Surpassing Torquoelectronic Effects in Conrotatory Ring Closures: Origins of Stereocontrol in Intramolecular Ketenimine – Imine [2+2] Cycloadditions

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Dedicated to Professor Kendall N. Houk

Abstract: Intramolecular ketenimine – imine [2+2] cycloadditions leading to 1,2-dihydroazeto[2,1-*b*]quinazolines occur in a notably stereocontrolled manner along the newly formed C – C single bond when prochiral ketenimine and imine fragments are combined. Computational studies support stepwise mechanisms for these reactions. In sharp contrast with other well-known [2+2] cycloadditions, the first step of the reaction determines its stereochemical outcome, thereby surpassing the low stereocontrol induced by torquoelectronic effects.

Keywords: ab initio calculations · cycloadditions · density functional calculations · ketenimines · stereochemistry

Introduction

Cycloadditions to construct carbon skeletons by the stereocontrolled formation of carbon – carbon bonds have widespread application and value.[1] [2+2] Cycloadditions of heterocumulenes[2] are of growing interest since they provide a general route to four-membered rings and constitute a testing ground for theoretical arguments on chemical reactivity. Ketenes are specially susceptible to [2+2] cycloadditions;[3] their reaction with imines, known as the Staudinger reaction, has been studied extensively and is now recognized as one of the most convenient approaches to β-lactams.[4] Keteniminium salts, as alternatives to free ketenes, have given excellent results in cycloadditions with imines.[5] By contrast, [2+2] cycloadditions of ketenimines with imines to provide azetidin-2-imines are scarce:[6] such intermolecular reactions proceed readily only if the electrophilic character of the ketenimine is enhanced by electron-withdrawing substituents on the nitrogen atom, such as tosyl[7] or cyano.[8]

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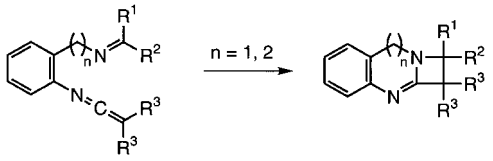
These *intermolecular* [2+2] cycloadditions of ketenimines with imines, in the few examples reported, have shown somewhat erratic degrees of diastereoselectivity at the 3,4-positions of the four-membered products, ranging from being completely in favour of the *trans* product in the reactions of several (*E*)-imines[7, 8] or a cyclic (*Z*)-imine[7] with *N*-cyano or tosyl *C*-monosubstituted ketenimines, to yielding equimolecular mixtures of *cis*- and *trans*-azetidin-2-imines in other closely related examples.[7]

We recently described the first examples of entropically assisted *intramolecular* [2+2] cycloadditions of ketenimines with imines that surpassed the electronic constraints mentioned above and could be conducted successfully on a variety of *N*-[2-(alkylideneaminomethyl)phenyl] ketenimines **1** ($n=1$),



1 **2**

leading to the previously unknown azeto[2,1-*b*]quinazolines **2** ($n=1$) in reasonable yields.[9] The scope and applicability of such processes, with regard to the chemical nature of the imine and ketenimine functions and to the length of the tether linking the reactive groups, were further evaluated,[10] one of the results being the successful preparation of azeto[2,1-*b*]-[1,3]benzodiazepines **2** ($n=2$).

As a continuation of these studies we have now explored diastereoselective versions of the intramolecular [2+2] cyclo-

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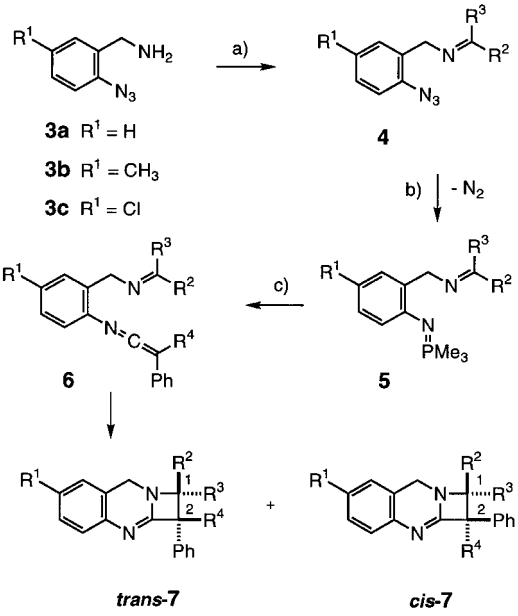
addition of ketenimines with imines, using adequately substituted derivatives of general structure **1**. Our first approach was the desymmetrization of the ketenimine fragment by placing two different substituents on its sp^2-carbon terminus, $-N{=}C{=}CR^1R^2$, thus making its two faces enantiotopic; we hoped that the combination with imine fragments of similar topicity, $-N{=}CR^3R^4$, would give rise diastereoselectively to products containing two stereogenic carbon atoms, C1 and C2.

The main problem with this approach was the limited availability[3] of prochiral ketenes $R^1R^2C{=}C{=}O$ stable enough to be used in the preparation of imino-ketenimines by aza-Wittig methodology.[10] For this task, in the present work we have employed methyl phenyl ketene and ethyl phenyl ketene, which are prepared routinely and are manageable under the usual working conditions.

Herein, we report the results obtained from this experimental work, including a computational study, in order to gain understanding of the origins of the reactivity and stereocontrol in these intramolecular reactions.



Scheme 1. Synthesis of azeto[2,1-*b*]quinazolines **7**. Reagents and conditions: a) Method A: R^2COR^3, Et_2O, anhyd. $MgSO_4$, 25 °C, 12 h; Method B: R^2COR^3, basic Al_2O_3, 25 °C, 12 h; Method C: R^2COR^3, cat. TsOH, toluene, reflux, 24 h; b) PMe_3, toluene, 25 °C, 30 min; c) $PhR^4C{=}C{=}O$, toluene, 25 °C, 1 h. For additional details, see Table 1.

Results and Discussion

Reaction of easily available 2-azidobenzylamines[11] **3a–3c** with a variety of aldehydes and ketones under standard conditions (Scheme 1) gave rise to nearly quantitative yields of the corresponding imines **4**, which were generally used as crude products in the next step because some of them underwent partial hydrolytic cleavage of the imino bond during attempts to purify them by crystallization or column chromatography. In all cases ^1H and ^{13}C NMR data of **4** showed only one set of signals, which were assigned to the *E* isomers. Treatment of crude imines **4** with one equivalent of 1M trimethylphosphane in toluene was followed by strong evolution of dinitrogen, indicating the conversion of the azide function into the corresponding λ^5-phosphazene **5**.[12, 13] The transformation **4**→**5**, which was monitored by IR spectroscopy (disappearance of the azide vibration near 2100 cm^{-1}) and ^{31}P NMR spectroscopy, was completed in less than 1 h.[14] The isolation and purification of **5** were prevented by the extreme hydrolytic sensitivity of the phosphazene group. When these compounds were treated in the same reaction flask with methyl phenyl ketene or ethyl phenyl ketene at room temperature, the pale yellow reaction mixture immediately turned orange and then slowly faded to a colourless solution. IR spectra of the orange reaction mixtures showed strong absorptions around 2000 cm^{-1} attributable to the C=C=N grouping of ketenimines **6** which resulted from an aza-Wittig reaction[15] of the phosphazene with the ketene. Transient ketenimines **6** were converted in solution at room temperature, through a formal [2+2] cycloaddition between the imino C=N and cumulated C=C bonds, into the corresponding azeto[2,1-*b*]quinazolines **7**, which were isolated in moderate to good yields from the final reaction mixture after column chromatography (Scheme 1 and Table 1).

Compounds **7** were characterized by their analytical and spectral data, which were essentially similar to those of compounds **2** reported previously.[10] Table 1 shows the results of reactions with a variety of imino-ketenimines in which the imino fragment was derived mainly from aromatic, hetero-

Table 1. Synthesis of azeto[2,1-*b*]quinazolines **7**.

R^1	R^2	R^3	R^4	Compound	*cis*-**7**:*trans*-**7**[a]	Yield [%][b]
H	4-O_2N-C_6H_4	H	CH_3	**7a**	> 98:2	73
H	4-Cl-C_6H_4	H	CH_3	**7b**	> 98:2	65
H	4-CH_3O-C_6H_4	H	CH_3	**7c**	> 98:2	58
H	2-CH_3O-C_6H_4	H	CH_3	**7d**	> 98:2	64
H	1-naphthyl	H	CH_3	**7e**	> 98:2	69
H	2-furyl	H	CH_3	**7f**	> 98:2	72
H	3-furyl	H	CH_3	**7g**	> 98:2	48
H	3-thienyl	H	CH_3	**7h**	> 98:2	67
H	(*E*)-C_6H_5-CH=CH	H	CH_3	**7i**	> 98:2	84
H	(*E*)-2-O_2N-C_6H_4-CH=CH	H	CH_3	**7j**	> 98:2	75
Cl	4-O_2N-C_6H_4	H	CH_3	**7k**	> 98:2	76
CH_3	(*E*)-C_6H_5-CH=CH	H	CH_3	**7l**	> 98:2	79
H	4-O_2N-C_6H_4	H	CH_3CH_2	**7m**	93:7	72
H	3-thienyl	H	CH_3CH_2	**7n**	> 98:2	46
Cl	4-O_2N-C_6H_4	H	CH_3CH_2	**7o**	90:10	82
H	$(CH_3)_2CH$	H	CH_3	**7p**	55:45	29
H	$(CH_3)_3C$	H	CH_3	**7q**	38:62	74
H	4-O_2N-C_6H_4	CH_3	CH_3	**7r**	> 98:2	63
H	C_6H_5	CF_3	CH_3	**7s**	50:50	77

[a] As determined by ^1H NMR (300 MHz) analysis of the crude reaction mixture. [b] Yield of pure isolated product.

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aromatic, vinylic and aliphatic aldehydes, as well from some ketones.

The *cis*/*trans* configuration of the diastereoisomeric reaction products was assigned on the basis of their NMR data and by nuclear Overhauser (NOE) experiments. When the reactions yielded mixtures of diastereoisomers, they were easily separated in a pure state by column chromatography, except for the two diastereoisomers of **7s**, which could not be separated. The ratio of the isomers was calculated in each case by integration of their respective signals in the ^{1}H NMR (300 MHz) spectra of the crude reaction mixtures, before the purification step.

When two diastereoisomeric products were isolated and successfully separated, for example azetoquinazolines **7m**, **7o**, **7p** and **7q**, the more notable differences observed in their respective ^{1}H NMR spectra appeared to be the chemical shifts of the signals assigned to the protons of the methyl or ethyl group at C2, as well those due to the proton at C1. We have assigned the *trans* configuration to the isomer showing the CH_3 or CH_3CH_2 protons at C2 shifted upfield, due to the magnetic shielding exerted by the adjacent aryl, heteroaryl, vinyl or alkyl group at C1 in the *cis* position. Similar shift differences have been found to support the assignment of 3,4-*cis* and -*trans*-β-lactams[16] and other substituted small rings,[17] with a similar interpretation. This effect is stronger when the groups causing the magnetic shielding are aromatic or vinylic rather than aliphatic.[16a, 17a] For this reason, this criterion could be used accurately to distinguish not only between C1-monosubstituted diastereoisomers but also in cases where one aryl and one alkyl group are placed at that carbon atom (for example, in compound **7s**). Similar reasoning, applied to the observed downfield shift of the proton at C1 in the *trans* isomers, corroborated the configurational assignment made above.

