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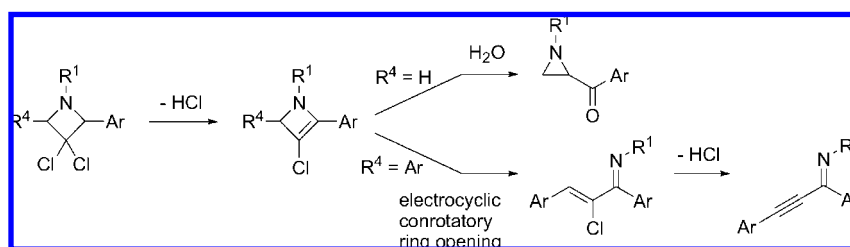
# Experimental and Computational Study of the Conrotatory Ring Opening of Various 3-Chloro-2-azetines

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A combined experimental and theoretical study is presented on 2-azetines, a class of azaheterocyclic compounds, which are difficult to access but have shown a unique reactivity as strained cyclic enamines. New highly substituted 2-azetines bearing aryl substituents at the 2- and 4-position were synthesized from 3,3-dichloroazetidines. Whereas 2-aryl-3,3-dichloroazetidines gave stable 2-aryl-3-chloro-2-azetines upon treatment with sodium hydride in DMSO, 2,4-diaryl-3,3-dichloroazetidines showed a remarkably different reactivity in that they afforded benzimidoyl-substituted alkynes under similar mild treatment with base. The formation of the alkynes involves electrocyclic ring opening of intermediate 2,4-diaryl-3-chloro-2-azetines and elimination of hydrogen chloride. Ab initio theoretical calculations confirmed the experimental findings and demonstrated that the 4-aryl substituent is responsible for this remarkably enhanced reactivity of 2-azetines toward electrocyclic conrotatory ring opening by a significant decrease in reaction barrier of about 30 kJ/mol. This activation effect by an aryl group in the allylic position toward electrocyclic ring opening of unsaturated four-membered rings is of general importance since a similar increased reactivity of 4-aryloxetes, 4-arylthiete-1,1-dioxides, and 3-arylcyclobutenes has been reported in literature as well.

## 1. Introduction

2-Azetines, which can be regarded as enamines with a highly constrained double bond and are difficult to access, are receiving increasing interest because they undergo intermolecular [2 + 2] photodimerization<sup>1</sup> or radical additions,<sup>2</sup> participate in [4 + 2] cycloadditions<sup>3</sup> or [2 + 2] cycloaddition reactions,<sup>4</sup> and can undergo ring opening by reaction with atmospheric oxygen.<sup>5</sup> The most studied, stable 2-azetines, such as *N*-acyl-, *N*-methanesulfonyl-, and *N*-nitro-2-azetines,<sup>1,6,7</sup> are mostly un-

substituted and mostly synthesized from the corresponding 3-(methanesulfonyloxy)azetidines via an elimination reaction in basic medium.<sup>8</sup> The synthesis and reactivity of 2-azetines bearing carbon-centered substituents at the 2- and 4-position is

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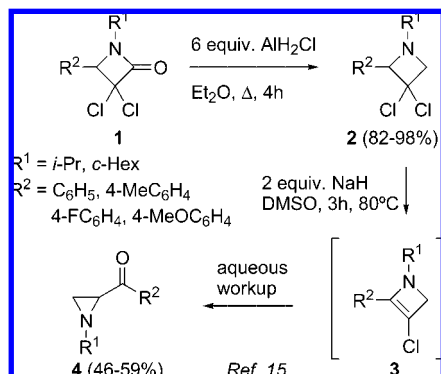
<sup>‡</sup> Center for Molecular Modeling.

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## SCHEME 1



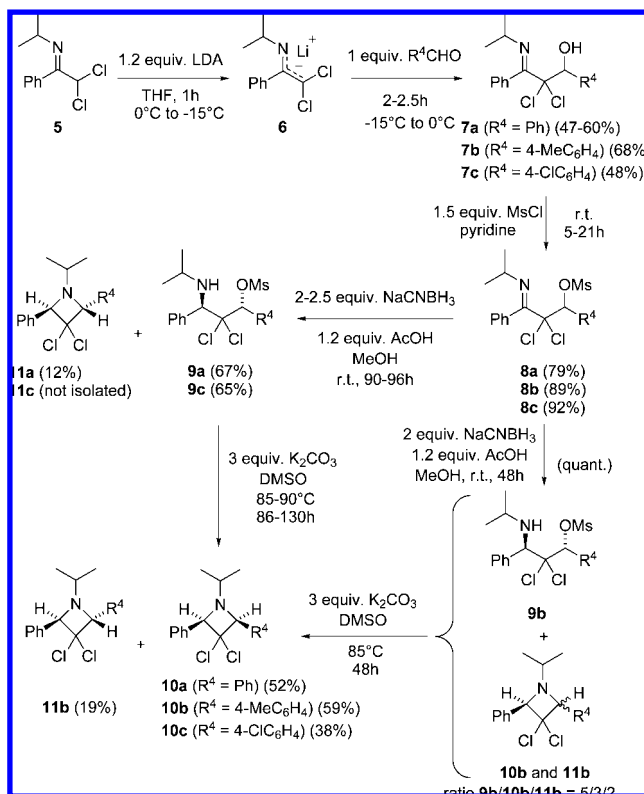
scarcely described in the literature. The formation of 1-amino-4-aryl-2-methyl-3-methoxy-2-azetidines, besides 3-pyrrolines, has been reported through reaction of  $\alpha$ -lithiomethoxyallene with aromatic hydrazones.<sup>9</sup> A series of 4-functionalized 2,3,4-*tert*-butyl-2-azetidines, as intermediates in the synthesis of 2*H*-pyrroles, 1,3-butadienes, and 2-aza-1,3-butadienes, has been reported from addition reactions of tri-*tert*-butylazete.<sup>10</sup> *N,N*-Diethylhydroxylamine reacted with dimethyl acetylenedicarboxylate to form dimethyl 1-ethyl-4-methyl-2-azetine-2,3-dicarboxylate,<sup>11</sup> while perfluorinated alkenes reacted with amines to give a variety of perfluorinated 2,3,4,4-tetraalkyl-2-azetidines.<sup>12</sup> It was envisaged that 2,4-disubstituted 3,3-dichloroazetidines could be precursors for the convenient preparation of synthetically valuable 2,4-disubstituted 3-chloro-2-azetidines.

