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# Regio- and stereoselective cycloadditions of (1*Z*,4*R**,5*R**)-1-arylmethylidene-4-benzoylamino-3-oxo-5-phenylpyrazolidin-1-ium-2-ides to methyl methacrylate

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ABSTRACT

[3+2] Cycloadditions of (1*Z*,4*R**,5*R**)-1-arylmethylidene-4-benzoylamino-3-oxo-5-phenylpyrazolidin-1-ium-2-ides **1a**–**e** to methyl methacrylate gave the 1-$CO_2$Me regioisomers **3**/**3′**, exclusively, in 1–67% yields. Stereocontrol was dependent on the *ortho*-substituents at the 1′-aryl group in dipole **1**: *ortho*-unsubstituted dipoles **1a**–**c** gave the major (1*R**,3*R**,5*R**,6*R**)-isomers **3a**–**c**, whilst *ortho*-disubstituted dipoles gave the major (1*R**,3*S**,5*R**,6*R**)-isomers **3′d**,**e**. The structures of cycloadducts were determined by NMR and X-ray diffraction.

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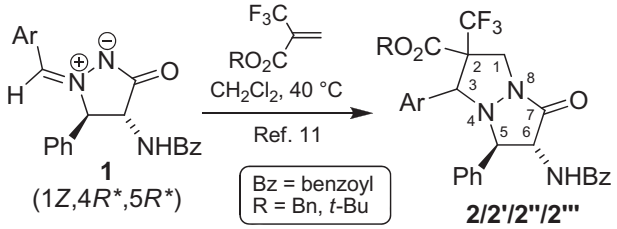
## 1. Introduction

1,3-Dipolar cycloadditions are useful reactions for the synthesis of polyfunctional heterocyclic compounds. They provide an easy access to five-membered heterocycles with multiple stereogenic centres, usually with excellent stereocontrol.[1] Asymmetric cycloadditions are well elaborated in chiral nitrone, nitrile oxide, and azomethine ylide series,[2] however, far fewer examples of asymmetric cycloadditions to chiral azomethine imines have been reported.[3]

The importance of pyrazolidin-3-one derivatives grew increasingly during the last decades due to their synthetic applicability and biological activity.[4] Recent applications of 3-pyrazolidinones include their use as templates in enantioselective Diels–Alder,[5] Michael,[6] and 'click' reactions,[3j,7] while Eli Lilly's antibiotics LY 186826, LY 193239, and LY 255262 are typical examples of bioactive pyrazolidinones.[8]

In the last decade, our studies on [3+2] cycloadditions of (1*Z*,4*R**,5*R**)-1-arylmethylidene-4-benzoylamino-3-oxo-5-phenyltetrahydropyrazol-1-ium-2-ides (1-arylmethylidene-4-benzoylamino-5-phenylpyrazolidin-3-on-1-azomethine imines) **1** to various dipolarophiles revealed general reactivity and selectivity of these cycloadditions,[9] as well as their applicability in high-throughput synthesis.[10]

Recently, Shibata and co-workers reported regioselective cycloadditions of 1-arylmethylidene-3-oxopyrazolidin-1-ium-2-ides **1** to alkyl 2-trifluoromethylacrylates, which led to mixtures of four diastereomers **2**/**2′**/**2″**/**2‴** with the ester group attached at position 2 (Scheme 1).[11]




**Scheme 1.**

However, regiochemistry of cycloadditions to alkyl 2-trifluoromethylacrylates, reported by Shibata and co-workers,[11] was not in agreement with our preliminary results on microwave-assisted cycloadditions of **1** to methyl methacrylate.[9b] Therefore, we decided to re-investigate these reactions with special focus on

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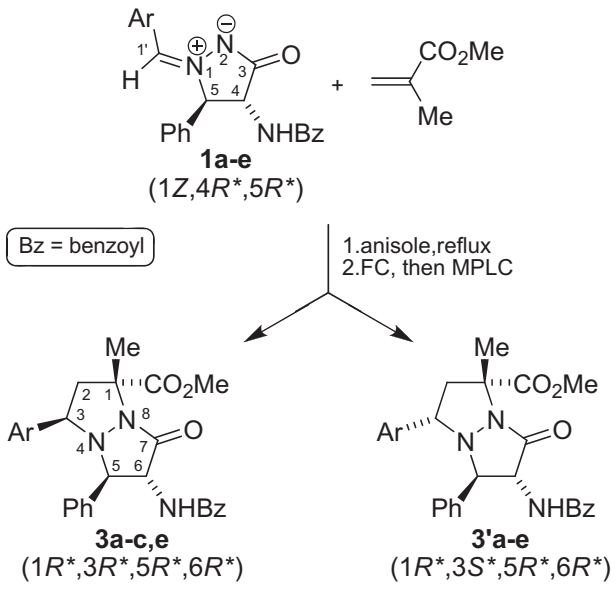
unambiguous structure determination. Herein, we report the results of this study, which established the regioselectivity and stereoselectivity of cycloadditions of azomethine imines **1** to methyl methacrylate.

## 2. Results and discussion

### 2.1. Synthesis of cycloadducts 3 and 3′

First of all, it turned out that conventional heating was equally effective for these cycloadditions as microwave-assisted heating, which had been used in the preliminary experiments.[9b] Thus, heating of dipoles **1a**–**e** with 1.2 equiv. of methyl methacrylate in anisole under reflux for 4 h, followed by evaporation in vacuo, first at 2 mbar/40 °C and then at 0.01 mbar/100 °C gave, exclusively, the 1-COOMe regioisomers as mixtures of diastereomers **3** and **3′**. Purification of the residues by flash chromatography (FC) gave purified mixtures of isomers **3**/**3′**, which were finally separated by medium pressure liquid chromatography (MPLC) to give isomerically pure cycloadducts **3a**–**c**,**e** and **3′a**–**e** in 1–67% yields (Scheme 2, Table 1).




**Scheme 2.**

### 2.2. Structure determination

The structures of cycloadducts were first determined by NMR experiments. The regiochemistry of cycloadducts **3** and **3′** was unambiguously established on the basis of chemical shifts ($\delta_{Ha}$ ~2.4 ppm, $\delta_{Hb}$ ~2.8 ppm) and the multiplicity of the signals for the methylene protons, which appeared as two doublets of a doublet with coupling constants, $^{2}J_{2Ha,2Hb}$ ~13 Hz, $^{3}J_{2Ha,3H}$ ~11 Hz, and $^{3}J_{2Hb,3H}$ ~6 Hz. In the case of the opposite regiochemistry, the signals for the methylene protons should appear as two doublets with geminal coupling constant, $^{2}J_{Ha,Hb}$ ~13 Hz, and with $\delta$ chemical shift ~4 ppm (Fig. 1, Table 2).[9,10,12]

Next, NOESY spectra of two representative cycloadducts **3b** and **3′e** were taken. The configuration at position 3 was essential for structure determination. In compound **3b**, an NOE between 3-H and 5-H supported the *syn*-orientation, while absence of an NOE enhancement between 3-H and 5-H in compound **3′e** was in agreement the *anti*-orientation between these two nuclei. Additionally, an NOE between 3-H and 6-H in compound **3′e** was in agreement with the *syn*-orientation of these protons. Accordingly, the (3*R**,5*R**,6*R**)-configuration was assigned to compound **3b** and the (3*S**,5*R**,6*R**)-configuration to compound **3′e**. Similarly, the (1*R**)-configuration of compounds **3b** and **3′e** was determined on the basis of an NOE between 1-Me and 2-Ha in **3b** and **3′e**, between 2-Hb and 3-H in **3b**, and between 2-Ha and 3-H in **3′e**. In summary, the (1*R**,3*R**,5*R**,6*R**)-configuration was assigned for compound **3b** and the (1*R**,3*S**,5*R**,6*R**)-configuration for compound **3′e**. NOE between the *trans*-oriented 5-H and 6-H in **3′e** is explainable by pseudoequatorial conformation of these two protons ($\theta$ ~90°), which is supported by negligible vicinal coupling constant, $^{3}J_{5H-6H}$ ~0 Hz (c.f. Fig. 1, Table 2).[13]

**Table 1**
Experimental data for compounds **3** and **3′**

| Compound | R | **3**/**3′** | Yield (%) | |
|---|---|---|---|---|
| | | | **3** | **3′** |
| **1a**, **3a**, **3′a** | Phenyl | 73:27 | 67 | 10 |
| **1b**, **3b**, **3′b** | 4-Nitrophenyl | 81:19 | 63 | 9 |
| **1c**, **3c**, **3′c** | 4-Methoxyphenyl | 68:32 | 29 | 13 |
| **1d**, **3d**, **3′d** | 2,6-Dichlorophenyl | 0:100 | — | 50 |
| **1e**, **3e**, **3′e** | 2,4,6-Trimethylphenyl | 11:89 | 1[a] | 15 |

[a] Characterized only by NMR.

