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Diastereoselective Aldol Reaction of Zincated 3-Chloro-3-methyl-1-azaallylic Anions as Key Step in the Synthesis of 1,2,3,4-Tetrasubstituted 3-Chloroazetidines

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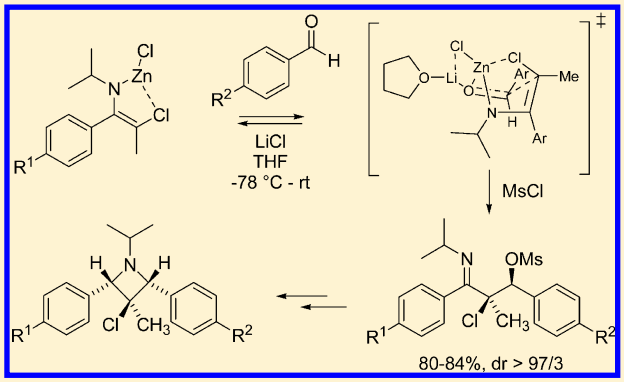
Supporting Information

ABSTRACT: Zincated 3-chloro-3-methyl-1-azaallylic anions undergo a stereoselective aldol addition across aromatic aldehydes and subsequent mesylation to produce *syn* α-chloro-β-mesyloxyketimines, which were isolated in 80−84% yield and high diastereomeric excess (dr > 97/3) after purification via flash chromatography. The *syn* α-chloro-β-mesyloxyketimines were further stereoselectively reduced to give stereochemically defined 3-aminopropyl mesylates, which were cyclized to 1,2,3,4-tetrasubstituted 3-chloroazetidines containing three contiguous stereogenic centers. DFT calculations on the key aldol addition revealed the presence of a highly ordered bimetallic six-membered twist-boat-like transition state structure with a tetra-coordinated metal cyclic structure. DFT calculations revealed that chelation of both zinc and lithium cations in the transition state structure leads to the experimentally observed high *syn* diastereoselectivity of aldol reactions.



INTRODUCTION

The stereoselective synthesis of azetidines, particularly of highly substituted derivatives, represents an underdeveloped research area, despite their importance as a class of strained azaheterocyclic compounds, which occur in a wide range of natural products and with application in medicinal chemistry for the synthesis of bioactive compound libraries.[1] 3-Haloazetidines, in particular, form an important subclass of functionalized four-membered azaheterocycles due to their potential physiological activities and their use as synthons in the synthesis of 3-substituted azetidine derivatives.[2] Only very recently, our group reported the first asymmetric synthesis of *trans*-2-aryl-3-chloroazetidines via cyclization of optically pure β-chloro-γ-sulfonylamino alcohols under Mitsunobu conditions.[3] The latter result, together with a variety of other examples,[1h,4] demonstrated that the cyclization of a preformed aminopropyl chain via nucleophilic substitution of a leaving group, such as a chloride, bromide, or an activated hydroxyl group, in the γ-position, forms a general method to prepare azetidines. The applicability of this method for the stereoselective synthesis of highly substituted 3-haloazetidines **3** depends, naturally, on the efficient synthetic accessibility of the corresponding stereochemically defined aminopropyl precursors **2** (Scheme 1). Metalated 3-chloro-1-azaallylic anions **1**[5] have proven to be suitable building blocks in organic synthesis by reaction with electrophiles and elaboration of the resulting functionalized α-chloroketimines.[6] More specifically, the aldol reaction of 3,3-dichloro-1-azaallylic anions **1** (R^3 = Cl) with aromatic aldehydes, followed by mesylation to the corresponding β-mesyloxyketimines,[7] and reduction afforded amines **2** (R^3 = Cl) as precursors of stereochemically defined 2,4-diaryl-3,3-dichloroazetidines **3** (R^3 = Cl).[8] In previous computational research, the 3-chloro-3-methyl-1-azaallylic anion **1** (R^3 = Me) was chosen as a model compound to obtain deeper insight into the structural features of 3-halo-1-azaallylic anions and a better

Scheme 1. Synthesis of Highly Substituted 3-Haloazetidines 3

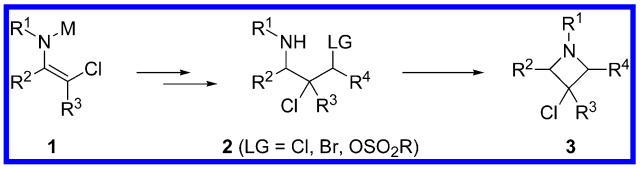


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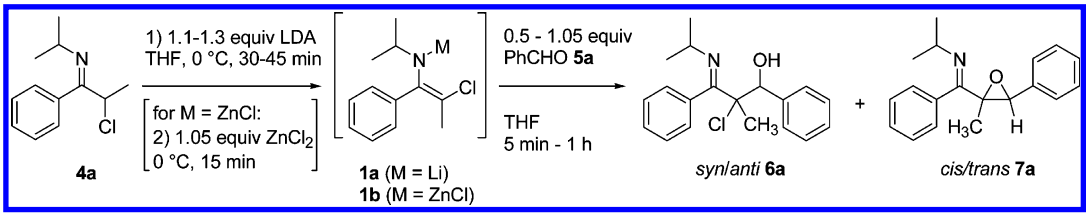
Table 1. Aldol Reaction of Anions 1a and 1b Derived from Imine 4a with Benzaldehyde 5a



entry	LDA (equiv)	M	reaction conditions	*syn* **6a**/*anti* **6a**/*cis* **7a**/*trans* **7a**[a]
1	1.1	Li	1.05 equiv **5a**, 0 °C, 1 h	47/0/6/47[b]
2	1.1	Li	1.05 equiv **5a**, −78 °C, 1 h	57/33/0/10
3	1.1	Li	0.5 equiv **5a**, −78 °C, 10 min	58/39/0/3
4	1.1	Li	1.05 equiv **5a**, −40 °C, 1 h	52/14/7/27
5	1.1	ZnCl	1.05 equiv **5a**, −40 °C, 1 h	66/32/0/2
6	1.1	ZnCl	1.05 equiv **5a**, −78 °C, 10 min	80/20/0/0
7	1.1	ZnCl	0.5 equiv **5a**, −78 °C, 5 min	89/11/0/0
8	1.1	ZnCl	0.5 equiv **5a**, −78 °C, 5 min then 0 °C, 1 h	85/12/0/3
9	1.3	ZnCl	1.05 equiv **5a**, −78 °C, 5 min then 0 °C, 1 h	75/17/0/8
10	1.3	ZnCl	1.05 equiv **5a**, −78 °C, 5 min then rt, 1 h	72/4/0/24[c]
11	1.3	ZnCl	0.5 equiv **5a**, −78 °C, 5 min then rt, 1 h	87/2/0/11[d]
12	1.3	ZnCl	0.75 equiv **5a**, −78 °C, 5 min then rt, 1 h	77/0/0/23
13	1.3	ZnCl	0.25 equiv **5a**, −78 °C, 5 min then rt, 1 h	80/0/0/20
14	1.3	ZnCl	0.5 equiv **5a**, rt, 1 h	85/0/0/15[e]
15	1.3	Li[f]	0.5 equiv **5a**, −78 °C, 5 min then rt, 1 h	63/0/0/37

[a]Determined via ^{1}H NMR analysis (300 MHz, $CDCl_3$) of the crude reaction mixture. [b]*syn* **6a** (dr >99/1) was isolated in 39% yield via crystallization from the reaction mixture in MeOH and an impure sample of *trans* **7a** was obtained via a second crystallization from the mother liquor. [c]*syn* **8a** (dr >95/5) was isolated via column chromatography in 68% yield after mesylation of the reaction mixture with 1.5 equiv MsCl in pyridine at room temperature for 22 h. [d]*syn* **8a** (dr >97/3) was isolated via column chromatography in 80% yield after mesylation of the reaction mixture with 1.5 equiv MsCl in pyridine at room temperature for 22 h. [e]*syn* **8a** (dr >99/1) was isolated via column chromatography in 63% yield after mesylation of the reaction mixture with 1.5 equiv MsCl in pyridine at room temperature for 22 h. [f]LiCl was added instead of $ZnCl_2$.