3,3-Dichloroazetidines form a virtually unknown class of strained azaheterocycles, the synthesis of which is scarcely reported in literature.<sup>13,14</sup> More recently, some authors have developed two straightforward syntheses to 3,3-dichloroazetidines. 2-Aryl-3,3-dichloroazetidines **2** were obtained by reduction of the corresponding 4-aryl-3,3-dichloro-2-azetidinones **1**, synthesized by a ketene-imine [2 + 2]-cycloaddition, with monochloroalane (Scheme 1).<sup>15</sup>

The second synthesis comprised aldol condensation of 3,3-dichloro-1-azaallylic anions **6**, generated from *N*-(1-aryl-2,2-dichloroethylidene)amines **5**, with aromatic aldehydes yielding the corresponding  $\alpha,\alpha$ -dichloro- $\beta$ -hydroxy ketimines **7**, which after mesylation and reduction afforded 2,4-diaryl-3,3-dichloroazetidines **10** in a stereospecific manner (Scheme 2).<sup>16</sup>

In the present paper, we wish to report on the reactivity of 2,4-diaryl-3,3-dichloroazetidines **10** under basic conditions that leads surprisingly to the synthesis of benzimidoyl-substituted alkynes via ring opening of intermediate 2,4-diaryl-3-chloro-2-azetidines. A complementary theoretical study on this unex-

## SCHEME 2



pected ring opening has the potential to explain the specific effects contributing to the stability of the 2,4-diaryl-3-chloro-2-azetidines. These effects might be of energetic, stereoelectronic, and steric origin.

## 2. Results and Discussion

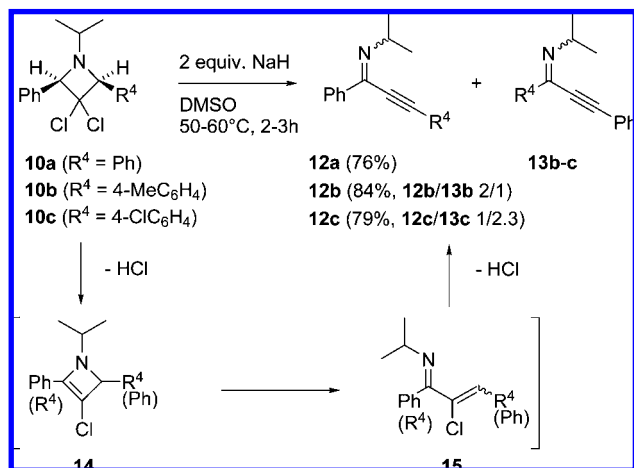
**2.1. Experimental Results.** *cis*-2,4-Diaryl-3,3-dichloroazetidines **10** (**a**,  $\text{R}^4 = \text{Ph}$ ; **b**,  $\text{R}^4 = 4\text{-MeC}_6\text{H}_4$ ; **c**,  $\text{R}^4 = 4\text{-ClC}_6\text{H}_4$ ) were prepared via a method reported earlier (Scheme 2).<sup>16</sup> However, the acid-catalyzed reduction of  $\alpha,\alpha$ -dichloro- $\beta$ -(mesyloxy) imines **8** with sodium cyanoborohydride in methanol was not completely diastereoselective as previously described. Before purification of the crude reaction mixtures of  $\beta$ -mesyloxyamines **9** about 15–20% of the *trans*-2,4-diaryl-3,3-dichloroazetidines **11** were clearly present (<sup>1</sup>H NMR analysis). Column chromatography led to the isolation of *trans*-azetidine **11a** in 12% yield, while single recrystallization of crude amine **9c** allowed the removal of the *trans*-azetidine **11c**, which was not isolated. Reduction of imine **8b** resulted in a mixture of amine **9b** and *cis*- and *trans*-azetidine **10b** and **11b**. The latter mixture was cyclized with potassium carbonate in DMSO at 85 °C to afford *cis*- and *trans*-azetidines **10b** and **11b**, which were separated by column chromatography as crystalline products in 59% and 19% yield, respectively. These results indicate that during the reduction with sodium cyanoborohydride



**FIGURE 1.** Conformers leading to the synthesis of *trans*-azetidines **11** (A) and *cis*-azetidines **10** (B) viewed along axis C1–C3 of propylamine **9** (B) and the corresponding diastereomer (A).

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SCHEME 3



the minor  $\beta$ -mesyloxyamine cyclized immediately to the corresponding *trans*-azetidine **11**, which is washed away from  $\beta$ -mesyloxyamine **9** with pentane/ether. The spontaneous formation of *trans*-azetidines **11** during the reduction can be reasonably explained from the reaction conformer A (Figure 1). The steric interaction between the aromatic substituents of  $\beta$ -mesyloxyamine **9** in conformation B disfavors the formation of the *cis*-disubstituted azetidines **10**, and a separate basic cyclization step under heating conditions is necessary to synthesize the latter.

With the *cis*-2,4-diaryl-3,3-dichloroazetidines **10a–c** in hand, their reactivity was studied with bases in non-nucleophilic solvents, in analogy with the study of the monoaryl derivatives, i.e., 2-aryl-3,3-dichloroazetidines **2**.<sup>15</sup> The latter azetidines were unreactive toward sodium hydride in THF, whereas sodium hydride in DMSO at 80 °C afforded the corresponding 2-azetines **3**, which hydrolyzed during workup and cyclized spontaneously to the aziridines **4**. Reacting 2,4-diaryl-3,3-dichloroazetidines **10** with sodium hydride in THF at room temperature for 20 h failed to give any reaction. However, treatment of azetidines **10** with sodium hydride in DMSO at 50–60 °C for 2–3 h afforded the alkynes **12** in high isolated yields, as a mixture with the regioisomers **13** in the case of unsymmetrically substituted azetidines **10b** and **10c** (Scheme 3).

This reaction is believed to proceed via the formation of the strained 2-azetines **14**, followed by thermal electrocyclic ring opening to 3-chloro-2,4-diaryl-1-aza-1,3-butadienes **15**. The latter undergo a second elimination reaction toward alkynes **12/13**, which should go faster if alkenes **15** are *Z*-configured with Cl and H on the opposite side of the carbon–carbon double bond.<sup>17</sup> The formation of these alkynes **12/13** was somewhat surprising in view of the results obtained with the 2-aryl-3,3-dichloroazetidines **2** under similar basic conditions at even higher temperature. Few examples are reported on the electrocyclic ring opening of 2-azetines to 1-aza-1,3-butadienes.<sup>6,18</sup> 1-Acyl-2-azetines, prepared via base-catalyzed  $\beta$ -elimination of 1-acyl-3-(mesyloxy)azetidines at 40–50 °C, were subjected to flash vacuum pyrolysis at 300–540 °C, to generate 1-acyl-1-azabutadienes.<sup>6</sup> More interesting, however, was the reaction of ynamines with arylsulfonylimines giving stereochemically defined  $\alpha,\beta$ -unsaturated arylsulfonamidines, after electrocyclic ring opening of initially formed 4-aryl-2-azetines at room temperature.<sup>18a</sup> The synthesis of  $\alpha,\beta$ -unsaturated thioimides has been described via 2-azetine intermediates formed via [2 + 2]-cycloaddition of imines with alkynyl sulfides.<sup>18b,c</sup> The

formation of stable 2-amino-4-phenyl-2-azetines<sup>19</sup> and more recently 1-amino-4-aryl-2-azetines was reported.<sup>9</sup> Theoretical calculations on the thermal ring opening of unsubstituted 2-azetine to 1-azabutadiene have confirmed that this reaction is a concerted, asynchronous, and, according to orbital symmetry rules, a conrotatory process and highly exothermic.<sup>20,21</sup> The additional 4-aryl substituent attached to the 2-azetine **14**, as compared to the characterized 4-unsubstituted 2-azetines **3**, which are stabilized by the conjugating 2-aryl substituent, is clearly responsible for the remarkably enhanced ring opening and makes the isolation of 2-azetines **14** difficult. It seems reasonable to assume that the 4-aryl group causes steric crowding which destabilizes the azetine ring **14** and conjugates with the 1-azabutadiene product **15** which makes the latter thermodynamically more stable. It is also likely that an aryl group lowers the reaction barrier as well.<sup>22</sup> A similar increase of reactivity of 4-phenyloxene,<sup>23</sup> 2,4-diarylthiete 1,1-dioxides,<sup>24</sup> and 3-phenylcyclobutene<sup>25</sup> toward electrocyclic ring opening has been reported as well.

