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Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 5582

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PAPER

Intramolecular cycloaddition of azomethine ylides, from imines of *O*-acylsalicylic aldehyde and ethyl diazoacetate, to ester carbonyl – experimental and DFT computational study†

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Received 5th April 2012, Accepted 1st June 2012
DOI: 10.1039/c2ob25676b

Intramolecular 1,3-dipolar cycloaddition of alkoxycarbonyl-substituted azomethine ylides to ester carbonyl was realized for the first time in the reaction of imines of *O*-acylsalicylic aldehyde with ethyl diazoacetate in the presence of $Cu(tfacac)_2$. The stereoselectivity of the cycloaddition is explained using DFT calculations.

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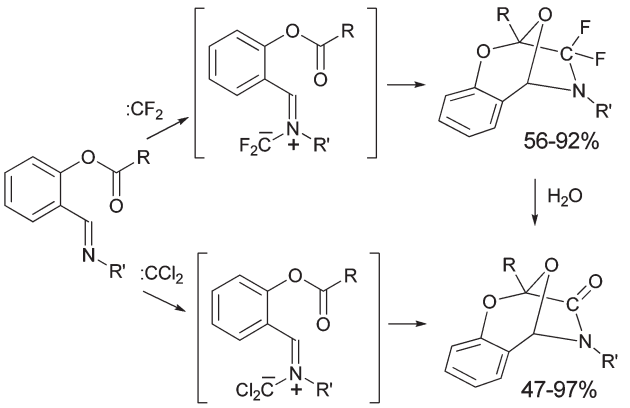
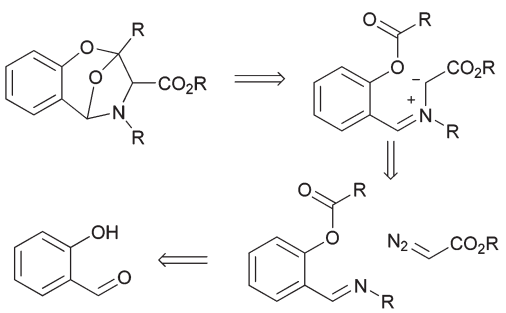
Introduction

1,3-Dipolar cycloaddition of azomethine ylides is an efficient synthetic tool for the synthesis of nitrogen containing heterocyclic compounds.[1,2] The intramolecular version of this reaction is very effective in the preparation of complex polycyclic molecules.[2a,r,t,u,y,3] Earlier we found that azomethine ylides generated from carbenes/carbenoids and imines of *O*-alkenyl- or *O*-alkynylsalicylic aldehyde undergo highly regio- and stereoselective intramolecular 1,3-dipolar cycloaddition to the multiple carbon–carbon bond to give chromenopyrrole derivatives.[4] Azomethine ylides generated from dihalocarbenes and imines of *O*-acylsalicylic aldehyde undergo the quite rare cycloaddition to ester carbonyl giving derivatives of 2,5-epoxy-1,4-benzoxazepine (Scheme 1).[5]

Though the biological activity of this heterocyclic system has yet to be investigated, derivatives of 2,5-epoxy-1,4-oxazepine-3-carboxylic acid were found among the products of decomposition of β-lactamase inhibitor clavulanic acid.[6] Derivatives of



Scheme 1 Reactions of imines of *O*-acylsalicylic aldehyde with dihalocarbenes.



Scheme 2 Retrosynthetic approach to derivatives of 2,5-epoxy-1,4-benzoxazepine.

2,5-epoxy-1,4-benzoxazepine-3-carboxylic acid could be prepared *via* the intramolecular cycloaddition to the C=O bond of the azomethine ylide, which was generated by reaction of imines of *O*-acylsalicylic aldehyde with metallocarbenoids from

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†Electronic supplementary information (ESI) available: X-Ray diffraction data, refinement information and Cartesian coordinates. CCDC 874425 for ***exo*-2a**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25676b

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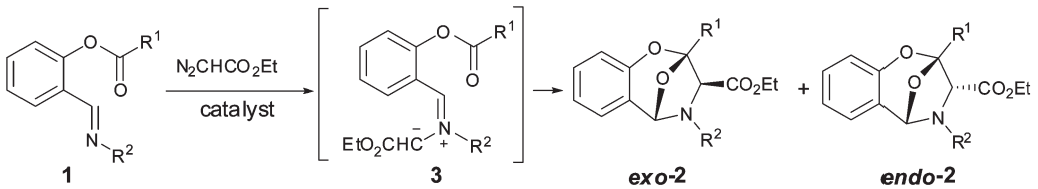

Scheme 3 Reaction of imines of *O*-acylsalicylic aldehyde with ethyl diazoacetate.

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diazocarbonyl compounds (Scheme 2). In this paper we present the results of the investigation of this reaction using ethyl diazoacetate (EDA) as the source of the carbenoid.

Results and discussion

Rh- and Cu-carbenoids, derived from diazo compounds and Rh(II)- and Cu-salts or complexes, are mostly used for the generation of azomethine ylides from imines.[1,7,8] Rh- and Cu-catalysts were, therefore, tested in a primary screening of catalysts for the generation of azomethine ylide from imine **1a** and ethyl diazoacetate (Scheme 3). Some of the tested catalysts decomposed ethyl diazoacetate (2 mol% $Rh_2(OAc)_4$, 10 mol% Cu-powder) but did not provide ylides **3a**, whereas others (10 mol% $Cu(acac)_2$, CuI, or $Fe(acac)_3$) did not even decompose the diazo compound. Probably in the latter cases the imine deactivates the catalyst.

Copper(II) trifluoroacetoacetate, $Cu(tfacac)_2$, proved to be the catalyst of choice. This catalyst decomposes ethyl diazoacetate with formation of a carbenoid which reacts with imine **1a**, giving ylide **3a**, and this in turn adds to the ester carbonyl with formation of 2,5-epoxy-1,4-benzoxazepine **2a**. It was found that the stereoselectivity of the reaction depends on temperature, thus in boiling methylene chloride the only product was the *endo*-isomer **2a**, whereas in boiling benzene both isomers were formed.

The former conditions (equivalent of $Cu(tfacac)_2/CH_2Cl_2$/40 °C) were employed to carry out the reactions of imines **1a–m** with ethyl diazoacetate. All the newly obtained compounds were fully characterized using standard spectral and analytical methods. To distinguish between *endo*- and *exo*-**2** it is possible to use the chemical shifts of the methylene protons of the ethoxy group. In the *endo*-isomer **2** the chemical shift of the methylene protons of the ethoxy group is 4.2–4.4 ppm and in the *exo*-isomer it is 3.6–3.9 ppm. The methylene protons in isomer *exo*-**2** are in the shielding area of the magnetic field generated by the 2-aryl ring which is *cis*-situated relatively to the oxazolidine ring (see structures *endo*- and *exo*-**2** ($R^1 = R^2 = Ph$) optimized at DFT B3LYP/6-31G(d) level in the ESI†). A similar shielding of the methylene protons of the ethoxy group was found in oxazolidine derivatives with a *cis*-situated ethoxycarbonyl and aryl groups.[9] The relative configuration of compound *exo*-**2a** was elucidated by X-ray analysis (Fig. 1).

Reaction of imines **1b–h** with ethyl diazoacetate in the presence of $Cu(tfacac)_2$ in CH_2Cl_2 also gave rise to the *endo*-isomers **2b–h** (Table 1). The absence of the *exo*-isomers was proved by an analysis of the ^1H NMR spectra of the corresponding reaction mixtures. Imines **1e–g**, containing electron withdrawing substituents in the benzoyl group, unexpectedly yielded both isomers under the same reaction conditions (Table 1). The cycloadducts *endo*-**2** can only have originated from the intramolecular cycloaddition of U-ylides **3**. The cycloadducts *exo*-**2** are derived only from the cycloaddition of S-ylides **3** (Scheme 4).[10] Several hypotheses can be proposed to explain the experimental stereoselectivity. The first hypothesis is that the stereoselectivity of the reaction is determined by the formation from (*E*)-imine and carbenoid of only the S- or only U-isomer of ylides **3**, or both, depending on the substituents in compounds **1**.

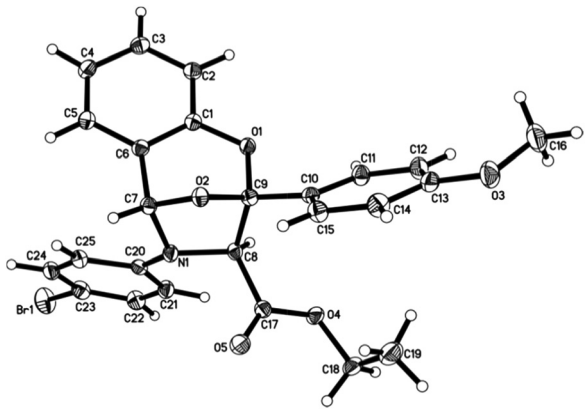

Fig. 1 X-Ray crystal structure of *exo*-**2a**.

