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Nitrilimine cycloaddition onto 2-azetidinones bearing alkenyl dipolarophile(s)

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Abstract—Silver acetate-promoted nitrilimines cycloaddition onto 3(*R**)-phenyl-4(*R**)-cinnamoyl-2-azetidinone **1** were highly stereoselective giving 4-(4,5-dihydropyrazol-5-yl) carbonyl-2-azetidinones **5** as the major products and regioisomeric 4-(4,5-dihydropyrazol-4-yl) carbonyl-2-azetidinones **6** as the minor one. When the same protocol was applied to the novel 3(*R**)-phenyl-4(*S**)-(4-benzoyl-*E*,*E*-1,3-butadienyl)-2-azetidinone **2** it resulted in site- and regioselective but not stereoselective cycloaddition, involving the formation of the four cycloadducts **10**–**13**.

1. Introduction

Since the discovery of penicillin in 1928, 2-azetidinone-based heterocycles have become one of the most widely used class of drugs for the systematic treatment of bacterial infections.[1] Due to their relevance in both clinic and economic fields, variously substituted 2-azetidinones represent a very attractive target for contemporary organic synthesis.[2] As a result, considerable efforts have been concerned with the design of new β-lactam antibiotics which cover a wide spectrum of antibacterial activity.[3] This scenario was further substantiated by the discovery that β-lactamases caused resistance against some penicillins and cephalosporins, thus stimulating the search for new drugs which should display enhanced stability towards the β-lactamases.[4] In a recent communication,[5] we presented the first stereoselective synthesis of a 4-(4,5-dihydropyrazol-5-yl)carbonyl-2-azetidinone and the regioisomeric 4-(4,5-dihydropyrazol-4-yl)carbonyl-2-azetidinone. We were intrigued by the chance to incorporate in the same molecule the 2-azetidinone and the pyrazole rings, the latter being found in several compounds which display biological activity as antinflammatory[6] and anti-coagulating[7] factors. As a good way to bring together the above-mentioned fragments we exploited nitrilimine 1,3-dipolar cycloaddition onto the 2-azetidinone bearing an ethylenic dipolarophile bond. To gain better insight about the site-, regio- and stereoselectivity outcome of this methodology, we decided to investigate further the behaviour of 3(*R**)-phenyl-4(*R**)-cinnamoyl-2-azetidinone **1**[5] towards nitrilimines and to undertake the study of the novel 3(*R**)-phenyl-4(*S**)-(4-benzoyl-*E*,*E*-1,3-butadienyl)-2-azetidinone **2** as dipolarophile (Fig. 1).

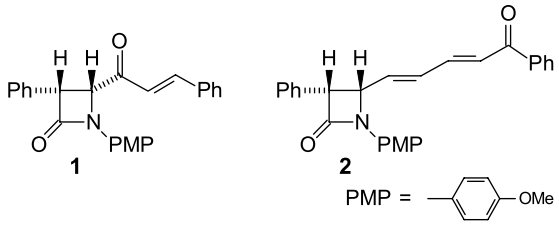

Figure 1.

2. Results and discussion

2.1. Nitrilimine cycloadditions to 3(*R**)-phenyl-4(*R**)-cinnamoyl-2-azetidinone 1

The generation of nitrilimine intermediate **4** was accomplished in situ by treatment of the corresponding hydrazonoyl chloride **3**[8] with an equimolecular amount of silver acetate in dry dioxane at room temperature in the presence of **1**[5]. Besides the recovery of some quantity of unreacted **1**, regioisomeric cycloadducts (4*R**,5′*S**)-**5** and (4*R**,4′*R**)-**6** were obtained (Scheme 1). Reaction times, overall product yields and regioisomeric ratio data are summarised in Table 1. Product separation was achieved by simple silica

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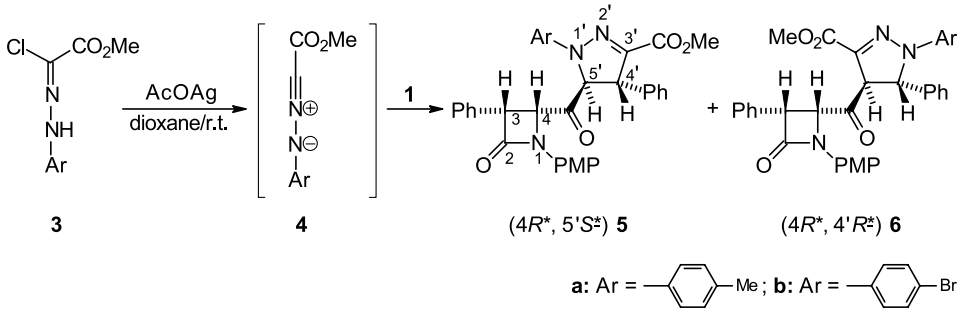


Scheme 1.