Attempts to isolate or identify intermediates **14** or **15** by performing the reaction of **10a** with 1.05 equiv of sodium hydride in DMSO at room temperature for 20 h or by following the reaction at 50–60 °C with repeated <sup>1</sup>H NMR analyses (300 MHz, DMSO-*d*<sub>6</sub>) did not give conclusive results. In the former case a reaction mixture was obtained which consisted (<sup>1</sup>H NMR analysis) of about 60% of starting azetine **10a**, together with 10% of alkyne **12a** and about 30% of two nonisolable olefinic compounds, which gave singlet CH-signals at 6.62 ppm and 6.70 ppm (CDCl<sub>3</sub>). Upon following the reaction with <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>), some minor appearing and subsequently disappearing signals, for instance, a singlet at 5.12 ppm and a singlet at 6.70 ppm, could be observed during the course of the reaction. These signals might correspond to methine protons from intermediate compounds **14a** and **15a**, respectively, but the amount of these intermediates was always small (<20%) as compared to the starting material **10a** or alkyne **12a** and did not allow the characterization of azetine **14a** by <sup>1</sup>H and <sup>13</sup>C NMR. This result seems to indicate that under the reaction conditions, the intermediate compounds are rapidly transformed further to the alkyne **12a** and that the slowest step in the pathway is the first elimination of hydrogen chloride to 2-azetine **14a**.

Transformation of *trans*-2,4-diphenyl-3,3-dichloroazetidine **11a** to alkyne **12a** upon reaction with sodium hydride in DMSO at 60 °C proved to be slower. A conversion of 64% was achieved after 6 h in the presence of 2.2 equiv of sodium hydride and 81% conversion after 24 h with 3 equiv of base. A plausible explanation for the reduced reactivity of the *trans*-azetine **11a**

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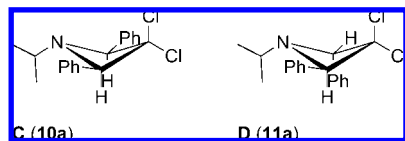
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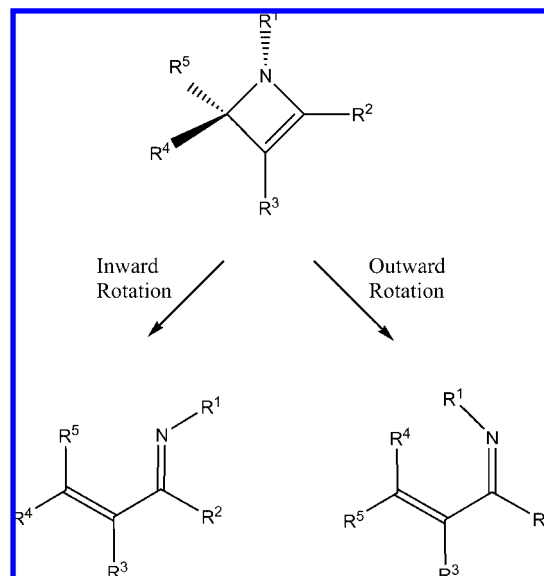


**FIGURE 2.** Conformers leading to the synthesis of 2-azetine **14a** from *cis*-azetidine **10a** (C) and *trans*-azetidine **11a** (D).

is that under the basic reaction conditions, a bimolecular E2 elimination is operative in the formation of 2-azetines from azetidines **10** and **11**. Calculations (*vide infra*) of the geometries of 3,3-dichloro-2,4-diphenylazetidines **10a** and **11a** confirmed that conformation C (Figure 2), with the carbon-centered substituents all pseudoequatorial, is clearly the most stable conformer of *cis*-azetidine **10a** with pseudoaxial protons on both C-2 and C-4 anti periplanar with pseudoaxial Cl on C-3. It is important to note that only the *trans*-invertomer occurs with the *N*-iPr-substituent and the two phenyl groups on opposite side of the ring. Conformer C is expected to give rapid E2 elimination, while in conformer D of *trans*-azetidine **11a** the pseudoaxial proton on C-2 is sterically hindered for attack by the base by the pseudoaxial phenyl on C-4 resulting in a slow E2 elimination.

One issue that still has to be discussed is the regiochemistry of the initial elimination reaction of the unsymmetrically substituted 2,4-diaryl-3,3-dichloroazetidines **10b** and **10c**, which gave rise to the formation of alkynes **12b,c** together with alkynes **13b,c**. The regioselectivity of elimination is dependent on the difference in acidity of the protons in the 2- and 4-position of azetidines **10**. The electron-donating *para*-substituted methyl group in azetidine **10b** increases the  $pK_a$  of the proton at the carbon substituted with the *p*-tolyl group and disfavors initial deprotonation in this position. Therefore, alkyne **12b** is the major regioisomer. On the contrary, the opposite regiochemistry is observed for the reaction of azetidine **10c**, since the electron-withdrawing *p*-chloro substituent decreases the  $pK_a$  of the corresponding benzylic proton, which makes the formation of alkyne **13c** more favored. The discrimination of alkynes **12** and **13**, confirming the proposed assignments, was possible through their independent separate synthesis via alkylation of 1-azaallylic anions **6** with the corresponding benzyl bromides and subsequent elimination of the  $\beta$ -arylated  $\alpha,\alpha$ -dichloro imines to the alkynes.<sup>26</sup>

**2.2. Theoretical Results.** To assess the influence of various substituents ( $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$ ) on the reactivity of 2-azetines toward ring opening, a large set of such heterocyclic compounds has been studied theoretically, as schematically presented in Figure 3. All theoretical calculations were performed within DFT framework at the mPW1B95/6-31+G(d,p) level of theory.<sup>27</sup> This level is expected to be a reliable method for reproducing accurate geometries and energy values of molecules with hetero elements in general.<sup>28,29</sup> In addition, this level was shown to perform fairly well in the description of four-membered rings with hetero elements.<sup>30,31</sup> More computational details are outlined in Supporting Information. The theoretical results provide us with a tool to shed light on the mechanistic details of the ring opening. The unsubstituted



**FIGURE 3.** Overview of studied compounds.  $R^1$  = H, Me, *i*Pr;  $R^2$  = H, Ph;  $R^3$  = Cl, H;  $R^4$  = H, Ph; and  $R^5$  = H, Ph.