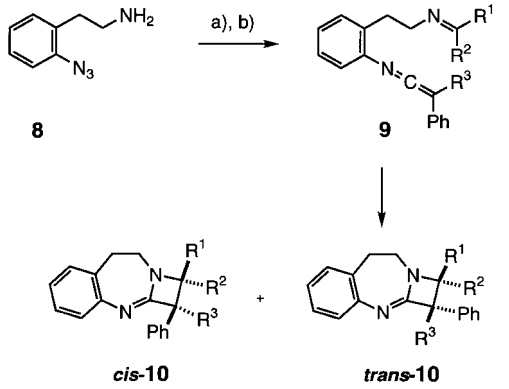
Moreover, the *cis* isomers of azetoquinazolines **7m**, **7o** and **7p** assigned in this way showed notable NOEs (7–15%) between the proton at C1 and the CH_3 or CH_2 protons at C2, whereas these signal enhancements could not be observed in the respective *trans* isomers, thus attesting to the validity of the configurational assignment. An additional feature common to *cis*-**7m**, -**7o** and -**7p** is the ^3J(C,H) coupling constant (3.5–4.2 Hz) between the CH_3 or CH_2 carbon atom linked to C2 and the proton at C1, as revealed in their gate-decoupled ^{13}C NMR spectra. From the values of this coupling constant, which is not observed in the *trans* isomers, a dihedral angle close to 35° between the two nuclei could be inferred.[18]

When only one diastereoisomer was detected (by ^{1}H NMR spectroscopy of the crude reaction mixture) and isolated (**7a**–**7l**, **7n**, **7r**), the *cis* configuration was assigned on the basis of NOE experiments similar to those described above and/or through observation of ^3J(C,H) coupling constants between the nuclei mentioned above for compounds **7a**–**7l** and **7n**, and by noting the chemical shift of the C2 CH_3 protons in the case of **7r**.

Table 1 reveals the high degree of stereocontrol which operated in most of the intramolecular [2+2] cycloadditions that have been carried out, leading to the formation of a clear excess of the *cis* diastereoisomer over the *trans*. The bulkiness of the substituents at C1 of the reaction products seems to play a role in reducing the diastereocontrol when imine fragments derived from aliphatic aldehydes are concerned, as in the reactions leading to **7p** and **7q**; the last example is the only one in which the usual sense of the stereocontrol is inverted. The electronic nature of the groups at C1 also seems to be important; this could be deduced from comparison of the diastereocontrol observed in the reactions leading to **7r** and **7s**, which was practically total in **7r** and zero in **7s**, where a CF_3 group instead of CH_3 is located at C1.

When the effects of solvent and temperature on the reaction leading to **7p** were examined, we found that lowering the reaction temperature led to a decrease in yield with no significant improvement in the *cis*/*trans* ratio of the diastereoisomers. The reaction in more polar solvents, such as dichloromethane or chloroform, provided similar stereoselectivities but in lower chemical yield.

Stereocontrol of the intramolecular [2+2] cycloadditions of imino-ketenimines **9**, obtained from 2-azidophenethylamine[11b] **8** by the sequence of events described in Scheme 1, yielded azeto[2,1-*b*][1,3] benzodiazepines **10** (Scheme 2).



Scheme 2. Synthesis of azeto[2,1-*b*][1,3]benzodiazepines **10**. Reagents and conditions: a) R^1COR^2, Et_2O, anhyd. $MgSO_4$, 25 °C, 12 h; b) 1, PMe_3, toluene, 25 °C, 30 min; 2, $PhR^3C{=}C{=}O$, toluene, 25 °C, 12 h. For additional details, see Table 2.

The results obtained from a representative selection of imino-ketenimines **9** are summarized in Table 2. The *cis* and *trans* configurations of the reaction products **10** were assigned by consideration of the same NMR data and experiments that we have already discussed for compounds **7**. The *cis*/*trans* ratios in Table 2 revealed, as a general trend, rather erratic degrees and senses of diastereocontrol, with some examples being notably selective in favour of either the *cis* (**10d**) or *trans* (**10c**, **10e**) isomer, whereas others showed minimal diastereoselectivity (**10a**, **10b**).

Thus, generally speaking, the high degree and the mostly predictable sense of the diastereocontrol observed in the

Table 2. Synthesis of azeto[2,1-*b*][1,3]benzodiazepines **10**.

R^1	R^2	R^3	Compound	*cis*-**10**:*trans*-**10**[a]	Yield [%][b]
4-O_2N-C_6H_4	H	CH_3	**10a**	54:46	71
4-Cl-C_6H_4	H	CH_3	**10b**	41:59	48
4-CH_3-C_6H_4	H	CH_3	**10c**	19:81	46
4-O_2N-C_6H_4	CH_3	CH_3	**10d**	> 98:2	63
4-Cl-C_6H_4	H	CH_3CH_2	**10e**	8:92	57

[a] As determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture. [b] Yield of pure isolated product.

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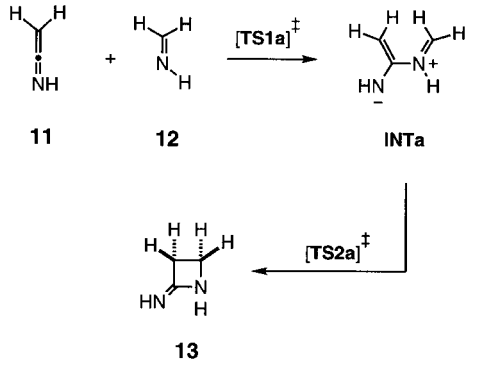
intramolecular [2+2] cycloadditions of imino-ketenimines **6** are lost when an additional methylene group is inserted into the aliphatic fragment of the tether linking the two reactive functionalities, imine and ketenimine, as is the case in substrates **9**.

Computational Studies

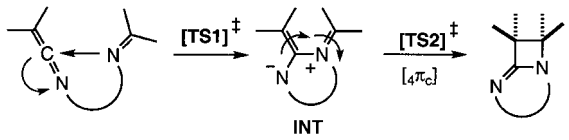
Since the mechanism of the [2+2] cycloaddition of neutral ketenimines and imines has not been reported previously, we first studied the *intermolecular* interaction between ketenimine **11** and methanimine **12** to yield azetidin-2-imine **13** (Scheme 3), so that the reaction path of this transformation could be used as a reference for the intramolecular version of the reaction.



Scheme 3. [2+2] Cycloaddition of ketenimine **11** and methanimine **12** to yield azetidin-2-imine **13**.

Intensive search along both the HF/6-31G* and B3LYP/6-31G* potential energy hypersurfaces led to a stepwise mechanism for the **11** + **12** → **13** transformation, either in the gas phase or in toluene solution[19] ($\varepsilon = 2.38$), involving the formation of a zwitterionic intermediate **INT** by nucleophilic addition of the iminic lone pair on the sp-hybridized atom of the ketenimine. The second step of the reaction is a conrotatory ring closure of **INT** to yield the corresponding four-membered ring.

This mechanism is quite similar to that proposed,[20] and obtained by computation,[21, 22] for the Staudinger reaction between ketenes and imines.[3, 4]



The qualitative profile of the reaction is depicted in Figure 1, and the corresponding values obtained at different theoretical levels are reported in Table 3. The chief geometrical features of the corresponding stationary points are reported in Figure 2. The HF/6-31G* geometries were found to be very similar to the B3LYP/6-31G* ones, both in the gas phase and in solution. In addition, the energy differences obtained at MP2/6-31G*//HF/6-31G*+ΔZPVE and B3LYP/6-31*+ΔZPVE levels are quite similar (Table 3). Therefore, for brevity, we shall comment on the B3LYP results only.

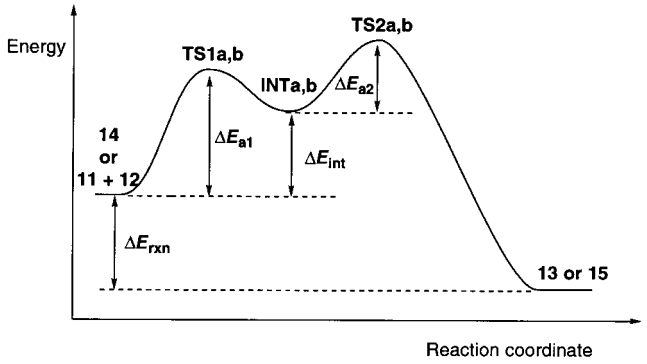


Figure 1. Qualitative reaction profile of the [2+2] reaction between ketenimines and imines.

The first step of the reaction consists in the formation of the N1 – C2 bond. The corresponding transition structure is **TS1a** (Figure 2). This step involves a nucleophilic addition of the iminic nitrogen lone pair on the LUMO of **11**, which lies in the σ_1 plane depicted in Figure 3. At this saddle point the interaction between the imine and the ketenimine moieties is not coplanar, as may be appreciated from the large values of the dihedral angle ω defined in Figure 3. As a consequence of this attack a positive charge is generated in the iminic part of **TS1a** (Figure 2). The activation energy at the B3LYP/6-31G* level is calculated to be 23.64 kcal mol^{-1}. Given that **TS1a** is

Table 3. Energy barriers (ΔE, kcal mol^{-1}) computed for the reactions included in Schemes 3 and 4.[a]

Method	**11** + **12** → **13**				**14** → **15**			
	ΔE_{a1}	ΔE_{int}	ΔE_{a2}	ΔE_{rxn}	ΔE_{a1}	ΔE_{int}	ΔE_{a2}	ΔE_{rxn}
		$\varepsilon = 1.00$				$\varepsilon = 1.00$		
HF/6-31G*[b]	+34.59	+30.72	+16.28	−26.61	+32.18	+24.49	+20.0	−24.38
MP2/6-31G*[b]	+23.94	+20.61	+6.84	−33.47	+18.25	+12.83	+7.44	−30.34
B3LYP/6-31G*[c]	+23.64	+20.54	+6.76	−27.22	+19.73	+14.04	+11.06	−22.57
		$\varepsilon = 2.38$				$\varepsilon = 2.38$		
HF(L1A1)/6-31G*[d]	+33.67	+28.93	+17.60	−26.55	+30.79	+21.76	+21.44	−24.94
MP2(L1A1)/6-31G*[d]	+23.22	+19.40	+7.94	−33.37	+17.10	+10.68	+8.88	−30.80
B3LYP(L1A1)/6-31G*[e]	+23.08	+19.29	+7.98	−27.18	+18.72	+12.56	+11.22	−23.16

[a] See Figure 1 for the notation of the energy barriers. $\varepsilon = 2.38$ corresponds to the dielectric constant for pure toluene at 25 °C. [b] Energies computed on fully optimized HF/6-31G* geometries. The ZPVE corrections, computed at the same level and conveniently scaled, have been included. [c] Energies computed on fully optimized B3LYP/6-31G* geometries. The ZPVE corrections, computed at the same level, have been included. [d] Energies computed on fully optimized HF(L1A1)/6-31G* geometries. The ZPVE corrections, computed at the same level and conveniently scaled, have been included. [e] Energies computed at the B3LYP(L1A1)/6-31G* level. The ZPVE corrections, computed at the same level, have been included.

