

Asymmetric Exo-Selective Diels–Alder Reactions by Steric Attenuation of Secondary Orbital Interactions

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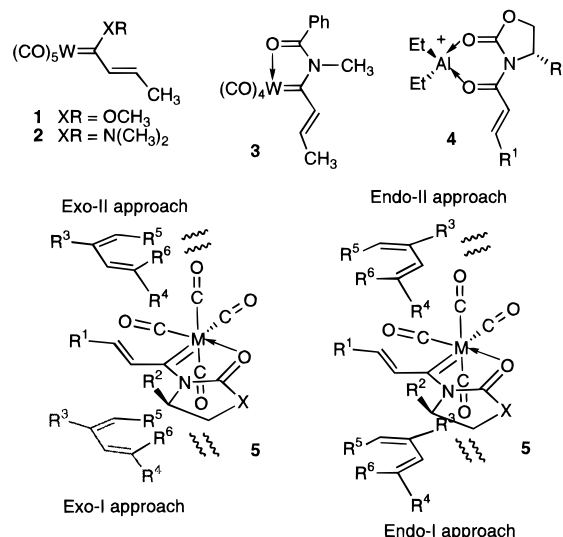
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At this point in time, a general exo-selective Diels–Alder reaction does not exist and its development constitutes one of the greatest remaining challenges for this reaction.² In previous work,^{2a} we have shown that it is possible to divert the Diels–Alder reaction to the exo-manifold by employing *N*-acylamino carbene complexes. It was proposed that the exo-selectivity is a result of a steric disfavoring of secondary orbital interactions in the transition state,³ and recently another solution for this general stratagem was reported.^{2f} Specifically, we observed that the *N*-acylamino carbene complex **3** is exo-selective which is in contrast to its methoxyl analog **1** which is endo-selective.^{2a} In lieu of experimental evidence, a proposal was made to account for this difference which involves a change in transition state from one involving an *s*-trans configuration in **1** to an *s*-cis configuration in **3**. Several examples of endo-selective Diels–Alder reactions have been proposed to involve *s*-cis conformations of the dienophile (i.e., **4**), but in all cases, these do not have the feature of apically disposed substituents on an atom directly bonded to the carbon involved in secondary orbital interactions.⁴ The octahedral configuration of the tungsten in **3** has the consequence of creating severe close contacts between the apical CO ligands and the diene in the endo but not the exo transition state. We report here the first examples of an asymmetric Diels–Alder reaction of a chiral carbene complex and an analysis of the asymmetric induction which was found to be in support the model previously proposed to account for the exo-selectivity of *N*-stabilized carbene complexes.

A key factor in this design of chiral carbene complexes for asymmetric Diels–Alder reactions is the nature of X in complex **5** (Scheme 1). The main limitation of the *N*-benzoyl complexes

Scheme 1



of the type **3** is that they are too reactive and unstable to decomposition pathways which compete with the desired Diels–Alder reactions. In some cases, the decomposition products have been identified as binuclear carbene complexes.^{2a} The dimethylamino carbene complex **2**, on the other hand, is inert to even reactive dienes as a result of strong resonance delocalization of the nitrogen atom.^{2a} Thus, the electronic nature of X in **5** was anticipated to be crucial in determining its reactivity/stability index and oxazolidinone (X = O) and imidazolidinone (X = NR) derivatives were considered likely candidates. The design also takes into account the fact that coordination of the oxazolidinone and imidazolidinone carbonyl group to the metal center should provide a rigid framework by which chiral derivatives would provide more predictable asymmetric inductions.

Initially, we decided to probe the effect of X in **5** on the reactions of *trans*-crotyl carbene complexes with *trans*-piperylene, since this represents one of the least reactive dienophile/diene pairs and should serve to better delineate the boundaries of the scope of this reaction.^{4a} It was with this diene that the largest difference between oxazolidinone and imidazolidinone carbene complexes was observed. The oxazolidinone complex **6**⁵ gave high yields of cycloadducts with reactive dienes; however, as can be seen from the data in Scheme 2, the yield of the reaction with *trans*-piperylene is definitely inferior to that of imidazolidinone complex **7**, which is less reactive but more stable than **6**. The stereoselectivities of these reactions were determined by GC analysis after oxidative conversion of the carbene complexes **9** and **10** to the imides **11** and **12**. The exo and endo isomers of the imide **12** are not separable, but the carbene complexes can be separated. If the exo isomer of the carbene complex **10** is purified on a silica gel column prior to oxidation, the exo isomer of the imide **12** can be obtained with greater than 97% stereoisomeric purity. It was also found that the use of the more stable tungsten complexes was necessary since, for example, the chromium analog **8** failed to produce any cycloadduct with *trans*-piperylene upon consumption of the carbene complex. However, the chromium complex **8** will react with the more reactive cyclopentadiene to give the cycloadduct **13** in nearly the same yield as the tungsten complex **7**. Complexes **6** and **7** are both exo-selective with *trans*-piperylene which is consistent with the model shown in Scheme 1. The chromium complex **8** is slightly more selective than the tungsten

(5) The tungsten complex **7** was prepared with the procedure that has been described for the corresponding chromium complex **8** in approximately the same overall yield.⁵ The preparation of complex **6** will be published separately.