**TABLE 1.** Summary of Reaction Barriers ( $\Delta E^{TS}$ ) and Reaction Energies ( $\Delta E^R$ ) of the Conrotatory Ring Opening of 2-Azetines

compound	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	inward rotation		outward rotation	
						$\Delta E^{\text{TS}}$	$\Delta E^{\text{R}}$	$\Delta E^{\text{TS}}$	$\Delta E^{\text{R}}$
Unsubstituted 2-Azetine									
<b>31</b>	H	H	H	H	H	132.86	−61.20	167.69	−56.60
Class I 3-Chloro-2-azetines: No Substitution at N <sup>a</sup>									
<b>16</b>	H	H	Cl	H	H	138.62	−60.90	166.76	−51.71
<b>17</b>	H	Ph	Cl	H	H	142.57	−32.64	168.18	−35.84
<b>18</b>	H	H	Cl	Ph	H	106.47	−71.70	171.25	−53.41
<b>19</b>	H	H	Cl	H	Ph	138.87	−46.88	133.26	−60.52
<b>20</b>	H	Ph	Cl	Ph	H	112.08	−40.24	172.07	−40.18
<b>21</b>	H	Ph	Cl	H	Ph	143.07	−27.06	137.00	−40.43
Class II 3-Chloro-2-azetines: Methyl Substitution at N									
<b>22</b>	Me	H	Cl	H	H	132.89	−66.28		
<b>23</b>	Me	Ph	Cl	H	H	143.85	−24.47		
<b>24</b>	Me	H	Cl	Ph	H	102.39	−75.74		
<b>25</b>	Me	H	Cl	H	Ph	115.86	−58.80		
<b>26</b>	Me	Ph	Cl	Ph	H	114.54	−31.66		
<b>27</b>	Me	Ph	Cl	H	Ph	125.97	−24.87		
Class III 3-Chloro-2-azetines: Isopropyl Substitution at N <sup>b</sup>									
<b>28</b>	<i>i</i> Pr	H	Cl	H	H	134.33	−66.70		
<b>3</b>	<i>i</i> Pr	Ph	Cl	H	H	143.49	−29.07		
<b>29</b>	<i>i</i> Pr	H	Cl	Ph	H	103.88	−76.06		
<b>30</b>	<i>i</i> Pr	H	Cl	H	Ph	117.93	−55.10		
<b>14aT</b>	<i>i</i> Pr	Ph	Cl	Ph	H	114.04	−36.29		
<b>14aC</b>	<i>i</i> Pr	Ph	Cl	H	Ph	124.06	−14.09		

<sup>a</sup> For  $R^1$  = H, barriers for both inward and outward rotation of the nitrogen lone pair are given. Energies in kJ/mol. <sup>b</sup> Energies for the isopropyl compounds with respect to the energetically most favored rotamer.

2-azetine (**31**,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ , and  $R^5$  = H; see Table 1) serves as a reference for the other substituted 3-chloro-2-azetines. For this compound theoretical calculations were already reported in literature.<sup>21</sup> A conrotatory electrocyclic ring opening was proposed with a clear preference for inward rotation of the nitrogen lone pair (7.8–8.6 kcal/mol as compared to outward

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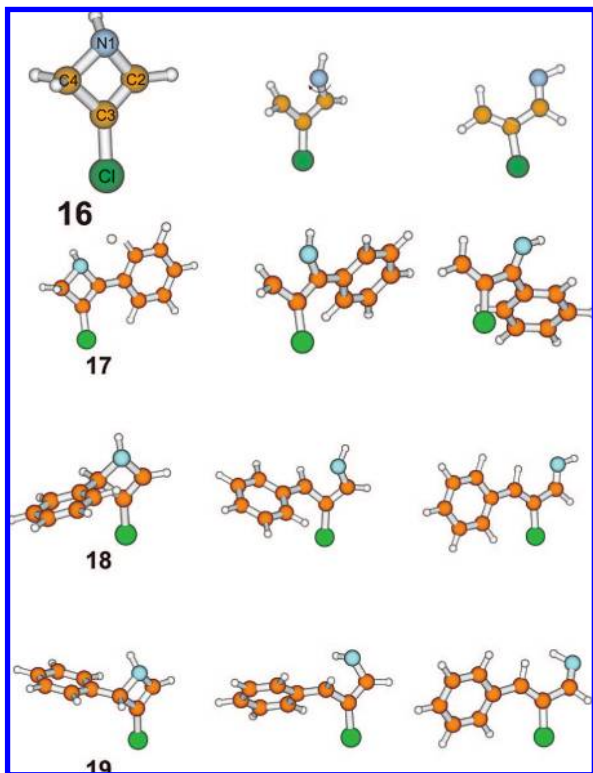
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**FIGURE 4.** Geometries of the reactants, transition states, and products for compounds **16**, **17**, **18**, and **19**.

rotation), which leads to torquoselectivity. In accordance with these results, our calculations also predict a preferable inward conrotatory ring opening path with a preference of 34.8 kJ/mol. The detailed results are given in Table 1. More details about the factors governing the inward rotation can be found in literature.<sup>32</sup>

**2.2.1. Class I 3-Chloro-2-azetines: No Substitution at N.** Compound **16**, the unsubstituted 3-chloro-2-azetidine, makes it possible to assess the influence of the chloro substitution at position 3. For azetidine **16**, in analogy with the unsubstituted 2-azetidine **31**, also the inward rotation of the lone pair on the nitrogen is preferred. Moreover, the reaction barriers and energies vary only slightly compared to the unsubstituted case. The difference between the *Z* and *E* configurations of the imine differ by 9.18 kJ/mol.

In the next part of this section, the further influence of phenyl groups at the 2- and 4-position is discussed. Compound **17** has a phenyl group at the 2-position. The ring opening occurs preferentially via a path in which the nitrogen lone pair rotates inwardly. The values for the activation energies are in the same order of magnitude compared to previous cases. The slight increase (142.57 kJ/mol for **17** compared to 138.62 kJ/mol for **16**) in the activation energy can be ascribed to the additional stabilization in the reactant molecule, where the phenyl group is almost planar with the C<sub>2</sub>=C<sub>3</sub> double bond inducing partial  $\pi$  conjugation. More striking is the difference in exothermicity of compound **17**, as compared to **16**. The reaction is less exothermic due to the additional steric hindrance in the product. The geometries of the reactants, transition states, and products for compounds **16**–**19** are given in Figure 4.

The phenyl substituent at the 4-position plays a substantial role in compound **18**. The barrier for ring opening is 106.47 kJ/mol compared to 138.62 kJ/mol in the unsubstituted com-

pound **16**. This is only the case for the *trans*-invertomer, in which the phenyl group is positioned at the opposite side of the ring as the hydrogen at the nitrogen. The *cis*-invertomer **19** of 4-phenyl-3-chloro-2-azetidine is a little bit more bound (calculated as 1.62 kJ/mol) than its *trans* counterpart **18**. This can probably be assigned to the occurrence of a slight stabilization effect due to a weak hydrogen bond interaction between the hydrogen on the 1-position with (the  $\pi$  orbital of) the aromatic phenyl ring (cf. Figure 4).<sup>33</sup>

The reaction routes found by gradual increase of the C<sub>4</sub>–N<sub>1</sub> distance reveal conrotatory ring opening in opposite directions for these two molecules. The *trans*-invertomer **18** follows the inward path as in the unsubstituted chloroazetidine **16**, whereas in the *cis*-invertomer **19** the opposite, outward rotation is slightly preferred. Due to the small energy difference between the two invertomers, all compounds with a phenyl group at the 4-position will follow the lower activated route via inward rotation of the nitrogen lone pair. Inspection of the molecular orbitals revealed that the transition state of **18** is stabilized by a larger extent of electron delocalization.