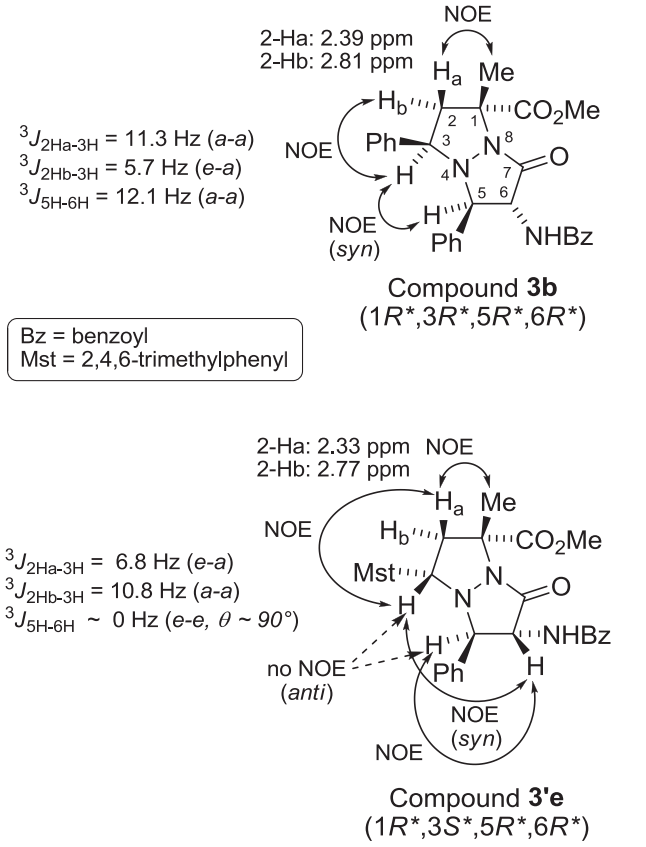



**Fig. 1.** Structure determination by $^{1}$H NMR and NOESY spectroscopy.

The configuration of compounds **3a**,**c**,**e** and **3′d** was determined by correlation of chemical shifts for the protons 2-Ha, 2-Hb, 3-H, 5-H, and 6-H and vicinal coupling constants, $^{3}J_{2Ha-3H}$, $^{3}J_{2Hb-3H}$, and $^{3}J_{5H-6H}$. Correlation data for compounds **3** and **3′** were also in agreement with the literature data for closely related known compounds (c.f. Fig. 1, Table 2).[9,10,12]

Finally, the structures of compounds **3b** and **3′d** were determined by X-ray diffraction (Figs. 2 and 3).

This structural study also revealed, that previous structural assignment of compounds **3a**–**c** was erroneous.[9b]

**Table 2**
Selected NMR data for compounds **3a**–**c**,**e** and **3′a**–**e**

| | $\delta$ (ppm) | | | | | $^3J_{H-H}$ (Hz) | | | Through-space H–H interactions (NOE) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2-Ha | 2-Hb | 3-H | 5-H | 6-H | 2a-3 | 2b-3 | 5–6 | 3–5 | Me-2a | Me-2b | 2a-3 | 2b-3 |
| **3a** | 2.46 | 2.76 | 4.12 | 4.25 | 5.42 | 11.4 | 5.6 | 11.9 | | | | | |
| **3b** | 2.39 | 2.81 | 4.26 | 4.29 | 5.49 | 11.3 | 5.7 | 12.1 | + | + | − | − | + |
| **3c** | 2.43 | 2.72 | 4.09 | 4.31 | 5.35 | 11.4 | 5.6 | 12.0 | | | | | |
| **3e** | 2.57 | 2.71 | 4.64 | 4.15 | 5.48 | 11.8 | 6.6 | 12.0 | | | | | |
| **3′a** | 2.54 | 2.63 | 3.63 | 4.29 | 5.23 | 6.8 | 9.0 | 2.6 | | | | | |
| **3′b** | 2.6[a] | 2.6[a] | 3.75 | 4.37 | 5.27 | 7.8 | 7.8 | 3.6 | | | | | |
| **3′c** | 2.52 | 2.62 | 3.60 | 4.22 | 5.21 | 6.8 | 8.7 | 3.0 | | | | | |
| **3′d** | 2.43 | 3.11 | 4.47 | 4.40 | 5.31 | 7.7 | 10.0 | 2.7 | | | | | |
| **3′e** | 2.33 | 2.77 | 3.92 | 4.33 | 5.13 | 6.8 | 10.8 | ~0 | − | + | − | + | − |

[a] The signals of 2-Ha and 2-Hb appeared as a multiplet.