Table 1. Cycloadditions between hydrazonoyl chlorides **3** and azetidinone **1**

Reactant	Time (h)	Product and yields (%)[a]			Product ratio[b]
		1	**5**	**6**	**5**:**6**
3a	30	15	56	14	80:20
3b	100	5	71	14	83:17

[a] Isolation yields.
[b] Deduced from ^{1}H NMR analysis of reaction crudes.

gel column chromatography, while analytical and spectroscopic data of the cycloadducts are in full agreement with the structures depicted. As far as cycloaddition regiochemistry is concerned, it reflects that observed in the reaction between nitrilimines and α,β-unsaturated carbonyls.[9] On the other hand, the stereochemical outcome of the cycloaddition deserves some comments. Both major product (4*R**,5′*S**)-**5** and minor product (4*R**,4′*R**)-**6** were detected as single stereoisomers thus making the cycloaddition fully stereoselective. This fact can be understood by close inspection of Dreiding stereomodels of **1**, which clearly shows that the phenyl ring in the 3-position of the 2-azetidinone moiety effectively hinders one of the two diastereofaces of the alkenyl dipolarophile. It needs to be added that the relative configurations of the newly-formed stereocentres of major **5** and minor **6** is dependent upon the conformation of **1**. In our preceding paper[5] we assumed that the free interchange between the four possible conformations of the cinnamoyl fragment in the 4-position of the 2-azetidinone ring of **1** is precluded by severe steric repulsion (Fig. 2), and we concluded that only the *syn* s-*cis* conformation should be the reasonable candidate describing the ground state conformation of **1**. Here, these assumptions find confirmation on the grounds of diffractometric analysis of the novel major cycloadduct (4*R**,5′*S**)-**5b** (Fig. 3).[10]

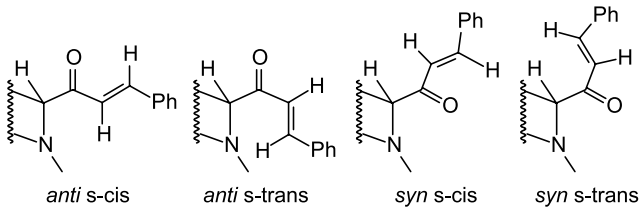


Figure 2.

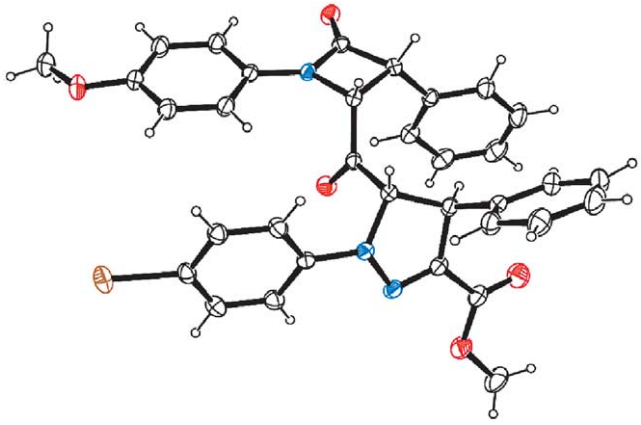
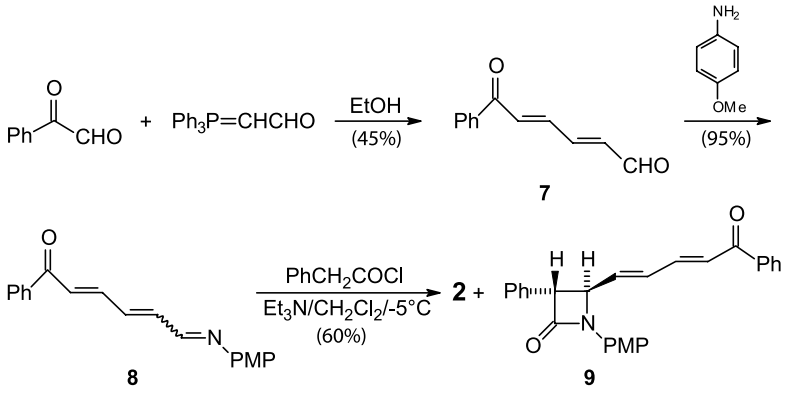


