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Highly Efficient Chiral 2-Oxazolidinone Auxiliaries Derived from Methylcyclopentadienes and 2-Oxazolone

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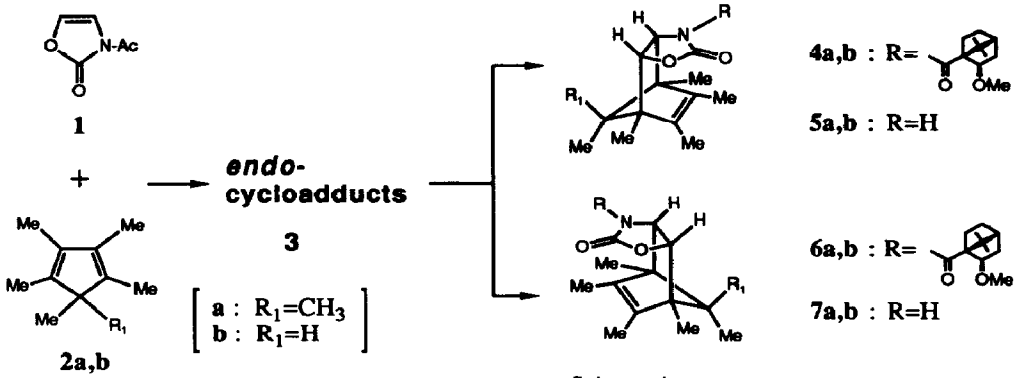
Abstract: Sterically congested [4+2]cycloadduct-based 2-oxazolidinones, (1*R*, 2*R*, 6*S*, 7*S*)-1, 7, 8, 9, 10, 10-hexamethyl- and (1*S*, 2*R*, 6*S*, 7*S*, 10*R*)-1, 7, 8, 9, 10, 10-pentamethyl-3-oxa-5-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-ones and their enantiomers, derived from hexamethyl- and pentamethylcyclopentadienes and 2-oxazolone, serve as extremely powerful chiral auxiliaries in the asymmetric alkylations and Diels-Alder reaction.

Stereochemically constrained camphor-based heterocycles such as 2-oxazolidinones,[1] sultams[2] and 2-oxazinone[3] have been widely used as auxiliaries to effect high levels of diastereoselective induction in a variety of asymmetric synthesis. We previously introduced conformationally rigid chiral 2-oxazolidinone auxiliaries derived from the Diels-Alder *endo*-adducts of 2-oxazolone using cyclopentadiene.[4] This non-camphor-derived auxiliaries were only of limited use due to their generally low induced diastereoselectivity.

This paper describes the versatile utility of the sterically congested chiral tricyclic 2-oxazolidinones (**5** and **7**) prepared by optical resolution of the *endo*-[4+2]cycloadducts (**3**)[5] derived from *N*-acetyl-2-oxazolone (**1**) and hexamethyl- and pentamethylcyclopentadienes (**2**), as the Evans' type auxiliaries.[6] The extremely enhanced asymmetric induction has been attained owing to the adjacent methyl substituents conformationally fixed, as compared with the parent cycloadduct auxiliaries.[4]

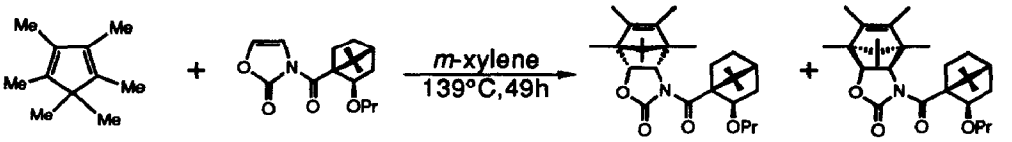
Both enantiomers **5a**[7] and **7a**[7] were readily prepared by the uncatalyzed cycloaddition of *N*-acetyl-2-oxazolone (**1**) to hexamethylcyclopentadiene(**2a**)[8] (at 139°C) followed by facile optical resolution with the aid of



Scheme 1

a versatile agent, (+)-Mac acid [(1*S*, 2*R*)-2-methoxy-1-apocamphanecarboxylic acid][9], analogous to the preparation of DMAOx.[10] Thus, chromatographic separation of the diastereomeric *N*-Mac cycloadducts **4a**[7] and **6a**[7] followed by reductive deacylation with $LiBH_4$/MeOH[11] resulted in the nearly quantitative formation of enantiomerically pure hexamethyl-5-aza-3-oxatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-ones (**5a** and **7a**)[7](Scheme 1). The absolute configurations of enantiomers **5a** and **7a** were determined as (*1R, 2R, 6S, 7S*)- and (*1S, 2S, 6R, 7R*)-forms, respectively, based on X-ray crystallographic analysis of the *N*-Mac isomer (**6a**).[12]

The uncatalyzed Diels-Alder reaction of **2a** and *N*-[(*1S,2R*)-2-propoxy-1-apocamphanecarbonyl] oxazolone (**8**) proceeded with moderate diastereoselectivity (72%d.e) in favor of **9**[13] to provide an alternative means for the facile preparation of the enantiomer **5a** (Scheme 2).



