Utilisation of chiral enaminones and azomethine imines in the synthesis of functionalised pyrazoles

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Abstract
Chiral enaminones, derived from commercially available enantipure starting materials, such as (+)-camphor and *α*-amino acids, were employed in cycloconcensation reactions with hydrazine derivatives to afford the corresponding pyrazoles, functionalised with terpene, alanine, 2-phenylethylamine, and *β*-amino alcohol moiety. On the other hand, recent study on stereocontrol in cycloadditions of racemic (1*Z*,4*R**,5*R**)-1-arylmethylidene-4-benzoylamino-5-phenylpyrazolidin-3-one-1-azomethine imines, available in three steps from hippuric acid, showed, that stereodirecting phenyl group, as well as *ortho*-substituents at the aromatic ring, control the selectivity of these cycloadditions. In extension, these results are now applied in a study, which is oriented towards combinatorial synthesis of pyrazolo[1,2–*a*]pyrazolone type of peptidomimetics with variable, yet predictable configuration.

Keywords: Enaminones, heterocycles, azomethine imines, cyclisations, cycloadditions, chiral pool

Contents

1. Introduction

Pyrazoles belong among the most reparesentative five-membered heterocyclic systems.[1] Despite the fact, that pyrazole ring is rarely a constituent of natural products, numerous synthetic pyrazole derivatives found use in various pharmaceutical, agrochemical, photographic, and other applications. Such examples of important pyrazole derivatives are natural products (*S*)-pyrazolylalanine,[2] pyrazomycin,[3] and withasomine[4] and synthetic compounds sildenafil (Viagra®),[5] lonazolac,[6] difenamizole,[7] mepirizole,[8] phenidone,[9] and bicyclic pyrazolidinone LY 186826.[10]

On the other hand, synthesis and transformations of heterocyclic compounds represent the major topics of our research interest, which is primarily focused on development of synthetic methodologies for the preparation of various heterocyclic systems. In extention, these methodologies are then used for preparation of various types of heterocyclic compunds, which are functionalised with an amino acid, hydroxy acid, amino alcohol, polyol, nucleoside, terpene, dipeptide, and realted structural motifs.[11] Within this context, a part of our studies was also focused on the synthesis of functionalised pyrazoles. For this purpose, we used two 3+2 heterocyclisation approaches, which are, also in general, the most frequently employed methods for the formation of the pyrazole ring:

a) cyclocondensation between a hydrazine derivative and a suitably functionalised chiral enaminone as enamino masked 1,3-dicarbonyl compound analogue and

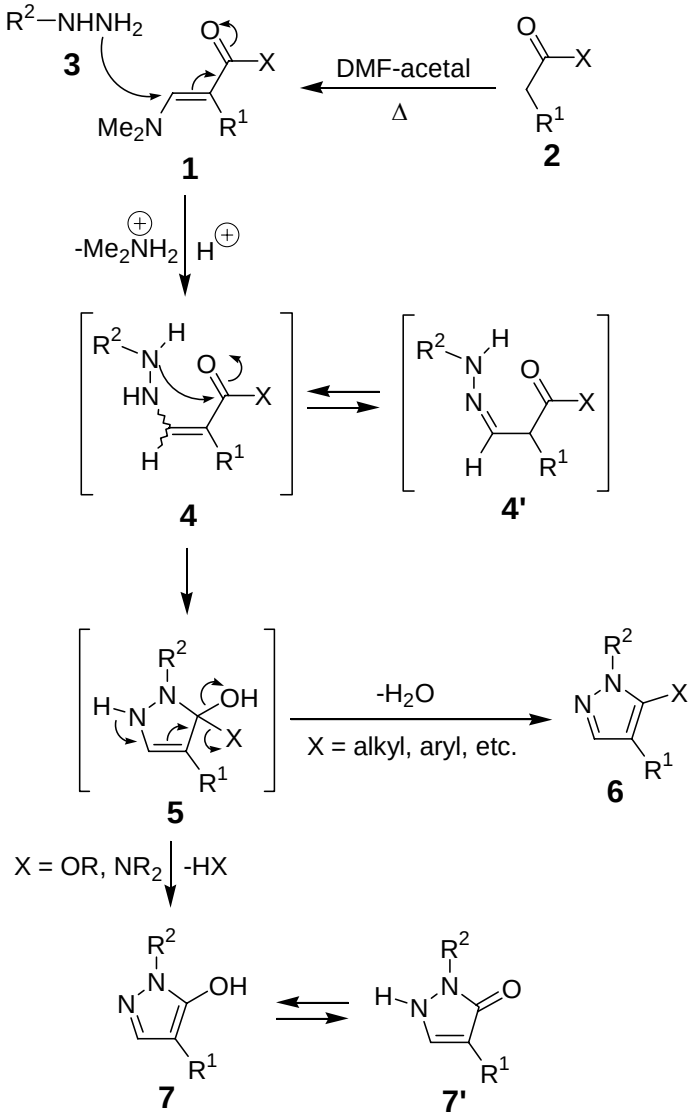
b) 1,3-dipolar cycloaddition of chiral 3-pyrazolidinone-1-azomethine imine to a suitable dipolarophile.

The present review represents a summary of our most recent results in the synthesis of functionalised pyrazoles.

2. Syntheses of functionalised pyrazoles from chiral enaminones

In the last two decades, a series of 2-substituted alkyl 3-(dimethylamino)propenoates **1** and related enaminones was synthesized and used for the preparation of various heterocyclic

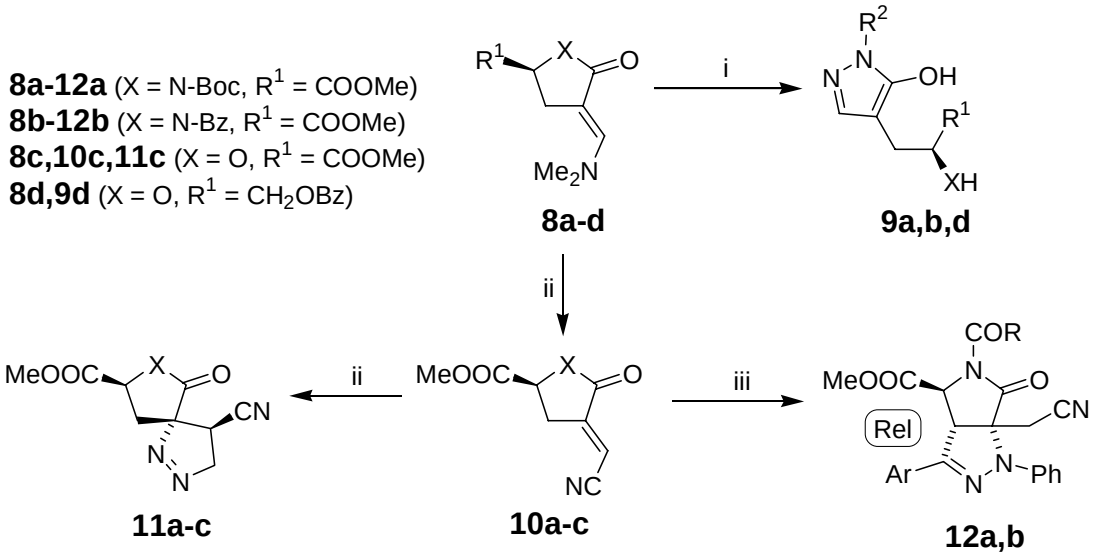
systems, functionalised heterocycles, and natural product analogues.[12,13] Recently, 3-(dimethylamino)propenoates **1** and analogs also found use in combinatorial synthesis.[14] The most usual synthesis of alkyl 3-(dimethylamino)propenoates **1** consists of a treatment of an active methylene compound **2** with a formamide acetal. Propenoates **1** exhibit similar reactivity as their parent 1,3-dicarbonyl compounds: a) they react with electrophiles at position 2 and b) two electrofilic sites at positons 3 and 1 enable cyclisations with various 1,2- and 1,3-dinucleophiles leading to five- and six-membered heterocyclic systems. Reactions of **1** with nucleophiles are acid-catalysed and proceed by initial substitution of the dimethylamino group, followed condensation to the carbonyl group.[12]



Scheme 1

For example, in the reactions of **1** with hydrazine derivatives **3**, substitution of the dimethylamino group takes place first to give the enehydrazines **4** (or tautomeric hydrazones **4'**), followed by cyclisation to the carbonyl group to give the intermediate **5**. In the case of enamino ketones (X = alkyl, aryl, etc.), elimination of water affords the 4,5-disubstituted pyrazole **6**, while in the case of enamino esters and enamino amides, 4-substituted 5-hydroxypyrazoles **7** and/or their tautomers **7'** are usually formed.[12] In some cases, the intermediates **4/4'**[15,16] and **5**[17] were isolated under mild reaction conditions and their structures were confirmed by X-Ray diffraction (Scheme 1).