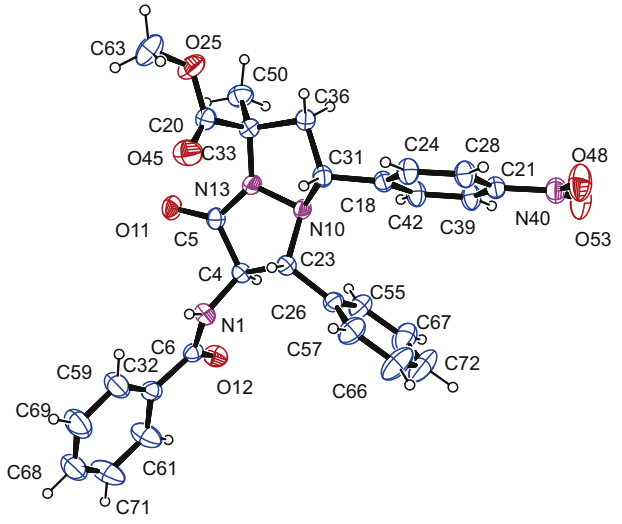



**Fig. 2.** The ORTEP drawing of compound **3b** showing the atom-numbering scheme.[14a,b]

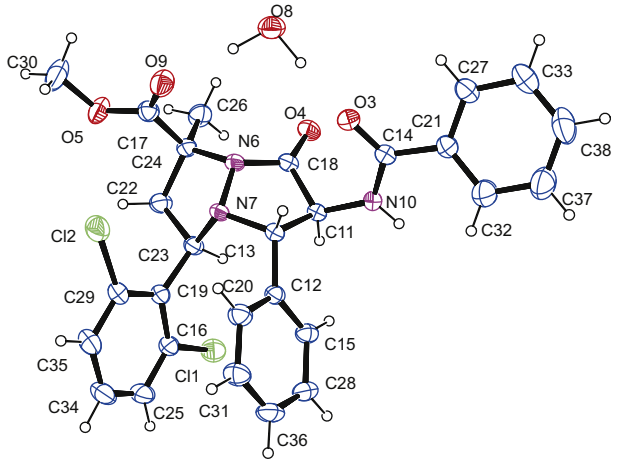
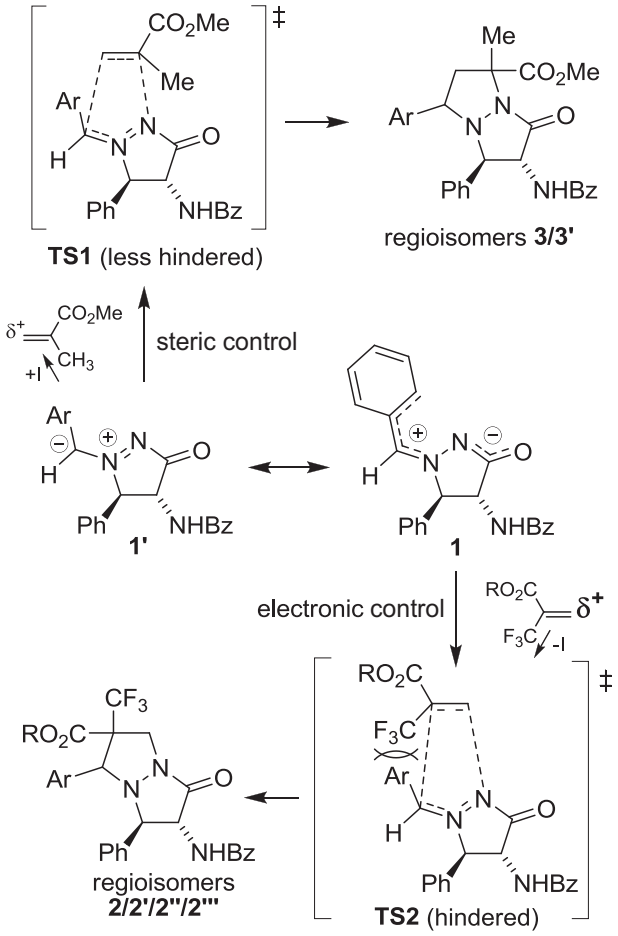



**Fig. 3.** The ORTEP drawing of the asymmetric unit of compound **3′d** showing the atom-numbering scheme.[14b]

## 2.3. Regio- and stereo-selectivity of cycloadditions

The regiochemistry and the stereochemistry of cycloadditions of **1a**–**e** to methyl methacrylate are explainable according to the Huisgen's concerted 1,3-dipolar cycloaddition mechanism.[15] Thus, a plausible rationale for the regioselectivity of cycloadditions of dipoles **1a**–**e** to methyl methacrylate is based on steric effects. In the proposed, less hindered transition state **TS1**, the disubstituted side of methacrylate is oriented away (*anti*) from the aryl substituent in the dipole **1′** and the 1-COOMe regioisomers **3**/**3′** are formed, selectively (Scheme 3).




**Scheme 3.**

On the other hand, the different regiochemistry of closely related cycloadditions to α-(trifluoromethyl)acrylates[11] might be explained by the electronic effects. In dipoles **1**, the negative charge is more likely located at the nitrogen N(2) atom due to stabilization of the negative charge by the carbonyl group, while the positive charge is stabilized by the 1′-aryl group. Preferential formation of the regioisomers **2**/**2′**/**2″**/**2‴** takes place by electrostatically controlled approach of the highly polarized α-(trifluoromethyl)acrylate to the mesomeric structure **1** via the proposed hindered transition state **TS2** (c.f. Scheme 3).

Regioselectivity of the above cycloadditions was correlated with frontier molecular orbital (FMO) energies and atomic Fukui indices,[16] obtained by density functional theory (DFT) calculations[17] for dipole **1a**, methyl methacrylate (MMA), and *tert*-butyl 2-(trifluoromethyl)acrylate (TMA). The calculated FMO energies and the largest values of Fukui indices for $N(2)_{HOMO}$ of dipole **1a** and $C(3)_{LUMO}$ of MMA and TMA were consistent with $dipole_{HOMO}$–$dipolarophile_{LUMO}$ controlled regioselective cycloadditions of **1a** to both dipolarophiles leading to the 2-$CO_2R$ regioisomers **2**/**2′**/**2″**/**2‴**.[15,18] This was clearly in agreement with the experimental results on cycloadditions of dipoles **1** to TMA.[11] On the other hand, the opposite regiochemistry of cycloadditions to MMA is explainable by the $dipole_{LUMO}$–$dipolarophile_{HOMO}$ control, which is feasible due to similar energy gaps ($\Delta E'-\Delta E$=0.5 eV) and large atomic Fukui indices for $C(1')_{LUMO}$ of dipole **1a** and $C(3)_{HOMO}$ of MMA. However, similar values of Fukui indices for C(2) and C(3) of $MMA_{HOMO}$ are not consistent with high regioselectivity of cycloadditions of dipoles **1** to MMA. Therefore, steric factors have to be taken into account in order to explain regioselective formation of the 1-$CO_2$Me regioisomers **3**/**3′** (c.f. Scheme 3).[15,18] The atomic Fukui indices for the terminal atoms of the HOMO and the LUMO of dipole **1a** and both dipolarophiles and their FMO energies are shown in Fig. 4.

The proposed transition state **TS1**. On the other hand, rotation around the C(1′)–Ar bond is not possible in *ortho*-disubstituted dipoles **1d**,**e**, which presumably adopt a twisted conformation **1″d**,**e**, where steric hindrance of the (1′*Re*)-face by the *ortho*-substituent pointing towards the N(2) becomes stronger than hindrance of the (1′*Si*)-face by the 5-Ph group.[15] Thus, the predominant *exo*-approach of the dipolarophile from the less hindered (1′*Si*)-face of the (*Z*)-dipoles **1″d**,**e** gives the major (1*R**,3*S**,5*R**,6*R**)-isomers **2′d**,**e** via the proposed transition state **TS1′**. The proposed conformations of dipoles **1a**–**c** and **1″d**,**e** are in agreement with the calculated conformational minima for dipoles **1a** and **1d** obtained by DFT calculations (Scheme 4).

## 3. Conclusion

In conclusion, cycloadducts **3a**–**c**,**e** and **3′a**–**e** were prepared by cycloadditions of dipoles **1a**–**e** to methyl methacrylate and the structures of the representative compounds **3b** and **3′d** were unambiguously determined by NMR and X-ray diffraction. Regiochemistry of cycloadditions was opposite to that observed by Shibata and co-workers in reactions with 2-trifluoromethyl acrylates.[11] This indicates that regiochemistry could be varied by the electronic effects of the α-substituent in alkyl methacrylate-type