Table 1 Reaction of imines **1** and ethyl diazoacetate in the presence of equivalent of $Cu(tfacac)_2$ in CH_2Cl_2 at 40 °C

Imine	R^1	R^2	Yield of *endo*/*exo*-**2**, %
1a	4-MeOC_6H_4	4-BrC_6H_4	41/0
1b	Ph	4-BrC_6H_4	39/0
1c	4-MeOC_6H_4	4-ClC_6H_4	27/0
1d	4-MeC_6H_4	4-BrC_6H_4	40/0
1h	*trans*-CH=CHPh	4-BrC_6H_4	18/0
1e	4-NCC_6H_4	4-BrC_6H_4	17/20
1f	$4\text{-O}_2\text{NC}_6H_4$	4-BrC_6H_4	29/9
1g	$3\text{-O}_2\text{NC}_6H_4$	4-BrC_6H_4	11/9
1i	*trans*-C(Ph)=CHPh	Ph	0/0
1j	4-MeOC_6H_4	4-MeOC_6H_4	0/0
1k	4-MeOC_6H_4	Ph	0/0
1l	Ph	Ph	0/0
1m	$4\text{-O}_2\text{NC}_6H_4$	4-MeOC_6H_4	0/0

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To check the possibility of formation of both isomeric ylides under conditions where the only the *endo*-**2** isomer of intramolecular cycloaddition was detected, we performed the catalytic reaction of EDA with imine **1d** in the presence of excess fumaronitrile as the external dipolarophile. In this case along with intramolecular cycloadduct *endo*-**2d** (29%) the sole intermolecular cycloadduct, compound **4**, was detected by ^{1}H NMR, and isolated by chromatography in 9% yield (Scheme 5).

The stereochemistry of cycloadduct **4** was established by 2D-^{1}H-NOESY (see the ESI†). Cycloaddition of the U- and S-ylides should lead to pyrrolidines of different configurations. As one can see from Scheme 5, compound **4** is the product of cycloaddition of the S-ylide to the C=C bond of fumaronitrile. Consequently, the product of intramolecular cycloaddition, compound *endo*-**2d**, and of intermolecular cycloaddition, compound **4**, are derived from ylides of different types. According to DFT B3LYP/6-31G(d) computations the barriers of intermolecular cycloaddition of the U-ylide are much higher than the corresponding barriers of the S-ylide and this is in accordance with the experimental result. We can conclude from this that both isomeric ylides are formed in the reactions and that we can reject the first hypothesis.

The second reason for the stereoselectivity found could be interconversion of isomers of compound **2** under the reaction conditions. Isomer *endo*-**2a** in the presence of $Cu(tfacac)_2$ in boiling CH_2Cl_2 for 8 h led to decomposition of 33% of the compound to a complex unidentified mixture and conversion of less than 5% to isomer *exo*-**2a**. Isomer *exo*-**2a** was shown to be stable under these conditions. It was also found that isomer *endo*-**2f**, containing an electron withdrawing substituent in the benzoyl group, did not convert into isomer *exo*-**2f** or other products under the reaction conditions. These results then disprove the second hypothesis.

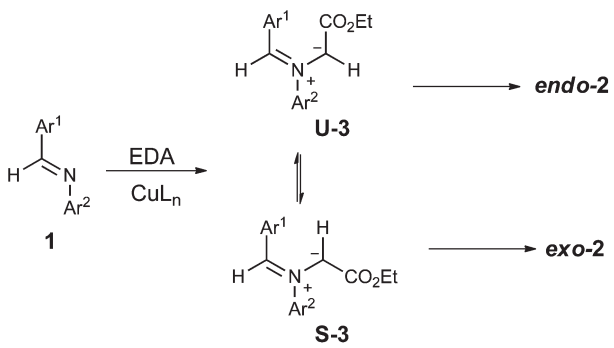
A third hypothesis assumes the formation of both the S- and U-ylides **3** in the reaction of imine **1** with ethyl diazoacetate, but considers that the barrier of transformation of the S-ylide to an *exo*-**2**, for substrates which do not contain electron withdrawing substituents in the benzoyl group, is higher than the barrier of transformation of the S- to the U-ylide **3** and higher than the barrier for transformation of the U-ylide **3** into the cycloadduct *endo*-**2**.

The computations at the DFT B3LYP/6-31G(d) level of the model compounds were used to check this third hypothesis. The sequence of transformations of the ylides **3**, generated from the imines **1** and the carbenoid (from diazoacetic acid for simplicity), leading to cycloadducts *exo*- and *endo*-**2** is shown in Fig. 2.

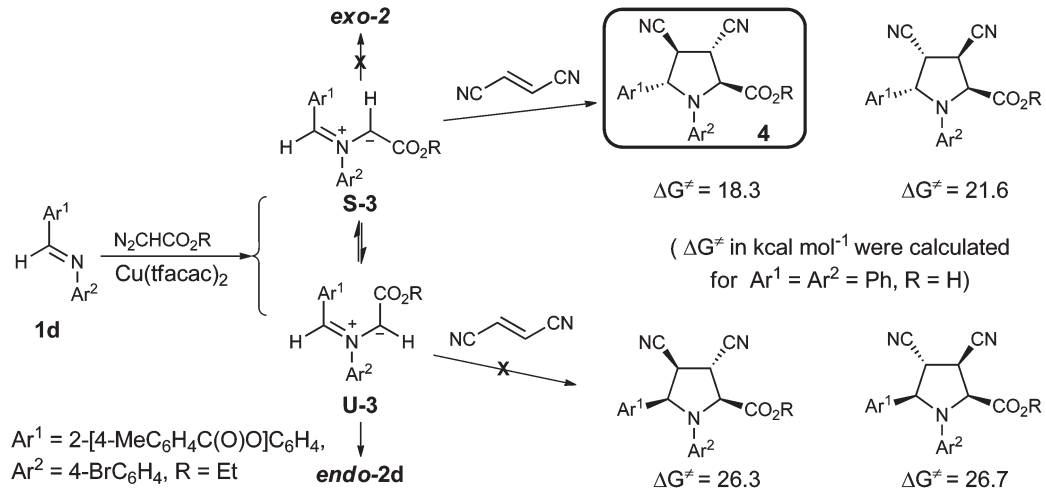
Interaction of the lowest energy conformation of (*E*)-imines **1** with the carbenoid leads to the formation of unfolded conformers of ylides **S-3′**, **S-3″** and **U-3′**, **U-3″**. These ylides can adopt the higher energy conformations of **S-3** and **U-3** *via* rotation about single bonds, and these are the immediate precursors of *exo*- and *endo*-**2**, respectively. The free energy profile of transformations of the model ylides **3l*** and **3n*** calculated at DFT B3LYP/6-31G(d) level is shown in Fig. 3.

The formation of the ylides **S-3** and **U-3** from ylides **S-3′** and **U-3′** occurs by rotation about single C–O and C–C bonds. Transformation of ylide **S-3′** to ylide **U-3′** (and back) can occur in two ways: (i) **S-3′** ⇄ **S-3″** ⇄ **U-3′**; (ii) **S-3′** ⇄ **U-3″** ⇄ **U-3′**. According to calculations (Fig. 3) the second pathway has a higher barrier than the first one.

For ylides containing an unsubstituted benzoyl group the free energy of the transition state for the formation of *endo*-cycloadduct ($TS_{S\text{-}3/exo\text{-}2}$) and the energy of the transition state for the transformation of ylide **S-3″** into ylide **U-3′** ($TS_{S\text{-}3''/U\text{-}3'}$) is



Scheme 4 Structure of ylides leading to stereoisomers of compound **2**.



Scheme 5 Reaction of imine **1d** with EDA in the presence of fumaronitrile.