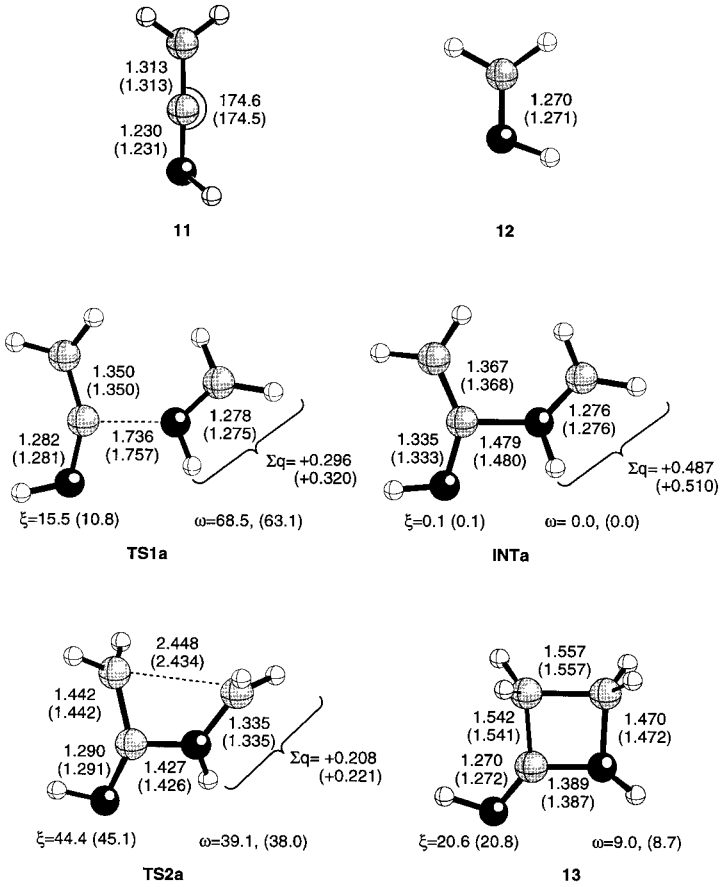


Figure 2. Computer plot of the stationary points found in the reaction between ketenimine **11** and methanimine **12**. Plain numbers correspond to the geometrical parameters computed at the B3LYP/6-31G* level. Numbers in parentheses correspond to the B3LYP(L1A1)/6-31G* data. Bond lengths and angles are given in Å and degrees, respectively. In this and in the subsequent figures which include ball-and-stick representations, atoms are represented by increasing depth of shading in the order: H, C, N.

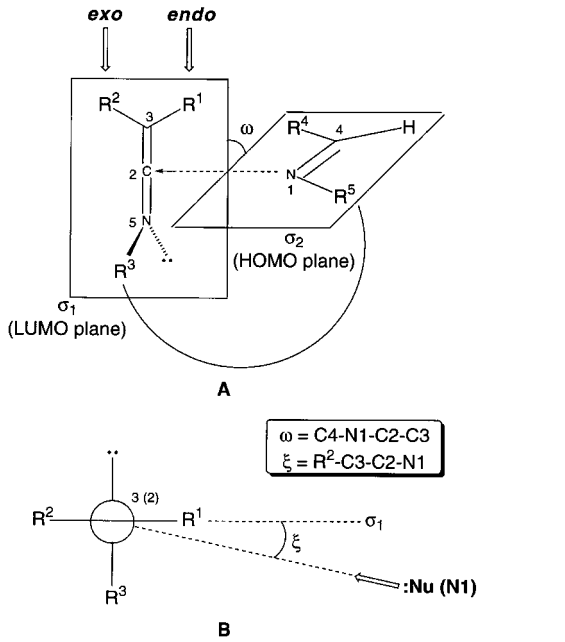
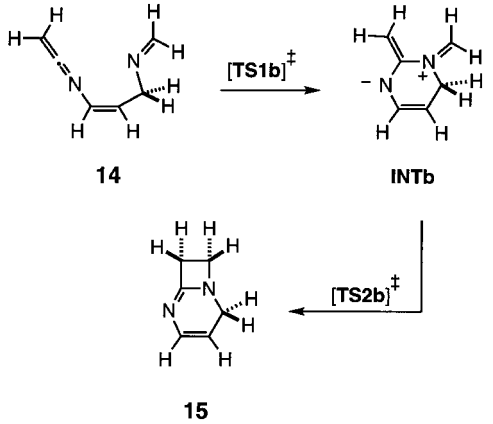


Figure 3. Schematic representation of the initial interaction between a ketenimine and an imine, together with the HOMO and LUMO planes of the interacting species and the more relevant dihedral angles discussed in the text.

more polar than the reactants and leads to the zwitterionic intermediate **INTa**, this activation barrier is slightly lower in simulated toluene solution (Table 3). We have also located a second transition structure denoted as **TS2a** in Figure 2. The computed geometrical features for this second saddle point are those one would expect for a conrotatory electrocyclic ring closure.[23] The energy barrier ΔE_{a2} associated with this second step is computed to be 6.76 kcal mol^{-1} at the B3LYP/6-31G* + ΔZPVE level (Table 3), but is slightly higher in solution, because of the loss of polarity on passing from **INTa** to **13**. This energy barrier is approximately 17 kcal mol^{-1} lower than that associated with the first step. It is noteworthy that in the Staudinger reaction between ketenes and imines the step with the highest activation energy is the second one, which corresponds to the formation of the C3 – C4 bond.

The **14** → **15** transformation (Scheme 4) is the simplest intramolecular case structurally related to the compounds included in the experimental study. The chief geometrical features of the stationary points are reported in Figure 4 and the energetic parameters are given in Table 3.



Scheme 4. Intramolecular [2+2] cycloaddition of **14** to yield cycloadduct **15**.

Our results indicate that the first transition structure, **TS1b** in Figure 4, is significantly earlier than **TS1a**, both in the gas phase and in solution, as may be readily appreciated from the N1 – C2 bond lengths. In addition, the restriction to rotational freedom imposed by formation of the six-membered ring promotes a non-coplanar approach between the imine and the ketenimine moieties of **14** (see the ω values for **TS1b** in Figure 4). Formation of the six-membered ring also makes it difficult to achieve the optimal dihedral angle of attack ξ (defined in Figure 3B) which, for a normal attack along the LUMO plane of the ketenimine moiety, should be $\xi = 0.0^\circ$. In contrast, for the **14** → **15** transformation ξ for **TS1b** is approximately 10° larger than in the parent reaction. Since **TS1b** occurs earlier than **TS1a**, this departure from the optimal trajectory does not induce an increase in the first activation barrier. The presence of the nitrogen-linked C=C bond in **14** promotes a higher electrophilicity of the ketenimine moiety because of the enamine – imine resonance.

This resonance is also present in **TS1b** and in the zwitterionic intermediate **INTb**.

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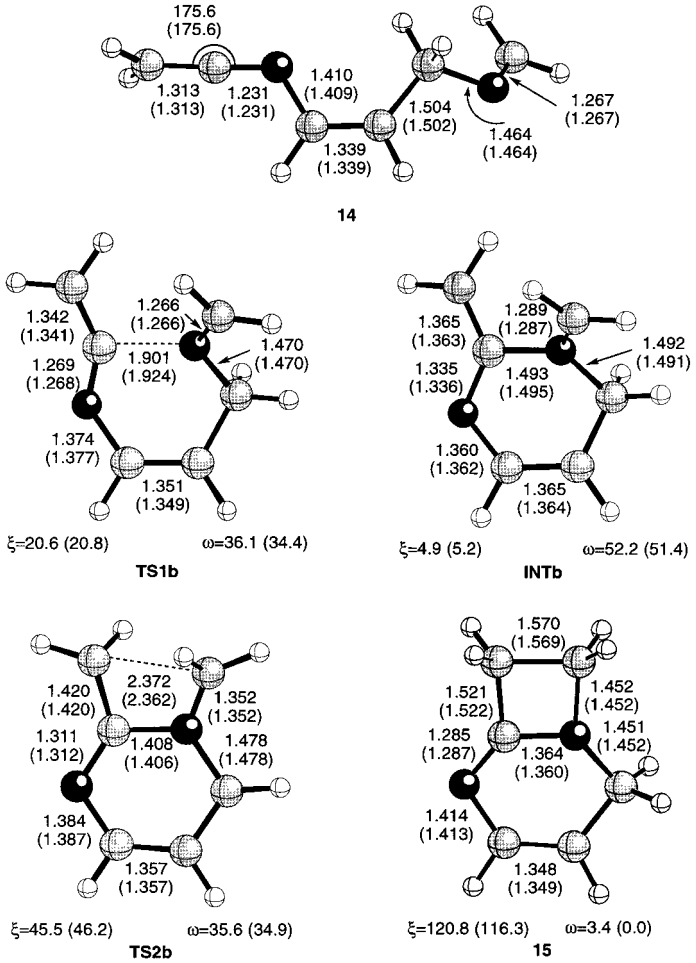
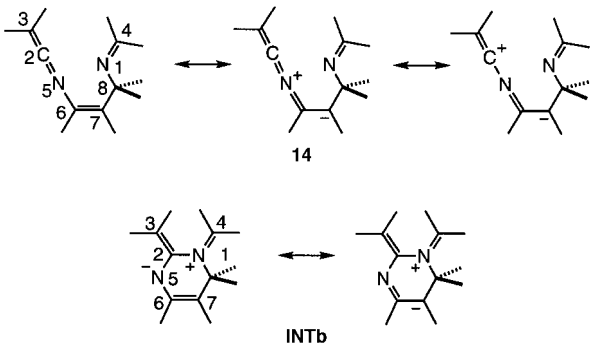


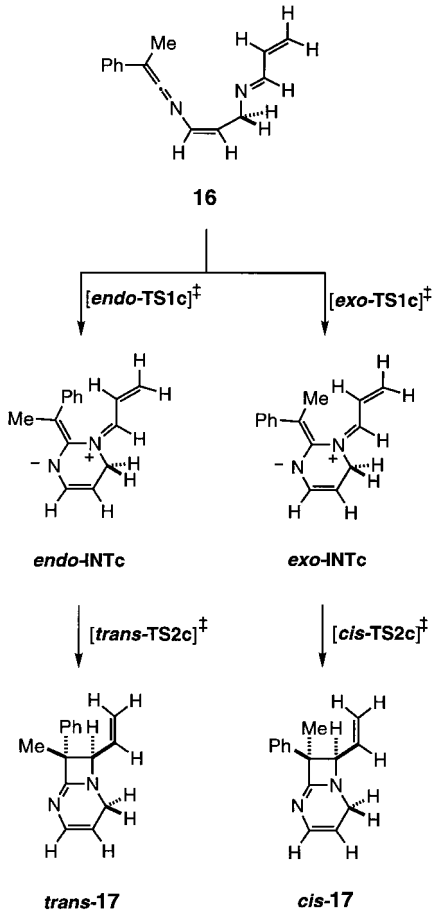
Figure 4. Computer plot of the stationary points found in the intramolecular reaction of **14** to yield cycloadduct **15**. Plain numbers correspond to the geometrical parameters computed at the B3LYP/6-31G* level. Numbers in parentheses correspond to the B3LYP(L1A1)/6-31G* data. See the caption of Figure 2 for additional details.



The progressive importance of the polar resonance forms along the reaction coordinate is readily apparent from the N5 – C6 and C6 – C7 bond lengths in **14**, **TS1b** and **INTb** (Figure 4). As a consequence of these combined effects, the first activation barrier for the **14** → **15** intramolecular reaction is calculated to be approximately 4 kcal mol^{-1} lower than that found in the parent intermolecular reaction (Table 3). In addition, the charge delocalization represented above is expected to be more efficient in the *ortho*-substituted phenyl systems present in the structures studied experimentally. Therefore, apart from entropic effects, N1 – C2 bond formation in the intramolecular reaction is considerably easier than in the intermolecular version, and it does not require the presence of electron-withdrawing groups on the ketenimine moiety to enhance the electrophilicity of the sp-hybridized carbon atom.