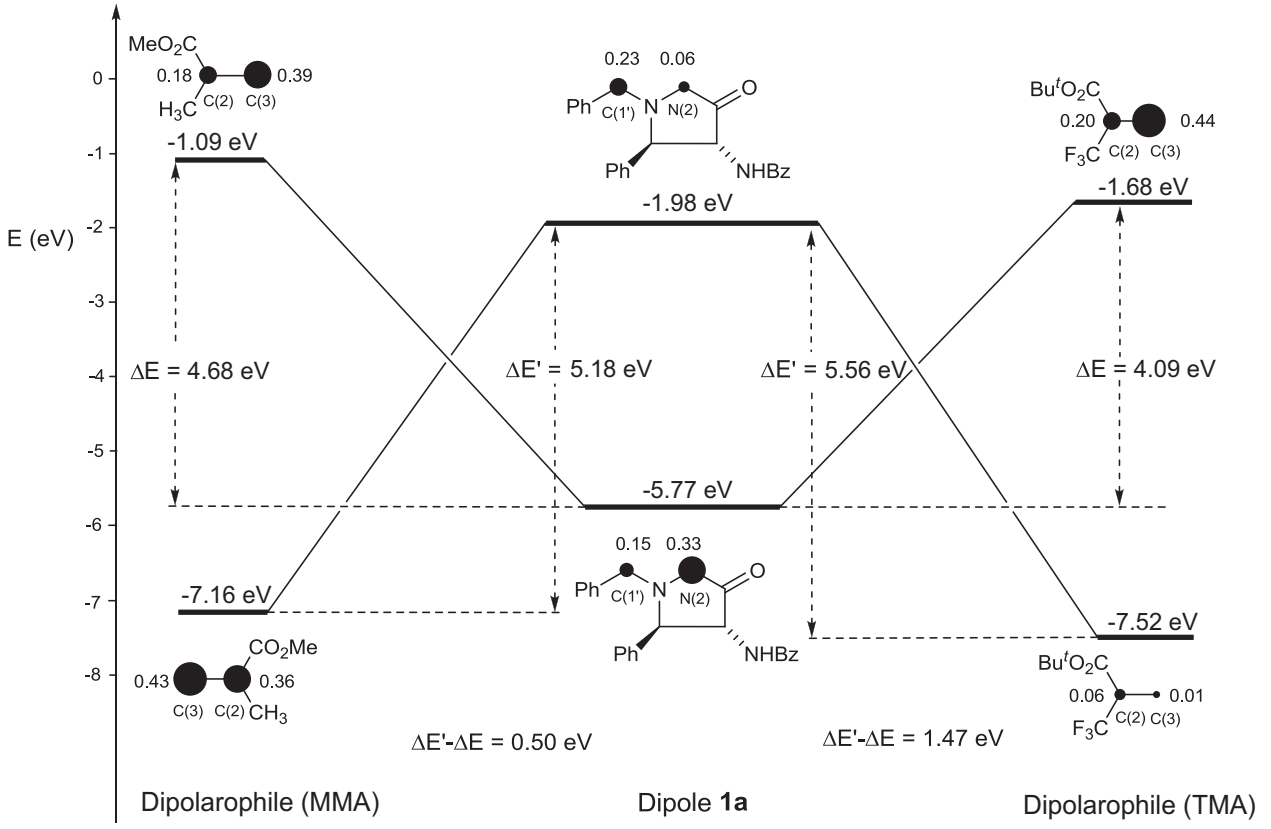


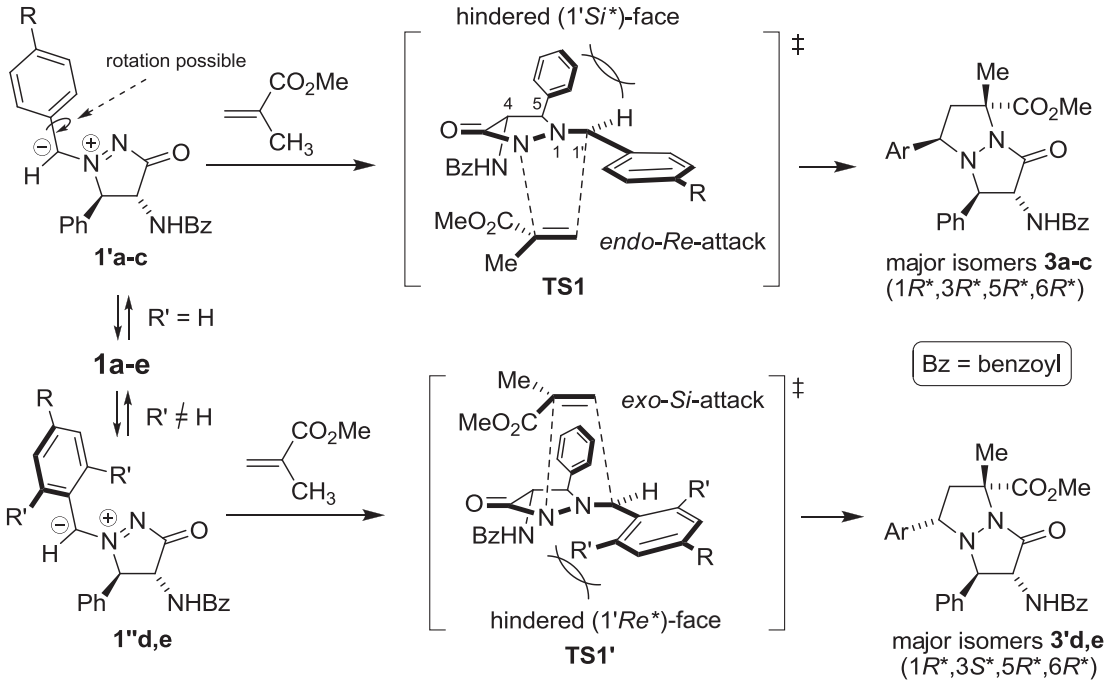

**Fig. 4.** FMO energies and atomic Fukui indices for **1a**, MMA, and TMA.

The stereoselectivity of the cycloadditions of dipoles **1a**–**e** to methyl methacrylate was in agreement with the stereochemistry observed by related cycloadditions[9,10,12] and could be explained in the following way: *ortho*-unsubstituted 1′-aryl group in dipoles **1a**–**c** can rotate around the C(1′)–Ar bond, thus shielding equally both faces of the dipole **1′a**–**c**. Consequently, the phenyl ring at position 5 is the stereodirecting group, which hinders the (1′*Si*)-face of the (*Z*)-dipole **1′**. Formation of the major (1*R**,3*R**,5*R**,6*R**)-isomers **3a**–**c** is explainable by preferential *endo*-attack of methyl methacrylate from the less hindered (1′*Re*)-face of dipole **1′a**–**c** via dipolarophiles. Such tunable regiochemistry would be useful in diversity-oriented synthesis of bicyclic pyrazolidinones as important scaffolds in the preparation of novel bioactive compounds.

## 4. Experimental

### 4.1. General

Melting points were determined on a Kofler micro hot stage. The NMR spectra were obtained on a Bruker Avance III UltraShield 500




**Scheme 4.**

plus at 500 MHz for $^1$H and 126 MHz for $^{13}$C nucleus, using acetone-$d_6$ and $CDCl_3$ with TMS as the internal standard, as solvents. Mass spectra were recorded on a Q-TOF Premier spectrometer and Agilent 6224 Accurate Mass TOF LC/MS, IR spectra on a Perkin–Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin–Elmer CHN Analyser 2400 II. Flash column chromatography (FC) was performed on silica gel (Fluka, Silica gel 60, particle size 0.035–0.070 mm). Medium pressure liquid chromatography was performed on a Büchi Flash Chromatography System (Büchi Fraction Collector C-660, Büchi Pump Module C-605, Büchi Control Unit C-620) on silica gel (LiChroprep® Si 60, 15–25 μm), dry filled column dimensions: 36×460 mm, backpressure: 10 bar, detection: UV (254 nm).

The ratios of isomers **3** and **3′** were determined by taking $^1$H NMR spectra of the crude reaction mixtures upon thorough evaporation in vacuo at 100 °C/0.01 mbar.

Methyl methacrylate was purchased by Sigma–Aldrich. Azomethine imines **1a**–**e** were prepared according to the literature procedures.[7c,10]

Density Functional Theory B3LYP/6-31G** was used for geometry optimisation and subsequent calculations of frontier molecular orbitals of **1a**, MMA, and TMA. All calculations were performed on Linux Workstation using Jaguar ver 7.8, rel 109 that is part of Schrodinger Suite 2011.

The Fukui indices, derived from Mulliken populations for the HOMO and LUMO orbitals calculated according to the method specified in Ref. 16 have been used for the quantification of the anticipated reactivity of a molecule. The atoms that are most reactive towards electrophilic attack are indicated by high positive values of atomic Fukui indices for the HOMO, while high positive values of the atomic Fukui indices for the LUMO indicates reactivity towards nucleophilic attack.

### 4.2. Synthesis of cycloadducts 3 and 3′. General procedure

A mixture of dipole **1** (1 mmol), methyl methacrylate (120 mg, 128 μL, 1.2 mmol), and anisole (4 mL) was heated under reflux for 4 h. The reaction mixture was cooled to room temperature and volatile components were evaporated in vacuo at 100 °C/0.01 Torr. The residue was purified by FC (75% EtOAc/hexanes). Fractions containing the products were combined and evaporated in vacuo to give mixtures of isomers **3** and **3′**, which were then separated by MPLC (50% EtOAc/hexanes). Fractions containing the products were combined and evaporated in vacuo to give the *title compounds* **3** and **3′**.