Scheme 2. Aldol Reaction of Imines 4 and Further Transformation to 3-Chloroazetidines 3

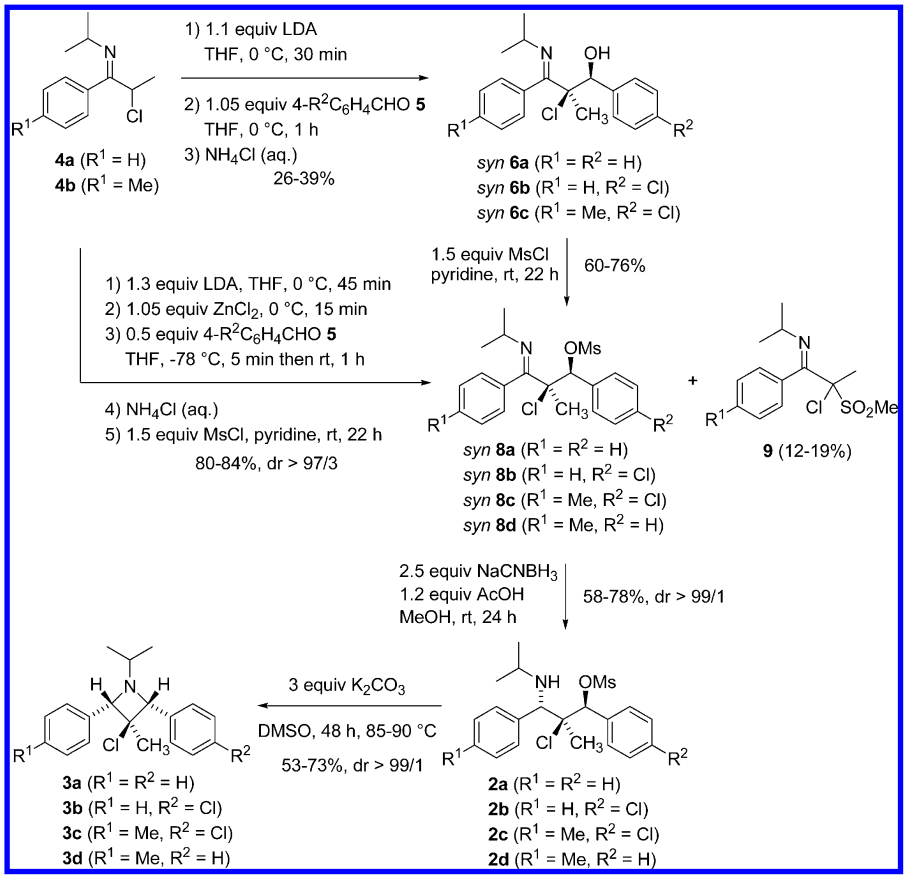


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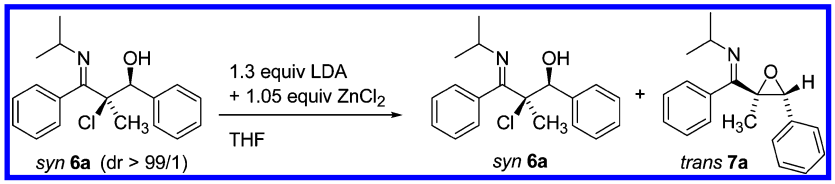
Table 2. Stability Study of *syn*-Chlorohydrin 6a



entry	temp (°C)/time (min)	*syn* **6a**/*trans* **7a**[a]
1	−78/5	97/3
2	0/5	96/4
3	0/5 + rt/60	96/4

[a]Determined via ^{1}H NMR analysis (300 MHz, $CDCl_3$) of the crude reaction mixture.

understanding of the factors that control the stereochemical outcome of the reactions involving these anions.[9,10]

Herein, the use of 3-chloro-3-methyl-1-azaallylic anions **1** (R^3 = Me) in aldol reactions with aromatic aldehydes is reported,[11,12] en route to the stereoselective synthesis of new azetidines **3** (R^3 = Me) with a chlorinated quaternary stereocenter at the 3-position and tertiary stereocenters at the 2- and 4-positions. To the best of our knowledge, the only report on the synthesis of such type of 3-haloazetidines with carbon-centered substituents at the 1-, 2-, 3-, and 4-positions involves the reaction of 1,2,2,3-tetrasubstituted aziridines or substituted 4-oxazolines, via the corresponding intermediate azomethine ylides, with sulfur ylides.[13] The aldol step has been investigated by means of theoretical calculations in order to better understand the effect of metal-coordination in the transition state structures and its effect on the diastereoselective outcome.

RESULT AND DISCUSSION

Experimental Results. Previous reported theoretical calculations demonstrated that the lithiated 3-chloro-3-methyl-1-azaallylic anion **1a** (M = Li, R^1 = *i*Pr, R^2 = C_6H_5, R^3 = Me) is present in a monosolvated monomeric *Z*-isomer form and should readily undergo transmetalation to the zincated *Z*-isomer **1b** (M = ZnCl, R^1 = *i*Pr, R^2 = C_6H_5, R^3 = Me).[9,10] In order the verify these calculations and to use these new fundamental insights in stereoselective organic synthesis, anions **1a** and **1b**, derived from the *N*-isopropylimine **4a** of *α*-chloropropiophenone, were reacted with aromatic aldehydes **5** (Table 1, Scheme 2). *N*-Isopropyl-*α*-chloro imine **4a** was prepared by condensation of *α*-chloropropiophenone with isopropylamine in the presence of titanium(IV) chloride.[14] Treatment of *N*-isopropyl-*α*-chloro imine **4a** with lithium diisopropylamide in tetrahydrofuran at 0 °C provided the lithiated 3-chloro-3-methyl-1-azaallylic anion **1a**,[9] which was further reacted with benzaldehyde **5a** at 0 °C for 1 h. After aqueous workup, a mixture of *syn* *α*-chloro-*β*-hydroxyketimine **6a** (*major* compound) together with the corresponding ring-closed *cis*- and *trans*-imidoylepoxides **7a** was obtained (Table 1, entry 1). The former *syn*-adduct **6a** was isolated in 39% yield from the reaction mixture via rapid crystallization in methanol, while all attempts to isolate other reaction products in pure form by a second crystallization from the mother liquor or through column chromatography on silica gel failed. Only an impure sample of *trans* epoxide **7a** was obtained after a second crystallization from the mother liquor and the *trans* stereochemistry was confirmed by the fact that a $^3J_{CH}$ of ∼0 Hz was observed for the *trans*-CH_3 and -H oxirane ring substituents.[15] No improvement on the stereoselectivity of the reaction could be accomplished upon lowering the reaction temperature to −40 or −78 °C, which resulted in even more tedious inseparable reaction mixtures due to the additional presence of significant amounts of the *anti*-aldol adduct **6a** (14−39%) besides the epoxides **7a** (entries 2−4). At 0 °C, the initially formed lithiated *anti*-adduct spontaneously cyclized to form the *trans*-imidoylepoxide **7a**, while the lithiated *syn*-adduct cyclized only to a minor extent due to sterical hindrance of the benzimidoyl and phenyl substituents during cyclization[16] and formed the *syn* *α*-chloro-*β*-hydroxyketimine **6a** after aqueous workup. Similar results were obtained for aldol reactions at 0 °C using imine **4b** and 4-chlorobenzaldehyde **5b**, resulting in the isolation of *syn* *α*-chloro-*β*-hydroxyketimines **6b,c** in low yields (Scheme 2).

Use of the zincated 3-chloro-3-methyl-1-azaallylic anion **1b**, obtained via transmetalation of the lithiated anion **1a** with $ZnCl_2$ at 0 °C, proved to be beneficial as it slightly improved the diastereoselectivity of the aldol reaction with benzaldehyde **5a** at −40 °C and afforded smaller amounts of the epoxides **7a** (Table 1, entry 5). The *syn*-diastereoselectivity of the aldol reaction with the zincated anion **1b** was, however, greatly improved (up to dr *syn*/*anti* 89/11) by further lowering the reaction temperature to −78 °C, shortening the reaction time, and increasing the amount of 1-azaallylic anion (Table 1, entries 6 and 7). Nevertheless, it was not possible to separate the *syn* *α*-chloro-*β*-hydroxyketimine **6a** from the *anti*-adduct **6a** via crystallization in good yield and good diastereomeric excess due to the occurrence of concomitant retro-aldol reactions. Therefore, to reduce the undesired amount of *anti* *α*-chloro-*β*-hydroxyketimine **6a** present in the reaction mixture, the initial temperature of the aldol reaction at −78 °C was increased again, resulting in some decrease of *syn*-diastereoselectivity and partial or full cyclization of the zincated *anti*-adduct to *trans*-epoxide **7a** (entries 8−13).

Eventually, it was found that at room temperature almost all of the zincated *anti*-adduct cyclized, conveniently providing the *syn* *α*-chloro-*β*-hydroxyketimine **6a** as the *major* compound (*syn* **6a**/*anti* **6a** = 98/2) in the reaction mixture after workup (entry 11). The latter adduct was chromatographically isolated as the corresponding *syn*-mesylate **8a** (to avoid retro-aldol reaction) in 80% yield (dr > 97/3) after treatment of the crude reaction mixture with mesyl chloride in pyridine for 22 h (Scheme 2). Changing the amount of benzaldehyde **5a** to 0.25 and 0.75 equiv, added under the latter optimized conditions, did not afford improved diastereoselectivities (entries 12 and 13). Furthermore, when benzaldehyde **5a** was added directly at room temperature to the zincated 1-azaallylic anion **1b**, only a small decrease of diastereoselectivity was observed, but after mesylation the corresponding *syn*-mesylate **8a** was isolated in a

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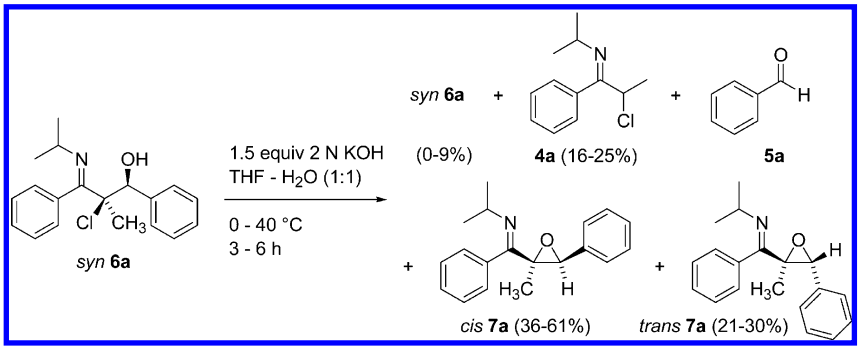
Scheme 3. Attempted Cyclization of *syn*-Chlorohydrin 6a to *cis*-Imidoylepoxide 7a



lower yield of 63% (dr > 99/1) (entry 14). When LiCl was used instead of $ZnCl_2$, a large decrease of diastereoselectivity was observed (entry 15).

