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Diastereoselective Diels–Alder Additions of Ethene to Substituted Homochiral 2(1*H*)-Pyrazinones

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Diels–Alder reactions of ethene with 2(1*H*)-pyrazinones bearing a homochiral auxiliary group are presented. The cycloaddition products form with diasteromeric excesses of up to 50 %. To the best of our knowledge, these are the first Diels–Alder reactions with ethene showing some degree of diastereoselectivity.

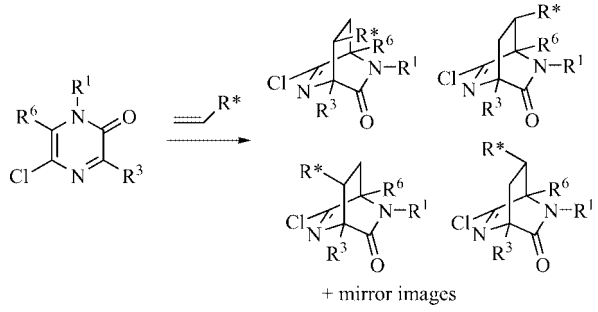
Introduction

The short and highly versatile synthesis of 3,5-dichloro-2(1*H*)-pyrazinones[1] is the starting point for many of the synthetic methods developed in our group.[2] One important research area is the application of Diels–Alder reactions with alkene dienophiles to the cyclic azadiene contained in these compounds. In these reactions, bicyclic adducts are formed as racemic mixtures which in turn are precursors for scaffolds with beta turn inducing properties.[3] So far, we were unsuccessful in modifying this reaction in an enantioselective fashion using homochiral catalysts.[4] For incorporation of the beta turn mimicking scaffolds in biomolecules it is important to obtain the 5-aminopiperidinone-2-carboxylate (APC) systems in their optically pure forms.[5] In this paper, we describe a modification of our original strategy with a homochiral auxiliary group in the system to produce diastereomeric reaction products.

Results and Discussion

Synthesis of Functionalized (α-Methylbenzyl)pyrazinones

In theory, a chiral auxiliary can be introduced either by the diene or the dienophile. However, because of the potential complexity of reaction mixtures resulting from Diels–Alder reactions with substituted dienophiles (Scheme 1), we prefer the method in which the auxiliary is introduced by the diene system. In the pyrazinones, used in our methodology, there are 3 potential attachment points for the auxiliary, the 1-, the 3- and the 6-position. Since the substituents at position 3 and 6 cannot be chosen freely in the design of the dipeptide mimics (they represent side chains of amino acids in the turn mimics), the 1-position was the only viable option left.



Scheme 1. Possible products from reaction of 2(1*H*)-pyrazinones with optically active dienophiles.

We therefore attached an (*R*)-α-methylbenzyl group to the lactam-nitrogen atom of the pyrazinone.[6] Since Diels–Alder reactions proceed at elevated temperature and the dienophile (ethene) is relatively small (and therefore hardly subject to steric interactions in the transition state), only minor diastereoselectivity was expected and our primary focus was on the purification and separation of the diastereoisomers of the products.

The pyrazinones bearing the homochiral α-methylbenzyl group were synthesized from an α-aminonitrile and oxalyl chloride (Scheme 2).[1] Synthesis of the aminonitrile by Strecker reaction did not pose any problems. In the cyclisation, rather low yields were obtained with increasing size of R^6. Bringing the substituents R^1 and R^6 close to each other in a planar system causes a lower yield because of steric hindrance. NMR spectra of the pyrazinones **1b** and **1c** show broad benzyl H signals, whereas for **1a** well-resolved quartets appear. This suggests the absence of free

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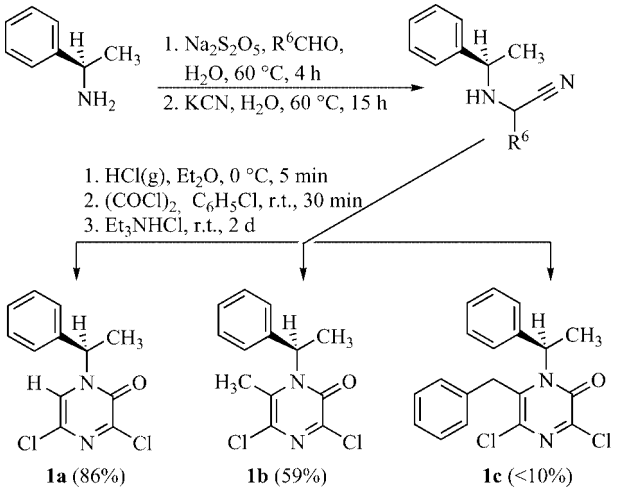
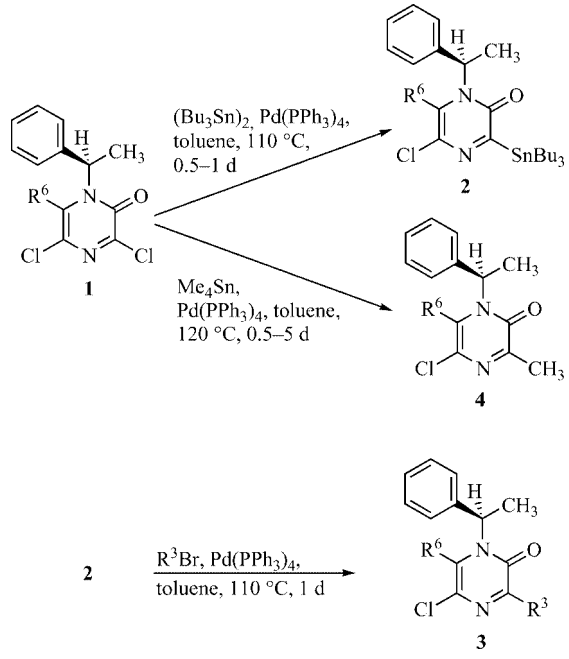
rotation of the α-methylbenzyl group in **1b** and **1c**, probably also due to steric hindrance by the substituent at the 6-position. Hindered rotation of a 6-substituent in pyrazinones has previously been reported to give rise to atropoisomeric compounds.[7]



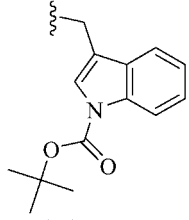
Scheme 2. Strecker synthesis of α-aminonitrile and direct conversion to dichloropyrazinones **1** bearing a homochiral α-methylbenzyl group.