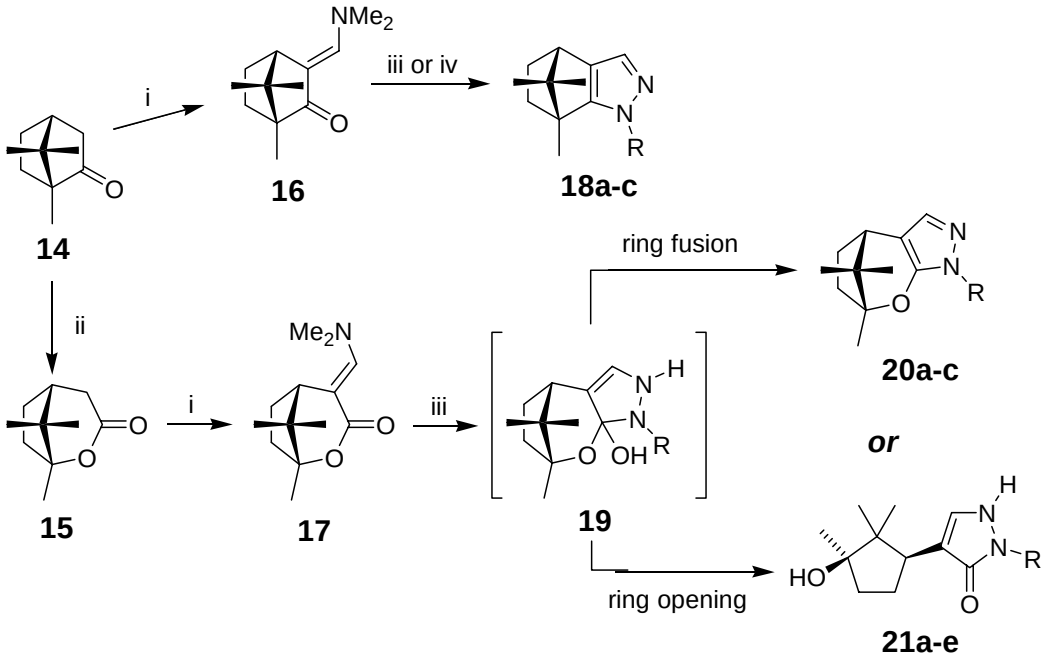
In the chiral enaminone series, our previous studies were based on tranformations of 5-substituted lactams **8a,b** and lactones **8c,d**. Acid-catalysed reactions of **8a,b,d** with various hydrazine derivatives **3**, resulted in 'ring switching' formation[18] of methyl (*S*)-*N*-acyl-3-(1-substituted-5-hydroxy-1*H*-pyrazol-4-yl)alanines **9a,b**[19] and (*S*)-1-*O*-benzoyl-3-(1-substituted-5-hydroxy-1*H*-pyrazol-4-yl)propane-1,2-diols **9c**.[20] In a recent extention, the 'ring switching' methodology was also applied in a parallel solution-phase synthesis of 3-pyrazolylalanines.[21] On the other hand, when the dimethylamino group in enaminones **8a–c** was substituted by the cyano group, nitriles **10a–c** were obtained and used as chiral dipolarophiles in 1,3-dipolar cycloadditons to diazomethane and nitrile imines to afford spiro pyrazoles **11a–c** and fused pyrazoles **12a,b** with a dipeptide or closely related structural unit (Scheme 2).[22]



Scheme 2. (i) R^2NHNH_2 **3**, AcOH, 80–120 °C; (ii) KCN, AcOH, r.t.; (iii) CH_2N_2–Et_2O, 0 °C; (iii) ArC(Cl)=NNHPh, Et_3N, CH_2Cl_2, reflux.

Similarly, 1-acyl-3-methyl-5-[(*Z*)-cyanomethylidene]imidazolidin-2,4-diones **13**, available in three steps from hydantoin, reacted with diazomethane, azomethine imines, and nitrile imines to give, depending on the reaction conditions, the spiro pyrazole hydantoins and the pyrazole-5-carboxamide derivatives.[23]

2.1 Synthesis of terpene-functionalised pyrazoles



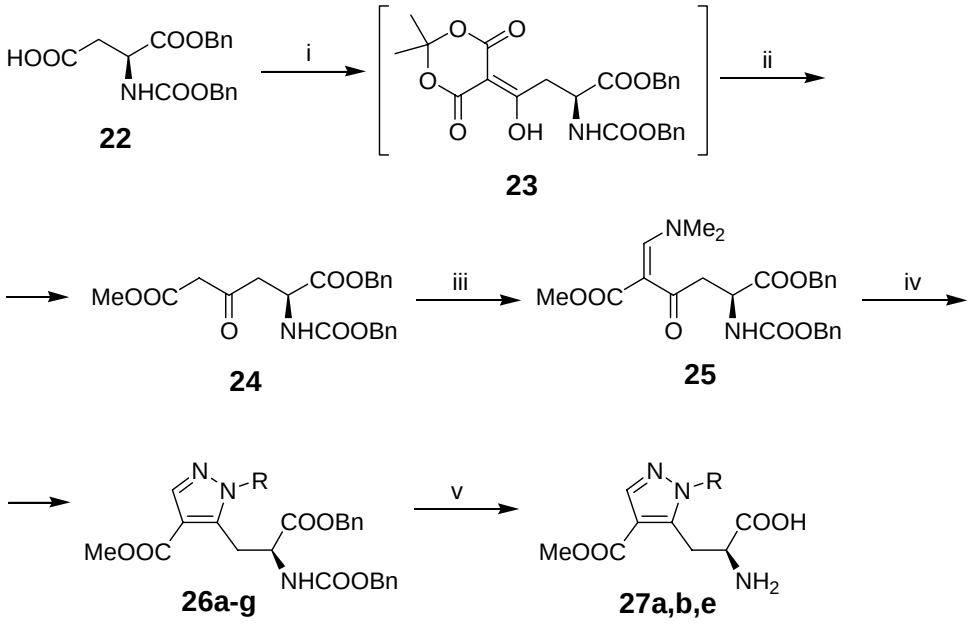
Compound	R	Yield (%)
3a, **18a**	H	81
3b, **18b**	Benzyl	63
3c	6-chloropyridazin-3-yl	-
18c	6-oxo-1,6-dihydropyridazin-3-yl	83
3d, **20a**	Ph	91
3e, **20b**	3-methylphenyl	74
3f, **20c**	4-methylphenyl	85
3a, **21a**	H	83
3g, **21b**	2-methylpehnyl	70
3h, **21c**	2-chlorophenyl	61
3i, **21d**	2-bromophenyl	63
3j, **21e**	Pentafluorophenyl	56

Scheme 3. (i) *t*-BuOCH(NMe_2)$_2$, DMF, reflux; (ii) AcOOH, AcOH, AcONa, r.t.; (iii) R^2–$NHNH_2$ (**3a,d–j**), *n*-PrOH, 37% HCl (1 equiv.), reflux; (iv) R^2–$NHNH_2$ **3b,c**, AcOH, reflux.