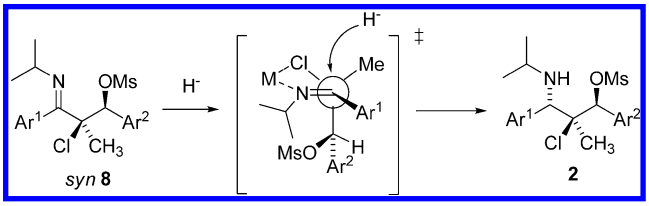
Noteworthy, only a negligible decrease of *syn*-diastereoselectivity was observed when the initial temperature of the aldol reaction at −78 °C was increased for 1 h to room temperature (entry 7, *syn*/*anti* 89/11 versus entry 11, *syn*/*anti* 87/13). Probably, this can be explained by the fact that the aldol reaction of zincated anion **1b** with benzaldehyde **5a** is not an equilibrated reaction, in which retro-aldol reaction of the formed zincated *syn*-adduct at room temperature is prevented or only occurs to a minor extent. This was confirmed by treating isolated *syn* α-chloro-β-hydroxyketimine **6a** under similar reaction conditions (Table 2). $ZnCl_2$ was added to LDA in THF at 0 °C for 15 min, after which *syn* α-chloro-β-hydroxyketimine **6a** was added and the reaction was stirred at −78 °C for 5 min (entry 1), at 0 °C for 5 min (entry 2) or at 0 °C, followed by 1 h at room temperature (entry 3). In all cases, the retro-aldol-mediated isomerization of adduct *syn* **6a** to epoxide *trans* **7a** was very limited (<5%) (Table 2).

Application of the optimized reaction conditions of the aldol reaction (Table 1, entry 11) allowed the isolation of *syn* α-chloro-β-mesyloxyketimines **8b−d** (dr > 97/3) in 80−84% yield after purification via flash chromatography (Scheme 2). It is noteworthy that in all cases α-chloro-α-methanesulfonylketimines **9** (formed by reaction of the excess of imines **4** with mesyl chloride) were also isolated as byproduct in 12−19% yield.

In order to confirm the *syn*-stereochemistry of chlorohydrin **6a**, attempts for a stereospecific cyclization to *cis*-imidoylepoxide **7a** via treatment with potassium hydroxide (1.5 equiv) in water/tetrahydrofuran (1:1) were made.[6c] However, all attempts (0 °C, 3 h; room temperature, 6 h; 40 °C, 4 h) failed due to the competitive retro-aldol reaction, resulting in inseparable mixtures of benzaldehyde **5a**, *syn*-chlorohydrin **6a** (0−9%), α-chloropropiophenone imine **4a** (16−25%), *cis*-epoxide **7a** (36−61%), and *trans*-epoxide **7a** (21−30%) (Scheme 3).

On the other hand, the *syn* β-hydroxyketimines **6** could be stereospecifically and stereoselectively converted into the targeted azetidines **3**. This transformation involved mesylation, followed by stereoselective reduction of the β-mesyloxyketimines **8** with $NaCNBH_3$ and base-induced cyclization of the stereochemically defined β-chloro-γ-mesyloxypropylamines **2** upon heating in DMSO (Scheme 2).[8] The observed stereoselectivity for the reduction of *syn* α-chloro-β-mesyloxyketimines **8** to amines **2** can be best rationalized by means of merging Evans' steric model for 1,3-induction[8a,17] and Cram's chelation model for 1,2-induction,[18] as shown in Scheme 4.[19]

Scheme 4. Model for the Stereoselective Reduction of Imine 8



Noteworthy, after reduction of β-mesyloxyketimine **8d** (R^1 = Me, R^2 = H), a mixture of β-chloro-γ-mesyloxypropylamine **2d** and 2,4-diaryl-3-chloro-3-methylazetidine **3d** was obtained in a ratio of 71:29. After flash chromatography, γ-mesyloxypropylamine **2d** and 2,4-diaryl-3-chloro-3-methylazetidine **3d** were isolated in 58% and 23% yield, respectively.

The *cis*-relationship of the methine C2- and C4-protons of azetidines **3** was ascertained by the chemical equivalence of these protons in ^{1}H NMR for symmetrical azetidine **3a**. Furthermore, the *cis*-relationship of the C3-methyl substituent and the C2- and C4-aromatic groups was concluded from the typical upfield chemical shift (0.71−0.72 ppm) of the methyl protons in ^{1}H NMR due to the shielding caused by the aromatic rings. Moreover, comparison with ^{1}H NMR chemical shift data of 3-methyl substituents of similar *cis*- and *trans*-3-methyl-2(,4-di)phenylazetidines and -oxetanes from literature confirmed this *cis*-relationship.[4a−d,h,20] The stereochemistry of azetidines **3** confirmed the previously assigned stereochemistry of the *syn*-chlorohydrins **6**.

From the experimental results mentioned above, it is clear that *syn*-chlorohydrins **6** are the kinetically favored products of the aldol reaction between lithiated and especially zincated azaallylic anions **1** and aromatic aldehydes **5**. On the other hand, a thermodynamic equilibration of the aldol products **6** via retro-aldol reaction under basic conditions (Scheme 3) results in the increased formation of the *trans*-imidoylepoxides **7**. Earlier theoretical literature showed that the bidentate monomeric *Z*/*anti* azaallylic anions **1a** and **1b** are the most favored configurations due to a strong internal halogen-metal interaction. Therefore, the formation of the kinetic *syn*-chlorohydrins **6** upon protonation of the metal-chelated *syn* adducts **10**,[21] the expected diastereomers from an enolate with *Z*-geometry,[22] is reasonably explained via the postulated boat-like transition state model in which the halogen-metal coordination is expected to be crucial (Scheme 5).[23]

In the six-membered chelated transition structure (*syn*-TS, Scheme 5), the phenyl group of benzaldehyde occupies the less-hindered pseudoequatorial position. The following section focuses on the theoretical elucidation of the stereochemical

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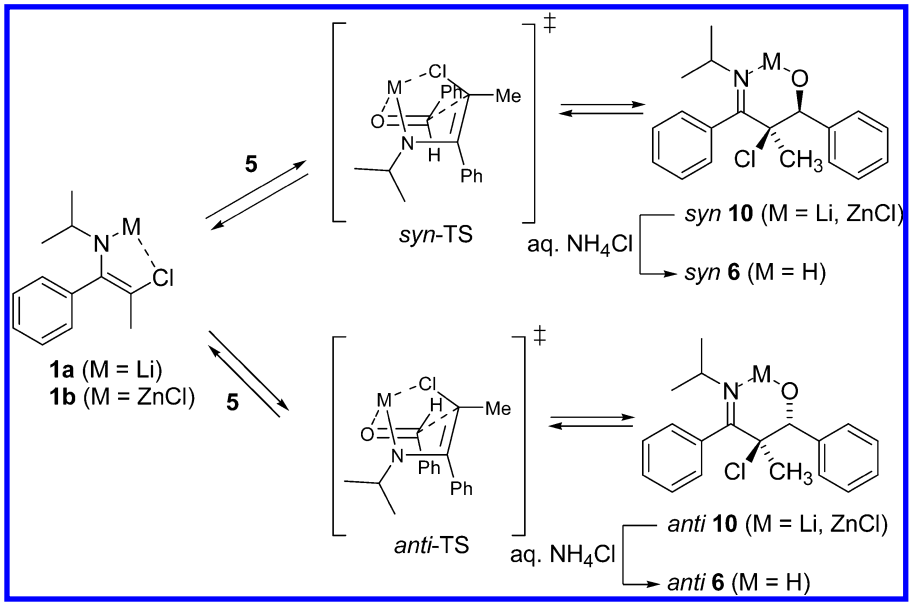
Scheme 5. Postulated Boat-Like Transition State Model for the Aldol Reaction of Azaallylic Anions 1



