Cu(I)-catalyzed [3+2] Cycloadditions of *tert*-Butyl (*S*)-(3-Oxopent-4-yn-2-yl)carbamate to 1-Benzylidenepyrazole-3-one-derived Azomethine Imines

Eva Pušavec[a], Jona Mirnik[a], Luka Šenica[a], Uroš Grošelj[a], Branko Stanovnik[a,b], and Jurij Svete[a,b]

[a] Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, 1000 Ljubljana, Slovenia

[b] EN-FIST, Centre of Excellence, Trg Osvobodilne fronte 13, 1000 Ljubljana, Slovenia

Reprint requests to Prof. Dr. Jurij Svete. Fax: +386 1 2419 220. E-mail: jurij.svete@fkkt.uni-lj.si

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Parallel screening of suitable reaction conditions for Cu(I)-catalyzed [3+2] cycloadditions of (1*Z*,4*R**,5*R**)-4-benzoylamino-1-benzylidene-5-phenyl-3-oxopyrazolidin-1-ium-2-ide (**1a**) to methyl propiolate (**2**) has established that this reaction proceeds smoothly at room temperature in acetonitrile in the presence of CuI and Hünig's base. The optimized reaction conditions were then applied in regio- and stereo-selective 1,3-dipolar cycloadditions of racemic azomethine imines **1a**–**e** to *tert*-butyl (*S*)-(3-oxopent-4-yn-2-yl)carbamate (**6**) leading to mixtures of diastereomeric non-racemic chromatographically separable cycloadducts **7a**–**d**, **7′a**–**d**, **8e**, and **8′e**. The structures of the products were confirmed by NMR spectroscopy.

Key words: 1,3-Dipolar Cycloaddition, 3-Pyrazolidinones, Catalysis, Copper, Acetylenes

Introduction

1,3-Dipolar cycloadditions are powerful methods for the preparation of five-membered heterocycles providing an easy access to polyfunctional compounds with multiple stereogenic centers, usually with excellent stereocontrol [1 – 3]. Within this context, asymmetric cycloadditions are well elaborated with chiral nitrones, nitrile oxides, and azomethine ylides [4 – 6], however, far fewer examples of highly selective asymmetric cycloadditions to cyclic chiral azomethine imines have so far been reported [7 – 16].

Copper(I)-catalyzed 1,3-dipolar cycloadditions of azides to terminal alkynes are the most outstanding examples within the emerging field of 'click' chemistry [17 – 19]. In contrast to the non-catalyzed reactions, copper(I)-catalyzed cycloadditions proceed regioselectively and under mild reaction conditions. Presumably, these reactions are not concerted reactions and proceed by a stepwise cycloaddition process [17 – 19]. Fu and co-workers reported regioselective and enantioselective copper(I)-catalyzed [3+2] coupling of achiral 3-pyrazolidinon-1-azomethine imines with terminal acetylenes to generate optically active pyrazolo[1,2-*a*]pyrazolone derivatives in 74 – 98 % *ee* [20, 21]. Since then, several other examples of catalyzed cycloadditions of 3-pyrazolidinone-derived azomethine imines to terminal acetylenes have been published comprising catalysis by CuI [22], di-copper-substituted silicotungstate [23], $[Cu(\mu\text{-OH})(tmen)]_2Cl_2$ [24], Cu-USY-zeolites [25, 26], $Cu(OH)_x/Al_2O_3$ [27], CuOAc [28], $AgN(SiMe_3)$, and $CuN(SiMe_3)_2$ [29]. Moreover, Kobayashi and co-workers also showed that regiochemistry of these reactions can be tuned by the choice of the ligand [29].

The importance of pyrazolidin-3-one derivatives grew increasingly during the last decades due to their synthetic applicability and biological activity [30 – 32] with Eli Lilly's antibiotics as typical examples of bioactive pyrazolo[1,2-*a*]pyrazolone derivatives [33 – 36]. Recent applications of 3-pyrazolidinones include their use as templates in enantioselective Diels-Alder [37, 38], Michael [39 – 42] and 'click' reactions [20 – 29].

Our previous 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** to various dipolarophiles revealed the general reactiv-

ity and selectivity of these cycloadditions [43, 44], as well as their applicability in high-throughput synthesis [45, 46]. The 4-benzyloxycarbonylamino analogs of **1** were also successfully employed in the synthesis of pyrazolo[1,2-*a*]pyrazole-based peptide mimetics [47–50]. However, the weakest link in the latter synthesis of peptide analogs was the [3+2] cycloaddition step, which had to be performed in refluxing anisole to assure a complete conversion of the starting dipole. Since epimerization of an α-amino acid (and their derivatives) is usually fast above 100 °C, the use of enantiopure azomethine imines for the synthesis of the non-racemic cycloadducts does not make sense. This drawback may be overcome by catalysis, which should significantly lower the required reaction temperature. This has been previously shown for regio- and stereo-selective copper(I) iodide-catalyzed cycloadditions of dipoles **1** to ethyl propiolate, which took place in refluxing dichloromethane [22]. In contrast, the non-catalyzed cycloadditions required harsh thermal activation (~150 °C) and led to mixtures of isomeric cycloadducts [51].

In extension, we decided to look for even milder reaction conditions, which would enable a full conversion at room temperature. Under such conditions, reactions of racemic dipoles **1** with a non-racemic dipolarophile would give a mixture of diastereomeric, yet non-racemic cycloadducts that could be separated by chromatography. Herein, we report the results of this study, showing that copper(I)-catalyzed cycloadditions of (1*Z*,4*R**,5*R**)-1-arylmethylidene-4-benzoylamino-3-oxo-5-phenyltetrahydropyrazol-1-ium-2-ides **1a**–**e** to methyl propiolate (**2**) and *tert*-butyl (*S*)-(3-oxopent-4-yn-2-yl)carbamate (**6**) proceed selectively and under mild conditions allowing the preparation of separable non-racemic products.

Results and Discussion

Cycloaddition of azomethine imine **1a** with methyl propiolate (**2**) was chosen as the model reaction in a search for suitable reaction conditions, which would enable a full conversion of reactants at room temperature. Parallel screening was performed on a 0.1 mmol scale in 2 mL glass vials using a magnetic stirrer and an aluminum block with 12 positions. Since the cycloadduct **3a** is highly fluorescent (bright-yellow fluorescence at 375 nm), simple and effective monitoring of the reaction progress was feasible by TLC. First, reactions of **1a** with 1 equiv. of **2** in the presence of 0.2 equiv. of CuI were performed in MeCN, DMF, EtOAc, CH_2Cl_2, THF, toluene, and MeOH at r. t., yet without noticeable conversion. However, addition of 0.3 equiv. of Et_3N significantly improved the result. Cycloaddition proceeded best in polar aprotic solvents (MeCN and DMF), where small weak spots of **1a** on TLC indicated almost complete conversion, while the insoluble dipole **1a** was completely dissolved (consumed). In non-polar aprotic solvents (EtOAc, CH_2Cl_2, THF), **1a** was not completely dissolved, and the conversion of **1a** into **3a** was also not complete according to TLC. On the other hand, formation of the cycloadduct **3a** was not detected in the reactions in toluene and MeOH. Acetonitrile was then chosen as standard solvent, since it is easily removable by evaporation at $\sim 30\,^{\circ}C/10$ mbar. Next, the influence of a base was explored. Among various tertiary amines (Et_3N, *i*-Pr_2NEt, 4-methylmorpholine, DMAP, and DBU), only 4-methylmorpholine did not give the reaction. Hünig's base was found to be the most suitable for complete conversion of the starting dipole **1a**. Finally, different copper salts were also tested as catalysts. Somewhat expectedly, copper(I) iodide exhibited the best performance (complete conversion of **1a**), but CuBr and $Cu(OAc)_2$ were also very good catalysts, while CuO, Cu_2O, $CuSO_4$, and CuCl did not catalyze the reaction (Table 1).

