,α-dichloro imines **8** with potassium cyanide and sodium borohydride in methanol under reflux furnished 2-cyano- and 2-methoxyazetidines **13d**−**f** and **13g**−**i**, respectively, which were obtained in pure form after recrystallization or flash chromatography (Table 2). 2-Cyanoazetidines have been reported scarcely in the literature.[7,8,22] Some 2-cyanoazetidines could be converted into useful medicinal products, such as appetite depressants and products that can control obesity.[23] Also, α-alkoxy azetidines have rarely been reported in the literature until now and they are only accessible in very special cases.[10,12,13,24] Although the rapid conversion of α-methoxy azetidines into β-(alkylamino) carbonyl compounds has been reported by us,[9,10] the 2,4-diaryl-3,3-dichloro-2-methoxyazetidines **13g**−**i** are rather stable under the reaction conditions mentioned in Table 2. The stabilizing character of the two chloro atoms at the

(21) An ORTEP diagram is included in the Supporting Information. The authors have deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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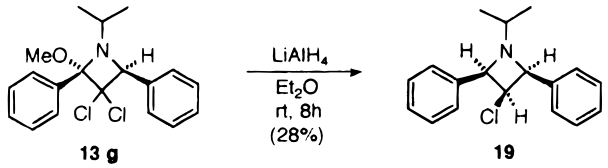
Scheme 6



3-position and the steric influence imposed by the aryl groups contribute to the fact that compounds **13g**−**i** are stable 2-methoxyazetidines.

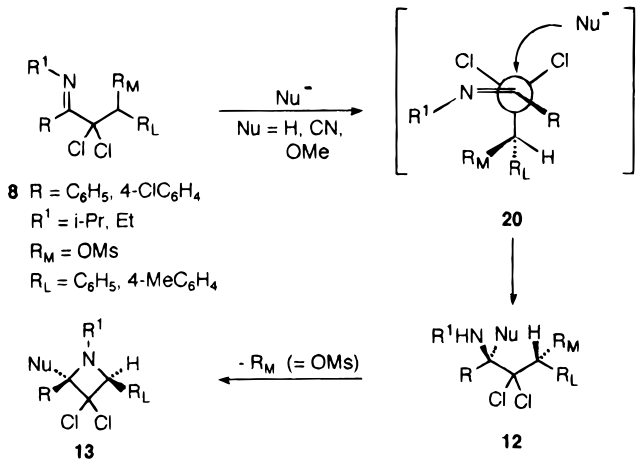
The nucleophilic attack of cyanide and methoxide across the imino function and following cyclization into four-membered azaheterocyclic rings **13d**−**i** was found to be highly stereoselective. X-ray crystallographic analysis revealed that the relative position of the two aryl groups at C2 and C4 of the azetidines **13d**−**i** was cis, as exemplified by azetidine **13f**.[21]

The reaction of 2-methoxyazetidine **13g** with lithium aluminum hydride in ether afforded 3-chloroazetidine **19** by nucleophilic substitution of the methoxy group by hydride via an azetinium intermediate (neighboring group participation of the adjacent amino group)[12] and subsequent conversion of the geminal dichloro derivative to the monochlorinated azetidine **19** via a single electron-transfer reaction[25] (Scheme 6). Some other minor components (probably ring-opening products), although clearly present in the reaction mixture (^{1}H NMR), could not be isolated in pure form. The spectroscopic data indicated that 3-chloroazetidine **19** is a symmetrical molecule. Only one chemical shift value is observed for the protons at C-2 and C-4. Also taking into account that a NOE effect between the vicinal protons at C-2, C-3, and C-4 was observed, the configuration of 3-chloroazetidine **19** can be depicted as *cis*-3-chloro-*cis*-2,4-diphenylazetidine (Scheme 6).