(6) Shi, Y.; Wulff, W. D. *J. Org. Chem.* **1994**, *59*, 5122.

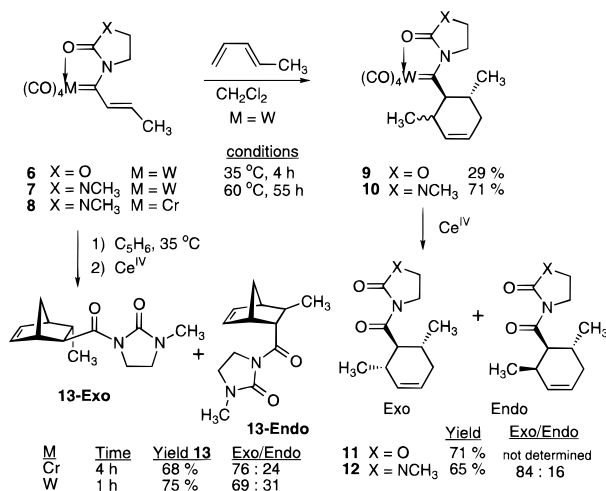
(1) (a) Department of Education GAANN Fellow, 1991–1992. (b) Department of Education GAANN Fellow, 1994–1995.

(2) For examples of exo-selective Diels–Alder reactions, see footnotes 29–32 in ref 2a and the following: (a) Anderson, B. A.; Wulff, W. D.; Powers, T. S.; Tribbitt, S.; Rheingold, A. L. *J. Am. Chem. Soc.* **1992**, *114*, 10784. (b) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1992**, *57*, 3380. (c) Gilbertson, S. R.; Zhao, X.; Dawson, D. P.; Marshall, K. L. *J. Am. Chem. Soc.* **1993**, *115*, 8517. (d) Pandey, B.; Dalvi, P. V. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1612. (e) Gouverneur, V. E.; Houk, N. N.; Pascual-Teresa, B.; Beno, B.; Janda, K. D.; Lerner, R. A. *Science* **1993**, *262*, 204. (f) Maruoka, K.; Imoto, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 12115. (g) Barluenga, J.; Canteli, R.-M.; Florez, J.; Garcia-Granda, S.; Cutierrez-Rodriguez, A. *J. Am. Chem. Soc.* **1994**, *116*, 6949. (h) Sabat, M.; Reynolds, K. A.; Finn, M. G. *Organometallics* **1994**, *13*, 2084. (i) Wright, M. W.; Smalley, T. L., Jr.; Welker, M. E.; Rheingold, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 6777. (j) Yoon, T.; Danishefsky, S. J.; de Gala, S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 853.

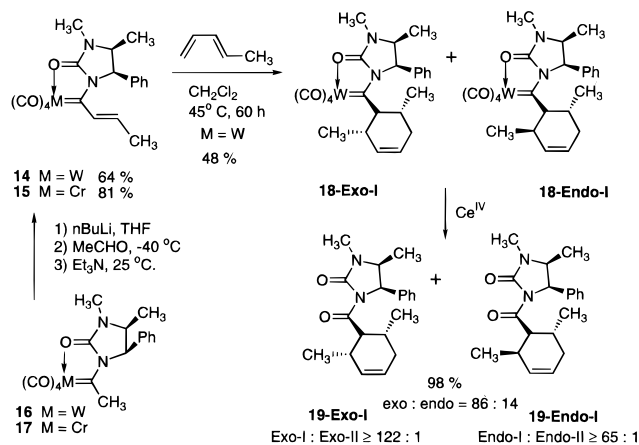
(3) The endo-selectivity of Diels–Alder reactions of alkoxyl carbene complexes is thought to be the result of secondary orbital interactions. For a discussion, see: Wulff, W. D.; Powers, T. S. *J. Org. Chem.* **1993**, *58*, 2381.

(4) (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. (b) Poll, T.; Metter, J. O.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 112. (c) Oppolzer, W.; Rodriguez, I.; Blagg, J.; Bernardinelli, G. *Helv. Chim. Acta* **1989**, *72*, 123. (d) Bueno, M. P.; Catiuela, C. A.; Mayoral, J. A.; Avenoza, A. *J. Org. Chem.* **1991**, *56*, 6551. (e) Waldmann, H. *J. Org. Chem.* **1988**, *53*, 6133. (f) Choy, W.; Reed, L. A., III; Masamune, S. *J. Org. Chem.* **1983**, *48*, 1137. (g) Masamune, S.; Reed, L. A., III; Davis, J. T.; Choy, W. *J. Org. Chem.* **1983**, *48*, 4441. (h) Tanaka, K.; Uno, H.; Osuga, H.; Suzuki, H. *Tetrahedron: Asymmetry* **1993**, *4*, 629. (i) Jensen, K. N.; Roos, G. H. P. *Tetrahedron: Asymmetry* **1992**, *3*, 1553.