Recently, (1*R*,3*E*,4*R*)-3-[(dimethylamino)methylidene]-1,7,7-trimethylbicyclo [2.2.1]-heptan-2-one (**16**)[16] and (1*R*,4*E*,5*R*)-4-[(dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one (**17**),[24] were prepared from (+)-camphor (**14**). Reactions of **16** and **17** with hydrazines **3a–j** afforded terpene-functionalised pyrazoles **18**, **20**, and **21**. Reactions of **16** were selective and gave the corresponding pyrazolo fused camphors **18a–c**. In the reaction of

16 with 6-chloro-3-hydrazinopyridazine (**3c**), substitution of the chloro by the hydroxy group took place. On the other hand, reactions of the lactone analogue **17** proceeded in two ways. Treatment of **17** with *ortho*-unsubstituted phenylhydrazines **3d–f** furnished the pyrazolo fused lactones **20a–c** as products of elimination of water from the intermediate **19**, while with *ortho*-substituted hydrazines **3g–j** and with hydrazine hydrochloride (**3a**), opening of the lactone ring took place to give the 'ring switched' products **21a–e**. It has to be emphasized, that also these reactions were higly selective and led to a single type of product, depending on the type of hydrazine derivative employed. Selectivity of these transformations might be attributed to steric, as well as to electronic effects (Scheme 3).[25]

2.2 Synthesis of (*S*)-3-(1-substituted-4-methoxycarbonyl-1*H*-pyrazol-5-yl)alanines from L-aspartic acid



Compound	R	Yield (%)	
		26	**27**
3a, **26a**, **27a**	H	57	82
3d, **26b**, **27b**	Ph	94	75
3j, **26c**	pentafluorophenyl	73	
3k, **26d**	4-methoxyphenyl	82	
3l, **26e**, **27e**	pyridin-2-yl	85	82
3m, **26f**	6-phenylpyridazin-3-yl	56	
3n, **26g**	pyrimidin-2-yl	80	

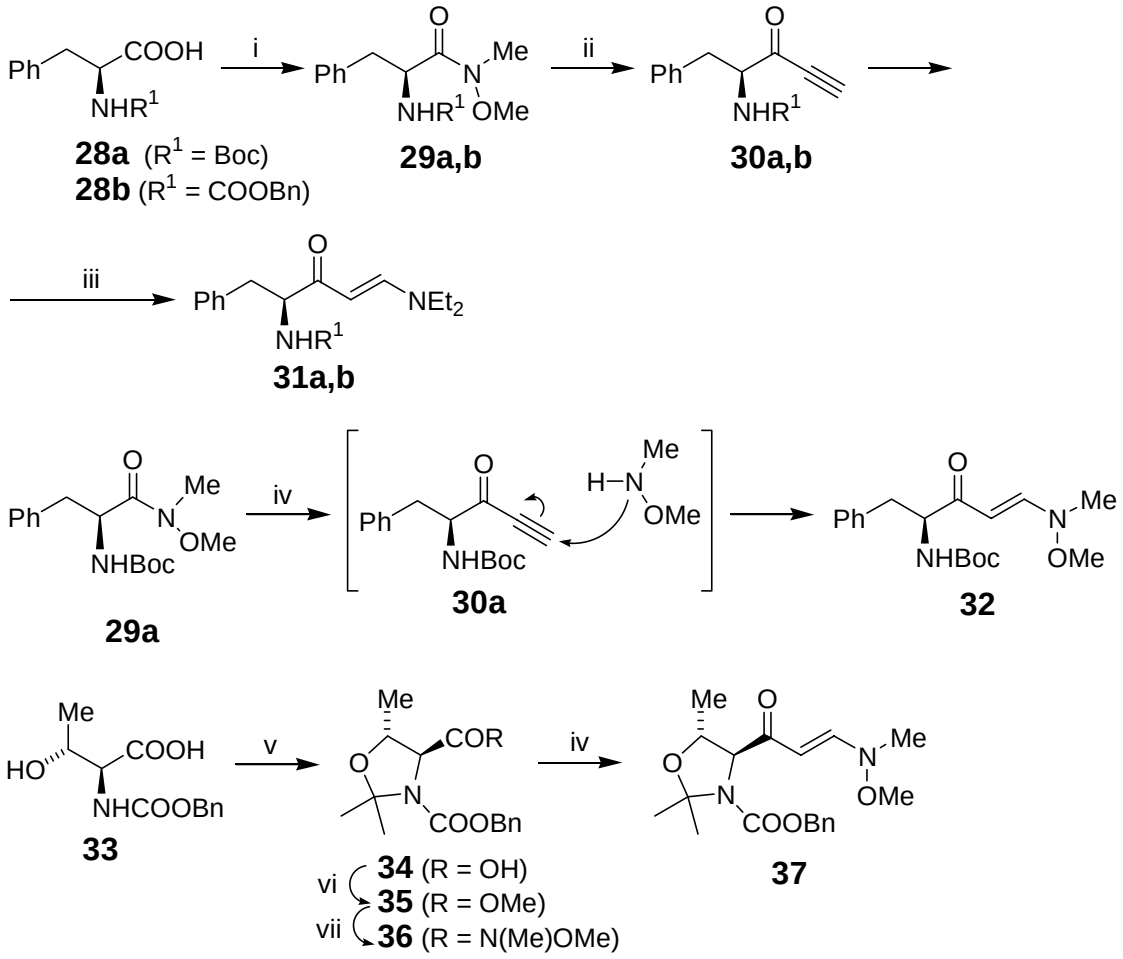
Scheme 4. (i) Meldrum's acid, DCC, CH_2Cl_2, DMAP, –5 °C (Ref.); (ii) MeOH, reflux; (iii) DMFDMA, CH_2Cl_2, r.t.; (iv) R–$NHNH_2$ × HCl **3a,d,j–n**, MeOH or EtOH, r.t.→reflux; (v) H_2 (1 bar), Pd–C, MeOH, r.t.

In search for alternative synthetic routes towards 3-pyrazolylalanines and other 3-heteroarylalanines, we have recently developped an enaminone-based methodology for the synthesis of (*S*)-3-(1*H*-pyrazol-5-yl)alanines. Starting from L-aspartic acid, the (*S*)-*N*-benzyloxycarbonylaspartic acid-1-benzyl ester (**22**) was prepared according to the literature procedure.[26] Following closely related literature examples,[27] compound **22** was then coupled with Meldrum's acid to give the intermediate **23**, which was transformed with methanol into 1-benzyl-6-methyl (*S*)-2-benzyloxycarbonylamino-4-oxohexanedioate (**24**) in 66% yield over two steps. Further treatment of **24** with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) in dichloromethane at r.t. furnished the desired enaminone **25** in 98% yield. Cyclocondensations of **25** with substituted hydrazine hydrochlorides **3a,d,j–n** gave the protected (*S*)-pyrazolylalanines **26a–g** in 56–94% yields. Deprotection of **26a,b,e** by catalytic hydrogenation furnished the free pyrazolylalanines **27a,b,e** (Scheme 4).[28]