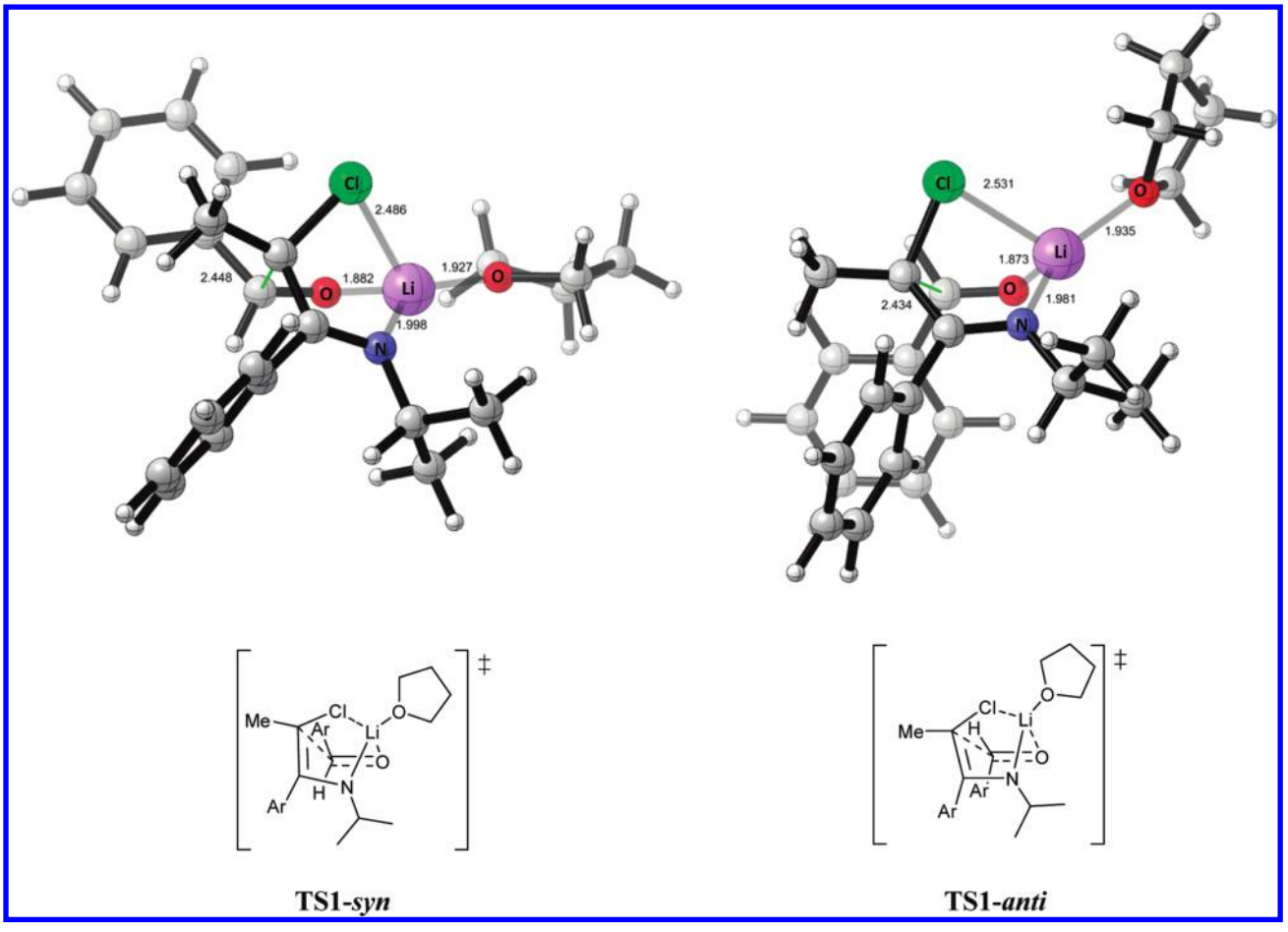


Figure 1. *Syn* and *anti* transition state structures for the aldol reaction of 3-chloro-3-methyl-1-azaallylic anions **1** and benzaldehyde **5a** in the presence of a Li^+ cation (with one solvating THF molecule). B3LYP/6-31+G(d,p) optimized geometries.

outcome of this aldol reaction, paying particular attention to metal coordination of the 1-azaallylic anion and its influence on the conformation of transition states involved. We will thus be able to further validate the proposed transition state in Scheme 5.

Theoretical Results. In order to explain the experimentally observed *syn* stereoselectivity, transition states leading to both the *syn* and *anti* adducts **10** were modeled in the presence of lithium and zinc counterions. Due to the strong coordination with these counterions, a very well-defined and low barrier

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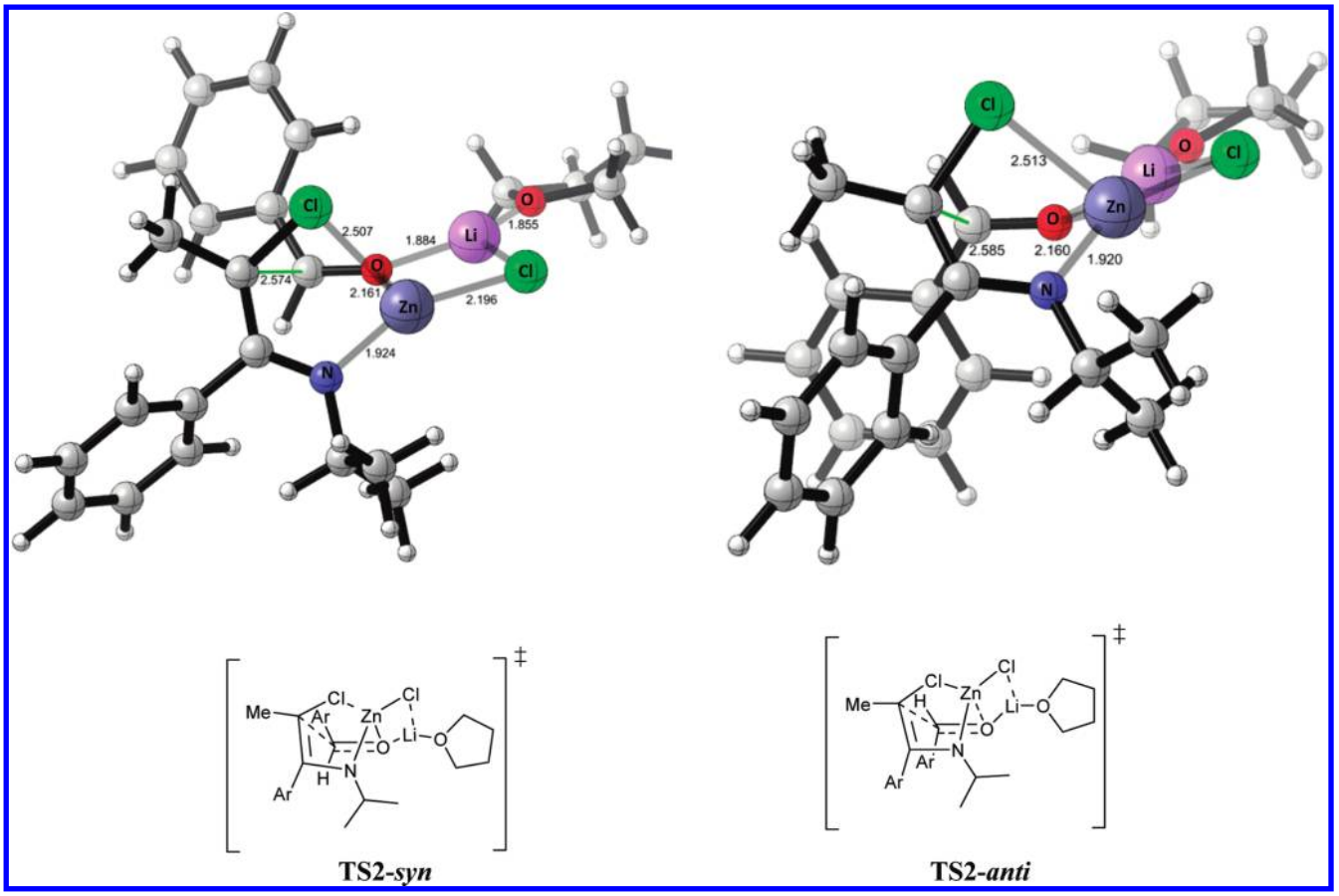

Figure 2. *Syn* and *anti* transition state structures for the aldol reaction of 3-chloro-3-methyl-1-azaallylic anions **1** and benzaldehyde **5a** in the presence of a $ZnCl^+$ and Li^+ cation (with one solvating THF molecule). B3LYP/6-31+G(d,p) optimized geometries.

transition state could be located for both the *anti* and *syn* addition of the 3-chloro-3-methyl-1-azaallylic anions **1** across benzaldehyde **5a**. These transition states are characterized by a "boat-like" geometry that is stabilized by the strong interaction between the metal cation, the halogen, and the benzaldehyde oxygen (Scheme 5 and Figure 1). Other possible transition state structures resulting from a rotation around the forming C−C bond were located; however, these structures all lack the beneficial metal−oxygen interaction and are less stable by 31.3 kJ/mol (for Li^+) and 70−88 kJ/mol (for $ZnCl^+$). In the literature, several crystallographic studies of aldol reactions are known in which the aldolate six-membered ring adopts boat-like and/or half-chair chelate conformations.[24]

All computations were performed using the Gaussian09 program package.[25] Geometry optimizations for the transition states were carried out using the B3LYP[26−28] hybrid functional and a 6-31+G(d,p) basis set. The nature of the transition states was confirmed by normal modes analysis. From these optimized structures, energy refinements were performed using recently developed density functionals B97D[29] and M06-2X[30] and a 6-311+G(d,p) basis set. Both electronic structure methods are able to account for dispersion interactions. In the case of B97D, this is realized by explicit inclusion of damped atom-pairwise dispersion corrections, whereas the M06-2X functional is a high-nonlocal functional shown to perform well in organic systems with dispersion effects.[31] The effect of solvation is taken into account as the sum of two contributions: one resulting from the coordination of solvent molecules to the solute by adding explicit THF molecules and the other originating from the bulk solvent effect by embedding the system in a polarizable continuum model. This approach, known as the explicit/implicit solvation model, has been used extensively to model organic reactions in solution.[32] The parameter set used for the description of the cavity and the solvent is crucial for obtaining reliable energies, and therefore the recently developed SMD model is used.[33]

Syn and *anti* transition state structures (**TS1-*syn*** and **TS1-*anti***, respectively) for the aldol reaction of azaallylic anions **1** and benzaldehyde **5a** in the presence of a Li^+ cation (with one solvating THF molecule) are shown in Figure 1. In our previous work,[9,10] it was shown that transmetalation of lithiated azaallylic anions **1a** to zincated anions **1b** takes place with ease. Subsequently, azaallylic anions **1b** are present as monomers and bear a $ZnCl^+$ cation; however, free lithium cations are also expected to interact with the benzaldehyde oxygen to which the negative charge will be transferred after the addition reaction. This interaction was modeled by including both lithium and zinc in the transition states, resulting in the bicoordinated structures shown in Figure 2 (**TS2-*syn*** and **TS2-*anti***). In both *syn* transition states (**TS1-*syn*** and **TS2-*syn***), the six-membered ring aldolate adopts a more energetically favored "twist-boat-like" conformation, whereas in the *anti* counterparts (**TS1-*anti*** and **TS2-*anti***) a less energetically favored "boat-like" conformation is observed. Furthermore, in the *syn* transition states, the phenyl group of benzaldehyde occupies the less-hindered pseudoequatorial position, whereas in the *anti*, the phenyl group of benzaldehyde occupies the more hindered pseudoaxial position leading to a more pronounced steric

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hindrance. In all four transition states, the benzaldehyde carbonyl moiety still has a double bond character; bond lengths in the 1-azaallylic anion show partial double bond character, which are indicative of early transition states. Figures 1 and 2 also indicate differences in metal coordination between the transition states. Noteworthy, **TS2-*syn*** and **TS2-*anti*** appear as four/six-membered bicyclic aldolates, in which the lithium is part of a four-membered metal cycle, coordinating with the benzaldehyde oxygen and with the chlorine atom attached to the zinc−metal.

