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Guidelines for stereocontrolled Diels–Alder reactions of chiral methylidene piperazine-2,5-diones with cyclopentadiene

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Abstract—The reactivities and stereoselectivities of Diels–Alder cycloaddition reactions of methylidene piperazine-2,5-diones with cyclopentadiene can be manipulated by appropriate choice of *N*- and α-carbon substituents. Good to excellent *exo*/*endo* and facial selectivities were obtained.

The use of cyclic dehydroalanine derivatives as dienophiles in Diels–Alder reactions has gained prominence in recent years.[1–5] With the appropriate choice of cyclic dehydroalanine systems, high regio- and stereoselectivities can frequently be achieved in cycloaddition reactions relative to acyclic systems.[6] Thus, cyclic dehydroalanine systems have been used as templates in the asymmetric synthesis of cycloaliphatic amino acids and derivatives.[3–5,7] Our recent studies have added to the repertoire of cyclic dehydroalanine derivatives available for the synthesis of amino acids and derivatives.[8] In particular, we have shown that methylidene piperazine-2,5-diones are excellent and versatile dienophiles in Diels–Alder reactions.[9] Our present studies suggest that chiral methylidene piperazine-2,5-diones have a distinct advantage over other cyclic dehydroalanine derivatives as templates in asymmetric synthesis as they offer three sites for reaction control. This in turn may allow for the attenuation or enhancement of reactivities and selectivities in Diels–Alder reactions. In this study, we demonstrate that by suitable choices of *N*- and *C*-substituents on the piperazine-2,5-dione template, good to excellent *exo*/*endo* and/or facial selectivities can be obtained.

Methylidene piperazine-2,5-diones **1a**–**3a**, **1b**–**3b** and **1c** were synthesised from the corresponding *cyclo*-(Ser-amino acid) derivatives.[10] Treatment of *cyclo*-(Ser-amino acid) with acetic anhydride under thermal conditions gave the *N*,*N*-diacetylated methylidene piperazine-2,5-diones whereas under basic conditions, only the monoacetylated methylidene derivatives were isolated (Scheme 1). Methylidene piperazine-2,5-dione **1c** was synthesised by treating *cyclo*-(Ser-*N*-MeAla) with acetic anhydride to form the intermediate *N*,*O*-diacetyl derivative, followed by treatment with 2 equiv. of potassium *tert*-butoxide (Scheme 1). The methylidene piperazine-2,5-diones were then treated with freshly cracked cyclopentadiene (10 equiv.) at room temperature.

The cycloadditions of chiral methylidene piperazine-2,5-diones **1**–**3** can potentially give rise to four diastereomers resulting from the approach of the diene *syn* or *anti* to the remote α-carbon substituent, in either an *exo* or *endo* orientation (Scheme 2). As summarised in Table 1, at least three of the four possible cycloadducts were observed in each of the reactive systems. The *exo* cycloadducts can be readily identified from the *endo* isomers by comparison of the ^{1}H NMR chemical shifts of the olefinic resonances.[†] In some cases this correlation is supported by X-ray data and 2D NMR correlation studies. The facial isomers are not easily identified and our assignments are based on X-ray studies as well as NOE experiments.

For a constant remote α-carbon substituent (Me) and a constant proximal *N*-substituent (*N*-H), reactivity towards Diels–Alder cycloaddition is sluggish when the distal *N*-substituent is Me versus Ac (entries 3 and 1 respectively, Table 1). This reactivity pattern is consis-

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[†] All new compounds gave satisfactory spectroscopic and analytical data.

