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CONFORMATIONALLY RIGID CHIRAL [4+2]CYCLOADDUCT-BASED 2-OXAZOLIDINONES AS NEW AUXILIARIES

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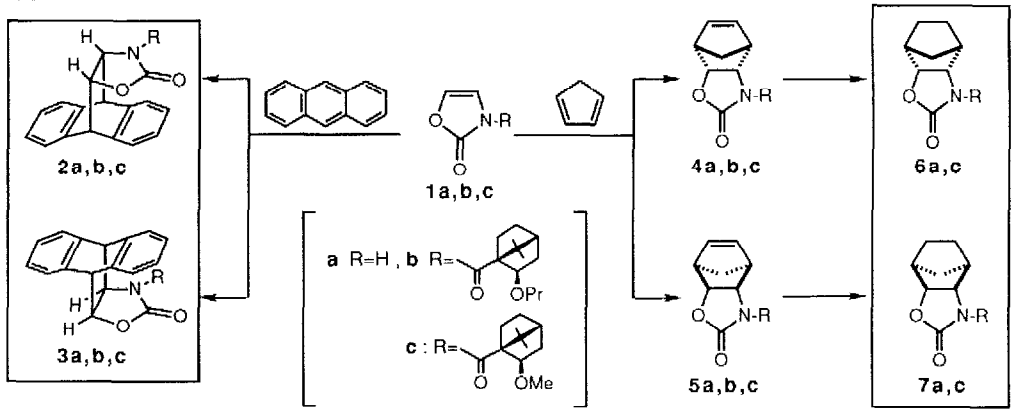
Abstract: Newly introduced enantiomerically pure [4+2]cycloadduct-based 2-oxazolidinones which are conformationally fixed by bicyclo[2.2.2] and [2.2.1] ring systems, serve well as exellent chiral auxiliaries in the Evans' asymmetric strategy.

The chiral 2-oxazolidinone heterocycles have been widely utilized as excellent auxiliaries in the Evans' asymmetric strategy which allows high levels of diastereoselection in a variety of chirality transfer reactions.[1] Apart from the (*S*)-4-substituted 2-oxazolidinones readily available from naturally occurring α-amino acids such as L-valine and L-phenylalanine,[2] their configurational antipodes as well as the well-designed chiral 2-oxazolidinones are not so easily accessible in a preparative quantity.

In this paper we describe the facile preparation and the practical utility for chiral auxiliaries of enantiomerically pure 4,5-disubstituted 2-oxazolidinones conformationally fixed by bicyclo[2.2.2] and [2.2.1] ring systems (**2a**,**3a**,**6a** and **7a**),[3] which are readily obtainable from the Diels-Alder reactions of 2-oxazolone with the cyclic dienes such as anthracene and cyclopentadiene. The advantage of such chiral derivatives for auxiliaries over the amino acid-derived heterocycles would be their high crystallinities and the steric congestions associated with the conformational rigidity, which have a precedent of camphor-derived auxiliaries.[4]

Scheme 1

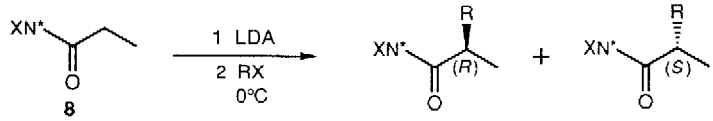


Two practical routes explored for the preparation of the chiral 2-oxazolidinones of high conformational rigidity have involved the diastereoselective Diels-Alder reactions of chiral 2-oxazolones with the cyclic dienes and the facile means for optical resolutions.

The 2-oxazolone heterocycles are known to serve as good dienophiles in the uncatalyzed [4+2]cycloadditions to anthracene and cyclopentadiene,[5] although attempted cycloadditions catalyzed by Lewis acids below ambient temperature have been unsuccessful.[6] We have recently introduced the chiral 2-alkoxy-1-apocamphanecarboxylic acids[7] which have proved to be highly potential as excellent auxiliaries for asymmetric reactions[8] and optical resolutions.[9] Thus the uncatalyzed cycloadditions of (-)-3-(2-propoxy and 2-methoxy-1-apocamphanecarbonyl)-2-oxazolones (**1b** and **1c**) to anthracene smoothly proceeded with unexpectedly high diastereoselectivity in xylene at 139°C to give the cycloadducts **2b** and **2c** in 94%d.e. (84% chemical yield) and 74%d.e. (97% chemical yield), respectively, which could be readily purified by column chromatography on silica gel or a single recrystallization. It should be noteworthy that such a high diastereofacial selection at the dienophiles has been attained in the *uncatalyzed* reactions. Deacylation of the sterically congested adducts thus obtained with lithium benzylmercaptide[10] or $LiBH_4$/MeOH gave good yield of the enantiomerically pure 2-oxazolidinone **2a**.[11] On the other hand, cyclopentadiene as an enophile gave the disappointingly low ratio of 1-2:1 of the diastereomeric *endo*-adducts **4b(c)** and **5b(c)**, which were highly separable by short column chromatography on silica gel The adducts **4b(c)** and **5b(c)** were deacylated analogously as above to **4a** and **5a**,[11] respectively, which were then catalytically hydrogenated to the cyclopentano-derivatives **6a** and **7a**,[11] respectively Absolute configurations of these adducts were conclusively determined as depicted in Scheme 1 through X-ray analysis of the key derivatives **2c** and **6c**.[12]

Easy separation of the diastereomeric cycloadducts described as above provides the alternative means for the facile preparation of both enantiomers by optical resolution. Thus, the Diels-Alder adducts[5] nicely prepared from 3-acetyl-2-oxazolone and the cyclic dienes were converted by treatment with cesium carbonate/methanol followed by 2-methoxy-1-apocamphane-

