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2,5-Diketopiperazines, New Chiral Auxiliaries for Asymmetric Diels-Alder Reactions.

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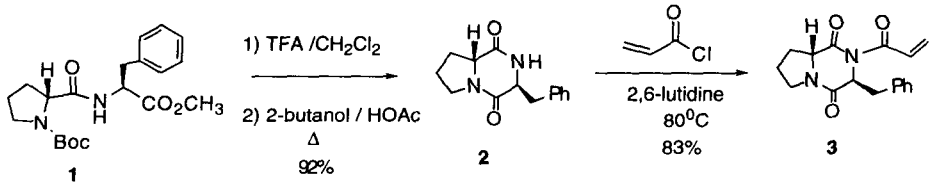
Abstract: Diketopiperazines have been utilized as chiral auxiliaries for asymetric Diels-Alder reactions. Cyclo-S-phenylalanyl-R-proline (**2**) was found to be the most promising of these auxiliaries and afforded Diels-Alder adducts in high chemical yield (78 -95%), with endo selectivities generally greater than 9:1. The diastereoselectivities observed were comparable to the best previously published values. © 1997 Elsevier Science Ltd.

The asymmetric Diels-Alder reaction using chiral auxiliaries is a powerful strategy for the stereoselective synthesis of organic compounds.[1-4] Oppolzer's sultam [3-7] and Evans oxazolidinone [8] are the gold standard for efficient chiral auxiliaries for Diels-Alder reactions. We now describe our studies involving chiral 2,5-diketopiperazines as efficient auxiliaries for these cycloadditions. 2,5-Diketopiperazines can be prepared from commercially available natural or unnatural amino acids, thus offering an attractive chiral template for asymmetric reactions.

The synthesis of cyclo-S-phenylalanyl-R-proline (**2**) can be accomplished in three steps from commercially available N-Boc-*D*-Proline and *L*-phenylalanine methyl ester hydrochloride. After a standard peptide coupling reaction to generate the Boc-N-prolyl-S-phenyalanine methyl ester **1**, deprotection, followed by cyclization gave cyclo-S-phenylalanine-R-proline in high yield (Scheme 1).

Scheme 1: Auxiliary Preparation

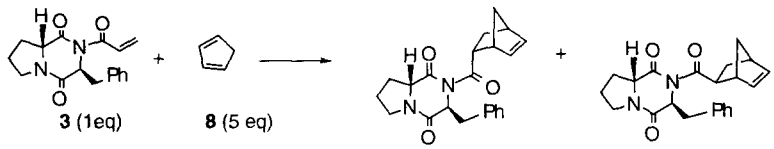


Alternatively, one can utilize N-Boc-*L*- proline as above and epimerize the S,S isomer to **2** in 79% yield.[9] Acylation of cyclo-S-phenylalanyl-R-proline (**2**) with acryloyl chloride in the presence of 2,6-lutidine provided cyclo-S-phenylalanyl-R-proline acrylate **3** in good yield.

Cycloaddition of **3** with cyclopentadiene in the presence of titanium tetrachloride at 0 °C in a mixture of dicholoromethane:toluene (1:5) provided 78% of 10:1 of a mixture of **4a** and **4b** (endo:exo) with 98% de

(Table1). The mixture of Diels-Alder adducts **4(a,b)** was then subjected to several operations. Previously reported cleavage methods caused ring opening of **4a** &**b**. The chiral auxiliaries were successfully removed using the lithium peroxide method of Evans.[8] The endo adduct **4a** was separated from the exo adduct **4b** and then subjected to the same conditions to provide 82% of the endo-2-carbomethoxybicyclo[2.2.1]hept-5-ene[10] and 70% yield of the unchanged chiral auxiliary **2**.

Table 1. Diels-Alder Cycloaddition of Cyclo- S-phenyl-alanyl-R-proline Acrylate with Cyclopentadiene

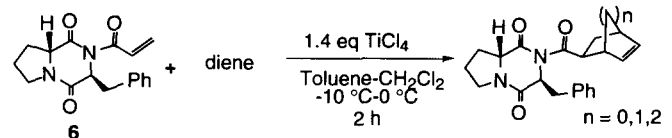


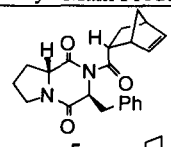
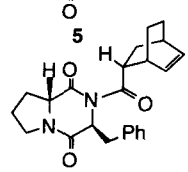
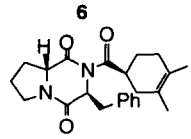
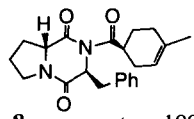
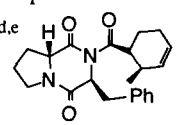
Conditions:	Yield:	endo -**4a**	exo-**4b**
1. 2 eq Et_2AlCl / CH_2Cl_2 / -78 °C/ 4 h	12%	100	0
2. 2 eq $TiCl_4$ / CH_2Cl_2-Toluene (1:5) / -78 °C / 4h	20%	92	1
3. 1.6 eq $TiCl_4$ / CH_2Cl_2-Toluene (1:5) / 0 °C / 3h	78%	10	1
4. 2.0 eq $ZnBr_2$ / THF / 0 °C- 25 °C / 3h	N.R.		