2.3 Synthesis of pyrazolyl and pyrazolo[1,5–*a*]pyrimidinyl substituted 2-phenylethylamines and *β*-amino alcohols

2.3.1 Synthesis of L-3-phenylalanine and L-threonine derived enamino ketones

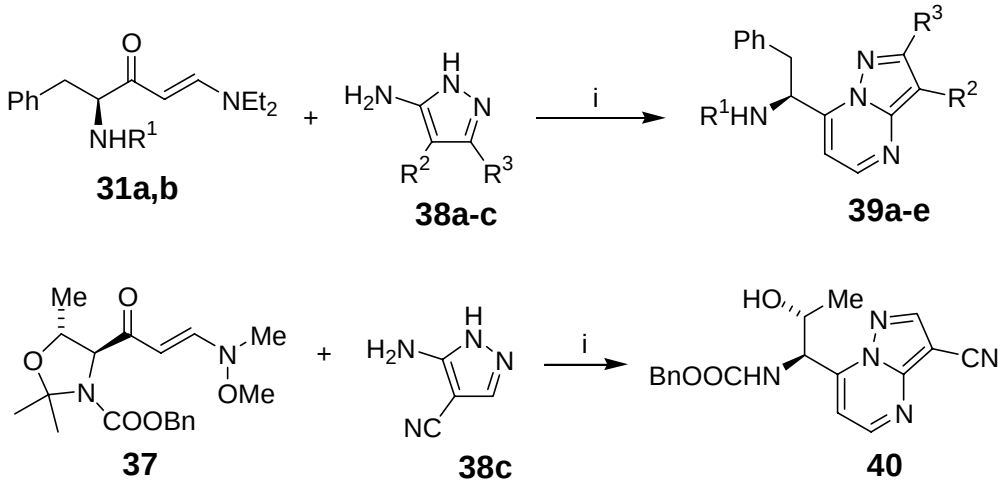
According to the literaturely known methodology,[29] the *N*-protected L-3-phenylalanines **28a,b** were transformed into the Weinreb amides **29a,b**, which were then treated with excess ethynylmagnesium bromide. Upon quenching excess Grignard reagent with aqueous $NaHSO_4$, the corresponding ethynyl ketones **30a,b** were obtained in 90 and 61% yield, respectively. Addition of diethylamine to the triple C≡C bond then afforded enamino ketones **31a,b** in 92% and 86% yield, respectively. On the other hand, upon treatment of **29a** with excess ethynylmagnesium bromide followed by quenching with aqueous NH_4Cl, the *N*-methyl-*N*-methoxy substituted enaminone **32** was obtained in 50% yield. Formation of **32** could be explained by initial formation of the ethynyl ketone **30a** followed by addition of *N*,*O*-dimethylhydroxylamine to the triple C≡C bond. Similarly, the enaminone **37** was prepared in four steps from *N*-benzyloxycarbonyl-L-threonine (**33**) (Scheme 5).[30]



Scheme 5. (i) ClCOOBu, *N*-methylmorpholine, EtOAc, 0 °C, then MeNHOMe, 0 °C→r.t.; (ii) HC≡CMgBr, THF, –78 °C→r.t., then aq. $NaHSO_4$; (iii) Et_2NH, CH_2Cl_2, 0 °C→r.t.; (iv) HC≡CMgBr, THF, –78 °C→r.t., then aq. NH_4Cl; (v) $Me_2C(OMe)_2$, $BF_3{\times}Et_2O$, r.t.; (vi) MeI, K_2CO_3, acetone, 0 °C→r.t.; (vii) *i*-PrMgBr, MeNHOMe, THF, –78 °C→–20 °C, then aq. NH_4Cl.

2.3.2 Synthesis of pyrazolo[1,5–*a*]pyrimidinyl substituted 2-phenylethylamines and *β*-amino alcohols

Enaminones **31a,b** and **37** reacted with 3-aminopyrazole derivatives **38a–c** as 1,3-dinucleophiles, to afford the corresponding (*S*)-1-(pyrazolo[1,5–*a*]pyrimidin-7-yl)-2-phenyletylamines **39a–e** and (*S*)-1-amino-1-(pyrazolo[1,5–*a*]pyrimidin-7-yl)propan-2-ol (**40**) in 20–77% yields. In the reaction of **37** with 5-amino-1*H*-pyrazole-4-carbonitrile (**38c**), simultaneous removal of the ketal protecting group also took place (Scheme 6).[30]

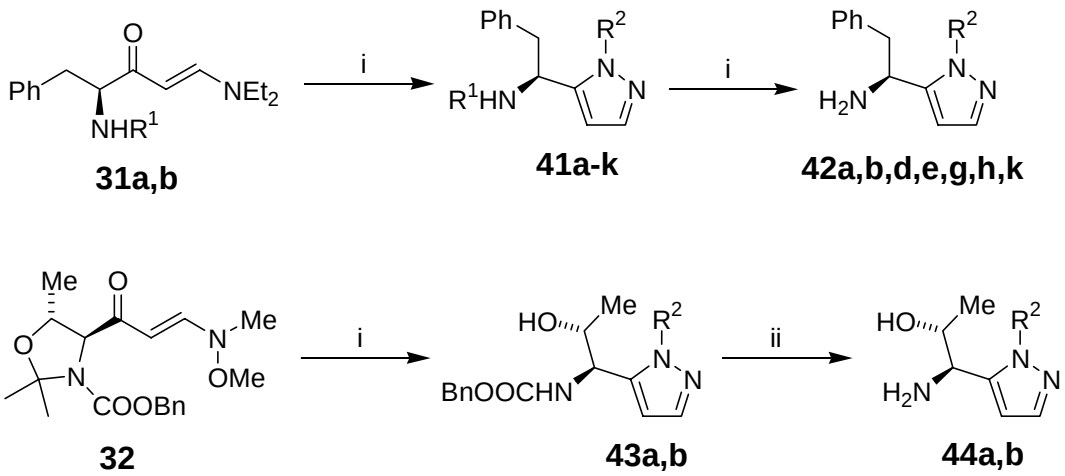


Compound	R^1	R^2	R^3	Yield (%)
38a, 39a	COOBn	H	H	76
38a, **39b**	Boc	H	H	44
38b, **39c**	COOBn	H	Me	32
38c, **39d**	COOBn	CN	H	73
38c, **39e**	Boc	CN	H	20
40				77

Scheme 6. (i) (i) EtOH, 37% HCl (1 equiv.), r.t.→reflux.

2.3.4 Synthesis of pyrazolyl substituted 2-phenylethylamines and *β*-amino alcohols

Acid-catalysed treatment of enaminones **31a,b** with substituted hydrazines **3a,c,d,i,h–o**, afforded the corresponding *N*-protected (*S*)-1-pyrazolyl-2-phenylethylamines **41a–k** in 54–98% yields. Deprotection of compounds **41a,b,d,e,g,h,k** by catalytic hydrogenation furnished free (*S*)-1-pyrazolyl-2-phenylethylamines **42a,b,d,e,g,h,k** in 69–98% yields. In the same manner, L-threonine derived enamino ketone **32** was transformed with phenylhydrazine (**3d**) and 3-hydrazino-6-phenylpyridazine (**3m**) into compounds **34a** and **34b**, respectively. Deprotection by catalytic hydrogenation afforded (2*S*,3*R*)-1-amino-1-(1-phenyl-1*H*-pyrazol-5-yl)propan-2-ol (**44a**) and (2*S*,3*R*)-1-amino-1-[1-(6-phenylpyridazin-3-yl)-1*H*-pyrazol-5-yl]propan-2-ol (**44b**) (Scheme 7).[30]



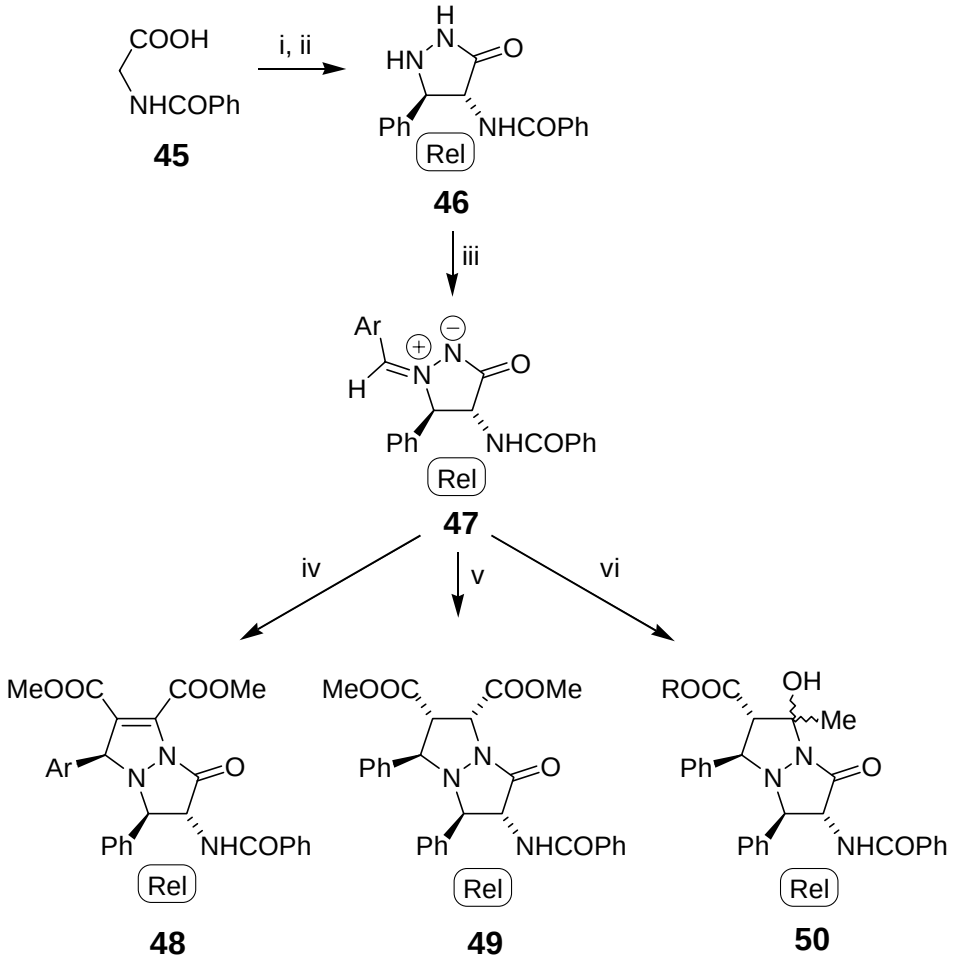
Compound	R^1	R^2	Yield (%)	
			41 or **43**	**42** or **44**
3a, **41a**, **42a**	COOBn	H	98	92
3a, **41b**, **42b**	Boc	H	86	82
3d, **41c**	COOBn	Ph	95	
3o, **41d**, **42d**	COOBn	4-nitrophenyl	80	95
3k, **41e**, **42e**	COOBn	4-methoxyphenyl	70	98
3i, **41f**	Boc	2-bromophenyl	90	
3l, **41g**, **42g**	COOBn	pyridin-2-yl	83	85
3n, **41h**, **42h**	COOBn	pyrimidin-2-yl	89	69
3c, **41i**	COOBn	6-chloropyridazin-3-yl	91	
3c, **41j**	Boc	6-chloropyridazin-3-yl	54	
3m, **41k**, **42k**	COOBn	6-phenylpyridazin-3-yl	78	70
3d, **43a**, **44a**		Ph	92	83
3m, **43b**, **44b**		6-phenylpyridazin-3-yl	63	64