Pyrazinones **1a** and **1b** were further functionalised at the 3-position using Stille chemistry, leading to compounds **3** (via intermediate **2**) and **4** (Scheme 3/Table 1).[2] Because of the low yield for compound **1c**, we did not further use it in this program. For product **4b**, again a broadened signal was observed in the proton NMR spectrum (suggesting the existence of atropoisomers at low temperature). In order to learn more about the energy barriers of the α-methylbenzyl rotation, we conducted a molecular modeling experiment on compound **4b**.[8]



Scheme 3. Functionalisation of the 3-position of the (α-methylbenzyl)pyrazinones.

Table 1. Functionalisation of the 3-position of (α-methylbenzyl)-pyrazinones.

	R^3	R^6	Yield
2	$SnBu_3$	H	76%
3a	Benzyl	H	65% (from **2**)
3b		H	57% (from **2**)
4a	Methyl	H	86%
4b	Methyl	Methyl	82%

In this experiment the torsion angle between the homochiral auxiliary group and the pyrazinone was set to certain fixed values (Figure 1), while all the other parameters were allowed to change freely.[8] The calculated energy profile suggests that indeed two energetically favoured conformations exist. The energy difference between these two low-energy conformations is 2.7 kJ/mol and the rotation barrier is about 43 kJ/mol. At room temperature, the structures are equilibrating. Otherwise it would be possible, at least in principle, to separate them as diastereoisomers, considering they contain a chiral centre as well as a chiral axis.

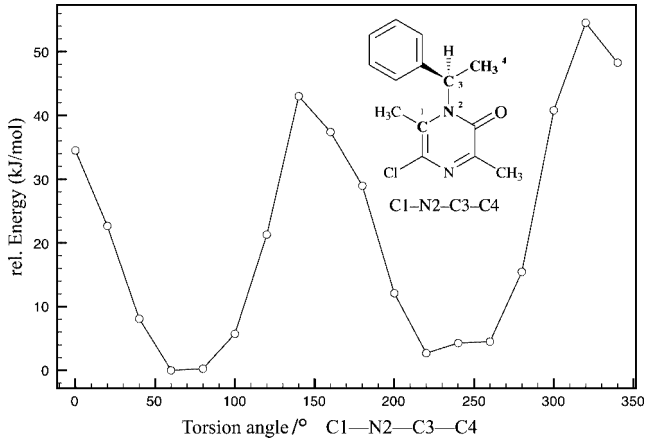
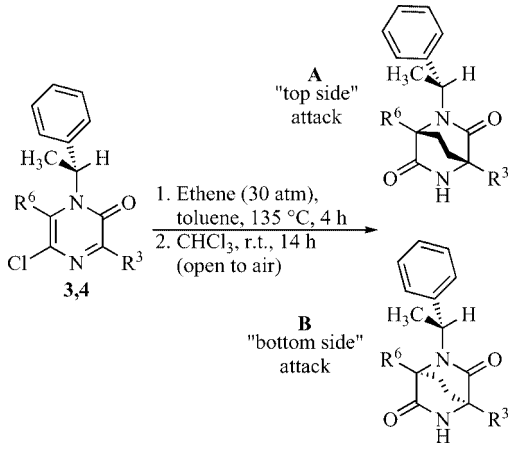


Figure 1. Energy profile of **4b**.

Synthesis of Stereochemically Pure Diels–Alder Adducts

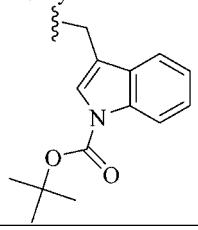
The subsequent cycloaddition with ethene and following hydrolysis step (Scheme 4) showed some interesting features. In spite of the previous (pertinent) remarks concerning the high temperature necessary to drive the reaction to completion (135 °C) and ethene being a small dienophile, a certain degree of diastereoselectivity could be observed in these Diels–Alder reactions (Table 2). As far as we know, these are the first diastereoselective Diels–Alder reactions

with ethene. The degree of diastereoselectivity parallels the degree of steric hindrance possibly exerted by the substituents at the 3- and 6-position of the pyrazinone. These steric effects will determine the most stable transition state for the adducts. The diastereomeric excess in the compounds formed (*de*) was deduced from NMR spectra of the concentrated crude reaction mixtures of the different isomers.



Scheme 4. Diels–Alder reaction/hydrolysis of functionalized (α-methylbenzyl)pyrazinones.

Table 2. Diels–Alder reaction/hydrolysis of functionalized (α-methylbenzyl)pyrazinones.

	R^3	R^6	*d.e.* (%)	Yield
5a I/II[a]	Methyl	H	**0**	77%
5b	Methyl	Methyl	**10**	79%
5c	Benzyl	H	**30**	81%
5d I/II[a]		H	**50**	54%

[a] The diastereoisomeric mixtures **5a** and **5d** could be separated in diastereoisomers by ways of column chromatography on silica gel. We labelled the isomers as **I** and **II**, with **I** being the compound eluting first from column on purification.

Compounds **5a** and **5d** could be separated in their different diastereomers by means of column chromatography on silica gel. At the current stage **5b** and **5c** were not resolved in the separate diastereomers after chromatography.

In an attempt to quantify the effect substituents on the pyrazinone have on the transition state energy of the adducts, a molecular modeling study has been performed on **5a** and **5b**. The energy and structure of the transition states of 4 Diels–Alder (2 pairs of diastereoisomers) adducts were calculated by using the standard features of the Spartan software (PM3 level). These calculations revealed small energy differences in the transition states of the different isomer pairs (data not shown).[9] The energy differences increased in parallel with the observed diastereoselectivities in the compounds. We do note however that the differences in the transition state energies as calculated are extremely small and cannot explain the diastereoselectivity we observed in this case.