Noteworthy, in Table 1 entries 10−13, it was shown in the aldol reaction that the best *syn*-diastereoselectivity was obtained using 0.5 equiv benzaldehyde **5a** (i.e., 2.0 equiv of the zincated anion **1b**) (entry 11) instead of 0.25, 0.75, or 1.05 equiv **5a** (entries 10, 12, 13). This may be explained by the possibility of the interference of a second azaallylic anion in the transition state structure **TS2**, in which lithium is replaced by this second azaallylic anion, leading to a more energetically favored conformation.

Table 3 shows the free energy difference $\Delta\Delta G_{syn\text{-}anti}$ between the transition state structures leading to the *syn* and *anti*

Table 3. Free Energy Difference $\Delta\Delta G^{\ddagger}_{syn\text{-}anti}$ (in kJ/mol) of the Transition State Structures Leading to the *syn* and *anti* Adducts 10 for the Studied Cases[a−c]

	$\Delta\Delta G^{\ddagger}_{syn\text{-}anti}$	
	M06-2X (SMD)	B97-D (SMD)
TS1 (Li-THF)	−3.6	−1.7
TS2 (ZnCl-Li-THF)	−11.3	−9.3

[a]B3LYP/6-31+G(d,p) optimized geometries. [b]SMD calculations in THF (ε = 7.4257). [c]$\Delta\Delta G^{\ddagger}_{syn\text{-}anti} = \Delta G^{\ddagger}_{syn} - \Delta G^{\ddagger}_{anti}$.

adducts **10**, where two different levels of theory, accounting for dispersive interactions, have been employed. M06-2X is known to perform very well in organic systems with long-range interactions,[31] as is the case in this study. The supermolecule comprising the metal ions and an explicit THF molecule is also embedded in a bulk continuum via the SMD solvation model, which is a universal solvent model based on solute electron density and is applicable to both charged and uncharged solutes in any solvent.

As indicated earlier, both *syn* transition states adopt a more energetically favored "twist-boat-like" conformation, whereas the *anti* counterparts are in a less energetically favored "boat-like" conformation. Energetics show that there is only a slight preference for the formation of the *syn* adduct in the case of coordination with a single metal cation (Li^+), which is in accordance with the experimental results from entries 1−4 in Table 1 (*syn* **6a**+*cis* **7a**/*anti* **6a**+*trans* **7a** 53:47 to 59:41). Meanwhile, *syn* selectivity is enhanced in the presence of a second coordinating metal cation, consistent with the experimental results from entries 6−14 in Table 1 (*syn* **6a**+*cis* **7a**/*anti* **6a**+*trans* **7a** 72:28 to 89:11). Compared to its *anti* counterpart (**TS2-*anti***), the *syn* transition state (**TS2-*syn***) is clearly more stabilized in the presence of two metal ions. This is due to the extra ordering caused by two coordinating metal ions, which favors the *syn* transition state structure more than the *anti*.

CONCLUSIONS

This combined experimental-theoretical study shows that the aldol reaction of lithiated and zincated 3-chloro-3-methyl-1-azaallylic anions **1** across aromatic aldehydes **5** mainly yields the kinetic *syn*-adducts. The proposed "twisted-boat-like" transition states associated with this diastereoselective reaction benefit from coordination of the carbonyl oxygen with a second metal cation, resulting in extra stabilization of the transition states leading to the *syn* adducts. This explains the increased *syn* selectivity in the reaction when lithium and zinc are both present in the reaction mixture. Furthermore, the stereochemically defined *syn*-chlorohydrins can be used in a stereoselective synthesis of new tetrasubstituted 3-chloroazetidines.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of *syn* α-Chloro-β-hydroxyketimines 6. Under a nitrogen atmosphere, *n*-butyl lithium (15.7 mmol, 2.5 N in hexanes, 6.3 mL) was added dropwise to a solution of diisopropylamine (15.7 mmol, 2.03 g) in THF (50 mL) at 0 °C. After 30 min of stirring at 0 °C, α-chloroketimine 4 (14.3 mmol), which was dissolved in 10 mL of THF, was added dropwise, and the reaction mixture was stirred for 30 min at 0 °C. Then benzaldehyde 5 (15.0 mmol), dissolved in 2 mL of THF, was added dropwise to the reaction mixture, after which stirring was continued for 1 h at 0 °C. After the addition of three drops of saturated aqueous ammonium chloride, 20 mL of an ice-cold solution of 0.5 N aqueous sodium hydroxide was added to the reaction mixture. The mixture was poured in a separatory funnel containing 30 mL of diethyl ether and 60 mL of 0.5 N aqueous sodium hydroxide. The aqueous layer was extracted three times with diethyl ether, and the combined organic extracts were washed with 30 mL of 0.5 N aqueous sodium hydroxide. After drying ($MgSO_4$), the solvent was evaporated in vacuo, and pure *syn* α-chloro-β-hydroxyketimines **6a−c** were isolated after recrystallization from methanol in 26−39%.

2-Chloro-3-isopropylimino-2-methyl-1,3-diphenylpropan-1-ol 6a. White crystals, 39% yield. Mp 103.9−104.5 °C. ^{1}H NMR ($CDCl_3$): δ 1.11 and 1.13 (2 × 3H, d, J = 6.2 Hz, $(C\underline{H}_3)_2$-CH), 1.32 (3H, s, CCl-CH_3); 3.26 (1H, septet, J = 6.2 Hz, $(CH_3)_2$-C$\underline{H}$), 5.28 (1H, d, J = 2.8 Hz, C$\underline{H}$-OH), 6.63 (1H, d, J = 2.8 Hz, CH-O$\underline{H}$), 7.29−7.43 (8H, m, 8 × CH_{ar}), 7.52−7.56 (2H, m, 2 × CHar). ^{13}C NMR ($CDCl_3$): δ 23.2, 23.5, 26.8, 52.9, 73.9, 79.0, 127.5 (3 × CH_{ar}), 128.0 (2 × CH_{ar}), 128.2, 128.5 (2 × CH_{ar}), 129.2 (2 × CH_{ar}), 134.3, 138.8, 171.9. IR (cm^{-1}): ν_{max} 3256, 1637. MS (ES) m/z (%): 316/318 (M + H^+, 100). Anal. Calcd for $C_{19}H_{22}ClNO$: C 72.25, H 7.02, N 4.43. Found: C 72.37, H 7.10, N 4.38.

2-Chloro-1-(4-chlorophenyl)-3-isopropylimino-2-methyl-3-phenylpropan-1-ol 6b. Yellow crystals, 34% yield. Mp 77.6−78.2 °C. ^{1}H NMR ($CDCl_3$): δ 1.10 and 1,12 (2 × 3H, d, J = 6.2 Hz, $(C\underline{H}_3)_2$-CH), 1.30 (3H, s, CCl-CH_3), 3.26 (1H, septet, J = 6.2 Hz, $(CH_3)_2$-C$\underline{H}$), 5.25 (1H, s, C$\underline{H}$−OH), 6.74 (1H, br. s, CH-O$\underline{H}$), 7.33 (2H, d, J = 8.5 Hz, 2 × CH_{ar}), 7.40−7.42 (5H, m, 5 × CH_{ar}), 7.48 (2H, d, J = 8.5 Hz, 2 × CH_{ar}). ^{13}C NMR ($CDCl_3$): δ 23.2, 23.5, 26.7, 52.9, 73.5, 78.4, 127.6, 127.7 (2 × CH_{ar}), 128.2, 128.6, 129.5, 130.6 (2 × CH_{ar}), 130.9, 133.9, 134.1, 137.3, 171.8. IR (cm^{-1}): ν_{max} 3401, 1634. MS (ES) m/z (%): 350/352 (M + H^+, 100). Anal. Calcd for $C_{19}H_{21}Cl_2NO$: C 65.15, H 6.04, N 4.00. Found: C 65.02, H 6.17, N 4.06.