Once suitable reaction conditions were found, cycloaddition of **1a** to methyl propiolate (**2**) was repeated on a 1 mmol scale. To our pleasant surprise, the conversion of **1a** was complete after 12 h, and the cycloadduct **3a** was isolated in 98 % yield upon chromatographic workup. The regio- and stereoselectivity of this reaction were in agreement with the closely related literature example for CuI-catalyzed cycloaddition of **1a** to ethyl acrylate [22]. Unfortunately, the *ortho*-disubstituted dipole **1f** did not react with **2** under these optimized conditions (Scheme 1).

Cycloadditions of the azomethine imines **1a**–**f** to *tert*-butyl (*S*)-(3-oxopent-4-yn-2-yl)carbamate (**6**) [52] were studied next. Dipolarophile **6** was prepared in two steps from commercially available (*S*)-Boc-alanine (**4**) *via* transformation into the corresponding Weinreb amide **5** [53] and treatment with ethynylmagnesium bromide following the literature procedure for the synthesis of closely related ynones [54]. Cycloadditions of **1a**–**f** to ynone **6** were performed under the same conditions as the above mentioned reaction of **1a** with

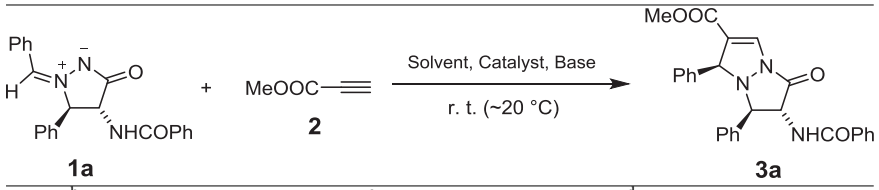
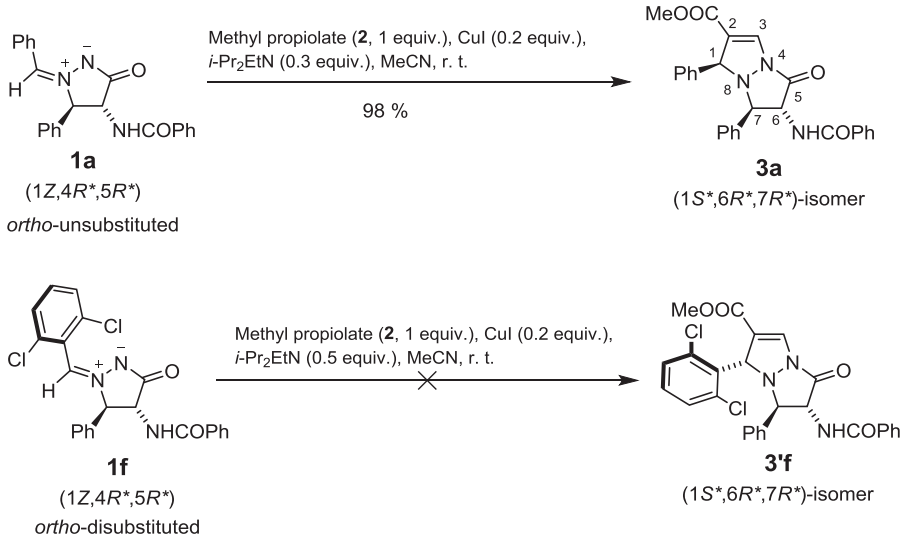


Table 1. Screening for suitable reaction conditions[a].

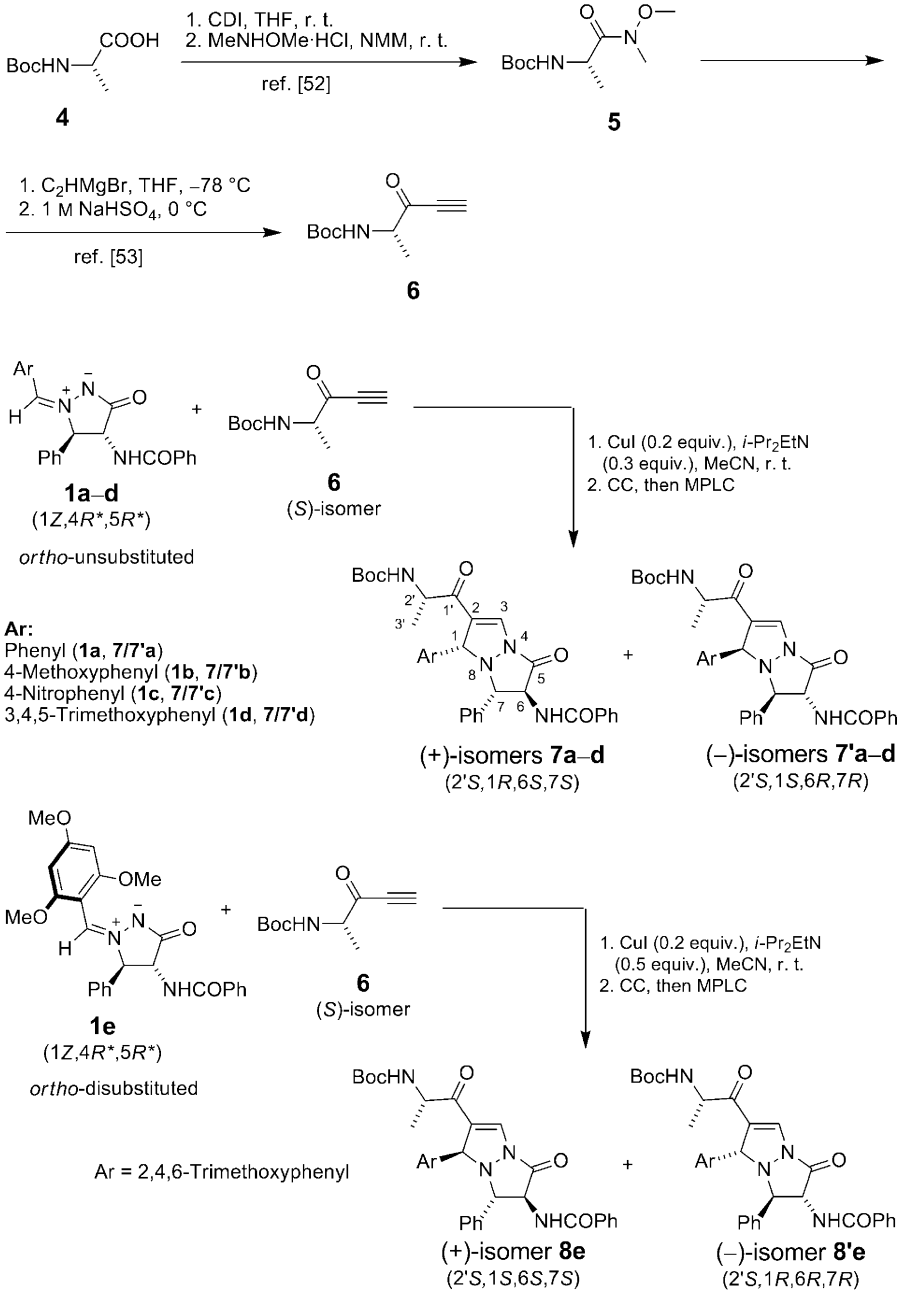
Solvent[b]		Catalyst[c]		Base[d]	
MeCN	++ ►	**CuI**	++ ►	***i*-Pr_2EtN**	++ ►
DMF	++	CuBr	+	Et_3N	+
EtOAc	+	$Cu(OAc)_2$	+	NMM	–
CH_2Cl_2	+	CuO	–	DBU	+
THF	+	Cu_2O	–	DMAP	+
toluene	–	$CuSO_4$	–		
MeOH	–	CuCl	–		

[a] Reactions were performed on a 0.1 mmol scale and were monitored by TLC on silica gel (EtOAc). The results were estimated qualitatively on the basis of intensities of spots of **1a** (dark violet, $R_f \sim 0.2$) and **3a** (yellow fluorescent, $R_f \sim 0.7$); [b] reaction conditions: CuI (0.2 equiv.), Et_3N (0.3 equiv.), r. t.; [c] reaction conditions: catalyst (0.2 equiv.), Et_3N (0.3 equiv.), MeCN, r. t.; [d] reaction conditions: CuI (0.2 equiv.), amine (0.3 equiv.), MeCN, r. t.