The following compounds were prepared in this manner.

*4.2.1. Methyl (1R*,3R*,5R*,6R*)-6-benzamido-1-methyl-7-oxo-3,5-diphenylhexahydropyrazolo-[1,2-a]pyrazole-1-carboxylate (**3a**) and its (1R*,3S*,5R*,6R*)-isomer **3′a**.* Prepared from **1a** (368 mg, 1 mmol).

*4.2.1.1. Methyl (1R*,3R*,5R*,6R*)-6-benzamido-1-methyl-7-oxo-3,5-diphenylhexahydropyrazolo[1,2-a]pyrazole-1-carboxylate (**3a**).* Yield: 315 mg (67%) of a white solid, mp 197–200 °C (from toluene). Found: C, 71.93; H, 6.01; N, 9.01. $C_{28}H_{27}N_3O_4$ requires C, 71.62; H, 5.80; N, 8.95%; $\nu_{max}$ (KBr) 3576, 3474, 3295, 3064, 2997, 2947, 1750, 1692, 1661, 1545, 1493, 1454, 1427, 1323, 1287, 1198, 1127, 756, 696 cm$^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 1.85 (3H, s, 1-*Me*), 2.46 (1H, dd, *J* 11.4, 13.2 Hz, 2-$H_a$), 2.76 (1H, dd, *J* 5.6, 13.2 Hz, 2-$H_b$), 3.91 (3H, s, O*Me*), 4.12 (1H, dd, *J* 5.6, 11.4 Hz, 3-*H*), 4.25 (1H, d, *J* 11.9 Hz, 5-*H*), 5.42 (1H, dd, *J* 8.2, 11.9 Hz, 6-*H*), 6.54 (1H, d, *J* 8.2 Hz, N*H*), 6.98–7.05 (6H, m, 6H of *Ph*), 7.09–7.14 (2H, m, 2H of *Ph*), 7.18–7.23 (2H, m, 2H of *Ph*), 7.34–7.40 (2H, m, 2H of *Ph*), 7.42–7.49 (1H, m, 1H of *Ph*), 7.69–7.74 (2H, m, 2H of *Ph*); $\delta_C$ (126 MHz, $CDCl_3$) 22.3, 40.9, 51.8, 53.2, 61.5, 61.8, 69.6, 77.1, 113.5, 127.2, 127.5, 127.7, 127.9, 127.9, 128.2, 131.5, 133.5, 135.3, 136.2, 162.4, 167.1, 171.9; HRMS (EI): [M–H]$^-$, found 468.1929. $C_{28}H_{26}N_3O_4$ requires 468.1929.

*4.2.1.2. Methyl (1R*,3S*,5R*,6R*)-6-benzamido-1-methyl-7-oxo-3,5-diphenylhexahydropyrazolo[1,2-a]pyrazole-1-carboxylate (**3′a**).* Yield: 48 mg (10%) of a colourless oil; $\nu_{max}$ (liquid film) 3323, 3061, 332, 2951, 1742, 1701, 1665, 1535, 1490, 1456, 1433, 1283, 1194, 1127, 762, 699 cm$^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 1.84 (3H, s, 1-*Me*), 2.54 (1H, dd, *J* 6.8, 13.0 Hz, 2-$H_a$), 2.63 (1H, dd, *J* 9.0, 13.0 Hz, 2-$H_b$), 3.60 (1H, dd, *J* 6.9, 8.8 Hz, 3-*H*), 3.88 (3H, s, O*Me*), 4.29 (1H, d, *J* 2.6 Hz, 5-

*H*), 5.23 (1H, dd, *J* 2.6, 7.8 Hz, 6-*H*), 7.05–7.10 (3H, m, 2H of *Ph*, N*H*), 7.10–7.14 (2H, m, 2H of *Ph*), 7.26–7.38 (6H, m, 6H of *Ph*), 7.46 (2H, br t, *J* 7.4 Hz, 2H of *Ph*), 7.53 (1H, br t, *J* 7.4 Hz, 1H of *Ph*), 7.85 (2H, br d, *J* 7.4 Hz, 2H of *Ph*); $\delta_C$ ($CDCl_3$, 126 MHz) 21.7, 51.8, 53.5, 60.0, 61.0, 63.0, 67.3, 127.5, 127.9, 128.5, 128.8, 128.8, 129.1, 132.0, 133.9, 134.7, 136.5, 162.4, 167.5, 172.0; HRMS (EI): $[M-H]^-$, found 468.1931. $C_{28}H_{26}N_3O_4$ requires 468.1929.

*4.2.2. Methyl (1R*,3R*,5R*,6R*)-6-benzamido-1-methyl-3-(4-nitrophenyl)-7-oxo-5-phenylhexahydropyrazolo[1,2-a]pyrazole-1-carboxylate (**3b**) and its (1R*,3S*,5R*,6R*)-isomer **3′b**.* Prepared from **1b** (411 mg, 1 mmol).

*4.2.2.1. Methyl (1R*,3R*,5R*,6R*)-6-benzamido-1-methyl-3-(4-nitrophenyl)-7-oxo-5-phenylhexahydropyrazolo[1,2-a]pyrazole-1-carboxylate hydrate (**3b**).* Yield: 322 mg (63%) of a yellowish solid, mp 222–223 °C (from toluene). Found: C, 64.53; H, 5.09; N, 10.75. $C_{28}H_{26}N_4O_6\cdot 1/3H_2O$ requires C, 64.61; H, 5.16; N, 10.76%; $\nu_{max}$ (KBr) 3344, 3065, 2992, 2947, 1744, 1704, 1647, 1603, 1518, 1493, 1348, 1286, 1203, 1132, 853, 748, 698 $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 1.85 (3H, s, 1-*Me*), 2.39 (1H, dd, *J* 11.3, 13.2 Hz, 2-$H_a$), 2.81 (1H, dd, *J* 5.7, 13.2 Hz, 2-$H_b$), 3.93 (3H, s, O*Me*), 4.26 (1H, dd, *J* 5.7, 11.3 Hz, 3-*H*), 4.29 (1H, d, *J* 12.1 Hz, 5-*H*), 5.49 (1H, dd, *J* 8.1, 12.1 Hz, 6-*H*), 6.58 (1H, d, *J* 8.1 Hz, N*H*), 7.00–7.06 (3H, m, 3H of *Ph*), 7.19–7.25 (2H, m, 2H of *Ph*), 7.29 (2H, td, *J* 2.0, 8.8 Hz, *o*-$C_6H_4$), 7.34–7.40 (2H, m, 2H of *Ph*), 7.47 (1H, tt, *J* 1.7, 7.3 Hz, *p*-*Ph*), 7.68–7.73 (2H, m, 2H of *Ph*), 7.88 (2H, td, *J* 2.0, 8.8 Hz, *m*-$C_6H_4$); $\delta_H$ (500 MHz, acetone-$d_6$) 1.78 (3H, s, 1-*Me*), 2.52 (1H, dd, *J* 11.3, 13.2 Hz, 2-$H_a$), 3.00 (1H, dd, *J* 5.8, 13.2 Hz, 2-$H_b$), 3.84 (3H, s, O*Me*), 4.41 (1H, dd, *J* 5.8, 11.3 Hz, 3-*H*), 4.53 (1H, d, *J* 12.5 Hz, 5-*H*), 5.52 (1H, dd, *J* 9.3, 12.5 Hz, 6-*H*), 6.99–7.08 (3H, m, 3H of *Ph*), 7.32–7.38 (2H, m, 2H of *Ph*), 7.41 (2H, br d, *J* 7.6 Hz, 2H of *Ph*), 7.49 (1H, tt, *J* 1.7, 7.3 Hz, *p*-*Ph*), 7.56 (2H, td, *J* 2.0, 8.8 Hz, *o*-$C_6H_4$), 7.80–7.86 (2H, m, 2H of *Ph*), 7.91 (2H, td, *J* 2.0, 8.8 Hz, *m*-$C_6H_4$), 8.21 (1H, d, *J* 9.3 Hz, N*H*); $\delta_C$ (126 MHz, $CDCl_3$) 22.2, 51.8, 53.5, 60.9, 62.3, 68.4, 78.1, 123.2, 127.2, 128.1, 128.1, 128.2, 128.4, 128.7, 131.8, 133.4, 134.6, 144.2, 147.3, 162.9, 167.2, 171.7; HRMS (EI): $MH^+$, found 515.1931. $C_{28}H_{27}N_4O_6$ requires 515.1897.

