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

Sven Mangelinckx,† Bart De Sterck,‡,# Filip Colpaert,† Saron Cataki,‡ Jan Jacobs,† Stijn Rooryck,† Michel Waroquier,‡ Veronique Van Speybroeck,‡ and Norbert De Kimpe*†

†Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium
‡Center for Molecular Modeling, Ghent University, Technologiepark 903, B-9052 Zwijnaarde, Belgium, Member of QCMM Alliance Ghent-Brussels

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. 3-Haloazetidines, in particular, form an important subclass of functionalized four-membered azaheterocycles due to their potential physiological activities and their use as synths in the synthesis of 3-substituted azetidine derivatives. 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. The latter result, together with a variety of other examples, 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 stereo-selective synthesis of highly substituted 3-haloazetidines depends, naturally, on the efficient synthetic accessibility of the corresponding stereochemically defined aminopropyl precursors. Metalated 3-chloro-1-azaallylic anions have proven to be suitable building blocks in organic synthesis by reaction with electrophiles and elaboration of the resulting functionalized α-chloroketimines. More specifically, the aldol reaction of 3,3-dichloro-1-azaallylic anions 1 (R3 = Cl) with aromatic aldehydes, followed by mesylation to the corresponding β-mesyloxyketimines, and reduction afforded amines 2 (R3 = Cl) as precursors of stereochemically defined 2,4-diaryl-3,3-dichloroazetidines. In previous computational research, the 3-chloro-3-methyl-1-azaallylic anion 1 (R3 = Me) was chosen as a model compound to obtain deeper insight into the structural features of 3-halo-1-azaallylic anions and a better understanding of the stereochemical course of the reaction.
### Table 1. Aldol Reaction of Anions 1a and 1b Derived from Imine 4a with Benzaldehyde 5a

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

*<sup>a</sup>Determined via 1H NMR analysis (300 MHz, CDCl₃) of the crude reaction mixture.

*<sup>b</sup>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.

*<sup>c</sup>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.

*<sup>d</sup>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.

*<sup>e</sup>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.

*<sup>f</sup>LiCl was added instead of ZnCl₂.

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

![Diagram of the reaction process](image-url)
understanding of the factors that control the stereochemochemical outcome of the reactions involving these anions.

Herein, the use of 3-chloro-3-methyl-1-azaallylic anions 1 (R³ = Me) in aldol reactions with aromatic aldehydes is reported en route to the stereoselective synthesis of new azetidines 3 (R³ = 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. 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, R¹ = iPr, R² = C₆H₅, R³ = Me) is present in a monosolvated monomeric Z-isomer form and should readily undergo transmetalation to the zincated Z-isomer 1b (M = ZnCl₂, R¹ = iPr, R² = C₆H₅, R³ = Me). 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-isopropylamine 4a of α-chloropropiophenone, were reacted with aromatic aldehydes S (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. Treatment of N-isopropyl-α-chloro imine 4a with lithium disopropylamide in tetrahydrofuran at 0 °C provided the lithiated 3-chloro-3-methyl-1-azaallylic anion 1a, 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-imidoyl epoxides 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 JCH of ~0 Hz was observed for the trans-CH₃ and -H oxirane ring substituents. 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-imidoyl epoxide 7a, while the lithiated syn-adduct cyclized only to a minor extent due to sterical hindrance of the benzimidoyl and phenyl substituents during cyclization 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 ZnCl₂ 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...
lower yield of 63% (dr > 99/1) (entry 14). When LiCl was used instead of ZnCl₂, 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 zinicated anion 1b with benzaldehyde 5a is not an equilibrated reaction, in which retro-aldol reaction of the formed zinicated 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). ZnCl₂ 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-imidoylpeioxide 7a via treatment with potassium hydroxide (1.5 equiv) in water/tetrahydrofuran (1:1) were made. 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 NaCNBH₃ and base-induced cyclization of the stereochemically defined β-chloro-γ-mesyloxypropylamines 2 upon heating in DMSO (Scheme 2). The observed stereo-selectivity 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 and Cram’s chelation model for 1,2-induction, as shown in Scheme 4.
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

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.
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.

All computations were performed using the Gaussian09 program package. Geometry optimizations for the transition states were carried out using the B3LYP 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 and M06-2X 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. 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. 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.

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, it was shown that transmetalation of lithiated azaallylic anions 1a to zinctated 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 pseudoaxial position, whereas in the anti, the phenyl group of benzaldehyde occupies the more hindered pseudoaxial position leading to a more pronounced steric...
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 zircated 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 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 ΔΔGsyn-anti between the transition state structures leading to the syn and 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, 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.

