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Stereocontrolled synthesis of azeto[2,1-*b*] quinazolines bearing three stereocenters via the intramolecular [2+2] cycloaddition between ketenimines and imines

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Abstract—A highly stereoselective synthesis of azeto[2,1-*b*]quinazolines bearing three stereocenters (C1, C2, and C8) has been achieved via intramolecular [2+2] cycloaddition between ketenimine and imine functions supported on an *ortho*-benzylic scaffold. An asymmetric center adjacent to the iminic nitrogen atom, the future C8 carbon of the bicyclic product, efficiently controls the absolute configuration of the two new stereogenic carbon atoms of the azetidine ring, C1 and C2.

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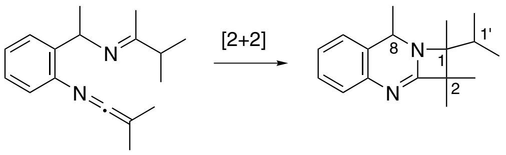
1. Introduction

The stereoselective synthesis of organic compounds with one or more stereogenic centers is one of the most challenging aspects of organic synthesis.[1] Cycloaddition reactions have proven to be very useful for achieving this goal in the synthesis of carbocyclic and heterocyclic ring systems.[2] The thermal [2+2] cycloaddition of cumulenes and heterocumulenes with alkenes, imines, and carbonyl compounds is one of the most useful routes to four-membered ring compounds.[3]

As a result of our studies on the chemistry of ketenimines, we have reported the first examples of the intramolecular [2+2] cycloaddition between ketenimine and imine functions, which took place efficiently when both functionalites were supported on an *ortho*-benzylic scaffold and yielded the previously unknown azeto[2,1-*b*]quinazolines (Scheme 1).[4] Next we explored diastereoselective versions of this process by the appropriate combination of ketenimine fragments with homotopic or enantiotopic faces and imine fragments with homotopic, enantiotopic, or diastereotopic faces.



Scheme 1. Intramolecular [2+2] cycloaddition between ketenimine and imine functions.

Thus we have reported several types of diastereoselective syntheses of azeto[2,1-*b*]quinazolines bearing two stereogenic carbon atoms. Simple diastereoselection along the newly formed C1–C2 bond occurred with good to excellent levels of stereocontrol.[5] Further we disclosed the efficient asymmetric induction that a stereogenic benzylic carbon atom in the iminoketenimine (C8 in the final azeto-quinazoline) achieved on the new C1 stereocenter (1,3-induction),[6] as well as on the more distant C2 (1,4-induction).[7] In addition we have shown that the absolute configuration of C1 can be also controlled by a stereogenic center linked to the iminic carbon atom (C1′ in the final cycloadduct).[6]

In parallel with the experimental work we performed a computational study of these imine–ketenimine [2+2] cycloadditions in order to gain a detailed understanding of their mechanism.[5,6] This study showed that these reactions occur by stepwise mechanisms. In the first step, blank;the nitrogen lone pair of the imine adds to the sp-hybridized carbon atom of the ketenimine. The

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Keywords: [2+2] Cycloadditions; Ketenimines; Imines.

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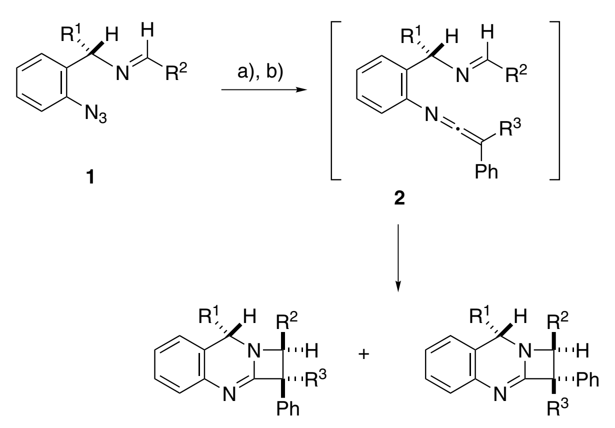
resulting zwitterionic intermediate undergoes, in a second step, a conrotatory ring closure to give the final [2+2] cycloadduct. In contrast with other stepwise [2+2] cycloadditions, such as the Staudinger reaction between ketenes and imines, in these reactions the step with the highest activation energy is the second one, corresponding to the formation of the C–C bond. Moreover, this mechanistic scheme was able to explain the degree and sense of the stereocontrol operating in the diastereoselective versions of these cycloadditions cited above.

Herein we describe the synthesis of racemic and nonracemic azeto[2,1-*b*]quinazolines bearing *three* stereogenic carbon atoms by means of a similar synthetic methodology, that is, the intramolecular keteniminе–imine [2+2] cycloaddition. It will be demonstrated that the absolute configuration of the stereogenic benzylic carbon in the substrate controls *simultaneously* that of the new stereocenters C1 and C2, in most of the cases with total efficiency as only one out of four possible diastereoisomers is obtained.

