Exo-Selective Diels–Alder Reaction Based on a Molecular Recognition Approach

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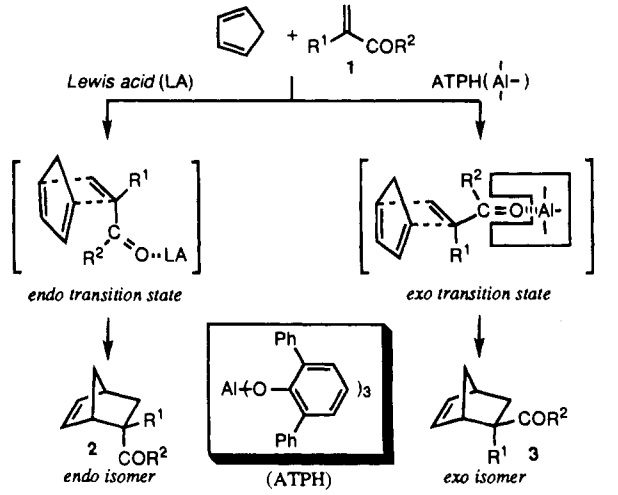
The Diels–Alder reaction and its variants (inverse-electron demand and hetero) offer many synthetic advantages in terms of simplicity and versatility, as exemplified by their broad application to the stereo- and regiochemically defined synthesis of a wide variety of natural products.[1] In particular, the use of Lewis acid catalysis in these cycloadditions allows rigorous creation of four contiguous stereocenters with largely predictable regio- and stereoselectivity. With regard to stereoselectivity, the most prominent feature is the *endo* selectivity, which is considered to be a general attribute of the Diels–Alder family of reactions.[2] In contrast, the opposite *exo* selectivity is usually not attainable by deliberate modification of existing methodologies, except in the case of several substrate-specific examples.[3,4] In this context, we have been interested in the possibility of obtaining *exo* selectivity by a molecular recognition approach using our recently developed Lewis acid receptors as described below.

The origin of the *endo* preference in Diels–Alder reactions is usually ascribed to "secondary orbital interactions" as suggested by Woodward and Hoffmann.[5,6] If the carbonyl groups of dienophilic α,β-unsaturated carbonyl substrates are effectively shielded by complexation with a specific Lewis acid receptor, the secondary interactions are significantly diminished, thereby disfavoring the *endo* transition state and facilitating reaction via the otherwise unfavorable *exo* transition state as illustrated in Scheme 1. Verification of this hypothesis has been demonstrated by the successful *exo*-selective Diels–Alder reaction of cyclopentadiene and α,β-unsaturated carbonyl substrate **1** in the presence of the complex aluminum tris(2,6-diphenylphenoxide) (ATPH), which provides an effective carbonyl pocket.[7]

Scheme 1



The Lewis acid-catalyzed Diels–Alder reaction of cyclopentadiene with vinyl ketone **1** (R^1 = H; R^2 = Ph) normally gave *endo* adduct **2** (R^1 = H; R^2 = Ph) preferentially. The ratio of **2**:**3** (R^1 = H; R^2 = Ph) was 97:3 with BF_3·OEt_2 and 98:2 with Me_3Al at −78 °C. However, initial complexation of the dienophile **1** (R^1 = H; R^2 = Ph) with ATPH (1.1 equiv) in CH_2Cl_2 and subsequent addition of cyclopentadiene at −78 °C resulted in stereochemical reversal to furnish *exo* adduct **3** (R^1 = H; R^2 = Ph) as the major product (72%, *endo/exo* = 27:73).[8] The selectivity was further increased to *endo/exo* = 18:82 with vinyl ketone **1** (R^1 = H; R^2 = 3,5-xylyl) [*cf.* *endo/exo* = 99:1 with Me_3Al]. It should be noted that the use of other modified organoaluminum reagents, such as methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD)[9] and methylaluminum bis(2,6-diphenylphenoxide) (MAPH),[10] gave less satisfactory results in the *exo*-selective Diels–Alder reaction of cyclopentadiene and the vinyl ketone **1** (R^1 = H; R^2 = Ph) (*endo/exo* = 81:19 with MAD and 34:66 with MAPH, respectively). In the case of α-substituted vinyl ketones **1**, high *exo* selectivity was observed with ATPH as a promotor. For example, the ATPH-promoted Diels–Alder reaction of cyclopentadiene with isopropenyl ketone **1** (R^1 = Me, R^2 = Ph or Me) or α-bromovinyl ketone **1** (R^1 = Br, R^2 = Me) afforded *exo* adducts **3** (R^1 = Me or Br, R^2 = Ph or Me) with more than 90% selectivity as shown in Table 1 (entries 1, 3, and 5). Catalytic use of ATPH lowered the selectivity (entry 4). Other dienophiles such as acylsilanes and acrylonitrile also gave *exo* selectivity (entries 6 and 7).

^{1}H NMR studies of the isopropenyl methyl ketone/ATPH complex (**5**) in CD_2Cl_2 solution at 20 °C have shown that ATPH shields the ketone carbonyl, as indicated by the upfield shift of each of the protons of isopropenyl methyl ketone (**4**),[11] particularly the protons of the two methyl groups (CH_{3a} and CH_{3d}) adjacent to the carbonyl. This is due to the ring current of the neighboring aromatic nucleus. In the ketone/ATPH

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(8) The *exo* selectivity is not greatly influenced by the reaction temperature (−78 → 0 °C) or solvent (CH_2Cl_2 or toluene).