Scheme 7. (i) R^2–$NHNH_2$ **3a,c,d,i,k–o**, EtOH, 37% HCl (1 equiv.), r.t.→reflux; (ii) H_2 (1 bar), EtOH–THF, 10% Pd–C, r.t.

3. Syntheses of functionalised pyrazoles from (1*Z*,4*R**,5*R**)-1-arylmethylidene-4-benzoylamino-5-phenylpyrazolidin-3-one-1-azomethine imines

1,3-Dipolar cycloaddition reactions are useful methods for preparation of five-membered heterocycles. They enable access to polyfunctional compounds with multiple asymmetric centers, often with excellent stereocontrol.[31] In contrast to well elaborated asymmetric cycloadditions in chiral nitrone, nitrile oxide, and azomethine ylide series,[32] much less examples of asymmetric cycloadditions to chiral azomethine imines have been reported.[33–37]

The importance of pyrazolidin-3-ones significantly rose in the last two decades, since several pyrazolidin-3-one derivatives exhibit biological activities and due to their applicability in industrial processes.[9,10,38,39] For example, 2-acylamino-1-oxo-1*H*,5*H*-pyrazolo[1,2–*a*]pyrazole-7-carboxylates are useful scaffolds for preparation of conformationally constrained peptidomimetics.[10,40] Since the first reports of *Dorn*[41] and *Oppolzer*,[42] 1,3-dipolar cycloaddition of stable, pyrazolidin-3-one derived, azomethine imines represent a simple and efficient method for preparation of 1*H*,5*H*-pyrazolo[1,2–*a*]pyrazol-1-ones. However, most of these studies were performed on achiral dipoles and on poorly substituted chiral azomethine imines.[10,38–40,43,44]
In connection with our studies in the field of 3-pyrazolidinones,[34,45–50] we have previously reported regio- and stereoselective 1,3-dipolar cycloadditions to polysubstituted racemic (1*Z*,4*R**,5*R**)-1-arylmethylidene-4-benzoylamino-5-phenylpyrazolidin-3-one-1-azomethine imines **47** leading to polysubstituted 1*H*,5*H*-pyrazolo[1,2–*a*]pyrazol-1-ones **48–50** (Scheme 8).[34]



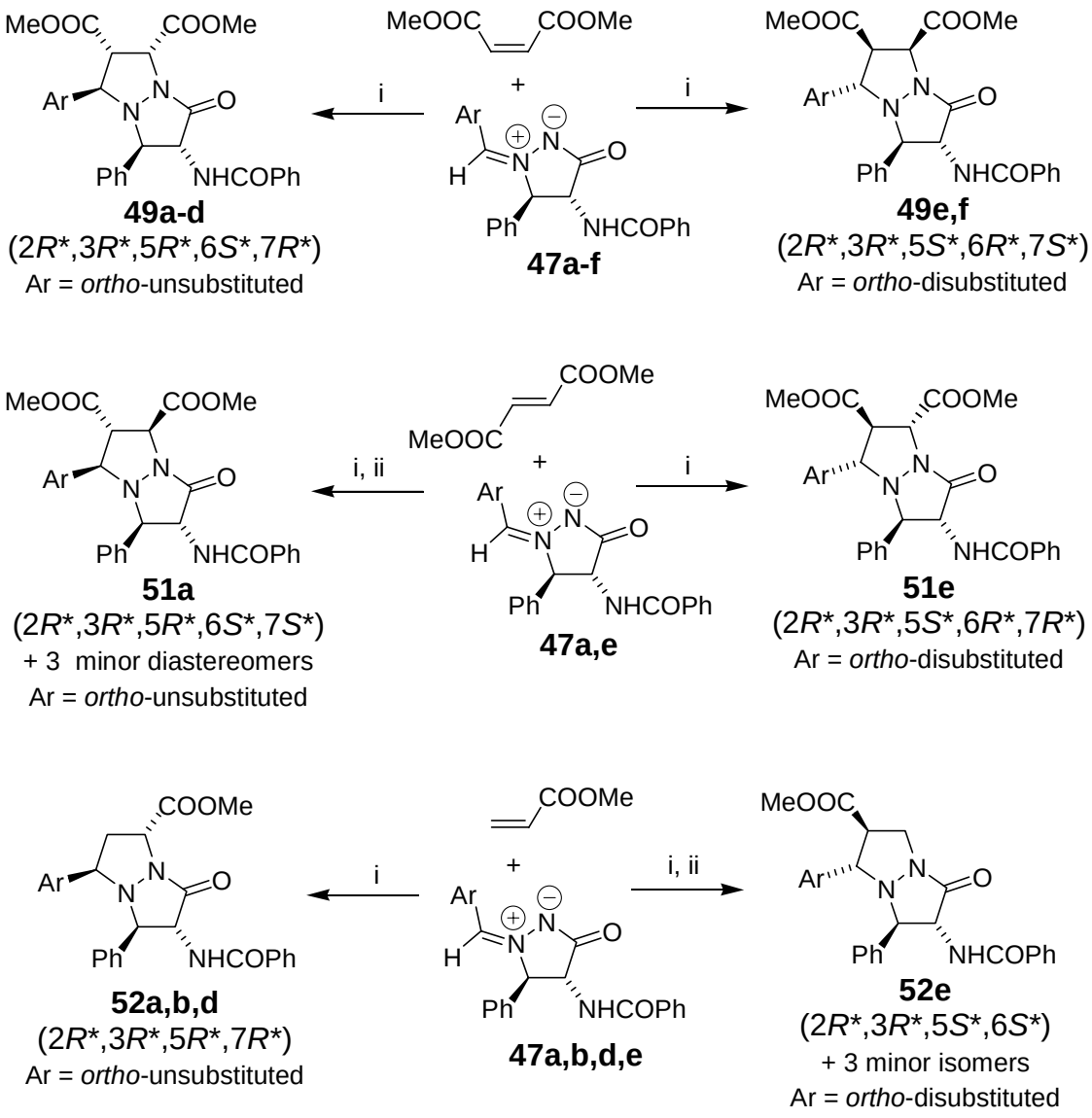
Scheme 8. (i) PhCHO, Ac_2O, AcONa, 100 °C; (ii) $N_2H_4 \times H_2O$ (80%), reflux; (iii) ArCHO, EtOH, TFA (cat.), reflux; (iv) dimethyl acetylenedicarboxylate, anisole, reflux; (v) dimethyl maleate, anisole reflux; (vi) methyl or ethyl acetoacetate, MeOH, Et_3N (1 equiv.), r.t.