The stereochemistry of **5a I** was undoubtedly established by single-crystal X-ray analysis. An ORTEP representation of the solid-state structure, given in Figure 2, identifies this compound as the (1*S*,4*S*) isomer (**5a I**, Scheme 4, **B**). However, as long as there are no X-ray data of **5d**, we make no attempt to draw any conclusion regarding preferential attack of ethene on either side.

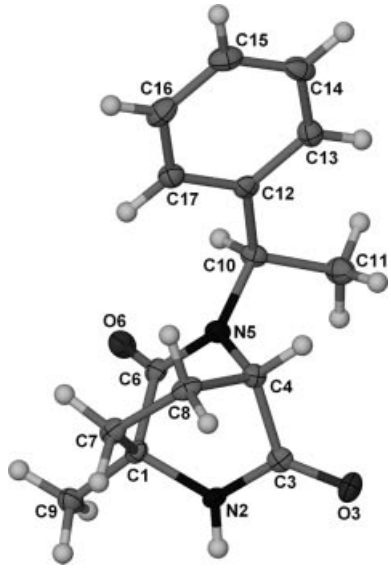
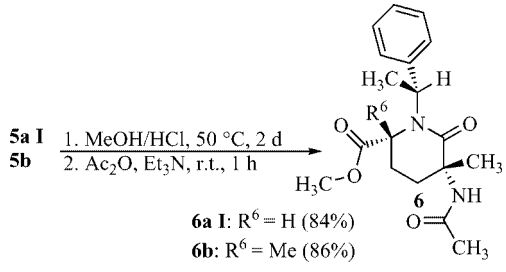


Figure 2. The molecular structure of **5a I**, with atom labels and 50% probability displacement ellipsoids for non-H atoms.

Conversion of the Diels–Alder Adducts to the APC Systems

Some closing tests were conducted to investigate whether these adducts experience the same selectivity in the methanolysis reaction as reported earlier for analogous systems.[13] The optically pure **5a I** and the diastereomeric mixture **5b** were submitted to the methanolysis procedure (Scheme 5). We observed selective methanolysis of the secondary amide function, leading to the APC systems **6a I** and **6b**, after capping of the amine with acetic anhydride. The diastereomers **6b I** and **6b II** could be separated by means of column chromatography.



Scheme 5. Selective methanolysis reaction of the (α-methylbenzyl)-pyrazinones.

Conclusions

We have developed a new and useful method to prepare diastereomeric Diels–Alder adducts of 2(1*H*)-pyrazinones through introduction of a homochiral α-methylbenzyl group. The diastereoisomers can be separated by column chromatography. Moreover, we report, to the best of our knowledge, on the first Diels–Alder reaction with ethene showing diastereoselectivity.

Experimental Section

General Methods: Melting points were taken using an Electrothermal IA 9000 digital melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 1600 Fourier transform spectrometer. Mass spectra were recorded on a Hewlett–Packard MS-Engine 5989A apparatus for EI and CI spectra, and a Kratos MS50TC instrument for exact mass measurements performed in the EI mode. For the NMR spectra (δ, ppm) a Bruker AMX 400 and a Bruker Avance 300 spectrometer were used. Analytical and preparative thin layer chromatography was carried out using Merck silica gel 60 PF-224, for column chromatography 70–230 mesh silica gel 60 (E.M. Merck) was used as the stationary phase.

3,5-Dichloro-1-[(1*R*)-1-phenylethyl]-2(1*H*)-pyrazinone (1a): (*R*)-Methylbenzylamine (0.1 mol) is added dropwise to a solution of sodium formaldehyde metabisulfite adduct (0.1 mol) in water (300 mL). After stirring for 4 h at ambient temperature, potassium cyanide (0.1 mol) is added and the reaction mixture is stirred overnight at 60 °C. The resulting amino nitrile is extracted with dichloromethane (3 × 200 mL), dried with $MgSO_4$ and concentrated under vacuum. The hydrochloric salt of this aminonitrile is prepared by passing gaseous HCl through the cooled solution of the aminonitrile in diethyl ether (300 mL) and filtration of the precipitated salt. Oxalyl chloride (0.2 mol) is added dropwise to a suspension of the hydrochloride of the amino nitrile (0.1 mol) in chlorobenzene (300 mL). After stirring for 30 min, triethylammonium chloride (10 g) is added and the resulting mixture is stirred at room temperature for 2 d under inert atmosphere. After evaporation of the solvent, the residue is purified by column chromatography (silica gel, CH_2Cl_2 → EtOAC/CH_2Cl_2) and subsequent crystallization (ethanol). Yield: 23.0 g, 86%; m.p. 88 °C (EtOH). IR (KBr): $\tilde{\nu}$ = 1654 (s, C=O), 1581 (s, C=N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.45–7.31 (m, 5 H, Ar-H), 7.02 (s, 1 H, 6-H), 6.23 (q, J = 7 Hz, 1 H, NCHPh), 1.75 (d, J = 7 Hz, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 151.6 (C-2), 147.2 (C-3), 137.3 (C-*ipso*), 129.4 (C-Ar), 129.2 (C-Ar), 127.0 (CH-Ar), 124.3 (C-5), 123.5 (C-6), 56.0 (CH), 18.5 (CH_3). EIMS: *m*/*z* (%) 268 [M^+, 6], 105 ($C_8H_9^+$, 100). HRMS: calcd. for $C_{12}H_{10}Cl_2N_2O$: 268.0170; found: 268.0162.

