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Asymmetric Catalysis of the Diels−Alder Reaction Using Dicationic Zirconocene Complexes

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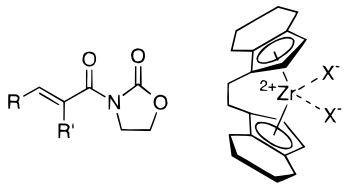
*Summary: Enantio- and diastereoselective Diels−Alder reactions between dienophiles **1** and cyclopentadiene are catalyzed by a chiral, dicationic complex formed on reaction of the chiral ansa-zirconocene **2** (X = Me) with 2 equiv of the strong acid [(Et$_2$O)$_2$H][B(Ar$_F$)$_4$] (**3**; Ar$_F$ = 3,5-(CF$_3$)$_2$C$_6$H$_3$), in either dichloromethane or 2-nitropropane solvent. The enantioselectivities are higher at lower catalyst loadings, particularly in dichloromethane solution, and spectroscopic studies suggest that this is related to competitive formation of ether-coordinated complexes at relatively low oxazolidinone:catalyst ratios.*

The use of chiral metallocene complexes of group 4 as catalysts for enantioselective transformations continues to attract significant interest.[1] We had reported that Diels−Alder reactions between oxazolidinone-based dienophiles **1** and cyclopentadiene are effectively and selectively catalyzed by chiral metallocene bis(triflate) catalysts (i.e., **2**; X = OTf)[2,3] and have investigated this system in a fair amount of detail from a mechanistic perspective.[4]



1 **2**

One of the outcomes of the latter work is that isomeric, five-coordinate, oxazolidinone−*mono(triflate)* complexes were formed from **2** (X = OTf) and **1** and that the minor isomer appeared to be the most reactive and selective toward dienes. It had occurred to us that generation of dicationic species[5] analogous to **2**, in which X is a noncoordinating counterion, might prove beneficial in eliminating isomerism in the substrate−catalyst

(1) For a relatively recent review, see: Hoveyda, A. H.; Morken, J. P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1262 and references therein.

(2) (a) Jaquith, J. B.; Guan, J.; Wang, S.; Collins, S. *Organometallics* **1995**, *14*, 1079. For other applications of group 4 metallocene bis(triflate) complexes see: (b) Odenkirk, W.; Bosnich, B. *J. Chem. Soc., Chem. Commun.* **1995**, 1181 and references therein. (c) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570 and references therein. (d) Li, S.; Bondar, G. V.; Levy, C. J.; Collins, S. *J. Org. Chem.* **1998**, *63*, 1885.

(3) For the use of other cyclopentadienyl (and related organometallic) complexes as catalysts for Diels−Alder reactions see e.g.: (a) Faller, J. W.; Smart, C. J. *Tetrahedron Lett.* **1989**, *30*, 1189. (b) Davies, D. L.; Fawcett, J.; Garratt, S. A.; Russell, D. R. *Tetrahedron Lett.* **1997**, 1351. (c) Davenport, A. J.; Davies, D. L.; Fawcett, J.; Garratt, S. A.; Lad, L.; Russell, D. R. *Tetrahedron Lett.* **1997**, 2347. (d) Carmona, D.; Cativiela, C.; Elipe, S.; Lahoz, F. J.; Lamata, M. P.; Lopez-Ram, M. P.; Oro, L.; Vega, C.; Viguri, F. *Tetrahedron Lett.* **1997**, 2351.

(4) Jaquith, J. B.; Levy, C. J.; Bondar, G. V.; Wang, S.; Collins, S. *Organometallics* **1998**, *17*, 914.

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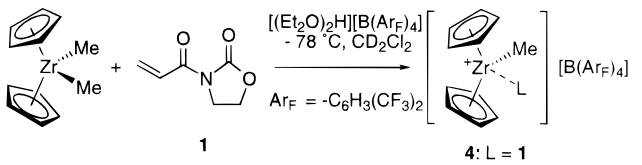
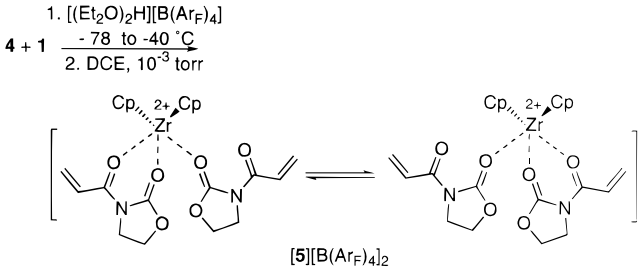
Scheme 1





complex.[6] We report herein that this approach is an effective alternative to the use of bis(triflate) catalysts and provide some preliminary details concerning the nature of the species present.