2-Chloro-1-(4-chlorophenyl)-3-isopropylimino-2-methyl-3-*p*-tolylpropan-1-ol 6c. White crystals, 26% yield. Mp 79.9−80.6 °C. ^{1}H NMR ($CDCl_3$): δ 1,10 and 1,11 (2 × 3H, d, J = 6.2 Hz, $(C\underline{H}_3)_2$-CH), 1.29 (3H, s, CCl-CH_3), 2.38 (3H, s, $C\underline{H}_3$-C_6H_4), 3.28 (1H, septet, J = 6.2 Hz, $(CH_3)_2$-C$\underline{H}$), 5.24 (1H, s, C$\underline{H}$−OH), 6.80 (1H, br. s, CH-O$\underline{H}$), 7.04 (2H, d, J = 7.7 Hz, 2 × CH_{ar}), 7.21 (2H, d, J = 7.7 Hz, 2 × CH_{ar}), 7.33 (2H, d, J = 8.5 Hz, 2 × CH_{ar}), 7.48 (2H, d, J = 8.5 Hz, 2 × CH_{ar}). ^{13}C NMR ($CDCl_3$): δ 21.3, 23.1, 23.5, 26.7, 52.8, 73.7, 78.4, 127.7 (4 × CH_{ar}), 128.9 (2 × CH_{ar}), 130.6 (2 × CH_{ar}), 131.0, 133.8, 137.4, 138.5, 172.0. IR (cm^{-1}): ν_{max} 3140, 1637. MS (ES) m/z

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(%): 364/366/368 (M + H^+, 100). Anal. Calcd for $C_{20}H_{23}Cl_2NO$: C 65.94, H 6.36, N 3.84. Found: C 66.03, H 6.44, N 3.89.

Synthesis of *syn* α-Chloro-β-mesyloxyketimines 8. *Procedure A: Starting from Pure Isolated syn α-Chloro-β-hydroxyketimines **6a–c**.* Methanesulfonyl chloride (8.26 mmol, 0.95 g) was added dropwise to a solution of α-chloro-β-hydroxyketimines **6** (5.5 mmol) in 15 mL of pyridine at room temperature. The reaction mixture was stirred at ambient temperature for 22 h, after which it was poured in 20 mL of ice-cold 0.5 N aqueous sodium hydroxide. The aqueous phase was extracted three times with dichloromethane, and the combined organic phases were dried ($MgSO_4$). After solvent evaporation in vacuo, the reaction crudes were recrystallized from hexane/diethyl ether (4:1) to yield *syn* α-chloro-β-mesyloxyketimines **8a–c** in a yield of 60–76%.

*Procedure B: Aldol Reaction of 3-Chloro-3-methyl-1-azaallylic Anions **1** Derived from Imines **4** with Aromatic Aldehydes **5**, Immediately Followed by Mesylation.* Under a nitrogen atmosphere, *n*-butyl lithium (15.7 mmol, 2.5 N in hexanes, 6.3 mL) was added dropwise to a solution of diisopropylamine (15.7 mmol, 2.03 g) in THF (50 mL) at 0 °C. After 30 min of stirring at 0 °C, α-chloroketimine **4** (12.1 mmol), which was dissolved in 10 mL of THF, was added dropwise, and the reaction mixture was stirred for 45 min at 0 °C. After deprotonation, a solution of zinc chloride (12.7 mmol) in 10 mL of THF was added, and the reaction mixture was stirred for 15 min at 0 °C. The reaction mixture was cooled to −78 °C, and then benzaldehyde **5** (6.05 mmol), which was dissolved in 2 mL of THF, was added dropwise to the reaction mixture, after which stirring was continued for 5 min at −78 °C, followed by 1 h at room temperature. After the addition of three drops of saturated aqueous ammonium chloride, 20 mL of an ice-cold solution of 0.5 N aqueous sodium hydroxide was added to the reaction mixture. The mixture was poured in a separatory funnel containing 30 mL of diethyl ether and 60 mL of 0.5 N aqueous sodium hydroxide. The aqueous layer was extracted three times with diethyl ether, and the combined organic extracts were washed with 30 mL of 0.5 N aqueous sodium hydroxide. After drying ($MgSO_4$), the solvent was evaporated in vacuo, and the crude mixture was dissolved in 16 mL of pyridine. Methanesulfonyl chloride (9.08 mmol, 1.04 g) was added dropwise, and the reaction mixture was stirred at room temperature for 22 h, after which it was poured in 22 mL of ice-cold 0.5 N aqueous sodium hydroxide. The aqueous phase was extracted three times with dichloromethane, and the combined organic phases were dried ($MgSO_4$). After solvent evaporation in vacuo, the reaction crudes were purified via flash chromatography to obtain pure *syn* α-chloro-β-mesyloxyketimines **8a–d** in a yield of 80–84% (dr >97/3). Noteworthy, in all cases α-chloro-α-methanesulfonylketimines **9** were also isolated as byproduct in 12–19% yield.

2-Chloro-3-isopropylimino-2-methyl-1,3-diphenylpropyl Methanesulfonate 8a. Yellow crystals, yield 76% (A), 80% (B). Mp 122.3–123.0 °C. R_f = 0.20, petroleum ether/Et_2O (80:20). ^{1}H NMR ($CDCl_3$): δ 1.10 and 1,11 (2 × 3H, d, J = 6.2 Hz, ($C\underline{H}_3$)$_2$-CH), 1.52 (3H, s, CCl-$C\underline{H}_3$), 2.80 (3H, s, CH_3SO_2), 3.27 (1H, septet, J = 6.2 Hz, (CH_3)$_2$-C$\underline{H}$), 6.59 (1H, s, C$\underline{H}$-OMs), 7.27–7.43 (8H, m, 8 × CH_{ar}), 7.57–7.64 (2H, m, 2 × CH_{ar}). ^{13}C NMR ($CDCl_3$): δ 23.2, 23.3, 26.9, 39.5, 53.9, 74.7, 87.1, 128.1 (3 × CH_{ar}), 128.2 (2 × CH_{ar}), 129.3 (2 × CH_{ar}), 129.6 (3 × CH_{ar}), 134.7, 135.7, 167.7. IR (cm^{-1}): ν_{max} 1640, 1177. MS (ES) m/z (%): 394/396 (M + H^+, 100). Anal. Calcd for $C_{20}H_{24}ClNO_3S$: C 60.98, H 6.14, N 3.56. Found: C 61.11, H 6.26, N 3.54.

2-Chloro-1-(4-chlorophenyl)-3-isopropylimino-2-methyl-3-phenylpropyl Methanesulfonate 8b. Yellow crystals, yield 70% (A), 83% (B). Mp 109.3–110.3 °C. R_f = 0.23, petroleum ether/Et_2O (80:20). ^{1}H NMR ($CDCl_3$): δ 1.08 and 1.11 (2 × 3H, d, J = 6.3 Hz, ($C\underline{H}_3$)$_2$-CH), 1.48 (3H, s, CCl-CH_3), 2.88 (3H, s, CH_3SO_2), 3.26 (1H, septet, J = 6.3 Hz, (CH_3)$_2$-C$\underline{H}$), 6.59 (1H, s, C$\underline{H}$-OMs), 7.37 (2H, d, J = 8.4 Hz, 2 × CH_{ar}), 7.30–7.42 (5H, m, 5 × CH_{ar}), 7.55 (2H, d, J = 8.4 Hz, 2 × CH_{ar}). ^{13}C NMR ($CDCl_3$): δ 23.2, 23.4, 26.6, 39.5, 53.8, 74.4, 86.0, 128.2 (2 × CH_{ar}), 128.3 (5 × CH_{ar}), 130.9 (2 × CH_{ar}), 133.5, 135.3, 135.4, 167.4. IR (cm^{-1}): ν_{max} 1645, 1176. MS (ES) m/z (%): 428/430/432 (M + H^+, 100). Anal. Calcd for $C_{20}H_{23}Cl_2NO_3S$: C 56.08, H 5.41, N 3.27. Found: C 56.23, H 5.57, N 3.34.

2-Chloro-1-(4-chlorophenyl)-3-isopropylimino-2-methyl-3-*p*-tolyl-propyl Methanesulfonate 8c. Yellow crystals, yield 60% (A), 84% (B). Mp 112.7–113.5 °C. R_f = 0.23, petroleum ether/Et_2O (80:20). ^{1}H NMR ($CDCl_3$): δ 1.08 and 1.10 (2 × 3H, d, J = 6.5 Hz, ($C\underline{H}_3$)$_2$-CH), 1.49 (3H, s, CCl-CH_3), 2.35 (3H, s, $C\underline{H}_3$-C_6H_4), 2.86 (3H, s, CH_3SO_2), 3.29 (1H, septet, J = 6.5 Hz, (CH_3)$_2$-C$\underline{H}$), 6.59 (1H, s, C$\underline{H}$-OMs), 7.11–7.22 (4H, m, 4 × CH_{ar}), 7.36 (2H, d, J = 8.7 Hz, 2 × CH_{ar}), 7.56 (2H, d, J = 8.7 Hz, 2 × CH_{ar}). ^{13}C NMR ($CDCl_3$): δ 21.5, 23.4, 23.6, 26.7, 39.7, 54.0, 74.8, 86.1, 127.0 (2 × CH_{ar}), 128.5 (2 × CH_{ar}), 129.1 (2 × CH_{ar}), 131.1 (2 × CH_{ar}), 132.6, 133.8, 135.5, 138.4, 167.9. IR (cm^{-1}): ν_{max} 1640, 1177. MS (ES) m/z (%): 442/444/446 (M + H^+, 100), 328/330 (20). Anal. Calcd for $C_{21}H_{25}Cl_2NO_3S$: C 57.01, H 5.70, N 3.17. Found: C 57.14, H 5.81, N 3.08.