3,5-Dichloro-6-methyl-1-[(1*R*)-1-phenylethyl]-2(1*H*)-pyrazinone (1b): Prepared according to the procedure given for compound **1a**. Yield: 16.6 g, 59%; m.p. 101 °C (EtOH). IR (KBr): $\tilde{\nu}$ = 1657 (s, C=O), 1561 (s, C=N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.40–7.17 (m, 5 H, Ph-H), 6.50 [br. s (q), 1 H, NCHPh], 2.20 (s, 3 H, CH_3), 1.99 (d, J = 7 Hz, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 153.1 (C-2), 144.1 (C-3), 138.1 (PhC-*ipso*), 135.9 (C-6), 129.0 (CH-Ar), 127.9 (CH-Ar), 126.0 (CH-Ar), 124.7 (C-5), 56.2 (CH), 17.6 (CH_3), 16.6 (CH_3). EIMS: *m*/*z* (%) 282 [M^+, 3], 105 ($C_8H_9^+$, 100). HRMS: calcd. for $C_{13}H_{12}Cl_2N_2O$: 282.0326; found: 282.0364.

6-Benzyl-3,5-dichloro-1-[(1*R*)-1-phenylethyl]-2(1*H*)-pyrazinone (1c): Prepared according to the procedure given for compound **1a**. The overlap of the signals, mainly caused by peak broadening, renders exact peak assessment impossible in the region 137.0–125.4 ppm of the ^{13}C NMR spectrum. Yield: 3.5 g, < 10%; m.p. 139 °C (EtOH). IR (KBr): $\tilde{\nu}$ = 1659 (s, C=O), 1559 (s, C=N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.49–7.06 (m, 10 H, Ph-H), 5.62 [br. s (q), 1 H, NCHPh], 4.41 (br. d, J = 15 Hz, 1 H, CHPh), 4.24 (br. d, J = 15 Hz, 1 H, CHPh), 1.61 (d, J = 7 Hz, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 152.1 (C-2), 146.6 (C-3), 137.4 (2× PhC-*ipso*), 137.0–125.4 (C-Ar, C-5, C-6), 58.9 (CH broad), 36.3 (CH_2Bn), 15.3 (CH_3). EIMS: *m*/*z* (%) 358 [M^+, 4], 105 ($C_8H_9^+$, 100). HRMS: calcd. for $C_{19}H_{16}Cl_2N_2O$: 358.0639; found: 358.0632.

5-Chloro-1-[(1*R*)-1-phenylethyl]-3-(tributylstannyl)-2(1*H*)-pyrazinone (2): A mixture of **1a** (0.02 mol), hexabutylditin (0.024 mol) and $Pd(PPh_3)_4$ (0.1 mmol) in toluene (50 mL) is stirred at 110 °C under inert atmosphere for 1 d. Upon completion of the reaction and removal of the solvent under vacuum, the residue is dissolved in EtOAc (60 mL) and stirred at room temp. for 4 h with excess KF. After filtration of the mixture, the filtrate is evaporated and purified by column chromatography (silica gel, 20:80 hexane/CH_2Cl_2 → 95:5 hexane/CH_2Cl_2). Yield: 8.0 g, 76%. IR (NaCl): $\tilde{\nu}$ = 1632 (s, C=O), 1575 (s, C=N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.41–7.26 (m, 5 H, Ph-H), 6.77 (s, 1 H, 6-H), 6.12 (q, J = 7 Hz, 1 H, NCHPh), 1.71 (d, J = 7 Hz, 3 H, CH_3), 1.58 (quintet, J = 7.5 Hz, 6 H, $SnCH_2CH_2$), 1.31 (quintet, J = 7.5 Hz, 6 H, CH_3CH_2), 1.18 (t, J = 7.5 Hz, 6 H, $SnCH_2$), 0.90 (t, J = 7.5 Hz, 9 H, CH_3).

3-Benzyl-5-chloro-1-[(1*R*)1-phenylethyl]-2(1*H*)-pyrazinone (3a): A suspension of 5-chloro-1-[(1*R*)-1-phenylethyl]-3-(tributylstannyl)-2(1*H*)-pyrazinone **2** (1 mmol), benzyl bromide (1.1 mmol) and $Pd(PPh_3)_4$ (0.005 mmol) in toluene (15 mL) is stirred at 110 °C under inert atmosphere for 1 d. After solvent removal under reduced pressure, the residue is dissolved in EtOAc (75 mL) and stirred at ambient temperature for 4 h with excess KF. After filtration of the mixture, the filtrate is evaporated and purified by column chromatography (silica gel, CH_2Cl_2 → EtOAc). Yield: 0.211 g, 65%. IR (NaCl): $\tilde{\nu}$ = 1650 (s, C=O), 1588 (s, C=N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.46–7.24 (m, 10 H, Ph-H), 6.91 (s, 1 H, 6-H), 6.20 (q, J = 7 Hz, 1 H, NCHPh), 4.18 (d, J = 14 Hz, 1 H, CH_2Ph), 4.10 (d, J = 14 Hz, 1 H, CH_2Ph), 1.68 (d, J = 7 Hz, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 158.6 (C-2), 154.2 (C-3), 138.0 (C-*ipso*), 136.5 (C-*ipso*), 129.4, 129.0, 128.7, 128.4, 127.3, 126.6 (all CH-Ar), 126.0 (C-5), 121.9 (C-6), 54.2 (N*C*HPh), 39.9 (*C*H_2Ph), 18.5 (CH_3). EIMS: *m*/*z* (%) 324 [M^+, 6], 105 ($C_8H_9^+$, 100). HRMS: calcd. for $C_{19}H_{17}ClN_2O$: 324.1029; found: 324.1029.

***tert*-Butyl 3-({6-Chloro-3-oxo-4-[(1*R*)-1-phenylethyl]-3,4-dihydro-2-pyrazinyl}methyl)-1*H*-indole-1-carboxylate (3b):** Prepared according to the procedure given for compound **3a**. Yield: 0.264 g, 57%. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.13 (d, J = 8 Hz, 1 H, indole-H), 7.72 (d, J = 7 Hz, 1 H, indole-H), 7.61 (s, 1 H, indole-H), 7.42–7.21 (m, 7 H, Ph-H, indole-H), 6.93 (s, 1 H, 6-H), 6.23 (q, J = 7 Hz, 1 H, NCHPh), 4.27 (d, J = 15 Hz, 1 H, indole-CH_2), 4.19 (d, J = 15 Hz, 1 H, indole-CH_2), 1.70 (d, J = 7 Hz, 3 H, CH_3), 1.66 (s, 9 H, *tert*-butyl CH_3). EIMS: *m*/*z* (%) 463 [M^+, 4], 407 (M^+ – C_4H_8, 5), 105 ($C_8H_9^+$, 100). HRMS: calcd. for $C_{26}H_{26}ClN_3O_3$: 463.1663; found: 463.1655.

