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DIASTEREOFACIAL SELECTIVITY IN INTRAMOLECULAR DIELS-ALDER REACTIONS OF CHIRAL TRIENE-N-ACYLOXAZOLIDONES

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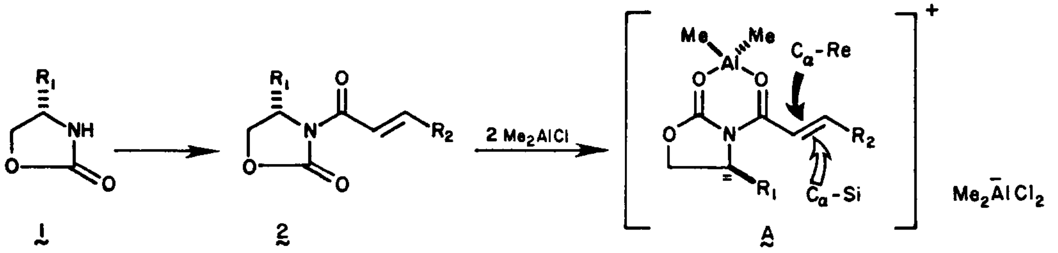
Abstract: Excellent diasterofacial selection has been observed in asymmetric Diels-Alder cycloadditions of E,E-triene-imides **3** and **6**.

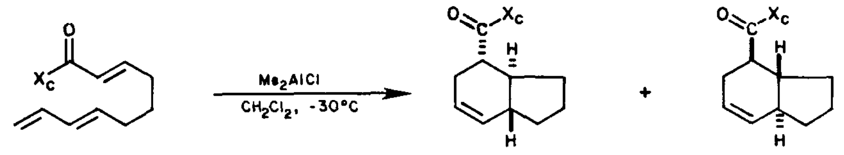
Few organic reactions rival the Diels-Alder process in scope and synthetic utility.[1] It is therefore not surprising that efforts to control the absolute stereochemical relationships established in this class of reactions have been a topic of long-standing interest.[2] The purpose of this Communication is to disclose further observations that we have made on the utility of oxazolidones such as **1** as chiral auxiliaries in the cycloaddition reactions of the derived carboximides **2** (R_2=H, alkyl).[2a] In principle, the Lewis acid-dienophile complex **A** satisfies the criteria necessary for effective asymmetric induction in the cycloaddition process. In practice, we have found that the stereochemical course of the Lewis-acid promoted Diels-Alder reactions of **2** (R_2=H, Me) is fully consistent with the intervention of an s-cis bidentate chelated dienophile **A**.[3] In conjunction with our interest in developing this class of chiral dienophiles we have carried out a detailed evaluation of the influence of the substituent, R_1, on the observed Diels-Alder reaction diastereoselection. The selection of intramolecular cycloaddition processes for this evaluation was stimulated by the paucity of documented examples of this family of asymmetric bond constructions.[2,4]



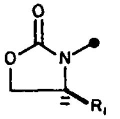
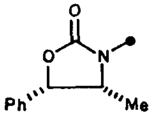
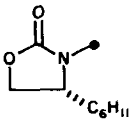
In the first case chosen for study, (E,E)-2,7,9-decatrienoic acid[4a] was converted to the corresponding acid chloride (1.4 equiv ClCOCOCl, 25°C, 8h) and subsequently employed to acylate[5] the lithiated chiral oxazolidones[6] illustrated in Scheme I in good overall yield (65-85%). Treatment of a 0.02 M solution of triene carboximides **3a**-**3d** in CH_2Cl_2 with 1.4 equiv of a 1.32 M solution of dimethylaluminum chloride (DMAC) in toluene (-30°C, 5h) resulted in the high-yield ($\geq$95%) conversion to the diastereomeric endo-cycloadducts **4** and **5** in the ratios indicated.[7] Based upon the data obtained from this series of cycloadditions, several important conclusions may be drawn. First, both the chiral carboximides **3a**-**3d** and the related methyl ester **3** (X_C=OMe) exhibit exceptional levels of endo selectivity (endo:exo $\geq$100:1);[9] however, the carboximides are far more reactive than the ester analogs in the Lewis-acid promoted Diels-Alder reaction. For example, complete conversion ($\geq$95%) of triene **3a** to the illustrated cycloadducts was effected at -30°C over a 5-h period. In contrast, the related methyl ester **3** (X_C=OMe) required 42 h at 25°C to achieve an 84% conversion under otherwise identical reaction conditions. Of prime interest to this study is the relationship between the C_4-oxazolidyl substituent, R_1, and the resultant endo diastereoselectivity. A comparison of the data obtained from trienes **3a** (R_1=i-C_3H_7 and **3b** (R_1=CH_2Ph) is instructive. Even though the steric requirements of i-C_3H_7 exceed those of CH_2Ph, the latter substrate, **3b**, exhibits a higher level of endo diastereoselection (**4b**:**5b** = 95:5) than that observed for **3a** (**4a**:**5a**=83:17). This same trend is also documented in the following case (Scheme II) and in bimolecular Diels-Alder reactions as well.[2a] We wish to suggest that the enhanced endo diastereoselection noted with triene **3b** (R_1=CH_2Ph) may be a consequence of a combination of complementary steric as well as electronic (π-stacking)[2e] effects. We therefore conclude that the (S)-phenylalanine-derived oxazolidone **1** (R=CH_2Ph) is the chiral auxiliary of choice when a C_α-Si diastereofacial bias (See **A**) is required for the cycloaddition process.