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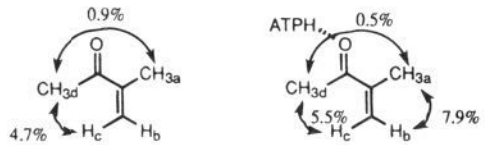
Table 1. ATPH-Promoted *Exo*-Selective Diels–Alder Reaction of Cyclopentadiene with Several Dienophiles[a]

entry	dienophile	yield[b] %	major adduct	*endo/exo* ratio[c] [ratio with Me_3Al]
1	CH_2=C(Me)COPh	81	**3** (R^1 = Me, R^2 = Ph)	4:96 [37:63]
2	CH_2=CHCOPh	72	**3** (R^1 = H, R^2 = Ph)	27:73 [98:2]
3	CH_2=C(Me)COMe	87	**3** (R^1 = R^2 = Me)	13:87 [66:34]
4		80		18:82[d]
5	CH_2=C(Br)COMe	84	**3** (R^1 = Br, R^2 = Me)	9:91 [51:49]
6	CH_2=CHCOSiMe_3	55	**3** (R^1 = H, R^2 = $SiMe_3$)	28:72 [99:1]
7	CH_2=CHCN	72		22:78 [71:29]

[a] The Diels–Alder reaction of cyclopentadiene with dienophile **1** or acrylonitrile was carried out with 1.1–1.5 equiv of ATPH in CH_2Cl_2 at −78 → 0 °C. [b] Isolated yield. [c] Determined by capillary GLC. [d] Use of catalytic ATPH (0.3 equiv).

complex **5**, the *s-trans* form predominates overwhelmingly in solution, as shown by ^{1}H NMR NOE studies in CD_2Cl_2.



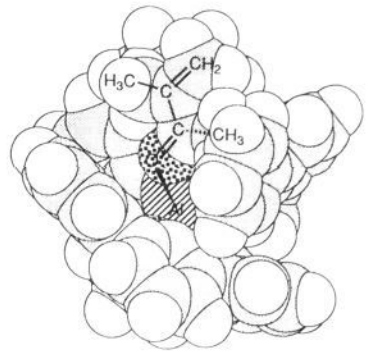
4 5

^{1}H NMR Data for **4** and **5** at 20 °C

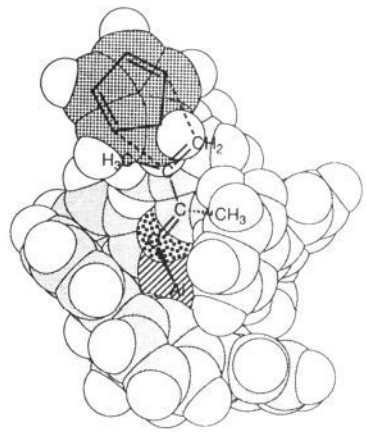
compound	CH_{3a}	H_b	H_c	CH_{3d}
4	1.87	5.83	5.99	2.33
5	1.16	5.48	5.74	1.01

Based on the ^{1}H NMR NOE data and the X-ray structure of the DMF-ATPH complex,[7] a plausible conformation of the isopropenyl methyl ketone/ATPH complex (**5**) and a possible transition state for the *exo*-selective Diels–Alder reaction of the complex **5** with cyclopentadiene are illustrated in Figure 1.[12] In Figure 1A, the α,β-unsaturated carbon (C=C) moiety appears to be stabilized by a π-stacking interaction with a phenyl group of ATPH. A second phenyl group of ATPH obstructs approach by cyclopentadiene from the *endo* side, as shown in Figure 1B.[13]

Our new approach is also applicable to the intramolecular Diels–Alder reaction of (*E*)-2-methyl-1,7,9-decatrien-3-one (**6**),[14] which gave *cis* adduct **7** preferentially via an *endo* transition state with Me_3Al in CH_2Cl_2 at −78 → −20 °C (75%, *cis/trans* = 88:12), whereas treatment of the substrate **6** with ATPH (1.1 equiv) in CH_2Cl_2 at −78 → −20 °C resulted in stereochemical reversal to furnish *trans* adduct **8** almost exclusively (69%, *cis/trans* = 4:96).[15]

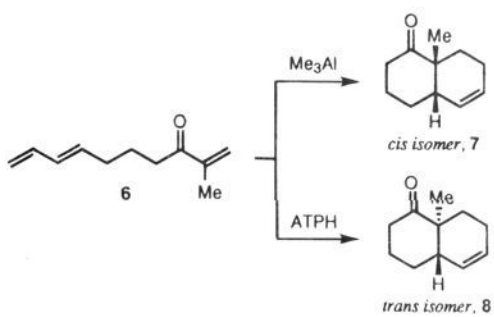


(A)



(B)

Figure 1. Space-filling models of (A) the isopropenyl methyl ketone/ATPH complex **5** and (B) its reaction with cyclopentadiene.



(12) These space-filling models are prepared on the basis of the X-ray data of the DMF–ATPH complex by using CSC Chem3D Plus.

(13) Participation by the *s-cis* conformer of isopropenyl methyl ketone in the complex **5** cannot be entirely ruled out in the transition state, as also seen in ref 6.

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