5-Chloro-3-methyl-1-[(1*R*)-1-phenylethyl]-2(1*H*)-pyrazinone (4a): A mixture of pyrazinone **1a** (7 mmol), tetramethyltin (8.4 mmol) and $Pd(PPh_3)_4$ (1 mol-%) in toluene (10 mL) is heated at 110 °C for 24 h. Upon completion of the reaction and removal of the solvent under vacuum, the residue is dissolved in EtOAc and stirred with an excess KF for 1/2 d at room temp. After filtration of the mixture, the filtrate is evaporated and purified by column chromatography

(silica gel, 10% EtOAc/CH_2Cl_2). Yield: 1.5 g, 86%; m.p. 84 °C (EtOH). IR (KBr): $\tilde{\nu}$ = 1663 (s, C=O), 1594 (s, C=N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.59–7.20 (m, 5 H, Ph-H), 6.96 (s, 1 H, 6-H), 6.23 (q, J = 7 Hz, 1 H, NCHPh), 2.48 (s, 3 H, CH_3), 1.72 (d, J = 7 Hz, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 157.8 (C-2), 154.5 (C-3), 137 (PhC-*ipso*), 128.9 (CH-Ar), 128.5 (CH-Ar), 127.3 (CH-Ar), 125.7 (C-5), 121.2 (C-6), 53.9 (CH), 20.8 (CH_3), 18.3 (CH_3). EIMS: *m*/*z* (%) 248 [M^+, 4], 105 ($C_8H_9^+$, 100). HRMS: calcd. for $C_{13}H_{13}ClN_2O$: 248.0716; found: 248.0716.

5-Chloro-3,6-dimethyl-1-[(1*R*)-1-phenylethyl]-2(1*H*)-pyrazinone (4b): Prepared according to the procedure given for compound **4a**. Yield: 1.5 g, 82%; m.p. 135 °C (EtOH). IR (KBr): $\tilde{\nu}$ = 1643 (s, C=O), 1568 (s, C=N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.41–7.17 (m, 5 H, Ar-H), 6.56 [br. s (q), 1 H, NCH], 2.46 (s, 3 H, CH_3), 2.18 (br. s, 3 H, CH_3), 1.88 (d, J = 7 Hz, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 156.3 (C-2), 154.4 (C-3), 139.0 (PhC-*ipso*), 133.0 (C-6), 128.8 (CH), 127.5 (CH), 126.5 (C-5), 125.8 (CH), 54.1 (broad) (CH), 20.8 (CH_3), 17.4 (CH_3), 16.7 (CH_3). EIMS: *m*/*z* (%) 262 [M^+, 3], 105 ($C_8H_9^+$, 100). HRMS: calcd. for $C_{14}H_{15}ClN_2O$: 262.0873; found: 262.0868.

(1*R*/*S*,4*R*/*S*)-1-Methyl-5-[(1*R*)-1-phenylethyl]-2,5-diazabicyclo-[2.2.2]octane-3,6-dione (5a I/II): The substituted pyrazinone **4a** (5 mmol) is dissolved in toluene and heated at 145 °C in a stainless steel bomb under ethene pressure (35 atm) for 4 h. The progress of the cycloaddition is monitored on TLC, by the disappearance of the starting pyrazinone. The resulting mixture is stirred for one night at room temperature open to the air to hydrolyse the imidoyl chloride. After evaporation of the solvent, the diastereoisomers can be separated by column chromatography (silica gel, Et_2O/EtOAc, 95:5), ratio of diastereoisomers 50:50; total yield: 1.0 g, 77%.

(1*S*,4*S*)-1-Methyl-5-[(1*R*)-1-phenylethyl]-2,5-diazabicyclo[2.2.2]-octane-3,6-dione (5a I): M.p. 174 °C (CH_2Cl_2/hexane). IR (KBr): $\tilde{\nu}$ = 1714 (s, C=O), 1655 (s, C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.35–7.26 (m, 5 H, Ar-H), 6.74 (s, 1 H, NH), 5.72 (q, J = 7 Hz, 1 H, NCHPh), 3.82 (dd, J = 4 Hz, J = 2 Hz, 1 H, 4-H), 1.82 (ddd, J = 13 Hz, 1 H, 11 Hz, 4 Hz, 7-H), 1.72 (ddd, J = 13 Hz, J = 10 Hz, J = 4 Hz, 1 H, 7-H), 1.65 (dddd, J = 13 Hz, J = 11 Hz, J = 4 Hz, J = 2 Hz, 1 H, 8-H), 1.30 (dddd, J = 13 Hz, J = 10 Hz, J = 4 Hz, J = 4 Hz, 1 H, 8-H), 1.54 (d, J = 7 Hz, 3 H, CH_3), 1.52 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.5 (C=O), 17.7 (C=O), 139.4 (PhC-*ipso*), 128.7 (CH-Ar), 128.0 (CH-Ar), 127.3 (CH-Ar), 58.3 (C-1), 54.7 (CH-Bn), 50.2 (CH), 32.0 [CH_2 (C-7)]; 24.6 [CH_2 (C-8)]; 18.3 [CH_3 (α-MeBn)]; 16.5 (CH_3). EIMS: *m*/*z* (%) 258 (100) [M^+], 153 ($M^+ - C_8H_9$, 80), 125 ($M^+ - C_8H_9 - CO$, 70), 105 ($C_8H_9^+$, 78). HRMS: calcd. for $C_{15}H_{18}N_2O_2$: 258.1368; found: 258.1369.