When the opposite sense of asymmetric induction is required for the cycloaddition process, either the (1S,2R)-norephedrine derived oxazolidone or the 4(R)-cyclohexyl-2-oxazolidone[6] may be conveniently employed. Each chiral heterocycle has its own individual asset and liability. For example, the ease of synthesis of

SCHEME I



3 **4** **5**

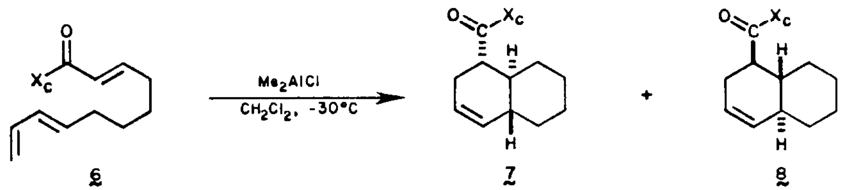
Chiral Aux. (X_C)	triene	Ratio (4:5)[7]	Isolated Yield[8]
 R_1 = i-C_3H_7	3a	83:17	60% (4a)
R_1 = CH_2Ph	3b	95:5	73% (4b)
	3c	15:85	70% (5c)
	3d	3:97	65% (5d)

the norephedrine-derived auxiliary is to be contrasted with the higher reaction diastereoselection of the 4-cyclohexyl-oxazolidone. It is most significant that, with all of the tabulated reactions, product diastereomer resolution by flash chromatography (silica gel) is exceptionally easy, and herein lies one of the important virtues of these chiral carboximide systems.

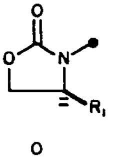
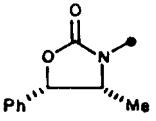
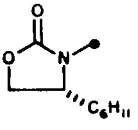
The (E,E)-2,8,10-undecatrienoic acid derivatives **6a-6d** were the next set of trienes chosen for study. The selection of this set of Diels-Alder substrates was prompted by Roush and co-workers who noted two major problems associated with the intramolecular cycloaddition of methyl trienoate **6** (X_c=OMe) and related congeners.[4d] First, these authors observed that **6** (X_c=OMe) failed to undergo Lewis-acid promoted cycloaddition in the face of competing diene polymerization. Second, transition state torsional effects appear to closely balance secondary orbital interactions in this system. For example, the thermal cycloaddition of **6** (X_c=OMe) affords a 1:1 mixture of cis- and trans-fused cycloadducts. In spite of the aforementioned complications, we found that the triene carboximides **6a-6d**, under the influence of dimethylaluminum chloride (1.4 equiv DMAC, -30°C, CH_2Cl_2, 5h), exhibited a pronounced propensity for endo cycloaddition (endo:exo $\geq$ 30:1). More significantly, the triene carboximides afforded good levels of endo diastereoselection and product diastereomers which were again readily purified by flash chromatography (Scheme II). As in the previous cases (Scheme I), triene **6b** (R_1=CH_2Ph) exhibited the highest levels of endo diastereoselection.

The nondestructive transesterification of the diastereomerically pure ($\geq$ 99%) carboximides **4b, 5d, 7b** and **8d** with lithium benzyloxide, <u>via</u> the published conditions,[10] afforded the pairs of enantiomeric esters **10** and **11** (Scheme III). Confirmation of the absolute stereochemistry of (+)**10** was established by $LiAlH_4$ reduction to the derived primary alcohol, $[\alpha]_D$ +43.3°(c 0.78, CCl_4), whose absolute configuration has been recently established, $[\alpha]_D$ +41.0° (c 1.94, CCl_4)[4a]. For the present, the absolute stereochemical assignments of (+)**11** and (-)**11** have been assigned by analogy with the other cases we have unambiguously established in this study.[2a]