Scheme 1.

methyl propiolate (**2**). Thus, dipoles **1a–f** were reacted with 1.1 equiv. of **6** in acetonitrile at room temperature in the presence of 0.2 equiv. of CuI and 0.3 equiv. of Hünig's base. Almost complete conversions of the *ortho*-unsubstituted dipoles **1a–d** were detected by TLC. Surprisingly, the 2,4,6-trimethoxyphenyl-substituted dipole **1e** also reacted with **6**, whereas the 2,6-dichlorophenyl-substituted dipole **1f** did not. Subsequent chromatographic work-up by flash column chromatography (FC) afforded mixtures of diastereomeric cycloadducts **7a–d**/**7′a–d** and **8e**/**8′e** in 66 – 98 % yields. The mixtures of isomers **7a–d**/**7′a–d** and **8e**/**8′e** were separated by medium-performance liquid chromatography (MPLC) to furnish diastereomerically pure non-racemic compounds **7a–d**, **7′a–d**, **8e**, and **8′e** in 3 – 44 % yields. Also here, the regio- and stereoselectivity of the cycloadditions and relative configurations of **7a–d**/**7′a–d** and **8e**/**8′e** were in agreement with previous results obtained by cycloadditions of dipoles **1a–e** to ethyl acrylate [22, 51]. Thus, all reactions furnished the 2-acyl regioisomers **7a–d**/**7′a–d** and **8e**/**8′e**, exclusively. Cycloadditions of *ortho*-unsubstituted dipoles **1a–d** afforded diastereoisomers **7a–d**/**7′a–d** with *syn*-oriented 1-H and 7-H,



Scheme 2.

whereas the *ortho*-disubstituted dipole **1e** afforded diastereoisomers **8e**/**8′e** with *anti*-oriented 1-H and 7-H (Scheme 2, Table 2).

The structures of the new compounds **3a**, **7a–d**, **7′a–d**, **8e**, and **8′e** were determined by spectroscopic methods (^{1}H NMR, ^{13}C NMR, IR, MS, HRMS) and by elemental analyses for C, H, and N. Compounds **7′c**, **7d**, **7′d**, **8e**, and **8′e** were not obtained in analytically pure form. Their identities were confirmed by ^{13}C NMR and HRMS.

Table 2. Yields of compounds **7a–d**, **7′a–d**, **8e**, and **8′e**.

Compound	Ar	Yield (%)[a]		
		7/**7′** or **8**/**8′**	**7** or **8**	**7′** or **8′**
7a, **7′a**	Ph	91	44	5
7b, **7′b**	4-methoxyphenyl	98	25	14
7c, **7′c**	4-nitrophenyl	95	39	17
7d, **7′d**	3,4,5-trimethoxyphenyl	66	30	14
8e, **8′e**	2,4,6-methoxyphenyl	88	10	3

[a] Much lesser combined yield of pure **7** and **7′** or **8** and **8′** than the original yield of **7**/**7′** or **8**/**8′** is due to material loss under chromatographic conditions.

The relative configurations of compounds **3a**, **7a–d**/**7′a–d** and **8e**/**8′e** were established by ^{1}H NMR and by NOESY spectroscopy. In the *ortho*-unsubstituted compounds **3a**, **7c**, **7′c**, **7d**, and **7′d**, a NOE between 1-H and 7-H supported the *syn*-orientation between these two nuclei. On the other hand, absence of NOE between 1-H and 7-H in the *ortho*-disubstituted compounds **8e** and **8′e** was in agreement with the *anti*-orientation of these two protons. The *trans*-configuration of 6-H and 7-H in compounds **3a**, **7a–d**/**7′a–d** and **8e**/**8′e** was determined on the basis of the vicinal coupling constant, $^3J_{6H-7H} \sim 11$ Hz, which was in agreement with a pseudoaxial conformation of these two nuclei (Fig. 1). The configurations of compounds **7a**, **7′a**, **7b**, and **7′b** were also confirmed by correlation of characteristic NMR data, which were also in agreement with the data for closely related compounds (Table 3) [22, 43, 44, 51].

So far, unambiguous determination of the absolute configuration of the non-racemic products **7a–d**, **7′a–d**, **8e**, and **8′e** was not possible as we were not able to obtain single crystals suitable for X-ray analysis. Nevertheless, compounds **7a–d**, **7′a–d**, **8e**, and **8′e** can be divided into two groups of isomers, the (+)-isomers **7a–d** and **8e** and the (–)-isomers **7′a–d** and **8′e**. Consequently, the tentative configurations of **7a–d**, **7′a–d**, **8e**, and **8′e** might be proposed on the basis of correlation of their specific rotations with the specific rotation of related fully saturated cycloadducts **9** and **9′** with known absolute configuration [50]. Accordingly, the tentative (2′*S*,1*R*,6*S*,7*S*)-configuration was assigned to the diastereomers **7a–d** with strong positive specific rotations, and the tentative (2′*S*,1*S*,6*R*,7*R*)-configuration was assigned to the diastereomers **7′a–d** with strong negative specific rotations. Similarly, the tentative (2′*S*,1*S*,6*S*,7*S*)-configuration was proposed for the (+)-isomers **8e** and *vice versa*, the (2′*S*,1*R*,6*R*,7*R*)-configuration for the (–)-isomers **8′e** (Fig. 2, *cf.* Table 3) [50].

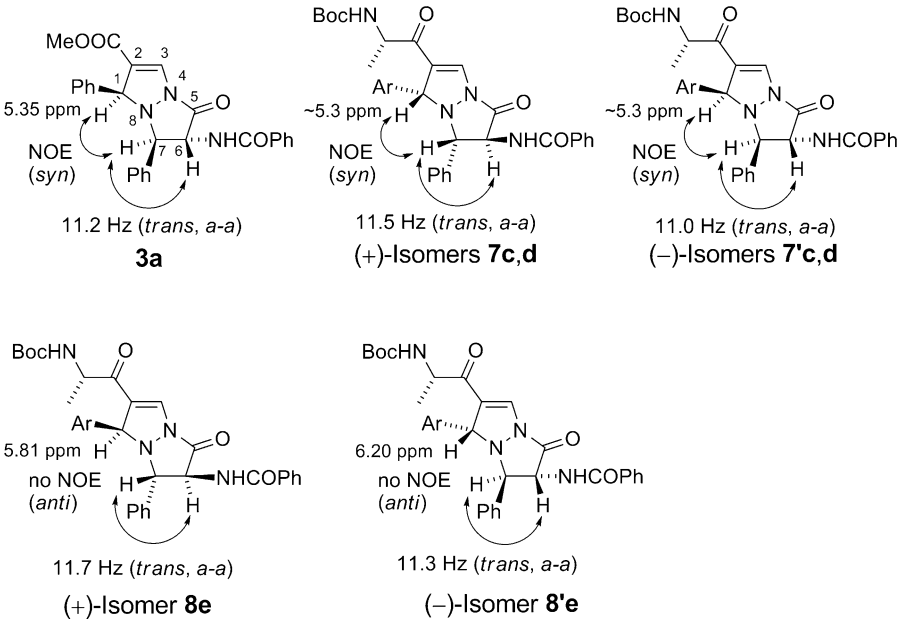


Fig. 1. Determination of the relative configuration of compounds **3a**, **7c**,**d**, **7′c**,**d**, **8e**, and **8′e** by ^{1}H NMR and by NOESY spectroscopy.

Table 3. Selected ^{1}H NMR data of compounds **3a**, **7a–e**, **7′a–e**, **8e**, and **8′e**.