The resulting products differ only in the configuration of the carbon–nitrogen double bond: *E* for the *trans* configured azetidine **18**, and *Z* for the route starting from the *cis*-azetidine **19**. The *E* isomer is more bound by some 9.56 kJ/mol, about the same energy difference as the *E/Z* difference of the products originating from compound **16**. The resulting reaction energies are –71.70 and –60.52 kJ/mol for the *trans* and *cis* starting invertomers, making these ring openings even more exothermic than the ring opening of unsubstituted 3-chloro-2-azetidine **16**. In the products the phenyl groups favor more extended electron delocalization (cf. Figure 4).

Compounds **20** and **21** have a phenyl group at both the 2- and 4-position, but **20** is the *trans*-invertomer whereas **21** is the *cis*-invertomer. The results are not altered with respect to the previous two azetines. The reaction barrier is 112.08 kJ/mol for **20**, which is only slightly higher than the activation barrier in compound **18**. A similar effect was observed for the difference of barriers for ring opening of **17** compared to **16**, which also differ only by a phenyl substituent at the 2-position. Apparently the various effects contributing to the reaction barrier are nearly additive. Conform previous findings on the exothermicity, all compounds having a phenyl substituent at the 2-position are less exothermic than their unsubstituted counterparts. The effect contributes to about 30 kJ/mol (–60.9 kJ/mol for compound **16** compared to –32.9 kJ/mol for compound **17** and –71.70 kJ/mol for compound **18** compared to –40.23 kJ/mol for compound **20**).

The main effects of phenyl substituents at the 2- and 4-position can be summarized as follows: (i) A phenyl substituent at the 4-position has a dramatic effect on the activation energies for ring

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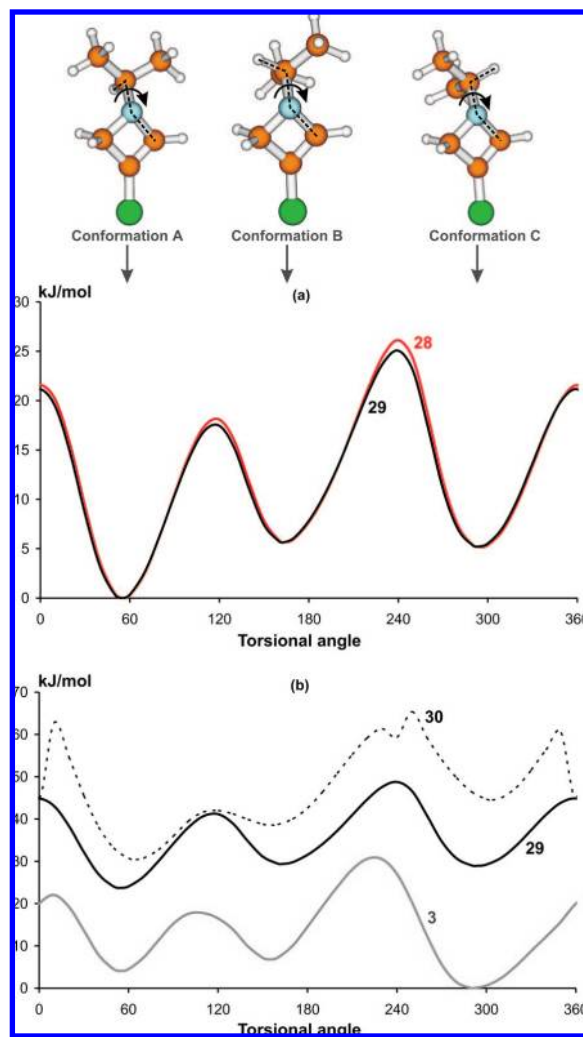
opening. A lowering of about 30 kJ/mol is noticed. This effect is only present for the *trans*-invertomers of these compounds, but as the barrier for inversion at the nitrogen center is very low, all ring opening routes will follow this lower activated pathway. The effect is primarily due to stereoelectronic effects in the transition states, which are stabilized due to  $\pi$  conjugation of the phenyl group with the forming C3=C4 double bond. (ii) A phenyl substitution at the 2-position does not alter the reaction barriers much but lowers considerably the degree of exothermicity due to additional steric hindrance in the product.

**2.2.2. Class II 3-Chloro-2-azetines: Methyl Substitution at N.** Class II consists of *N*-methyl-3-chloro-2-azetines in which the substitution at the 2- and 4-position is varied. The results for the reaction barriers and reaction enthalpies are summarized in Table 1. All conrotatory ring openings occur in the same direction, i.e., inward rotation of the nitrogen lone pair; the other direction would cause too much steric hindrance. The results for barriers follow the same qualitative trends as for compounds of class I. The exothermicity of compounds having a phenyl substitution at the 2-position is reduced as compared to similar species of class I, due to a larger steric hindrance between the methyl group and the aromatic ring. Substitution at the 4-position with a phenyl group has the same dramatic influence on the activation energies, which are reduced by about 30 kJ/mol. The barriers for ring opening of *cis*- and *trans*-invertomers is much smaller, which must again be traced back to the degree of delocalization of reactive orbitals in the transition state. As in class I the additivity of energetic effects induced by substitution at the 2- and 4-position is maintained.

**2.2.3. Class III 3-Chloro-2-azetines: Isopropyl Substitution at N.** Class III consists of *N*-isopropyl-3-chloro-2-azetines, which were also the species studied in the experimental part. The isopropyl group is subject to an internal rotation, giving rise to several conformers. It is thus important to study this rotation before starting the discussion of the ring opening reaction.

All compounds of this class are subject to an internal rotation of the isopropyl group, giving rise to a variety of rotamers, each having a different energy and possibly different reactivity. In the normal mode spectrum of these molecules, one low lying frequency corresponds to an internal rotation rather than an harmonic oscillator.<sup>34</sup> The torsional potential for *N*-isopropyl-3-chloro-2-azetine **28** is shown in Figure 5a. It has the expected form with three energy minima. The lowest energy rotamer **28A** has both methyl groups of the isopropyl function as far as possible from the four-membered ring. Geometrical considerations suggest that this profile should not be altered much by the presence of a phenyl group at the 4-position in the *trans*-invertomer **29**. This is indeed the case as confirmed by the torsional potentials (given in Figure 5) of both species relative to conformation A.

Additionally, the effect of substitution at the 2- and 4-position on the torsional energy is examined. The torsional energy profiles of compounds **3**, **29**, and **30** are shown in Figure 5b. Due to the same composition stoichiometry of compounds **3**, **29**, and **30**, the energies can be directly compared. The torsional potential energies are given in absolute values and as zero energy the energetically most favored conformation C of compound **3** is chosen.