The bond lengths in **INTb** are similar to those found in **INTa**. However, it is noteworthy that in **INTb** the exocyclic and endocyclic multiple bonds generate a *sofa* conformation of the six-membered ring, in which the methylene protons occupy axial and equatorial positions (Figure 4). This feature could be exploited to induce stereocontrol from an asymmetrically substituted C8 atom. The conrotatory transition structure **TS2b** is also similar to **TS2a**, and the energy barrier associated with the formation of the C3 – C4 bond is approximately 8.0 kcal mol^{-1} lower than that associated with the formation of the N1 – C2 bond (Table 3).

We investigated the different reaction paths for the more highly substituted compound **16** (Scheme 5), in which phenyl and methyl groups have been included in the ketenimine moiety. In addition, there is an (*E*)-vinyl group in the iminic part to model either the (*E*)-styryl or aryl groups present in the experimental studies (vide supra). Cyclization of **16** can yield either *cis*- or *trans*-**17**, which can be considered as computational analogues of *cis*- and *trans*-**7a** – **7l** (Table 1). Given the size of structures **16** and **17**, the two stereoisomeric



Scheme 5. Intramolecular [2+2] cycloaddition of **16** to yield cycloadducts *cis*- and *trans*-**17**.

reaction paths were explored at the HF/3-21G level, and the corresponding energies were computed at both the B3LYP/6-31G* and the B3LYP(L1A1)/6-31G* level. Model analyses with the simpler reactions depicted in Schemes 3 and 4 revealed that this approach is valid, the relative energies being similar.

The possible reaction intermediates and the corresponding reaction profiles are depicted in Scheme 5 and Figure 5, respectively. The energy barriers reported in Table 4 are also defined in Figure 5. The minimum-energy conformation of **16** is shown in Figure 6. From this structure, nucleophilic attack on the sp-hybridized carbon atom can occur by two alternative routes, in which the phenyl group is either *endo* or *exo* with respect to the N1–C2 bond being formed (Figure 3). Both transition structures are depicted in Figure 6, where it can be seen that *exo*-**TS1c** is earlier than *endo*-**TS1c**, with a longer N1–C2 bond. Interestingly, in *endo*-**TS1c** the steric interaction between the *endo*-phenyl group and the (*E*)-vinyl group at C4 promotes a severe distortion of the C2–C3 bond, which is longer than that computed for the reactant. For *endo*-**TS1c** ξ is 48.1°, much larger than the value computed for its *exo* analogue (Figure 6). In *endo*-**TS1c** there is therefore a large departure from the optimal trajectory of attack leading to the formation of the N1–C2 bond and this transition structure is calculated to be approximately 2.0 kcal mol^{-1} higher in energy than *exo*-**TS1c** (Table 4).

In contrast with the first transition structures, the two zwitterionic intermediates *exo*- and *endo*-**INTc** are each calculated to be virtually isoenergetic, both in the gas phase and in solution, as is reflected by the similar ΔE_{int} values reported in Table 4. From the structural point of view, the bond lengths and dihedral angles ω and ξ reflect the similar geometrical parameters of the two intermediates.

As we have commented previously, the second transition structures associated with C3–C4 bond formation in cycloadducts *cis*- and *trans*-**17** (Figure 7) correspond to conrotatory electrocyclic ring closures. Conrotation of *endo*-**INTc** leads to *trans*-**17** via saddle point *trans*-**TS2c**. In this latter transition structure, the methyl group is outward and the phenyl and vinyl groups are inward with respect to the C3–C4 bond being

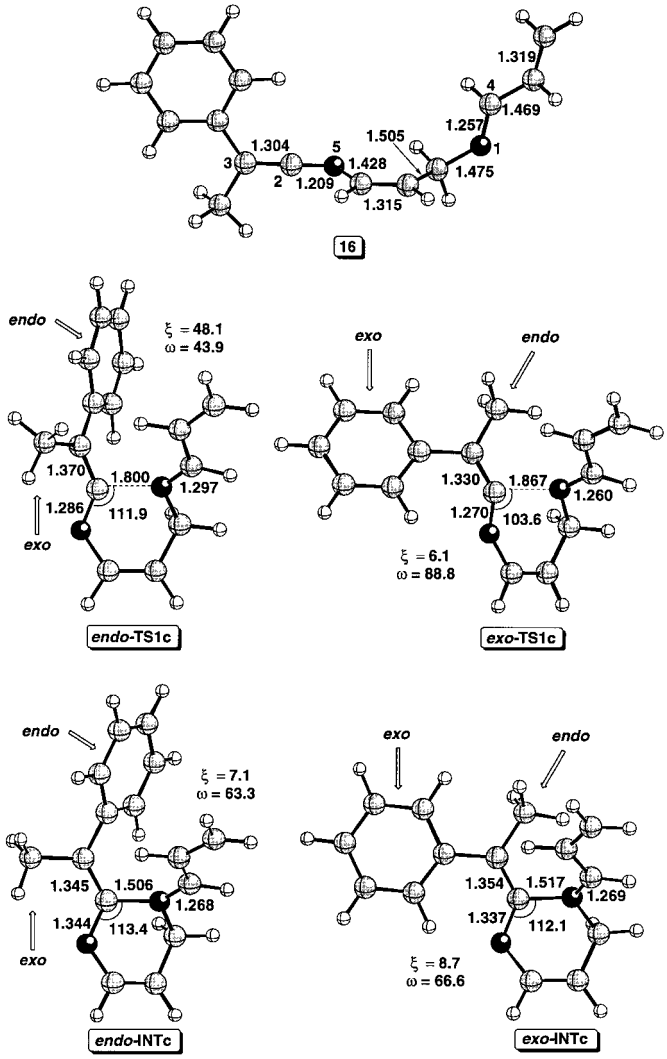


Figure 6. HF/3-21G geometrical data of **16** and the two possible first transition structures **TS1c** and zwitterionic intermediates **INTc**. See the caption of Figure 2 for additional details.

formed. Similarly, the conrotatory ring closure of *exo*-**INTc** yields *cis*-**17** via *cis*-**TS2c**, in which the vinyl group is also inward, whereas the methyl and phenyl groups occupy the inward and outward positions respectively. According to torquoelectronic theory,[24] the relative energies of both transition structures are determined mainly by the donor character of the methyl and phenyl groups. Houk and co-workers[25] have found a linear correlation between the outward preference for a given substituent and its electron-releasing or -withdrawing character, quantified by the Taft parameter.[26] Since for both the phenyl and the methyl groups $\sigma_R^0 = 0.11$,[27] the stereocontrol in the conrotatory step of the reaction is

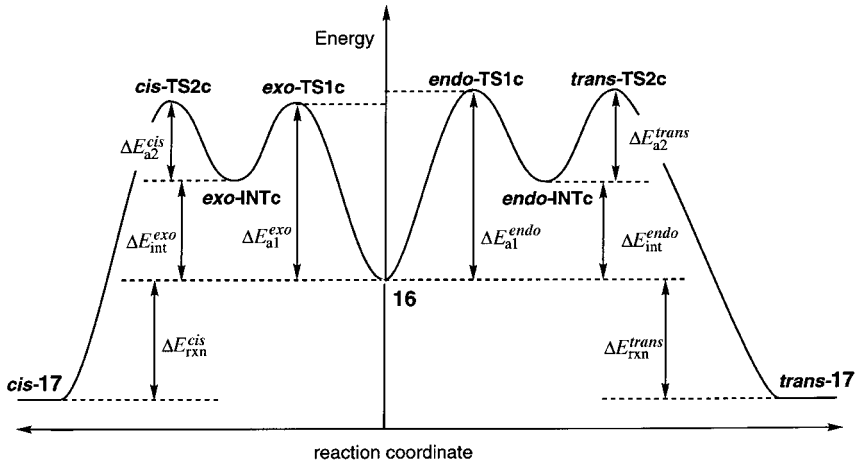


Figure 5. Qualitative reaction profile of the intramolecular [2+2] cycloaddition of **16** to yield cycloadducts *cis*- and *trans*-**17**.

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Table 4. Relative energies[a,b] [kcal mol^{-1}] for the intramolecular reaction of compound **16** to yield *cis*- and *trans*-**17**.

Method	ΔE_{a1} *endo*	ΔE_{a1} *exo*	ΔE_{int} *endo*	ΔE_{int} *exo*	ΔE_{a2} *trans*	ΔE_{a2} *cis*	ΔE_{rxn} *trans*	ΔE_{rxn} *cis*
HF/3–21G*	27.1	25.1	21.0	22.2	19.2	18.8	– 20.2	– 20.5
B3LYP/6–31G*//HF/3–21G*	22.1	20.2	13.6	13.8	7.7	7.5	– 12.3	– 12.6
B3LYP/6–31G*(L1A1)//HF/3–21G*[c]	21.5	19.4	12.5	12.5	8.5	8.4	– 12.5	– 12.8

[a] Single-point energies computed on HF/6–31G* geometries. [b] ZPVEs have been computed at the HF/3–21G* level and conveniently scaled. [c] Values obtained in simulated toluene solution ($\varepsilon = 2.38$)

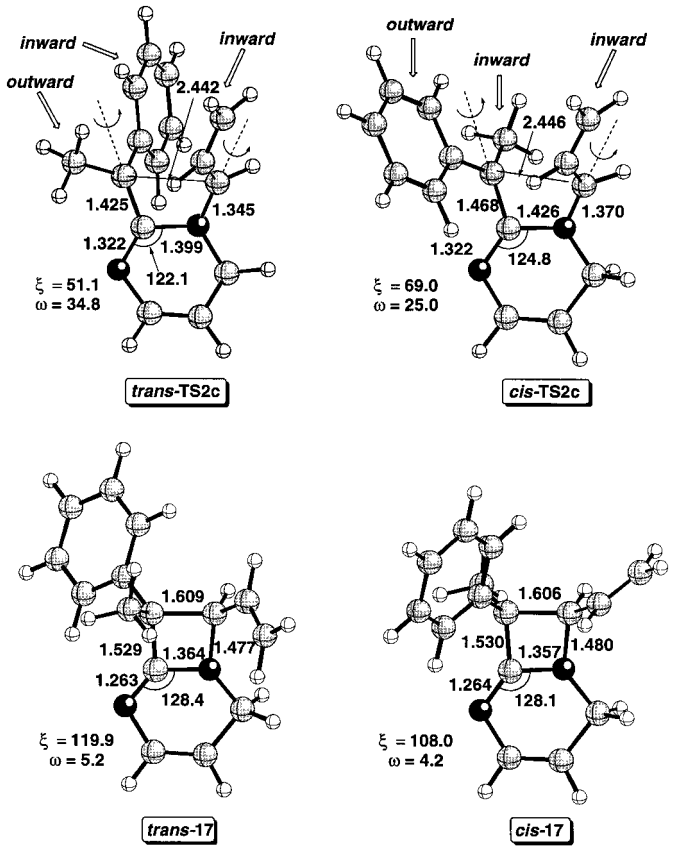

Figure 7. HF/3-21G geometrical data of the two possible second transition structures **TS2c** and cycloadducts *cis*- and *trans*-**17**. See the caption of Figure 2 for additional details.

expected to be negligible. As reported in Table 4, the ΔE_{a2} values for both *cis*- and *trans*-**TS2c** are almost identical, but significantly lower than the ΔE_{a1} values.

If we consider the kinetic equations [Eqs. (1) and (2)], from the computational results and the experimental evidence we can assume that [**INTc**] $\ll$ [**16**] + [**17**] for both *cis* and *trans* stereoisomers. Therefore, the steady-state approximation,[28] if applied to both *endo* and *exo*-**INTc**, yields Equation (3).

From Equation (3) and the data reported in Table 4 the theoretical stereoselectivity of the reaction can be estimated[29] by means of Equations (4) – (6).