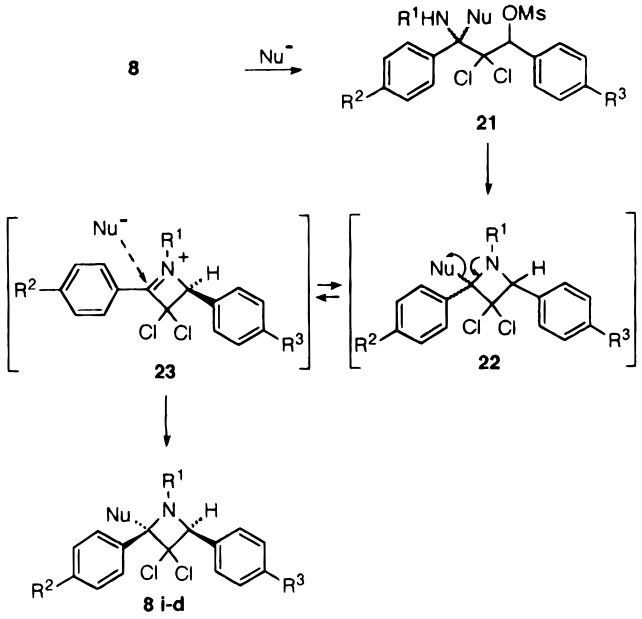
Although the Cram steric model for 1,3-induction has been widely recognized,[26] we suggest that the observed stereoselectivity (**8** → **12** → **13a**−**c** and **8** → **13d**−**i**) is best rationalized by a steric model proposed by Evans,[27] based on a study by Jacques and co-workers[28] (Scheme 7). In this model, (a) staggered rather than eclipsed transition structures **20** are preferred, having an anti orientation between C_β and the forming bond,[29] and (b) the dominant destabilizing interactions are between the imidoyl carbon substituent (R) and the β-aryl substituents (Scheme 7).

Of course, this rule applies only to reactions that are kinetically controlled, i.e., where the product isolated is that formed in a rate-controlled process, not the more

Scheme 7



Scheme 8



stable product formed in a subsequent equilibration. Indeed, one might propose that in a first step a nonstereospecific addition occurs, providing a mixture of 1,3-syn- and 1,3-anti-adducts **21**, which lead to *cis*- and *trans*-2,4-diarylazetidines **22** after ring closure (Scheme 8). Subsequent equilibration via the azetinium intermediate **23** and attack of the nucleophile at the opposite side of the 4-aryl substituent also gives *cis*-2,4-diarylazetidines **13d**−**i** exclusively. Evidently, this is only applicable to the synthesis of 2-cyano- and 2-methoxyazetidines **13d**−**i** where the reacting nucleophile is also a leaving group.

In conclusion, the reaction of 3,3-dichloro-1-azaallylic carbanions with aromatic aldehydes and subsequent mesylation leads to α,α-dichloro-β-(mesyloxy) ketimines that were converted into rare classes of azetidines, including 3,3-dichloroazetidines and 2-methoxyazetidines, in a highly stereoselective way.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded at 270 and 68 MHz. The type of carbon and hydrogen atom was determined via DEPT and ^{13}C−^{1}H and ^{1}H−^{1}H COSY techniques. Mass spectra were performed at 70 eV. Ether and THF were freshly

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distilled from sodium wire and sodium benzophenone ketyl, respectively. Melting points are uncorrected.

Synthesis of β-Hydroxy Imines 7. The synthesis of *N*-(2,2-dichloro-3-hydroxy-1,3-diphenyl-1-propylidene)isopropylamine (**7a**) is representative (Table 1). To an ice- cooled solution of diisopropylamine (3.51 g, 34.70 mmol) in THF (35 mL) was added under an N_2 atmosphere *n*-BuLi (12.83 mL 2.5 M in hexane, 32.07 mmol) followed after 10 min by a solution of *N*-(2,2-dichloro-1-phenyl-1-ethylidene)isopropylamine (**6a**)[16] (6.15 g, 26.70 mmol) in THF (25 mL). After 35 min of stirring at 0 °C, the reaction mixture was cooled to −15 °C and stirred additionally for 10 min at −15 °C. Then, a solution of freshly distilled benzaldehyde (2.83 g, 26.70 mmol) in THF (15 mL) was added dropwise. The mixture was gradually warmed to 0 °C during 1 h and then poured into an ice-cooled 0.5 N NaOH solution (150 mL) and extracted with ether (3 × 100 mL), and the combined organic extracts were dried with K_2CO_3. Evaporation of the solvent in vacuo yielded 8.04 g (90%) of crude **7a**, which was purified by recrystallization (pentane/ether 1/1) to afford 5.39 g (60%) of the pure substance.