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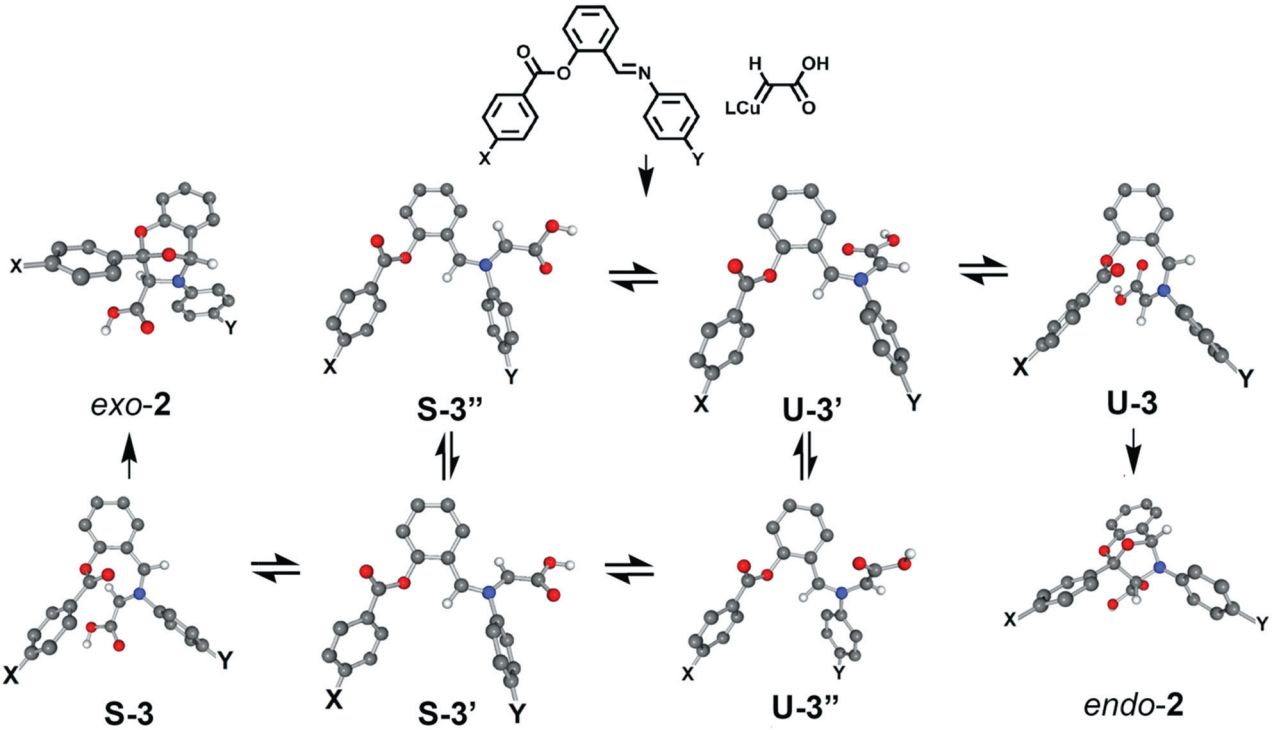

Fig. 2 The sequence of transformations of ylides **3*** leading to cycloadducts **2*** (See formulas in Fig. 3). The molecules presented correspond to the stationary points (minima) on the potential energy surface. Hydrogen atoms on aromatic rings are omitted for clarity.

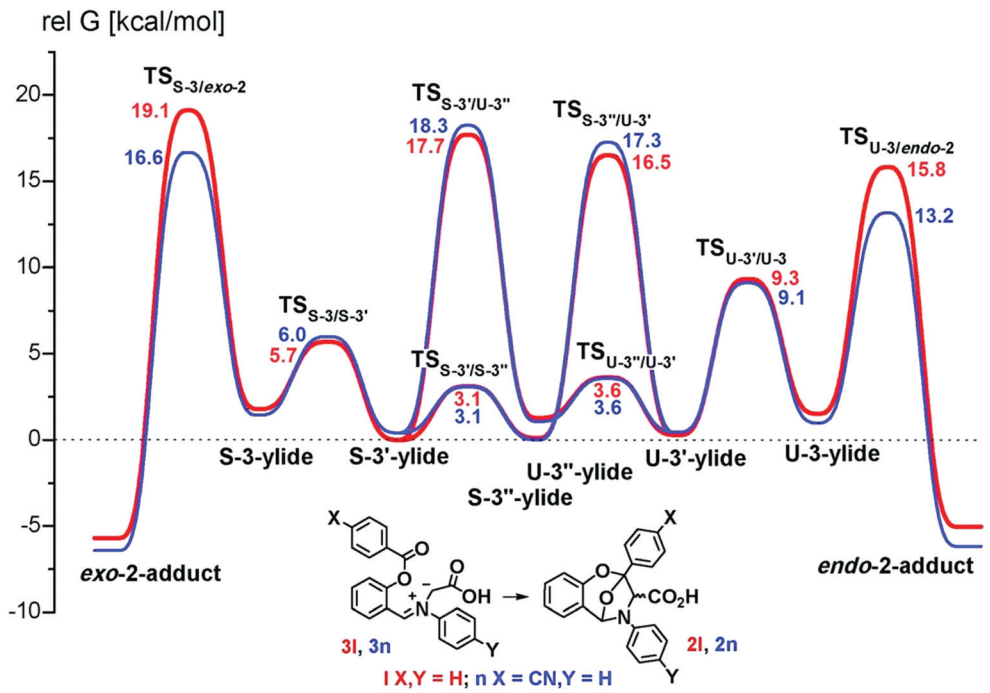

Fig. 3 Energy profiles for transformations of ylides **3***. Relative free energies [kcal mol^{-1}, 298K] computed at the B3LYP/6-31G(d) level.

higher than the energy of the transition state for the formation of *exo*-cycloadduct ($TS_{U\text{-}3/endo\text{-}2}$). In this case therefore, according to the calculations, the *endo*-cycloadduct has to be the main product. The situation became quite different for compounds containing electron-withdrawing substituents in the benzoyl group. Introduction of a cyano group leads to a small increase in the free energy of the transition state for the interconversion of the ylides and a relatively big decrease in energy of the transition state for the transformation of the ylides into cycloadducts (Fig. 3). This permits an easier transformation of ylide **S-3** into

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Table 2 Energy barriers of transformation of ylides **S-3** into cycloadducts *exo*-**2** and ylides **U-3** into cycloadducts *endo*-**2** (See formulas in Fig. 2 and 3). $\Delta G^{\#}$ [kcal mol^{-1}, 297 K] computed at the B3LYP/6-31G(d) level

X	Y	ylide **S-3** → cycloadduct *exo*-**2**	ylide **U-3** → cycloadduct *endo*-**2**
H	H	17.3	14.3
CN	H	15.3	12.2
H	Cl	17.1	13.3
OH	H	18.1	15.3
H	OH	17.5	14.5

the *exo*-**2** cycloadduct, than for the transformation into ylide **U-3**, the precursor of the *endo*-**2** cycloadduct.

Introduction of an electron-donating substituent into the benzoyl fragment leads as expected to an enlarged barrier to cycloaddition, and it has a small effect on the barrier for the interconversion of the ylides (Table 2).

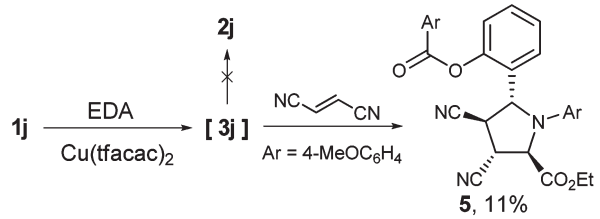
Thus the found stereoselectivity of the reaction of the substrates without electron withdrawing substituents on the benzoyl group is due to the free energy of the transition state for the formation of cycloadduct *exo*-**2** being higher than the energy of the transition state for the isomerization of the S-ylide **3** to the U-ylide **3**. The latter undergoes transformation into the *endo*-**2** cycloadduct through a relatively low-energy transition state. Introduction of an electron withdrawing substituent in the *p*-position of the benzoyl group of the starting imine makes the cycloaddition of S-ylide **3**, leading to cycloadduct *exo*-**2**, more favorable than the S-ylide ⇄ U-ylide interconversion.

The reaction of EDA with imine **1h** containing both C═O and C═C dipolarophilic fragments yielded only the cycloadduct *endo*-**2h**. The lack of cycloadducts to the C═C bond is probably explained by a high rigidity of the 4-atomic linker with three sp^2 centers, preventing effective overlap of orbitals of the 1,3-dipole and the C═C bond. Imine **1h** demonstrated a similar behavior in the reaction with difluorocarbene.[5a]

Unexpectedly, the reaction of EDA with imines **1i–1m**, which do not contain halogen in the *N*-aryl group, gave no cycloaddition to the C═O bond. This is maybe due to (i) the ylide not being formed in this case, (ii) the intramolecular cycloaddition having a higher activation barrier so the ylide undergoes nonselective decomposition or reacts faster with the external dipolarophiles, dimethyl maleate and dimethyl fumarate, which are both practically always formed as byproducts during catalytic decomposition of ethyl diazoacetate.[7] In fact, according to calculations at the DFT B3LYP/6-31G(d) level, the introduction of a chlorine atom into the *N*-phenyl ring diminishes the barrier for the intramolecular cycloaddition, making this process more competitive and leading to the formation of the *endo*-**2** cycloadduct (Table 2).