Initial work focused on the generation of a dicationic complex from Cp_2ZrMe_2 and oxazolidinone **1** (R = R′ = H). A variety of approaches for in situ formation of these species were investigated, but the one that proved effective involved protonolysis of Cp_2ZrMe_2, using the Brookhart acid **3**.[7]

Addition of 1 equiv of **3** to a solution of Cp_2ZrMe_2 and **1** in CD_2Cl_2 at −78 °C cleanly furnished the cationic methyl complex **4** (Scheme 1);[8] a further addition of 1 equiv of **3** in the presence of an additional 1 equiv of **1** led to the formation of a mixture of several complexes, some of which appear to contain coordinated Et_2O in addition to coordinated oxazolidinone. Complex **5** could be obtained as a white solid, by removal of the solvent in vacuo and dissolution in dichloroethane, followed by removal of this solvent under high vacuum to remove Et_2O and washing with hexane.

Although analytically pure material could not be obtained,[9] the spectroscopic data of the major species present leave little doubt as to its composition as the bis(oxazolidinone) complex **5** (Scheme 1).[8] In particular, both ^{1}H and ^{13}C NMR spectra indicate the presence of a single, *symmetrical* compound, in which both C═O groups are shifted 5−10 ppm downfield from free oxazolidinone. This implies either that both coordinated oxazolidinones are bidentate (which seems unlikely as the complex would be 20 e) or that one is bidentate and the other monodentate with rapid, intramolecular interconversion occurring on the ^{1}H and ^{13}C NMR time scales (Scheme 1).[10]

This approach was then extended to the in situ formation of an analogous species from the chiral complex (*S*)-**2** (X = Me)[11] under catalytic conditions (Table 1).[12] As can be appreciated from the results, both the endo:exo selectivity and the level of enantioselectivity are usefully high for the dienophiles examined, with the exception of the methacryloyl oxazolidinone **1** (R = H, R′ = Me), which has been included mainly to illustrate the unique reactivity of this type of catalyst in promoting normally very sluggish Diels−Alder reactions. Also, note that the diastereo- and enantioselectivity observed in dichloromethane is somewhat lower than that observed in 2-nitropropane solvent at similar catalyst loadings using dienophile **1** (R = R′ = H) (e.g., entries 3 vs 6) and that, in the former solvent, the level of enantioselectivity (and to a lesser extent diastereoselectivity) is dependent on catalyst loading. Similar behavior was observed with the other oxazolidinone substrates (e.g., entries 7−10), although comparisons between the two solvents etc. are difficult because of the different temperatures employed.

While a detailed interpretation of the results seen awaits future work, some initial observations are revealing. ^{1}H and ^{13}C NMR spectroscopic studies indicate that, in CD_2Cl_2 solvent, at least two different complexes are present, both of which have coordinated oxazolidinone and one of which also has signals that can be attributed to coordinated ether (see the Supporting Information for details). The ratio of the ether-coordinated complex to the other complex present is sensitive to the ratio of **1**:**2**, being ca. 4:1 at a 2:1 ratio and about

(5) For work on dicationic, zirconocene complexes see: (a) Jordan, R. F.; Echols, S. F. *Inorg. Chem.* **1987**, *26*, 383. (b) Jordan, R. F.; Dasher, W. E.; Echols, S. F. *J. Am. Chem. Soc.* **1986**, *108*, 1718. (c) Thewalt, U.; Lasser, W. *J. Organomet. Chem.* **1984**, *276*, 341. (d) Thewalt, U.; Klein, H. P. *J. Organomet. Chem.* **1980**, *194*, 297.

(6) This idea was also suggested to us by Prof. D. F. Taber (University of Delaware).