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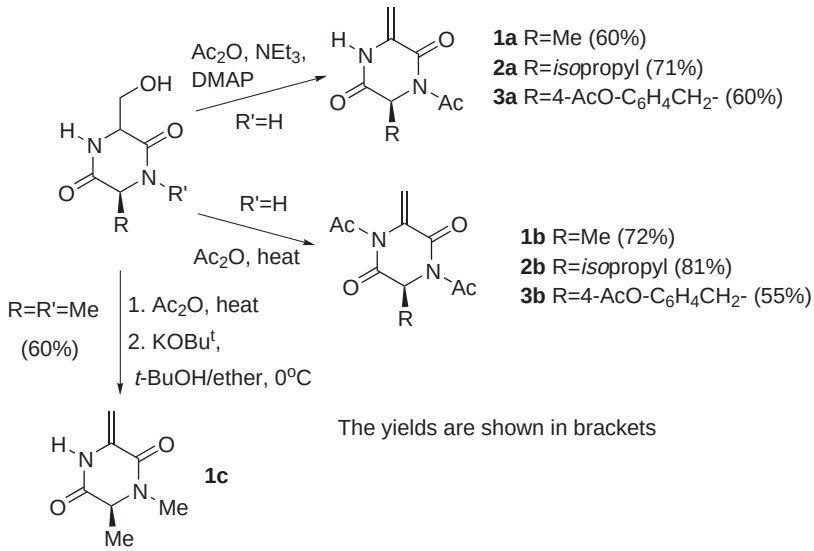
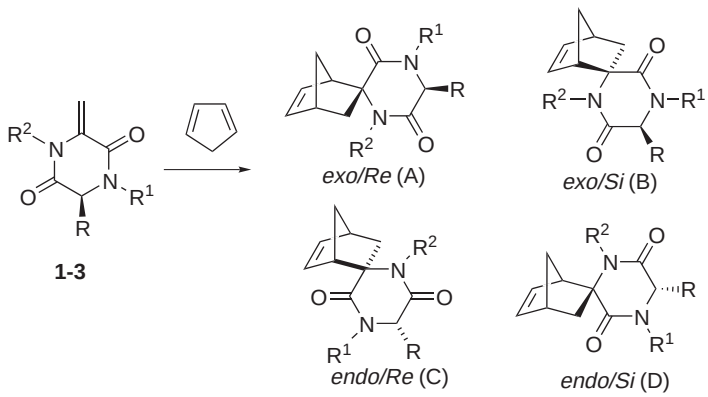


Scheme 1. Routes to methylidene piperazine-2,5-diones.



Scheme 2. The four possible diastereomers from cycloaddition.

Table 1. Outcomes of cycloadditions of methylidene piperazinediones with cyclopentadiene

Entry	Methylidene piperazinedione	Isolated yields	Product distribution (A:B:C:D)
1	**1a**	60%[a]	10:17:1:1
2	**1b**	50%[b]	Trace:1.2:trace:1
3	**1c**	$<10\%$[a]	Not determined
4	**2a**	60%[a]	12:1.4:1:0
5	**2b**	Trace[c]	Not determined
6	**3a**	60%[a]	7:1:1:0
7	**3b**	Trace[c]	Not determined

[a] Conditions: cyclopentadiene (10 equiv.), room temperature, 16 h.
[b] Conditions: cyclopentadiene (10 equiv.), room temperature, 72 h with addition of fresh cyclopentadiene (10 equiv.) after every 16 h.
[c] Conditions: cyclopentadiene (10 equiv.), toluene, 100°C, 16 h.

tent with our previous observations with achiral methylidene piperazine-2,5-diones.[9] Thus in the first instance, in order to fulfil the reactivity requirement for synthetically useful conversions to cycloadducts, a distal *N*-Ac group is deemed a necessary but not exclusive requirement.

Comparisons of the reactivities of methylidene piperazine-2,5-diones **1a** and **b** (constant distal *N*- and α-substituent) via competitive rate studies show that reactivity is attenuated for systems where the proximal *N*-substituent is Ac versus H. Similar observations are also made for methylidene piperazine-2,5-diones **2a** and **b** as well as **3a** and **b**.