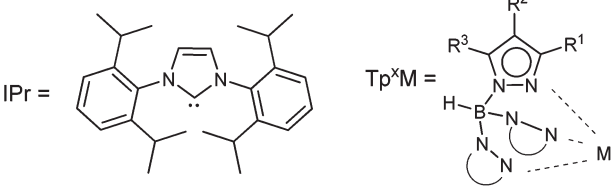
As mentioned above, imines **1i–m**, in the catalytic reaction with EDA, did not give the products of intramolecular cycloaddition of their corresponding ylides. To check whether the ylides **2i–m** were still formed under the conditions used, the reaction of imine **1j** was performed in the presence of excess fumaronitrile as external dipolarophile, and cycloadduct **5** was isolated as the sole product (Scheme 6).

The configuration of cycloadduct **5** was the same as the configuration of cycloadduct **4**, therefore also being derived



Scheme 6 Reaction of imine **1j** with EDA in the presence of fumaronitrile.

6 IPrCuCl; **7** IPrCuCl/NaB[2-$(F_3C)_2C_6H_3]_4$; **8** $Tp^{Br,iPr}Cu$, R^1= iPr, R^2= Br, R^3= H; **9** $Tp^{Ph}Cu$, R^1= Ph, R^2= H, R^3= H; **10** $Tp^{Br3}Cu$, R^1= R^2= R^3= Br; **11** $Tp^{*Br}Cu$, R^1= Me, R^2= Br, R^3= Me; **12** $Tp^{Br3}Ag$, R^1= R^2= R^3= Br



Scheme 7 Catalysts used in the reaction of **1a** with EDA.

from the S-ylide. This result confirms the formation of ylide **3j**, which however does not undergo intramolecular cycloaddition to the C═O bond. As one can see from Table 2 the electron donating substituents both on the benzoyl and on the *N*-phenyl groups lead to an enlarging of barriers to intramolecular cycloaddition to the C═O bond making this reaction noncompetitive with reactions leading to byproducts. In accordance with this assumption the reaction of imine **1f**, containing electron withdrawing substituents, led exclusively to products of intramolecular cycloaddition to the C═O bond, even in the presence of excess fumaronitrile as external dipolarophile.

Choice of catalyst is often the critical point in the reactions of alkyl diazoacetates with imines.[7] Rhodium derivatives which were most widely used as catalysts in the reaction of alkyl diazoacetates with olefinic substrates can be used in reactions with some simple imines. It usually failed, however, in the reactions with imines containing functional groups.[6] For example, $Rh_2(AcO)_4$ does not work as catalyst in the reaction of salicylic aldehyde derived imines with EDA.[4e]

The results obtained show that it is also important that the catalyst should not promote the formation of carbene dimers, which can react as external dipolarophiles. It prompted us to look at catalysts based on Cu complexes with neutral (NHC) or anionic (Tp^x) ligands which are known to decompose EDA in the presence of olefinic substrates without producing the carbene dimers.[11] Here we investigated their capability of forming of azomethine ylides from EDA and imines. Reactions of imine **1a** with EDA in CH_2Cl_2 at r.t. were performed in the presence of catalysts **6–12** (Scheme 7), but only catalyst **7** gave any corresponding cycloadduct of ylide **3** (compound *endo*-**2a**, 23%).

Conclusions

The products of the intramolecular 1,3-dipolar cycloaddition of alkoxycarbonyl-substituted azomethine ylides to ester carbonyl

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were obtained for the first time in the reaction of imines of *O*-acylsalicylic aldehyde with ethyl diazoacetate in the presence of $Cu(tfacac)_2$. It was found that the stereoselectivity of the cycloaddition depends on the substituents on the benzoyl group of the substrate. Imines with electron withdrawing substituents in the *p*- or *m*-position of the benzoyl group gave a mixture of *endo*- and *exo*-isomers of ethyl 2,5-epoxy-1,4-benzoxazepine-3-carboxylates, whereas substrates without such substituents gave the *endo*-isomers exclusively. According to DFT computations the change of stereoselectivity of cycloaddition is caused by a decrease of the barrier to cycloaddition and a small increase of the barrier to the U- and S-ylide interconversion when an electron withdrawing substituent is introduced on the benzoyl group of the reactant.

Experimental section

General methods

Melting points were determined on a hot stage microscope (Boetius) and are uncorrected. IR spectra were recorded on a Specord M80 spectrometer. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were determined in $CDCl_3$ or DMSO-d_6 with a Bruker DPX 300 spectrometer. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane. Elemental analysis was performed on a Hewlett-Packard 185B CHN-analyser. The single crystal X-ray data were collected at 120(1)K on a Bruker SMART CCD 6000 diffractometer equipped with a Cryostream (Oxford Cryosystems) cryostat using graphite monochromated MoKα radiation (λ = 0.71073 Å). The structure was solved by direct method and refined by full-matrix least squares on F^2 for all data using OLEX2 software. All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms were located on the difference map and refined isotropically. Flash chromatography was performed using Merck silica (0.040–0.063 mm). TLC analysis was performed on glass backed plates (Merck) coated with 0.2 mm silica layer with UV-indicator 60F254.

Imines 1

O-Acylsalicylaldehydes were synthesized by acylation of salicylaldehyde with the corresponding acid chlorides in dry DMF in the presence of anhydrous K_2CO_3. Imines were prepared by condensation of aldehydes with amines in ethanol.[12] Imines **1a**, **b**, **e**, **i–l** were described earlier.[5]

2-(4-Chlorophenyliminomethyl)phenyl 4-methoxybenzoate (1c). (1.14 g, 78%) was obtained from 2-formylphenyl 4-methoxybenzoate (1.0 g, 4 mmol) and 4-chloroaniline (510 mg, 4 mmol). Mp = 101–102 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ = 3.90 (3H, s, OC*H*$_3$), 6.99–8.22 (12H, m, H$_{Ar}$), 8.57 (1H, s, C*H*=N). ^{13}C NMR ($CDCl_3$): δ = 55.5 (OC*H*$_3$), 114.0, 121.1, 122.1, 123.2, 126.3, 128.3, 128.5, 129.2, 131.6, 132.4, 150.5, 151.1, 155.3 (C$_{Ar}$), 164.2 (*C*H=N), 164.7 (*C*O$_2$R). IR ($CHCl_3$) ν_{max}: 1730 (CO_2R), 1603 (CH=N) cm^{-1}. Anal. calcd for $C_{21}H_{16}ClNO_3$, %: C, 68.95; H, 4.4; N, 3.8. Found, %: C, 69.15; H, 4.5; N, 3.9.

2-(4-Bromophenyliminomethyl)phenyl 4-methylbenzoate (1d). (1.4 g, 75%) was obtained from 2-formylphenyl 4-methylbenzoate (1.13 g, 4.7 mmol) and 4-bromoaniline (0.81 g, 4.7 mmol). Mp = 133.5–134.5 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ = 2.47 (3H, s, C*H*$_3$), 6.95–8.22 (12H, m, H$_{Ar}$), 8.56 (1H, s, C*H*=N). ^{13}C NMR ($CDCl_3$): δ = 21.8 (*C*H$_3$), 119.5, 122.5, 123.1, 126.1, 126.3, 128.2, 128.6, 129.5, 130.3, 132.1, 132.5, 144.9, 150.9, 151.1 (C$_{Ar}$), 155.4 (*C*H=N), 165.1 (*C*O$_2$R). IR ($CHCl_3$) ν_{max}: 1750 (CO_2R), 1625 (CH=N) cm^{-1}. Anal. calcd for $C_{21}H_{16}BrNO_2$, %: C, 64.0; H, 4.1; N, 3.55. Found, %: C, 63.9; H, 4.2; N, 3.7.

2-(4-Bromophenyliminomethyl)phenyl 4-nitrobenzoate (1f). (3.7 g, 87%) was obtained from 2-formylphenyl 4-nitrobenzoate (2.8 g, 10 mmol) and 4-bromoaniline (1.72 g, 10 mmol). Mp = 115–117 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ = 6.86–8.42 (12H, m, H$_{Ar}$), 8.48 (1H, s, C*H*=N). ^{13}C NMR ($CDCl_3$): δ = 119.7, 122.3, 123.1, 123.8, 126.9, 127.8, 130.5, 131.4, 132.2, 132.5, 134.6, 149.9, 150.6, 150.9 (C$_{Ar}$), 155.6 (*C*H=N), 163.3 (*C*O$_2$R). IR ($CHCl_3$) ν_{max}: 1740 (CO_2R), 1620 (CH=N) cm^{-1}. Anal. calcd for $C_{20}H_{13}BrN_2O_4$, %: C, 56.5; H, 3.1; N, 6.6. Found, %: C, 56.5; H, 3.1; N, 6.4.