***N*-(2,2-Dichloro-3-hydroxy-1,3-diphenyl-1-propylidene)isopropylamine (7a):** mp 112−113 °C; ^{1}H NMR ($CDCl_3$) δ 1.12 and 1.13 (2 × 3H, 2 × d, J = 6.1 Hz, Me_2CH), 3.29 (1H, septet, J = 6.1 Hz, C*H*Me$_2$), 5.61 (1H, br s, C*H*OH), 6.12 (1H, br s, CHO*H*), 7.25−7.43 and 7.63−7.69 (10H, m, 2 × C_6H_5); ^{13}C NMR ($CDCl_3$) δ 23.1 and 23.2 (Me_2), 53.1 (*C*HMe$_2$), 79.5 (CHOH), 89.7 (CCl_2), 127.3, 127.9, 128.4, 129.0, and 130.0 (C_o, C_m and C_p), 132.6 and 136.8 (C_q), 167.9 (C=N); IR (KBr) 3120−3470 (OH), 1635 cm^{-1} (C=N); MS *m*/*z* no M$^+$, 300/302 (M$^+$ − Cl; 9), 194/196 (21), 146 (23), 106 (28), 105 (46), 104 (100), 77 (44). Anal. Calcd for $C_{18}H_{19}Cl_2NO$: C, 64.32; H, 5.70; N, 4.17. Found: C, 64.41; H, 5.59; N, 4.29.

***N*-[2-Chloro-2,3-epoxy-4-ethyl-1-phenyl-1-hexylidene]-isopropylamine (10).** The same procedure as described for the preparation of the β-hydroxy imines **7** provided **10** in 86% yield (*cis*/*trans* : 1/1): ^{1}H NMR ($CDCl_3$) δ 0.92−1.29 (2 × 12H, m, NCH*Me*$_2$ and *Me*CH$_2$), 1.35−1.82 (2 × 5H, m, C*H*(C*H*$_2$Me)$_2$), 2.88 and 3.11 (2 × 1H, 2 × d, J = 8.58 Hz, CHO), 3.47 (1H, septet, J = 6.27 Hz, C*H*Me$_2$), 4.37 (1H, septet, J = 5.94 Hz, C*H*Me$_2$), 7.16−7.47 and 7.85−7.89 (2 × 5H, 2 × m, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 10.5, 11.0, and 11.1 (*Me*CH$_2$), 23.1 and 23.4 (CH*Me*$_2$), 21.7, 23.6 and 24.8 (*C*H$_2$CH$_3$), 40.2 (*C*HCH$_2$), 52.3 and 52.5 (*C*HMe$_2$), 65.4 and 67.0 (CHO), 75.5 and 83.4 (CCl), 127.6, 127.6, 128.2, 128.4, 128.9 and 129.9 (CH=), 134.2 and 136.0 (C_q), 157.9 and 162.5 (C=N); IR (NaCl) 1630−1640 cm^{-1} (C=N); MS *m*/*z* 293/5 (M$^+$; 0.5), 146 (42), 104 (100), 77 (27), 51 (13), 43 (20). Anal. Calcd for $C_{17}H_{24}ClNO$: C, 69.49; H, 8.23; N, 4.77. Found: C, 69.57; H, 8.20; N, 4.66.