2-Chloro-3-isopropylimino-2-methyl-1-phenyl-3-*p*-tolyl-propyl Methanesulfonate 8d. Yellow crystals, yield 81% (B). Mp 123.7–124.0 °C. R_f = 0.22, petroleum ether/Et_2O (80:20). ^{1}H NMR ($CDCl_3$): δ 1.09 and 1.10 (2 × 3H, d, J = 6.2 Hz, ($C\underline{H}_3$)$_2$-CH), 1.51 (3H, s, CCl-CH_3), 2.35 (3H, s, $C\underline{H}_3$-C_6H_4), 2.80 (3H, s, CH_3SO_2), 3.28 (1H, septet, J = 6.2 Hz, (CH_3)$_2$-C$\underline{H}$), 6.57 (1H, s, C$\underline{H}$-OMs), 7.02–7.28 (3H, m, 3 × CH_{ar}), 7.31–7.41 (4H, m, 4 × CH_{ar}), 7.56–7.63 (2H, m, 2 × CH_{ar}). ^{13}C NMR ($CDCl_3$): δ 21.3, 23.2, 23.4, 26.8, 39.5, 53.7, 74.8, 87.1, 128.0 (3 × CH_{ar}), 128.8 (2 × CH_{ar}), 129.2 (2 × CH_{ar}), 129.6 (2 × CH_{ar}), 132.7, 134.8, 138.0, 167.8. IR (cm^{-1}): ν_{max} 1641, 1174. MS (ES) m/z (%): 408/410 (M + H^+, 100). Anal. Calcd for $C_{21}H_{26}ClNO_3S$: C 61.83, H 6.42, N 3.43. Found: C 61.64, H 6.61, N 3.28.

(2-Chloro-2-methanesulfonyl-1-phenylpropylidene)-isopropylamine 9a. Yellow oil, yield 19%. R_f = 0.35, petroleum ether/Et_2O (80:20). ^{1}H NMR ($CDCl_3$): δ 1.09 (6H, d, J = 6.1 Hz, ($C\underline{H}_3$)$_2$-CH), 1.89 (3H, s, CCl-$C\underline{H}_3$), 3.31 (1H, septet, J = 6.1 Hz, (CH_3)$_2$-C$\underline{H}$), 3.34 (3H, s, CH_3SO_2), 7.18–7.25 (2H, m, 2 × CH_{ar}), 7.38–7.46 (3H, m, 3 × CH_{ar}). ^{13}C NMR ($CDCl_3$): δ 22.8, 22.9, 23.0, 37.9, 53.9, 83.9, 127.3 (2 × CH_{ar}), 128.5 (2 × CH_{ar}), 129.0, 134.1, 163.9. IR (cm^{-1}): ν_{max} 2967, 1638, 1311, 1144. MS (ES) m/z (%): 288/290 (M + H^+, 100). HRMS: calcd for $C_{13}H_{18}ClNO_2S$ 288.0819 [M + H^+], found 288.0819 [M + H^+].

(2-Chloro-2-methanesulfonyl-1-*p*-tolylpropylidene)-isopropylamine 9b. Yellow oil, yield 15%. R_f = 0.31, petroleum ether/Et_2O (80:20). ^{1}H NMR ($CDCl_3$): δ 1.08 (6H, d, J = 6.1 Hz, ($C\underline{H}_3$)$_2$-CH), 1.89 (3H, s, CCl-$C\underline{H}_3$), 2.38 (3H, s, $C\underline{H}_3$-C_6H_4), 3.32 (3H, s, CH_3SO_2), 3.33 (1H, septet, J = 6.1 Hz, (CH_3)$_2$-C$\underline{H}$), 7.09 (2H, d, J = 8.3 Hz, 2 × CH_{ar}), 7.22 (2H, d, J = 7.7 Hz, 2 × CH_{ar}). ^{13}C NMR ($CDCl_3$): δ 21.3, 22.7, 22.9, 23.0, 37.9, 53.8, 84.1, 127.2 (2 × CH_{ar}), 129.1 (2 × CH_{ar}), 131.0, 138.9, 164.1. IR (cm^{-1}): ν_{max} 2968, 1638, 1310, 1146. MS (ES) m/z (%): 302/304 (M + H^+, 100). HRMS: calcd for $C_{14}H_{20}ClNO_2S$ 302.0976 [M + H^+], found 302.0972 [M + H^+].

General Procedure for the Synthesis of β-Chloro-γ-mesyloxyamines 2. Sodium cyanoborohydride (10.5 mmol) and acetic acid (5.03 mmol) were subsequently added to a solution of α-chloro-β-mesyloxyketimines **8** (4.20 mmol) in 20 mL of methanol, and the reaction mixture was stirred for 24 h at room temperature. The reaction mixture was poured in 20 mL of 0.5 N aqueous sodium hydroxide, and the aqueous phase was extracted three times with dichloromethane. The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated in vacuo. The reaction crudes were purified by a recrystallization from hexane/diethyl ether (9:1) to give β-chloro-γ-mesyloxyamines **2a–c** in 63–78% yield. Reduction of β-mesyloxyketimine **8d** (R^1 = Me, R^2 = H) afforded a mixture of β-chloro-γ-mesyloxypropylamine **2d** and 2,4-diaryl-3-chloro-3-methylazetidine **3d** in a ratio of 71:29. After purification via flash chromatography, β-chloro-γ-mesyloxypropylamine **2d** and 2,4-diaryl-3-chloro-3-methylazetidine **3d** were isolated in 23% and 58% yield, respectively.

2-Chloro-3-isopropylamino-2-methyl-1,3-diphenylpropyl methanesulfonate 2a. Yellow crystals, yield 78%. Mp 138.0–139.4 °C. ^{1}H NMR ($CDCl_3$): δ 0.95 en 1.07 (2 × 3H, d, J = 6.2 Hz, ($C\underline{H}_3$)$_2$-CH), 1.22 (3H, s, CCl-CH_3), 1.51 (1H, br s, NH), 2.59 (3H, s,

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CH_3SO_2), 2.66 (1H, septet, J = 6.2 Hz, $(CH_3)_2$-CH), 4.32 (1H, s, CHNH), 6.27 (1H, s, CH-OMs), 7.32−7.40 (8H, m, 8 × CH_{ar}), 7.56−7.58 (2H, m, 2 × CH_{ar}). ^{13}C NMR ($CDCl_3$): δ 22.0 (2 × CH_3), 24.6, 39.9, 47.1, 65.0, 74.8, 85.0, 127.5, 127.7 (2 × CH_{ar}), 128.2 (2 × CH_{ar}), 129.5, 129.7 (2 × CH_{ar}), 129.8 (2 × CH_{ar}), 134.6, 139.1. IR (cm^{-1}): ν_{max} 3335, 1172. MS (ES) m/z (%): 396/398 (M + H^+, 100). Anal. Calcd for $C_{20}H_{26}ClNO_3S$: C 60.67, H 6.62, N 3.54. Found: C 60.39, H 6.71, N 3.62.

2-Chloro-1-(4-chlorophenyl)-3-isopropylamino-2-methyl-3-phenylpropyl Methanesulfonate 2b. Yellow crystals, yield 67%. Mp 111.1−111.3 °C. ^{1}H NMR ($CDCl_3$): δ 0.94 en 1.06 (2 × 3H, d, J = 6.3 Hz, $(CH_3)_2$-CH), 1.20 (3H, s, CCl-CH_3), 1.55 (1H, br s, NH), 2.66 (1H, septet, J = 6.3 Hz, $(CH_3)_2$-CH), 2.68 (3H, s, CH_3SO_2), 4.28 (1H, s, CHNH), 6.27 (1H, s, CH-OMs), 7.30−7.40 (7H, m, 7 × CH_{ar}), 7.52 (2H, d, J = 8.3 Hz, 2 × CH_{ar}). ^{13}C NMR ($CDCl_3$): δ 22.0 (2 × CH_3), 24.6, 40.0, 47.1, 65.0, 74.6, 84.0, 127.6, 127.7 (2 × CH_{ar}), 128.5 (2 × CH_{ar}), 129.7 (2 × CH_{ar}), 130.9 (2 × CH_{ar}), 133.3, 135.6, 138.9. IR (cm^{-1}): ν_{max} 3359, 1176. MS (ES) m/z (%): 430/432/434 (M + H^+, 100). Anal. Calcd for $C_{20}H_{25}Cl_2NO_3S$: C 55.81, H 5.85, N 3.25. Found: C 55.73, H 5.97, N 3.33.

2-Chloro-1-(4-chlorophenyl)-3-isopropylamino-2-methyl-3-*p*-tolylpropyl Methanesulfonate 2c. Yellow crystals, yield 63%. Mp 123.0−123.6 °C. ^{1}H NMR ($CDCl_3$): δ 0.94 and 1.05 (2 × 3H, d, J = 6.3 Hz, $(CH_3)_2$-CH), 1.20 (3H, s, CCl-CH_3), 1.47 (1H, br s, NH), 2.36 (3H, s, CH_3-C_6H_4), 2.65 (1H, septet, J = 6.3 Hz, $(CH_3)_2$-CH), 2.68 (3H, s, CH_3SO_2), 4.23 (1H, s, CHNH), 6.26 (1H, s, CH-OMs), 7.16 (2H, d, = 8.1 Hz, 2 × CH_{ar}), 7.23 (2H, d, J = 8.1 Hz, 2 × CH_{ar}), 7.37 (2H, d, J = 8.5 Hz, 2 × CH_{ar}), 7.51 (2H, d, J = 8.5 Hz, 2 × CH_{ar}). ^{13}C NMR ($CDCl_3$): δ 21.1, 22.0 (2 × CH_3), 24.6, 40.0, 47.1, 64.7, 74.9, 84.0, 128.5 (4 × CH_{ar}), 129.5 (2 × CH_{ar}), 130.9 (2 × CH_{ar}), 133.3, 135.5, 135.8, 137.3. IR (cm^{-1}): ν_{max} 3326, 1176. MS (ES) m/z (%): 444/446/448 (M + H^+, 100). Anal. Calcd for $C_{21}H_{27}Cl_2NO_3S$: C 56.75, H 6.12, N 3.15. Found: C 56.62, H 6.05, N 3.17.