2-(4-Bromophenyliminomethyl)phenyl 3-nitrobenzoate (1g)

(a) 2-Formylphenyl 3-nitrobenzoate. (14.1 g, 87%) was obtained from salicylic aldehyde (7.3 g, 0.06 mol), K_2CO_3 (12.4 g, 0.09 mol) and 3-nitrobenzoyl chloride (14.5 g, 0.078 mol). Mp = 119–121 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ = 7.31–9.04 (8H, m, H$_{Ar}$), 10.10 (1H, s, C*H*O). ^{13}C NMR ($CDCl_3$): δ = 123.4, 125.3, 127.0, 128.0, 128.2, 139.0, 130.7, 132.4, 135.5, 135.9, 148.4, 150.7 (C$_{Ar}$), 163.0 (*C*O$_2$R), 188.6 (*C*H=O). IR (KBr) ν_{max}: 1760 (CO_2R), 1700 (CH=O) cm^{-1}. Anal. calcd for $C_{14}H_9NO_5$, %: C, 62.0; H, 3.3; N, 5.2. Found, %: C, 61.95; H, 3.1; N, 5.05.

*(b) 2-(4-Bromophenyliminomethyl)phenyl 3-nitrobenzoate (**1g**).* (7.01 g, 82%) was obtained from 2-formylphenyl 3-nitrobenzoate (5.4 g, 20 mmol) and 4-bromoaniline (3.44 g, 20 mmol). Mp = 129–131 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ = 6.88–8.55 (12H, m, H$_{Ar}$), 9.07 (1H, s, C*H*=N). ^{13}C NMR ($CDCl_3$): δ = 119.7, 122.3, 123.1, 125.2, 126.9, 127.9, 128.1, 130.0, 130.4, 131.0, 132.2, 132.5, 135.8, 148.4, 150.0, 150.7 (C$_{Ar}$), 155.6 (*C*H=N), 163.1 (*C*O$_2$R). IR ($CHCl_3$): ν_{max}: 1760 (CO_2R), 1635 (CH=N) cm^{-1}. Anal. calcd for $C_{20}H_{13}BrN_2O_4$, %: 56.5; H, 3.1; N, 6.6. Found, %: C, 56.3; H, 3.1; N, 6.6.

2-(4-Bromophenyliminomethyl)phenyl cinnamate (1h). (1.58 g, 78%) was obtained from 2-formylphenyl cinnamate (1.26 g, 5 mmol) and 4-bromoaniline (0.86 g, 5 mmol). Mp = 111–112 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ = 6.71 (1H, d, J = 16 Hz, C*H*=CHPh), 7.05–7.64 (12H, m, H$_{Ar}$), 7.95 (1H, d, J = 16 Hz, CH=C*H*Ph), 8.20–8.23 (1H, m, H$_{Ar}$), 8.58 (1H, s, C*H*=N). ^{13}C NMR ($CDCl_3$): δ = 116.4, 119.5, 122.6, 123.0, 126.3, 128.1, 128.4, 128.5, 129.0, 131.0, 132.2, 132.5, 133.9, 147.5, 150.9, 151.1 (C$_{Ar}$, CH=*C*HPh, *C*H=CHPh), 155.5 (*C*H=N), 165.2 (*C*O$_2$R). IR ($CHCl_3$) ν_{max}: 1740 (CO_2R), 1640 (CH=N), 1590 (C=C) cm^{-1}. Anal. calcd for $C_{22}H_{16}BrNO_2$, %: C, 65.0; H, 4.0; N, 3.45. Found, %: C, 65.0; H, 3.7; N, 3.5.

2-(4-Methoxyphenyliminomethyl)phenyl 4-methoxybenzoate (1j). (1.53 g, 85%) was obtained from 2-formylphenyl 4-

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Published on 13 June 2012 on http://pubs.rsc.org | doi:10.1039/C2OB25676B

methoxybenzoate (1.28 g, 5 mmol) and 4-methoxyaniline (738 mg, 6 mmol). Mp = 74–76 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ = 3.79 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 6.85–8.24 (12H, m, H_{Ar}), 8.62 (1H, s, C*H*═N). ^{13}C NMR ($CDCl_3$): δ = 55.4 (OCH_3), 55.5 (OCH_3), 114.0, 114.3, 121.4, 122.2, 123.1, 126.2, 128.4, 128.8, 131.8, 132.4, 150.0, 150.9, 152.9, 158.4 (C_{Ar}), 164.1 (*C*H═N), 164.8 (*C*O_2R). IR ($CHCl_3$) ν_{max}: 1740 (CO_2R), 1620 (CH═N) cm^{-1}. Anal. calcd for $C_{22}H_{19}NO_4$, %: C, 73.1; H, 5.3; N, 3.9. Found, %: C, 73.1; H, 5.3; N, 3.9.

2-(4-Methoxyphenyliminomethyl)phenyl 4-nitrobenzoate (1m). (1.32 g, 95%) was obtained from 2-formylphenyl 4-nitrobenzoate (1.0 g, 3.7 mmol) and 4-methoxyaniline (585 mg, 3.7 mmol). Mp = 97.5–98.5 °C (EtOH). ^{1}H NMR ($CDCl_3$): δ = 3.77 (3H, s, OCH_3), 6.81–8.42 (12H, m, H_{Ar}), 8.52 (1H, s, C*H*═N). ^{13}C NMR ($CDCl_3$): δ = 55.4 (OCH_3), 114.3, 122.0, 123.0, 123.7, 126.8, 128.3, 130.3, 131.4, 131.8, 134.8, 144.5, 149.7, 150.9, 153.0 (C_{Ar}), 158.5 (*C*H═N), 163.4 (*C*O_2R). IR ($CHCl_3$) ν_{max}: 1740 (CO_2R), 1620 (CH═N) cm^{-1}. Anal. calcd for $C_{21}H_{16}N_2O_5$, %: C, 67.0; H, 4.3; N, 7.4. Found, %: C, 67.1; H, 4.2; N, 7.5.

General procedures for the reactions of imines 1 with EDA

A: A solution of EDA in dry CH_2Cl_2 was added using a syringe pump to a solution of imine **1** and equivalent of Cu(tfacac)$_2$ in dry CH_2Cl_2 at 40 °C under Ar (*ca*. 8 h). The reaction was monitored by TLC (hexane–EtOAc, 5 : 1). After completion of the reaction the solvent was removed on rotary evaporator and the residue was separated by column chromatography on silica gel (hexane–EtOAc).

B: A solution of EDA in dry benzene was added using a syringe pump to a solution of imine **1** and Cu(tfacac)$_2$ (10 mol%) in dry benzene at 80 °C under Ar. The reaction was monitored by TLC (hexane–EtOAc, 5 : 1). After completion of the reaction the solvent was removed on rotary evaporator and the residue was separated by column chromatography on silica gel (hexane–EtOAc).

Ethyl (2*RS*,3*SR*,5*RS*)-4-(4-bromophenyl)-2-(4-methoxyphenyl)-2,3,4,5-tetrahydro-2,5-epoxy-1,4-benzoxazepine-3-carboxylate (*endo*-2a) (32 mg, 13%), and ethyl (2*RS*,3*RS*,5*RS*)-4-(4-bromophenyl)-2-(4-methoxyphenyl)-2,3,4,5-tetrahydro-2,5-epoxy-1,4-benzoxazepine-3-carboxylate (*exo*-2a) (35 mg, 14%) were obtained using procedure B from imine **1a** (205 mg, 0.5 mmol) and EDA (684 mg, 6 mmol). Compound *endo*-**2a** (102 mg, 41%) was obtained using procedure A from imine **1a** (205 mg, 0.5 mmol) and EDA (684 mg, 6 mmol).

endo-**2a**: Mp = 130.5–131.5 °C (ether–hexane). ^{1}H NMR ($CDCl_3$): δ = 1.06 (3H, t, J = 7.1 Hz, CH_2CH_3), 3.85 (3H, s, OCH_3), 4.03–4.16 (2H, m, CH_2CH_3), 4.64 (1H, s, C^{3}H), 6.43 (1H, s, C^{5}H), 6.51–6.54 (2H, m, C_{Ar}H), 6.86–6.99 (4H, m, C_{Ar}H), 7.21–7.36 (4H, m, C_{Ar}H), 7.72–7.75 (2H, m, C_{Ar}H). ^{13}C NMR ($CDCl_3$): δ = 13.9 (CH_2CH_3), 55.3 (OCH_3), 61.5 (CH_2CH_3), 74.2 (C^3), 88.4 (C^5), 106.4 (C^2), 111.2, 113.7, 113.8, 115.6, 121.0, 123.5, 123.6, 127.1, 128.3, 129.9, 132.3, 143.1, 151.0, 160.5 (C_{Ar}), 167.3 (*C*O_2Et). IR ($CHCl_3$) ν_{max}: 1750 (CO_2Et) cm^{-1}. Anal. calcd for $C_{25}H_{22}BrNO_5$, %: C, 60.5; H, 4.5; N, 2.8. Found, %: C, 60.5; H, 4.6; N, 2.6.