2. Results and discussion

Sequential treatment of readily available[6] azidoimines **1** with trimethylphosphane and the prochiral ketenes $Ph(CH_3)C{=}C{=}O$ or $Ph(CH_3CH_2)C{=}C{=}O$ provided iminoketenimines **2**, which bear a diastereotopic imine fragment and a ketenimine portion with a prostereogenic terminal carbon atom. Transient iminoketenimines **2** underwent the expected intramolecular formal [2+2] cycloaddition to give the azeto[2,1-*b*]quinazolines **3**, bearing three stereogenic carbon atoms C1, C2, and C8 (Scheme 2).

The study of the ^{1}H NMR spectra of each one of the final reaction mixtures before the purification step showed that when the imine fragment was derived from an aromatic, heteroaromatic, or α,β-unsaturated aldehyde (Table 1, entries **a**–**j**) the [2+2] cycloaddition of the corresponding iminoketenimine **2** led to a single diastereoisomer, which was identified as (1*S**,2*R**,8*S**)-1,2-*cis*-1,8-*trans*-**3** (see below). On the other hand, when the imine fragment was derived from isobutyraldehyde (Table 1, entries **k** and **l**) the reaction mixtures contained two diastereoisomeric azetoquinazolines, the corresponding (1*S**,2*R**,8*S**)-1,2-*cis*-1,8-*trans*-**3** and (1*S**,2*S**,8*S**)-1,2-*trans*-1,8-*trans*-**3**, in a ratio close to 3:2 as calculated by integration of the signals corresponding to *H*-C1, *H*-C8, and C*H*$_3$-C2 in the ^{1}H NMR spectra of the mixtures.



(1*S**,2*R**,8*S**)-1,2-*cis*-1,8-*trans*-**3** (1*S**,2*S**,8*S**)-1,2-*trans*-1,8-*trans*-**3**

Scheme 2. Reagents and conditions: (a) PMe_3, toluene, 25 °C, 30 min; (b) $PhR^3\ C{=}C{=}O$, toluene, 25 °C, 1 h.

Compounds **3** were obtained in moderate to good total yields after purification by column chromatography (Table 1), and characterized by their analytical and spectral data, which were essentially similar to those of the analogous structures previously reported.[4–7] In the reactions that yielded mixtures of diastereoisomers these were successfully separated by column chromatography.

The relative configuration of the three stereogenic centers (C1, C2, and C8) of compounds **3a**–**j** could be determined on the basis of nuclear Overhauser (NOE) experiments and *gate-decoupled* ^{13}C NMR spectra. For instance, irradiation of the signal at 5.11 ppm corresponding to the *H*-C1 proton in compound **3c** ($R^1 = CH_3$; $R^2 = 4\text{-}O_2N\text{–}C_6H_4$; $R^3 = CH_3$) induced a 10.9% and a 14.3% enhancement of the signals assigned to the protons of the C*H*$_3$-C8 and C*H*$_3$-C2 methyl groups, respectively. This result shows that those nuclei are on the same side of the mean molecular plane. Moreover, the gate-decoupled ^{13}C NMR spectrum of compound **3c** showed a $^3J(\mathrm{C,\ H}) = 3.7$ Hz coupling

Table 1. Azeto[2,1-*b*]quinazolines **3**

Compound	R^1	R^2	R^3	*cis–trans*-**3**:*trans–trans*-**3**	Yield (%)
a	CH_3	4-Cl–C_6H_4	CH_3	>98:2	48
b	CH_3	4-CH_3O–C_6H_4	CH_3	>98:2	76
c	CH_3	4-O_2N–C_6H_4	CH_3	>98:2	75
d	CH_3	2-Furyl	CH_3	>98:2	70
e	CH_3	(*E*)-2-O_2N–C_6H_4–CH=CH	CH_3	>98:2	80
f	CH_3	4-O_2N–C_6H_4	CH_3–CH_2	>98:2	77
g	CH_3	3-Thienyl	CH_3–CH_2	>98:2	80
h	CH_3	(*E*)-2-O_2N–C_6H_4–CH=CH	CH_3–CH_2	>98:2	85
i	C_6H_5	4-O_2N–C_6H_4	CH_3	>98:2	80
j	C_6H_5	2-Furyl	CH_3–CH_2	>98:2	72
k	CH_3	$(CH_3)_2CH$	CH_3	60:40	42
l	C_6H_5	$(CH_3)_2CH$	CH_3	58:42	66

