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EXTREMELY POWERFUL CHIRAL AUXILIARIES: ENANTIOMERIC [4+2] CYCLOADDUCTS OF 2-OXAZOLONE AND 9,10-DIMETHYLANTHRACENE

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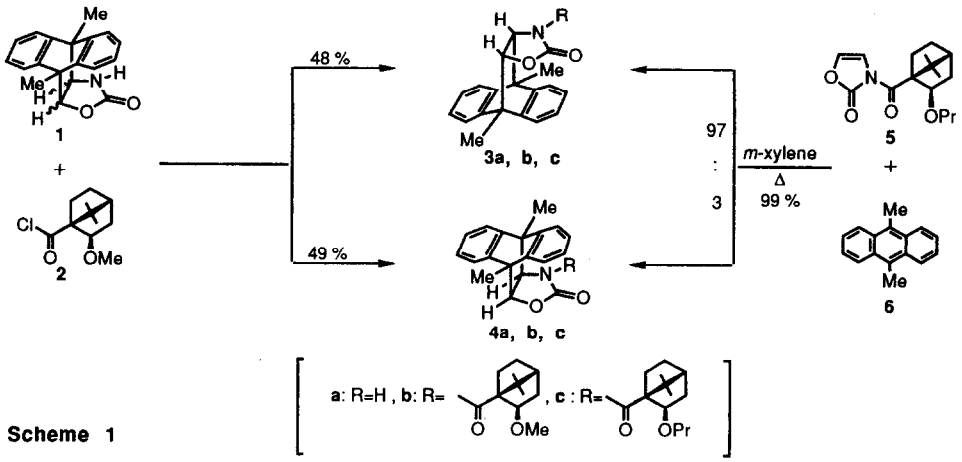
Abstract: Enantiomeric [4+2] cycloadduct-based 2-oxazolidinones (**3a** and **4a**), newly derived from 9,10-dimethylanthracene and 2-oxazolone, serve as the most effective Evans' auxiliaries so far developed in diastereoselective alkylations and Diels-Alder reactions.

Compounds with chiral 2-oxazolidinone skeletons have been utilized as Evans' auxiliaries in a variety of asymmetric chemical conversions such as alkylations,[1a,1b,1d] cycloadditions[1c,1d] and aldol condensations.[1a,1e] We have recently reported the promising use of enantiomeric 4,5-disubstituted 2-oxazolidinones conformationally fixed by bicyclo[2.2.1] and bicyclo[2.2.2] ring systems, which could be derived from the cycloadditions of the 2-oxazolone to the appropriate cyclic dienes and serve generally as good chiral auxiliaries in the Evans' asymmetric strategy.[2] There is an ongoing requirement to improve their efficiency as sterically constrained chiral auxiliaries, particularly in the diastereoselective methylation and ethylation of the chiral enolates derived from *N*-acyl-2-oxazolidinones, where only poor levels of diastereoselection have been attained so far.[1a,1b,1d]

In this paper we describe the preparation and the greatly improved utility of the enantiomeric [4+2] cycloadduct-based 2-oxazolidinones (**3a** and **4a**) sterically congested by the constrained 1,1-diphenylethyl groups at the 4- and 5-positions, which could be the most powerful auxiliaries among the chiral 2-oxazolidinones explored so far.

Both the enantiomers **3a** and **4a** were readily obtained by the uncatalyzed cycloaddition of 2-oxazolone to 9,10-dimethylanthracene followed by facile optical resolution, by analogy with the preparation of the same types of 2-oxazolidinone auxiliaries.[2] Thus, the diastereomeric mixture derived from the acylation of the cycloadducts (**1**) with (1*S*,2*R*)-2-methoxy-1-apocamphanecarbonyl chloride (**2**) was readily separated chromatographically on silica gel to give in