*4.2.2.2. Methyl (1R*,3S*,5R*,6R*)-6-benzamido-1-methyl-3-(4-nitrophenyl)-7-oxo-5-phenylhexahydropyrazolo[1,2-a]pyrazole-1-carboxylate (**3′b**).* Yield: 48 mg (9%) of a pale yellowish oil; $\nu_{max}$ (liquid film) 3405, 3372, 3062, 2949, 1741, 1704, 1666, 1603, 1522, 1490, 1455, 1347, 1286, 1127, 854, 699 $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 1.87 (3H, s, 1-*Me*), 2.57–2.64 (2H, m, 2-$CH_2$), 3.72 (1H, t, *J* 7.9 Hz, 3-*H*), 3.89 (3H, s, O*Me*), 4.36 (1H, br d, *J* 3.3 Hz, 5-*H*), 5.25 (1H, dd, *J* 3.3, 7.5 Hz, 6-*H*), 7.16 (2H, br d, *J* 7.2 Hz, 2H of *Ph*), 7.29–7.34 (2H, m, 2H of *Ph*), 7.32 (2H, d, *J* 8.7 Hz, *o*-$C_6H_4$), 7.36 (1H, br t, *J* 7.3 Hz, 1H of *Ph*), 7.46 (2H, br t, *J* 7.6 Hz, 2H of *Ph*), 7.55 (1H, br t, *J* 7.4 Hz, 1H of *Ph*), 7.85 (2H, br t, *J* 7.6 Hz, 2H of *Ph*), 8.13 (2H, d, *J* 8.7 Hz, *m*-$C_6H_4$); $\delta_C$ (126 MHz, $CDCl_3$) 21.6, 51.4, 53.7, 59.7, 61.5, 62.1, 66.9, 124.0, 127.5, 128.7, 128.7, 128.8, 128.8, 129.4, 132.2, 133.6, 134.1, 144.6, 147.9, 163.1, 167.6, 171.9; HRMS (EI): $MH^+$, found 515.1917. $C_{28}H_{27}N_4O_6$ requires 515.1925.

*4.2.3. Methyl (1R*,3R*,5R*,6R*)-6-benzamido-3-(4-methoxyphenyl)-1-methyl-7-oxo-5-phenylhexahydropyrazolo[1,2-a]pyrazole-1-carboxylate (**3c**) and its (1R*,3S*,5R*,6R*)-isomer **3′c**.* Prepared from **1c** (400 mg, 1 mmol).

*4.2.3.1. Methyl (1R*,3R*,5R*,6R*)-6-benzamido-3-(4-methoxyphenyl)-1-methyl-7-oxo-5-phenylhexahydropyrazolo[1,2-a]pyrazole-1-carboxylate (**3c**).* Yield: 145 mg (29%) of a white solid, mp 162–163 °C (from toluene). Found: C, 69.44; H, 6.01; N, 8.34. $C_{29}H_{29}N_3O_5$ requires C, 69.72; H, 5.85; N, 8.41%; $\nu_{max}$ (KBr) 3413, 3370, 3293, 1749, 1698, 1639, 1615, 1538, 1515, 1446, 1410, 1281, 1246, 1206, 1175, 1121, 1088, 1028, 837, 697 $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 1.84 (3H, s, 1-*Me*), 2.43 (1H, dd, *J* 11.4, 13.2 Hz, 2-$H_a$), 2.72 (1H, dd, *J* 5.6, 13.2 Hz, 2-$H_b$), 3.64 (3H, s, O*Me*), 3.87 (3H, s, O*Me*), 4.09 (1H, dd, *J* 5.6, 11.4 Hz, 3-*H*), 4.31 (1H, d, *J* 12.0 Hz, 5-*H*), 5.35 (1H, dd, *J* 8.4, 12.0 Hz, 6-*H*), 6.54 (2H, d, *J* 8.8 Hz, *m*-$C_6H_4$), 6.95–7.05 (6H, m, 3H of *Ph*, *o*-$C_6H_4$, and N*H*), 7.14–7.22 (2H, m, 2H of *Ph*), 7.31 (2H, br t, *J* 7.4 Hz, 2H of *Ph*), 7.40 (1H, tt, *J* 1.3, 7.4 Hz, *p*-*Ph*), 7.65–7.71 (2H, m, 2H of *Ph*); $\delta_C$ (126 MHz, $CDCl_3$) 22.5, 51.9, 53.6, 55.4, 61.8, 62.1, 69.3, 77.6, 113.6, 127.4, 128.0, 128.1, 127.2, 128.3, 128.6, 128.9, 131.8, 133.8, 135.6, 159.3, 162.6, 167.4, 172.2; HRMS (EI): $MH^+$, found 500.2172. $C_{29}H_{30}N_3O_5$ requires 500.2180.

*4.2.3.2. Methyl (1R*,3S*,5R*,6R*)-6-benzamido-3-(4-methoxyphenyl)-1-methyl-7-oxo-5-phenylhexahydropyrazolo[1,2-a]pyrazole-1-carboxylate (**3′c**).* Yield: 67 mg (13%) of a colourless oil; $\nu_{max}$ (liquid film) 3349, 3062, 3033, 2998, 2954, 1742, 1699, 1666, 1612, 1538, 1515, 1456, 1432, 1294, 1249, 1180, 1126, 1032, 834, 700 $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 1.83 (3H, s, 1-*Me*), 2.52 (1H, dd, *J* 6.8, 13.1 Hz, 2-$H_a$); 2.62 (1H, dd, *J* 8.7, 13.1 Hz, 2-$H_b$), 3.60 (1H, br t, *J* 7.7 Hz, 3-*H*), 3.79 and 3.88 (6H, 2s, 1:1, O*Me*), 4.22 (1H, br d, *J* 3.0 Hz, 5-*H*), 5.21 (1H, dd, *J* 3.0, 7.9 Hz, 6-*H*), 6.55 (1H, br d, *J* 8.6 Hz, N*H*), 6.81 and 7.04 (4H, 2d, 1:1, *J* 8.7 Hz, $C_6H_4$), 7.03–7.05 (2H, m, 2H of *Ph*), 7.09 (2*H*, br d, *J* 7.0 Hz, 2H of *Ph*), 7.29–7.40 (3H, m, 3H of *Ph*), 7.46 (2H, br t, *J* 7.5 Hz, 2H of *Ph*), 7.52 (1H, br t, *J* 7.4 Hz, 1H of *Ph*), 7.84 (2H, br d, *J* 7.3 Hz, 2H of *Ph*); $\delta_C$ (126 MHz, $CDCl_3$) 21.5, 51.4, 53.3, 55.2, 59.4, 60.7, 62.8, 67.1, 113.9, 127.2, 127.3, 128.1, 128.4, 128.51, 128.5, 128.6, 128.6, 128.8, 129.0, 159.5, 162.0, 167.2, 171.8; *m*/*z* (EI) 498 (100, $[M-H]^-$); HRMS (EI): $[M-H]^-$, found 498.2034. $C_{29}H_{28}N_3O_5$ requires 498.2033.