Scheme 2



HXN*	RX	Yield (%)	(*R*)-isomer	(*S*)-isomer
2a	$PhCH_2Br$	71	120	1[a]
2a	CH_2=$CHCH_2Br$	72	19	1[a]
6a	$PhCH_2Br$	70	58	1[a]
6a	CH_2=$CHCH_2Br$	66	16	1[b]

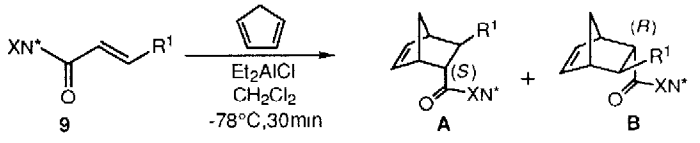
a) These ratios were determined by HPLC b) This ratio was determined by capillary GC

carbonyl chloride/sodium hydride into the diastereomeric mixtures of **2c** and **3c**, and of **4c** and **5c**. Chromatographic separation followed by nondestructive removal of the chiral auxiliaries gave nearly quantitative yield of **2a** and **3a**, and **4a** and **5a**,[11] respectively, in absolutely pure form. Smooth hydrogenation of **4a** and **5a** gave **6a** and **7a**,[11] respectively. The method involving simple and high yield processes is of practical use for a relatively large scale production.

The utility of these chiral 2-oxazolidinones of high rigidity as new auxiliaries was explored by comparison with that of the valine-derived oxazolidinones.[1] The versatility was verified by high asymmetric induction attained in the typical reactions such as the alkylations of *N*-propionyl-2-oxazolidinones (**8**)[1a] and the Diels-Alder reactions of *N*-crotonyl and *N*-acryloyl-2-oxazolidinones (**9**) with cyclopentadiene.[1b] The alkylations of the derived lithium enolates with alkyl halides proceeded with high diastereofacial selectivities even at 0°C as shown in Scheme 2.[13] Thus, the anthracene-based (+)-chiral auxiliary **2a** worked well to give the diastereoselectivity of 120:1 in favor of (*R*)-isomer as predicted from chelation control.[1a]

The Scheme 3 shows the promising results of the Lewis acid mediated cycloadditions of the anthracene-based *N*-crotonyl and *N*-acryloyl-2-oxazolidinones (**9**) to cyclopentadiene, indicative of the practical advantage of these conformationally rigid heterocycles over the conventionally used derivatives.[13] The transition states should be similar to those described previously.[1b] A noteworthy feature of the conformationally rigid chiral heterocycles is their remarkably high crystallinities associated with bicyclo[2.2.2] and [2.2.1]systems, which can significantly enhance the diastereomeric purities of the crude product mixture upon a single recrystallization as exemplified in the above reactions. The major isomers presented here were all highly crystalline and could be readily isolated in a purity above 99%d e. upon a single recrystallization.

Scheme 3



9 **A** **B**

IIXN*	R^1	Yield (%)	Σ*exo* Σ*endo*	*endo* d.s **A**(*S*) **B**(*R*)
2a	$-CH_3$	100	2 98	1 55[a)]
2a	-H	98	2 98	1 17[a)]

a) These ratios were determined by HPLC

In conclusion we have showed that both anthracene-based and cyclopentadiene-based chiral 2-oxazolidinones **2a**(**3a**) and **6a**(**7a**) which are conformationally fixed are equally useful as new chiral auxiliaries and in particular the former may be choice of agents. Further applications along this line are in progress.

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3) The systematic skeleton-names of **2a**, **4a** and **6a** are as 3-oxa-5-azadibenzo[h,k]tricyclo-[5.2.2.$0^{2,6}$]undeca-8,10-dien-4-one, 3-oxa-5-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-one and 3-oxa-5-azatricyclo[5.2.1.$0^{2,6}$]decan-4-one, respectively.

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11) **2a**: mp.244°C (from hexane-CH_2Cl_2), $[\alpha]_D$=+60.6° (c=1 0, MeOH) **3a**: mp.244°C (from hexane-CH_2Cl_2), $[\alpha]_D$=-60.7° (c=1.0, MeOH). **4a** mp 189°C (from AcOEt), $[\alpha]_D$=+85.5° (c= 1 0, MeOH) **5a**: mp.190°C (from AcOEt), $[\alpha]_D$=-85.3° (c=1.0, MeOH). **6a**: mp.181°C (from CCl_4-$CHCl_3$), $[\alpha]_D$=+51.3° (c=1.0, $CHCl_3$). **7a**: mp.181°C (from CCl_4-$CHCl_3$), $[\alpha]_D$=-50.0° (c= 1.0, $CHCl_3$).

12) X-ray crystal data. **2c** [mp.227°C (from CCl_4), $[\alpha]_D$=+79 2° (c=1 0, $CHCl_3$)]. monoclinic, $P2_1$, a=11.324(2)Å, b=12.438(3)Å, c=8 130(1)Å, β=90.12(1)°, V=1145.1Å^3, Z=2, μ=0.648mm^{-1}. The structure was refined to R-value of 4.1%. **6c** [mp.113°C (from hexane), $[\alpha]_D$=+72.2° (c=1.0, $CHCl_3$)]: monoclinic, P2, a=15.533(2)Å, b=7.575(1)Å, c=15 373(5)Å, β=94 41(2)°, V=1803.5Å^3, Z=4, μ=0.655mm^{-1} The structure was refined to R-value of 7.6%.

13) We are indebted to Naoko Inada of Kumamoto University for her skillful technical assistance in this part of studies

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