Scheme 1

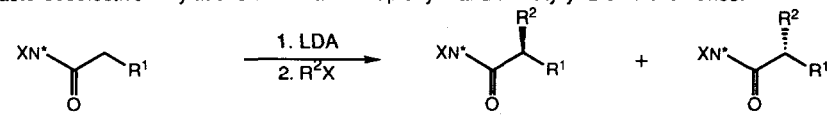
quantitative yield **3b** and **4b**, which were smoothly deacylated with the $LiBH_4$/MeOH reducing system[3] to give the (+)- and (-)-enantiomers (**3a** and **4a**),[4] respectively, in 90% yield each.[5] The configurations of the enantiomers **3a** and **4a** were based on the unequivocal assignment made by X-ray crystal analysis of the isomer **3b** (Fig.1).[6]

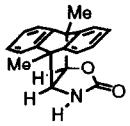
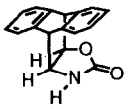
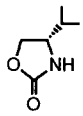
An alternative means for the preparation of such chiral 2-oxazolidinones was provided by highly diastereoselective Diels-Alder reaction of dimethylanthracene with 3-(2-alkoxy-1-apocamphanecarbonyl)-2-oxazolones. Thus, when the 2-propoxy-1-apocamphanecarbonylated derivative (**5**) was used as a dienophile, the reaction proceeded in boiling xylene with good diastereoselectivity of 94% d.e. in favor of the (4*R*,5*S*)-2-oxazolidinone derivative (**3c**) (Scheme 1), while the use of the 2-methoxy-1-apocamphane derivative resulted in lower selectivity (70% d.e.) of the cycloadduct **3b**.

The synthetic utility of the above sterically constrained heterocycles as chiral auxiliaries in diastereoselective alkylations and cycloadditions was explored in comparison with those of the widely employed conventional 2-oxazolidinones[1a,1b,1d], as well as the anthracene-based cycloadducts[2], and the results are summarized together with the literature values for comparison in Tables 1 and 2. As shown, excellent diastereoselectivity was obtained in all the reactions examined, providing, to our knowledge, the highest selectivity so far observed. These sterically constrained chiral auxiliaries seem to offer a substantial advantage over the conventional 2-oxazolidinones. Thus, the typical alkylations of the lithium enolates derived from *N*-propionyl-2-oxazolidinone with benzyl, allyl and ethyl halides could be *completely* controlled with regard to the diastereofacial selection (Table 1). It is noteworthy that the methylation of the derived *N*-butyryl 2-oxazolidinone enolates with methyl iodide at -30°C could be regulated with excellent diastereoselectivity (155 : 1), since the reaction is notoriously difficult to control diastereoselectively.[7]

Much higher diastereoselectivity than those induced by any other oxazolidinone auxiliaries was also obtained in the Lewis acid-catalyzed cycloadditions of *N*-crotonyl- and *N*-acryloyl-2-oxa-

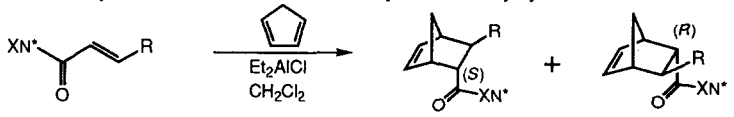
Table 1 Diastereoselective Alkylations of Chiral *N*-Propionyl- and *N*-Butyryl-2-oxazolidinones.

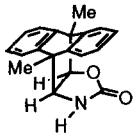
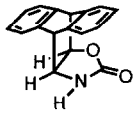
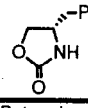


HXN*	R^1	R^2X	Temp. (°C)	Yield (%)	**A** : **B**[a]
	-Me	$PhCH_2Br$	0	76	>500 : 1[b]
	-Me	$CH_2=CHCH_2Br$	0	92	>500 : 1[b]
	-Me	CH_3CH_2I	0	51	>500 : 1[b]
	-Et	CH_3I	-30	96	155 : 1
	-Me	$PhCH_2Br$	0	71	120 : 1[c]
	-Me	$CH_2=CHCH_2Br$	0	72	19 :1[c]
	-Me	CH_3CH_2I	0	20	10 : 1
	-Et	CH_3I	-30	92	2.5 : 1
	-Me	$PhCH_2Br$	0	92	99 : 1[d]
	-Me	$CH_2=CHCH_2Br$	0	71	49 : 1[d]
	-Me	CH_3CH_2I	0	36	16 : 1[d]
	-Et	CH_3I	-78	79	9 : 1[d]

a) Determined by HPLC analysis. b) Exceeding the limit of detection. c) Taken from ref.2. d) Taken from ref.1b.