Thus, at 298 K we have obtained a value of 4.2:1 for the *cis*-**17**/*trans*-**17** ratio at the B3LYP/6-31G*//HF/3-21G* + ΔZPVE level, which is in good agreement with our experimental findings for cycloadducts **7a** – **7l**, **7n** and **7r** (Table 1), in which the *cis* stereoisomers are formed with virtually complete stereocontrol. In simulated toluene solution the calculated ratio is 3.7:1, which is also in qualitative agreement with the experimental results. Since the ΔE_{a2} values are very similar for both *cis*- and *trans*-**17**, the difference between the ΔE_{a1} values is responsible for the large *cis*/*trans* ratio obtained from Equation (3). Therefore, in these systems the loss of stereocontrol imposed by torquoelectronic effects is avoided because the reactant transfers stereocontrol of the reaction to the formation of the N1 – C2 bond. The geometry of the first transition structure favours the formation of the *exo* zwitterionic intermediates and hence the corresponding *cis* stereoisomers. From these results, it can be expected that a less rigid reactant should lead to a significant loss of stereocontrol, since the restrictions imposed on the first transition structure should be relaxed, the features of the second transition structures being similar. This explains the lower stereoselectivity found in the cyclization of compounds **9** to yield **10a** – **10c**[30] (Scheme 2), in which there is an additional methylene group in the central diazepine ring.

In summary, our experimental and computational studies indicate that in these reactions high stereoselectivity can be achieved in spite of the low stereocontrol of the step in which

$$\mathbf{16} \underset{k_{-1}^{c}}{\overset{k_{1}^{c}}{\rightleftharpoons}} \textit{exo}\text{-}\mathbf{INTc} \xrightarrow{k_{2}^{c}} \textit{cis}\text{-}\mathbf{17} \tag{1}$$

$$\mathbf{16} \underset{k_{-1}^{t}}{\overset{k_{1}^{t}}{\rightleftharpoons}} \textit{endo}\text{-}\mathbf{INTc} \xrightarrow{k_{2}^{t}} \textit{trans}\text{-}\mathbf{17} \tag{2}$$

$$\frac{[\textit{cis}\text{-}\mathbf{17}]}{[\textit{trans}\text{-}\mathbf{17}]} = \frac{k_1^c k_2^c}{k_1^t k_2^t}\left(\frac{k_{-1}^t + k_2^t}{k_{-1}^c + k_2^c}\right) \tag{3}$$

$$\frac{[\textit{cis}\text{-}\mathbf{17}]}{[\textit{trans}\text{-}\mathbf{17}]} \approx \frac{\exp\left[-\left(\Delta E_{a1}^{exo} + \Delta E_{a2}^{cis}\right)/\mathrm{RT}\right]\left[\exp\left(-\Delta E_{-a1}^{endo}/\mathrm{RT}\right) + \exp\left(-\Delta E_{a2}^{trans}/RT\right)\right]}{\exp\left[-\left(\Delta E_{a1}^{endo} + \Delta E_{a2}^{trans}\right)/\mathrm{RT}\right]\left[\exp\left(-\Delta E_{-a1}^{exo}/\mathrm{RT}\right) + \exp\left(-\Delta E_{a2}^{cis}/RT\right)\right]} \tag{4}$$

$$\Delta E_{-a1}^{endo} = \Delta E_{a1}^{endo} - \Delta E_{int}^{endo} \tag{5}$$

$$\Delta E_{-a1}^{exo} = \Delta E_{a1}^{exo} - \Delta E_{int}^{exo} \tag{6}$$

the new chiral centres are formed. We think that this stereocontrol transfer model can be extended to other stepwise mechanisms or tandem reactions which include at least one reversible step.

Experimental Section

All melting points were determined on a Kofler hot-plate melting-point apparatus and are uncorrected. IR spectra were obtained as Nujol emulsions or films on a Nicolet Impact 400 spectrophotometer. NMR spectra were recorded on a Bruker AC-200 or a Varian Unity 300 instrument. Chemical shifts are given relative to tetramethylsilane (TMS). Mass spectra were recorded on a Hewlett-Packard 5993C spectrometer (EI) or on a VG-Autospec spectrometer (FAB$^+$). Microanalyses were performed on a Carlo Erba EA-1108 instrument.

Materials: 2-Azidobenzylamine (**3a**),[11a] 5-methyl-2-azidobenzylamine (**3b**),[11b] 5-chloro-2-azidobenzylamine (**3c**),[11c] ethyl phenyl ketene[31] and methyl phenyl ketene[32] were prepared following previously reported procedures. *N*-(2-Azidobenzyl)imines (**4**) and *N*-(2-azidophenethyl)imines were obtained by standard procedures (Scheme 1, Methods A, B and C).[10]

General procedure for the preparation of azeto[2,1-*b*]quinazolines 7 and azeto[2,1-*b*][1,3]benzodiazepines 10: Trimethylphosphane (3 mmol) was added to a solution of the corresponding imine (3 mmol) in dry toluene (15 mL) and the reaction mixture was stirred at room temperature until the evolution of nitrogen ceased (15 – 30 min). Then methyl phenyl ketene or ethyl phenyl ketene (3 mmol) was added, and the reaction mixture was stirred at room temperature until the ketenimine band around 2000 cm^{-1} was not observed by IR spectroscopy (1 – 12 h). The solvent was removed under reduced pressure and the resulting material was chromatographed on a silica gel column, with hexanes/ethyl acetate as eluent.

***cis*-2-Methyl-1-(4-nitrophenyl)-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline (7a)**: Yield 73%; m.p. 159 – 161 °C (colourless prisms from diethyl ether); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.01$ (s, 3H), 4.48 (d, J(H,H) = 12.7 Hz, 1H), 4.52 (d, J(H,H) = 12.7 Hz, 1H), 4.87 (s, 1H), 6.93 (d, J(H,H) = 7.8 Hz, 1H), 7.02 – 7.10 (m, 6H), 7.19 (d, J(H,H) = 8.7 Hz, 2H), 7.26 – 7.29 (m, 2H), 7.97 (d, J(H,H) = 8.7 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 24.01$, 45.13, 63.49 (s), 74.89, 121.12 (s), 123.37, 125.02, 125.49, 126.97, 127.17, 127.26, 127.92, 128.24, 128.90, 137.33 (s), 142.15 (s), 143.34 (s), 147.49 (s), 166.20 (s); IR (Nujol): $\tilde{\nu} = 1679$, 1520, 1346 cm^{-1}; MS (70 eV, EI): m/z (%): 369 (79) [M^+], 77 (100); $C_{23}H_{19}N_3O_2$ (369.42): calcd C 74.78, H 5.18, N 11.37; found C 74.65, H 5.01, N 11.21.

***cis*-1-(4-Chlorophenyl)-2-methyl-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline (7b)**: Yield 65%; m.p. 137 °C (colourless prisms from diethyl ether); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.93$ (s, 3H), 4.45 (d, J(H,H) = 12.6 Hz, 1H), 4.52 (d, J(H,H) = 12.6 Hz, 1H), 4.73 (s, 1H), 6.91 – 7.12 (m, 11H), 7.23 – 7.26 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 24.39$, 44.86, 62.86 (s), 75.26, 121.32(s), 124.73, 125.50, 126.93, 127.20, 128.11, 128.41, 128.60, 128.80, 133.92 (s), 134.33 (s), 138.06 (s), 142.71 (s), 166.63 (s) (a methine carbon was not observed); IR (Nujol): $\tilde{\nu} = 1674$, 1601, 1084 cm^{-1}; MS (70 eV, EI): m/z (%): 360 (35) [M^++2], 358 (100) [M^+], 204 (48); $C_{23}H_{19}ClN_2$ (358.87): calcd C 76.98, H 5.34, N 7.80; found C 76.80, H 5.24, N 7.93.

***cis*-1-(4-Methoxyphenyl)-2-methyl-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline (7c)**: Yield 58%; oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.92$ (s, 3H), 3.69 (s, 3H), 4.47 (s, 2H), 4.73 (s, 1H), 6.64 (d, J(H,H) = 8.7 Hz, 2H), 6.86 – 6.92 (m, 3H), 6.99 – 7.08 (m, 6H), 7.23 – 7.25 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 24.52$, 44.51, 55.09, 62.46 (s), 75.44, 113.45, 121.33 (s), 124.33, 125.28, 126.46, 127.07, 127.17, 127.54 (s), 127.79, 128.46, 128.54, 138.50 (s), 142.94 (s), 159.32 (s), 166.77 (s); IR (film): $\tilde{\nu} = 1669$, 1511, 1248 cm^{-1}; MS (70 eV, EI): m/z (%): 354 (60) [M^+], 77 (100); $C_{24}H_{22}N_2O$ (354.45): calcd C 81.33, H 6.25, N 7.90; found C 81.55, H 5.98, N 7.75.

***cis*-1-(2-Methoxyphenyl)-2-methyl-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline (7d)**: Yield 64%; m.p. 192 – 193 °C (colourless prisms from diethyl ether); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.01$ (s, 3H), 3.85 (s, 3H), 4.50 (d, J(H,H) = 12.7 Hz, 1H), 4.57 (d, J(H,H) = 12.7 Hz, 1H), 5.12 (s, 1H), 6.64 – 6.71 (m, 2H), 6.91 – 7.19 (m, 9H), 7.24 (d, J(H,H) = 8.6 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 23.29$, 45.63, 55.20, 61.96 (s), 70.91, 109.64, 120.25, 121.52 (s), 124.47, 124.96 (s), 125.38, 126.58, 126.69, 126.78, 127.10, 127.66, 128.59, 128.67, 138.60 (s), 143.10 (s), 156.69 (s), 167.87 (s); IR (Nujol): $\tilde{\nu} = 1681$, 1243, 765 cm^{-1}; MS (70 eV, EI): m/z (%): 354 (70) [M^+], 261 (100); $C_{24}H_{22}N_2O$ (354.45): calcd C 81.33, H 6.25, N 7.90; found C 81.18, H 6.32, N 7.73.

***cis*-2-Methyl-1-(1-naphthyl)-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline (7e)**: Yield 69%; m.p. 158 – 159 °C (colourless prisms from diethyl ether); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.17$ (s, 3H), 4.53 (d, J(H,H) = 12.5 Hz, 1H), 4.61 (d, J(H,H) = 12.5 Hz, 1H), 5.56 (s, 1H), 6.77 – 7.18 (m, 9H), 7.26 – 7.28 (m, 2H), 7.47 – 7.64 (m, 3H), 7.79 (d, J(H,H) = 8.0 Hz, 1H), 8.85 (d, J(H,H) = 8.7 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 23.75$, 45.51, 63.10 (s), 72.56, 121.48 (s), 122.43, 124.13, 124.69, 125.19, 125.44, 125.67, 126.51, 126.69, 126.74, 127.17, 127.62, 128.08, 128.78, 129.09, 131.23 (s), 131.62 (s), 133.45 (s), 138.03 (s), 142.91 (s), 167.30 (s); IR (Nujol): $\tilde{\nu} = 1669$, 764, 700 cm^{-1}; MS (70 eV, EI): m/z (%): 374 (100) [M^+], 243 (47); $C_{27}H_{22}N_2$ (374.49): calcd C 86.60, H 5.92, N 7.48; found C 86.73, H 5.84, N 7.29.