(7) Brookhart, M.; Grant, B.; Volpe, A. F. *Organometallics* **1992**, *11*, 3290 and references therein. We thank Prof. Richard Jordan (University of Chicago) for suggesting the use of this material.

(8) NMR spectroscopic data for [**4**][$B(Ar_F)_4$]: ^{1}H NMR (200 MHz, CD_2Cl_2, 220 K) δ 7.73 (s, 8 H, *o*-H Ar_F), 7.54 (s, 4H, *p*-H Ar_F), 6.80 (br d, 1H, J = 16 Hz, H_2C═), 6.17−6.50 (m, 2H, H_2C═ superimposed on ═CHCO), 6.03 (s, 10H, CpH), 4.72 (t, 2H, CH_2O), 4.29 (t, 2H, CH_2N), 0.29 (s, 3H, Me); ^{13}C NMR (75 MHz, CD_2Cl_2, 220 K) δ 169.5 [br, CH_2═$CHC(O)N$], 161.3 (q, J_{BC} = 50 Hz, *i*-C), 156.5 [br, OC(═O)N], 143.9 (H_2C═), 134.2 (*o*-C), 128.3 (q, J_{CF} = 31.5 Hz, *m*-C), 124.0 (q, J_{CF} = 272.5 Hz, CF_3), 122.9 [CH_2═CHC(═O)], 117.1 (*p*-C), 112.0 (Cp), 64.7 (CH_2O), 42.9 (CH_2N), 36.1 (ZrMe). NMR spectroscopic data for [**5**][$B(ArF)_4$]$_2$: ^{1}H NMR (200 MHz, CD_2Cl_2, 298 K) δ 7.71 (s, 16 H, *o*-H Ar_F), 7.56 (s, 8H, p-H Ar_F), 6.88 (d, 2H, J = 16.6 Hz, H_2C═), 6.31−6.61 [s at 6.43 superimposed on m, 14H, CpH + (H_2C═) + (═CHCO)], 4.87 (t, 4H, CH_2O), 4.41 (t, 4H, CH_2N); ^{19}F (188 MHz, CD_2Cl_2) δ −63.0; ^{13}C NMR (75 MHz, CD_2Cl_2, 293 K) δ 167.0 [CH_2═CHC(═O)N], 162.1 (q, J_{BC} = 50 Hz, *i*-C), 160.7 [OC(═O)N], 142.9 (H_2C═), 135.2 (*o*-C), 129.2 (q, J_{CF} = 31.5 Hz, *m*-C), 125.0 (q, J_{CF} = 272.5 Hz, CF_3), 124.3 [CH_2═CHC(═O)], 118.2 (Cp), 117.9 (*p*-C), 67.5 (CH_2O), 44.8 (CH_2N).

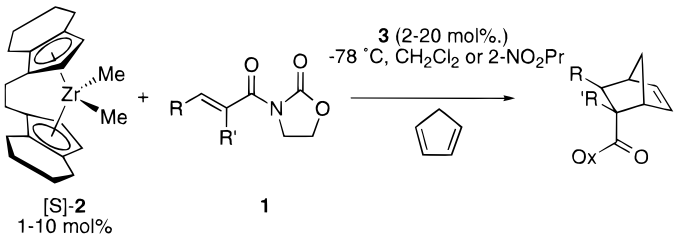
(9) Under these conditions, complex **5** is contaminated with a small amount of a complex (ca. 5 mol %) containing coordinated ether. Coordinated ether can be removed by the use of an excess of **1** (ca. 5 equiv) during preparation of **5**, followed by removal of solvent in vacuo. Unfortunately, separation of **5** from excess **1** by attempted crystallization leads to the formation of oils which are contaminated by **1**.

(10) Preliminary variable-temperature ^{1}H NMR experiments suggest the latter scenario is likely.

(11) For efficient resolutions of this *ansa*-metallocene see: Chin, B.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 2267 and references therein.