<table>
<thead>
<tr>
<th>ΔΔGsyn-anti (in kJ/mol)</th>
<th>M06-2X (SMD)</th>
<th>B97-D (SMD)</th>
</tr>
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<tbody>
<tr>
<td>TS1 (Li–THF)</td>
<td>−3.6</td>
<td>−1.7</td>
</tr>
<tr>
<td>TS2 (ZnCl2–Li–THF)</td>
<td>−11.3</td>
<td>−9.3</td>
</tr>
</tbody>
</table>

4B3LYP/6-31+G(d,p) optimized geometries. SMD calculations in THF (ε = 7.425). ΔΔGsyn-anti = ΔGsyn − ΔGanti.

### EXPERIMENTAL SECTION

**General Procedure for the Synthesis of syn α-Chloro-β-hydroxyketimines 6.** Under a nitrogen atmosphere, n-butylium (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-chloro ketimine 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. 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 (MgSO4), 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-isopropylmimo-2-methyl-1,3-dipropylpropan-1-ol 6a.

White crystals, 39% yield. Mp 103.9–104.5 °C. H NMR (CDCl3): δ 1.11 and 1.13 (2 × 3H, d, J = 6.2 Hz, (CH3)2–CH), 1.32 (3H, s, CCl–CH3), 3.26 (1H, septet, J = 6.2 Hz, (CH2)–CH2), 5.28 (1H, d, J = 2.8 Hz, CH–OH), 6.63 (1H, d, J = 2.8 Hz, CH–OH), 7.29–7.45 (8H, m, 8 × CH). IR (cm−1): νmax 3425, 1637. MS (ES) m/z (%): 316/318 (M + H+, 100). Anal. Calcd for C19H22ClNO: 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-isopropylmimo-2-methyl-3-phenylpropan-1-ol 6b.

Yellow crystals, 34% yield. Mp 77.6–78.2 °C. 1H NMR (CDCl3): δ 1.10 and 1.12 (2 × 3H, d, J = 6.2 Hz, (CH3)2–CH), 1.30 (3H, s, CCl–CH3), 3.26 (1H, septet, J = 6.2 Hz, (CH2)–CH2), 5.25 (1H, s, CH–OH), 6.74 (1H, br, CH–OH), 7.33 (2H, d, J = 8.5 Hz, 2 × CH), 7.40–7.42 (5H, m, 5 × CH). 13C NMR (CDCl3): δ 23.2, 23.5, 26.7, 52.9, 73.8, 75.8, 124.6, 127.7 (2 × CH2), 128.2, 128.5 (2 × CH2), 129.2 (2 × CH3), 134.3, 138.8, 171.8 IR (cm−1): νmax 2913, 2530, 1630, 1524, 1429, 1317, 1294, 1272, 1251, 1198, 1158, 1028, 917, 751, 727, 691, 638, 618, 576, 560, 540, 522, 492, 461 (M + H+, 100). Anal. Calcd for C21H18Cl3NO: C 69.92, H 6.04, N 4.00. Found: C 69.62, H 6.17, N 4.06.

#### 2-Chloro-1-(4-chlorophenyl)-3-isopropylmimo-2-methyl-3-p-tolylpropan-1-ol 6c.

White crystals, 26% yield. Mp 79.9–80.6 °C. 1H NMR (CDCl3): δ 1.10 and 1.11 (2 × 3H, d, J = 6.2 Hz, (CH3)2–CH), 1.29 (3H, s, CCl–CH3), 2.38 (3H, s, CH–C(CH3)3), 3.28 (1H, septet, J = 6.2 Hz, (CH2)–CH2), 5.24 (1H, s, CH–OH), 6.80 (1H, br, CH–OH), 7.04 (2H, d, J = 7.7 Hz, 2 × CH2). 2.71 (2H, d, J = 7.7 Hz, 2 × CH2). 7.33 (2H, d, J = 8.5 Hz, 2 × CH2), 7.48 (2H, d, J = 8.5 Hz, 2 × CH2). 13C NMR (CDCl3): δ 21.3, 23.1, 23.5, 26.7, 52.8, 73.7, 78.4, 127.7 (4 × CH2), 128.9 (2 × CH2), 131.0, 133.8, 137.4, 138.5, 172.0 IR (cm−1): νmax 3160, 1360, MS (ES) m/z (%): 316/318 (M + H+, 100). Anal. Calcd for C19H18Cl3NO: C 69.92, H 6.04, N 4.00. Found: C 69.62, H 6.17, N 4.06.