***cis*-1-(2-Furyl)-2-methyl-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline (7f)**: Yield 72%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.94$ (s, 3H), 4.51 (s, 2H), 4.84 (s, 1H), 5.96 (d, J(H,H) = 3.4 Hz, 1H), 6.11 – 6.14 (m, 1H), 6.88 (d, J(H,H) = 7.5 Hz, 1H), 6.98 – 7.24 (m, 9H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 24.62$, 44.53, 62.53 (s), 69.03, 108.98, 110.51, 121.41 (s), 124.56, 125.52, 126.61, 126.84, 127.16, 128.00, 128.66, 139.01 (s), 142.61, 142.84 (s), 149.73 (s), 166.18 (s); IR (film): $\tilde{\nu} = 1672$, 780, 739, 702 cm^{-1}; MS (70 eV, EI): m/z (%): 314 (63) [M^+], 184 (100); $C_{21}H_{18}N_2O$ (314.39): calcd C 80.23, H 5.77, N 8.91; found C 79.98, H 5.57, N 9.01.

***cis*-1-(3-Furyl)-2-methyl-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline (7g)**: Yield 48%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.47$ (s, 3H), 4.46 (d, J(H,H) = 12.7 Hz, 1H), 4.54 (d, J(H,H) = 12.7 Hz, 1H), 4.87 (s, 1H), 6.49 (s, 1H), 6.87 (d, J(H,H) = 7.4 Hz, 1H), 6.98 – 7.01 (m, 1H), 7.19 – 7.41 (m, 5H), 7.49 – 7.58 (m, 4H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 21.44$, 43.84, 59.59 (s), 67.10, 109.53, 120.69 (s), 121.03 (s), 124.52, 125.25, 125.98, 127.15, 127.23, 128.64, 140.92, 142.11 (s), 142.52 (s), 144.01, 166.93 (s), (a methine carbon was not observed); IR (film): $\tilde{\nu} = 1681$, 1161, 876 cm^{-1}; MS (70 eV, EI): m/z (%): 314 (51) [M^+], 184 (100); $C_{21}H_{18}N_2O$ (314.39): calcd C 80.23, H 5.77, N 8.91; found C 80.55, H 5.47, N 8.70.

***cis*-2-Methyl-2-phenyl-1-(3-thienyl)-1,2-dihydroazeto[2,1-*b*]quinazoline (7h)**: Yield 67%; m.p. 137 – 138 °C (colourless prisms from diethyl ether); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.92$ (s, 3H), 4.49 (s, 2H), 4.86 (s, 1H), 6.57 (dd, J(H,H) = 1.2, 4.9 Hz, 1H), 6.90 – 7.26 (m, 11H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 24.48$, 44.71, 62.34 (s), 71.65, 121.49 (s), 123.20, 124.50, 125.47, 125.81, 126.37, 126.73, 127.00, 127.19, 127.96, 128.67, 137.89 (s), 138.78 (s), 142.96 (s), 166.57 (s); IR (Nujol): $\tilde{\nu} = 1673$, 1597, 789 cm^{-1}; MS (70 eV, EI): m/z (%): 330 (100) [M^+], 203 (60); $C_{21}H_{18}N_2S$ (330.45): calcd C 76.33, H 5.49, N 8.48; found C 76.11, H 5.34, N 8.39.

***cis*-2-Methyl-2-phenyl-1-(*E*-2-phenylethenyl)-1,2-dihydroazeto[2,1-*b*]quinazoline (7i)**: Yield 84%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.92$ (s, 3H), 4.36 (d, J(H,H) = 8.9 Hz, 1H), 4.55 (s, 2H), 5.60 (dd, J(H,H) = 8.9, 15.8 Hz, 1H), 6.65 (d, J(H,H) = 15.8 Hz, 1H), 6.94 – 7.47 (m, 14H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 24.15$, 44.39, 60.80 (s), 74.23, 121.38 (s), 124.38, 125.25, 126.15, 126.59, 127.10, 127.16, 128.11, 128.34, 128.58, 134.57, 136.03 (s), 138.69 (s), 142.88 (s), 166.41(s) (two methine carbons were not observed); IR (film): $\tilde{\nu} = 1676$, 1602, 1148 cm^{-1}; MS (70 eV, EI): m/z (%): 350 (32) [M^+], 77 (100); $C_{25}H_{22}N_2$ (350.46): calcd C 85.68, H 6.32, N 7.99; found C 85.43, H 6.11, N 8.21.

***cis*-2-Methyl-1-[*E*-2-(2-nitrophenyl)ethenyl]-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline (7j)**: Yield 75%; m.p. 277 °C (colourless prisms from diethyl ether); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.93$ (s, 3H), 4.39 (d, J(H,H) = 8.1 Hz, 1H), 4.58 (s, 2H), 5.55 (dd, J(H,H) = 8.1, 15.6 Hz, 1H), 6.89 – 7.04 (m, 3H), 7.08 (d, J(H,H) = 15.6 Hz, 1H), 7.20 – 7.45 (m, 9H), 7.93 (dd, J(H,H) = 1.2, 7.8 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 23.88$, 44.71, 61.23 (s), 73.39, 121.37 (s), 124.59, 125.48, 127.21, 127.30, 128.39, 128.59, 128.67, 129.08, 129.67, 131.74, 132.28 (s), 133.38, 138.59 (s), 142.77 (s), 147.53 (s), 166.16 (s) (two methine carbons were not observed); IR (Nujol): $\tilde{\nu} = 1672$, 1520, 1343 cm^{-1}; MS (70 eV, EI): m/z (%): 395 (52) [M^+], 77 (100); $C_{25}H_{21}N_3O_2$ (395.46): calcd C 75.93, H 5.35, N 10.62; found C 75.75, H 5.17, N 10.75.

***cis*-6-Chloro-2-methyl-1-(4-nitrophenyl)-2-phenyl-1,2-dihydroazeto[2,1-*b*]-quinazoline (7k)**: Yield 76%; m.p. 200 – 201 °C (colourless prisms from $CHCl_3$/*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.01$ (s, 3H), 4.44 (d, J(H,H) = 12.9 Hz, 1H), 4.55 (d, J(H,H) = 12.9 Hz, 1H), 4.87 (s, 1H), 6.92

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(d, J(H,H) = 1.1 Hz, 1H), 7.03 (s, 5H), 7.16 – 7.22 (m, 4H), 7.98 (d, J(H,H) = 8.7 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 24.07, 44.88, 63.55 (s), 74.91, 122.69 (s), 123.47, 126.75, 126.93, 127.08, 127.41, 127.93, 128.34, 128.88, 129.78 (s), 136.17 (s), 140.99 (s), 143.05 (s), 147.61 (s), 166.37 (s); IR (Nujol): $\tilde{\nu}$ = 1672, 1519, 1346 cm^{-1}; MS (70 eV, EI): m/z (%): 406 (35) [M^++2], 404 (12) [M^+], 77 (100); $C_{23}H_{18}ClN_3O_2$ (403.87): calcd C 68.40, H 4.49, N 10.40; found C 68.55, H 4.60, N 10.58.

***cis*-2,6-Dimethyl-2-phenyl-1-(*E*-2-phenylethenyl)-1,2-dihydroazeto[2,1-*b*]-quinazoline (71)**: Yield 79%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.78 (s, 3H), 2.17 (s, 3H), 4.17 (d, J(H,H) = 8.7 Hz, 1H), 4.35 (s, 2H), 5.48 (dd, J(H,H) = 8.7, 15.7 Hz, 1H), 6.49 (d, J(H,H) = 15.7 Hz, 1H), 6.59 (s, 1H), 6.90 – 6.93 (m, 1H), 7.01 – 7.04 (m, 3H), 7.09 – 7.21 (m, 6H), 7.29 – 7.32 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 20.84, 24.12, 44.51, 60.77 (s), 74.18, 121.13 (s), 125.13, 126.41, 126.58, 127.04, 127.19, 127.66, 128.04, 128.30, 128.56, 129.05, 133.95 (s), 134.36, 136.13 (s), 138.88 (s), 140.46 (s), 165.81 (s); IR (film): $\tilde{\nu}$ = 1683, 1597, 1520 cm^{-1}; MS (FAB$^+$): m/z: 365 [MH$^+$]; $C_{26}H_{24}N_2$ (364.49): calcd C 85.68, H 6.63, N 7.68; found C 85.33, H 6.79, N 7.51.

***trans*-2-Ethyl-1-(4-nitrophenyl)-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline (*trans*-7m)**: Yield 12%; m.p. 168 – 169 °C (colourless prisms from diethyl ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.75 (t, J(H,H) = 7.3 Hz, 3H), 1.48 (m, 1H), 1.75 (m, 1H), 4.51 (s, 2H), 4.95 (s, 1H), 6.93 (d, J(H,H) = 7.4 Hz, 1H), 7.03 – 7.11 (m, 1H), 7.21 – 7.47 (m, 5H), 7.62 – 7.69 (m, 4H), 8.32 (d, J(H,H) = 8.6 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 9.31, 28.27, 44.94, 65.12 (s), 73.06, 121.18 (s), 124.09, 124.95, 125.75, 126.83, 127.13, 127.53, 127.97, 128.86, 128.94, 139.70 (s), 143.44 (s), 147.97 (s), 152.22 (s), 165.86 (s); IR (Nujol): $\tilde{\nu}$ = 1668, 1602, 1515, 1344 cm^{-1}; MS (FAB$^+$): m/z : 384 [MH$^+$]; $C_{24}H_{21}N_3O_2$ (383.45): calcd C 75.17, H 5.52, N 10.96; found C 75.31, H 5.38, N 10.79.

***cis*-2-Ethyl-1-(4-nitrophenyl)-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline (*cis*-7m)**: Yield 60%; m.p. 237 – 238 °C (colourless prisms from diethyl ether); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (t, J(H,H) = 7.4 Hz, 3H), 2.30 – 2.43 (m, 2H), 4.43 (d, J(H,H) = 12.4 Hz, 1H), 4.55 (d, J(H,H) = 12.4 Hz, 1H), 4.89 (s, 1H), 6.92 (d, J(H,H) = 7.2 Hz, 1H), 7.04 – 7.09 (m, 6H), 7.20 (d, J(H,H) = 8.7 Hz, 2H), 7.26 – 7.29 (m, 2H), 7.98 (d, J(H,H) = 8.7 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 10.19, 31.24, 44.53, 69.33 (s), 72.41, 121.18 (s), 123.37, 124.86, 125.78, 127.15, 127.18, 127.53, 128.19, 128.25, 128.53, 136.33 (s), 142.60 (s), 143.60 (s), 147.55 (s), 165.26 (s); IR (Nujol): $\tilde{\nu}$ = 1668, 1599, 1521, 1343 cm^{-1}; MS (70 eV, EI): m/z (%): 383 (100) [M^+], 368 (78), 204 (62); $C_{24}H_{21}N_3O_2$ (383.45): calcd C 75.17, H 5.52, N 10.96; found C 75.26, H 5.43, N 10.78.

***cis*-2-Ethyl-2-phenyl-1-(3-thienyl)-1,2-dihydroazeto[2,1-*b*]quinazoline (7n)**: Yield 46%; m.p. 175 – 177 °C (colourless prisms from *n*-hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.11 (t, J(H,H) = 7.3 Hz, 3H), 2.20 – 2.31 (m, 2H), 4.43 (d, J(H,H) = 12.6 Hz, 1H), 4.49 (d, J(H,H) = 12.6 Hz, 1H), 4.91 (s, 1H), 6.57 (dd, J(H,H) = 1.3, 5.0 Hz, 1H), 6.85 – 6.88 (m, 1H), 6.96 – 7.28 (m, 10H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 10.10, 31.51, 44.30, 66.96 (s), 68.97, 121.41 (s), 123.42, 124.36, 125.53, 125.74, 126.63, 126.67, 127.17, 127.52, 127.86, 128.60, 137.65 (s), 137.92 (s), 143.13 (s), 165.76 (s); IR (Nujol): $\tilde{\nu}$ = 1667, 1217, 702 cm^{-1}; MS (FAB$^+$): m/z: 345 [MH$^+$]; $C_{22}H_{20}N_2S$ (344.48): calcd C 76.71, H 5.83, N 8.13; found C 76.90, H 5.65, N 8.00.