Similarly, *Chuang* and *Sharpless*,[36] as well as *Husson*, *Bonin*, *Micouin*, and coworkers,[35,37] reported high facial selectivity of 1,3-dipolar cycloadditions to chiral azomethine imines, derived from pyrazolidinones and related 1,3,4-oxadiazinones.

On the other hand, our previous study on reactions of 1-arylmethylidene-5,5-dimethylpyrazolidin-3-on-1-azomethine imines with methyl propiolate showed, that the regioselectivity was strongly dependent on the *ortho*-substituents at the aromatic ring.[49] This results prompted us to investigate also the influence of *ortho*-substituents in chiral azomethine imines **47** on stereoselectivity and regioselectivity of cycloadditions.

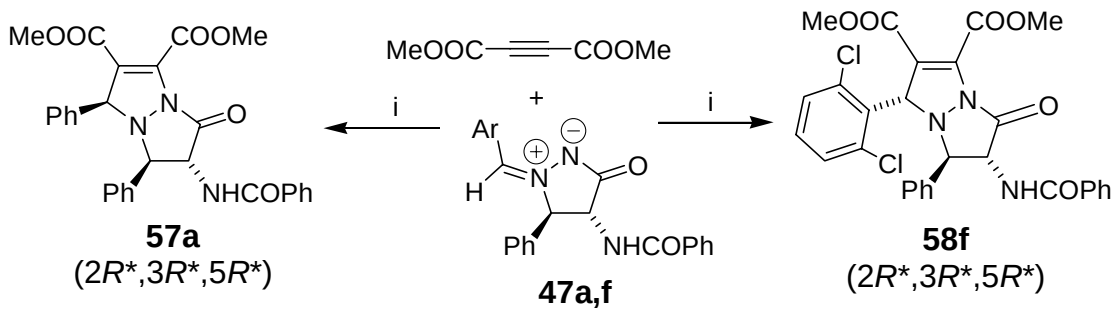
3.1 Stereocontrol in cycloadditions to dimethyl maleate, dimethyl fumarate, methyl acrylate, and dimethyl acetylenedicarboxylate

Azomethine imines **47a–f** with the following aryl substituents attached to the exocyclic C=N double bond were chosen as the model 1,3-dipoles: phenyl (**47a**), 4-nitrophenyl (**47b**), 4-methoxyphenyl (**47c**), 3,4,5-trimethoxyphenyl (**47d**), 2,4,6-trimethylphenyl (**47e**), and 2,6-dichlorophenyl (**47f**). Cycloadditions were carried out with dimethyl maleate, dimethyl fumarate, and methyl acrylate as the model dipolarophiles. Cycloadditions of dipoles **47a–f** to dimethyl maleate were all stereoselective, however, two diastereomeric types of cycloadducts were formed, depending on *ortho*-substituents at the aromatic ring. *ortho*-Unsubstituted dipoles **47a–d** afforded the cycloadducts **49a–d** with (2*R**,3*R**,5*R**,6*S**,7*R**)-configuration, while *ortho*-disubstituted azomethine imines **47e,f** gave, stereoselectively, the major (2*R**,3*R**,5*S**,6*R**,7*S**)-isomers **49e,f**. In contrast, cycloaddition of *ortho*-unsubstituted **47a** to dimethyl fumarate (**5**) was not stereoselective and gave a mixture of **51a** and three isomeric cycloadducts in a ratio of 33:30:22:15, which were separated by chromatography. On the other hand, reaction of dimethyl fumarate with *ortho*-disubstituted **47e** afforded the major (2*R**,3*R**,5*S**,6*R**,7*R**)-isomer **51e** in 68% d.e.. Reactions of *ortho*-unsubstituted **47a,b,d** with methyl acrylate proceeded regioselectively and stereoselectively to give the (2*R**,3*R**,5*R**,7*R**)-isomers **55a,b,d**, while cycloaddition of *ortho*-disubstituted **47e** was not selective and furnished a mixture of the major (2*R**,3*R**,5*S**,6*S**)-isomer **52e** and three minor isomers in a ratio of 34:30:21:15, which were separated by chromatography (Scheme 9).[51]



Scheme 9. (i) Anisole, reflux; (ii) chromatographic separation (CC followed by MPLC).

These results prompted us to reinvestigate the configuration of compounds, formed upon cycloaddition of dipoles **47a** and **47f** to dimethylacetylene dicarboxylate.[34] Also in this case, stereocontrol was dependent on *ortho*-substituents. Thus, **47a** gave cycloadduct **48a** with (2*R**,3*R**,5*R**)-configuration, while the *ortho*-disubstituted **48f** gave cycloadduct **58f** with the opposite sense of configuration at position 5 (Scheme 10).[51]



Scheme 10. (i) Anisole, reflux.

Stereochemistry of these cycloadditions, which is apparently controlled by the stereodirecting phenyl group at position 3, as well as by the *ortho*-substituents at the aromatic ring, might be summarized in the following way:

(a) *ortho*-unsubstituted dipoles favoured formation of the major isomers with *syn*-oriented *H*–C(3) and *H*–C(5), while *ortho*-disubstituted dipoles favoured formation of the major isomers with *anti*-oriented *H*–C(3) and *H*–C(5),

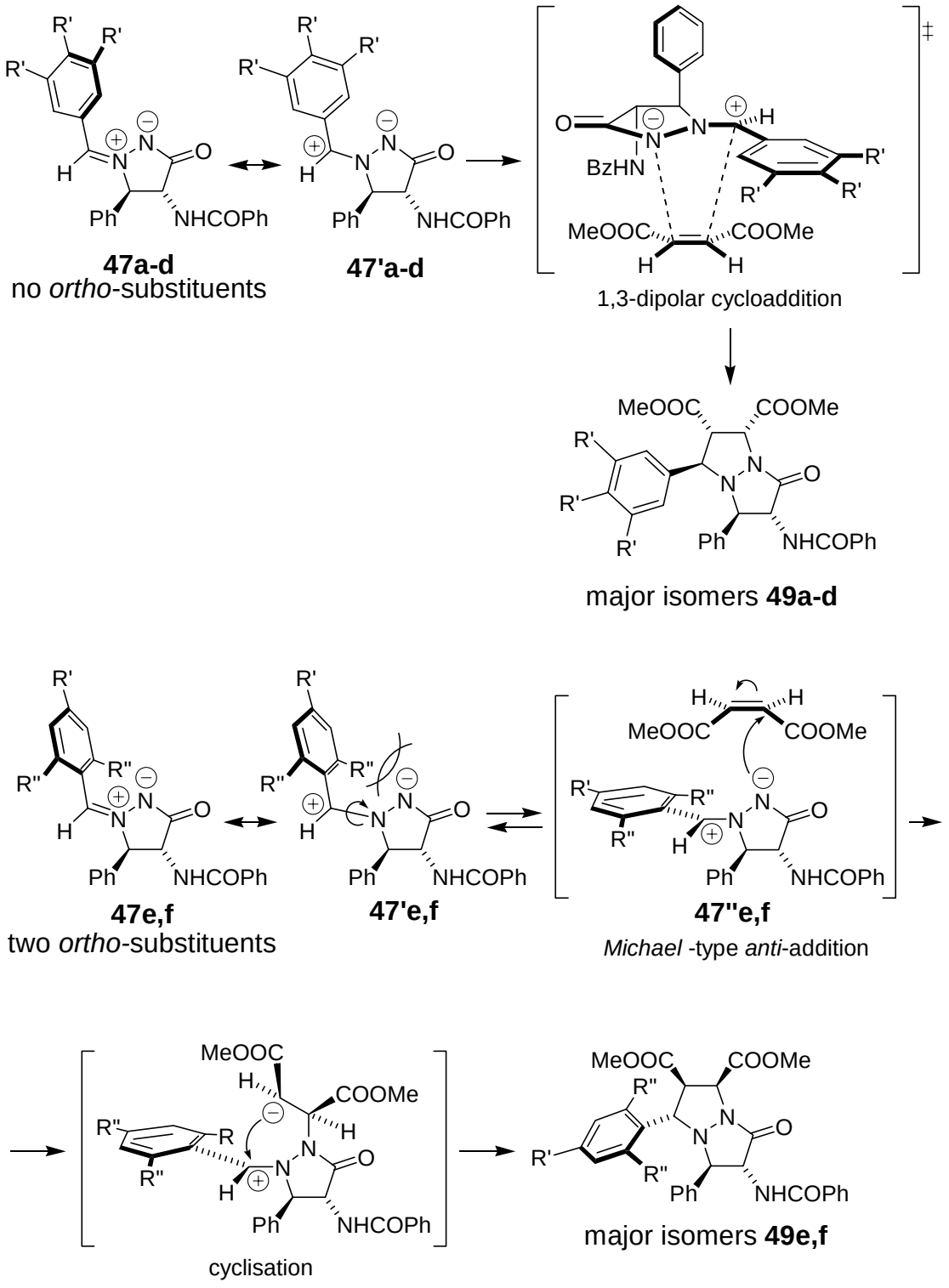
(b) in all major isomers with a stereocenter at position 6, the *H*–C(5) and *H*–C(6) were alway *trans*-oriented,