exo-**2a**: Mp = 150–151.5 °C (ether–hexane). ^{1}H NMR ($CDCl_3$): δ = 0.88 (3H, t, J = 7.2 Hz, CH_2CH_3), 3.84 (3H, s, OCH_3), 3.60–3.88 (2H, m, CH_2CH_3), 4.55 (1H, s, C^{3}H), 6.56 (1H, s, C^{5}H), 6.45–6.48 (2H, m, C_{Ar}H), 6.81–6.97 (4H, m, C_{Ar}H), 7.17–7.32 (4H, m, C_{Ar}H), 7.70–7.73 (2H, m, C_{Ar}H). ^{13}C NMR ($CDCl_3$): δ = 13.6 (CH_2CH_3), 55.4 (OCH_3), 61.6 (CH_2CH_3), 72.0 (C^3), 87.3 (C^5), 107.6 (C^2), 111.3, 113.3, 115.5, 116.3, 120.6, 122.0, 125.0, 126.2, 127.5, 130.3, 132.2, 140.8, 150.0, 160.6 (C_{Ar}), 168.1 (*C*O_2Et). IR ($CHCl_3$) ν_{max}: 1750 (CO_2Et) cm^{-1}. Anal. calcd for $C_{25}H_{22}BrNO_5$, %: C, 60.5; H, 4.5; N, 2.8. Found, %: C, 60.4; H, 4.6; N, 2.5. Crystal data for *exo*-**2a**: $C_{25}H_{22}BrNO_5$, M = 496.35, triclinic, a = 8.1931(2), b = 11.5561(3), c = 13.5965(4) Å, α = 65.4650(10), β = 89.4570(10), γ = 70.3560(10)°, U = 1090.13(5) Å^3, T = 120(2), space group $P\bar{1}$ (no. 2), Z = 2, μ(Mo-Kα) = 1.923, 12 682 reflections measured, 6586 unique (R_{int} = 0.0155) which were used in all calculations. Final w$R_2(F^2)$ = 0.070 for all data (377 refined parameters), conventional $R_1(F)$ = 0.0283 for 5629 reflections with $I \geq 2\sigma$, GOF = 1.097. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 874425.

Ethyl (2*RS*,3*SR*,5*RS*)-4-(4-bromophenyl)-2-phenyl-2,3,4,5-tetrahydro-2,5-epoxy-1,4-benzoxazepine-3-carboxylate (*endo*-2b). (90 mg, 39%) was obtained using procedure A from imine **1b** (190 mg, 0.5 mmol) and EDA (798 mg, 7 mmol). Mp = 120–122 °C (ether–hexane). ^{1}H NMR ($CDCl_3$): δ = 1.06 (3H, t, J = 7.1 Hz, CH_2CH_3), 4.02–4.18 (2H, m, CH_2CH_3), 4.65 (1H, s, C^{3}H), 6.47 (1H, s, C^{5}H), 6.52–6.55 (2H, m, C_{Ar}H), 6.88–6.99 (2H, m, C_{Ar}H), 7.22–7.49 (7H, m, C_{Ar}H), 7.80–7.83 (2H, m, C_{Ar}H). ^{13}C NMR ($CDCl_3$): δ = 13.9 (CH_2CH_3), 61.5 (CH_2CH_3), 74.3 (C^3), 88.6 (C^5), 106.2 (C^2), 111.4, 114.0, 115.6, 121.1, 123.5, 123.7, 125.7, 128.3, 129.6, 129.9, 132.3, 136.1, 143.2, 150.9 (C_{Ar}), 167.3 (*C*O_2Et). IR ($CHCl_3$) ν_{max}: 1750 (CO_2Et) cm^{-1}. Anal. calcd for $C_{24}H_{20}BrNO_4$, %: C, 61.8; H, 4.3; N, 3.0. Found, %: C, 61.8; H, 4.5; N, 2.7.

Ethyl (2*RS*,3*SR*,5*RS*)-4-(4-chlorophenyl)-2-(4-methoxyphenyl)-2,3,4,5-tetrahydro-2,5-epoxy-1,4-benzoxazepine-3-carboxylate (*endo*-2c). (61 mg, 27%) was obtained using procedure A from imine **1c** (183 mg, 0.5 mmol) and EDA (844 mg, 10 mmol). Mp = 133–134 °C (ether–hexane). ^{1}H NMR ($CDCl_3$): δ = 1.06 (3H, t, J = 7.1 Hz, CH_2CH_3), 3.85 (3H, s, OCH_3), 4.02–4.18 (2H, m, CH_2CH_3), 4.65 (1H, s, C^{3}H), 6.44 (1H, s, C^{5}H), 6.57–6.60 (2H, m, C_{Ar}H), 6.87–6.99 (4H, m, C_{Ar}H), 7.21–7.24 (4H, m, C_{Ar}H), 7.73–7.77 (2H, m, C_{Ar}H). ^{13}C NMR ($CDCl_3$): δ = 13.9 (CH_2CH_3), 55.3 (OCH_3), 61.5 (CH_2CH_3), 74.4 (C^3), 88.6 (C^5), 106.4 (C^2), 113.5, 113.7, 115.6, 121.0, 123.5, 123.6, 124.2, 127.1, 128.4, 129.4, 129.9, 142.8, 151.0, 160.5 (C_{Ar}), 167.4 (*C*O_2Et). IR ($CHCl_3$) ν_{max}: 1750 (CO_2Et) cm^{-1}. Anal. calcd for $C_{25}H_{22}ClNO_5$, %: C, 66.45; H, 4.9; N, 3.1. Found, %: C, 66.5; H, 5.0; N, 2.8.

Ethyl (2*RS*,3*SR*,5*RS*)-4-(4-bromophenyl)-2-(4-methylphenyl)-2,3,4,5-tetrahydro-2,5-epoxy-1,4-benzoxazepine-3-carboxylate (*endo*-2d). (94 mg, 40%) was obtained using procedure A from imine **1d** (197 mg, 0.5 mmol) and EDA (684 mg, 6 mmol). Mp = 120–124 °C (ether–hexane). ^{1}H NMR ($CDCl_3$): δ = 1.06 (3H, t, J = 7.1 Hz, CH_2CH_3), 2.41 (3H, s, CH_3), 4.01–4.18 (2H, m, CH_2CH_3), 4.64 (1H, s, C^{3}H), 6.45 (1H, s, C^{5}H), 6.51–6.54

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Published on 13 June 2012 on http://pubs.rsc.org | doi:10.1039/C2OB25676B

(2H, m, $C_{Ar}H$), 6.87–6.98 (2H, m, $C_{Ar}H$), 7.22–7.36 (6H, m, $C_{Ar}H$), 7.68–7.70 (2H, m, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$): δ = 13.9 (CH_2CH_3), 21.3 (CH_3), 61.5 (CH_2CH_3), 74.2 (C^3), 88.4 (C^5), 106.3 (C^2), 111.2, 113.9, 115.6, 121.0, 123.5, 123.6, 125.5, 129.0, 129.9, 132.3, 133.2, 139.5, 143.1, 150.9 (C_{Ar}), 167.3 (CO_2Et). IR (KBr) ν_{max}: 1750 (CO_2Et) cm^{-1}. Anal. calcd for $C_{25}H_{22}BrNO_4$, %: C, 62.5; H, 4.6; N, 2.9. Found, %: C, 62.5; H, 4.6; N, 2.75.