**FIGURE 5.** Isopropyl torsional potentials (in kJ/mol) for compounds **28**, **3**, **29**, and **30**. The structures of the three conformations are shown for the case of *N*-isopropyl-3-chloro-2-azetine **28**. (a) Torsional potentials of isopropyl in *N*-isopropyl-3-chloro-2-azetine **28** and in *N*-isopropyl-4-phenyl-3-chloro-2-azetine **29** relative to conformation A. (b) Torsional potentials of isopropyl in absolute values of 3-chloro-2-azetines of class III, **3**, **29** and **30**. Zero energy at the energetically most favored conformation C of *N*-isopropyl-2-phenyl-3-chloro-2-azetine **3**.

Several conclusions can be drawn:

(i) The presence of a 2-phenyl group provides an additional stabilization effect. It seems that the (partial) electron delocalization by the 2-phenyl group over the C2=C3 double bond lowers the energy by 20–25 kJ/mol for most values of the isopropyl dihedral angle, with a maximal stabilization of about 30 kJ/mol around conformation C. This fluctuation of stabilization can be directly related to the alignment of the phenyl ring with C2=C3 and therefore to the extent of  $\pi$  conjugation. For dihedral angles of the isopropyl substituent around conformers A and B, the tilt angle of the phenyl ring with respect to C2=C3 is up to 35°, whereas it is 25° around conformer C.

(ii) A second observation concerns the difference in the torsional energy profile for the *cis*- and *trans*-invertomer of *N*-isopropyl-4-phenyl-3-chloro-2-azetines **30** and **29**. The rotation of the isopropyl group in the *cis*-invertomer is subject to more steric hindrance with the phenyl group at the 4-position giving rise to larger torsional barriers. This effect is most pronounced around conformation **30C**,

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where both methyl groups of the isopropyl group are in close proximity of the 4-phenyl. The energy difference between **30A** and **30C** is 14.07 kJ/mol, compared to 5.22 kJ/mol between the *trans*-conformations **29A** and **29C**. Another peculiarity of the isopropyl internal rotation profile in *cis*-invertomer **30** is that the orientation of *iPr<sub>cis</sub>* will invert to the *trans*-configured geometry of the torsional profile **29** when the isopropyl dihedral angle is forced to 0°. At typical temperatures needed to overcome the ring opening barriers (> 100 kJ/mol), most of the molecules will adopt the *trans*-configuration, as the molecules are in thermodynamic equilibrium and can overcome either torsional barriers or barriers for pyramidal inversion.<sup>35</sup>

(iii) The *N*-isopropyl-2,4-diphenyl-3-chloro-2-azetines **14** having a substitution both at the 2- and 4-position show the same qualitative features of the torsional profile.

(iv) In all torsional energy profiles the barriers between the different rotamers are not very high. This means that all conformers A, B, and C can be expected to be in thermodynamic equilibrium. In the following section the barriers are only discussed starting from the energetically most favored rotamers.

**2.2.4. Ring Opening of Compounds of Class III: Comparative Study Experiment versus Theory.** The ring opening of compounds of class III shows similar features as those observed in the two previous classes. Inspection of Table 1 shows that the energy predictions for reaction barriers and enthalpies behave in a similar way in the three classes of azetines for various substituents. All azetines studied in the experimental section of this paper have an isopropyl substitution at the nitrogen, and direct comparison with the experimental observations can take place for the 3-chloro-2-azetines of Class III.

The most striking observation is the different reactivity toward ring opening of the experimentally observed 2-aryl-3-chloro-2-azetine **3** and the 2,4-diaryl-3-chloro-2-azetine **14aT**. Compound **3** has a large energy barrier of 143.49 kJ/mol for ring opening, whereas compound **14aT** with an additional aryl group at the 4-position has a barrier of 114.04 kJ/mol. This reduction of the energy barrier by about 30 kJ/mol for the electrocyclic ring opening of chlorinated 2-azetines with an aryl substitution at the 4-position explains the experimentally observed behavior. Chlorinated 2-azetines without the additional substituent at the 4-position could be easily transformed into functionalized aziridines (compounds **4** in Scheme 1), whereas similar starting compounds with the additional substituent at the 4-position gave rise to substituted alkynes under similar basic conditions.

A second observation concerns the slightly higher activation energy for electrocyclic ring opening starting from the *cis*-invertomer (**14aC**) (114 kJ/mol for **14aT** compared to 124 kJ/mol for **14aC**). It is interesting to have some idea about the distribution of the various invertomers. For compounds **30** and **29**, having no substitution at the 2-position, the barrier between the two invertomers amounts to 35 kJ/mol. For the experimentally used derivatives with a phenyl group at both the 2- and 4-position, no clear transition state between the two invertomers could be located as the transition involved a combined reaction coordinate in which the inversion at the nitrogen center took place with simultaneous rotations of the phenyl group and isopropyl group. It is expected that inversion is rather improbable for these heavily substituted constrained heterocyclic compounds.

The probability that azetine **14a** occurs as the *trans*-invertomer **14aT** can however also be traced back to the

precursor azetidines **10a** and **11a**. It was found that conformation C (Figure 2) with the carbon-centered substituents all pseudo-equatorial is clearly the most stable conformer of *cis*-azetidine **10a** with pseudoaxial protons on both C-2 and C-4 antiperiplanar with pseudoaxial Cl on C-3. Conformations with both phenyls at the same side of the ring as the *iPr* have not been found. On the other hand, for azetidine **11a** some conformers like D (Figure 2) with one phenyl ring at the same side of the four-membered ring as the *iPr* and the other phenyl ring at the opposite side could be identified as stable conformers (see Figure 2, conformer D), but having an energy at least 20 kJ/mol higher than the conformer C of azetidine **10a**. Conformer C is expected to give rapid E2 elimination toward the *trans*-invertomer **14aT**, whereas elimination of the pseudoaxial proton on C-2 in conformer D is inhibited by steric hindrance caused by the pseudoaxial phenyl group on C-4. These arguments provide evidence for the major occurrence of the *trans*-invertomers **14aT**, which are characterized by the lowest barriers for electrocyclic ring opening.

Although the *trans/cis* relation of the *N*-methyl-4-phenyl-2-azetines **24–27** was not examined, it is expected that similar effects are operative, making only the *trans* forms **24** and **26** relevant.

### 3. Conclusion

In this paper, 3-chloro-2-azetines were synthesized in order to understand the reactivity of this highly unstable class of azaheterocyclic compounds. Representatives of this class of compounds without a 4-substituent (2-aryl-3-chloro-2-azetines **3**) are smoothly transformed into functionalized aziridines after an aqueous workup procedure, whereas the 4-phenyl derivatives (2,4-diaryl-3,3-dichloroazetidines **10**) undergo a conrotatory electrocyclic ring opening toward benzimidoyl-substituted alkynes upon treatment with sodium hydride in DMSO under mild conditions.