(1*S**,6*R**,7*R**)-Isomer **3a**								
Compound	δ (ppm)						$^3J_{6H-7H}$	
	1-H	2′-H	3-H	6-H	7-H	NH		
3a[a]	5.27	–	7.70	4.75[b]	4.75[b]	6.58	[b]	
3a[c]	5.35	–	8.00	4.93	4.76	9.10	11.2	
(+)-Isomers **7a–d** and **8e**								
Compound	δ (ppm)						$^3J_{6H-7H}$	$[\alpha]_{589}^{23}$
	1-H	2′-H	3-H	6-H	7-H	NH		
7a[a]	5.26	4.73	8.35	5.36	4.50	5.47/7.88	11.5	+260
7b[a]	5.23	4.73	8.31	5.33	4.49	5.46/7.81	11.5	+509
7c[a]	5.43	4.71	8.13	5.11	4.65	5.22/7.10	11.5	+686
7d[a]	5.27	4.80	8.28	5.31	4.53	5.44/7.60	11.4	+117
8e[a]	5.81	4.74	8.37	5.28	4.50	5.65/8.17	11.7	+373
(–)-Isomers **7′a–d** and **8′e**								
Compound	1-H	2′-H	3-H	6-H	7-H	NH	$^3J_{6H-7H}$	$[\alpha]_{589}^{23}$
7′a[a]	5.29	4.68	7.91	4.70	4.80	5.06/6.97	11.0	–532
7′b[a]	5.27	4.69	7.89	4.70	4.79	5.08/6.88	11.0	–607
7′c[a]	5.42	4.71	7.60	4.66	4.86	4.94/6.61	10.9	−769
7′d[a]	5.28	4.78	7.98	4.72	4.82	5.05/6.83	11.1	−194
8′e[a]	6.20	4.72	7.69	5.00	4.21	5.30/6.52	11.3	−112

[a] In $CDCl_3$; [b] the signals for 6-H and 7-H were overlapping and appeared as a multiplet; [c] in $[D_6]$DMSO.

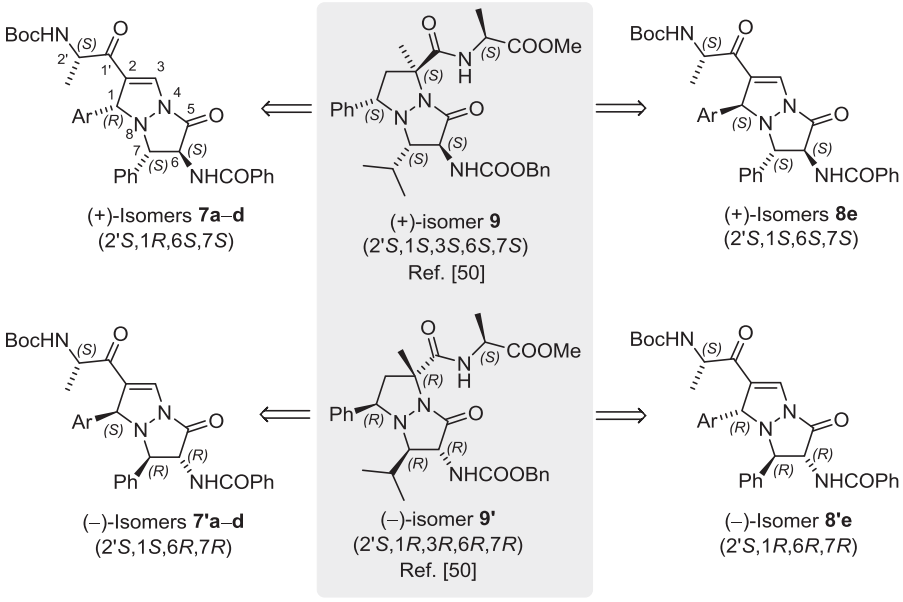


Fig. 2. Proposed tentative configurations of compounds **7a–d**, **7′a–d**, **8e**, and **8′e**.

Conclusion

In summary, regioselective and stereoselective CuI-catalyzed [3+2] cycloadditions of azomethine imine dipoles **1** to ynones **2** and **6** can be performed at room temperature in acetonitrile in the presence of Hünig's base to afford 2-acyl-substituted 1-aryl-6-benzamido-5-oxo-7-phenyl-6,7-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazoles **7**, **7′**, **8**, and **8′** in very good yields. Suitable reaction conditions were found upon

combinatorial screening on a 0.1 mmol scale using dipole **1a** and methyl propiolate (**2**) as model compounds. In contrast to harsh thermal activation (∼ 150 °C) required for the non-catalyzed [3+2] cycloadditions of azomethine imines **1** [43, 44, 50, 51], these optimized reaction conditions allow preparation of the non-racemic cycloadducts by the use of the non-racemic dipoles or/and dipolarophiles. This has been demonstrated by cycloadditions of racemic dipoles **1a–e** to the non-racemic dipolarophile **6**, which afforded mixtures of diastereomeric non-racemic cycloadducts **7a–d**, **7′a–d**, **8e**, and **8′e** that were separable by preparative liquid chromatography (MPLC). Furthermore, this CuI-catalyzed method could also be useful for asymmetric applications, *e. g.* for the synthesis of non-racemic dipoles and cycloadducts *via* kinetic resolution as shown by Fu and co-workers [21].

Experimental Section

Melting points were determined on a Stanford Research Systems MPA100 OptiMelt automated system. The NMR spectra were obtained on a Bruker Avance III UltraShield 500 plus at 500 MHz for ^{1}H and 126 MHz for ^{13}C, using $CDCl_3$ and [D$_6$]DMSO (with TMS as the internal standard) as solvents. Mass spectra were recorded on an Agilent 6224 Accurate Mass TOF LC/MS spectrometer, IR spectra on a Bruker FTIR Alpha Platinum ATR spectrophotometer. Microanalyses were performed on a Perkin-Elmer CHN analyzer 2400 II. Column chromatography (CC) and flash column chromatography (FC) were performed on silica gel (Fluka, silica gel 60, particle size 35 – 70 μm). Medium-performance liquid chromatography (MPLC) was done 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), column dimensions: 23 × 460 mm, backpressure: 10 bar, detection: UV (254 nm).

Methyl propiolate (**2**) (TCI Europe), CuI, *i*-Pr$_2$EtN, (*S*)-*N*-Boc-alanine (**4**), *N*,*O*-dimethylhydroxylamine, CDI, and ethynylmagnesium bromide (Sigma Aldrich) are commercially available. Azomethine imines **1a–c**,**f** [9], **1d** [55], **1e** [22], and Weinreb amide **5** [53] were prepared following the literature procedures.

Methyl (1S,6R*,7R*)-6-benzamido-5-oxo-1,7-diphenyl-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazole-2-carboxylate (**3a**)*

CuI (39 mg, 0.2 mmol) and Hünig's base (52 μL, 0.3 mmol) were added to a stirred suspension of **1a** (369 mg, 1 mmol) and methyl propiolate (**2**) (107 μL, 1.2 mmol) in acetonitrile (10 mL), and stirring at r. t. was continued until complete dissolution of the starting dipole **1a** (~12 h). Volatile components were evaporated *in vacuo* (35 °C, 10 mbar), and the residue was purified by FC (EtOAc-hexanes, 4 : 1). Fractions containing the product were combined, and the solvent was evaporated *in vacuo* (40 °C, 10 mbar) to give **3a**. Yield: 444 mg (98 %) of a pale-brown solid. M. p. 218 – 219 °C. – IR (ATR): ν = 3318, 3264, 3116, 3063, 3017, 2956, 2924, 1732 (C=O), 1696 (C=O), 1635, 1601, 1580, 1531, 1491, 1444, 1415, 1331, 1256, 1233, 1217, 1196, 1158, 1107, 1088, 1065, 1028, 1002, 966, 918, 888, 853, 838, 779, 766, 739, 696, 642, 604 cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 3.56 (3H, s, OMe), 4.76 (1H, d, J = 11.2 Hz, 7-H), 4.93 (1H, dd, J = 11.2, 8.2 Hz, 6-H), 5.35 (1H, d, J = 1.7 Hz, 1-H), 7.07 – 7.86 (15H, m, 3 × Ph), 8.00 (1H, d, J = 1.6 Hz, 3-H), 9.10 (1H, d, J = 8.3 Hz, NH) ppm. – ^{1}H NMR ($CDCl_3$): δ = 3.63 (3H, s, OMe), 4.73 – 4.79 (2H, m, 6-H, 7-H), 5.27 (1H, d, J = 1.7 Hz, 1-H), 6.58 (1H, d, J = 5.3 Hz, NH), 7.12 – 7.16 (4H, m, 4H of Ph), 7.17 – 7.22 (6H, m, 6H of Ph), 7.43 (2H, t, J = 7.7 Hz, 2H of Ph), 7.53 (1H, t, J = 7.4 Hz, 1H of Ph), 7.70 (1H, d, J = 1.7 Hz, 3-H), 7.75 (2H, d, J = 7.4 Hz, 2H of Ph) ppm. – ^{13}C NMR ([D$_6$]DMSO): δ = 51.4, 60.7, 72.6, 73.3, 115.5, 127.2, 127.4, 127.6, 127.8, 127.9, 128.1, 128.3, 128.5, 131.1, 131.9, 133.0, 135.6, 140.6, 163.3, 164.6, 166.1 ppm. – HRMS ((+)-ESI): m/z = 453.1687 (calcd. 453.1689 for $C_{27}H_{23}N_3O_4$, $[M]^+$). – $C_{27}H_{23}N_3O_5 \cdot 1/3H_2O$ (459.5): calcd. C 70.58, H 5.19, N 9.14; found C 70.85, H, 5.26, N 9.12.

