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The Unusual Role of CO Transfer in Molybdenum-Catalyzed Asymmetric Alkylations

Shane W. Krska,* David L. Hughes, Robert A. Reamer, David J. Mathre, and Yongkui Sun

Departments of Process Research, Chemical Engineering R & D, Merck and Co., Inc., Rahway, New Jersey 07065

Barry M. Trost

Department of Chemistry, Stanford University, Stanford, California 94305-5080

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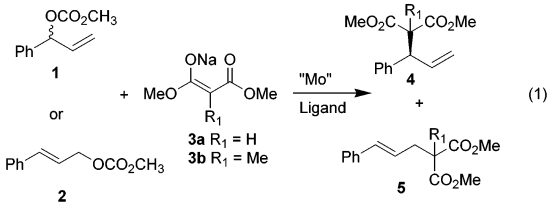
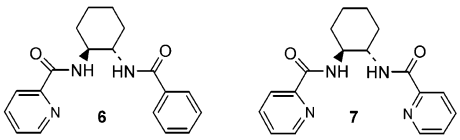
Over the past few years, the molybdenum-catalyzed asymmetric alkylation reaction (eq 1) has been developed into a powerful synthetic method, providing branched product **4** in high yield, ee, and regioselectivity.[1−4] Recently we reported a systematic study

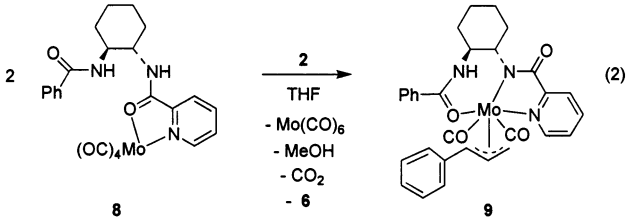


of the effects of ligand structure on the rate and regio- and stereoselectivity of molybdenum-catalyzed asymmetric alkylations.[5] This study revealed that unsymmetrical ligands such as **6** perform as well as (or, in some cases, better than) previously reported symmetrical ligands such as **7** and that the ligand appears to be binding to the metal through one pyridine ring and one or more of the amide moieties.



While a number of ligands of varying structure have now been successfully designed for this reaction, the nature of the catalytic species remains unknown. Herein we describe spectroscopic and crystallographic studies that provide definitive structures of intermediates in the catalytic cycle and disclose the unusual role played by CO transfer in catalyst turnover.

To gain more insight into the nature of the catalytic species, a series of stoichiometric reactions designed to model various steps in the catalytic cycle were followed by NMR. Reaction of Mo(CO)$_4$(norbornadiene) with ligand **6** produced complex **8**, with two-point binding through the pyridine nitrogen and amide group.[6] This neutral Mo−ligand complex reacted with linear carbonate **2** in THF-d_8 at 50 °C in a sealed NMR tube to form the π-allyl intermediate **9**. The stoichiometry of this reaction, as shown in eq 2, involves formation of 1 equiv each of **9**, MeOH, and free ligand from 2 equiv of complex **8**. In addition, a significant amount (presumably 1 equiv) of Mo(CO)$_6$ is observed by ^{13}C NMR spectroscopy. The methanol observed is formed, along with CO_2, from the methyl carbonate-leaving group upon deprotonation of one of the amide



groups of the ligand; the resulting anionic ligand ultimately becomes a part of the π-allyl complex **9**.

A suitable crystal of **9** was grown, and the X-ray structure is shown in Figure 1.[7] Noteworthy features of this structure include

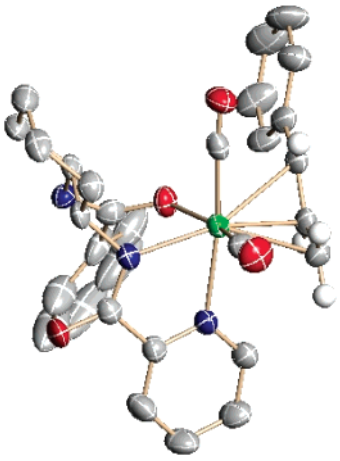


Figure 1. Crystal structure of π-allyl complex **9**. Thermal ellipsoids are drawn at the 50% probability level. Solvent (THF) and nonallylic H atoms are omitted for clarity. Carbon atoms are shown in gray, hydrogen in white, molybdenum in green, nitrogen in blue, and oxygen in red.