(12) Typical experimental procedure: a solution of **3** (0.05 mmol) in dichloromethane (1.0 mL) was prepared in the glovebox and then brought outside and cooled to −78 °C. To this was added a solution of **1** (2.5 mmol) in dichloromethane (4.4 mL) and (*S*)-**2** (>98% ee) in dichloromethane (25 μL of a 1.0 M solution), precooled to −78 °C, by syringe. After 1 h at −78 °C, freshly distilled cyclopentadiene (5 mmol) was added in one portion by syringe with vigorous stirring. After completion of the reaction, as monitored by TLC, the solution was quenched with 100 μL of pH 7 buffer followed by addition of 3.0 mL of dichloromethane. The reaction mixture was warmed to room temperature, dried over anhydrous $MgSO_4$, and filtered through a short pad of dry silica gel. The filtrate was concentrated to dryness in vacuo, and the crude products were analyzed by ^{1}H NMR spectroscopy to determine endo:exo ratios (the olefinic signals for the two diastereomers are well separated[4]). The substantially pure products (being contaminated only by small quantities of dicyclopentadiene) were further purified by flash chromatography on silica, with dichloromethaneas eluent (R_f = 0.24 for the adducts derived from **1** (R = R′ = H) and CpH). The fractions were concentrated to dryness in vacuo, and the purified adducts (isolated in 85−95% yield) were analyzed by HPLC on a Chiracel OD column as described in detail elsewhere.[4]

Table 1. Diels-Alder Reactions of Oxazolidinones 1 and Cyclopentadiene[a]



[S]-**2**
1-10 mol%

1

entry	substrate	amt of **2** (mol %)	solvent	*T* (°C)	*t* (h)[b]	endo:exo	% ee[c]
1	**1** (R = R′ = H)	10	CH_2Cl_2	−78	1	14.7	72.0
2	**1** (R = R′ = H)	5	CH_2Cl_2	−78	1	15.9	79.0
3	**1** (R = R′ = H)	1	CH_2Cl_2	−78	1	22.1	91.0
4	**1** (R = R′ = H)	10	2-NO_2Pr	−78	1	21.9	88.0
5	**1** (R = R′ = H)	5	2-NO_2Pr	−78	1	22.1	94.0
6	**1** (R = R′ = H)	1	2-NO_2Pr	−78	1	22.4	94.0
7	**1** (R = Me; R′ = H)	1	CH_2Cl_2	−20	67	6.1	76.0
8	**1** (R = Me; R′ = H)	1	2-NO_2Pr	−40	31	8.1	95.0
9	**1** (R = H; R′ = Me)	5	CH_2Cl_2	−20	59	1.2	53.0[d]
10	**1** (R = H; R′ = Me)	5	2-NO_2Pr	−40	34	1.3	83.0[d]

[a] For a typical experimental procedure, see ref 10. [b] Time taken for consumption of **1** as monitored by TLC; isolated yields were 85−95%. [c] The % ee is reported for the major, (2*R*)-endo enantiomer, except where noted, and was determined by HPLC on a Chiracel OD column (see ref 4 for details). [d] The % ee is reported for the major, exo enantiomer; the endo enantiomers do not separate under these conditions.

1:1 at a 4:1 ratio. We suspect that the other complex present is analogous to **5**, on the basis of the observation that excess oxazolidinone is required to displace coordinated ether.

Also, the level of enantioselectivity is sensitive to the presence of residual ether. For example, the selectivity for formation of a (2*R*)-endo adduct derived from **1** (R = R′ = H) improved to 85% ee with an endo:exo ratio of 21.4:1 at a 5 mol % catalyst loading (cf. entry 2, Table 1), when the solvent was removed in vacuo at −35 °C and replaced with fresh dichloromethane at that temperature, prior to addition of cyclopentadiene at −78 °C.

We can tentatively suggest that the ether-coordinated complex may react with cyclopentadiene to give a product with lower selectivity and that the use of low catalyst loadings (i.e., high **1**:**2** ratios) reduces the concentration of this complex to low enough levels that it does not effectively intervene in the catalysis until conversion of **1** approaches 100%.

In conclusion, dicationic zirconium complexes exhibit significant promise as a new class of asymmetric catalyst for the Diels−Alder reaction. Future work will concentrate on modifications to catalyst structure, as well as reaction conditions, in an attempt to improve on the levels of selectivity and to investigate the utility of such species in other Lewis-acid-mediated organic reactions.

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Supporting Information Available: Figures giving NMR spectral data for complexes **4** and **5** and ^{1}H NMR spectra for the complexes generated from the reaction of **2** and **3** in the presence of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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