Ethyl (2*RS*,3*SR*,5*RS*)-4-(4-bromophenyl)-2-(4-cyanophenyl)-2,3,4,5-tetrahydro-2,5-epoxy-1,4-benzoxazepine-3-carboxylate (*endo*-2e) (42 mg, 17%) and (2*RS*,3*RS*,5*RS*)-4-(4-bromophenyl)-2-(4-cyanophenyl)-2,3,4,5-tetrahydro-2,5-epoxy-1,4-benzoxazepine-3-carboxylate (*exo*-2e) (48 mg, 20%). Obtained using procedure A from imine **1e** (203 mg, 0.5 mmol) and EDA (684 mg, 6 mmol).

endo-**2e**: Mp = 144–148 °C (EtOAc–hexane). ^{1}H NMR ($CDCl_3$): δ = 1.05 (3H, t, J = 7.1 Hz, CH_2CH_3), 4.02–4.17 (2H, m, CH_2CH_3), 4.56 (1H, s, C^3H), 6.50 (1H, s, C^5H), 6.54–6.57 (2H, m, $C_{Ar}H$), 6.88–7.00 (2H, m, $C_{Ar}H$), 7.27–7.39 (4H, m, $C_{Ar}H$), 7.75–7.95 (4H, m, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$): δ = 13.8 (CH_2CH_3), 61.8 (CH_2CH_3), 74.4 (C^3), 88.9 (C^5), 105.3 (C^2), 112.0, 113.5, 114.2, 115.6, 118.3 (CN), 121.6, 123.2, 123.9, 126.6, 130.2, 132.2, 132.4, 141.0, 143.1, 150.9 (C_{Ar}), 166.9 (CO_2Et). IR (KBr) ν_{max}: 1715 (CO_2Et), 2230 (CN) cm^{-1}. Anal. calcd for $C_{25}H_{19}BrN_2O_4$, %: C, 61.1; H, 3.9; N, 5.7. Found, %: C, 61.0; H, 3.8; N, 5.8.

exo-**2e**: Mp = 163–166 °C (dec.) (ether–hexane). ^{1}H NMR ($CDCl_3$): δ = 0.85 (3H, t, J = 7.1 Hz, CH_2CH_3), 3.58–3.87 (2H, m, CH_2CH_3), 4.58 (1H, s, C^3H), 6.59 (1H, s, C^5H), 6.45–6.48 (2H, m, $C_{Ar}H$), 6.86–6.91 (2H, m, $C_{Ar}H$), 7.20–7.33 (4H, m, $C_{Ar}H$), 7.74–7.95 (4H, m, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$): δ = 13.5 (CH_2CH_3), 61.9 (CH_2CH_3), 71.8 (C^3), 87.6 (C^2), 106.6 (C^5), 111.8, 113.7, 115.6, 116.3, 118.1 (CN), 121.2, 121.7, 125.1, 127.1, 130.6, 131.8, 132.3, 138.8, 140.3, 149.4 (C_{Ar}), 167.7 (CO_2Et). IR ($CHCl_3$) ν_{max}: 1760 (CO_2Et), 2240 (CN) cm^{-1}. Anal. calcd for $C_{25}H_{19}BrN_2O_4$, %: C, 61.1; H, 3.9; N, 5.7. Found, %: C, 61.0; H, 3.9; N, 5.5.

Ethyl (2*RS*,3*SR*,5*RS*)-4-(4-bromophenyl)-2-(4-nitrophenyl)-2,3,4,5-tetrahydro-2,5-epoxy-1,4-benzoxazepine-3-carboxylate (*endo*-2f) (75 mg, 29%) and (2*RS*,3*RS*,5*RS*)-4-(4-bromophenyl)-2-(4-nitrophenyl)-2,3,4,5-tetrahydro-2,5-epoxy-1,4-benzoxazepine-3-carboxylate (*exo*-2f) (23 mg, 9%). Obtained using procedure A from imine **1f** (213 mg, 0.5 mmol) and EDA (1140 mg, 10 mmol).

endo-**2f**: Mp = 157–160 °C (dec.) (CH_2Cl_2–hexane). ^{1}H NMR ($CDCl_3$): δ = 1.06 (3H, t, J = 7.1 Hz, CH_2CH_3), 4.02–4.19 (2H, m, CH_2CH_3), 4.58 (1H, s, C^3H), 6.52 (1H, s, C^5H), 6.55–6.58 (2H, m, $C_{Ar}H$), 6.90–7.04 (2H, m, $C_{Ar}H$), 7.28–7.39 (4H, m, $C_{Ar}H$), 7.99–8.01 (2H, m, $C_{Ar}H$), 8.31–8.34 (2H, m, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$): δ = 13.9 (CH_2CH_3), 61.8 (CH_2CH_3), 74.5 (C^3), 89.0 (C^5), 105.3 (C^2), 112.1, 114.3, 115.6, 121.7, 123.2, 123.6, 123.9, 127.0, 130.2, 132.5, 142.8, 143.2, 150.3 (C_{Ar}), 166.9 (CO_2Et). IR (KBr) ν_{max}: 1745 (CO_2Et) cm^{-1}. Anal. calcd for $C_{24}H_{19}BrN_2O_4$, %: C, 56.4; H, 3.75; N, 5.5. Found, %: C, 56.4; H, 3.7; N, 5.5.

exo-**2f**: Mp = 149–158 °C (dec.) (CH_2Cl_2–hexane). ^{1}H NMR ($CDCl_3$): δ = 0.86 (3H, t, J = 7.1 Hz, CH_2CH_3), 3.59–3.88 (2H, m, CH_2CH_3), 4.61 (1H, s, C^3H), 6.61 (1H, s, C^5H), 6.46–6.49 (2H, m, $C_{Ar}H$), 6.87–6.93 (2H, m, $C_{Ar}H$), 7.21–7.24 (2H, m, $C_{Ar}H$), 7.31–7.34 (2H, m, $C_{Ar}H$), 7.99–8.02 (2H, m, $C_{Ar}H$), 8.30–8.33 (2H, m, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$): δ = 13.6 (CH_2CH_3), 61.9 (CH_2CH_3), 71.9 (C^3), 87.7 (C^5), 106.7 (C^2), 111.8, 115.6, 116.4, 121.2, 121.7, 123.2, 125.1, 127.6, 130.6, 132.3, 140.5, 148.7, 149.4 (C_{Ar}), 167.7 (CO_2Et). IR (KBr) ν_{max}: 1745 (CO_2Et) cm^{-1}. Anal. calcd for $C_{24}H_{19}BrN_2O_4$, %: C, 56.4; H, 3.75; N, 5.5. Found, %: C, 56.5; H, 3.9; N, 5.6.

Ethyl (2*RS*,3*SR*,5*RS*)-4-(4-bromophenyl)-2-(3-nitrophenyl)-2,3,4,5-tetrahydro-2,5-epoxy-1,4-benzoxazepine-3-carboxylate (*endo*-2g) (27 mg, 11%) and (2*RS*,3*RS*,5*RS*)-4-(4-bromophenyl)-2-(3-nitrophenyl)-2,3,4,5-tetrahydro-2,5-epoxy-1,4-benzoxazepine-3-carboxylate (*exo*-2g) (23 mg, 9%). Obtained using procedure A from imine **1g** (213 mg, 0.5 mmol) and EDA (912 mg, 8 mmol).

endo-**2g**: Mp = 138–141 °C (EtOAc–hexane). ^{1}H NMR ($CDCl_3$): δ = 1.10 (3H, t, J = 7.1 Hz, CH_2CH_3), 4.04–4.23 (2H, m, CH_2CH_3), 4.60 (1H, s, C^3H), 6.52 (1H, s, C^5H), 6.54–6.57 (2H, m, $C_{Ar}H$), 6.92–7.04 (2H, m, $C_{Ar}H$), 7.28–7.39 (4H, m, $C_{Ar}H$), 7.64–7.68 (1H, m, $C_{Ar}H$), 8.12–8.15 (1H, m, $C_{Ar}H$), 8.31–8.35 (1H, m, $C_{Ar}H$), 8.71–8.73 (1H, m, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$): δ = 13.9 (CH_2CH_3), 61.9 (CH_2CH_3), 74.3 (C^3), 88.9 (C^5), 105.1 (C^2), 112.0, 114.2, 115.6, 121.5, 121.7, 123.2, 123.9, 124.5, 129.5, 130.2, 131.7, 132.4, 138.4, 143.1, 148.2, 150.3 (C_{Ar}), 166.8 (CO_2Et). IR (KBr) ν_{max}: 1755 (CO_2Et) cm^{-1}. Anal. calcd for $C_{24}H_{19}BrN_2O_4$, %: C, 56.4; H, 3.75; N, 5.5. Found, %: C, 56.6; H, 3.7; N, 5.6.

exo-**2g**: Mp = 137–140 °C (EtOAc–hexane). ^{1}H NMR ($CDCl_3$): δ = 0.84 (3H, t, J = 7.2 Hz, CH_2CH_3), 3.59–3.87 (2H, m, CH_2CH_3), 4.61 (1H, s, C^3H), 6.62 (1H, s, C^5H), 6.46–6.49 (2H, m, $C_{Ar}H$), 6.87–6.95 (2H, m, $C_{Ar}H$), 7.22–7.34 (4H, m, $C_{Ar}H$), 7.63–7.68 (1H, m, $C_{Ar}H$), 8.12–8.14 (1H, m, $C_{Ar}H$), 8.32–8.34 (1H, m, $C_{Ar}H$), 8.70–8.72 (1H, m, $C_{Ar}H$). ^{13}C NMR ($CDCl_3$): δ = 13.5 (CH_2CH_3), 61.9 (CH_2CH_3), 71.8 (C^3), 87.7 (C^5), 106.5 (C^2), 111.8, 115.7, 116.4, 121.2, 121.8, 124.6, 125.1, 129.2, 130.6, 132.2, 132.3, 136.2, 140.4, 148.0, 149.4 (C_{Ar}), 167.8 (CO_2Et). IR (KBr) ν_{max}: 1745 (CO_2Et) cm^{-1}. Anal. calcd for $C_{24}H_{19}BrN_2O_4$, %: C, 56.4; H, 3.75; N, 5.5. Found, %: C, 56.5; H, 3.8; N, 5.2.