*tert-Butyl (S)-(3-oxopent-4-yn-2-yl)carbamate (**6**)* [52]

Compound **6** was prepared from the Weinreb amide **5** [53] following the literature procedure for the preparation of closely related ynones [54]. At –78 °C under argon, ethynylmagnesium bromide (0.5 M in THF, 80 mL, 40 mmol) was slowly added to a stirred solution of **5** (2.323 g, 10 mmol) in anh. THF, and the mixture was stirred at –78 °C under argon for 1 h and then at r. t. for 12 h. The mixture was poured into a cold (0 °C) 1 M aq. $NaHSO_4$ solution (150 mL) and stirred for 1 h. THF was evaporated *in vacuo* (35 °C, 10 mbar), and the aqueous residue was extracted with ether (2 × 150 mL). The combined organic phase was washed successively with 1 M aq. $NaHSO_4$ (150 mL), sat. aq. $NaHCO_3$ (150 mL), and brine (150 mL), dried over anh. Na_2SO_4, filtered, and the filtrate was evaporated *in vacuo* (40 °C, 10 mbar). The residue was purified by CC (EtOAc-hexanes, 1 : 2) to give **6**. Yield: 1.576 g (80 %) of brownish crystals. Physical and spectral data of **6** were in agreement with the literature data [52].

*Synthesis of tert-butyl ((S)-1-((1R,6S,7S)-1-aryl-6-benzamido-5-oxo-7-phenyl-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamates **7a–d**, their (2′S,1S,6R,7R)-diastereomers **7′a–d**, tert-butyl ((S)-1-((1S,6S,7S)-6-benzamido-5-oxo-7-phenyl-1-(2,4,6-trimethoxyphenyl)-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate (**8e**) and its (2′S,1R,6R,7R)-diastereomer (**8′e**)*

CuI (117 mg, 0.6 mmol) and Hünig's base (156 μL, 0.9 mmol) were added to a stirred suspension of **1a–e** (3 mmol) and *tert*-butyl (*S*)-(3-oxopent-4-yn-2-yl)carbamate (**6**) (651 mg, 3.3 mmol) in anh. acetonitrile (20 mL), and stirring at r. t. was continued until complete dissolution of the starting dipole **1** (1 – 4 h for **1a–d**, 72 h for **1e**). Volatile components were evaporated *in vacuo* (35 °C, 10 mbar), and the residue was purified by FC (EtOAc-hexanes). Fractions containing the product were combined, and the solvent was evaporated *in vacuo* (40 °C, 10 mbar) to give a mixture of diastereomers **7a–d**, **7′a–d**, **8e**, and **8′e** which were separated by MPLC. From fractions containing the products, the solvent was evaporated *in vacuo* to give two diastereomeric non-racemic compounds **7a–d**, **7′a–d**, **8e**, and **8′e**.

The following compounds were prepared in this manner:

*tert-Butyl (+)-((S)-1-((1R,6S,7S)-6-benzamido-5-oxo-1,7-diphenyl-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate (**7a**) and its (–)-(2′S,1S,6R,7R)-diastereomer (**7′a**)*

Prepared from **1a** (1.064 g, 2.88 mmol) and **6** (0.6136 g, 3.11 mmol), stirring for 2 h; FC (EtOAc-hexanes, 2 : 1). – Yield of **7a/7′a**: 1.49 g (91 %) of a yellow solid. – MPLC (EtOAc-hexanes, 1 : 1).

*(+)-Isomer **7a***. Yield: 232 mg (14 %) of a yellow solid. M. p. 169 – 172 °C. – $[\alpha]_{589}^{23} = +260$ ($c = 0.32$, CH_2Cl_2). – IR (ATR): $\nu = 3353, 3103, 2976, 1731$ (C=O), 1677 (C=O), 1657 (C=O), 1641 (C=O), 1595, 1526, 1489, 1392, 1368, 1348, 1325, 1267, 1236, 1194, 1152, 1120, 1089, 1062, 1030, 958, 899, 875, 849, 782, 760, 715, 693, 641, 608 cm^{-1}. – ^{1}H NMR ($CDCl_3$): $\delta = 1.14$ (3H, d, $J = 7.1$ Hz, CH_3), 1.44 (9H, s, Boc), 4.50 (1H, d, $J = 11.5$ Hz, 7-H), 4.73 (1H, br p, $J = 7.3$ Hz, 2′-H), 5.26 (1H, d, $J = 1.6$ Hz, 1-H), 5.36 (1H, dd, $J = 8.8$, 11.5 Hz, 6-H), 5.47 (1H, d, $J = 8.0$ Hz, N*H*Boc), 7.08 – 7.12 (4H, m, 4H of Ph), 7.14 – 7.16 (3H, m, 3H of Ph), 7.17 – 7.20 (3H, m, 3H of Ph), 7.36 (2H, br t, $J = 7.6$ Hz, 2H of Ph), 7.41 (1H, br t, $J = 7.5$ Hz, 1H of Ph), 7.76 (2H, br d, $J = 7.6$ Hz, 2H of Ph), 7.88 (1H, br d, $J = 8.9$ Hz, N*H*COPh), 8.35 (1H, br s, 3-H) ppm. – ^{13}C NMR ($CDCl_3$): $\delta = 20.5$, 28.6, 52.2, 61.3, 73.6, 76.0, 80.2, 123.8, 127.5, 127.8, 127.9, 127.9, 128.2, 128.5, 128.5, 129.0, 130.6, 132.0, 133.2, 133.9, 139.8, 155.8, 165.6, 167.7, 194.4 ppm. – HRMS ((+)-ESI): $m/z = 567.2595$ (calcd. 567.2602 for $C_{33}H_{35}N_4O_5$, $[M+H]^+$) – $C_{33}H_{34}N_4O_5$ (566.7): calcd. C 69.95, H 6.05, N 9.89; found C 69.55, H, 6.09, N 9.74.

