Notes

Complete Characterization of a Chiral Lewis Acid−Product Complex for the Enantioselective Diels−Alder Reaction between Methacrolein and Cyclopentadiene: Mechanistic Considerations

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Summary: The Diels−Alder reaction between methacrolein and cyclopentadiene catalyzed by [(η^5-C_5Me_5)Ir{(R)-Prophos}-(methacrolein)][SbF_6]$_2$ is inhibited by the products, this feature allowing, for the first time, the spectroscopic and crystallographic characterization of the major Lewis acid−product intermediate involving an enal as a dienophile.

Introduction

The Diels−Alder (DA) reaction is one of the most versatile and powerful synthetic transformations for the construction of the cyclohexane framework, allowing the formation of up to four contiguous stereocenters in a concerted fashion.[1] Since the first reports on chiral Lewis acid catalyzed DA reactions,[2] great progress has been made in the development of enantioselective versions of this reaction.[3] Aluminum- and boron-based catalysts with chiral ligands were initially employed, but the use of transition-metal-based Lewis acid catalysts has now become dominant. It is commonly assumed that the pathway of the Lewis acid DA catalyzed reaction involves three steps: (i) formation of the Lewis acid−dienophile complex (the true catalyst); (ii) its interaction with the diene; and (iii) product dissociation with concomitant regeneration of the catalyst.[3]

Spectroscopic and solid-state characterizations of catalysts and intermediate complexes involved in catalysis, along with knowledge of their solution behavior, are invaluable for achieving a deep understanding of the details and nuances of a catalytic system. Methacrolein has been extensively used as a dienophile in enantioselectively catalyzed DA reactions because of its high reactivity and versatility. Its *s-cis*/*s-trans* equilibrium plays a major role due to its influence on the stereochemistry of the process, and although the *s-trans* conformer has been experimentally found in some Lewis acid−methacrolein complexes,[4] the preferred conformation in the transition state has been a subject of some debate.[5] Furthermore, to the best of our knowledge, no experimental data about the Lewis acid−DA product complex have been previously reported for DA reactions involving 2-enals.

Here, we report the spectroscopic and crystallographic characterization of [(η^5-C_5Me_5)Ir{(*R*)-Prophos}(*exo*-(*S*)-adduct)]-[SbF_6]$_2$ (**1**) ((*R*)-Prophos = (*R*)-1,2-bis(diphenylphosphino)-propane, *exo*-(*S*)-adduct = (1*R*,2*S*,4*R*)-2-methylbicyclo[2.2.1]-hept-5-ene-2-carbaldehyde), a Lewis acid−DA product complex involved in the reaction between methacrolein and cyclopentadiene catalyzed by the iridium compound [(η^5-C_5Me_5)Ir{(*R*)-Prophos}(methacrolein)][SbF_6]$_2$ (**2**). This characterization, together with that of the Lewis acid−dienophile complex **2** and that of the catalyst precursor [(η^5-C_5Me_5)Ir{(*R*)-Prophos}(H_2O)]-[SbF_6]$_2$ (**3**) recently reported by us,[4g,h] completes the structural elucidation of the organometallic species involved in this DA reaction (see Scheme 1). Additionally, solution spectroscopic studies, under catalytic conditions, corroborate the validity of the proposed cycle and provide interesting information about the characteristics of the catalytic steps. In particular, these studies reveal that, unexpectedly, the products act as competitive inhibitors of the reaction.

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Scheme 1. Catalytic Cycle and Molecular Views of the Structures of the Intermediates Involved

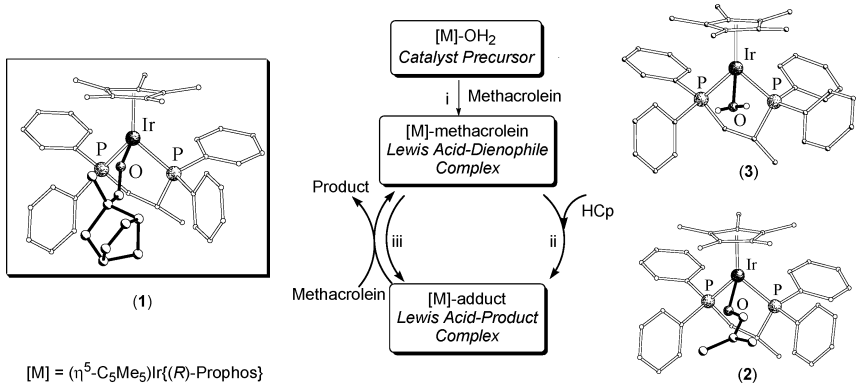
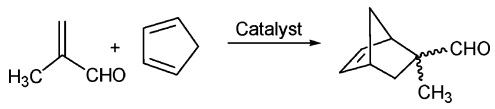