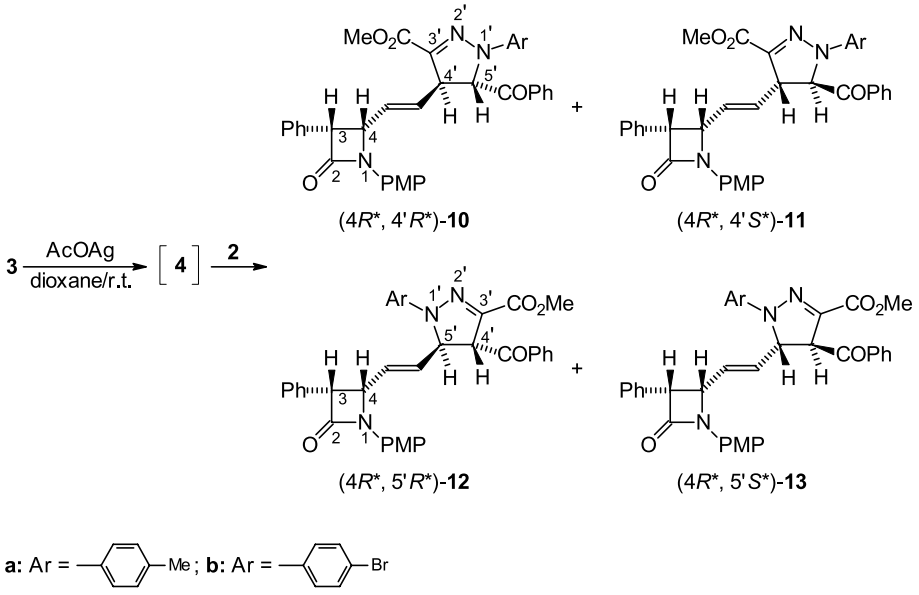
Figure 3. ORTEP plot of (4*R**,5′*S**)-**5b**. Ellipsoid at 20% of probability level; H atoms not to scale. Black=C,H; red=O; blue=N; brown=Br.

2.2. Nitrilimine cycloadditions to 3(*R**)-phenyl-4(*S**)-(4-benzoyl-*E*,*E*-1,3-butadienyl)-2-azetidinone 2

In order to obtain the 2-azetidinone derivative **2**, we followed the three-step synthetic sequence outlined in the Scheme 2. First, phenylglyoxal was submitted to Wittig reaction in the presence of (triphenylphosphoranylidene)-acetaldehyde. The resulting dienal **7**, which was obtained as the only isolable product, was readily converted to the imine derivative **8** which was then reacted with phenylacetyl chloride in the presence of triethylamine, thus following the Staudinger [2+2] cycloaddition protocol. Compound **2** was obtained as the major one (48%) and isolated in the analytically pure state after chromatographic separation from isomeric 3,4-*trans* **9** (12%). Next, 2-azetidinone **2** was treated with hydrazonoyl chlorides **3** as described before with **1**. Since both of the conjugated olefins of **2** are suitable position for dipolar attack, which can proceed with two opposite orientations, both site-, regio- and stereoselectivity phenomena can be involved in their cycloadditions. In fact,



Scheme 2.



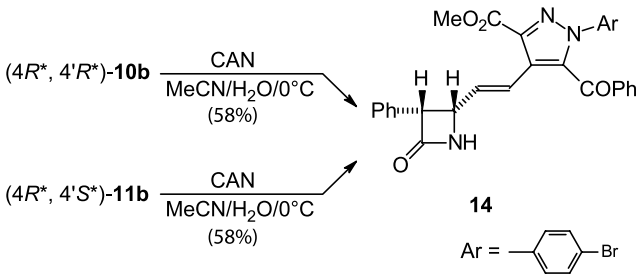
Scheme 3.

Table 2. Cycloadditions between hydrazonoyl chlorides **6** and azetidinone **2**

Reactant	Time (h)	Product and yields (%)[a]				Product ratio[b]
		10	**11**	**12**	**13**	**10**:**11**:**12**:**13**
6a	48	31	31	13	13	35:35:15:15
6b	190	25	25	9	9	37:37:13:13

[a] Isolation yields.
[b] Deduced from ^{1}H NMR analysis of reaction crudes.