We examined the reaction of **3** with various dienes (Table 2). The optimal conditions found for cycloaddition of **3** and dienes employed 1.4 eq of titanium tetrachloride and 5 eq of the diene in a mixture of dicholoromethane-toluene (1:5) at 0 °C for 2 h. The chemical yields are very high and with the exception of entry 5, the reactions proceed with high endo selectivity and good diastereoselectivity. The adduct acids of **5** - **9** were cleaved using litium peroxide as above in from 82 - 88% yield. [11]

During this study we also surveyed other diketopiperazines in Diels-Alder reaction with cyclopentadiene. We observed that N-acryloyl-cyclo-S-valinyl-R-proline **10** and N-acryloyl-cyclo-S-t-butyl leucinyl-R-proline **11** reacted with poor endo:exo selectivity and poor diastereoselectivity. (Table 3). Similar observations by Evans[12] point to the importance of the phenyl ring and its ability to participate in a π-stacking interaction with the electron deficient dienophile moiety. We proposed a transition state model in which the complexed α,β-unsaturated carbonyl moiety will exist in the s-cis conformation, avoiding the severe steric interaction between the vinyl proton of the olefin and the chiral auxiliary. Conformational analysis of the s-cis and s-trans titanium tetrachloride/cyclo-

Table 2: Diels-Alder Reactions of Compound 3 with Dienes



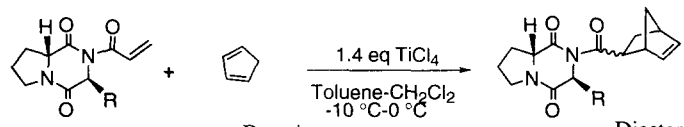
Diene	Yield (%)[a]	endo:exo	Diastereoselectivity[c]	Main Product
1. 	78%	9 : 1[b]	90 : 1	 **5**
2. 	88%	99 : 1[b]	76 : 1	 **6**
3. 	92%	—	68 : 3	 **7**
4. 	94%	—	100 : 0	 **8** para : meta = 100 :0
5. 	95%	—	2 : 15 : 6 : 55[d,e]	 **9**

[a] Yield of isolated, purified cycloadducts. [b] Ratios determined by ^{1}H NMR
[c] Ratios were determined by GC/MS, and chiral HPLC with Chiral OD column.
[d] No attempt was made to assign minor diastereomers. [e]Assigment of major adduct **9** proceeded by performing 2-D-COSY.

S-phenylalanyl-R-proline complexes was performed with MM2 calculations using the CAche program.[13] These calculations showed the s-cis complex is 3 Kcal/mole more stable than the s-trans complex. Furthermore, a π-stacking interaction involving the imides phenyl ring, and thus the olefin would hold the molecule in this conformation and block the top face of the molecule. This allows the diene to approach from the bottom face.

Despite the fact that the isopropyl group is more sterically demanding than the benzyl substituent it can not participate in π-stacking interactions with the olefin moiety.

Table 3: $TiCl_4$-Promoted Diels Alder Reaction of Dienophiles with Cylopentadiene



entry	dienophile	Reaction Time (h)	Yield (%)[a]	endo : exo[b]	Diastereo-selectivity[c]
1	**3**, R = CH_2Ph	2 h	78%	9 : 1	90 : 1
2	**10**, R = $CH(CH_3)_2$	3.5 h	71%	3: 1	52 : 29
3	**11**, R = $C(CH_3)_3$	16 h	67%	2 :1	32 : 40

[a] Yield of isolated, purified cycloadducts. [b] Ratios determined by ^1H NMR. [c]Ratios were determined by Chiral HPLC with Chiral OD column.

In summary, our preliminary results have shown that diketopiperazines can be used as chiral auxiliaries for Lewis acid catalyzed Diels-Alder cycloadditions to afford high yields, high endo selectivity and high diastereoselectivity. Futher studies utilizing other diketopiperazines in these reactions are presently being carried out. The results of these studies will be reported in due course.

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(10) $[\alpha]_D^{22}$ + 145 (c 0.5, EtOH). Lit. $[\alpha]_D^{26}$ + 141 (c 0.5, EtOH).
(11) Diastereomeric ratios for cleaved acid adducts (by NMR) were: endo-2-carboxybicyclo[2.2.1]hept-5-ene (**5**), 90:1; : endo-2-carboxybicyclo[2.2.2]oct-6-ene (**6**), 75:1; The acid adducts of **7** and **8** were derivatized with (S) -(-)-α–Methylbenzylamine. The diastereomeric ratios of the methylbenzylamide derivatives of the cleaved acid adduct of **7** was 23:1 and **8** was 100:0 each by chiral HPLC.
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