Table 2 Diastereoselective Cycloadditions of Chiral *N*-Crotonyl- and *N*-Acryloyl-2-oxazolidinones to Cyclopentadiene.



HXN*	R	Temp. (°C)	Yield (%)	Σ*exo*:Σ*endo*[a]	*endo* d.s.[a] **A**(*S*):**B**(*R*)
	$-CH_3$	-78	97	1 : 99	1 : 327
	-H	-78	94	1 : 99	1 : 33
	$-CH_3$	-78	100	1 : 49	1 : 55[b]
	-H	-78	98	1 : 49	1 : 17[b]
	$-CH_3$	-100	82	1 : 48	1 : 32[c]
	-H	-100	82	1 : 100	1 : 19[c]

a) Determined by HPLC analysis. b) Taken from ref.2. c) Taken from ref.1c.

zolidinone derivatives with cyclopentadiene as shown in Table 2.

Since both types of the reactions should go through chelation-restricted transition states similar to those described previously,[1] the satisfactory diastereoselectivity attained would result from the enhanced bulkiness at the C_4-position of the 2-oxazolidinone skeletons congested by the constrained 1,1-diphenylethyl groups.

In conclusion, we can recommend both enantiomers of the dimethylanthracene-based cycloadducts (**3a** and **4a**) as the chiral auxiliaries of choice for Evans' asymmetric reactions. Further applications to different types of asymmetric reactions are being investigated.

References and Notes

1 a) Evans, D.A. *Aldrichimica Acta.* Vol.15, No.2, **1982**, 23.
b) Evans, D.A., Ennis, M.D., Mathre, D.J. *J.Am.Chem.Soc.*, **82**, 1737 (1982).
c) Evans, D.A., Chapman, K.T., Bisaha, J. *J.Am.Chem.Soc.*, **110**, 1238 (1988).
d) Evans, D.A., Chapman, K.T., Hung, D.T., Kawaguchi, A.T. *Angew.Chem.Int.Ed.Engl.*, **26**, 1184 (1987).
e) Evans, D.A., Bartroli, J., Smih, T.L. *J.Am.Chem.Soc.*, **103**, 2127 (1981).

2 Matsunaga, H., Kimura, K., Ishizuka, T., Haratake, M., Kunieda, T. *Tetrahedron Lett.*, **32**,7715 (1991).

3 Matsunaga, H., Ishizuka, T., Marubayashi, N., Kunieda, T. *Chem. Pharm. Bull.*, in press.

4 **3a**: mp. 287°C (from hexane-CH_2Cl_2), $[\alpha]_D$ +48.6° (c.1.0, MeOH).
4a: mp. 287°C (from hexane-CH_2Cl_2), $[\alpha]_D$ -48.4° (c.1.0, MeOH).

5 On the attempted deacylation with $LiSCH_2Ph$[6] at room temperature, **3b** and **4b** were recovered unchanged nearly quantitatively.

6 X-ray crystal data for **3b**
[mp. 271°C (from hexane-CH_2Cl_2),
$[\alpha]_D$ +86.6° (c.1.0, $CHCl_3$)]:
Orthorhombic,
$P2_12_12_1$, a=12.152(2) Å, b=21.469(0) Å,
c=8.749(1) Å, β=90.00(1)°, V=2470.5Å^3,
Z=4, μ=0.629mm^{-1}.
The structure was refined to the R-value of 4.7%.

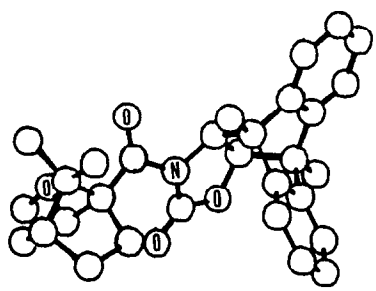


Fig.1

7 The 4-*tert*-butyl-2-oxazolidinone was reported to give exceptionally high selectivity of 97% d.e. [1d]

8 Damon, R.E., Coppola, G.M. *Tetrahedron Lett.*, **31**,2849 (1990).

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