1,3-dipolar cycloaddition of nitrilimine **4** gave a complex mixture of the four cycloadducts **10**–**13** (Scheme 3). Reaction times, product yields and product ratio data are given in Table 2. Structural assignment of cycloadducts **10**–**13** was somewhat laborious. ^{1}H NMR spectroscopy of crude reaction products showed the disappearance of the signal due to the α-hydrogen to the benzoyl group of **2**, which resonates as a doublet at 6.91 δ. This indicates that only the activated alkenyl dipolarophile of **2** is involved in cycloaddition, thus making the process fully site-selective. To this point, due to the stereoconservativity typical of 1,3-dipolar cycloadditions, it is possible envisage the formation of up to four regio- and stereoisomeric cycloadducts. After laborious chromatographic separation, the two major products **10b** and **11b** were isolated in the pure state. The latter products were submitted to oxidation with cerium (IV) ammonium nitrate giving the same pyrazole derivative, namely *E*-1-(azetidin-4-yl)-2-(pyrazol-4-yl)-ethylene **14** (Scheme 4). Following this chemical correlation experiment, it can be argued that: (i) major cycloadducts **10** and **11** must be stereoisomers, and (ii) minor cycloadducts **12** and **13** also must be stereoisomers and regioisomeric with



Scheme 4.

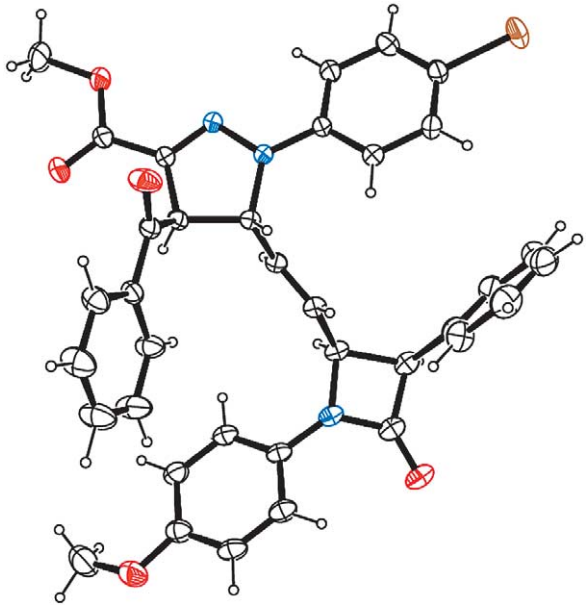


Figure 4. ORTEP plot of (4*R**,5′*R**)-**12b**. Ellipsoid at 20% of probability level; H atoms not to scale. Black = C,H; red = O; blue = N; brown = Br.

respect to **10** and **11**. Slow evaporation of a chloroformic solution of **12b** gave crystals suitable for X-ray diffractometric analysis (Fig. 4)[10] thus enabling us to the unequivocal assignment of structures (4*R**,5′*R**)-**12** and (4*R**,5′*S**)-**13** to the two minor cycloadducts. Structural assignment of major **10** and **11** rely upon NOE experiment. As can be seen from Figure 5, NOE enhancements between H_A–H_B and H_C–H_D occurs in the case of (4*R**,4′*R**)-**10b**, while (4*R**,4′*S**)-**11b** did not show any NOE enhancement. This picture is consistent with the ground state conformations of both major cycloadducts optimised at the AM1[11]

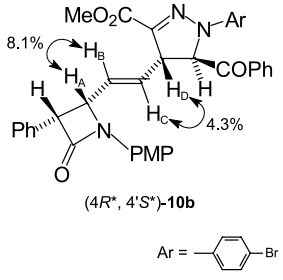


Figure 5.