(1*R*,4*R*)-1-Methyl-5-[(1*R*)-1-phenylethyl]-2,5-diazabicyclo[2.2.2]-octane-3,6-dione (5a II): M.p. 182 °C (CH_2Cl_2/hexane). IR (KBr): $\tilde{\nu}$ = 1681 (br. s, C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.34–7.24 (m, 5 H, Ph-H), 6.38 (s, 1 H, NH), 5.67 (q, J = 7 Hz, 1 H, NCHPh), 3.88 (dd, J = 4 Hz, J = 2 Hz, 1 H, 4-H), 2.01–1.86 (m, 4 H, 7-H, 8-H), 1.56 (d, J = 7 Hz, 3 H, CH_3), 1.50 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 171.7 (C=O), 170.7 (C=O), 139.8 (PhC-*ipso*), 128.8 (CH-Ar), 128.0 (CH-Ar), 126.8 (CH-Ar), 58.1 (C-1), 55.3 (C-Bn), 50.9 (CH), 32.5 [CH_2 (C-7)]; 25.8 [CH_2 (C-8)]; 18.3 (CH_3), 17.0 (CH_3). EIMS: *m*/*z* (%) 258 (100) [M^+], 153 ($M^+ - C_8H_9$, 67), 125 ($M^+ - C_8H_9 - CO$, 66), 105 ($C_8H_9^+$, 74). HRMS: calcd. for $C_{15}H_{18}N_2O_2$: 258.1368; found: 258.1369.

(1*R,4*R**)-1,4-Dimethyl-2-[(1*R*)-1-phenylethyl]-2,5-diazabicyclo-[2.2.2]octane-3,6-dione (5b): 5b** was synthesized according to the procedure given for compound **5a I/II**, and purified by column chromatography [EtOAc → EtOAc/EtOH (95:5)]. The diastereoisomers however could not be separated and therefore 2 signal sets are observed in the ^1H NMR spectrum (ratio of diastereoisomers 55:45). The^1H NMR spectrum (integration normalised to 20 protons per product) shows that several signals are broadened due to hindered rotation The 1-methyl signal and C-1 signal are not observed in the ^{13}C-NMR due to this signal broadening. Total yield: 1.1 g, 79%; m.p. unrelevant (diastereoisomeric mixture). IR (KBr): $\tilde{\nu}$ = 1696 (br. s, CO) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.35–7.22 (m, 5 H + 5 H, Ar-H), 6.93 (br. s, 1 H, NH minor isomer), 6.48 (br. s, 1 H, NH major isomer), 5.40 and 5.29 (br. s, 1 H, NCHPh major and minor isomer), 2.07–1.79 (m, 2× 4 H, 7-H and 8-H), 1.75 (d, J = 7 Hz, 3 H, CH_3 major isomer), 1.72 (d, J = 7 Hz, 3 H, CH_3 minor isomer), 1.48 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 1.44 (br. s, 3 H, CH_3), 1.43 (br. s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C), major isomer: δ = 173.9 (C=O), 172.8 (C=O), 141.8 (PhC-*ipso*), 128.9 (CH-Ar), 127.4 (CH-Ar), 126.6 (CH-Ar), 62.8 (C-4), 57.9 (NCH), 34.4 (CH_2), 32.3 (CH_2), 19.0 (CH_3), 18.3 (CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C), minor isomer: δ = 173.9 (C=O), 172.8 (C=O), 142.4 (PhC-*ipso*), 128.8 (CH-Ar), 127.3 (CH-Ar), 126.8 (CH-Ar), 62.8 (C-4), 57.8 (NCH), 34.3 (CH_2), 32.2 (CH_2), 19.1 (CH_3), 17.9 (CH_3). EIMS: *m*/*z* (%) 272 [M^+, 54], 167 ($M^+ - C_8H_9$, 6), 139 ($M^+ - C_8H_9 - CO$, 23), 124 ($M^+ - C_8H_9 - HNCO$, 100), 105 ($C_8H_9^+$, 68). HRMS: calcd. for $C_{16}H_{20}N_2O_2$: 272.1525; found: 272.1525.

(1*R,4*S**)-1-Benzyl-5-[(1*R*)-1-phenylethyl]-2,5-diazabicyclo[2.2.2]-octane-3,6-dione (5c):** Prepared according to the procedure given for compound **5a**. The diastereoisomers however could not be separated and therefore 2 signal sets are observed in the ^1H NMR spectrum (ratio of diastereoisomers 65:35). Some signals in the ^{13}C NMR spectrum cannot be assigned to the major or minor isomer (indicated with *). Yield: 1.4 g, 81%; m.p. unrelevant (diastereoisomeric mixture). IR (KBr): $\tilde{\nu}$ = 1704 (br. s, CO) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.50–7.20 (m, 10 H + 10 H, Ar-H), 6.90–6.50 (m, 2 H + 2 H, NH and NCHPh), 3.86 (dd, J = 4 Hz, J = 2 Hz, 1 H, 4-H major isomer), 3.82 (dd, J = 4 Hz, J = 2 Hz, 1 H, 6-H major isomer), 3.48 (d, J = 15 Hz, 1 H, Bn-H major isomer), 3.45 (d, J = 15 Hz, 1 H, Bn-H minor isomer), 3.13 (d, J = 15 Hz, 1 H, Bn-H minor isomer), 3.09 (d, J = 15 Hz, 1 H, Bn-H major isomer), 2.15–1.20 (m, 4 H + 4 H, 2× CH_2 major and minor isomer), 1.88 (d, J = 7 Hz, 3 H, CH_3 major isomer), 1.58 (d, J = 8 Hz, 3 H, CH_3 minor isomer). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C), major isomer: δ = 172.0 (C=O), 170.7 (C=O), 139.7 (PhC-*ipso*), 135.2 (PhC-*ipso*), 130.8 (CH-Ar), 129.5 (CH-Ar), 129.1 (CH-Ar), 128.5 (CH-Ar), 127.7 (CH-Ar), 127.2 (CH-Ar), 60.9 (C-3), 55.1 (NCH), 50.8 (CH), 37.7 (C-8)*, 30.7 (C-7)*, 25.0 (CH_3)*, 16.9 (CH_2Ph)*. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C), minor isomer: δ = 171.5 (C=O), 170.7 (C=O), 140.0 (PhC-*ipso*), 135.2 (PhC-*ipso*), 130.8 (CH-Ar), 129.5 (CH-Ar), 129.2 (CH-Ar), 128.4 (CH-Ar), 127.9 (CH-Ar), 127.2 (CH-Ar), 60.7 (C-3), 55.7 (NCH), 51.5 (CH), 37.6 (C-8)*, 30.9 (C-7)*, 26.4 (CH_3)*, 17.5 (CH_2Ph)*. EIMS: *m*/*z* (%) 334 (100) [M^+], 229 ($M^+ - C_8H_9$, 71), 201 ($M^+ - C_8H_9 - CO$, 47), 105 ($C_8H_9^+$, 61). HRMS: calcd. for $C_{21}H_{22}N_2O_2$: 334.1681; found: 334.1681.