***trans*-6-Chloro-2-ethyl-1-(4-nitrophenyl)-2-phenyl-1,2-dihydroazeto[2,1-*b*]-quinazoline (*trans*-7o)**: Yield 8%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.73 (t, J(H,H) = 7.3 Hz, 3H), 1.36 – 1.51 (m, 1H), 1.68 – 1.83 (m, 1H), 4.83 (s, 2H), 4.97 (s, 1H), 6.92 (s, 1H), 7.20 – 7.48 (m, 5H), 7.61 – 7.67 (m, 4H), 8.33 (d, J(H,H) = 8.6 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 9.28, 28.30, 44.60, 65.18 (s), 73.03, 122.62 (s), 124.17, 126.79, 126.88, 127.01, 127.65, 127.96, 128.81, 128.99, 129.72 (s), 139.45 (s), 143.05 (s), 148.06 (s), 166.04 (s) (a quaternary carbon was not observed); IR (film): $\tilde{\nu}$ = 1672, 1601 cm^{-1}; MS (70 eV, EI): m/z (%): 420 (45) [M^++2], 418 (16) [M^+], 77 (100); $C_{24}H_{20}ClN_3O_2$ (417.90): calcd C 68.98, H 4.82, N 10.05; found C 68.87, H 5.01, N 9.89.

***cis*-6-Chloro-2-ethyl-1-(4-nitrophenyl)-2-phenyl-1,2-dihydroazeto[2,1-*b*]-quinazoline (*cis*-7o)**: Yield 74%; m.p. 180 °C (colourless prisms from diethyl ether); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, J(H,H) = 7.4 Hz, 3H), 2.31 – 2.41 (m, 2H), 4.39 (d, J(H,H) = 12.7 Hz, 1H), 4.53 (d, J(H,H) = 12.7 Hz, 1H), 4.90 (s, 1H), 6.89 (s, 1H), 7.07 (s, 5H), 7.16 – 7.26 (m, 4H), 7.98 (d, J(H,H) = 8.5 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 10.03, 31.12, 44.06, 68.23 (s), 72.36, 122.49 (s), 123.32, 126.75, 126.93, 127.16, 127.34, 128.12, 128.14, 128.68, 129.59 (s), 135.90 (s), 141.04 (s), 143.06 (s), 147.48 (s), 165.39 (s); IR (Nujol): $\tilde{\nu}$ = 1666, 1518, 853, 758, 703 cm^{-1}; MS (70 eV, EI): m/z (%): 420 (39) [M^++2], 418 (13) [M^+], 77 (100); $C_{24}H_{20}ClN_3O_2$ (417.90): calcd C 68.98, H 4.82, N 10.05; found C 68.83, H 4.70, N 9.88.

***trans*-1-Isopropyl-2-methyl-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline (*trans*-7p)**: Yield 13%; oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (d, J(H,H) = 6.5 Hz, 3H), 1.08 (d, J(H,H) = 6.5 Hz, 3H), 1.72 (s, 3H), 2.09 – 2.21 (m, 1H), 3.43 (d, J(H,H) = 10.3 Hz, 1H), 4.52 (d, J(H,H) = 12.4 Hz, 1H), 4.57 (d, J(H,H) = 12.4 Hz, 1H), 6.82 – 6.86 (m, 1H), 6.94 – 6.99 (m, 1H), 7.15 – 7.26 (m, 3H), 7.31 – 7.36 (m, 2H), 7.54 – 7.58 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 19.78, 19.93, 20.59, 30.03, 46.90, 56.62 (s), 78.05, 121.46 (s), 124.07, 124.92, 126.46, 126.65, 126.78, 128.36, 128.48, 142.23 (s), 142.79 (s), 168.02 (s); IR (film): $\tilde{\nu}$ = 1664, 1599, 1145 cm^{-1}; MS (70 eV, EI): m/z (%): 290 (23) [M^+], 261 (100); $C_{20}H_{22}N_2$ (290.41): calcd C 82.72, H 7.63, N 9.64; found C 82.91, H 7.54, N 9.35.

***cis*-1-Isopropyl-2-methyl-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline (*cis*-7p)**: Yield 16%; oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.60 (d, J(H,H) = 6.8 Hz, 3H), 0.87 (d, J(H,H) = 6.8 Hz, 3H), 1.43 – 1.55 (m, 1H), 1.86 (s, 3H), 3.18 (d, J(H,H) = 9.6 Hz, 1H), 4.53 (d, J(H,H) = 12.4 Hz, 1H), 4.58 (d, J(H,H) = 12.4 Hz, 1H), 7.40 – 7.89 (m, 9H) ; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 18.56, 19.69, 21.68, 29.59, 47.92, 57.17 (s), 80.50, 121.60 (s), 124.29, 124.95, 126.70, 127.18, 127.51, 128.07, 128.46, 137.93 (s), 142.69 (s), 168.07 (s); IR (film): $\tilde{\nu}$ = 1667, 1601, 732 cm^{-1}; MS (70 eV, EI): m/z (%): 290 (20) [M^+], 103 (100); $C_{20}H_{22}N_2$ (290.41): calcd C 82.72, H 7.63, N 9.64; found C 82.95, H 7.41, N 9.31.

***trans*-2-Methyl-2-phenyl-1-*tert*-butyl-1,2-dihydroazeto[2,1-*b*]quinazoline (*trans*-7q)**: Yield 46%; m.p. 114 – 116 °C (colourless prisms from diethyl ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.53 (s, 9H), 1.81 (s, 3H), 3.61 (s, 1H), 4.59 (s, 2H), 6.87 (d, J(H,H) = 7.1 Hz, 1H), 6.95 – 7.03 (m, 1H), 7.14 – 7.38 (m, 5H), 7.56 – 7.60 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.01, 27.75, 34.36 (s), 47.03, 58.52 (s), 81.14, 121.40 (s), 124.18, 125.18, 126.41, 126.86, 126.92, 128.58, 128.68, 143.15 (s), 143.55 (s), 167.74 (s); IR (Nujol): $\tilde{\nu}$ = 1682, 1650, 1608 cm^{-1}; MS (70 eV, EI): m/z (%): 304 (40) [M^+], 261 (100); $C_{21}H_{24}N_2$ (304.43): calcd C 82.85, H 7.95, N 9.20; found C 82.67, H 7.78, N 9.08.

***cis*-2-Methyl-2-phenyl-1-*tert*-butyl-1,2-dihydroazeto[2,1-*b*]quinazoline (*cis*-7q)**: Yield 28%; m.p. 196 °C (colourless prisms from diethyl ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.71 (s, 9H), 1.86 (s, 3H), 3.41 (s, 1H), 4.56 (s, 2H), 6.89 – 7.46 (m, 9H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 24.37, 26.57, 34.49 (s), 48.47, 58.34 (s), 83.53, 121.71 (s), 124.42, 125.05, 126.89, 127.34, 128.13, 128.66, 138.57 (s), 142.94 (s), 168.29 (s) (a methine carbon was not observed); IR (Nujol): $\tilde{\nu}$ = 1665, 1394, 1126, 1082 cm^{-1}; MS (70 eV, EI): m/z (%): 304 (43) [M^+], 247 (100); $C_{21}H_{24}N_2$ (304.43): calcd C 82.85, H 7.95, N 9.20; found C 82.67, H 7.79, N 9.34.

***cis*-1,2-Dimethyl-1-(4-nitrophenyl)-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline (7r)**: Yield 63%; m.p. 171 °C (yellow prisms from diethyl ether); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.89 (s, 3H), 1.98 (s, 3H), 4.46 (d, J(H,H) = 12.4 Hz, 1H), 4.70 (d, J(H,H) = 12.4 Hz, 1H), 6.95 – 7.07 (m, 7H), 7.21 – 7.24 (m, 4H), 7.89 (d, J(H,H) = 8.7 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 19.28, 19.51, 40.77, 64.30 (s), 77.64 (s), 120.66 (s), 122.92, 124.72, 125.51, 126.83, 126.88, 126.95, 127.24, 127.95, 128.76, 139.17 (s), 142.71 (s), 146.53 (s), 148.63 (s), 165.62 (s); IR (Nujol): $\tilde{\nu}$ = 1665, 1514, 1348 cm^{-1}; MS (70 eV, EI): m/z (%): 383 (95) [M^+], 77 (100); $C_{24}H_{21}N_3O_2$ (383.45): calcd C 75.17, H 5.52, N 10.96; found C 75.01, H 5.37, N 10.78.

(*trans* + *cis*)-1,2-Diphenyl-2-methyl-1-trifluoromethyl-1,2-dihydroazeto-[2,1-*b*]quinazoline (*trans*-7s and *cis*-7s): Yield 77%; oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 3H), 2.07 (s, 3H), 4.76 (s, 2H), 4.84 (s, 2H), 6.51 – 7.61 (m, 26H), 7.73 – 7.76 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 19.69 (q, J(F,C) = 3.0 Hz), 25.19, 43.10, 43.93, 62.85 (s), 65.93 (s), 120.79 (s), 121.08 (s), 122.84 (s), 123.81 (s), 125.16, 125.19, 125.89, 126.04, 126.89, 126.91, 127.13, 127.16, 127.24, 127.37, 127.66, 127.91, 128.15, 128.32, 128.43, 128.91, 129.10, 129.27, 132.28 (s), 132.75 (s), 136.83 (s), 138.52 (s), 142.06 (s), 142.04 (s), 164.36 (s), 164.90 (s); IR (film): $\tilde{\nu}$ = 1685, 1602, 1158 cm^{-1}; MS (70 eV, EI): m/z (%): 392 (100) [M^+], 77 (53); $C_{24}H_{19}F_3N_2$ (392.42): calcd C 73.46, H 4.88, N 7.14; found C 73.13, H 4.99, N 7.34.