(c) cycloadditions to dimethyl maleate and dimethyl acetylenedicarboxylate were always stereoselective,

(d) cycloaddition to dimethyl fumarate was stereoselective only in the case of two *ortho*-substituents, and

(e) cycloadditions to methyl acrylate were selective only in the case of no *ortho*-substituents.

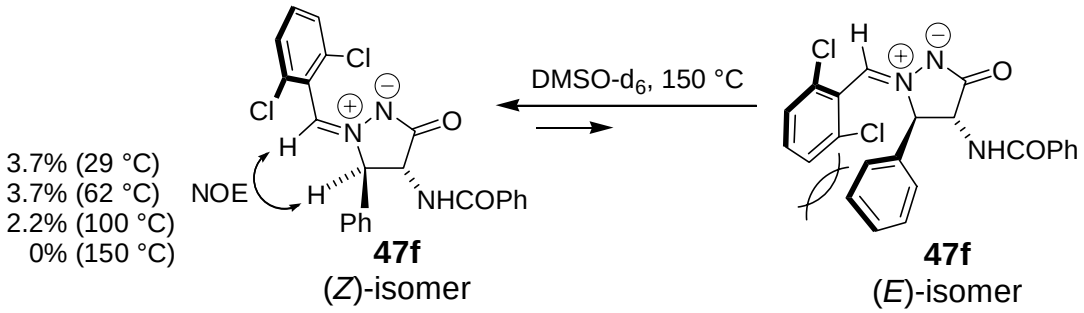
Possible explanation for different selectivity might be examplified at best by cycloadditions of **47a–f** to dimethyl maleate. Dipoles **47a–d** with free *ortho*-positions in the aromatic ring can adopt the planar conformation **47'a–d** allowing transition state for the concerted 1,3-dipolar cycloaddition. Formation of the compounds **49a–d** could be explained by preferential *endo*-approach of dipolarophile from the less hindered face of the (1*Z*,4*R**,5*R**)-dipole. On the other hand, such planar conformation is not possible in the case of dipoles **47e,f** with two *ortho*-substituents. Alternatively, stereoselective formation of **49e,f** might be explained by a two-step 1,4-addition–cyclization mechanism.[52] In the mezomeric structures **47'e,f**, rotation around the N(1)–C(1') single bond gives the rotamers **47''e,f** with the bulky aryl group twisted away from the phenyl ring at position 3. Conformers **47''e,f** can undego *Michael*-type *anti*-addition to the dipolarophile to form the intermediate zwitterions (or a biradicals),[52] which cyclise into the final products **49e,f** (Scheme 11).[51]



Scheme 11

Stereoselective formation of compounds **49e,f** could also be in agreement with the *exo*-approach of the dipolarophile from the less hindered face of the (1*E*,4*R**,5*R**)-dipoles **47e,f**.

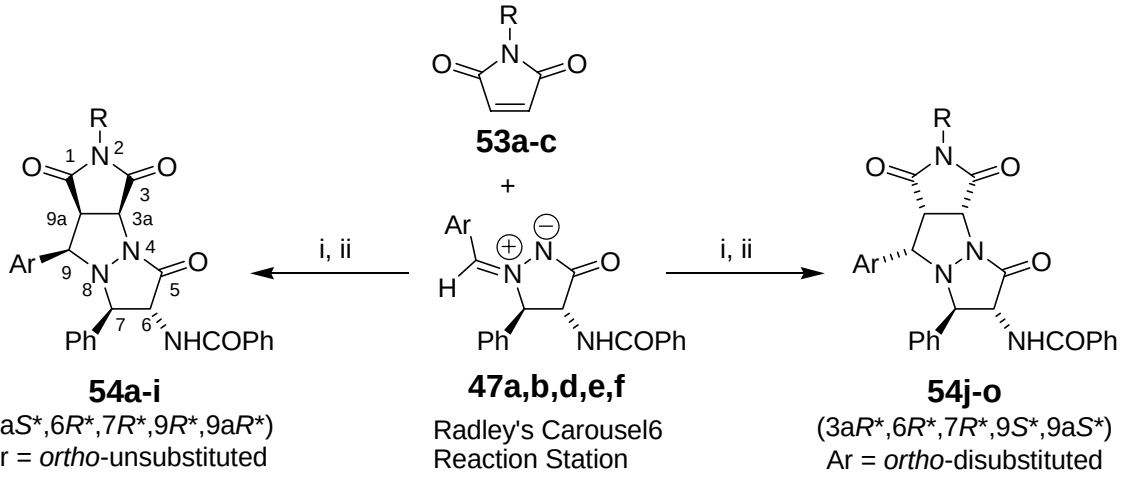
However, this explanation does not seem suitable, since both, (*Z*)- and (*E*)-planar conformation of dipoles **47'e,f** would be sterically unfavourable due to two *ortho*-substituents and because *Z*/*E*-isomerization of dipoles **47e,f** at 150 °C would consequently lead to a mixture of isomeric cycloadducts. In order to determine the possible *Z*/*E*-isomerisation, ^{1}H NMR and NOESY spectra of azomethine imine **47f** were recorded at 29, 62, 100, and 150 °C. Only one set of signals, observed in ^{1}H NMR spectra even at 150 °C, was in agreement with retention of the (Z)-configuration. On the other hand, decreasing NOE between 1'–H and 5–H did not exclude the possibility of *Z*/*E*-isomerisation (Scheme 12).[51]



Scheme 12

3.2 Combinatorial synthesis of 5*H*-pyrazolo[1,2–*a*]pyrrolo[3,4–*c*]pyrazole-1,3,5(2*H*,3a*H*)-triones

In continuation, we focused our attention also on combinatorial studies. Since the reaction and isolation conditions for azomethine imines **47** are allways the same (the dipoles precipitate from the reaction mixture), a series of azomethine imines **47** has recently been prepared by the parallel solution-phase approach and isolated simply by filtration, washing, and drying. In extention, the solution-phase approach was applied for the combinatorial synthesis of 15 tetrahydro-5*H*-pyrazolo[1,2–*a*]pyrrolo[3,4–*c*]pyrazole-1,3,5(2*H*,3a*H*)-triones **54a–o** by reacting five azomethine imines **47a,b,d,e,f** with three maleimides **53a–c**. Maleimides were chosen, since they are also, like dimethyl maleate, the *cisoid*-dipolarophiles and cycloadditions were exspected to proceed stereoselectively regardles to the *ortho*-substituents at the aromatic ring (*c.f.* Scheme 9). Upon heating in anisole followed by cooling, evaporation, trituration with ether, filtration, washing, and thorough drying, all products **54a–i** and **54j–o** were isolated in analytically pure form in 18–89% yields.[53] According to exspectations, two stereochemical types of cycloadducts, **54a–i** and **54j–o**, were formed, depending on *ortho*-substituents at the aromatic ring. Surprisingly, recent NMR and X-ray structural determinations showed, that the configurations at positions 6, 7 and 9 were in agreement with the previously established stereocontrol, while the configurations at positions 3a and 9a were not.[51] This might be due to possible isomerisation at positions 3a and 9a in cycloadduct **54** or/and due to different steric demand of the dipolarophile **53** in comparison to dimethyl maleate (Scheme 13).[53]