*(–)-Isomer **7′a***. Yield: 74 mg (5 %) of a yellow solid. M. p. 193 – 195 °C. – $[\alpha]_{589}^{23} = -532$ ($c = 0.25$, CH_2Cl_2). – IR (ATR): $\nu = 3369, 2979, 1733$ (C=O), 1675 (C=O), 1644 (C=O), 1582, 1527, 1507, 1417, 1345, 1323, 1250, 1157, 1120, 1068, 1028, 958, 917, 876, 852, 762, 719, 695, 653, 610 cm^{-1}. – ^{1}H NMR ($CDCl_3$): $\delta = 1.24$ (3H, d, $J = 6.7$ Hz, CH_3), 1.40 (9H, s, Boc), 4.68 (1H, br p, $J = 7.6$ Hz, 2′-H), 4.70 (1H, dd, $J = 7.7$, 11.0 Hz, 6-H), 4.80 (1H, d, $J = 11.0$ Hz, 7-H), 5.06 (1H, d, $J = 8.5$ Hz, N*H*Boc), 5.29 (1H, d, $J = 1.5$ Hz, 1-H), 6.97 (1H, br d, $J = 7.7$ Hz, N*H*COPh), 7.05 – 7.11 (2H, m, 2H of Ph), 7.12 – 7.16 (7H, m, 7H of Ph), 7.17 – 7.21 (1H, m, 1H of Ph), 7.39 (2H, br t, $J = 7.8$ Hz, 2H of Ph), 7.51 (1H, br t, $J = 7.4$ Hz, 1H of Ph), 7.73 (2H, br d, $J = 7.3$ Hz, 2H of Ph), 7.91 (1H, br s, 3-H) ppm. – ^{13}C NMR ($CDCl_3$): $\delta = 19.0$, 28.3, 51.2, 62.6, 73.2, 74.1, 79.9, 122.8, 127.2, 127.7, 127.8, 127.8, 128.1, 128.5, 128.7, 128.8, 130.6, 132.2, 132.8, 134.4, 140.1, 155.0, 164.2, 167.4, 194.5 ppm. – HRMS ((+)-ESI): $m/z = 567.2599$ (calcd. 567.2602 for $C_{33}H_{35}N_4O_5$, $[M+H]^+$) – $C_{33}H_{34}N_4O_5 \cdot 1/3H_2O$ (572.7): calcd. C 69.21, H 6.10, N 9.78; found C 69.37, H, 6.34, N 9.78.

*tert-Butyl (+)-((S)-1-((1R,6S,7S)-6-benzamido-1-(4-methoxyphenyl)-5-oxo-7-phenyl-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate (**7b**) and its (–)-(2′S,1S,6R,7R)-diastereomer (**7′b**)*

Prepared from **1b** (0.6046 g, 1.51 mmol) and **6** (0.3468 g, 1.76 mmol), stirring for 4 h; FC (EtOAc-hexanes, 2 : 1). – Yield of **7b/7′b**: 883 mg (98 %) of a yellow solid. – MPLC (EtOAc-hexanes, 1 : 1).

*(+)-Isomer **7b***. Yield: 227 mg (25 %) of a yellow solid. M. p. 177 – 180 °C. – $[\alpha]_{589}^{23} = +509$ ($c = 0.25$, CH_2Cl_2). – IR (ATR): $\nu = 3360, 3090, 2982, 2934, 1741$ (C=O), 1710 (C=O), 1671 (C=O), 1652 (C=O), 1593, 1582, 1514, 1490, 1437, 1417, 1369, 1351, 1323, 1304, 1267, 1200, 1153, 1121, 1065, 1029, 966, 918, 874, 852, 823, 784, 761, 693 cm^{-1}. – ^{1}H NMR ($CDCl_3$): $\delta = 1.16$ (3H, d, $J = 7.1$ Hz, CH_3), 1.44 (9H, s, Boc), 3.73 (3H, s, OCH_3), 4.49 (1H, d, $J = 11.5$ Hz, 7-H), 4.73 (1H, p, $J = 7.3$ Hz, 2′-H), 5.23 (1H, br s, 1-H), 5.33 (1H, dd, $J = 8.8$, 11.5 Hz, 6-H), 5.46 (1H, d, $J = 8.0$ Hz, N*H*Boc), 6.68 and 6.99 (4H, 2d, 1 : 1, $J = 8.6$ Hz, C_6H_4), 7.11 – 7.15 (2H, m, 2H of Ph), 7.17 – 7.21 (3H, m, 3H of Ph), 7.34 – 7.38 (2H, m, 2H of Ph), 7.45 – 7.48 (1H, m, 1H of Ph), 7.75 (2H, m, 2H of Ph), 7.81 (1H, d, $J = 8.7$ Hz, N*H*COPh), 8.31 (1H, br s, 3-H) ppm. – ^{13}C NMR ($CDCl_3$): $\delta = 20.4$, 28.5, 52.0, 55.2, 61.3, 72.9, 75.9, 80.1, 113.5, 123.7, 127.3, 127.8, 128.4, 128.4, 128.7, 128.8, 130.4, 131.9, 131.9, 133.2, 133.8, 155.6, 159.0, 165.4, 167.5, 194.4 ppm. – HRMS ((+)-ESI): $m/z = 597.2702$ (calcd. 597.2708 for

$C_{34}H_{37}N_4O_6$, $[M+H]^+$) – $C_{34}H_{36}N_4O_6$ (596.7): calcd. C 68.44, H 6.08, N 9.39; found C 68.57, H, 6.02, N 9.36.

(–)-Isomer ***7′b***. Yield: 122 mg (14 %) of a yellow solid. M. p. 192 – 195 °C. – $[\alpha]_{589}^{23} = -607$ ($c = 0.32$, CH_2Cl_2). – IR (ATR): $\nu = 3384, 3108, 2932, 1713$ (C=O), 1682 (C=O), 1645 (C=O), 1615, 1583, 1505, 1455, 1424, 1385, 1367, 1345, 1322, 1240, 1161, 1112, 1071, 1043, 1028, 968, 922, 902, 879, 858, 840, 800, 783, 753, 717, 698, 653, 616 cm^{-1}. – ^{1}H NMR ($CDCl_3$): $\delta = 1.26$ (3H, d, $J = 7.1$ Hz, CH_3), 1.41 (9H, s, Boc), 3.73 (3H, s, OCH_3), 4.69 (1H, br p, $J = 7.0$ Hz, 2′-H), 4.70 (1H, dd, $J = 7.6, 11.0$ Hz, 6-H), 4.79 (1H, d, $J = 11.0$ Hz, 7-H), 5.08 (1H, d, $J = 8.5$ Hz, N*H*Boc), 5.27 (1H, d, $J = 1.5$ Hz, 1-H), 6.68 and 6.98 (4H, 2d, 1 : 1, $J = 8.5$ Hz, C_6H_4), 6.88 (1H, br s, N*H*COPh), 7.13 – 7.22 (5H, m, Ph), 7.39 – 7.42 (2H, br t, $J = 7.9$ Hz, 2H of Ph), 7.52 (1H, br t, $J = 7.5$ Hz, 1H of Ph), 7.74 (2H, br d, $J = 7.9$ Hz, 2H of Ph), 7.89 (1H, br s, 3-H) ppm. – ^{13}C NMR ($CDCl_3$): $\delta = 19.1$, 28.3, 51.3, 55.1, 62.7, 72.7, 74.2, 79.9, 113.5, 122.9, 127.2, 127.8, 128.5, 128.7, 128.8, 128.9, 130.5, 132.3, 132.3, 132.8, 134.4, 155.0, 159.0, 164.2, 167.4, 194.7 ppm. – HRMS ((+)-ESI): $m/z = 597.27$ (calcd. 597.2708 for $C_{34}H_{37}N_4O_6$, $[M+H]^+$) – $C_{34}H_{36}N_4O_6 \cdot 1/3H_2O$ (602.7): calcd. C 67.76, H 6.13, N 9.30; found C 67.92, H, 5.91, N 9.04.

*tert-Butyl (+)-((S)-1-((1R,6S,7S)-6-benzamido-1-(4-nitrophenyl)-5-oxo-7-phenyl-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate (**7c**) and its (–)-(2′S,1S,6R,7R)-diastereomer (**7′c**)*

Prepared from **1c** (1.0247 g, 2.47 mmol) and **6** (0.5018 g, 2.54 mmol), stirring for 1 h; FC (EtOAc-hexanes, 2 : 3). – Yield of **7c/7′c**: 1.429 g (95 %) of a yellow solid. – MPLC (EtOAc-hexanes, 1 : 1).