Ethyl (2*RS*,3*SR*,5*RS*)-4-(4-bromophenyl)-2-[(*E*)-2-phenylvinyl)]-2,3,4,5-tetrahydro-2,5-epoxy-1,4-benzoxazepine-3-carboxylate (*endo*-2h). (44 mg, 18%) Obtained using procedure A from imine **1h** (246 mg, 0.5 mmol) and EDA (456 mg, 4 mmol). Mp = 129.5–130.5 °C (dec.) (EtOAc–hexane). ^{1}H NMR ($CDCl_3$): δ = 1.11 (3H, t, J = 7.1 Hz, CH_2CH_3), 4.10–4.20 (2H, m, CH_2CH_3), 4.59 (1H, s, C^3H), 6.37 (1H, s, C^5H), 6.51–6.54 (2H, m, $C_{Ar}H$), 6.59 (1H, d, J = 16.1 Hz, C*H*=CHPh), 6.84–6.98 (2H, m, $C_{Ar}H$), 7.18–7.51 (10H, m, $C_{Ar}H$, CH=C*H*Ph). ^{13}C NMR ($CDCl_3$): δ = 13.9 (CH_2CH_3), 61.6 (CH_2CH_3), 74.9 (C^3), 88.5 (C^5), 105.4 (C^2), 111.2, 113.8, 115.5, 121.0 (C_{Ar}), 122.4 (C*H*=CHPh), 123.5, 127.2, 128.7, 128.8, 129.9, 132.3 (C_{Ar}), 133.6 (CH=C*H*Ph), 135.2, 143.1, 150.8 (C_{Ar}), 167.2 (CO_2Et). IR (KBr) ν_{max}: 1720 (CO_2Et) cm^{-1}. Anal. calcd for $C_{26}H_{22}BrNO_4$, %: C, 63.4; H, 4.5; N, 2.8. Found, %: C, 63.2; H,4.3; N, 3.1.

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General procedure for the reactions of imines 1 with EDA in the presence of fumaronitrile

A solution of EDA in dry CH_2Cl_2 was added using a syringe pump to a solution of fumaronitrile, imine **1** and 10 mol% of $Cu(tfacac)_2$ in dry CH_2Cl_2 at 40 °C under Ar (*ca*. 8 h). The reaction was monitored by TLC (hexane–EtOAc, 5 : 1). After completion of the reaction the solvent was removed on rotary evaporator and the residue was separated by column chromatography on silica gel (hexane–EtOAc).

Ethyl (2*RS*,3*RS*,4*RS*,5*RS*)-1-(4-bromophenyl)-3,4-dicyano-5-(2-(4-methylbenzoyloxy)phenyl)pyrrolidine-2-carboxylate (4). Compound **4** (25 mg, 9%) and *endo*-**2d** (69 mg, 29%) were obtained from imine **1d** (197 mg, 0.5 mmol), fumaronitrile (312 mg, 4 mmol), and EDA (912 mg, 8 mmol). Compound **4**: Mp = 194–196 °C (CH_2Cl_2–hexane). ^{1}H NMR ($CDCl_3$): δ = 1.08 (3H, t, J = 7.1 Hz, CH_2CH_3), 2.46 (3H, s, CH_3), 3.60–3.63 (1H, dd, J = ^{1} 4.2 Hz, J = 2.9 Hz, C^4H), 3.71–3.73 (1H, dd, J = 2.9 Hz, J = 2 Hz, C^3H), 4.02–4.20 (2H, m, CH_2CH_3), 5.10 (1H, d, J = 2 Hz, C^2H), 5.38 (1H, d, J = 4.2 Hz, C^5H), 6.45–6.48 (2H, m, C_{Ar}H), 7.21–7.44 (8H, m, C_{Ar}H), 8.16–8.19 (2H, m, C_{Ar}H). ^{13}C NMR ($CDCl_3$): δ = 13.7 (CH_2CH_3), 21.8 (CH_3), 35.4 (C^4), 39.8 (C^3), 61.5 (C^2), 62.8 (CH_2CH_3), 65.9 (C^5), 113.1, 116.9 (2*CN), 117.8, 123.5, 125.5, 126.9, 127.2, 129.5, 130.3, 130.6, 132.2, 142.4, 145.3, 148.6 (C_{Ar}), 165.4 (CO_2R), 167.2 (CO_2Et). IR (KBr) ν_{max}: 1730 (CO_2R), 2250 (CN) cm^{-1}. Anal. calcd for $C_{29}H_{24}BrN_3O_4$, %: C, 62.4; H, 4.3; N, 7.5. Found, %: C, 62.4; H, 4.3; N, 7.4.

Ethyl (2*RS*,3*RS*,4*RS*,5*RS*)-3,4-dicyano-5-(2-(4-methoxybenzoyloxy)phenyl)-1-(4-methoxyphenyl)pyrrolidine-2-carboxylate (5). Compound **(5)** (30 mg, 11%) was obtained from imine **1j** (180 mg, 0.5 mmol), fumaronitrile (156 mg, 2 mmol), and EDA (912 mg, 8 mmol). **5**: Mp = 173–174 °C (CH_2Cl_2–hexane). ^{1}H NMR ($CDCl_3$): δ = 1.03 (3H, t, 7.1 Hz, CH_2CH_3), 3.55–3.57 (1H, dd, J = 5.4 Hz, J = 3.8 Hz, C^4H), 3.67–3.69 (1H, dd, J = 3.8 Hz, J = 2 Hz, C^3H), 3.69 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.96–4.14 (2H, m, CH_2CH_3), 5.05 (1H, d, J = 2 Hz, C^2H), 5.40 (1H, d, J = 5.4 Hz, C^5H), 6.60–6.63 (2H, m, C_{Ar}H), 6.73–6.76 (2H, m, C_{Ar}H), 7.01–7.04 (2H, m, C_{Ar}H), 7.19–7.49 (4H, m, C_{Ar}H), 8.25–8.28 (2H, m, C_{Ar}H). ^{13}C NMR ($CDCl_3$): δ = 13.7 (CH_2CH_3), 35.2 (C^4), 40.2 (C^3), 55.3 (OCH_3), 55.5 (OCH_3), 61.0 (C^2), 62.3 (CH_2CH_3), 66.8 (C^5), 114.0 (CN), 114.5 (CN), 117.2, 117.4, 118.5, 120.7, 123.3, 127.0, 129.9, 132.8, 136.7, 148.8, 154.1, 164.3, 165.0 (CO_2R), 169.1 (CO_2Et). IR (KBr) ν_{max}: 1720 (CO_2Et), 2250 (CN) cm^{-1}. Anal. calcd for $C_{30}H_{27}N_3O_6$, %: C, 68.6; H, 5.2; N, 8.0. Found, %: C, 68.6; H, 5.2; N, 8.1.

Computational details

All calculations were performed with the B3LYP density functional method[13] by using the Gaussian suite of quantum chemical programs. Geometry optimizations of intermediates, transition states, reactants, and products in the gas phase were performed at the B3LYP/6-31G(d) level using Gaussian 03.[14] Stationary points on the respective potential-energy surfaces were characterized at the same level of theory by evaluating the corresponding Hessian indices. Careful verification of the unique imaginary frequencies for transition states was carried out to check whether the frequency indeed pertains to the desired reaction coordinate. Intrinsic reaction coordinates (IRC) were calculated to authenticate all transition states.[15]

Acknowledgements

We gratefully acknowledge the financial support of the Russian Foundation for Basic Research (project 11-03-00186), Federal Grant-in-Aid Program "Human Capital for Science and Education in Innovative Russia" (Governmental Contract no. 16.740.11.0442), and Saint Petersburg State University for a research grant (№ 12.38.78.2012).

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