***N*-[3-Chloro-4-ethyl-2-oxo-1-hexylidene]isopropylamine (11).** This compound was formed during distillation of the epoxide **10**: bp 89−94 °C/0.015 mmHg; ^{1}H NMR ($CDCl_3$) δ 0.89 and 0.99 (2 × 3H, 2 × t, J = 7.4 Hz, 2 × *Me*CH$_2$), 1.15 and 1.17 (2 × 3H, 2 × d, J = 6.1 Hz, Me_2CH), 1.35−1.65 (4H, m, 2 × C*H*$_2$CH$_3$), 1.99−2.10 (1H, m, C*H*CHCl), 3.69 (1H, septet, J = 6.1 Hz, C*H*Me$_2$), 5.92 (1H, d, J = 5.28 Hz, CHCl), 7.03−7.15 and 7.30−7.46 (5H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 11.3 and 11.4 (*Me*CH$_2$), 21.9 and 23.2 (2 × CH$_2$), 23.4 and 23.5 (Me_2CH), 44.0 (*C*HCHCl), 53.6 (*C*HMe$_2$), 62.2 (CHCl), 127.5, 128.3, and 129.1 (CH=), 132.7 (C_q), 163.1 (C=N), 195.6 (C=O); IR (NaCl) 1712 (C=O), 1626 cm^{-1} (C=N); MS *m*/*z* no M$^+$; 258 (M$^+$ − Cl, 1), 163 (6), 146 (33), 104 (100), 77 (31), 51 (14), 43 (18). Anal. Calcd for $C_{17}H_{24}ClNO$: C, 69.49; H, 8.23; N, 4.77. Found: C, 69.51; H, 8.14; N, 4.69.

Synthesis of β-(Mesyloxy) Imines 8. The synthesis of *N*-(2,2-dichloro-3-(mesyloxy)-1,3-diphenyl-1-propylidene)isopropylamine (**8a**) is representative (Table 1). To a solution of α,α-dichloro-β-hydroxy imine **7a** (3.31 g, 9.85 mmol) in pyridine (30 mL) was added dropwise at room temperature mesyl chloride (1.69 g, 14.77 mmol). After 5 h of stirring at room temperature, the reaction mixture was poured into an ice-cooled 0.5 N NaOH solution (100 mL) and extracted with CH_2Cl_2 (3 × 75 mL). The organic layer was dried ($MgSO_4$) and evaporated in vacuo to give **8a** as a crude solid product, which was purified by recrystallization (pentane/ether 4/1) to afford 3.12 g (77%) of pure white needles.

***N*-[2,2-Dichloro-3-(mesyloxy)-1,3-diphenyl-1-propylidene]isopropylamine (8a):** mp 115 °C; ^{1}H NMR ($CDCl_3$) δ 1.09 and 1.16 (2 × 3H, 2 × d, J = 6.27 Hz, Me_2CH), 2.76 (3H, s, $MeSO_2$), 3.31 (1H, septet, J = 6.27 Hz, C*H*Me$_2$), 6.83 (1H, s, CHO), 7.00−7.20, 7.34−7.47, and 7.68−7.76 (10H, m, 2 × C_6H_5); ^{13}C NMR ($CDCl_3$) δ 23.0 and 23.1 (Me_2CH), 39.9 ($MeSO_2$), 54.2 (*C*HMe$_2$), 85.0 (CHO), 89.4 (CCl_2), 127.8, 127.9, 128.1, 128.8, 129.8, and 130.6 (C_o, C_m, and C_p), 133.3 and 133.9 (C_q), 163.1 (C=N); IR (KBr) 1636 cm^{-1} (C=N); MS *m*/*z* no M$^+$, 378/380 (M$^+$ − Cl; 5), 172 (5), 146 (55), 107 (6), 104 (100), 77 (10), 43 (9). Anal. Calcd for $C_{19}H_{21}Cl_2NO_3S$: C, 55.07; H, 5.11; N, 3.38. Found: C, 55.19; H, 5.01; N, 3.44.

Synthesis of 3-(Mesyloxy) Amines 12. The synthesis of *N*-isopropyl-*N*-(2,2-dichloro-3-(mesyloxy)-1,3-diphenylpropyl)-amine (**12a**) is representative (Table 1). To a solution of α,α-dichloro-β-(mesyloxy) imine **8a** (1.24 g, 3 mmol) in methanol (15 mL) was added $NaCNBH_3$ (0.47 g, 7.5 mmol), followed by acetic acid (0.22 g, 3.6 mmol). The mixture was stirred for 24 h at room temperature, poured into a 0.5 N NaOH solution (50 mL), and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo to yield 1.21 g (97%) of crude **12a**, which was washed with 20 mL of a solution of pentane/ether (9/1) to give 1.10 g (88%) of pure white solid.