(+)-Isomer ***7c***. Yield: 587 mg (39 %) of a yellow solid. M. p. 165 – 166 °C. – $[\alpha]_{589}^{23} = +686$ ($c = 0.27$, CH_2Cl_2). – IR (ATR): $\nu = 3433, 3366, 3089, 2983, 2932, 1716$ (C=O), 1673 (C=O), 1651 (C=O), 1580, 1516, 1433, 1349, 1325, 1266, 1238, 1201, 1153, 1119, 1090, 1065, 965, 845, 832, 755 cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 1.07$ (3H, d, $J = 7.3$ Hz, CH_3), 1.37 (9H, s, Boc), 4.63 (1H, p, $J = 7.2$ Hz, 2′-H), 4.79 (1H, d, $J = 11.2$ Hz, 7-H), 5.03 (1H, dd, $J = 8.2, 11.2$ Hz, 6-H), 5.60 (1H, br s, 1-H), 7.11 – 7.17 (4H, m, 3H of Ph and N*H*Boc), 7.25 – 7.27 (2H, m, 2H of Ph), 7.40 (2H, br d, $J = 8.7$ Hz, 2H of C_6H_4), 7.49 (2H, br t, $J = 7.5$ Hz, 2H of Ph), 7.57 (1H, br t, $J = 7.4$ Hz, 1H of Ph), 7.83 (2H, br d, $J = 7.3$ Hz, 2H of Ph), 8.00 (2H, d, $J = 8.7$ Hz, 2H of C_6H_4), 8.65 (1H, br s, 3-H), 9.13 (1H, br d, $J = 8.3$ Hz, N*H*COPh) ppm. – ^{1}H NMR ($CDCl_3$): $\delta = 1.17$ (3H, d, $J = 7.1$ Hz, CH_3), 1.44 (9H, s, Boc), 4.65 (1H, d, $J = 11.5$ Hz, 7-H), 4.71 (1H, p, $J = 7.4$ Hz, 2′-H), 5.11 (1H, dd, $J = 7.8, 11.5$ Hz, 6-H), 5.22 (1H, d, $J = 7.8$ Hz, N*H*Boc), 5.43 (1H, br s, 1-H), 7.10 (1H, br d, $J = 8.2$ Hz, N*H*COPh), 7.13 – 7.18 (2H, m, 2H of Ph), 7.18 – 7.24 (3H, m, 3H of Ph), 7.35 (2H, br d, $J = 8.7$ Hz, 2H of C_6H_4), 7.42 (2H, br t, $J = 7.5$ Hz, 2H of Ph), 7.52 (1H, br t, $J = 7.3$ Hz, 1H of Ph), 7.75 (2H, br d, $J = 7.4$ Hz, 2H of Ph), 8.03 (2H, d, $J = 8.7$ Hz, 2H of C_6H_4), 8.13 (1H, br s, 3-H) ppm. – ^{13}C NMR ([D$_6$]DMSO): $\delta = 17.4$, 28.3, 52.3, 60.8, 72.2, 73.2, 78.1, 121.5, 122.9, 127.3, 128.0, 128.3, 128.5, 128.6, 129.1, 131.4, 132.0, 133.0, 135.2, 146.6, 148.6, 155.2, 164.7, 166.1, 196.1 ppm. – HRMS ((+)-ESI): $m/z = 612.2454$ (calcd. 612.2453 for $C_{33}H_{34}N_5O_7$, $[M+H]^+$). – $C_{34}H_{33}N_5O_7$ (611.7): calcd. C 64.80, H 5.44, N 11.45; found C 64.59, H, 5.23, N 11.33.

(–)-Isomer ***7′c***. Yield: 253 mg (17 %) of a yellow solid. M. p. 208 – 211 °C. – $[\alpha]_{589}^{23} = -769$ ($c = 0.22$, CH_2Cl_2). – IR (ATR): $\nu = 3380$, 3328, 3110, 2981, 1736 (C=O), 1678 (C=O), 1641 (C=O), 1581, 1519, 1421, 1368, 1324, 1295, 1250, 1159, 1110, 1071, 1028, 954, 879, 832, 802, 784, 757, 716, 697, 614 cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 1.12$ (3H, d, $J = 6.9$ Hz, CH_3), 1.33 (9H, s, Boc), 4.56 (1H, p, $J = 7.0$ Hz, 2′-H), 4.79 (1H, d, $J = 11.1$ Hz, 7-H), 5.01 (1H, dd, $J = 8.1, 11.1$ Hz, 6-H), 5.57 (1H, br s, 1-H), 7.14 – 7.19 (3H, m, 3H of Ph), 7.26 – 7.28 (3H, m, 2H of Ph and N*H*Boc), 7.33 (2H, d, $J = 8.6$ Hz, 2H of C_6H_4), 7.48 (2H, br t, $J = 7.6$ Hz, 2H of Ph), 7.56 (1H, br t, $J = 7.4$ Hz, 1H of Ph), 7.82 (2H, br d, $J = 7.2$ Hz, 2H of Ph), 7.95 (2H, d, $J = 8.6$ Hz, 2H of C_6H_4), 8.53 (1H, br s, 3-H), 9.13 (1H, d, $J = 8.2$ Hz, N*H*COPh) ppm. – ^{1}H NMR ($CDCl_3$): $\delta = 1.33$ (3H, d, $J = 6.9$ Hz, CH_3), 1.39 (9H, s, Boc), 4.66 (1H, dd, $J = 7.5, 10.9$ Hz, 6-H), 4.71 (1H, p, $J = 7.6$ Hz, 2′-H), 4.86 (1H, d, $J = 10.9$ Hz, 7-H), 4.94 (1H, d, $J = 8.3$ Hz, N*H*Boc), 5.42 (1H, br s, 1-H), 6.61 (1H, br d, $J = 7.5$ Hz, N*H*COPh), 7.15 – 7.19 (4H, m, 4H of Ph), 7.21 – 7.26 (1H, m, 1H of Ph), 7.31 (2H, br d, $J = 8.3$ Hz, 2H of C_6H_4), 7.45 (2H, br t, $J = 7.7$ Hz, 2H of Ph), 7.55 (1H, br t, $J = 7.4$ Hz, 1H of Ph), 7.76 (2H, br d, $J = 7.2$ Hz, 2H of Ph), 7.60 (1H, br s, 3-H), 8.01 (2H, d, $J = 8.3$ Hz, 2H of C_6H_4) ppm. – ^{13}C NMR ($CDCl_3$): $\delta = 16.9$, 28.2, 51.4, 60.9, 72.0, 73.0, 78.3, 121.4, 122.7, 127.3, 128.2, 128.3, 128.6, 128.6, 129.2, 131.4, 132.0, 133.0, 135.2, 146.5, 148.4, 155.0, 164.8, 166.2, 195.6 ppm. – HRMS ((+)-ESI): $m/z = 612.2449$ (calcd. 612.2453 for $C_{33}H_{34}N_5O_7$, $[M+H]^+$).

*tert-Butyl (+)-((S)-1-((1R,6S,7S)-6-benzamido-1-(3,4,5-trimethoxyphenyl)-5-oxo-7-phenyl-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate (**7d**) and its (–)-(2′S,1S,6R,7R)-diastereomer (**7′d**)*

Prepared from **1d** (1.1054 g, 2.41 mmol) and **6** (0.490 g, 2.48 mmol), stirring for 1 h; FC (EtOAc-hexanes, 2 : 1). Yield of **7d/7′d**: 1.046 g (66 %) of a yellow solid. – MPLC (EtOAc-hexanes, 1 : 1).

(+)-Isomer ***7d***. Yield: 474 mg (30 %) of a yellow solid. M. p. 178 – 183 °C. – $[\alpha]_{589}^{23} = +117$ ($c = 0.23$, CH_2Cl_2). –

IR (ATR): ν = 3333, 2975, 2934, 1733 (C=O), 1708 (C=O), 1658 (C=O), 1584, 1504, 1467, 1455, 1416, 1366, 1324, 1237, 1162, 1125, 1064, 1003, 944, 851, 758, 697 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.28 (3H, d, J = 7.1 Hz, CH_3), 1.45 (9H, s, Boc), 3.62 and 3.77 (9H, 2s, 2 : 1 3×OMe), 4.53 (1H, d, J = 11.4 Hz, 7-H), 4.80 (1H, p, J = 7.0 Hz, 2′-H), 5.27 (1H, br s, 1-H), 5.31 (1H, dd, J = 8.2, 11.4 Hz, 6-H), 5.44 (1H, d, J = 7.9 Hz, N*H*Boc), 6.18 (2H, s, 2H of Ph), 7.17 – 7.25 (5H, m, Ph), 7.39 (2H, t, J = 7.6 Hz, 2H of Ph), 7.49 (1H, t, J = 7.4 Hz, 1H of Ph), 7.60 (1H, d, J = 8.2 Hz, N*H*COPh), 7.78 (2H, d, J = 7.5 Hz, 2H of Ph), 8.28 (1H, s, 3-H) ppm. – ^{13}C NMR ($CDCl_3$): δ = 20.4, 28.5, 52.2, 55.8, 60.7, 61.3, 73.5, 75.9, 80.1, 104.5, 122.6, 127.3, 128.3, 128.6, 128.7, 129.2, 131.1, 132.2, 133.1, 133.9, 135.4, 137.4, 152.9, 155.5, 165.3, 167.4, 194.6 ppm. – HRMS ((+)-ESI): m/z = 657.2912 (calcd. 657.2919 for $C_{36}H_{41}N_4O_8$, $[M+H]^+$).