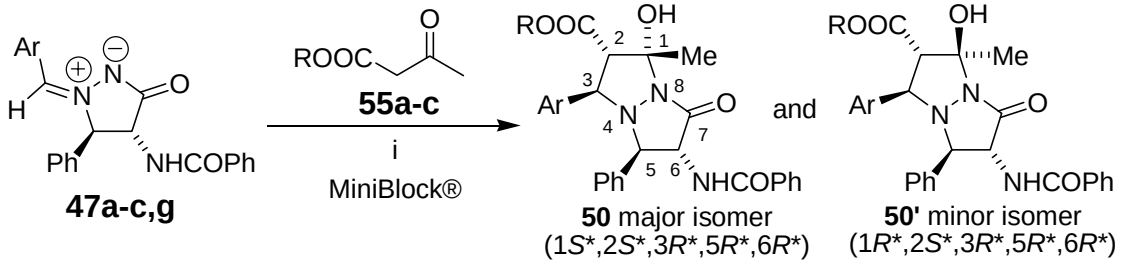
Compound	Ar	R	Yield (%)
	(3a*S**,6*R**,7*R**,9*R**,9a*R**)-isomers		
54a	Ph	Ph	74
54b	4-nitrophenyl	Ph	84
54c	3,4,5-trimethoxyphenyl	Ph	75
54d	Ph	4-methylphenyl	48
54e	4-nitrophenyl	4-methylphenyl	57
54f	3,4,5-trimethoxyphenyl	4-methylphenyl	76
54g	Ph	Me	55
54h	4-nitrophenyl	Me	73
54i	3,4,5-trimethoxyphenyl	Me	85
	(3a*R**,6*R**,7*R**,9*S**,9a*S**)-isomers		
54j	2,4,6-trimethylphenyl	Ph	63
54k	2,6-dichlorophenyl	Ph	82
54l	2,4,6-trimethylphenyl	4-methylphenyl	55
54m	2,6-dichlorophenyl	4-methylphenyl	89
54n	2,4,6-trimethylphenyl	Me	18
54o	2,6-dichlorophenyl	Me	84

Scheme 13. (i) maleimide **53a–c**, anisole, reflux; (ii) evaporation, trituration with Et_2O, filtration, washing with Et_2O, drying *in vacuo*.

3.3 Combinatorial studies on cycloadditions to *β*-keto esters.

Next, we investigated cycloadditons of azomethine imines **47** to *β*-keto esters **55**,[34] which result in the formation of two epimeric alkyl 3-aryl-6-benzoylamino-1-hydroxy-1-methyl-7-oxo-5-phenyltetrahydro-1*H*,5*H*-pyrazolo[1,2–*a*]pyrazole-2-carboxylates, the major (1*S**,2*S**,3*R**,5*R**,6*R**)-isomers **50** and the minor (1*R**,2*S**,3*R**,5*R**,6*R**)-isomers **50'**. During the preliminary studies it turned out, that *ortho*-disubstituted dipoles **47e,f** do not react.

Therefore, we have chosen three model *ortho*-unsubstituted azomethine imines **47a–c** and one model *ortho*-monosubstituted azomethine imine **47g** and nine model *β*-keto esters **55a–i** for a combinatorial study on cycloaddition reactions. First, 12 reactions were carried out with ethyl (**55a**), benzyl (**55b**), and *tert*-butyl acetoacetate (**55c**). With exception of **50**{47b; 55c}, the products were isolated as mixtures of epimers **50** and **50'**. Phenyl (**47a**) and 4-nitrophenyl (**47b**) susbtituted dipoles reacted with all three acetoacetates **55a–c**, while 4-methoxyphenyl (**47c**) and 2,4-dichlorophenyl substituted azomethine imine (**47g**) did not react in all cases. On the other hand, *tert*-butyl acetoacetate (**55c**) was the most reactive, since it underwent cycloadditions with all four azomethine imines **47a–c,g**. (Scheme 14).[53]



50/50'{47a-c,g; 55a-c}

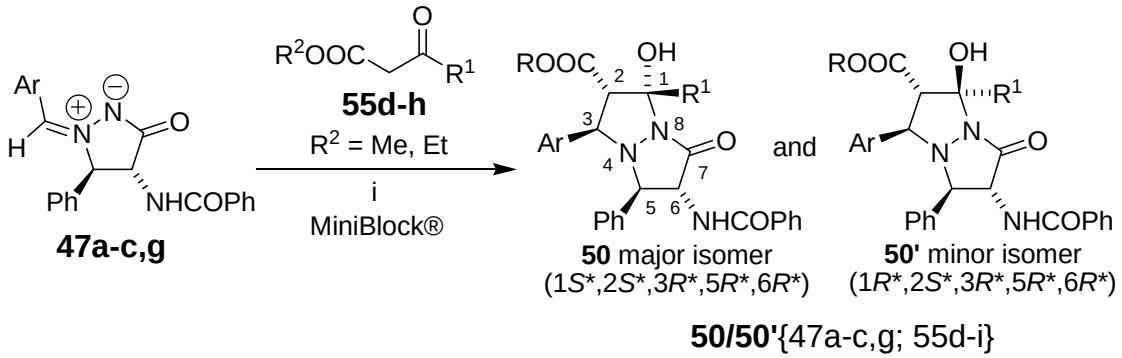
	Yield/D.e. (%)		
R (**55a–c**) →	**55a**	**55b**	**55c**
Ar (**47**)↓	Et	Bn	*t*-Bu
47a phenyl	76/48	60/14	78/46
47b 4-nitrophenyl	75/62	89/60	86/100
47c 4-methoxyphenyl	*n.c.*	34/16	80/68
47g 2,4-dichlorophenyl	*n.c.*	*n.c.*	66/64

n.c.) No conversion detected by TLC.

Scheme 14. (i) MeOH, Et_3N (1 equiv.), r.t..

Finally, 24 cycloadditions were performed with dipoles **47a–c,g** and *β*-keto esters **55d–i** with variable substituents at the *β*-position (**55d** (R = Et), **55e** (R = *n*-Pr), **55f** (R = *i*-Rr), **55g** (R = *t*-Bu), **55h** (R = Ph), and **55i** (R = CH_2COOMe). In contrast to cycloadditions to alkyl acetoacetates **55a–c**, isomerically pure cycloaccudcts were isolated upon reactions of **47a–c,g** with *β*-keto esters **55d–i**. An exception was compound **50/50'** {47a; 55d}, which was obtained in 72% d.e. 4-Nitrophenyl substituted azomethine imine **47b** was again the most reactive and gave cycloadducts also with sterically more demanding keto esters **55g–i** (R = *t*-Bu, Ph, CH_2COOMe), while the other three dipoles **47a,c,g** reacted only with sterically less demanding keto esters **55d–f** (R = Et, *n*-Pr, *i*-Rr). These results also support the indication, that, besides steric factors, the

electronic effects should also be taken into account by planning a combinatorial synthesis of pyrazolo[1,2–*a*]pyrazolone type of peptidomimetics (Scheme 15).[53]



	Yield/D.e.[a] (%)					
R^1 (**55d–i**)→	**55d**	**55e**	**55f**	**55g**	**55h**	**55i**
Ar (**47a–c,g**)↓	Et	*n*-Pr	*i*-Pr	*t*-Bu	Ph	CH_2COOMe
47a phenyl	60/72	19	32	*n.c.*	*n.c.*	76
47b 4-nitrophenyl	85	85	49	41	14	86
47c 4-methoxyphenyl	29	22	43	*n.c.*	*n.c.*	*n.c.*
47g 2,4-dichlorophenyl	45	54	23	*n.c.*	6	*n.c.*

n.c.) No conversion detected by TLC.
[a]) Unless otherwise stated, the d.e. was 100%.

Scheme 15. (i) MeOH, Et_3N (1 equiv.), r.t..

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