***N*-Isopropyl-*N*-[2,2-dichloro-3-(mesyloxy)-1,3-diphenylpropyl]amine (12a):** mp 129 °C; ^{1}H NMR ($CDCl_3$) δ 0.98 and 1.10 (2 × 3H, 2 × d, J = 6.27 Hz, Me_2CH), 1.70−1.90 (1H, br s, NH), 2.60 (3H, s, $MeSO_2$), 2.69 (1H, septet, J = 6.27 Hz, C*H*Me$_2$), 4.54 (1H, s, Cl_2CCHN), 6.65 (1H, s, CHO), 7.28−7.49 and 7.66−7.74 (10H, m, 10 × CH=); ^{13}C NMR ($CDCl_3$) δ 22.0 and 24.5 (Me_2CH), 40.1 ($MeSO_2$), 46.5 (*C*HMe$_2$), 66.0 (Cl_2*C*CHN), 83.5 (CHO), 95.1 (CCl_2), 127.8, 128.0, 128.1, 129.9, and 130.6 (C_o, C_m, and C_p), 133.1 and 137.6 (C_q); IR (KBr) 3320 (NH, weak), 1354, 1170 cm^{-1}; MS *m*/*z* no M$^+$; 319/321 (M$^+$ − OSO_2Me; 7), 172 (13), 148 (20), 147 (59), 132 (100), 105 (15), 104 (20), 43 (18). Anal. Calcd for $C_{19}H_{23}Cl_2NO_3S$: C, 54.81; H, 5.57; N, 3.36. Found: C, 54.98; H, 5.42; N, 3.44.

Reaction of Amines 7a−c with Potassium Carbonate. Synthesis of 3,3-Dichloroazetidines 13a−c. The synthesis of 3,3-dichloro-1-isopropyl-2,4-diphenylazetidine (**13a**) is representative (Table 2). To a solution of β,β-dichloro-γ-(mesyloxy) amine **12a** (0.62 g, 1.5 mmol) in DMSO (10 mL) was added potassium carbonate (0.62 g, 4.5 mmol). The mixture was stirred for 48 h at 90 °C, poured into H_2O (30 mL), and extracted with CH_2Cl_2 (4 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give crude 3,3-dichloroazetidine **13a** as a solid material, which was purified by recrystallization (pentane/ether 4/1) to afford 0.30 g (63%) of pure crystals.

3,3-Dichloro-1-isopropyl-2,4-diphenylazetidine (13a): mp 90−91 °C; ^{1}H NMR ($CDCl_3$) δ 0.85 (6H, d, J = 6.27 Hz, Me_2), 2.84 (1H, septet, J = 6.27 Hz, C*H*Me$_2$), 4.73 (2H, s, NCHCCl_2), 7.33−7.45 (6H, m, C_m, and C_p), 7.61 (4H, dd, J = 7.92, 1.65 Hz, C_o); ^{13}C NMR ($CDCl_3$) δ 21.6 (Me_2), 59.2 (*C*HMe$_2$), 80.8 (CCl_2*C*HN), 85.2 (CCl_2), 128.0, 128.3, and 128.5 (C_o, C_m, and C_p), 137.6 (C_q); IR (KBr) 2965, 1452, 1330, 1025; MS *m*/*z* 319/321/323 (M$^+$; 5), 172 (11), 148 (12), 147 (58), 146 (17), 132 (100), 105 (15), 104 (19). Anal. Calcd for $C_{18}H_{19}Cl_2N$: C, 67.50; H, 5.98; N, 4.37. Found: C, 67.59; H, 6.09; N, 4.30.

3,3-Dichloro-2-(4-chlorophenyl)-1-ethyl-4-phenylazetidine (13b). Purification by flash chromatography hexane/ethyl acetate 98/2 (R_f = 0.46): ^{1}H NMR ($CDCl_3$) δ 0.90 (3H, t, J = 7.26 Hz, Me), 2.75 and 2.77 (2 × 1H, 2 × q, J = 7.26 Hz, CH_2), 4.60 and 4.64 (2 × 1H, 2 × s, CHN), 7.36−7.61 (9H, m, C_o, C_m, and C_p); ^{13}C NMR ($CDCl_3$) δ 13.7 (Me), 51.4 (CH_2), 80.7 and 81.3 (CHN), 85.3 (CCl_2), 128.0, 128.2, 128.4, 128.7, and 129.5 (C_o, C_m, and C_p), 134.5, 134.8, and 136.0 (C_q); IR (NaCl) 1488, 1180, 1086, 1011, 696 cm^{-1}; MS *m*/*z* 339/341/343 (M$^+$; 9), 304/306 (38), 208 (34), 206 (35), 174 (67), 172 (100), 152 (71), 133 (72), 132 (95), 118 (87). Anal. Calcd for $C_{17}H_{16}Cl_3N$: C, 59.93; H, 4.73; N, 4.11. Found: C, 60.09; H, 4.61; N, 4.03.