Table 1. Enantioselective DA Reaction between Methacrolein and Cyclopentadiene Catalyzed by 2 in CH_2Cl_2[a]



entry	*T* (°C)	*t* (h)	yield[b,c] (%)	isomer ratio[c] (exo:endo)	*ee*[d] (%)
1	RT	2.8×10^{-3}	59		
		3.3×10^{-2}	91		
		8.3×10^{-2}	92		
		0.25	92	95:5	70
2	−20	1.7×10^{-2}	15.5		
		4.2×10^{-2}	40		
		8.3×10^{-2}	72		
		0.5	91		
		3	91	97.7:2.3	85
3	−35	0.5	40		
		1	74		
		3	90		
		14.5	91		
		24	91	98:2	90
4	−50	3	29		
		14.5	78.5		
		24	85		
		62	91		
		86	91	98:2	90

[a] Reaction conditions: catalyst 1.25×10^{-2} mmol (5.0 mol %), methacrolein 20.7 μL (0.25 mmol), HCp 412.0 μL (5.0 mmol), 4 mL of CH_2Cl_2, 50 mg of 4 Å molecular sieves. [b] Based on methacrolein. [c] Determined by GC. [d] In the *exo* isomers. Determined by ^{1}H NMR with the chiral shift reagent (+)-Eu(hfc)$_3$.

Results and Discussion

Complex **2** is a very active catalyst for the DA reaction between methacrolein and cyclopentadiene. Table 1 collects a selection of the results obtained along with the reaction conditions. Excellent *exo* diastereoselectivity and enantioselectivity from 70 to 90%, for the *exo S* at C2 isomer, were achieved. Interestingly, conversions listed in Table 1 unambiguously establish that the rate dramatically drops to very low values at around 91% conversion. To obtain more information about this surprising feature, we monitored the reaction under catalytic conditions. At −50 °C, ^{31}P NMR spectra of a 1/20/40 molar ratio mixture of **2**/methacrolein/HCp show the immediate formation of three new (*R*)-Prophos iridium complexes in an 89/8/3 molar ratio. We have characterized the major compound as the adduct-containing complex [(η^5-C_5Me_5)Ir{(*R*)-Prophos}(*exo*-*S*-adduct)][SbF_6]$_2$ (**1**) (see below), and due to the similarity

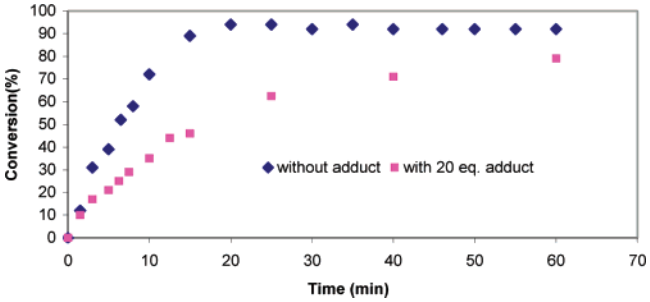


Figure 1. Reaction conditions: compound **2**, 6.25×10^{-3} mmol, methacrolein 0.125 mmol, HCp 2.50 mmol, 2 mL of CH_2Cl_2, 50 mg of 4 Å molecular sieves.

of their ^{31}P NMR spectra (see Experimental Section) and relative abundance, most probably, the other two isomeric compounds are the related [(η^5-C_5Me_5)Ir{(*R*)-Prophos}(*exo*-*R*-adduct)][SbF_6]$_2$ (**4**) and one of the two possible *endo* adduct-containing [(η^5-C_5Me_5)Ir{(*R*)-Prophos}(*endo*-adduct)][SbF_6]$_2$ (**5**) intermediates. As at −50 °C the DA reaction is too slow to be monitored, the mixture was allowed to react at −20 °C. As the reaction proceeds, the relative amount of the adduct-containing complexes increases at the expense of complex **2** indicating that the adduct dissociation step accounts for the rate of the process. During catalysis, a constant 89/8/3, **1**/**4**/**5** molar ratio was observed. Notably, this ratio closely resembles the measured selectivity at −20 °C. At the end, the amount of complex **2** is less than 3% of the total and the product dissociation step stops, accounting for the low rate observed at high conversions. Further addition of methacrolein restarts catalysis (see eq 1).