In order to understand the dramatic role of the phenyl substituent at the 4-position of the azetines, a systematic theoretical study was conducted. The phenyl substitution at the 4-position destabilized the 2-azetine ring, thereby facilitating the ring opening by about 30 kJ/mol. Moreover, stereoelectronic effects in the transition state additionally stabilize the activated complexes with an additional aryl substitution at the 4-position. All ring opening reactions start from the *trans*-invertomer as the barrier for inversion is much smaller than the barrier for ring opening. Only for the most substituted derivatives that were also synthesized experimentally the selectivity for the *trans*-invertomer can be traced back to the originating azetidines.

A small effect for a phenyl substitution at the 2-position was found, which slightly stabilizes the 2-azetines and increases the ring opening barriers by about 5–10 kJ/mol. This stabilization can be explained by  $\pi$  conjugation of the phenyl group with the C2=C3 double bond.

### 4. Experimental Section

**Synthesis of  $\beta$ -Hydroxy Imines 7.** The synthesis of *N*-(2,2-dichloro-3-hydroxy-1,3-diphenyl-1-propylidene)-isopropylamine (**7a**) is representative.<sup>16</sup> To an ice-cooled solution of diisopropylamine (1.32 g, 13 mmol) in THF (10 mL) was added under an  $N_2$  atmosphere *n*-BuLi (4.8 mL, 2.5 M in hexane, 12 mmol) followed after 10 min by a solution of *N*-(2,2-dichloro-1-phenyl-1-ethylidene)-isopropylamine (**5**) (2.3 g, 10 mmol) in THF (5 mL). The reaction was cooled over the period of 1 h to –15 °C and then a solution of freshly distilled benzaldehyde (1.06 g, 10 mmol) in THF (2 mL) was added dropwise. The mixture was gradually warmed to 0 °C during 2.5 h, then poured into an ice-cooled 0.5 N NaOH solution (15 mL), and extracted with ether (3  $\times$  30 mL), and the combined organic extracts were dried with

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K<sub>2</sub>CO<sub>3</sub>. Evaporation of the solvent in vacuo yielded 2.97 g (88%) of crude **7a**, which was purified by recrystallization (pentane/ether 1:1) to afford 1.59 g (47%) of the pure substance.

***N*-[2,2-Dichloro-3-(4-chlorophenyl)-3-hydroxy-1-phenyl-1-propylidene]-isopropylamine 7c.** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.13 and 1.14 (2 × d, 2 × 3H, *J* = 6.33 Hz), 3.30 (septet, 1H, *J* = 6.33 Hz), 5.58 (d, 1H, *J* = 2.20 Hz), 6.16 (d, 1H, *J* = 2.75 Hz), 7.28–7.46 (m, 7H), 7.57–7.62 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 23.1, 23.3, 53.2, 78.9, 89.5, 127.5, 127.9, 129.0, 129.1, 131.4, 132.4, 134.4, 135.4, 167.9; IR (KBr, cm<sup>-1</sup>) ν 3401 (OH), 1642 (C=N); MS (ES, pos. mode) *m/z* (%) 370/72/74/76 (M + H<sup>+</sup>, 100). Anal. Calcd for C<sub>18</sub>H<sub>18</sub>Cl<sub>3</sub>NO: C 58.32; H 4.89; N 3.78. Found: C 58.07; H 4.82; N 3.61. Yield = 48%. Mp = 115.9–116.8 °C. Amorphous light brown solid.

**Synthesis of β-(Mesyloxy) Imines 8.** The synthesis of *N*-[2,2-dichloro-3-(mesyloxy)-1,3-diphenyl-1-propylidene]-isopropylamine (**8a**) is representative.<sup>16</sup> To a solution of α,α-dichloro-β-hydroxy imine **7a** (4.10 g, 12.2 mmol) in pyridine (30 mL) was added dropwise at room temperature mesyl chloride (2.09 g, 18.2 mmol). After 5 h of stirring at room temperature, the reaction mixture was poured into an ice-cooled 0.5 N NaOH solution (90 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 60 mL). The organic layer was dried (MgSO<sub>4</sub>) and evaporated in vacuo to give **8a** as a crude solid product, which was purified by recrystallization (pentane/ether 4:1) to afford 3.98 g (79%) of pure white crystals.

***N*-[2,2-Dichloro-3-(4-chlorophenyl)-3-(mesyloxy)-1-phenyl-1-propylidene]-isopropylamine 8c.** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.08 and 1.15 (2 × d, 2 × 3H, *J* = 6.33 Hz), 2.86 (s, 3H), 3.31 (septet, 1H, *J* = 6.33 Hz), 6.83 (s, 1H), 7.00–7.46 (m, 7H), 7.65–7.70 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 23.17, 23.22, 40.0, 54.3, 84.0, 89.4, 128.0, 128.2, 128.3, 129.0, 131.9, 132.2, 133.7, 136.0, 164.1; IR (KBr, cm<sup>-1</sup>) ν 1642 (C=N); MS (ES, pos. mode) *m/z* (%) 448/50/52/54 (M + H<sup>+</sup>, 100). Anal. Calcd for C<sub>19</sub>H<sub>20</sub>Cl<sub>2</sub>NO<sub>3</sub>S: C 50.85; H 4.49; N 3.12. Found: C 50.63; H 4.54; N 3.05. Yield = 92%. Mp = 93.0–96.9 °C. Amorphous brown solid.

**Synthesis of β-(Mesyloxy) Amines 9.** The synthesis of *N*-isopropyl-*N*-(2,2-dichloro-3-(mesyloxy)-1,3-diphenylpropyl)amine (**9a**) is representative.<sup>16</sup> To a solution of α,α-dichloro-β-(mesyloxy) imine **8a** (0.83 g, 2 mmol) in methanol (10 mL) was added NaCNBH<sub>3</sub> (0.31 g, 5 mmol), followed by acetic acid (0.15 g, 2.4 mmol). The mixture was stirred for 96 h at room temperature, poured into a 0.5 N NaOH solution (35 mL), and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL). The combined organic extracts were dried (MgSO<sub>4</sub>) and evaporated in vacuo. The reaction mixture obtained was purified by column chromatography (pentane/diethyl ether 9/1) to afford 0.56 g (67%) of pure **9a** (*R*<sub>f</sub> = 0.12) and 0.078 g (12%) of pure *trans*-azetidine **11a** (*R*<sub>f</sub> = 0.54).

***trans*-3,3-Dichloro-1-isopropyl-2,4-diphenylazetidine 11a.** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 0.69 (d, 3H, *J* = 6.05 Hz), 0.71 (d, 3H, *J* = 6.60 Hz), 3.07 (septet, 1H, *J* = 6.2 Hz), 5.27 (s, 2H), 7.36–7.57 (m, 10H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 21.1, 21.9, 48.6, 82.3, 85.2, 127.9, 128.6, 129.7, 136.5; IR (KBr, cm<sup>-1</sup>) ν 1453, 1230, 1200, 929, 698; MS (ES, pos. mode) *m/z* (%) 320/22/24 (M + H<sup>+</sup>, 100). Anal. Calcd for C<sub>18</sub>H<sub>19</sub>Cl<sub>2</sub>N: C 67.51; H 5.98; N 4.37. Found: C 67.44; H 6.03; N 4.28. Yield = 12%. *R*<sub>f</sub> = 0.54 (pentane/diethyl ether 9:1). Mp = 114.1–115.1 °C. White crystals.