2-Chloro-3-isopropylamino-2-methyl-1-phenyl-3-*p*-tolylpropyl Methanesulfonate 2d. White crystals, yield 58%. Mp 131.4−131.8 °C. R_f = 0.09, petroleum ether/EtOAc (95:5). ^{1}H NMR ($CDCl_3$): δ 0.95 and 1.06 (2 × 3H, d, J = 6.2 Hz, $(CH_3)_2$-CH), 1.22 (3H, s, CCl-CH_3), 1.47 (1H, br s, NH), 2.36 (3H, s, CH_3-C_6H_4), 2.59 (3H, s, CH_3SO_2), 2.65 (1H, septet, J = 6.2 Hz, $(CH_3)_2$-CH), 4.27 (1H, s, CHNH), 6.26 (1H, s, CH-OMs), 7.16 (2H, d, = 8.3 Hz, 2 × CH_{ar}), 7.25 (2H, d, J = 7.2 Hz, 2 × CH_{ar}), 7.34−7.46 (3H, m, 3 × CH_{ar}), 7.52−7.64 (2H, m, 2 × CH_{ar}). ^{13}C NMR ($CDCl_3$): δ 21.2, 22.0, 22.1, 24.6, 39.9, 47.1, 64.8, 75.0, 85.1, 128.2 (2 × CH_{ar}), 128.5 (2 × CH_{ar}), 129.5, 129.6 (2 × CH_{ar}), 129.7 (2 × CH_{ar}), 134.7, 136.0, 137.2. IR (cm^{-1}): ν_{max} 3347, 1352, 1174. MS (ES) m/z (%): 410/412 (M + H^+, 100). Anal. Calcd for $C_{21}H_{28}ClNO_3S$: C 61.52, H 6.88, N 3.42. Found: C 61.88, H 6.53, N 3.14.

General Procedure for the Synthesis of 2,4-Diaryl-3-chloro-3-methylazetidines 3. Potassium carbonate (4.56 mmol) was added to a solution of β-chloro-γ-mesyloxyamines 2 (1.52 mmol) in DMSO (10 mL), and the reaction mixture was stirred for 48 h at 85−90 °C. The reaction mixture was poured in water, and the aqueous phase was extracted three times with dichloromethane. The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated in vacuo. The reaction crudes were purified via flash chromatography, which gave 2,4-diaryl-3-chloro-3-methylazetidines **3** in 53−73% yield.

3-Chloro-1-isopropyl-3-methyl-2,4-diphenylazetidine 3a. Colorless oil, yield 53%. R_f = 0.34, petroleum ether/EtOAc (95:5). ^{1}H NMR ($CDCl_3$): δ 0.72 (3H, s, CCl-CH_3), 0.87 (6H, d, J = 6.3 Hz, $(CH_3)_2$-CH), 2.83 (1H, septet, J = 6.3 Hz, $(CH_3)_2$-CH), 4.51 (2H, s, 2 × CH), 7.27−7.40 (6H, m, 6 × CH_{ar}), 7.52−7.58 (4H, m, 4 × CH_{ar}). ^{13}C NMR ($CDCl_3$): δ 21.7 (2 × CH_3), 22.5, 60.0, 66.8, 77.7 (2 × CH), 127.3 (4 × CH_{ar}), 127.5 (2 × CH_{ar}), 128.0 (4 × CH_{ar}), 138.9 (2 × C_{quat}). IR (cm^{-1}): ν_{max} 2970, 1454, 1334, 1069. MS (ES) m/z (%): 300/302 (M + H^+, 57), 150/152 (100). Anal. Calcd for $C_{19}H_{22}ClN$: C 76.11, H 7.40, N 4.67. Found: C 76.22, H 7.53, N 4.70.

3-Chloro-2-(4-chlorophenyl)-1-isopropyl-3-methyl-4-phenylazetidine 3b. Colorless oil, yield 60%. R_f = 0.30, petroleum ether/EtOAc (95:5). ^{1}H NMR ($CDCl_3$): δ 0.71 (3H, s, CCl-CH_3), 0.85 and 0.86 (2 × 3H, d, J = 6.3 Hz, $(CH_3)_2$-CH), 2.82 (1H, septet, J = 6.3 Hz, $(CH_3)_2$-CH), 4.46 and 4.50 (2H, s, 2 × CH), 7.29−7.40 (5H, m, 5 × CH_{ar}), 7.47−7.55 (4H, m, 4 × CH_{ar}). ^{13}C NMR ($CDCl_3$): δ 21.6, 21.7, 22.5, 60.0, 66.5, 77.7 (2 × CH), 127.3 (2 × CH_{ar}), 127.7, 128.1 (2 × CH_{ar}), 128.3 (2 × CH_{ar}), 128.6 (2 × CH_{ar}), 133.3, 137.5, 138.6. IR (cm^{-1}): ν_{max} 2970, 1489, 1332, 1070. MS (ES) m/z (%): 334/336/338 (M + H^+, 70), 286 (100), 268 (35). Anal. Calcd for $C_{19}H_{21}Cl_2N$: C 68.27, H 6.33, N 4.19. Found: C 68.16, H 6.43, N 4.15.

3-Chloro-2-(4-chlorophenyl)-1-isopropyl-3-methyl-4-*p*-tolylazetidine 3c. Colorless oil, yield 73%. R_f = 0.32, petroleum ether/EtOAc (95:5). ^{1}H NMR ($CDCl_3$): δ 0.71 (3H, s, CCl-CH_3), 0.84 and 0.85 (2 × 3H, d, J = 6.3 Hz, $(CH_3)_2$-CH), 2.36 (3H, s, CH_3-C_6H_4), 2.80 (1H, septet, J = 6.3 Hz, $(CH_3)_2$-CH), 4.44 and 4.46 (2H, s, 2 × CH), 7.17 (2H, d, J = 8.0 Hz, 2 × CH_{ar}), 7.33 (2H, d, J = 8.4 Hz, 2 × CH_{ar}), 7.40 (2H, d, J = 8.0 Hz, 2 × CH_{ar}), 7.49 (2H, d, J = 8.4 Hz, 2 × CH_{ar}). ^{13}C NMR ($CDCl_3$): δ 21.2, 21,7 (2 × CH_3), 22.4, 60.0, 66.6, 77.6 (2 × CH), 127.2 (2 × CH_{ar}), 128.3 (2 × CH_{ar}), 128.7 (2 × CH_{ar}), 128.8 (2 × CH_{ar}), 133.3, 135.7, 137.3, 137.6. IR (cm^{-1}): ν_{max} 2977, 1489, 1371, 1328, 1070. MS (ES) m/z (%): 348/350/352 (M + H^+, 100), 349 (30), 312 (45). Anal. Calcd for $C_{20}H_{23}Cl_2N$: C 68.97, H 6.66, N 4.02. Found: C 69.10, H 6.82, N 4.09.

3-Chloro-1-isopropyl-3-methyl-2-phenyl-4-*p*-tolylazetidine 3d. Colorless oil, yield 64%. R_f = 0.36, petroleum ether/EtOAc (95:5). ^{1}H NMR ($CDCl_3$): δ 0.72 (3H, s, CCl-CH_3), 0.86 (6H, d, J = 6.2 Hz, $(CH_3)_2$-CH), 2.35 (3H, s, CH_3-C_6H_4), 2.81 (1H, septet, J = 6.2 Hz, $(CH_3)_2$-CH), 4.47 and 4.46 (2H, s, 2 × CH), 7.16 (2H, d, J = 8.3 Hz, 2 × CH_{ar}), 7.22−7.38 (3H, m, 3 × CH_{ar}), 7.43 (2H, d, J = 8.3 Hz, 2 × CH_{ar}), 7.52−7.58 (2H, m, 2 × CH_{ar}). ^{13}C NMR ($CDCl_3$): δ 21.2, 21.7 (2 × CH_3), 22.4, 59.9, 67.0, 77.6, 77.7, 127.2 (2 × CH_{ar}), 127.3 (2 × CH_{ar}), 127.5, 128.0 (2 × CH_{ar}), 128.7 (2 × CH_{ar}), 135.9, 137.1, 139.0. IR (cm^{-1}): ν_{max} 2969, 1439, 1374, 1331, 1199, 1069. MS (ES) m/z (%): 314/316 (M + H^+, 100), 276 (48). Anal. Calcd for $C_{20}H_{24}ClN$: C 76.53, H 7.71, N 4.46. Found: C 76.18, H 7.49, N 4.31.

■ ASSOCIATED CONTENT

Supporting Information

General experimental conditions and copies of ^{1}H NMR and ^{13}C NMR spectra for *syn* α-chloro-β-hydroxyketimines **6**, *syn* α-chloro-β-mesyloxyketimines **8**, α-chloro-α-methanesulfonylketimines **9**, β-chloro-γ-mesyloxyamines **2**, and 2,4-diaryl-3-chloro-3-methylazetidines **3**. Cartesian coordinates of B3LYP/6-31++G(d,p) optimized transition state structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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