***N*-[1-(4-Chlorophenyl)-3-phenyl-2-propyn-1-ylidene]-ethylamine (18).** This compound was formed as a byproduct during the synthesis of (**13b**). Flash chromatography with hexane/ethyl acetate 98/2 ($R_f = 0.24$) afforded it as an oil: ^{1}H NMR ($CDCl_3$) δ 1.38 (3H, t, $J = 7.4$ Hz, Me), 3.94 (2H, q, $J = 7.4$ Hz, CH_2), 7.35−7.46 and 7.58−7.63 (7H, m, C_o, C_m, C_p), 8.02 (2H, d, $J = 8.58$ Hz, 2 × CH=); ^{13}C NMR ($CDCl_3$) δ 15.6 (Me), 51.0 (CH_2), 81.0 and 98.2 (C≡C), 128.5, 128.6, 128.8, 129.8, and 132.2 (C_o, C_m, and C_p), 121.4, 136.1, and 136.4 (C_q), 149.3 (C=N); IR (NaCl) 2196 cm^{-1} (C≡C); MS *m*/*z* 267/269 (M^+; 100), 266/268 (60), 191 (64), 139 (69), 128 (46), 125 (55), 115 (81). Anal. Calcd for $C_{17}H_{14}ClN$: C, 76.26; H, 5.27; N, 5.23. Found: C, 76.13; H, 5.39; N, 5.39.

Reaction of Imines 8a−c with Potassium Cyanide. Synthesis of 2-Cyanoazetidines 13d−f. The synthesis of 3,3-dichloro-2-cyano-1-isopropyl-2,4-diphenylazetidine (**13d**) is representative (Table 2). Potassium cyanide (0.39 g, 6 mmol) was added to a solution of β-(mesyloxy) imine (**8a**) (1.24 g, 3 mmol) in methanol (15 mL). The mixture was then refluxed for 6 h after which it was cooled to room temperature, poured into water (50 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give crude **13d**, which was purified by flash chromatography (hexane/ethyl acetate 97/3; $R_f = 0.38$) to afford 0.56 g (54%) of pure azetidine **13d**.

3,3-Dichloro-2-cyano-1-isopropyl-2,4-diphenylazetidine (13d): ^{1}H NMR ($CDCl_3$) δ 0.89 and 0.94 (2 × 3H, 2 × d, $J = 6.27$ Hz, *Me*$_2$CH), 3.25 (1H, septet, $J = 6.27$ Hz, C*H*Me$_2$), 4.90 (1H, s, CCl_2CHN), 7.38−7.60 and 7.80−7.88 (10H, m, 2 × C_6H_5); ^{13}C NMR ($CDCl_3$) δ 21.8 and 22.3 (*Me*$_2$CH), 56.1 (*C*HMe$_2$), 79.9 (*CC*≡N), 80.2 (CCl_2CHN), 85.7 (CCl_2), 115.6 (CN), 127.8, 128.2, 128.3, 128.5, 129.3, and 130.1 (C_o, C_m, and C_p), 134.8 and 135.9 (C_q); IR (NaCl) 1451, 1390, 1237, 1188 cm^{-1}; MS *m*/*z* 344/346/348 (M^+; 6), 311 (10), 172 (100), 147 (40), 132 (56), 104 (29). Anal. Calcd for $C_{19}H_{18}Cl_2N_2$: C, 66.09; H, 5.25; N, 8.11. Found: C, 66.16; H, 5.36; N, 8.01.