constant between the CH_3 carbon atom linked to C2 and the *H*-C1 proton, which agrees with a 1,2-*cis* relative configuration.[5] The configurational assignment made above was proved by an X-ray structure determination of **3c**, which revealed that the hydrogen at C1 and the methyl groups at C2 and C8 present a relative *cis* disposition (Fig. 1). Similarly, the results of NOE experiments and the gate-decoupled ^{13}C NMR spectra of both isomers of compound **3k** [$R^1 = CH_3$; $R^2 = (CH_3)_2CH$; $R^3 = CH_3$] were in accord with a 1,2-*cis*-1,8-*trans* configuration of the major isomers of the azetoquinazolines **3k** and **3l**, and a 1,2-*trans*-1,8-*trans* configuration of the minor isomers. That is, both stereoisomers of compounds **3k**,**l** are epimers at the C2 carbon atom (Scheme 3).

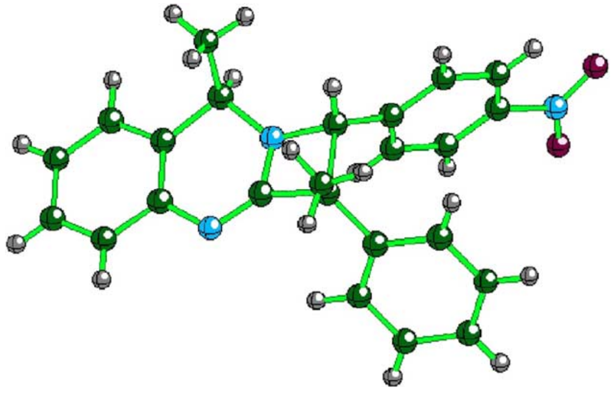
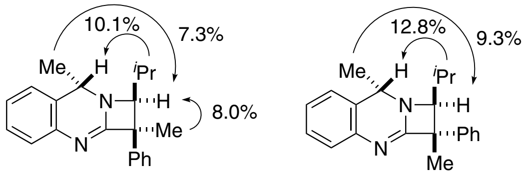


Figure 1. Ball and stick representation of the crystal structure of compound **3c**.



1,2-*cis*-1,8-*trans*-**3k**

^3J(C,H) = 4.3 Hz

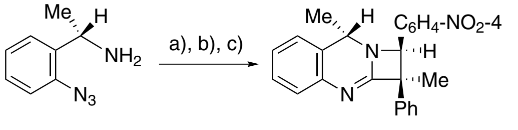
1,2-*trans*-1,8-*trans*-**3k**

^3J(C,H) = 0 Hz

Scheme 3. Configurational assignment of compounds 1,2-*cis*-1,8-*trans*-**3k** and 1,2-*trans*-1,8-*trans*-**3k**.

By utilizing the same synthetic methodology we prepared optically active **3c** $[\alpha]_D = +216.0$ (*c* 5×10^{-3}, CH_2Cl_2), starting from enantioenriched (*S*)-1-(2-azidophenyl)-ethylamine **4** (ee > 97%)[8] (Scheme 4).

Table 1 reveals the high degree of stereocontrol operating in the intramolecular cycloaddition of the iminoketenimines **2a**–**j**, yielding only one out of four possible diastereoisomers. For compounds **2k**,**l** in which the imino fragment derives from isobutyraldehyde, the cycloaddition took place with complete control of the configuration at the C1 carbon atom of the azetoquinazolines **3k**,**3l**, but the control over C2 was nearly null. This result is precedented by the low stereocontrol observed in examples of simple diastereoselection along the C1–C2 bond with imines derived from the same aldehyde.[5]

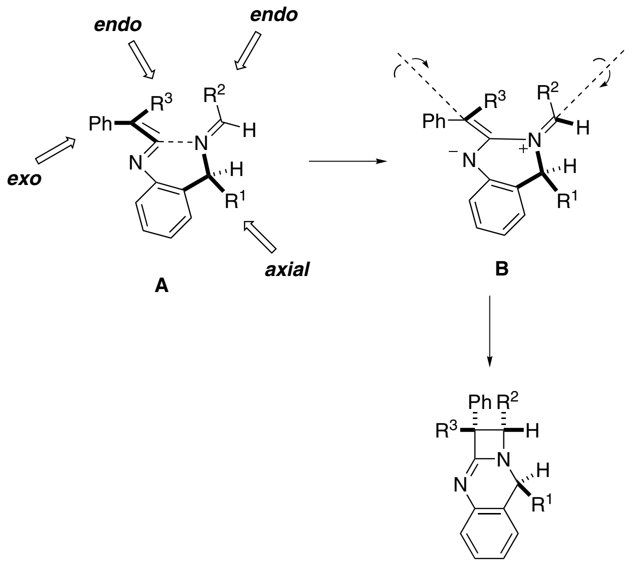


(*S*)-**4**

(1*S*,2*R*,8*S*)-**3c**

Scheme 4. Reagents and conditions: (a) 4-O_2N–C_6H_4–CHO, Et_2O, anhyd $MgSO_4$, 25 °C, 12 h; (b) PMe_3, toluene, 25 °C, 30 min; (c) PhMeC=C=O, toluene, 25 °C, 1 h.