*4.2.4. Methyl (1R*,3S*,5R*,6R*)-6-benzamido-3-(2,6-dichlorophenyl)-1-methyl-7-oxo-5-phenylhexahydropyrazolo[1,2-a]pyrazole-1-carboxylate (**3′d**).* Prepared from **1d** (438 mg, 1 mmol). Yield: 269 mg (50%) of a white solid, mp 144–146 °C (from toluene). Found: C, 62.62; H, 4.74; N, 7.76. $C_{28}H_{25}Cl_2N_3O_4$ requires C, 62.46; H, 4.68; N, 7.80%; $\nu_{max}$ (KBr) 3482, 3334, 3069, 2951, 1751, 1725, 1638, 1543, 1439, 1353, 1272, 1160, 787, 698 $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 1.92 (3H, s, 1-*Me*), 2.43 (1H, dd, *J* 7.7, 12.9 Hz, 2-$H_a$), 3.11 (1H, dd, *J* 10.0, 12.9 Hz, 2-$H_b$), 3.86 (3H, s, O*Me*), 4.40 (1H, d, *J* 2.7 Hz, 5-*H*), 4.47 (1H, dd, *J* 7.7, 10.0 Hz, 3-*H*), 5.31 (1H, dd, *J* 2.7, 8.2 Hz, 6-*H*), 7.08 (1H, t, *J* 7.9 Hz, *p*-$C_6H_3$), 7.12–7.22 (3H, m, 2H of *Ar*, N*H*), 7.27–7.32 (5H, m, 5H of *Ar*), 7.41–7.56 (3H, m, 3H of *Ar*), 7.83–7.88 (2H, m, 2H of *Ar*); $\delta_C$ (126 MHz, $CDCl_3$) 22.0, 46.2, 53.5, 56.2, 61.7, 62.0, 66.9, 77.4, 100.2, 127.4, 128.5, 128.8, 129.1, 129.2, 129.6, 130.4, 132.0, 133.8, 134.1, 164.9, 167.4, 172.5; *m*/*z* (EI) 536 (100, $[M-H]^-$); HRMS (EI): $[M-H]^-$, found 536.1146. $C_{28}H_{24}^{35}Cl_2N_3O_4$ requires 536.1149.

*4.2.5. Methyl (1R*,3S*,5R*,6R*)-6-benzamido-3-mesityl-1-methyl-7-oxo-5-phenylhexahydropyrazolo[1,2-a]pyrazole-1-carboxylate (**3′e**) and its (1R*,3R*,5R*,6R*)-isomer **3e**.* Prepared from **1e** (411 mg, 1 mmol).

*4.2.5.1. Methyl (1R*,3S*,5R*,6R*)-6-benzamido-3-mesityl-1-methyl-7-oxo-5-phenylhexahydropyrazolo-[1,2-a]pyrazole-1-carboxylate (**3′e**).* Yield: 75 mg (15%) of a yellow oil; $\nu_{max}$ (liquid film) 3399, 2925, 1737, 1698, 1661, 1530, 1449, 1375, 1267, 1174, 1121, 1089, 841, 725 $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 1.89 (3H, s, 1-*Me*), 1.42, 2.20, and 2.52 (9H, 3s, 1:1:1, 3×*Me*–Ar), 2.33 (1H, dd, *J* 6.8, 12.9 Hz, 2-$H_a$), 2.77 (1H, dd, *J* 10.8, 12.9 Hz, 2-$H_b$), 3.87 (3H, s, O*Me*), 3.92 (1H, dd, *J* 6.8, 10.8 Hz, 3-*H*), 4.33 (1H, s, 5-*H*), 5.13 (1H, d, *J* 7.4 Hz, 6-*H*), 6.63 and 6.76 (2H, 2s, 1:1, $C_6H_2$), 7.04–7.10 (1H, m, *p*-*Ph*), 7.07 (1H, d, *J* 7.4 Hz, N*H*), 7.25–7.37 (4H, m, 4H of *Ph*), 7.43–7.57 (3H, m, 3H of *Ph*), 7.84–7.89 (2H, m, 2H of *Ph*); $\delta_H$ (500 MHz, acetone-$d_6$) 1.85 (3H, s, 1-*Me*), 1.55, 2.14, and 2.57 (9H, 3s, 1:1:1, 3×*Me*–Ar), 2.49 (1H, dd, *J* 7.1, 12.9 Hz, 2-$H_a$), 2.80 (1H, dd, *J* 10.6, 12.9 Hz, 2-$H_b$), 3.84 (3H, s, O*Me*), 4.17 (1H, dd, *J* 7.1, 10.6 Hz, 3-*H*), 4.52 (1H, d, *J* 3.7 Hz, 5-*H*), 5.30

(1H, dd, *J* 3.7, 8.2 Hz, 6-*H*), 6.56 and 6.73 (2H, 2s, 1:1, $C_6H_2$), 7.14–7.20 (2H, m, 2H of *Ph*), 7.25–7.33 (3H, m, 3H of *Ph*), 7.45–7.60 (3H, m, 3H of *Ph*), 7.87–7.93 (2H, m, 2H of *Ph*), 8.04 (1H, d, *J* 8.2 Hz, N*H*); $\delta_C$ (126 MHz, $CDCl_3$) 19.7, 20.7, 21.5, 47.3, 53.3, 56.1, 60.8, 63.5, 66.9, 127.1, 128.6, 128.7, 128.8, 128.9, 129.2, 131.5, 131.8, 133.8, 134.6, 137.1, 137.2, 137.4, 162.9, 167.2, 172.3; *m*/*z* (EI) 511 (76, $M^+$), 434 (23), 390 (65), 331 (19), 291 (11), 231 (35), 223 (11), 205 (8), 171 (56), 151 (7), 131 (7), 105 (100), 77 (44%); HRMS (EI): $M^+$, found 511.2471. $C_{31}H_{33}N_3O_4$ requires 511.2480.

*4.2.5.2. Methyl (1R*,3R*,5R*,6R*)-6-benzamido-3-mesityl-1-methyl-7-oxo-5-phenylhexahydropyrazolo-[1,2-a]pyrazole-1-carboxylate (**3e**).* Yield: 6 mg (1%) of a colourless oil; $\delta_H$ (500 MHz, $CDCl_3$) 1.83 (3H, s, 1-*Me*), 2.06, 2.22, and 2.48 (9H, 3s, 1:1:1, 3×*Me*–Ar), 2.57 (1H, dd, *J* 6.6, 13.4 Hz, 2-$H_a$), 2.71 (1H, dd, *J* 11.8, 13.4 Hz, 2-$H_b$), 3.91 (3H, s, O*Me*), 4.15 (1H, d, *J* 12.0 Hz, 5-*H*), 4.64 (1H, dd, *J* 6.6, 11.8 Hz, 3-*H*), 5.48 (1H, dd, *J* 8.4, 12.0 Hz, 6-*H*), 6.51 and 6.53 (2H, 2s, 1:1, $C_6H_2$), 6.62 (1H, d, *J* 8.4 Hz, N*H*), 6.97–7.05 (3H, m, 3H of *Ph*), 7.18–7.22 (2H, m, 2H of *Ph*), 7.37 (2H, br t, *J* 7.6 Hz, 2H of *Ph*), 7.46 (1H, br t, *J* 7.4 Hz, 1H of *Ph*), 7.72 (2H, br d, *J* 7.4 Hz, 2H of *Ph*); $\delta_C$ (126 MHz, $CDCl_3$) 20.6, 20.8, 21.3, 22.8, 47.0, 53.6, 61.2, 67.6, 127.4, 127.6, 127.9, 128.0, 128.4, 128.6, 128.9, 129.2, 131.3, 131.9, 133.9, 135.0, 136.2, 137.2, 137.7, 163.1, 167.4, 172.6; HRMS (EI): $[M-H]^-$, found 510.2389. $C_{31}H_{32}N_3O_4$ requires 510.2398.