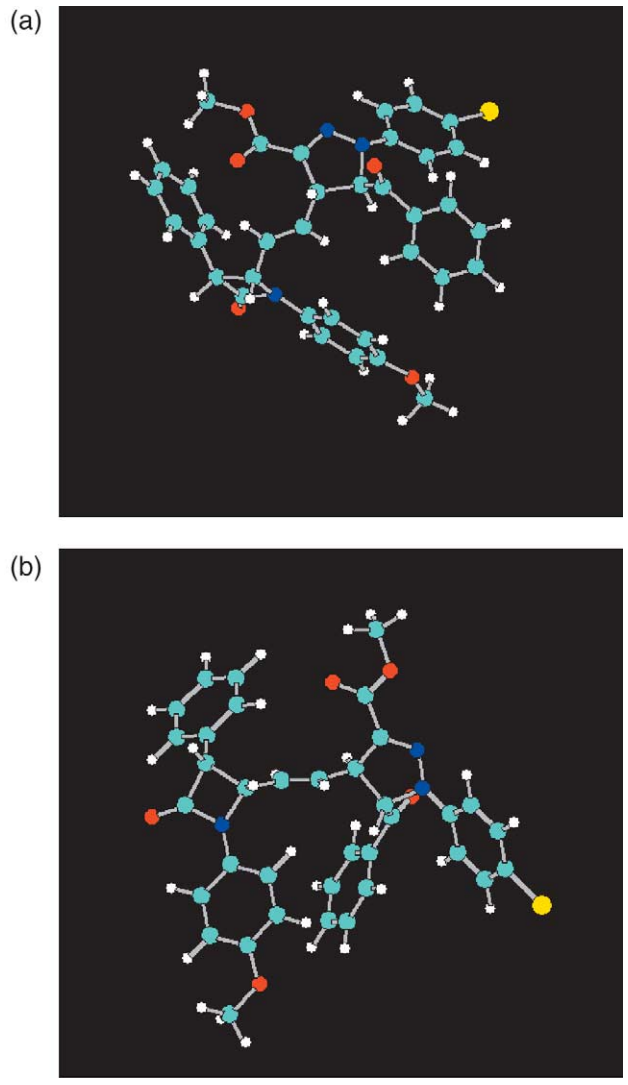


Figure 6. AM1 optimised ground state conformations of the two major cycloadducts: (a) (4*R**,4′*R**)-**10b**; (b) (4*R**,4′*S**)-**11b**.

Table 3. AM1 computed distances H_A–H_B, H_C–H_D of major cycloadducts (4*R**,4′*R**)-**10b** and (4*R**,4′*S**)-**11b**

Product	Distance (Å)	
	H_A–H_B	H_C–H_D
(4*R**,4′*R**)-**10b**	2.56	2.87
(4*R**,4′*S**)-**11b**	3.12	3.13

level (Fig. 6),[12] while H_A–H_B and H_C–H_D computed distances are given in Table 3. As can be inferred from Table 2, nitrilimine cycloaddition to 4-butadienyl-2-azetidinone **2** occurs with a moderate degree of regioselectivity but was not stereoselective. A comparison with the behaviour of 4-cinnamoyl-2-azetidinone **1** suggest that the distance between the reactive dipolarophile and the 2-azetidinone core is critical in determining cycloaddition stereoselectivity. The phenyl ring in the 3-position of the 2-azetidinone ring of **2** cannot hinder one of the two diastereofaces of the outer alkenyl dipolarophile thus causing the lack of stereoselectivity.

3. Conclusions

The site-, regio- and stereoselectivity involved in nitrilimine 1,3-dipolar cycloaddition to highly-functionalised 2-azetidinones have been studied. Although regioselectivities obeys the known rules dictated from FMO theory, stereoselectivies depend upon the length of the tether joining the reactive dipolarophile to the 2-azetidinone core.

4. Experimental

4.1. General

Melting points were determined with a Büchi apparatus in open tubes and are uncorrected. IR spectra were recorded with a Perkin–Elmer 1725× spectrophotometer. Mass spectra were determined with a VG-70EQ apparatus. ^{1}H NMR (300 MHz) spectra were taken with a Bruker AC 300 or a Bruker AMX 300 instrument (in $CDCl_3$ solutions at room temperature). Chemical shifts are given as ppm from tetramethylsilane and *J* values are given in Hz. The NOESY experiments were acquired with 1024 data points for 512 increments, without zero-filling. A relaxation delay (d1) of 2 s and a mixing time (d8) of 800 ms (compound **10b**) or 700 ms (compound **11b**) was used.

4.1.1. 6-Oxo-6-phenyl-hexa-2,4-*E*,*E*-dien-1-al 7. A suspension of methyltriphenylphosphonium chloride (3.64 g, 10.7 mmol) in ethanol (16 mL) was warmed to 50 °C to obtain a clear solution. Triethylamine (1.23 g, 12.2 mmol) was added and the resulting dark solution was warmed to 50 °C for 0.5 h. The mixture was added dropwise to a stirred solution of phenylglyoxal monohydrate (0.74 g, 4.9 mmol) in ethanol (16 mL) under nitrogen athmosphere and then warmed to 70 °C for 1.5 h. The reaction was monitored by TLC (eluent: dichloromethane/ethyl acetate 95:5). Brine (20 mL) was added and the resulting mixture was extracted with dichloromethane (4×20 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure giving 6-oxo-6-phenyl-hexa-2,4-*E*,*E*-dien-1-al **7** (0.41 g, 45%) as pale yellow powder, mp 86 °C (from diisopropyl ether). IR (nujol) 1690, 1660, 1615 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.51 (1H, dd, J=15.3, 7.7 Hz), 7.32 (1H, dd, J=15.3, 7.9 Hz), 7.37 (1H, d, J=15.0 Hz), 7.51 (1H, dd, J=15.0, 7.9 Hz), 7.5–7.8 (5H, m), 9.72 (1H, d, J=7.7 Hz); MS *m*/*z* 186 (M^+). Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.46; H, 5.46.