***tert*-Butyl 3-({(1*R**,4*S**)-5-[(1*R*)-3,6-Dioxo-1-phenylethyl]-2,5-diazabicyclo[2.2.2]oct-1-yl}methyl)-1*H*-indole-1-carboxylate (5d I/II):** Prepared according to the procedure given for compound **5a**. The diastereoisomers can be separated via column chromatography (silica gel, EtOAc/CH_2Cl_2, 10:90). The CO signal of the Boc group is unresolved in the ^{13}C NMR spectrum. Ratio of diastereoisomers 75:25; total yield: 1.3 g, 54%.

5d I: Minor isomer; m.p. 100 °C (hexane/CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.16 (d, J = 8 Hz, 1 H, indole-H),

7.54 (d, J = 7 H, 1 H, indole-H), 7.53 (s, 1 H, indole-H), 7.36–7.24 (m, 7 H, Ar-H + indole-H), 5.74 (s, 1 H, NH), 5.72 (q, J = 7 Hz, 1 H, CHPh), 3.86 (m, 1 H, 4-H), 3.51 (d, J = 15 Hz, 1 H, indole-CH), 3.24 (d, J = 7 Hz, 1 H, indole-CH), 2.09–1.85 (m, 4 H, 2× CH_2), 1.68 (s, 9 H, CH_3), 1.59 (d, J = 7 Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.1 (C=O), 170.3 (C=O), 139.7 (C-*ipso*), 130.8–113.6 (CH-Ar + indole CH), 84.1 (indole C), 60.5 (C-1), 55.3 (NCH), 51.2 (C-4), 30.9 (CH_2), 28.2 (CH_3 BOC), 26.4 (CH_2), 25.9 (CH_2), 17.2 (CH_3). EIMS: *m*/*z* (%) 473 [M^+, 40], 417 (M^+ – C_4H_8, 63), 374 (M^+ – BOC, 94), 268 (M^+ – BOC – indolyl, 40), 224 (268 – H_2NCO, 100), 105 ($C_8H_9^+$, 92). HRMS: calcd. for $C_{28}H_{31}N_3O_4$: 473.2315; found: 473.2317.

5d II: Major isomer; m.p. 172 °C (hexane/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.15 (d, J = 8 Hz, 1 H, indole-H), 7.55 (m, 2 H, indole-H), 7.31 (m, 9 H, Ar-H, indole-H), 5.80 (s, 1 H, NH), 5.79 (q, J = 7 Hz, 1 H, NCHPh), 3.81 (dd, J = 4 Hz, J = 2 Hz, 1 H, J = 2 Hz, 4-H), 3.52 (d, J = 15 Hz, 1 H, indole-CH_2), 3.23 (d, J = 15 Hz, 1 H, indole 2-H), 2.01 (ddd, J = 13 Hz, J = 11 Hz, J = 4 Hz, 1 H, 7-H), 1.80 (ddd, J = 13 Hz, J = 10 Hz, J = 4 Hz, 1 H, 7-H), 1.69 (s, 9 H, CH_3), 1.60 (dddd, J = 13 Hz, J = 11 Hz, J = 4 Hz, J = 2 Hz, 1 H, 8-H), 1.56 (d, J = 7 Hz, 3 H, CH_3), 1.31 (dddd, J = 13 Hz, J = 10 Hz, J = 4 Hz, J = 4 Hz, 1 H, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.6 (C=O), 170.3 (C=O), 139.4 (C-*ipso*), 130.8–113.6 (CH-Ar, indole-CH), 84.1 (indole-C), 60.7 (C-1), 54.6 (NCH), 50.5 (C-4), 30.5 (CH_2), 28.2 (CH_3 BOC), 26.4 (CH_2), 24.7 (CH_2), 16.6 (CH_3). EIMS: *m*/*z* (%) 473 [M^+, 40], 417 (M^+ – C_4H_8, 63), 374 (M^+ – BOC, 94), 268 (M^+ – BOC – indolyl, 40), 224 (268 – H_2NCO, 100), 105 ($C_8H_9^+$, 92). HRMS: calcd. for $C_{28}H_{31}N_3O_4$: 473.2315; found: 473.2317.