The major cycloadducts resulting from the reaction of methylidene piperazine-2,5-dione **1a** with cyclopentadiene are the *exo* cycloadducts (*exo*/*endo* selectivity

Table 2. Summary of stereochemical outcomes with manipulations of substituents on methylidene piperazinediones

Desired outcome	Proximal *N*-substituent	Distal *N*-substituent	Remote α-carbon substituent for best facial selectivity
High *exo* selectivity	H	Ac	> Me (e.g. *i*Pr)
High *endo* selectivity	Ac	Ac	Me

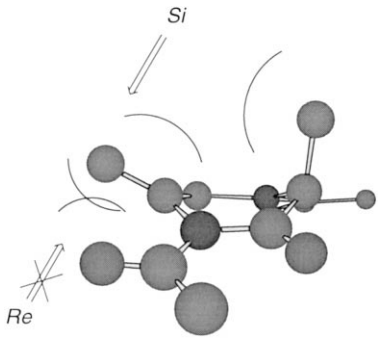


Figure 1. AM1 calculated ground-state structure of **1b**.

~13:1), with facial selectivity only slightly in favour of the approach of cyclopentadiene *syn* to the remote α-Me substituent (i.e. *Si* addition) as determined by X-ray crystallography of the deacetylated derivative. In contrast, cycloaddition of **1b** occurred with complete facial selectivity to favour *Si* addition but the *exo*/*endo* selectivity is severely compromised. This supports previous observations that the presence of the proximal *N*-H group strongly enhances *exo*/*endo* selectivity.[9] The extremely high *Si* facial selectivity observed for methylidene piperazine-2,5-dione **1b** may be rationalised by comparing the ground-state structures of the methylidene piperazine-2,5-diones **1a** and **b**. Molecular modelling studies[‡] suggest that piperazine-2,5-dione **1b** adopts a more boat-like conformation as compared to **1a**, presumably in order to reduce 1,3-allylic strain. This in turn results in greater shielding of the *Re* face of the olefin to attack by cyclopentadiene. Thus the steric shielding by the proximal *N*-Ac group (1,3-relationship) is greater than that due to the presence of the remote α-methyl substituent (1,5-relationship) and *Si* face attack is favoured (Fig. 1). The role of *N*-substituents in influencing the stereochemical outcomes of reactions in heterocyclic systems is well documented[11] and has recently been exploited in piperazine-2,5-dione chiral relay systems.[12,13]

Comparisons of the Diels–Alder reactions of methylidene piperazine-2,5-diones **1a**, **2a** and **3a** with cyclopentadiene show that for a constant proximal and distal *N*-H and *N*-Ac groups respectively, high *exo*/*endo* selectivities are obtained (typically >8:1). In addition, with increasing bulk of the remote α-carbon substituent, facial selectivity improves from 1.7:1 in R = Me, to 8.6:1 in R = *iso*propyl, to 7:1, in R = CH_2Ar. The major isomer in the latter two cases were determined by NOE studies and X-ray crystallography to be that resulting from *Re* addition to the olefin (i.e. *anti* to the remote α-carbon substituent). These studies suggest that high facial discrimination of the two faces of the olefin can be effected by the choice of a remote α-carbon substituent larger than a methyl group.

Thus in the presence of a distal *N*-Ac group (to fulfil the reactivity requirement), the manipulations required for the best control of *exo*/*endo* and facial selectivity are summarised in Table 2.

As the methods for cleavage of piperazine-2,5-diones to the constituent α-amino acids are well established,[12–15] the studies described here enable the utilisation of one type of cyclic dehydroalanine template to provide access to all the stereoisomers of the biologically active norbornyl amino acids.[16] For example, the use of D-amino acids as the directing groups in methylidene piperazine-2,5-diones will lead to cycloadducts with the opposite configuration to that when the L-amino acids are used.

From our studies here, it is apparent that methylidene piperazine-2,5-diones have several advantages over existing cyclic dehydroalanine templates. In particular, a feature of the piperazine-2,5-dione systems is that the *exo*/*endo* and facial selectivity can be easily manipulated by appropriate choice of *N*- and remote α-carbon substituents.

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[‡] Molecular modeling calculations were carried out with Spartan SG1 Ver. 5.0.1© Wavefunction, Inc., using AM1 parameters. We note that care must be exercised in the over-interpretation of molecular modeling studies due to the Curtin–Hammett principle.

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