2a **8** **9** (6 : 1) **10**

Scheme 2

On the other hand, the reaction of pentamethylcyclopentadiene(**2b**) with 2-oxazolone (at 139°C) gave a mixture of the 10-*anti*- and 10-*syn*-methylcycloadducts (**17** and **18**) in a ratio of 3:1.[14] The major anti-diastereomer was purely isolated by repeated recrystallization from CCl_4 and cleanly resolved into enantiomers **5b**[7] and **7b**[7] *via* **4b**[7] and **6b**[7], respectively, in the same way as above.

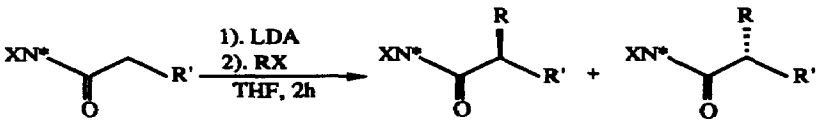
We wish to demonstrate the high potential of the sterically constrained cycloadduct-based 2-oxazolidinones thus obtained as the chiral auxiliaries for alkylations (**Table 1**) and Lewis acid-catalyzed Diels-Alder reactions (**Table 2**). Alkylations of *N*-propionyl-oxazolidinone (**11**) derived from **5a** *via* lithium enolates with benzyl bromide and allyl bromide proceeded smoothly with diastereoselectivity above 99.6 % d.e.(Entries 1 and 2). Even in the methylation of *N*-butyryl-2-oxazolidinone enolates with methyl iodide, which was generally difficult to control with high diastereoselectivity, an excellent diastereomer ratio of 140:1 was obtained in favor of (*S*)-**12** at -30 °C (Entry 4). This is, to our knowledge, the highest ranked selectivity so far observed. And both the hexamethyl and pentamethyloxazolidinones (**5a, b**) apparently work as excellent chiral auxiliaries with greatly improved utility.

The Et_2AlCl-catalyzed Diels-Alder reactions of *N*-crotonyl- and *N*-acryloyl-2-oxazolidinone derivatives (**14**) with cyclopentadiene proceeded with extremely high diastereoselectivity as shown in **Table 2**. This is also the highest selectivity so far obtained by oxazolidinone-control of this sort of cycloadditions. It may be interesting that reversal of the diastereoselection was not observed between the Lewis acids $EtAlCl_2$ and $SnCl_4$ during the reaction of *N*-crotonyl-2-oxazolidinones with cyclopentadiene, in contrast to the recent report on the stereodichotomy depending on the Lewis acids used.[1b]

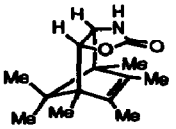
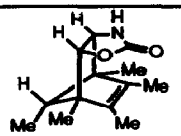
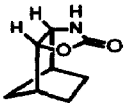
The satisfactory diastereofacial differentiation attained in either reaction would result from the steric congestion enhanced by the methyl substituents adjacently introduced to the parent bicyclo[2.2.1] skeleton.

In conclusion, the enantiomers of hexamethyl and pentamethyl substituted cycloadducts (**5a, b** and **7a, b**) are recommended as non-camphor-derived chiral 2-oxazolidinone auxiliaries extremely powered up for the asymmetric methodology.

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

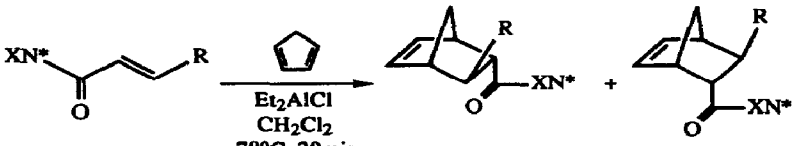


11 **12** **13**

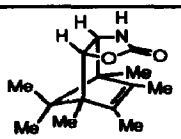
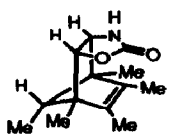
Entry	HXN*	R'	RX	Temp(°C)	Yield(%)	**12 : 13**[a]
1		Me	$PhCH_2Br$	0	100	>500 : 1
2		Me	$CH_2{=}CHCH_2Br$	0	100	>500 : 1
3		Et	CH_3I	0	81	120 : 1
4		Et	CH_3I	-30	85	139 : 1
5		Me	$PhCH_2Br$	0	76	99 : 1
6		Et	CH_3I	0	98	89 : 1
7		Me	$PhCH_2Br$	0	70	58 : 1[b]
8		Me	$CH_2{=}CHCH_2Br$	0	66	16 : 1[b]

a) Determined by capillary GC. b) Taken from ref. 4.

