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Stereocontrolled Diels-Alder Reactions with Chiral Tricyclic Oxazolidinones

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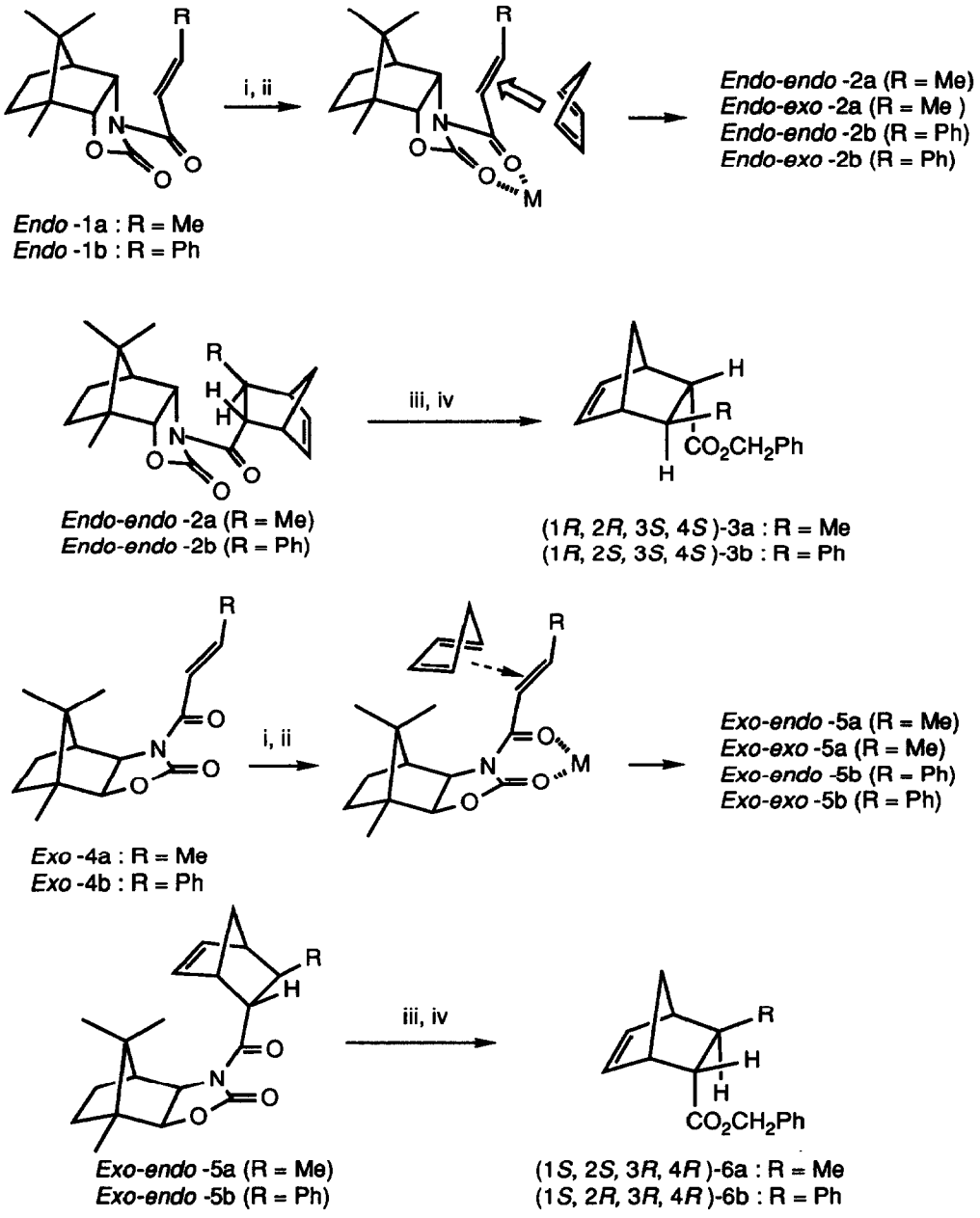
Abstract: (1*R*,2*R*,6*S*,7*S*)-5-Aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one (*endo*-oxazolidinone) and (1*R*,2*S*,6*R*,7*S*)-isomer (*exo*-oxazolidinone) are found to be efficient diastereomeric auxiliaries for Diels-Alder reactions, which are promoted by Lewis acid catalysts with predictable absolute stereochemistry. Thus, the reaction of cyclopentadiene with *N*-crotonyl- or *N*-cinnamoyl-*endo*-oxazolidinones gave (1*R*,2*R*,3*S*,4*S*)-3-methyl- or (1*R*,2*S*,3*S*,4*S*)-3-phenylbicyclo[2.2.1]hept-5-ene-2-carboxylates, while their enantiomers, *i.e.* (1*S*,2*S*,3*R*,4*R*)-3-methyl- or (1*S*,2*R*,3*R*,4*R*)-3-phenylbicyclo[2.2.1]hept-5-ene-2-carboxylates were obtained stereoselectively from the corresponding *exo*-oxazolidinone derivatives.