The sense of the stereocontrol operating in the cycloaddition of compounds **2a**–**j** can be explained by our mechanistic model based on computational calculations.[5,6] In accordance with this model, the first step determines the stereochemical outcome of these processes. After analyzing in detail the four possible diastereoisomeric first transition structures one can easily infer that the one represented as **A** in Scheme 5 must be the most stable. The key features of the structure **A** are that the phenyl group on the ketenimine moiety occupies the *exo* position in preference to R^3, and that R^1 is *axial* leaving H in the more sterically congested equatorial position. The *endo* position of the substituent R^2 at the iminic carbon atom is due to the *E* geometry of the imines used as starting materials. Therefore, clockwise[9] conrotation of the zwitterionic intermediate **B**, resulting from transition structure **A**, leads to the formation of (1*S**,2*R**,8*S**)-1,2-*cis*-1,8-*trans*-**3** in full accordance with the experimental results.



1,2-*cis*-1,8-*trans*-**3**

Scheme 5. Mechanistic model for the formation of azeto[2,1-*b*]-quinazolines 1,2-*cis*-1,8-*trans*-**3** from ketenimines **2**.

In other words, the benzylic stereocenter determines the observed facial stereodifferentiation between the two preferred[5] *ul* approaches of the imine and ketenimine stereotopic faces, in favor of the $\mathit{Re}_{\text{imine}}$–$\mathit{Si}_{\text{ketenimine}}$ facial interaction. This stereodifferentiation relies on the 1,3-induction that the configuration of the benzylic carbon atom exerts over the new C1 stereocenter in the cycloadduct.[6]

3. Conclusion

In summary, this study on the intramolecular [2+2] cycloaddition between ketenimine and imine fragments placed on an *ortho*-benzylic scaffolding has provided a highly stereocontrolled preparation of azeto[2,1-*b*]quinazolines bearing three stereocenters, two of them formed during the cycloaddition process. To this end, we have combined ketenimine fragments derived from prochiral ketenes and imine fragments derived from chiral amines and achiral aldehydes. The stereochemical outcome at the two new stereocenters of the cycloadducts (C1 and C2) is controlled simultaneously by the stereogenic benzylic carbon adjacent to the imine nitrogen atom of the iminoketenimines, in spite of both stereocenters are not formed in the rate-determining mechanistic step.

4. Experimental

4.1. General methods

All melting point were determined on a Kofler hot-plate melting point apparatus and are uncorrected. IR spectra were obtained as Nujol emulsion or films on a Nicolet impact 400 spectrophotometer. NMR spectra were recorded on a Bruker AC-200 or on a Varian Unity-300. Mass spectra were recorded on a Hewlett–Packard 5993C spectrometer. Microanalyzes were performed on a Carlo Erba EA-1108 instrument.

4.2. Materials

N-(2-Azidobenzyl)imines **1**,[6] (*S*)-1-(2-azidophenyl)ethylamine **4**,[8] diphenyl ketene,[10] ethyl phenyl ketene,[11] and methyl phenyl ketene[12] were prepared following previously reported procedures.

4.2.1. General procedure for the preparation of azeto[2,1-*b*]quinazolines 3. Trimethylphosphane (3 mmol, 1 M toluene solution) was added to a solution of the corresponding azide **1** (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 ethyl phenyl ketene or methyl 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 (0.5–1 h). The solvent was removed under reduced pressure, and the resulting material was chromatographed on a silica gel column, with hexanes/ethyl acetate (4:1 v/v) as eluent.

4.2.2. (1*S,2*R**,8*S**)-1,2-*cis*-1,8-*trans*-1-(4-Chlorophenyl)-2,8-dimethyl-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline 3a.** Yield 48%; mp 176 °C; colorless prisms (diethyl ether). ^{1}H NMR (CDCl$_3$) δ: 1.45 (d, 3H, $J = 6.3$ Hz), 1.94 (s, 3H), 4.65 (q, 1H, $J = 6.3$ Hz), 4.96 (s, 1H), 6.92–6.99 (m, 3H), 7.02–7.12 (m, 8H), 7.23–7.26 (m, 2H). ^{13}C NMR (CDCl$_3$) δ: 21.6, 24.1, 48.6, 61.3 (s), 71.3, 124.6, 125.3, 126.9, 127.0, 127.2 (s), 127.3, 128.1, 128.4, 128.6, 128.7, 133.9 (s), 134.3 (s), 138.1 (s), 142.5 (s), 165.6 (s). MS *m*/*z* (I%): 374 (M$^+$+2, 29), 372 (M$^+$, 54), 217 (100). IR (Nujol) ν cm^{-1}: 1668 (N=C). Anal. Calcd for $C_{24}H_{21}ClN_2$: C, 77.30; H, 5.68; N, 7.51. Found: C, 77.39; H, 5.49; N, 7.73.