#### CONCLUSIONS

This combined experimental-theoretical study shows that the aldol reaction of lithiated and zircated 3-chloro-3-methyl-1-azaallylic anions 1 across aromatic aldehydes 5 mainly yields the kinetic syn-adducts. The proposed “twist-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-chloroalkylides can be used in a stereoselective synthesis of new tetrastituted 3-chloroazetidines.
nlyketimines 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 disopropylamine (15.7 mmol, 2.03 g) in THF (50 mL) at 0 °C. After 30 min of stirring at 0 °C, 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 dichloromethane. The combined organic extracts were dried (MgSO4). After solvent evaporation in vacuo, the reaction crude were recrystallized from hexane/diethyl ether (4:1) to yield syn α-chloro-β-mesyloxyketimines 8a–c in a yield of 60−76%.

2-Chloro-2-methanesulfonyl-1-phenyl-3-p-tolyl-propyl Methanesulfonate 8d. Yellow crystals, yield 81% (B). Mp 123.7−124.0 °C. Rf = 0.22, petroleum ether/EtO (80:20). H NMR (CDCl3): δ 1.09 and 1.10 (2 × 3H, d, J = 6.2 Hz, (CH3)2-CH), 1.51 (3H, s, C(α)-CH3), 2.35 (3H, s, CH3-CH), 2.80 (3H, s, CH2-SO2), 3.28 (1H, septet, J = 6.2 Hz, (CH3)2-CH), 6.57 (1H, s, CH-OM), 7.02–7.28 (3H, m, 3 × CH2), 7.31–7.41 (4H, m, 2 × CH2), 7.56–7.63 (2H, m, 2 × CH2). 13C NMR (CDCl3): δ 21.3, 23.3, 23.4, 26.8, 39.5, 53.7, 57.4, 87.1, 128.0 (3 × CH2), 128.8 (2 × CH2), 112.9 (2 × CH2), 129.6 (2 × CH2), 129.6 (2 × CH2). IR (cm−1): νmax 3322, 3034, 2928, 1747, 1639, 1641, 1614, 1174. MS (ES) m/z (%): 408/410 (M + H+, 100). Anal. Calcld for C18H16NO2S: C 61.31, H 6.42, N 3.43. Found: C 61.64, H 6.61, N 3.28.

(2-Chloro-2-methanesulfonyl-1-phenylpropyldiene) isomylamine 9a. Yellow oil, yield 15%. Rf = 0.35, petroleum ether/EtO (80:20). H NMR (CDCl3): δ 1.09 (6H, d, J = 6.1 Hz, (CH3)2-CH), 1.89 (3H, s, C(α)-CH3), 3.31 (1H, septet, J = 6.1 Hz, (CH3)2-CH), 3.34 (3H, s, CH3-SO2), 7.18–7.25 (2H, m, 2 × CH2), 7.36–7.46 (3H, m, 3 × CH2). 13C NMR (CDCl3): δ 22.8, 22.9, 23.0, 37.9, 53.7, 53.8, 84.1, 127.2 (2 × CH2), 128.5 (2 × CH2), 129.0, 134.1, 163.9. IR (cm−1): νmax 3069, 1638, 1311. 1H NMR (CDCl3): δ 3.31 (1H, septet, J = 10.0 Hz, (CH3)2-CH), 3.34 (3H, s, CH3-SO2), 127.2 (2 × CH2), 128.5 (2 × CH2), 129.0, 134.1, 163.9. MS (ES) m/z (%): 288/290 (M + H+, 100). HRMS: calcld for C15H14NO2S, 288.0819 [M + H+], found 288.0819 [M + H+].

(2-Chloro-2-methanesulfonyl-1-p-tolylpropyldiene) isomylamine 9b. Yellow oil, yield 15%. Rf = 0.31, petroleum ether/EtO (80:20). H NMR (CDCl3): δ 1.08 (6H, d, J = 6.1 Hz, (CH3)2-CH), 1.89 (3H, s, C(α)-CH3), 2.35 (3H, s, CH3-CH), 3.32 (3H, s, CH3-SO2), 3.33 (1H, septet, J = 6.1 Hz, (CH3)2-CH), 7.09 (2H, d, J = 8.3 Hz, 2 × CH2), 7.22 (2H, d, J = 7.7 Hz, 2 × CH2). 13C NMR (CDCl3): δ 21.3, 22.7, 22.9, 23.0, 37.9, 53.8, 84.1, 127.2 (2 × CH2), 128.5 (2 × CH2), 129.0, 134.1, 163.9. IR (cm−1): νmax 3069, 1638, 1311. 1H NMR (CDCl3): δ 3.31 (1H, septet, J = 10.0 Hz, (CH3)2-CH), 3.34 (3H, s, CH3-SO2), 127.2 (2 × CH2), 128.5 (2 × CH2), 129.0, 134.1, 163.9. MS (ES) m/z (%): 302/304 (M + H+, 100). HRMS: calcld for C16H14NO2S, 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 8a–c 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 (MgSO4), and the solvent was evaporated in vacuo. The reaction crude were purified by recrystallization from hexane/diethyl ether (9:1) to give β-chloro-γ-mesyloxyamines 2a–c in 63−78% yield. Reduction of β-chloro-γ-mesyloxyamines 8d (R′ = Me, R″ = H) afforded a mixture of β-chloro-γ-mesyloxypropyldiene 2d and 2,4-diaryl-3-chloro-3-methylazetidine 3d in a ratio of 71:29. After purification via flash chromatography, β-chloro-γ-mesyloxypropyldiene 2d and 2,4-diaryl-3-chloro-3-methylazetidine 3d were isolated in 23% and 58% yield, respectively.