The asymmetric Diels-Alder reaction constitutes a powerful route to chiral cyclohexene derivatives, because high levels of diastereoface differentiation and *endo/exo* selectivity have been achieved either by use of a variety of chiral dienophiles,[1,2] or by use of prochiral dienophiles in the presence of chiral Lewis acid catalysts such as titanium or aluminum reagents.[3,4,5] In this reaction, both optical antipodes are necessary as chiral sources for the preparation of both enantiomeric products. Since both chiral auxiliaries are not always readily available, the method which provides both enantiomers of products by using chiral auxiliaries derived from a single chiral pool would be most attractive and desirable from a synthetic viewpoint.

We now wish to report the first stereocontrolled Diels-Alder reaction using diastereomers of tricyclic-oxazolidinones, which have been prepared in optically pure form in our laboratory for the asymmetric synthesis of (*R*)-(-)-muscone of high enantiomeric purity.[6,7] The reaction of *endo*-**1a**, derived from (1*R*,2*R*,6*S*,7*S*)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one (*endo*-oxazolidinone) and crotonyl chloride, with cyclopentadiene in toluene at -30 °C in the presence of $TiCl_2(O\text{-}i\text{-}Pr)_2$ gave a mixture of *endo-endo*-**2a** and *endo-exo*-**2a** in a ratio of 88:12. The *endo-endo*-**2a** separated by column chromatography was transformed into benzyl (1*R*,2*R*,3*S*,4*S*)-3-methylbicyclo[2.2.1]hept-5-ene-2-carboxylate (**3a**) of 84% ee (Table 1) by the procedure developed by Evans.[2a] In constrast, the reaction of *exo*-**4a** afforded its enantiomer of **3a**, namely (1*S*,2*S*,3*R*,4*R*)-**6a** in 68% ee by hydrolysis of *exo-endo*-**5a**. *N*-Cinnamoyl-tricyclic-oxazolidinones (**1b** and **4b**) are highly diastereoselective dienophiles, leading to the formation of 100% ee of (1*R*,2*S*,3*S*,4*S*)-adduct (**3b**) via *endo-endo*-**2b**, and (1*S*,2*R*,3*R*,4*R*)-adduct (**6b**) via *exo-endo*-**5b**, respectively. Banks and co-workers recently reported the diastereoselectivities of 20-99% in the reaction of *endo*-**1a** or **1b** with cyclopentadiene in dichloromethane.[8]

It is interesting to note that the diastereoface differentiation depends upon the Lewis acid used in the reaction of *endo*-**1a** or *exo*-**4a** ("stereodichotomy"[2i]). Thus the use of $EtAlCl_2$, $TiCl_2(O\text{-}i\text{-}Pr)_2$, and $TiCl_4$ uniformly afforded (1*R*,2*R*,3*S*,4*S*)-**3a** from *endo*-**1a** and (1*S*,2*S*,3*R*,4*R*)-**6a** from *exo*-**4a**, respectively. On



Scheme 1 i) 5 eq. of cyclopentadiene in dry toluene, ii) Lewis Acid
iii) 2 eq. of $PhCH_2OH$ in dry THF, iv) 1.5 eq. of *n*-BuLi .

the other hand, the stereoselectivity is reversed with $SnCl_4$ and the reaction afforded (1*S*,2*S*,3*R*,4*R*)-**6a** from *endo*-**1a**, and (1*R*,2*R*,3*S*,4*S*)-**3a** from *exo*-**4a**. The reversal of the stereoselection, however, was not observed in the reaction of *N*-cinnamoyl-tricyclic-oxazolidinones (*endo*-**1b** and *exo*-**4b**).