(–)-Isomer ***7′d***. Yield: 216 mg (14 %) of a yellow solid. M. p. 157 – 163 °C. – $[\alpha]_{589}^{23}$ = –194 (c = 0.11, CH_2Cl_2). – IR (ATR): ν = 3337, 2934, 1736 (C=O), 1673 (C=O), 1643 (C=O), 1588, 1507, 1456, 1415, 1328, 1238, 1156, 1125, 1002, 954, 852, 693 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.32 (3H, d, J = 7.0 Hz, CH_3), 1.40 (9H, s, Boc), 3.64 and 3.76 (9H, 2s, 2 : 1, 3 ×OCH_3), 4.72 (1H, dd, J = 7.5, 11.1 Hz, 6-H), 4.78 (1H, br p, J = 7.6 Hz, 2′-H), 4.82 (1H, d, J = 11.0 Hz, 7-H), 5.05 (1H, d, J = 8.5 Hz, N*H*Boc), 5.28 (1H, br s, 1-H), 6.18 (2H, s, C_6H_2), 6.83 (1H, br s, N*H*COPh), 7.19 – 7.26 (5H, m, Ph), 7.42 (2H, br t, J = 7.6 Hz, 2H of Ph), 7.53 (1H, br t, J = 7.3 Hz, 1H of Ph), 7.76 (2H, br d, J = 7.6 Hz, 2H of Ph), 7.98 (1H, br s, 3-H) ppm. – ^{13}C NMR ($CDCl_3$): δ = 18.8, 28.3, 51.2, 55.8, 60.7, 62.6, 73.5, 74.2, 80.1, 104.6, 122.0, 127.3, 128.3, 128.7, 128.8, 129.1, 131.0, 132.3, 132.7, 134.5, 135.6, 137.2, 152.8, 155.1, 164.2, 167.4, 194.8 ppm. – HRMS ((+)-ESI): m/z = 657.2915 (calcd. 657.2919 for $C_{36}H_{41}N_4O_8$, $[M+H]^+$).

*tert-Butyl (+)-((S)-1-((1S,6S,7S)-6-benzamido-1-(2,4,6-trimethoxyphenyl)-5-oxo-7-phenyl-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-1-oxopropan-2-yl)carbamate (**8e**) and its (–)-(2′S,1R,6R,7R)-diastereomer (**8′e**)*

Prepared from **1e** (0.7544 g, 1.64 mmol) and **6** (0.3312 g, 1.68 mmol), stirring for 72 h; FC (EtOAc-hexanes, 3 : 2). – Yield of **8e/8′e**: 0.9544 g (88 %) of a yellow solid. – MPLC (EtOAc-hexanes, 2 : 3).

(+)-Isomer ***8e***. Yield: 111 mg (10 %) of a yellow solid. M. p. 123 – 128 °C. – $[\alpha]_{589}^{23}$ = +373 (c = 0.20, CH_2Cl_2). – IR (ATR): ν = 3307, 2935, 1714 (C=O), 1652 (C=O), 1590, 1531, 1490, 1434, 1355, 1321, 1227, 1203, 1151, 1118, 1058, 950, 915, 852, 813, 756, 696 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.27 (3H, d, J = 7.1 Hz, CH_3), 1.47 (9H, s, Boc), 3.08, 3.72, and 3.75 (9H, 3s, 1 : 1 : 1, 3 × OCH_3), 4.50 (1H, d, J = 11.7 Hz, 7-H), 4.74 (1H, p, J = 7.3 Hz, 2′-H), 5.28 (1H, dd, J = 9.0, 11.7 Hz, 6-H), 5.65 (1H, br d, J = 7.7 Hz, N*H*Boc), 5.66 and 6.05 (2H, 2d, 1 : 1, J = 1.5 Hz, C_6H_2), 5.81 (1H, br s, 1-H), 7.04 – 7.08 (2H, m, 2H of Ph), 7.09 – 7.13 (1H, m, 1H of Ph), 7.18 (2H, br d, J = 7.3 Hz, 2H of Ph), 7.36 (2H, br t, J = 7.7 Hz, 2H of Ph), 7.46 (1H, br t, J = 7.3 Hz, 1H of Ph), 7.81 (2H, br d, J = 7.6 Hz, 2H of Ph), 8.17 (1H, br d, J = 7.9 Hz, N*H*COPh), 8.37 (1H, br s, 3-H) ppm. – ^{13}C NMR ($CDCl_3$): δ = 21.3, 28.5, 51.9, 55.1, 55.2, 55.6, 61.8, 64.2, 76.0, 79.8, 90.0, 91.0, 106.8, 126.0, 127.0, 127.4, 127.9, 128.0, 128.3, 129.4, 131.7, 133.5, 135.6, 155.7, 158.7, 159.9, 161.0, 164.7, 167.4, 193.9 ppm. – HRMS ((+)-ESI): m/z = 657.2913 (calcd. 657.2919 for $C_{36}H_{41}N_4O_8$, $[M+H]^+$).

(–)-Isomer ***8′e***. Yield: 25 mg (3 %) of a yellow solid. M. p. 128 – 132 °C. – $[\alpha]_{589}^{23}$ = −112 (c = 0.22, CH_2Cl_2). – IR (ATR): ν = 3319, 2932, 1712 (C=O), 1660 (C=O), 1651 (C=O), 1587, 1531, 1489, 1434, 1366, 1324, 1225, 1205, 1150, 1118, 1058, 1027, 951, 853, 812, 695 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.25 (3H, d, J = 7.2 Hz, CH_3), 1.41 (9H, s, Boc), 3.21, 3.76, and 3.81 (9H, 3s, 1 : 1 : 1, 3× OCH_3), 4.21 (1H, d, J = 11.3 Hz, 7-H), 4.72 (1H, dq, J = 7.4–7.9 Hz, 2′-H), 5.00 (1H, dd, J = 7.8–11.6 Hz, 6-H), 5.30 (1H, d, J = 7.8 Hz, N*H*Boc), 5.84 and 6.07 (2H, 2d, 1 : 1, J = 2.2 Hz, C_6H_2), 6.20 (1H, s, 1-H), 6.52 (1H, br d, J = 7.8 Hz, N*H*COPh), 7.05 – 7.07 (2H, m, 2H of Ph), 7.20 – 7.22 (3H, m, 3H of Ph), 7.37 (2H, br t, J = 7.6 Hz, 2H of Ph), 7.47 (1H, br t, J = 7.5 Hz, 1H of Ph), 7.67 – 7.69 (2H, m, 2H of Ph), 7.69 (1H, br s, 3-H) ppm. – ^{13}C NMR ($CDCl_3$): δ = 19.9, 28.4, 51.4, 55.2, 55.4, 55.6, 57.2, 62.6, 67.9, 79.6, 90.3, 90.8, 102.8, 124.0, 127.1, 127.5, 128.2, 128.3, 128.5, 128.6, 131.9, 133.5, 136.1, 155.0, 159.6, 160.9, 161.7, 162.1, 167.1, 194.0 ppm. – HRMS ((+)-ESI): m/z = 657.2914 (calcd. 657.2919 for $C_{36}H_{41}N_4O_8$, $[M+H]^+$).

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