3,3-Dichloro-2-(4-chlorophenyl)-2-cyano-1-ethyl-4-phenylazetidine (13e). Purification by flash chromatography hexane/ethyl acetate 98/2 ($R_f = 0.26$): ^{1}H NMR ($CDCl_3$) δ 0.98 (3H, t, $J = 7.2$ Hz, Me), 2.93 and 2.93 (2 × 1H, 2 × q, $J = 7.2$ Hz, CH_2), 4.86 (1H, s, NCH), 7.39−7.56 (7H, m, C_o, C_m, and C_p), 7.73 (2H, d, $J = 8.58$ Hz, 2 × CH=); ^{13}C NMR ($CDCl_3$) δ 13.8 (Me), 47.4 (CH_2), 79.8 (*CC*≡N), 80.4 (NCH), 86.1 (CCl_2), 114.9 (C≡N), 128.1, 128.4, 128.8, 128.9, and 129.5 (C_o, C_m, C_p), 132.2, 133.9, and 136.4 (C_q); IR (NaCl) 2250 (C≡N, weak), 1488, 760, and 698 cm^{-1}; MS *m*/*z* 364/366/368 (M^+; 1), 176 (19), 172 (100), 132 (41), 118 (32), 84 (35). Anal. Calcd for $C_{18}H_{15}Cl_3N_2$: C, 59.12; H, 4.13; N, 7.66. Found: C, 59.19; H, 4.02; N, 7.69.

Reaction of Imines 8a−c with Sodium Borohydride. Synthesis of 2-Methoxyazetidines 13g−i. The synthesis of 3,3-dichloro-1-isopropyl-2-methoxy-2,4-diphenylazetidine (**13g**) is representative (Table 2). To a solution of β-(mesyloxy) imine (**8a**) (0.82 g, 2 mmol) in methanol (10 mL) was added sodium borohydride (0.15 g, 4 mmol). After 30 h of reflux, the mixture was poured into water (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give crude **13g** as a solid material, which was purified by recrystallization (pentane/ether 4/1) to afford 0.46 g (66%) of pure product.

3,3-Dichloro-1-isopropyl-2-methoxy-2,4-diphenylazetidine (13g): mp 89 °C; ^{1}H NMR ($CDCl_3$) δ 1.01 and 1.15 (2 × 3H, 2 × d, $J = 6.4$ Hz, *Me*$_2$CH), 3.49 (1H, septet, $J = 6.4$ Hz, C*H*Me$_2$), 3.50 (3H, s, OMe), 5.16 (1H, s, $CHCCl_2$), 7.26−7.70 (10H, m, 2 × C_6H_5); ^{13}C NMR ($CDCl_3$) δ 20.9 and 24.4 (*Me*$_2$-CH), 48.2 (*C*HMe$_2$), 56.5 (OMe), 76.4 (*C*HCCl_2), 89.5 (CCl_2), 103.7 (N*C*OMe), 127.7, 128.0, 128.4, 128.5, and 128.8 (C_o, C_m, and C_p), 136.7 and 137.4 (C_q); IR (KBr) 1250, 1190, 1101, 870 cm^{-1}; MS *m*/*z* 318 (M^+ − OMe; 1), 177 (51), 176 (77), 162 (100) 105 (44), 104 (40), 77 (22). Anal. Calcd for $C_{19}H_{21}Cl_2NO$: C, 65.15; H, 6.04; N, 4.00. Found: C, 65.24; H, 6.01; N, 4.12.

3,3-Dichloro-2-(4-chlorophenyl)-1-ethyl-2-methoxy-4-phenylazetidine (13h). This azetidine was obtained as an oil (purity 95%) and could not be purified by recrystallization or chromatography: ^{1}H NMR ($CDCl_3$) δ 1.01 (3H, t, $J = 7.3$ Hz, *Me*CH_2), 2.89 and 3.09 (2H, AB × q, $J = 12.3$, 7.3 Hz, CH_2), 3.42 (3H, s, OMe), 4.95 (1H, s, NCH), 7.31−7.60 (9H, m, C_6H_5 and C_6H_4), ^{13}C NMR ($CDCl_3$) δ 14.3 (*Me*CH_2), 43.2 (CH_2), 56.3 (OMe), 78.7 (NCH), 88.8 (CCl_2), 102.1 (N*C*OMe), 127.7, 128.1, 128.3, 128.4, and 129.2 (C_o, C_m and C_p), 134.5, 134.6, and 135.9 (C_q); IR (KBr) 1090, 1045, 698 cm^{-1}; MS *m*/*z* 369/371/373 (M^+; 11), 196 (75), 182 (36), 172 (42), 139 (49), 57 (44), 43 (100). Anal. Calcd for $C_{18}H_{18}Cl_3NO$: C, 58.32; H, 4.89; N, 3.78. Found C, 58.19; H, 4.99; N, 3.61.