To assess the product inhibition effect, two series of independent experiments, without and with added adduct, were carried out at −20 °C. All the remaining conditions were the same. Each reaction was quenched by addition of an excess of N(^{n}Bu)$_4$Cl in CH_2Cl_2, at the specified time (Figure 1). From the comparison of the plots of conversions versus time, the reduction in rate, due to the presence of the product as a competitive inhibitor, becomes apparent. Additionally, we have reached the equilibrium shown in eq 1 starting from both sides of the corresponding equation (see step iii, in Scheme 1), and assuming a similar stability for the diastereomeric adduct complexes, an equilibrium constant, at −20 °C, of about 8 has been spectroscopically estimated. This result contrasts with the well-known Lewis acid preference for unsaturated aldehydes rather than for their saturated counterparts.[6]

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$$[(\eta^5\text{-}C_5Me_5)Ir\{(R)\text{-Prophos}\}(\text{methacrolein})]^{2+} + \text{adduct} \rightleftharpoons [(\eta^5\text{-}C_5Me_5)Ir\{(R)\text{-Prophos}\}(\text{adduct})]^{2+} + \text{methacrolein} \quad (1)$$

An 84/14/2 molar ratio mixture of **1**/**4**/**5** was prepared by reacting the aqua-complex **3** with 2 equiv of the reaction product of entry 2, Table 1 (90.4% *exo*-*S*-adduct, 7.3% *exo*-*R*-adduct, 2.3% *endo*-adducts), in the presence of 4 Å MS as a water scavenger. From the isolated solid, single crystals of **1** were obtained and its crystal structure was determined (Figure 2). The iridium atom is pseudo-octahedral being coordinated to an η^5-C_5Me_5 ring, to the two phosphorus atoms of the (*R*)-Prophos ligand, and to the aldehyde oxygen of the (1*R*,2*S*,4*R*) DA adduct. It has *S* absolute configuration,[7] and the metallacycle Ir−P−C−C−P presents a λ conformation. Comparing the geometric parameters of the fragment O−C(38)−C(39)−C(45) with those of the methacrolein moiety in the parent Lewis acid−dienophile complex $[(\eta^5\text{-}C_5Me_5)Ir\{(R)\text{-Prophos}\}(\text{methacrolein})]^+$ (**2**), it is clear that diene addition originates the expected elongation of C(38)−C(39) and C(39)−C(45) bond lengths (from 1.443(9) and 1.322(12) in **2** to 1.482(7) and 1.570(8) Å in **1**) and the rupture of planarity (torsion angle along the fragment −179.4(4) in **2** versus 141.0(5)° in **1**), both modifications being associated with the loss of conjugation.

In summary, we have presented the complete spectroscopic and crystallographic characterization of the key intermediate **1** for the DA cycloaddition reaction of HCp with methacrolein catalyzed by the iridium complex **2**, along with NMR studies of the system in catalytic conditions. The results obtained allow us to substantiate the catalytic cycle and to propose that product dissociation is an equilibrium step. In contrast with previous studies on other catalyzed DA reactions,[8] our system provides the first example of a proven preference of the catalyst for the DA adduct rather than for the corresponding dienophile.

Experimental Section

General Comments. All solvents were dried over appropriate drying agents, distilled under nitrogen, and degassed prior to use. All preparations have been carried out under nitrogen. Carbon, hydrogen, and nitrogen analyses were performed using a Perkin-Elmer 240 B microanalyzer. ^{1}H, ^{31}P{^{1}H}, and ^{13}C{^{1}H}NMR spectra were recorded on a Varian UNITY 300 (299.95 MHz) or a Brucker 300 ARX (300.10 MHz) spectrometer. Chemical shifts are expressed in ppm upfield from $SiMe_4$ or 85% H_3PO_4 (^{31}P). NOEDIFF and ROESY spectra were obtained using standard procedures.