***trans*-2-Methyl-1-(4-nitrophenyl)-2-phenyl-1,2,8,9-tetrahydroazeto[2,1-*b*]-[1,3]benzodiazepine (*trans*-10a)**: Yield 32%; m.p. 204 °C (yellow prisms from diethyl ether); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (s, 3H), 3.03 – 3.22 (m, 2H), 3.55 (ddd, J(H,H) = 2.8, 4.7, 12.1 Hz, 1H), 3.83 (ddd, J(H,H) = 2.2, 9.3, 12.1 Hz, 1H), 4.87 (s, 1H), 7.04 (td, J(H,H) = 1.6, 6.8 Hz, 1H), 7.13 (dd, J(H,H) = 1.6, 7.5 Hz, 1H), 7.24 – 7.34 (m, 3H), 7.41 (m, 2H), 7.50 (d, J(H,H) = 8.7 Hz, 2H), 7.61 – 7.65 (m, 2H), 8.28 (d, J(H,H) = 8.7 Hz,

2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 20.44, 36.14, 54.29, 57.51$ (s), 73.54, 123.58, 124.05, 126.19, 127.34, 127.37, 127.78, 128.99, 130.27, 133.72 (s), 142.77 (s), 144.79 (s), 147.69 (s), 147.82 (s), 161.52 (s) (a methine carbon was not observed); IR (Nujol): $\tilde{\nu} = 1680, 1593, 1517, 1343$ cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 383 (100) [M^+], 103 (53); $C_{24}H_{21}N_3O_2$ (383.45): calcd C 75.17, H 5.52, N 10.96; found C 75.01, H 5.37, N 10.82.

cis*-2-Methyl-1-(4-nitrophenyl)-2-phenyl-1,2,8,9-tetrahydroazeto[2,1-*b*]-[1,3]benzodiazepine** (cis*-10a**): Yield 39%; oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.99$ (s, 3H), 3.05–3.17 (m, 2H), 3.50 (ddd, J(H,H) = 3.1, 4.6, 11.8 Hz, 1H), 3.67 (ddd, J(H,H) = 3.7, 8.0, 11.8 Hz, 1H), 4.78 (s, 1H), 6.99–7.41 (m, 11H), 7.93 (d, J(H,H) = 8.7 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 24.81, 36.00, 53.75, 60.08$ (s), 74.38, 123.26, 123.68, 126.96, 127.32, 127.36, 127.81, 128.08, 130.23, 133.80 (s), 138.10 (s), 144.62 (s), 147.35 (s), 161.13 (s) (a methine carbon and a quaternary carbon were not observed); IR (film): $\tilde{\nu} = 1681, 1598, 1522, 1347$ cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 383 (100) [M^+], 232 (99); $C_{24}H_{21}N_3O_2$ (383.45): calcd C 75.17, H 5.52, N 10.96; found C 74.98, H 5.70, N 10.70.

trans*-1-(4-Chlorophenyl)-2-methyl-2-phenyl-1,2,8,9-tetrahydroazeto[2,1-*b*]-[1,3]-benzodiazepine** (trans*-10b**): Yield 28%; m.p. 159–160 °C (colourless prisms from diethyl ether); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.93$ (s, 3H), 3.04 (ddd, J(H,H) = 2.5, 5.0, 13.6 Hz, 1H), 3.13 (ddd, J(H,H) = 2.8, 9.0, 13.6 Hz, 1H), 3.49 (ddd, J(H,H) = 2.8, 4.9, 12.1 Hz, 1H), 3.75 (ddd, J(H,H) = 2.5, 9.0, 12.1 Hz, 1H), 4.75 (s, 1H), 7.00 (td, J(H,H) = 1.5, 6.9 Hz, 1H), 7.08 (dd, J(H,H) = 1.5, 7.5 Hz, 1H), 7.22–7.40 (m, 9H), 7.61 (d, J(H,H) = 7.5 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 20.42$, 36.25, 53.43, 57.06 (s), 73.58, 123.31, 126.23, 127.05, 127.34, 127.69, 128.40, 128.84, 128.99, 130.26, 133.73 (s), 134.01 (s), 135.46 (s), 143.34 (s), 147.92 (s), 162.01 (s); IR (Nujol): $\tilde{\nu} = 1683$, 1594 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 375 (11) [M^++2], 373 (31) [M^+], 132 (100); $C_{24}H_{21}ClN_2$ (372.90): calcd C 77.30, H 5.67, N 7.51; found C 77.45, H 5.70, N 7.64.

cis*-1-(4-Chlorophenyl)-2-methyl-2-phenyl-1,2,8,9-tetrahydroazeto[2,1-*b*]-[1,3]-benzodiazepine** (cis*-10b**): Yield 20%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.93$ (s, 3H), 3.05–3.09 (m, 2H), 3.54–3.66 (m, 2H), 4.66 (s, 1H), 6.86 (d, J(H,H) = 8.4 Hz, 2H), 7.02–7.38 (m, 11H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 25.05$, 36.09, 52.91, 59.48 (s), 74.50, 123.39, 126.58, 127.28, 127.45, 127.70, 127.90, 128.23, 128.77, 130.24, 133.56 (s), 133.80 (s), 135.25 (s), 138.69 (s), 147.59 (s), 161.66 (s); IR (film): $\tilde{\nu} = 1685$, 1602, 1265 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 375 (14) [M^++2], 373 (43) [M^+], 132 (100); $C_{24}H_{21}ClN_2$ (372.90): calcd C 77.30, H 5.67, N 7.51; found C 77.02, H 5.55, N 7.25.

trans*-2-Methyl-1-(4-methylphenyl)-2-phenyl-1,2,8,9-tetrahydroazeto[2,1-*b*]-[1,3]benzodiazepine** (trans*-10c**): Yield 37%; m.p. 194–195 °C (colourless prisms from diethyl ether); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.27$ (s, 3H), 2.37 (s, 3H), 3.06–3.13 (m, 2H), 3.47 (ddd, J(H,H) = 2.9, 5.0, 12.1 Hz, 1H), 3.74 (ddd, J(H,H) = 3.2, 8.2, 12.1 Hz, 1H), 4.75 (s, 1H), 6.88–7.10 (m, 3H), 7.16–7.41 (m, 8H), 7.63 (d, J(H,H) = 7.0 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 20.36$, 21.21, 36.34, 52.86, 56.93 (s), 74.00, 123.08, 126.26, 126.85, 127.08, 127.27, 127.60, 128.71, 129.41, 130.26, 133.58 (s), 133.77 (s), 137.94 (s), 143.73 (s), 148.11 (s), 162.36 (s); IR (Nujol): $\tilde{\nu} = 1680, 1597$ cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 352 (20) [M^+], 132 (100); $C_{25}H_{24}N_2$ (352.48): calcd C 85.19, H 6.86, N 7.94; found C 85.00, H 6.68, N 7.79.

cis*-2-Methyl-1-(4-methylphenyl)-2-phenyl-1,2,8,9-tetrahydroazeto[2,1-*b*]-[1,3]benzodiazepine** (cis*-10c**): Yield 9%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.87$ (s, 3H), 2.19 (s, 3H), 3.00–3.11 (m, 2H), 3.39–3.66 (m, 2H), 4.66 (s, 1H), 6.81 (d, J(H,H) = 8.1 Hz, 2H), 6.89 (d, J(H,H) = 8.1 Hz, 2H), 6.96–7.42 (m, 9H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 21.12$, 29.75, 36.21, 52.54, 59.30 (s), 75.05, 123.14, 126.25, 127.27, 127.49, 127.56, 127.61, 127.70, 128.73, 130.24, 133.45 (s), 133.88 (s), 137.50 (s), 139.22 (s), 147.91 (s), 162.03 (s); IR (film): $\tilde{\nu} = 1676$, 1596 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 352 (100) [M^+], 132 (68); $C_{25}H_{24}N_2$ (352.48): calcd C 85.19, H 6.86, N 7.94; found C 85.43, H 6.65, N 7.71.

***cis*-1,2-Dimethyl-1-(4-nitrophenyl)-2-phenyl-1,2,8,9-tetrahydroazeto[2,1-*b*]-[1,3]-benzodiazepine** (**10d**): Yield 63%; m.p. 250–252 °C (yellow prisms from diethyl ether); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.90$ (s, 3H), 1.91 (s, 3H), 2.99–3.24 (m, 2H), 3.61–3.66 (m, 2H), 6.92–7.14 (m, 9H), 7.27–7.33 (m, 2H), 7.83 (d, J(H,H) = 6.9 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta =$ 19.60, 20.14, 36.88, 48.81, 62.30 (s), 72.53 (s), 122.79, 123.43, 126.69, 127.22, 127.40, 127.73, 127.87, 130.29, 133.61 (s), 140.08 (s), 146.32 (s), 147.64 (s), 150.12 (s), 160.86 (s) (a methine carbon was not observed); IR (Nujol): $\tilde{\nu} =$ 1678, 1597, 1518, 1346 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 397 (100) [M^+], 233 (75); $C_{25}H_{23}N_3O_2$ (397.48): calcd C 75.54, H 5.83, N 10.57; found C 75.38, H 5.97, N 10.41.

trans*-1-(4-Chlorophenyl)-2-ethyl-2-phenyl-1,2,8,9-tetrahydroazeto[2,1-*b*]-[1,3]benzodiazepine** (trans*-10e**): Yield 51%; oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.75$ (t, J(H,H) = 7.3 Hz, 3H), 1.43–1.50 (m, 1H), 1.69–1.76 (m, 1H), 2.95–3.11 (m, 2H), 3.41 (ddd, J(H,H) = 2.6, 4.7, 12.0 Hz, 1H), 3.72 (ddd, J(H,H) = 2.5, 9.5, 12.0 Hz, 1H), 4.77 (s, 1H), 6.99 (td, J(H,H) = 1.5, 7.3 Hz, 1H), 7.07 (dd, J(H,H) = 1.8, 7.3 Hz, 1H), 7.23–7.42 (m, 9H), 7.68 (d, J(H,H) = 7.0 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 8.90$, 28.17, 35.85, 53.92, 60.74 (s), 72.89, 123.12, 126.82, 127.11, 127.47, 127.56, 128.56, 128.59, 128.83, 130.04, 133.82 (s), 133.89 (s), 135.62 (s), 141.62 (s), 148.04 (s), 161.17 (s); IR (Nujol): $\tilde{\nu} = 1676, 1596, 1216, 1092$ cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 389 (36) [M^++2], 387 (12) [M^+], 132 (100); $C_{25}H_{23}ClN_2$ (386.93): calcd C 77.60, H 5.99, N 7.24; found C 77.32, H 6.20, N 7.41

cis*-1-(4-Chlorophenyl)-2-ethyl-2-phenyl-1,2,8,9-tetrahydroazeto[2,1-*b*][1,3]-benzodiazepine** (cis*-10e**): Yield 6%; oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 1.81 (t, J(H,H) = 7.3 Hz, 3H), 2.26 (q, J(H,H) = 7.3 Hz, 2H), 2.99–3.14 (m, 2H), 3.42–3.59 (m, 2H), 4.71 (s, 1H), 6.86 (d, J(H,H) = 8.4 Hz, 2H), 6.89–7.09 (m, 6H), 7.16–7.20 (m, 2H), 7.25–7.30 (m, 2H), 7.42 (d, J(H,H) = 8.1 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 9.68$, 31.57, 36.21, 52.55, 63.75 (s), 71.22, 123.35, 126.47, 127.48, 127.71, 127.80, 127.93, 128.27, 129.18, 130.26, 133.64 (s), 133.78 (s), 135.45 (s), 138.18 (s), 147.78 (s), 160.40 (s); IR (film): $\tilde{\nu} = 1677, 1599, 1219, 759$ cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 389 (41) [M^++2], 387 (14) [M^+], 132 (100); $C_{25}H_{23}ClN_2$ (386.93): calcd C 77.60, H 5.99, N 7.24; found C 77.88, H 5.65, N 7.59.

Computations: All calculations reported in this study have been performed using the GAUSSIAN 94[33] series of programs, with the 3-21G and 6-31G* basis sets.[34] Electron correlation was partially taken into account by means of either Møller–Plesset theory up to the second order[35] (MP2) or density functional theory[36] using the hybrid functional developed by Becke and customarily denoted as B3LYP.[37] All the reported stationary points were fully optimized by analytical gradient techniques and characterized by frequency calculations.[38] Zero-point vibrational energies (ZPVEs) obtained at either the HF/6-31G* or HF/3-21G* level were scaled by 0.89.[39] The ZPVEs obtained at the B3LYP/6-31G* level were not scaled. Solute–solvent interactions were computed by means of the Onsager model,[40] which is denoted as L1A1,[41] and in which the solute is modelled as a sphere and the solvation energy ΔG_s is approximated by Equation (7), where ε is the dielectric constant of the solvent, μ is the dipole moment of the solute and a_0 is its spherical cavity radius. Atomic charges[42] were calculated by

$$\Delta G_s \approx -\frac{\varepsilon - 1}{2\varepsilon + 1}\frac{\mu^2}{a_0^3} \qquad (7)$$

the natural bond orbital (NBO) method.[43]

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