Scheme 2



Scheme 3



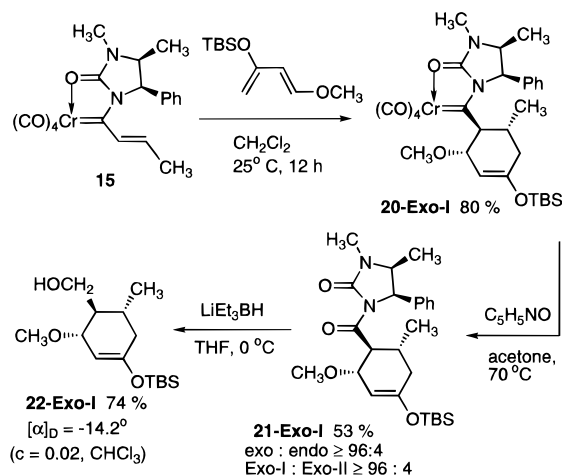
complex **7** in its reaction with cyclopentadiene, and this is consistent with the expectation that the metal carbene carbon bond length will be slightly shorter for the chromium complex. However, it was found difficult to predict from the drawings in Scheme 1 that these reactions with cyclopentadiene would be exo-selective, since in either the endo or exo approaches there will be close contacts with the apical CO ligand ($R^3, R^4 = H, R^5, R^6 = CH_2$). However, when the exo and endo approaches of cyclopentadiene are examined by space-filling models, it is clear that the methylene unit of cyclopentadiene in an exo approach does not have as close a contact with the apical CO as does one of the vinyl hydrogens (C-2 position) in the endo approach.

Given the increased stability and ease of handling and the increased yield with *trans*-piperylene, the imidazolidinone complexes appear to be the complexes of choice for Diels–Alder reactions. For these reasons the chiral imidazolidinone complexes **14** and **15** were prepared and evaluated (Scheme 3).⁷ The reaction of the chiral tungsten imidazolidinone complex **14** with *trans*-piperylene gave a single diastereomer of the exo adduct **18** consistent with the model in Scheme 1, since with $R^4 = CH_3$ there should be a significantly greater preference for Exo-I approach over Exo-II approach such that a close contact between R^4 and R^2 (Ph) is avoided. Also as expected the exo:endo ratio is unchanged from that observed with the achiral complex **7**. The stereoselectivities of this reaction were determined by capillary GC with the aid of authentic samples of the four diastereomers of the imide **19**

(7) Complexes **14** and **15** were prepared by the indicated aldol reaction from the chiral complexes **16** and **17**.⁸

(8) Powers, T. S.; Shi, Y.; Wilson, K. J.; Wulff, W. D.; Rheingold, A. L. *J. Org. Chem.* **1994**, *59*, 6882.

Scheme 4



resulting from the oxidative removal of the metal from the cycloadduct **18**. The assignment of stereochemistry of the endo adduct of **18** as **18-Endo-I** was made possible by independent syntheses of the two endo diastereomers of the corresponding imides which relied on chemistry developed by Evans and co-workers.^{4a,9} The stereochemical assignment of the major exo isomer of **18** was made on the basis of the expectation that it is the same as that determined for the major exo isomer of **20**.

The cycloadduct **20** was obtained as a single diastereomer from the Diels–Alder reaction of complex **15** with Danishefsky's diene, which occurred with both high exo:endo selectivity and high facial selectivity at the dienophile.¹⁰ This is consistent with the model shown in Scheme 1 which predicts that Danishefsky's diene will give higher levels of exo-selection than *trans*-piperylene ($R^3 = H$ vs $R^3 = OTBS$). The adduct **20** was obtained in 80% yield and was determined to have the stereochemistry shown by X-ray analysis (Scheme 4).⁹ The degree of the stereoselection in this reaction was rigorously determined by ¹H NMR to be greater than 96% exo and greater than 96% Exo-I with the aid of authentic samples of all four of the possible diastereomers of the imide **21** that were prepared by independent synthesis.⁹ If it is assumed that Danishefsky's diene approaches the dienophile **15** anti to the phenyl group of the chiral auxiliary, then the stereochemistry observed for **20** can only result from reaction of an *s-cis* conformation of the carbene complex **15**. Thus, the structure of **20-Exo-I** provides experimental evidence for the model developed to explain the unusual exo-selectivity of *N*-stabilized carbene complexes. The availability of dienophiles of the type **14** and **15** has provided an element of control in asymmetric Diels–Alder reactions that has previously not been possible. The examples here show that these complexes can give exo products with high enantioselectivity for dienophiles with substitution patterns that do not normally give exo products. We intend to further establish whether the scope of the exo-selective Diels–Alder reactions of imidazolidinone carbene complexes will be as broad as the model presented here suggests.

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Supporting Information Available: Procedures and spectral data for all new compounds and crystal structure data for **20-Exo-I** including atomic parameters, anisotropic thermal parameters, bond distances, and bond angles (43 pages). See any current masthead page for ordering and Internet access instructions.

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(9) Details can be found in the Supporting Information.

(10) The reaction of the tungsten complex **14** with Danishefsky's diene gave a much lower yield of the Diels–Alder adduct as the result of the formation of a dinuclear carbene complex in a side reaction.