[(η^5-C_5Me_5)Ir{(*R*)-Prophos}(*exo*-(*S*)-adduct)][SbF_6]$_2$ (1). At −10 °C, under argon, to a solution of [(η^5-C_5Me_5)Ir{(*R*)-Prophos}-(H_2O)][SbF_6]$_2$ (**3**) (100.0 mg, 0.081 mmol) in CH_2Cl_2 (4 mL) a mixture of *exo*-*S*-isomer/*exo*-*R*-isomer/*endo*-isomers at a 90.4/7.3/2.3 molar ratio (22.1 mg, 0.162 mmol) and 4 Å molecular sieves (100 mg) were added. The solution was stirred for 1 h, and then the solvent was vacuum-evaporated. The residue was washed with 3 × 4 mL of *n*-hexane and extracted with 6 mL of CH_2Cl_2 at 0 °C. The addition of 20 mL of dry *n*-hexane to the yellow filtrate afforded a yellow solid that was washed with *n*-hexane and vacuum-dried (81.0 mg, 93% yield, **1**: 84%; **4**: 14%; **5**: 2%)(Chart 1). **1**: ^{1}H NMR (300 MHz, CD_2Cl_2, −50 °C): δ = 7.85 (s, 1H, CHO), 7.1−7.8 (m, 20H, Ph), 6.21 (dd, J_{H6H5} = 5.1 Hz, J_{H4H5} = 2.5 Hz, 1H, H_5), 5.82 (dd, J_{H1H6} = 2.8 Hz, 1H, H_6), 3.66 (dm, J_{PH} = 47.6 Hz, 1H, H_c), 2.84 (m, 1H, H_g), 2.78 (bs, 1H, H_4) 2.65 (m, 1H, H_t), 1.43 (d, 1H, H_1), 1.38 (bs, 15H, C_5Me_5), 1.31 (partially overlapped)

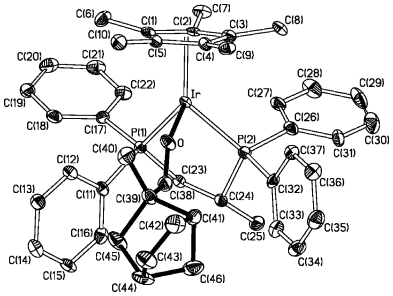
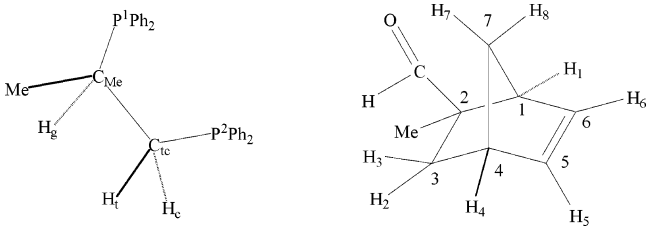


Figure 2. Molecular view of the Lewis acid−product complex **1**. Selected bond distances (Å) and angles (deg): Ir−O 2.132(3), O−C(38) 1.234(6), C(38)−C(39) 1.482(7), C(39)−C(41) 1.591-(7), C(39)−C(45) 1.570(8), C(41)−C(42) 1.510(8), C(42)−C(43) 1.319(9), C(43)−C(44) 1.483(9), C(44)−C(45) 1.533(8); Ir−O−C(38) 139.8(4), O−C(38)−C(39) 121.2(5), C(38)−C(39)−C(45) 109.8(5), C(41)−C(42)−C(43) 108.6(6), C(42)−C(43)−C(44) 108.3-(6).