4.2.3. (1*S,2*R**,8*S**)-1,2-*cis*-1,8-*trans*-1-(4-Methoxyphenyl)-2,8-dimethyl-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline 3b.** Yield 76%. ^{1}H NMR (CDCl$_3$) δ: 1.44 (d, 3H, $J = 6.3$ Hz), 1.92 (s, 3H), 3.68 (s, 3H), 4.66 (q, 1H, $J = 6.3$ Hz), 4.97 (s, 1H), 6.64 (d, 2H, $J = 8.7$ Hz), 6.91–6.99 (m, 3H), 7.01–7.12 (m, 6H), 7.22–7.25 (m, 2H). ^{13}C NMR (CDCl$_3$) δ: 21.7, 24.2, 48.4, 55.2, 61.0 (s), 71.7, 113.5, 124.3, 125.0, 126.5, 126.9, 127.2 (s), 127.3, 127.5 (s), 127.8, 128.4, 128.6, 138.5 (s), 142.6 (s), 159.4 (s), 165.8 (s). MS *m*/*z* (I%): 368 (M$^+$, 37), 238 (100). IR (Nujol) ν cm^{-1}: 1665 (N=C). Anal. Calcd for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.56; N, 7.60. Found: C, 81.53; H, 6.49; N, 7.78.

4.2.4. (1*S,2*R**,8*S**)-1,2-*cis*-1,8-*trans*-2,8-Dimethyl-1-(4-nitrophenyl)-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline 3c.** Yield 75%; mp 143 °C; yellow prisms (diethyl ether). ^{1}H NMR (CDCl$_3$) δ: 1.48 (d, 3H, $J = 6.3$ Hz), 2.00 (s, 3H), 4.68 (q, 1H, $J = 6.3$ Hz), 5.11 (s, 1H), 6.96–7.13 (m, 8H), 7.21–7.28 (m, 3H), 7.97 (d, 2H, $J = 8.7$ Hz). ^{13}C NMR (CDCl$_3$) δ: 21.5, 23.5, 48.8, 61.8 (s), 70.7, 123.3, 124.8, 125.2, 126.9, 127.1, 127.9, 128.1, 128.6, 137.2 (s), 141.9 (s), 143.3 (s), 147.4 (s), 165.0 (s). MS *m*/*z* (I%): 383 (M$^+$, 56), 368 (100). IR (Nujol) ν cm^{-1}: 1668 (N=C), 1517, 1349. Anal. Calcd for $C_{24}H_{21}N_3O_2$: C, 75.17; H, 5.52; N, 10.96. Found: C, 75.01; H, 5.49; N, 10.80.

4.2.5. (1*R,2*R**,8*S**)-1,2-*cis*-1,8-*trans*-1-(2-Furyl)-2,8-dimethyl-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline 3d.** Yield 70%. ^{1}H NMR (CDCl$_3$) δ: 1.45 (d, 3H, $J = 6.3$ Hz), 1.91 (s, 3H), 4.71 (q, 1H, $J = 6.3$ Hz), 5.05 (s, 1H), 5.97 (d, 1H, $J = 3.2$ Hz), 6.12 (dd, 1H, $J = 1.8$, 3.2 Hz), 6.94 (d, 1H, $J = 7.3$ Hz), 7.03 (dd, 1H, $J = 4.3$, 8.6 Hz), 7.09–7.26 (m, 8H). ^{13}C NMR (CDCl$_3$) δ: 21.6, 24.1, 48.5, 61.1 (s), 65.6, 108.9, 110.5, 124.5, 125.2, 126.6, 126.8, 127.2 (s), 127.9, 128.5, 138.9 (s), 142.4 (s), 142.6, 149.7 (s), 165.2 (s). MS *m*/*z* (I%): 328 (M$^+$, 67), 313 (100). IR (Nujol) ν cm^{-1}: 1679 (N=C). Anal. Calcd for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53. Found: C, 80.29; H, 6.03; N, 8.74.