### 4.3. X-ray structure analysis for compounds 3b and 3′d

For X-ray structure determination, the crystals of compounds **3b** and **3′d** were mounted on the tip of glass fibres. Data were collected on a Nonius Kappa CCD diffractometer using monochromated Mo Kα radiation at room temperature by using Nonius Collect software.[19] Data reduction and integration were performed with the software package DENZO-SMN.[20] The coordinates of all of the non-hydrogen atoms were found via direct methods using the SIR97[21] structure solution program. A full-matrix least-squares refinement on $F^2$ magnitudes with anisotropic displacement parameters for all non-hydrogen atoms using SHELXL-97[22] was employed. All H atoms were initially located in difference Fourier maps. H atoms bonded to C atoms were subsequently treated as riding atoms in geometrically idealized positions, with C–H=0.93 for aromatic, 0.96 for methyl, 0.97 for methylene, 0.98 for methine and 0.86 Å for N–H bonds, respectively, with $U_{iso}(H)=kU_{eq}(C, N)$, where $k=1.5$ for methyl groups, which were permitted to rotate but not to tilt, and 1.2 for all other H atoms. Water hydrogen atoms were not refined; an exception is H2w in structure **3b**, which was restrained to be 1.00(2) Å away from oxygen and refined isotropically. Figures depicting the structures were prepared by ORTEP3.[23]

CCDC 828734 and 828735 contain the supplementary crystallographic data for structures **3b** and **3′d**, respectively. 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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## Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.09.140. These data include MOL files and InChiKeys of the most important compounds described in this article.

## References and notes

1. (a) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: Hoboken, NJ, 2003; (b) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, NY, 1984; Vol. 1; (c) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, NY, 1984; Vol. 2.
2. (a) Gothelf, V. K.; Jørgensen, K. A. Asymmetric reactions In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: Hoboken, NJ, 2003; pp 817–899; (b) Grashey, R. Azomethine imines In. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, NY, 1984; Vol. 1, pp 733–814; (c) Schantl, J. G. Azomethine imines In. *Science of Synthesis: Houben-Weyl Methods of Organic Transformations*; Georg Thieme: Stuttgart, 2004; Vol. 27, pp 731–824.
3. (a) Stanovnik, B. *Tetrahedron* **1991**, *47*, 2925–2945; (b) Žličar, M.; Stanovnik, B.; Tišler, M. *Tetrahedron* **1992**, *48*, 7965–7972; (c) Svete, J.; Prešeren, A.; Stanovnik, B.; Golič, L.; Golič Grdadolnik, S. *J. Heterocycl. Chem.* **1997**, *34*, 1323–1328; (d) Roussi, F.; Bonin, M.; Chiaroni, A.; Micouin, L.; Riche, C.; Husson, H.-P. *Tetrahedron Lett.* **1999**, *40*, 3727–3730; (e) Roussi, F.; Chauveau, A.; Bonin, M.; Micouin, L.; Husson, H.-P. *Synthesis* **2000**, 1170–1179; (f) Chuang, T.-H.; Sharpless, K. B. *Helv. Chim. Acta* **2000**, *83*, 1734–1743; (g) Chauveau, A.; Martens, T.; Bonin, M.; Micouin, L.; Husson, H.-P. *Synthesis* **2002**, 1885–1890; (h) Panfil, I.; Urbanczyk-Lipkowska, Z.; Suwinska, K.; Solecka, J.; Chmielewski, M. *Tetrahedron* **2002**, *58*, 1199–1212; (i) Chung, F.; Chauveau, A.; Seltki, M.; Bonin, M.; Micouin, L. *Tetrahedron Lett.* **2004**, *45*, 3127–3130; (j) Suarez, A.; Downey, C. W.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11244–11245; (k) Chen, W.; Yuan, X.-H.; Li, R.; Du, W.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Adv. Synth. Catal.* **2006**, *348*, 1818–1822.
4. (a) Dorn, H. *Chem. Heterocycl. Compd. USSR* **1981**, 3–31; (b) Claramunt, R. M.; Elguero, J. *Org. Proc. Prep. Int.* **1991**, *23*, 273–320; (c) Elguero, J. Pyrazoles In. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science Ltd.: Oxford, 1996; Vol. 3, pp 1–75.
5. (a) Sibi, M. P.; Stanley, L. M.; Nie, X.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2007**, *129*, 395–405; (b) Nakano, H.; Tsugawa, N.; Takahashi, K.; Okuyama, Y.; Fujita, R. *Tetrahedron* **2006**, *62*, 10879–10887.
6. (a) Sibi, M. P.; Soeta, T. *J. Am. Chem. Soc.* **2007**, *129*, 4522–4523; (b) Sibi, M. P.; Prabagaran, N. *Synlett* **2004**, 2421–2424; (c) Sibi, M. P.; Liu, M. *Org. Lett.* **2001**, *3*, 4181–4184; (d) Lin, C.-H.; Yang, K.-S.; Pan, J.-F.; Chen, K. *Tetrahedron Lett.* **2000**, *41*, 6815–6819.
7. (a) Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778–10779; (b) Pezdirc, L.; Stanovnik, B.; Svete, J. *Aust. J. Chem.* **2009**, *62*, 1661–1666; (c) Keller, M.; Sido, A. S. S.; Pale, P.; Sommer, J. *Chem.—Eur. J.* **2009**, *15*, 2810–2817.
8. (a) Ternansky, R. J.; Draheim, S. E. *Tetrahedron* **1992**, *48*, 777–796; (b) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789–12854.
9. (a) Svete, J. *ARKIVOC* **2006**, *vii*, 35–46; (b) Svete, J. In *(4R*,5R*)-4-Benzoylamino-5-Phenyl-3-Pyrazolidinone—A Useful Building Block in the Synthesis of Functionalized Pyrazoles*; Horvat, M. A., Golob, J. H., Eds.; Nova Science: New York, NY, 2008; pp 129–193.
10. (a) Pezdirc, L.; Cerkovnik, J.; Pirc, S.; Stanovnik, B.; Svete, J. *Tetrahedron* **2007**, *63*, 991–999; (b) Pezdirc, L.; Grošelj, U.; Meden, A.; Stanovnik, B.; Svete, J. *J. Comb. Chem.* **2007**, *9*, 717–723.
11. Ogawa, S.; Nishimine, T.; Tokunaga, E.; Shibata, N. *Synthesis* **2010**, 3274–3281.
12. Pezdirc, L.; Jovanovski, V.; Bevk, D.; Jakše, R.; Pirc, S.; Meden, A.; Stanovnik, B.; Svete, J. *Tetrahedron* **2005**, *61*, 3977–3990.
13. Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11–15.
14. (a) For clarity, only one of organic molecules with its atom numbering scheme is depicted (there are two such molecules in the asymmetric unit). For the same reason, the water molecule is omitted as well. (b) Displacement ellipsoids are drawn at 30% probability level and hydrogen atoms are shown as small spheres of arbitrary radii.
15. (a) Huisgen, R. 1,3-Dipolar cycloadditions—introduction, survey, mechanism In. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, NY, 1984; Vol. 1, pp 1–176; (b) Houk, K. N.; Yamaguchi, K. Theory of 1,3-dipolar cycloadditions In. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, NY, 1984; Vol 2, pp 407–450.
16. (a) Contreras, R. R.; Fuentealba, P.; Galvan, M.; Pérez, P. *Chem. Phys. Lett.* **1999**, *304*, 405–413; (b) Chamorro, E.; Pérez, P. *J. Chem. Phys.* **2005**, *123*, 114107/1–114107/10.
17. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372–1377.
18. Sustmann, R. *Pure Appl. Chem.* **1975**, *40*, 569–593.
19. *Collect Software*; Nonius, BV: Delft, The Netherlands, 2000.
20. Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, *276*, 307–326.
21. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115–119.
22. Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.
23. Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.