4.1.2. *N*-(4-Methoxyphenyl)-1-(5-oxo-5-phenyl-penta-1,3-*E*,*E*-dienyl)methanimine 8. A solution of 4-methoxyaniline (0.30 g, 2.5 mmol) in ethanol (0.75 mL) was added dropwise to **7** (0.46 g, 2.5 mmol) in ethanol (5.0 mL). The mixture was stirred at room temperature for 5 min and the solid material was filtered off giving **8** as yellow powder, mp 108 °C (from ethanol). IR (nujol) 1650, 1590, 1560 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.86 (3H, s), 6.9–7.1 (4H, m), 7.21 (1H, d, J=14.6 Hz), 7.25–7.60 (8H, m), 8.30 (1H, d, J=8.1 Hz); MS *m*/*z* 291 (M^+). Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.32; H, 5.88; N, 4.81. Found: C, 78.27; H, 5.84; N, 4.75.

4.1.3. 3(*R)-Phenyl-4(*S**)-(4-benzoyl-*E*,*E*−1,3-butadienyl)-2-azetidinone 2 and 3(*R**)-phenyl-4(*R**)-(4-benzoyl-*E*,*E*-1,3-butadienyl)-2-azetidinone 9.** A solution of **8** (0.40 g, 1.4 mmol) and triethylamine (0.61 g, 6.0 mmol) in dry dichloromethane (25 mL) was cooled to −5 °C. Phenylacetyl chloride (0.70 g, 4.5 mmol) in dry dichloromethane (13 mL) was added under nitrogen athmosphere and the resulting mixture was stirred and cooled to 0 °C for 1 h, then at room temperature for 6 h. The reaction was monitored by TLC (eluent: dichloromethane/ethyl acetate 95:5). Brine (20 mL) was added and the resulting mixture was extracted with dichloromethane (2×20 mL). The organic layer was washed with water, dried over sodium sulfate and evaporated under reduced pressure giving a solid. The residue was chromatographed on a silica gel column with *t*-butylmethyl ether/light petroleum 3:2. First fractions gave 3,4-*cis* **2**, further elution gave isomeric 3,4-*trans* **9**.

Compound **2**. (0.27 g, 48%). IR (nujol) 1745, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.80 (3H, s), 4.86 (1H, d, J=6.0 Hz), 4.93 (1H, dd, J=7.5, 6.0 Hz), 5.81 (1H, dd, J=15.2, 7.5 Hz), 6.55 (1H, dd, J=15.2, 10.7 Hz), 6.8–6.9 (2H, m), 6.92 (1H, d, J=15.0 Hz), 7.14 (1H, dd, J=15.0, 10.7 Hz), 7.4–7.9 (12H, m); MS *m*/*z* 409 (M^+). Anal. Calcd for $C_{27}H_{23}NO_3$: C, 79.19; H, 5.66; N, 3.42. Found: C, 79.15; H, 5.63; N, 3.38.

Compound **9**. (70 mg, 12%). IR (nujol) 1745, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.79 (3H, s), 4.26 (1H, d, J=2.5 Hz), 4.54 (1H, dd, J=7.7, 2.5 Hz), 6.42 (1H, dd, J=15.2, 7.7 Hz), 6.69 (1H, dd, J=15.2, 10.8 Hz), 6.8–6.9 (4H, m), 7.03 (1H, d, J=15.0 Hz), 7.32 (1H, dd, J=15.0, 10.8 Hz), 7.40–7.95 (10H, m); MS *m*/*z* 409 (M^+). Anal. Calcd for $C_{27}H_{23}NO_3$: C, 79.19; H, 5.66; N, 3.42. Found: C, 79.26; H, 5.70; N, 3.47.

4.1.4. Nitrilimine cycloadditions to 3(*R)-phenyl-4(*R**)-cinnamoyl-2-azetidinone 1 and 3(*R**)-phenyl-4(*S**)-(4-benzoyl-*E*,*E*-1,3-butadienyl)-2-azetidinone 2.** To a solution of **1**[5] or **2** (1.0 mmol) and the appropriate hydrazonoyl chloride **3** (2.0 mmol) in dry dioxane (25 mL) was added silver acetate (0.17 g, 1.0 mmol). The mixture was kept under vigorous stirring in the dark for 24 h at room temperature. Hydrazonoyl chloride **3** (1.0 mmol) and silver acetate (0.5 mmol) were added again, and the mixture was stirred for further 24 h. The reaction was monitored by TLC (eluent: light petroleum/ethyl acetate 65:35). The undissolved material was filtered off and dichloromethane (40 mL) was added. The organic layer was washed firstly with 5% aqueous sodium hydrogencarbonate, then with water (25 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was chromatographed on a silica gel column with *t*-butylmethyl ether/light petroleum 65:35.