4.2.6. (1*S,2*R**,8*S**)-1,2-*cis*-1,8-*trans*-2,8-Dimethyl-1-[(*E*)-2-(2-nitrophenyl)ethenyl]-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline 3e.** Yield 80%; mp 133 °C; colorless prisms (diethyl ether). ^{1}H NMR (CDCl$_3$) δ: 1.52 (d, 3H,

$J = 6.2$ Hz), 1.92 (s, 3H), 4.61 (d, 1H, $J = 7.9$ Hz), 4.79 (q, 1H, $J = 6.2$ Hz), 5.53 (dd, 1H, $J = 7.9$, 15.6 Hz), 6.88–7.08 (m, 3H), 7.10 (d, 1H, $J = 15.6$ Hz), 7.17–7.45 (m, 9H), 7.93 (dd, 1H, $J = 1.7$, 7.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 21.8, 23.5, 48.9, 59.8 (s), 69.9, 124.5, 124.6, 125.1, 126.9, 127.2, 127.3, 128.5, 128.6, 129.1, 129.7, 131.6, 132.3 (s), 133.4, 138.6 (s), 142.5 (s), 147.5 (s), 165.1 (s). MS *m/z* (I%): 409 (M^+, 40), 394 (100). IR (Nujol) ν cm^{-1}: 1668 (N=C), 1521, 1343. Anal. Calcd for $C_{26}H_{23}N_3O_2$: C, 76.26; H, 5.66; N, 10.26. Found: C, 76.32; H, 5.43; N, 10.40.

4.2.7. (1*S,2*R**,8*S**)-1,2-*cis*-1,8-*trans*-2-Ethyl-8-methyl-1-(4-nitrophenyl)-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline 3f.** Yield 77%; mp 146 °C; yellow prisms (diethyl ether). ^{1}H NMR ($CDCl_3$) δ: 1.18 (t, 3H, $J = 7.3$ Hz), 1.48 (d, 3H, $J = 6.3$ Hz), 2.36 (q, 2H, $J = 7.3$ Hz), 4.65 (q, 1H, $J = 6.3$ Hz), 5.16 (s, 1H), 6.95 (d, 1H, $J = 7.2$ Hz), 7.00–7.11 (m, 6H), 7.20 (d, 2H, $J = 8.7$ Hz), 7.22–7.28 (m, 2H), 7.97 (d, 2H, $J = 8.7$ Hz). ^{13}C NMR ($CDCl_3$) δ: 10.1, 21.9, 31.0, 48.7, 66.8 (s), 68.5, 123.4, 124.7, 125.5, 126.9 (s), 127.0, 127.1, 127.5, 128.2, 128.3, 128.8, 136.4 (s), 142.2 (s), 143.5 (s), 147.6 (s), 164.1 (s). MS *m/z* (I%): 397 (M^+, 84), 382 (100). IR (Nujol) ν cm^{-1}: 1662 (N=C), 1523, 1346. Anal. Calcd for $C_{25}H_{23}N_3O_2$: C, 75.54; H, 5.83; N, 10.57. Found: C, 75.35; H, 5.69; N, 10.40.

4.2.8. (1*R,2*R**,8*S**)-1,2-*cis*-1,8-*trans*-2-Ethyl-8-methyl-2-phenyl-1-(3-thienyl)-1,2-dihydroazeto[2,1-*b*]quinazoline 3g.** Yield 80%. ^{1}H NMR ($CDCl_3$) δ: 1.14 (t, 3H, $J = 7.3$ Hz), 1.44 (d, 3H, $J = 6.3$ Hz), 2.26 (q, 2H, $J = 7.3$ Hz), 4.65 (q, 1H, $J = 6.3$ Hz), 5.17 (s, 1H), 6.56 (dd, 1H, $J = 2.0$, 4.3 Hz), 6.91 (d, 1H, $J = 8.3$ Hz), 6.99–7.19 (m, 8H), 7.22–7.28 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 10.1, 22.1, 31.3, 48.3, 65.3, 65.6 (s), 123.5, 124.3, 125.3, 125.7, 126.6, 126.8, 126.9, 127.2 (s), 127.5, 127.8, 128.4, 137.8 (s), 137.9 (s), 142.8 (s), 164.6 (s). MS *m/z* (I%): 358 (M^+, 96), 343 (100). IR (Nujol) ν cm^{-1}: 1669 (N=C). Anal. Calcd for $C_{23}H_{22}N_2S$: C, 77.06; H, 6.19; N, 7.81. Found: C, 76.88; H, 6.33; N, 7.59.