In contrast to these results, the stereodichotomy between $TiCl_4$ and $EtAlCl_2$ was reported in the reaction of (*S*)-lactyl acrylate[2i] or *N*-acryroyl-(*S*)-proline benzyl ester.[9] The diastereoselectivities of the present results may be rationalized by assuming a model proposed by Helmchen.[2i] Thus, in the presence of titanium or aluminum reagents, *N*-crotonyl- and *N*-cinnamoyl-oxazolidinones would form chelate complexes with the syn conformation of the amide moieties.[8,9] The attack of cyclopentadiene from the front side of the complex of *endo*-**1a** is favored to give *endo-endo*-**2a**, and the approach of the diene from the rear face of the complex of the *exo*-**4a** provides *exo-endo*-**5a** . Assumption of a non-chelate complex with $SnCl_4$ can explain the reversal of the stereoselection.[2i] However, the formation of the non-chelate complex is less favored in the case of *N*-cinnamoyl derivatives, due to steric hindrance between the phenyl group and the bornane skeleton.

Table 1. Asymmetric Diels-Alder reactions of *endo*-oxazolidinone-**1** or *exo*-oxazolidinone-**4** with cyclopentadiene.[a]

dieno-phile	Lewis acid	equiv.	temp. (°C)	time (h)	yield of adduct	*endo*/*exo* ratio	% ee of *endo*-product
1a	$EtAlCl_2$	0.2	0	18	97	79/21	69 (**3a**)
1a	$EtAlCl_2$	0.2	0	4	94	82/18	48 (**3a**)[b]
1a	$EtAlCl_2$	1	0	18	96	80/20	68 (**3a**)
1a	$TiCl_2(O\text{-}i\text{-}Pr)_2$	0.2	0	5	82	90/10	71 (**3a**)
1a	$TiCl_2(O\text{-}i\text{-}Pr)_2$	1	0	5	78	88/12	84 (**3a**)
1a	$TiCl_2(O\text{-}i\text{-}Pr)_2$	1	0	5	98	87/13	47 (**3a**)[b]
1a	$TiCl_2(O\text{-}i\text{-}Pr)_2$	1	-30	10	78	94/6	87 (**3a**)
1a	$BF_3{\cdot}OEt_2$	0.2	0 ~ r.t.	18	52	94/6	57 (**3a**)
1a	$SnCl_4$	0.2	0	18	99	88/12	51 (**6a**)
1b	$TiCl_2(O\text{-}i\text{-}Pr)_2$	1	0	10	97	90/10	100 (**3b**)
1b	$TiCl_2(O\text{-}i\text{-}Pr)_2$	0.05	0	10	8	87/13	93 (**3b**)
1b	$SnCl_4$	1	0	10	24	95/5	50 (**3b**)
4a	$TiCl_2(O\text{-}i\text{-}Pr)_2$	1	-40 ~ -10	18	94	87/13	68 (**6a**)
4a	$TiCl_2(O\text{-}i\text{-}Pr)_2$	1	-40 ~ -10	18	40	84/16	37 (**6a**)[b]
4a	$SnCl_4$	1	0	18	96	93/7	27 (**3a**)
4b	$TiCl_2(O\text{-}i\text{-}Pr)_2$	1	0	10	71	85/15	100 (**6b**)
4b	$SnCl_4$	1	0	10	79	91/9	93 (**6b**)

[a] Toluene was used as solvent. [b] Dichloromethane was used.

Although more work is clearly needed to elucidate the general picture of the Diels-Alder reaction, the present study provides a remarkable example of how the stereochemistry of the reaction may be altered by simple

changing the diastereomeric chiral auxiliary from *endo* to *exo*, which can be readily prepared from a single chiral pool precursor, D-camphor.

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