In the case of compounds **5** and **6** (from 2-azetidinone **1**) first fractions gave major **5**, further elution gave minor **6**.

Compounds (4*R**,5′*S**)-**5b** and (4*R**,4′*R**)-**6b** were obtained as previously described.[5]

Compound (4*R**,5′*S**)-**5b**. (0.45 g, 71%) as yellow prisms, mp 203 °C (from diisopropyl ether). IR (nujol) 1750, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.67 (3H, s), 3.81 (3H,

s), 4.05 (1H, d, $J=3.3$ Hz), 4.65 (1H, d, $J=3.3$ Hz), 4.84 (1H, d, $J=6.3$ Hz), 5.09 (1H, d, $J=6.3$ Hz), 6.8–7.5 (18H, m); MS *m/z* 638 (M^+). Anal. Calcd for $C_{34}H_{28}BrN_3O_5$: C, 63.96; H, 4.42; N, 6.58. Found: C, 64.01; H, 4.45; N, 6.63.

Compound (4*R**,4′*R**)-**6b**. (0.09 g, 14%) as pale yellow powder, mp 182 °C (from diisopropyl ether). IR (nujol) 1745, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.73 (3H, s), 3.80 (3H, s), 4.95 (1H, d, $J=6.6$ Hz), 5.31 (1H, d, $J=4.1$ Hz), 5.86 (1H, d, $J=6.6$ Hz), 6.32 (1H, d, $J=4.1$ Hz), 6.8–7.5 (18H, m); MS *m/z* 638 (M^+). Anal. Calcd for $C_{34}H_{28}BrN_3O_5$: C, 63.96; H, 4.42; N, 6.58. Found: C, 63.91; H, 4.46; N, 6.52.

In the case of compounds **10a**–**13a** (from 2-azetidinone **2**), first fractions gave major **10a**, further elution gave a mixture of **11a**–**13a**.

Compound (4*R**,4′*R**)-**10a**. (0.19 g, 31%). IR (nujol) 1740, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.29 (3H, s), 3.74 (3H, s), 3.82 (3H, s), 3.85 (1H, dd, $J=8.5$, 4.4 Hz), 4.82–4.88 (2H, m), 5.12 (1H, d, $J=4.4$ Hz), 5.45 (1H, dd, $J=15.7$, 5.0 Hz), 6.02 (1H, dd, $J=15.7$, 8.5 Hz), 6.8–7.6 (18H, m); MS *m/z* 599 (M^+). Anal. Calcd for $C_{37}H_{33}N_3O_5$: C, 74.11; H, 5.55; N, 7.01. Found: C, 74.16; H, 5.58; N, 7.08.

The mixture of compounds **11a**–**13a** was chromatographed on a silica gel column with ethyl acetate/light petroleum 3:2. First fractions gave major **11a**, further elution gave a mixture of minor **12a** and **13a**.

Compound (4*R**,4′*S**)-**11a**. (0.19 g, 31%). IR (nujol) 1750, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (3H, s), 3.72 (3H, s), 3.81 (3H, s), 3.89 (1H, dd, $J=8.0$, 4.0 Hz), 4.80–4.86 (2H, m), 5.19 (1H, d, $J=4.0$ Hz), 5.50 (1H, dd, $J=15.6$, 5.3 Hz), 6.01 (1H, dd, $J=15.6$, 8.0 Hz), 6.7–7.8 (18H, m); MS *m/z* 599 (M^+). Anal. Calcd for $C_{37}H_{33}N_3O_5$: C, 74.11; H, 5.55; N, 7.01. Found: C, 74.08; H, 5.51; N, 6.94.

Compounds (4*R**,5′*R**)-**12a** and (4*R**,5′*S**)-**13a** (156 mg, 26%) were as 1:1 mixture on the basis of ^1H NMR spectrum. Diagnostic signals were at δ 4.42 (1H, d, $J=5.0$ Hz), first minor diastereoisomer, and at δ 4.57 (1H, d, $J=5.5$ Hz), second minor diastereoisomer.

In the case of compounds **10b**–**13b** (from 2-azetidinone **2**), first fractions gave a mixture of major **10b** and minor **13b**, further elution gave a mixture of major **11b** and minor **12b**.