***N*-Isopropyl-*N*-[2,2-dichloro-3-(4-chlorophenyl)-3-(mesyloxy)-1-phenylpropyl]amine 9c.** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 0.97 and 1.09 (2 × d, 2 × 3H, *J* = 6.33 Hz), 1.80 (broad s, 1H), 2.68 (s, 3H), 2.69 (septet, 1H, *J* = 6.33 Hz), 4.51 (s, 1H), 6.65 (s, 1H), 7.32–7.47 (m, 7H), 7.61–7.66 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 22.0, 24.5, 40.1, 46.6, 65.9, 82.5, 94.9, 127.8, 128.2, 128.3, 129.8, 131.8, 136.1, 137.3; IR (KBr, cm<sup>-1</sup>) ν 3349 (NH, weak), 1371, 1179, 945, 847; MS (ES, pos. mode) *m/z* (%) 450/52/54/56 (M + H<sup>+</sup>, 100). Anal. Calcd for C<sub>19</sub>H<sub>22</sub>Cl<sub>2</sub>NO<sub>3</sub>S: C 50.62; H 4.92; N 3.11. Found: C 50.24; H 4.85; N 3.00. Yield (after washing of the reaction crude with petroleum ether/EtOAc 9/1) = 65%. Mp = 118.7–120.3 °C. Amorphous yellow-brown solid.

**Synthesis of *cis*-3,3-Dichloroazetidines 10.** The synthesis of 3,3-dichloro-1-isopropyl-2,4-diphenylazetidine (**10a**) is representative.<sup>16</sup> To a solution of β,β-dichloro-γ-(mesyloxy) amine **9a** (2.36 g, 5.67 mmol) in DMSO (30 mL) was added potassium carbonate (2.35 g, 17.01 mmol). The mixture was stirred for 86 h at 90 °C, poured into H<sub>2</sub>O (90 mL), and extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 × 45 mL). The combined organic extracts were washed with H<sub>2</sub>O (30 mL) and brine (2 × 30 mL), dried (MgSO<sub>4</sub>), and evaporated to give crude 3,3-dichloroazetidine **10a** as a solid material, which was purified by column chromatography (petroleum ether/EtOAc 98:2) to afford 0.94 g (52%) of pure **10a** (*R*<sub>f</sub> = 0.33).

***trans*-3,3-Dichloro-1-isopropyl-4-(4-methylphenyl)-2-phenylazetidine 11b.** This compound was isolated via column chromatography from the reaction crude of the cyclization reaction of the crude β,β-dichloro-γ-(mesyloxy)amine **9b** to azetidine **10b**. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 0.69 (d, 3H, *J* = 6.05 Hz), 0.70 (d, 3H, *J* = 6.33 Hz), 2.40 (s, 3H), 3.06 (septet, 1H, *J* = 6.1 Hz), 5.23 and 5.25 (each s, each 1H), 7.22–7.25 and 7.36–7.46 and 7.51–7.56 (m, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 21.3, 21.4, 22.0, 48.7, 82.3, 85.5, 127.9, 128.7, 129.6, 129.8, 133.4, 136.9, 138.6; IR (KBr, cm<sup>-1</sup>) ν 1455, 1229, 1194, 1059, 699; MS (ES, pos. mode) *m/z* (%) 334/36/38 (M + H<sup>+</sup>, 100). Anal. Calcd for C<sub>19</sub>H<sub>21</sub>Cl<sub>2</sub>N: C 68.27; H 6.33; N 4.19. Found: C 67.98; H 6.39; N 4.13. Yield = 19%. *R*<sub>f</sub> = 0.13 (petroleum ether/EtOAc 99:1). Mp = 82.5–84.4 °C. White crystals.

***cis*-3,3-Dichloro-2-(4-chlorophenyl)-1-isopropyl-4-phenylazetidine 10c.** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 0.83 (d, 3H, *J* = 6.05 Hz), 0.84 (d, 3H, *J* = 6.33 Hz), 2.84 (septet, 1H, *J* = 6.2 Hz), 4.69 and 4.72 (each s, each 1H), 7.34–7.44 (m, 5H), 7.52–7.61 (m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 21.5, 21.6, 59.2, 80.1, 80.7, 84.8, 128.0, 128.2, 128.5, 129.6, 134.3, 136.1, 137.3; IR (KBr, cm<sup>-1</sup>) ν 1489, 1248, 1087, 1016, 699; MS (ES, pos. mode) *m/z* (%) 354/56/58/60 (M + H<sup>+</sup>, 100). Anal. Calcd for C<sub>18</sub>H<sub>18</sub>Cl<sub>2</sub>N: C 60.95; H 5.11; N 3.95. Found: C 60.85; H 5.26; N 4.12. Yield = 38%. *R*<sub>f</sub> = 0.25 (petroleum ether/EtOAc 99/1). Mp = 83.7–84.5 °C. White crystals.

**Synthesis of Alkynes 12 and 13.** The synthesis of *N*-(1,3-diphenylprop-2-yn-1-ylidene)propyl-2-amine (**12a**) is representative. To sodium hydride (0.08 g, 2 mmol, 60% dispersion in oil) was added DMSO (2 mL) and the mixture was stirred for 20 min at room temperature to generate dimethylsodium. Subsequently, 3,3-dichloro-1-isopropyl-2,4-diphenylazetidine **10a** (0.32 g, 1 mmol), dissolved in DMSO (3 mL), was added dropwise at room temperature. After the addition was completed, the mixture was kept at 55 °C for 3 h. After cooling, water (10 mL) was added, and the aqueous phase was extracted with diethyl ether (3 × 15 mL). The combined organic phases were dried (MgSO<sub>4</sub>), and after filtration and evaporation of the solvent, the crude *N*-(1,3-diphenylprop-2-yn-1-ylidene)propyl-2-amine (**12a**) was obtained. Further purification was performed by column chromatography to yield 0.27 g (76%) of the pure compound. **12a.** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.32 (d, 6H, *J* = 6.33 Hz), 4.33 (septet, 1H, *J* = 6.33 Hz), 7.37–7.44 (m, 6H), 7.56–7.61 (m, 2H), 8.04–8.09 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 23.5, 56.3, 81.5, 97.5, 121.7, 127.5, 128.2, 128.6, 129.5, 130.2, 132.1, 137.9, 148.3; IR (NaCl, cm<sup>-1</sup>) ν 2204 (C≡C), 1591 (C=N); MS (ES, pos. mode) *m/z* (%) 248 (M + H<sup>+</sup>, 100). Anal. Calcd for C<sub>18</sub>H<sub>17</sub>N: C 87.41; H 6.93; N 5.66. Found: C 87.29; H 6.95; N 5.62. Yield = 76%. *R*<sub>f</sub> = 0.35 (petroleum ether/EtOAc 9:1). Colorless viscous oil.

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**Supporting Information Available:** General information, spectroscopic data of compounds **12b,c**, **13b,c** and computational details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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