Synthesis of 3-Chloroazetidine (19). To an ice-cooled solution of 3,3-dichloroazetidine (**13c**) (0.35 g, 1 mmol) in diethyl ether (5 mL) was added $LiAlH_4$ (0.08 g, 2 mmol). The mixture was stirred at room temperature for 8 h, poured into ice-cooled water (30 mL), and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residual oil was purified by flash chromatography to yield 0.08 g (28%) of pure 3-chloroazetidine **19** as white needles (hexane/ethyl acetate 96/4; $R_f = 0.42$): mp 101 °C; ^{1}H NMR ($CDCl_3$) δ 0.80 (6H, d, $J = 6.3$ Hz, Me$_2$), 2.70 (1H, septet, $J = 6.3$ Hz, C*H*Me$_2$), 4.52 (2H, d, $J = 6.7$ Hz, C*H*NC*H*), 4.88 (1H, t, $J = 6.7$ Hz, CHCl), 7.25−7.42 and 7.50−7.59 (10H, m, 2 × C_6H_5); ^{13}C NMR ($CDCl_3$) δ 21.5 (Me$_2$), 58.5 (CHCl), 58.8 (*C*HMe$_2$), 68.7 (*C*HNC*H*), 127.6, 127.7, 128.6 (C_o, C_m, and C_p), 139.3 (C_q); IR (KBr) 1457, 763 cm^{-1}; MS *m*/*z* 285/287 (M^+; 3), 250(14), 147 (19), 132 (100), 104 (13), 77 (9). Anal. Calcd for $C_{18}H_{20}ClN$: C, 75.64; H, 7.05; N, 4.90. Found: C, 75.73; H, 6.98; N, 4.98.

X-ray Crystallographic Analysis of 13c.[21] Pure crystals were obtained by recrystallization from pentane/ether (4/1). The principal crystallographic parameters of compound **13c** are as follows:[21] $M = 334.27$; monoclinic; space group *P*21/*C*; $a = 5.925(2)$ Å, $b = 16.225(8)$ Å, $c = 18.739(10)$ A; $\alpha = 90°$, $\beta = 94.95(4)°$, $\gamma = 90°$; $V = 1795(2)$ A^3; $Z = 4$; $D_c = 1.237$ g/cm^3; Mo K$_\alpha$; $\lambda = 1.541\,78$ A, $\mu = 3.204$ mm^{-1}; $F(000) = 704$. The structure was refined to a final $R = 0.0782$, $R_w = 0.2368$ for 3225 reflections, $I > 2\sigma(I)$.

X-ray Crystallographic Analysis of 13f.[21] Pure crystals were obtained by recrystallization from pentane/ether (4/1). The principal crystallographic parameters of compound **13f** are as follows:[21] $M = 359.28$; monoclinic; space group *P*21/n; $a = 10.897(7)$ Å, $b = 14.379(3)$ Å, $c = 12.105(11)$ A; $\alpha = 90°$, $\beta = 92.40(6)°$, $\gamma = 90°$; $V = 1895(2)$ A^3; $Z = 4$; $D_c = 1.259$ g/cm^3; Mo K$_\alpha$; $\lambda = 0.710\,69$ A, $\mu = 0.346$ mm^{-1}; $F(000) = 752$. The structure was refined to a final $R = 0.0460$, $R_w = 0.1273$ for 3730 reflections, $I > 2\sigma(I)$.

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Supporting Information Available: An ORTEP presentation for **13c** and **13f**. Detailed ^{1}H NMR, ^{13}C NMR, IR, and MS data for all compounds **7**, **8**, **10**−**13**, **17**, and **19** (13 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.

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