The mixture of compounds **10b** and **13b** was chromatographed on a silica gel column with dichloromethane/light petroleum 9:1. First fractions gave major **10b**, further elution gave minor **13b**.

Compound (4*R**,4′*R**)-**10b**. (0.17 g, 25%). IR (nujol) 1745, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.81 (3H, s), 3.84 (3H, s), 3.87 (1H, dd, $J=7.9$, 3.9 Hz), 4.82–4.88 (2H, m), 5.14 (1H, d, $J=3.9$ Hz), 5.50 (1H, dd, $J=15.7$, 5.2 Hz), 6.01 (1H, dd, $J=15.7$, 7.9 Hz), 6.9–7.7 (18H, m); MS *m/z* 664 (M^+). Anal. Calcd for $C_{36}H_{30}BrN_3O_5$: C, 65.07; H, 4.55; N, 6.32. Found: C, 65.12; H, 4.59; N, 6.39.

Compound (4*R**,5′*S**)-**13b**. (60 mg, 9%). IR (nujol) 1740, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.73 (6H, s), 4.50 (1H, d, $J=4.9$ Hz), 4.79 (1H, dd, $J=7.5$, 4.9 Hz), 4.80–4.85 (2H, m), 5.50 (1H, dd, $J=15.7$, 3.8 Hz), 5.84 (1H, dd, $J=15.7$, 7.5 Hz), 6.9–7.7 (18H, m); MS *m/z* 664 (M^+). Anal. Calcd for $C_{36}H_{30}BrN_3O_5$: C, 65.07; H, 4.55; N, 6.32. Found: C, 65.10; H, 4.51; N, 6.27.

The mixture of compounds **11b** and **12b** was crystallised with chloroform. Minor **12b** was obtained as a crystalline solid while the mother liquor contained major **11b**.

Compound (4*R**,4′*S**)-**11b**. (0.17 g, 25%). IR (nujol) 1745, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.74 (3H, s), 3.82 (3H, s), 3.86 (1H, dd, $J=8.5$, 4.3 Hz), 4.85–4.90 (2H, m), 5.07 (1H, d, $J=4.3$ Hz), 5.45 (1H, dd, $J=15.7$, 4.9 Hz), 6.02 (1H, dd, $J=15.7$, 8.5 Hz), 6.9–7.6 (18H, m); MS *m/z* 664 (M^+). Anal. Calcd for $C_{36}H_{30}BrN_3O_5$: C, 65.07; H, 4.55; N, 6.32. Found: C, 65.14; H, 4.58; N, 6.37.

Compound (4*R**,5′*R**)-**12b**. (60 mg, 9%). Mp 186 °C (from chloroform). IR (nujol) 1750, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.83 (6H, s), 4.58 (1H, d, $J=5.2$ Hz), 4.75 (1H, dd, $J=7.9$, 5.2 Hz), 4.80–4.85 (2H, m), 5.48 (1H, dd, $J=15.7$, 3.5 Hz), 5.83 (1H, dd, $J=15.7$, 7.9 Hz), 6.8–7.7 (18H, m); MS *m/z* 664 (M^+). Anal. Calcd for $C_{36}H_{30}BrN_3O_5$: C, 65.07; H, 4.55; N, 6.32. Found: C, 65.03; H, 4.55; N, 6.36.

4.1.5. Cerium(IV) ammonium nitrate oxidation of major cycloadducts 10b and 11b. A solution of **10b** or **11b** (0.17 g, 0.26 mmol) in acetonitrile (15 mL) was cooled to 0 °C. Cerium(IV) ammonium nitrate (0.55 g, 1.0 mmol) in water (8.0 mL) was added dropwise under vigorous stirring and ice-cooling. The reaction was monitored by TLC (eluent: light petroleum/ethyl acetate 3:2). After 2 h water (15 mL) and saturated aqueous sodium dithionite (10 mL) were added. The resulting mixture was extracted with ethyl acetate (4×25 mL), the organic layer was washed with water (2×25 mL) and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave **14** as a dark oil.

Compound **14**. (85 mg, 58%). IR (nujol) 1750, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.99 (3H, s), 4.47 (1H, dd, $J=7.7$, 5.2 Hz), 4.62 (1H, d, $J=5.2$ Hz), 5.50 (1H, dd, $J=16.2$, 7.7 Hz), 5.73 (1H, br s), 6.95 (1H, d, $J=16.2$ Hz), 7.1–7.1 (14H, m); MS *m/z* 572 (M^+). Anal. Calcd for $C_{29}H_{22}BrN_3O_4$: C, 62.60; H, 3.99; N, 7.55. Found: C, 62.58; H, 3.97; N, 7.58.

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