SCHEME II

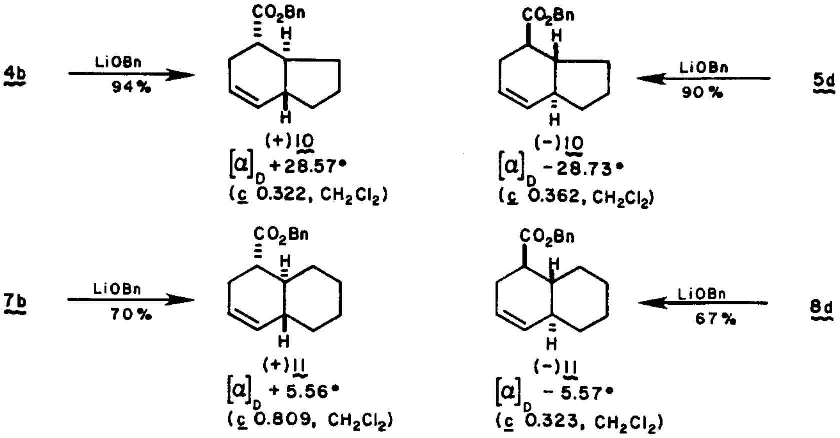


6 7 8

Chiral Aux. (X_c)		triene	Ratio (7:8)[7]	Isolated Yield[8]
	R_1= i-C_3H_7	6a	92 : 8	65% (7a)
	R_1= CH_2Ph	6b	97 : 3	88% (7b)
		6c	9 : 91	70% (8c)
		6d	6 : 94	70% (8d)

In all examples that we have encountered in both intermolecular and intramolecular cycloadditions, dienophile π-facial selection is readily predicted by assuming that the oxazolidone C$_4$-substituent, R$_1$, directs the cycloaddition process to the opposite face of the cisoid dienophile-Lewis acid complex. For example, in the dienophile complex **A** , the accessible π-face is predicted and is found to be C$_\alpha$-Si.

SCHEME III



In summary, the oxazolidyl carboximides **2** should prove to be a useful class of chiral dienophiles in the Diels-Alder process. The ease with which these chiral heterocycles may be synthesized from readily available chiral precursors stands as an important criterion by which these systems should be evaluated.[11]

References and Notes

(1) For recent reviews see: (a) Brieger, G.; Bennet, J.N. Chem. Rev. **1980**, 80, 63. (b) Oppolzer, W. Angew. Chem. Int. Ed. Engl. **1977**, 16, 10. (c) Oppolzer, W. Synthesis, **1978**, 793. (d) Funk, R.L.; Vollhardt, K.P.C. Chem. Soc. Rev. **1980**, 9, 41. (e) Fallis, A.G. Can. J. Chem. **1984**, 62, 183.

(2) We refer here to chirality transfer in which the inducing chiral moiety is subsequently removed. (a) Evans, D.A.; Chapman, K.T.; Bisaha, J. J. Am. Chem. Soc. **1984**, in press. (b) Corey, E.J.; Ensley, H.E. ibid. **1975**, 97, 6908. (c) Oppolzer, W.; Chapuis, C.; Kelley, M. Helv. Chim. Acta **1983**, 48, 4781. (d) Choy, W.; Masamune, S. J. Org. Chem. **1983**, 48, 4441. (e) Trost, B.M.; O'Krongly, D.; Belletire, J.L. J. Am. Chem. Soc. **1980**, 102, 7595, and references cited in each.

(3) After an extensive study of Lewis-acid catalysts which included $SnCl_4$, $TiCl_4$, $ZrCl_4$, Me_2ZrCl_2, $AlCl_3$, BF_3 and numerous others, we found that either diethylaluminum chloride (DEAC) or dimethylaluminum chloride (DMAC) employed in excess of one equiv was clearly the Lewis acid of choice for high levels of reaction diastereoselection.

(4) (a) Roush, W.R.; Gillis, H.R.; Ko, A.I. J. Am. Chem. Soc. **1982**, 104, 2269. (b) Roush, W.R.; Ko, A.I.; Gillis, H.R. J. Org. Chem. **1980**, 45, 4264. (c) Roush, W.R.; Gillis, H.R. ibid. **1980**, 45, 4267. (d) Roush, W.R.; Hall, S.E. J. Am. Chem. Soc. **1981**, 103, 5200. (e) Mukaiyama. T.; Iwasawa, N. Chem. Lett. **1981**, 29.

(5) Evans, D.A.; Bartroli, J.; Shih, T. J. Am. Chem. Soc. **1981**, 103, 2127.

(6) The illustrated optically pure 2-oxazolidones, with one exception, were prepared from the respective β-amino alcohol precursors via the Newman procedure: Newman, M.S.; Kutmer, A. J. Am. Chem. Soc. **1951**, 73, 4199. The chiral auxiliary, 4(R)-cyclohexyl-2-oxazolidone, mp 119.5-121.2°C, $[\alpha]_D$ +2.3° (c 1.26, CH_2Cl_2) was prepared from the 4(R)-phenyl precursor by hydrogenation (Rh-Al_2O_3, 15 psi H_2, MeOH, 25°C, 15h).

(7) All diastereomer ratios were determined by capillary gas chromatography.

(8) The diastereomeric purity (Ref. 7) of all cycloadducts exceeded 99%.

(9) Roush (Ref. 4a) reports an endo : exo ratio for **3** (X_C = OMe) of 100:0 as determined by high-field NMR analysis. Under the conditions reported in this study we have observed an analogous 115:1 ratio (footnote 7).

(10) Evans, D.A.; Ennis, M.D.; Mathre, D.J. J. Am. Chem. Soc. **1982**, 104, 1737.

(11) This research has been supported by the National Science Foundation (CHE-834256).

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