4.2.9. (1*S,2*R**,8*S**)-1,2-*cis*-1,8-*trans*-2-Ethyl-8-methyl-1-[(*E*)-2-(2-nitrophenyl)ethenyl]-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline 3h.** Yield 85%. ^{1}H NMR ($CDCl_3$) δ: 1.15 (t, 3H, $J = 7.3$ Hz), 1.52 (d, 3H, $J = 6.3$ Hz), 2.27 (q, 2H, $J = 7.3$ Hz), 4.68 (d, 1H, $J = 8.3$ Hz), 4.76 (q, 1H, $J = 6.3$ Hz), 5.28 (s, 1H), 5.55 (dd, 1H, $J = 8.3$, 15.6 Hz), 6.91–7.05 (m, 4H), 7.10 (d, 1H, $J = 15.6$ Hz), 7.21–7.47 (m, 7H), 7.93 (dd, 1H, $J = 1.7$, 7.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 9.8, 22.1, 30.8, 48.7, 64.5 (s), 67.5, 124.3, 124.6, 125.2, 126.7, 127.0 (s), 127.1, 127.8, 128.4, 128.5, 129.1, 129.7, 131.8, 132.3 (s), 133.4, 137.7 (s), 142.6 (s), 147.5 (s), 163.9 (s). MS *m/z* (I%): 423 (M^+, 55), 408 (100). IR (Nujol) ν cm^{-1}: 1667 (N=C), 1521, 1345. Anal. Calcd for $C_{27}H_{25}N_3O_2$: C, 76.57; H, 5.95; N, 9.92. Found: C, 76.33; H, 5.74; N, 9.80.

4.2.10. (1*S,2*R**,8*S**)-1,2-*cis*-1,8-*trans*-2-Methyl-1-(4-nitrophenyl)-2,8-diphenyl-1,2-dihydroazeto[2,1-*b*]quinazoline 3i.** Yield 80%; mp 146 °C; yellow prisms (diethyl ether). ^{1}H NMR ($CDCl_3$) δ: 1.84 (s, 3H), 4.49 (s, 1H), 5.52 (s, 1H), 6.85 (d, 1H, $J = 7.6$ Hz), 7.00–7.18 (m, 10H), 7.26–7.37 (m, 5H), 7.95 (d, 2H, $J = 8.6$ Hz). ^{13}C NMR ($CDCl_3$) δ: 23.0, 58.1, 62.0 (s), 70.9, 123.4, 125.1, 125.2 (s), 125.8, 127.0, 127.2, 127.8, 128.0, 128.2, 128.5, 128.6, 128.9, 129.2, 137.4 (s), 140.5 (s), 142.1 (s), 143.3 (s), 147.5 (s), 164.6 (s). MS *m/z* (I%): 445 (M^+, 100). IR (Nujol) ν cm^{-1}: 1661 (N=C), 1523, 1352. Anal. Calcd for $C_{29}H_{23}N_3O_2$: C, 78.18; H, 5.20; N, 9.43. Found: C, 78.37; H, 5.39; N, 9.35.

4.2.11. (1*R,2*R**,8*S**)-1,2-*cis*-1,8-*trans*-2-Ethyl-1-(2-furyl)-2,8-diphenyl-1,2-dihydroazeto[2,1-*b*]quinazoline 3j.** Yield 72%. ^{1}H NMR ($CDCl_3$) δ: 0.99 (t, 3H, $J = 7.3$ Hz), 2.12 (qd, 2H, $J = 2.6$, 7.3 Hz), 4.58 (s, 1H), 5.57 (s, 1H), 5.98 (d, 1H, $J = 3.1$ Hz), 6.13 (dd, 1H, $J = 1.8$, 3.1 Hz), 6.76 (d, 1H, $J = 6.8$ Hz), 6.96 (td, 1H, $J = 1.3$, 7.3 Hz), 7.10–7.27 (m, 9H), 7.30–7.37 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 9.9, 31.0, 57.6, 65.6, 66.0 (s), 109.4, 110.5, 124.6, 125.2 (s), 125.6, 126.7, 127.1, 127.9, 128.3, 128.5, 128.7, 129.0, 137.9 (s), 141.2 (s), 142.6, 142.7 (s), 149.5 (s), 163.8 (s). MS *m/z* (I%): 404 (M^+, 95), 375 (100). IR (Nujol) ν cm^{-1}: 1665 (N=C). Anal. Calcd for $C_{28}H_{24}N_2O$: C, 83.14; H, 5.98; N, 6.93. Found: C, 83.32; H, 5.79; N, 6.81.

4.2.12. (1*S,2*R**,8*S**)-1,2-*cis*-1,8-*trans*-1-Isopropyl-2,8-dimethyl-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline 3k.** Yield 26%. ^{1}H NMR ($CDCl_3$) δ: 0.57 (d, 3H, $J = 6.6$ Hz), 0.91 (d, 3H, $J = 6.6$ Hz), 1.45 (d, 3H, $J = 6.4$ Hz), 1.46–1.66 (m, 1H), 1.85 (s, 3H), 3.53 (d, 1H, $J = 9.6$ Hz), 4.76 (q, 1H, $J = 6.4$ Hz), 6.94–7.41 (m, 9H). ^{13}C NMR ($CDCl_3$) δ: 18.7, 19.8, 21.1, 21.2, 30.1, 51.5, 55.6 (s), 75.8, 124.3, 124.7, 126.7, 127.2, 127.4 (s), 127.8, 128.1, 128.3, 137.9 (s), 142.2 (s), 167.1 (s). MS *m/z* (I%): 304 (M+, 9), 77 (100). IR (Nujol) ν cm^{-1}: 1665 (N=C). Anal. Calcd for $C_{21}H_{24}N_2$: C, 82.85; H, 7.94; N, 9.20. Found: C, 82.74; H, 8.11; N, 9.12.