Methyl (2*S*,5*S*)-5-(Acetylamino)-1-[(1*R*)-1-phenylethyl]-5-methyl-6-oxo-2-piperidinecarboxylate (6a I): A cooled solution of adduct **5a I** (1 mmol) in methanol is flushed with gaseous HCl for 10 min. After stirring the acidified solution for 2 d at 50 °C, the solvent is removed under reduced pressure. The oily residue is dissolved in acetic anhydride and triethylamine is added till precipitate formation is observed. After additional stirring for 1 h at ambient temperature, the ammonium salts are filtered off. The filtrate is evaporated and purified by column chromatography (silica gel, EtOAc). Yield: 0.279 g, 84%; m.p. 99 °C (hexane/CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 1739 (s, C=O), 1682, (s, C=O), 1641 (s, C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.42–7.21 (m, 5 H, Ar-H), 6.75 (s, 1 H, NH), 5.89 (q, J = 7 Hz, 1 H, NCHPh), 3.75 (m, 4 H, OCH_3, 2-H), 2.78 (ddd, J = 14 Hz, J = 6 Hz, J = 3 Hz, 1 H, bridge-H), 2.13–2.00 (m, 2 H, bridge-H), 1.99 (s, 3 H, CH_3), 1.89 (m, 1 H, bridge-H), 1.63 (s, 3 H, CH_3), 1.40 (d, J = 7 Hz, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 173.9 (C=O), 173.0 (C=O), 170.0 (C=O), 139.9 (PhC-*ipso*), 129.0 (CH-Ar), 127.8 (CH-Ar), 127.0 (CH-Ar), 57.6 (C), 54.7 (CH), 52.7 (C-Bn), 52.5 (OCH_3), 30.0 (CH_2), 25.2 (CH_3), 24.3 (CH_3), 23.7 (CH_2), 15.3 (CH_3). EIMS: *m*/*z* (%) 332 [M^+, 16], 273 (M^+ – CO_2CH_3, 26), 245 (M^+ – NH_2COCH_3 – CO, 100), 185 (45), 120 ($C_8H_{10}N^+$, 29), 105 ($C_8H_9^+$, 74). HRMS: calcd. for $C_{18}H_{24}N_2O_4$: 332.1736; found: 332.1738.

Methyl (2*R,5*R**)-5-(Acetylamino)-1-[(1*R*)-1-phenylethyl]-2,5-dimethyl-6-oxo-2-piperidinecarboxylate (6b I/II):** Prepared according to the procedure given for compound **6a I**. The absolute configurations on C-2 and C-5 are unknown (relative configuration of amine and carboxylate unambiguously *cis*). Total yield: 0.298 g, 86%

6b I: Minor isomer; m.p. 91 °C (hexane/CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 1733 (s, C=O), 1644 (s, C=O), 1636 (s,C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.30–7.50 (m, 5 H, Ar-H), 6.79 (s, 1 H, NH), 5.41 (br. s, 1 H, NCHPh), 3.58 (s, 3 H, OMe), 2.77 (ddd, J = 14 Hz, J = 4 Hz, J = 4 Hz, 1 H, bridge$_{eq}$-H), 2.20 (ddd, J = 14 Hz, J = 14 Hz, J = 5 Hz, 1 H, bridge$_{ax}$-H), 2.10–1.50 (m, 2 H, bridge-H), 1.97 (s, 3 H,CH_3), 1.68 (s, 3 H, CH_3), 1.65 (d, J = 7 Hz, 3 H, CH_3), 1.41 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 174.6 (C=O), 173.9 (C=O), 169.7 (C=O), 142.2 (PhC-*ipso*), 128.1 (CH-Ar), 126.8 (CH-Ar), 126.7 (CH-Ar), 64.1–57.2 (C-2, C-5), 52.6 (OMe), 33.4 (CH_3), 28.9 (CH_2), 25.6–24.6–24.4–19.3 (3×CH_3, CH_2). EIMS: *m*/*z* (%) 346 [M^+, 15], 287 (M^+ – CO_2CH_3,16), 259 (M^+ – NH_2COCH_3 – CO, 3), 120 ($C_8H_{10}N^+$, 100), 105 ($C_8H_9^+$, 55). HRMS: calcd. for $C_{19}H_{26}N_2O_4$: 346.1893; found: 346.1895.

6b II: Major isomer; m.p. 125 °C (hexane/CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 1727 (s, C=O), 1647 (br. s, C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.35–7.10 (m, 5 H, Ar-H), 6.65 (s, 1 H, NH), 4.39 (q, J = 7 Hz, 1 H, NCHPh), 2.80–2.70 (m, 1 H, bridge-H), 2.23 (m, 3 H, 3× bridge-H), 1.94 (s, 3 H, CH_3), 1.84 (d, J = 7 Hz, 3 H, CH_3), 1.61 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 173.8 (C=O), 173.2 (C=O), 169.7 (C=O), 142.4 (PhC-*ipso*), 128.2 (CH-Ar), 126.5 (CH-Ar), 125.9 (CH-Ar), 65.5–57.7 (C-2, C-5), 56.9 (CH-Bn), 52.8 (OMe), 32.9 (CH_3), 28.8 (CH_2) 25.6–24.3–23.9–19.3 (3× CH_3, CH_2). EIMS: *m*/*z* (%) 346 [M^+, 23], 287 (M^+ – CO_2CH_3,47), 259 (M^+ – NH_2COCH_3 – CO, 4), 120 ($C_8H_{10}N^+$, 100), 105 ($C_8H_9^+$, 78). HRMS: calcd. for $C_{19}H_{26}N_2O_4$: 346.1893; found: 346.1893.

Crystal Data for 5a I: $C_{15}H_{18}N_2O_2$, M = 258.31, colorless block, 0.42 × 0.22 × 0.18 mm^3, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 6.9623(18), b = 11.418(3), c = 16.932(4) Å, V = 1346.1(6) Å^3, Z = 4, D_c = 1.275 g/cm^3, F(000) = 552, Bruker APEX CCD area detector, Mo-K_α radiation, λ = 0.71073 Å, T = 100(2) K, $2\theta_{max}$ = 56.7°, 8211 reflections collected, 1835 unique (R_{int} = 0.0706). Final *GooF* = 1.034, R_1 = 0.0501, wR_2 = 0.0931, R indices based on 1463 reflections with $I > 2\sigma(I)$ (refinement on F^2), 174 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.086 mm^{-1}. The structure was solved and refined using the SHELX-97 suite of programs[10] and the X-Seed[11] interface. Friedel pairs (1289) were merged before final refinement. Figure 2 was prepared using X-SEED[11] and POV-Ray.[12]

CCDC-620133 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[9] The calculations reveal a difference of 0.2661 kJ/mol in the case of **5a** and 0.4867 kJ/mol in the case of **5b** on an average transition state energy of respectively 217.7309 and 199.2635 kJ/mol and point towards a preferred tendency for attack of ethene from the "top side". However, the reliability of these results is questionable, due to the small energy differences.

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