2-Chloro-3-isopropylimino-2-methyl-1,3-diphenylpropyl Methanesulfonate 2a. Yellow crystals, yield 78%. Mp 138.0−139.4 °C. H NMR (CDCl3): δ 0.95 en 1.07 (2 × 3H, d, J = 6.2 Hz, (CH3)2-CH), 1.22 (3H, s, C(α)-CH3), 1.51 (1H, br s, NH), 2.59 (3H, s, C6H5-CH2), 2.59 (3H, s, C6H5-CH2), 3.98 (3H, s, CH3-CO), 3.71 (3H, s, CH3-CO), 7.40–7.53 (8H, m, 8 × CH), 7.46 (3H, m, 3 × CH2), 7.47 (3H, m, 3 × CH2), 7.48 (2H, d, J = 6.0 Hz, (CH3)2-CH).
CH₃SO₃)₂, 2.66 (1H, septet, J = 6.2 Hz, (CH₃)₂-CH), 4.32 (1H, s, CH₃NH), 6.27 (1H, s, CH-OMs), 7.32–7.40 (8H, m, 8 × CH₃), 7.56–7.58 (2H, m, 2 × CH₃). 13C NMR (CDCl₃): δ 22.0 (2 × CH₃), 24.6, 39.1, 47.1, 65.0, 74.8, 85.0, 127.5, 127.7 (2 × CH₃), 128.2 (2 × CH₃), 129.5, 129.7 (2 × CH₃), 129.8 (2 × CH₃), 134.6, 139.1. IR (cm⁻¹): νmax 3359, 1176. MS (ES) m/z (?): 348/350/352 (M + H⁺, 100), 349 (30), 312 (45). Anal. Calc'd for C₂₁H₂₈ClNO₃S: C 61.52, H 6.88, N 3.42. Found: C 61.7, H 6.63, N 3.15. Found: C 68.16, H 6.43, N 4.15.

3-Chloro-2-(4-chlorophenyl)-1-isopropyl-3-methyl-4-p-toly lazetidine 3c. Colorless oil, yield 73%. Rf: 0.32, petrol ether/EtOAc (95:5). 1H NMR (CDCl₃): δ 0.73 (3H, s, CCl-CH₃), 1.47 (1H, br s, NH), 2.36 (6H, s, 2 × CH₃), 7.28 (2H, d, J = 8.3 Hz, 2 × CH₃), 7.43 (2H, d, J = 8.3 Hz, 2 × CH₃), 7.52–7.58 (2H, m, 2 × CH₃). 13C NMR (CDCl₃): δ 21.2, 21.7, 22.4, 60.1, 66.6, 77.6 (2 × CH₃), 127.2 (2 × CH₃), 128.7 (2 × CH₃), 128.8 (2 × CH₃), 133.3, 135.7, 137.3, 137.6. IR (cm⁻¹): νmax 2977, 1489, 1371, 1328, 1070. MS (ES) m/z (%): 334/336/338 (M + H⁺, 70), 286 (100), 268 (35). Anal. Calc'd for C₁₉H₁₈Cl₂N: C 68.27, H 6.35, N 4.13. Found: C 68.16, H 6.43, N 4.15.

**ASSOCIATED CONTENT**

**Supporting Information**

General experimental conditions and copies of 1H NMR and 13C NMR spectra for syn α-chloro-β-hydroxyketimines 6, syn α-chloro-β-mesyloxyketimines 8, α-chloro-α-mesulfonylketimines 9, β-chloro-γ-mesyloxyamines 2, and 2,4-diaryl-3-chloro-3-methylopyrazidines 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.

**AUTHOR INFORMATION**

**Corresponding Author**
Tel: +32 (0)9 264 59 51. Fax: +32 (0)9 264 62 43. E-mail: norbert.dekimpe@ugent.be.

**Present Address**
LANEXX Rubber N.V., BTR - Competence Center Technology Process Technologist, Haven 1009 - Canadastraat 21, 2070 Zwijndrecht, Belgium.

**Notes**
The authors declare no competing financial interest.
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REFERENCES


(6) For a similar diastereospecific ring closure to cis-3-aryl-2-chloro-2-imidoylaziridines, see ref. 6c.