Chart 1. Labeling of (*R*)-Prophos and *exo*-(*S*)-Adduct for NMR Assignments



(m, 3H, Me), 0.98 (m, 1H, H_8), 0.76 (d, J_{H8H7} = 9.7 Hz, H_7), 0.73 (d, J_{H3H2} = 16.9 Hz, H_2), 0.25 (s, 3H, *Me*CCHO), 0.24 (partially overlapped) (m, 1H, H_3). ^{13}C NMR (75.47 MHz, CD_2Cl_2, −50 °C): δ = 230.25 (CHO), 134−118 (Ph), 141.20 (C_5), 133.78 (C_6), 101.59 (C_5Me_5), 57.49 (C_2), 53.27 (C_1), 47.70 (C_7), 44.69 (C_4), 35.83 (C_3), 34.76 (dd, J_{PC} = 53.5, 11.9 Hz, C_{tc}), 32.13 (dd, J_{PC} = 36.8 Hz, J_{PC} = 8.3 Hz, C_{Me}), 19.60 (*Me*CCHO), 16.16 (dd, J_{PC} = 17.6 Hz, J_{PC} = 5.2 Hz, Me), 8.91 (C_5Me_5). ^{31}P NMR (121.5 MHz, CD_2Cl_2, −50 °C): δ = 48.88 (d, J_{P2P1} = 6.7 Hz, P^1), 29.43 (d, P^2). Anal. Calcd for $C_{46}H_{54}F_{12}OP_2IrSb_2$: C, 40.96; H, 4.03. Found: C, 40.74; H, 4.09. IR (KBr pellets, cm^{-1}): ν(CO) 1618 (s), ν(SbF_6) 657 (s).

4: ^{1}H NMR (300 MHz, CD_2Cl_2, −50 °C): δ = 7.88 (s, 1H, CHO). ^{31}P NMR (121.5 MHz, CD_2Cl_2, −50 °C): δ = 49.18 (d, J_{P2P1} = 6.7 Hz, P^1), 28.93 (d, P^2).

5: ^{31}P NMR (121.5 MHz, CD_2Cl_2, −50 °C): δ = 50.08 (d, J_{P2P1} = 8.1 Hz, P^1), 28.46 (d, P^2).

Catalytic Procedure. The metallic complex [(η^5-C_5Me_5)Ir{(*R*)-Prophos}(H_2O)][SbF_6]$_2$ (1.25 × 10^{-2} mmol, 5 mol %) was dissolved in 2 mL of dry CH_2Cl_2 under argon at −20 °C, and 50 mg of 4 Å molecular sieves and freshly distilled methacrolein (20.7 μL, 0.25 mmol) were added. After 30 min of reaction the mixture was allowed to warm up to room temperature or was introduced in a cryogenic bath at the appropriate temperature. At the same temperature, cyclopentadiene (412.0 μL, 5.0 mmol) in 2 mL of CH_2Cl_2 was added. The reaction was quenched by addition of an excess of N(^{n}Bu)$_4$Cl in CH_2Cl_2, at the specified times. The absolute configuration of the major adduct was assigned by comparing the sign of $[\alpha]_D$ with that in the literature.[9]

X-ray Structure Analysis. Crystals were mounted in oil on a glass fiber, and intensity data were collected at 100(2) K on a CCD Bruker SMART APEX diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å) using ω rotations (0.3°). Data treatment and structure solution were carried out as described

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in ref 6b.[10] Anisotropic displacement parameters were applied for all non-hydrogen atoms. Hydrogen atoms were included in calculated positions and refined riding on carbon atoms. Refinements were performed by full-matrix least-squares on F^2 (SHELXL-97).[10]

Crystal Data for 1. $C_{46}H_{53}F_{12}IrOP_2Sb_2 \cdot CH_2Cl_2$, $M = 1432.45$; crystal size $0.14 \times 0.13 \times 0.08$ mm^3; monoclinic, $P2_1$; $a = 11.6093(7)$ Å, $b = 15.8413(10)$ Å, $c = 14.8090(9)$ Å; $\beta = 111.8230(10)°$; $Z = 2$; $V = 2528.3(3)$ Å^3; $\mu = 3.935$ mm^{-1}, min and max trans. factors 0.601 and 0.736; $2\theta_{max} = 57.8°$; 31 640 reflections collected, 12 071 unique [$R_{int} = 0.0296$]; number of data/restrains/parameters 12071/1/611; final GOF 1.069, $R_1 = 0.0311$ [11 581 reflections $I > 2\sigma(I)$], $wR_2 = 0.0557$ for all data; Flack parameter $x = 0.006(3)$. CCDC-628466 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge on application to the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: + 44 1223/336-033; e-mail: deposit@ccdc.cam.ac.uk).

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