4.2.13. (1*S,2*S**,8*S**)-1,2-*trans*-1,8-*trans*-1-Isopropyl-2,8-dimethyl-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline 3k.** Yield 16%. ^{1}H NMR ($CDCl_3$) δ: 1.05 (d, 3H, $J = 6.5$ Hz), 1.11 (d, 3H, $J = 6.5$ Hz), 1.37 (d, 3H, $J = 6.3$ Hz), 1.71 (s, 3H), 2.03–2.27 (m, 1H), 3.71 (d, 1H, $J = 10.3$ Hz), 4.77 (q, 1H, $J = 6.3$ Hz), 6.87–7.00 (m, 2H), 7.15–7.38 (m, 5H), 7.54–7.58 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 19.6, 20.1, 20.8, 21.9, 30.7, 51.4, 55.6 (s), 74.5, 124.1, 124.7, 126.4, 126.7, 127.0, 127.3 (s), 128.4, 128.7, 142.3 (s), 167.0 (s). MS *m/z* (I%): 304 (M^+, 29), 77 (100). IR (Nujol) ν cm^{-1}: 1662 (N=C). Anal. Calcd for $C_{21}H_{24}N_2$: C, 82.85; H, 7.94; N, 9.20. Found: C, 82.79; H, 7.79; N, 9.38.

4.2.14. (1*S,2*R**,8*S**)-1,2-*cis*-1,8-*trans*-1-Isopropyl-2-methyl-2,8-diphenyl-1,2-dihydroazeto[2,1-*b*]quinazoline 3l.** Yield 36%. ^{1}H NMR ($CDCl_3$) δ: 0.43 (d, 3H,

$J = 6.6$ Hz), 0.87 (d, 3H, $J = 6.7$ Hz), 1.49–1.60 (m, 1H), 1.72 (s, 3H), 3.04 (d, 1H, $J = 9.6$ Hz), 5.60 (s, 1H), 6.80 (d, 1H, $J = 7.7$ Hz), 6.95 (td, 1H, $J = 2.2$, 7.6 Hz), 7.15–7.42 (m, 12H). ^{13}C NMR (CDCl$_3$) δ: 18.6, 20.4, 21.4, 29.9, 56.0 (s), 60.6, 76.0, 124.6, 125.4, 126.0 (s), 126.6, 127.3, 127.8, 128.0, 128.2, 128.3, 128.6, 129.0, 138.1 (s), 141.4 (s), 142.2 (s), 166.5 (s). MS m/z (I%): 366 (M$^+$, 100). IR (Nujol) ν cm^{-1}: 1665 (N=C). Anal. Calcd for $C_{26}H_{26}N_2$: C, 85.21; H, 7.15; N, 7.64. Found: C, 85.13; H, 7.36; N, 7.51.

4.2.15. (1*S,2*S**,8*S**)-1,2-*trans*-1,8-*trans*-1-Isopropyl-2-methyl-2,8-diphenyl-1,2-dihydroazeto[2,1-*b*]quinazoline 3l.** Yield 30%. ^{1}H NMR (CDCl$_3$) δ: 0.95 (d, 3H, $J = 6.5$ Hz), 1.06 (d, 3H, $J = 6.6$ Hz), 1.74 (s, 3H), 2.17–2.32 (m, 1H), 3.38 (d, 1H, $J = 10.3$ Hz), 5.65 (s, 1H), 6.77 (d, 1H, $J = 7.3$ Hz), 6.92 (td, 1H, $J = 1.6$, 7.4 Hz), 7.50–7.55 (m, 12H). ^{13}C NMR (CDCl$_3$) δ: 20.1, 20.6, 21.3, 30.4, 56.2 (s), 60.5, 74.2, 124.4, 125.3, 125.9 (s), 126.6, 126.9, 127.7, 128.2, 128.5, 128.6, 128.8, 141.6 (s), 142.0 (s), 142.2 (s), 166.5 (s). MS m/z (I%): 366 (M$^+$, 89), 77 (100). IR (Nujol) ν cm^{-1}: 1668 (N=C). Anal. Calcd for $C_{26}H_{26}N_2$: C, 85.21; H, 7.15; N, 7.64. Found: C, 85.36; H, 7.06; N, 7.58.

4.3. X-ray diffraction study

Crystallographic data for the structure **3c** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 222577. Copies of the data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk).

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