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



14 **15** **16**

Entry	HXN*	R	Yield(%)	Σ *endo* : Σ *exo*	*endo* d.s.[a] **15 : 16**
1		H	100	>99 : 1	89 : 1
2		Me	100	>99 : 1	>500 : 1
3		H	75.2	99 : 1	115 : 1
4		Me	96.3	>99 : 1	336 : 1

a) Determined by capillary GC.

References and Notes

1. a) Bonner, M. P.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 1299. b) Tanaka, K.; Uno, H.; Osuga, H.; Suzuki, H. *Tetrahedron : Asymmetry* **1993**, *4*, 629. c) Yan, T. H.; Lin, T. C.; Tseng,.W. H.; Chen, T. W. *Tetrahedron Lett.* **1991**, *32*, 5563. d) Yan, T. H.; Tan, C. W.; Lo, H. C.; Hung, T. Y. *J. Am. Chem. Soc.* **1993**, *115*, 2613.
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4. Matsunaga, H.; Kimura, K.; Ishizuka, T.; Haratake, M.; Kunieda, T. *Tetrahedron Lett.* **1991**, *32*, 7715.
5. As expected, the hexamethyl- and the pentamethyl-*endo*-cycloadducts (**3**), which were solely isolable, were completely unreactive to catalytic hydrogenation under a variety of conditions.
6. a) Evans, D. A.; Bartroli, J.; Smith, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. b) Evans, D. A. *Aldrichimica Acta.* **1982**, *15*, 23. c) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *82*, 1737.d) Evans, D. A.; Chapman, K. T.; Hung, D. T.; Kawaguchi, A. T. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1184. e) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.
7. **4a**: mp 142.5° C(from EtOH), $[\alpha]_D$ +123.3°(c 1.0, $CHCl_3$), **4b**: mp 147.5 °C(from EtOH), $[\alpha]_D$ +147.5°(c 1.0, $CHCl_3$). **5a**: mp 192.5 °C(from EtOH), $[\alpha]_D$ +57.6°(c 1.0, $CHCl_3$), **5b**: mp 160.5 °C(from EtOH), $[\alpha]_D$ +70.0°(c 1.0, $CHCl_3$). **6a**: mp 165.0 °C(from EtOH), $[\alpha]_D$ -163.3°(c 1.0, $CHCl_3$), **6b**: mp 153.0 °C(from EtOH), $[\alpha]_D$ -167.2°(c 1.0, $CHCl_3$). **7a**: mp 191.5 °C(from EtOH), $[\alpha]_D$ -56.7°(c 1.0, $CHCl_3$), **7b**: mp 161.5 °C(from EtOH), $[\alpha]_D$ -70.5°(c 1.0, $CHCl_3$).
8. Hexamethylcyclopentadiene was readily prepared by methylation of the commercially available pentamethyl compound with MeI / *n*-BuLi in THF at 0 °C.
9. Ishizuka, T.; Kimura, K.; Ishibuchi, S.; Kunieda, T. *Chem. Lett.* **1992**, 991.
10. Kimura, K.; Murata, K.; Otsuka, K.; Ishizuka, T.; Haratake, M.; Kunieda, T. *Tetrahedron Lett.* **1992**, *32*, 4461.
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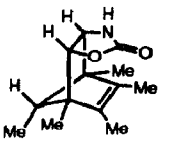
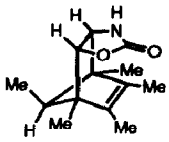
12. X-ray crystal data for **6a**: orthorhombic, $P2_12_12_1$, a=12.566(2) Å, b=22.732(3) Å, c=8.229(1) Å, β=90.00(1) °, V=2347.6 $Å^3$, Z=4, μ=0.590 mm^{-1}. The structure was refined to the R-value of 6.25 %.
    Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre.
    We are indebted to Dr. T. Nakao, The Yoshitomi Research Laboratories, for the X-ray analysis.
13. Determined by capillary GC using the authentic both isomers separately prepared.
14. The assignment was made on the basis of the doublet peaks at δ 0.65 (**17**) and δ 0.75 (**18**) attributable to the 10-methyl protons in the ^{1}H-NMR-spectrum (400MHz).



17 (anti)



18 (syn)

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