the following: (1) the allyl moiety binds in an η^3 fashion to Mo, with one face clearly open for reaction with a nucleophile; (2) the ligand is coordinated to the metal via three-point binding: the pyridine nitrogen, the nitrogen of the deprotonated amide, and the carbonyl oxygen of the undeprotonated amide; and (3) the complex contains two CO ligands. The overall geometry of the complex, including the syn orientation of the allyl moiety with respect to the CO ligands, is similar to other structurally characterized $L_2(CO)_2XMo(\eta^3$-allyl) complexes.[8,9] The solution structure, as determined by multinuclear NMR, is consistent with the crystal structure.[10,11]

Two important findings of the crystal structure are the deprotonation of the amide nitrogen,[12,13] and the three-point binding of the ligand to Mo. Both are likely key factors in providing strong

* To whom correspondence should be addressed. E-mail: shane_krska@merck.com.

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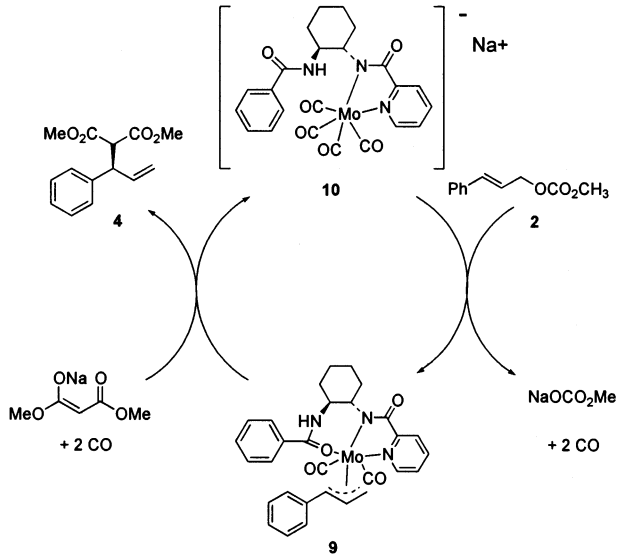
complexation and the rigidity required for producing high ee's in the allylic alkylation, even at temperatures of >100 °C in toluene.[14] While the crystal structure indicates one face of the π-allyl moiety is clearly open for approach of a nucleophile, attack of malonate in this direction predicts stereochemistry opposite to that which is observed. Thus, the π-allyl complex observed as the major species in solution is likely not the reactive species.[15]

A further surprise was in store when we initiated studies on the reactivity of **9**. When **9** is formed in situ from **8** and **2**, it smoothly reacts with sodium dimethyl malonate to produce the branched product **4** with ee >95%. However, when isolated **9** is redissolved in THF-d_8 and combined with sodium dimethyl malonate, no reaction occurs. Since the complex formed in situ also has $Mo(CO)_6$ and methanol present, we concluded one of these components must be necessary for reactivity. Indeed, addition of $Mo(CO)_6$ to the reaction mixture of the isolated π-allyl complex and malonate resulted in clean formation of the branched product **4** in 82% yield with ee >95%. The major molybdenum-containing product of this reaction is complex **10**, formed in 90% yield (Scheme 1). The

Scheme 1



reaction between isolated **9** and **3a** also occurs in the presence of 1 atm CO(g) to give **4** in 80% yield and >95% ee. Under these conditions, complex **10** is formed in 58% yield along with 13% free ligand according to ^{1}H NMR spectroscopy. Thus, the role of the $Mo(CO)_6$ is to serve as a source of CO in the reaction of the bis(carbonyl) complex **9** to the tetra(carbonyl) complex **10**. In effect, $Mo(CO)_6$ provides complex **9** with the necessary CO's to enhance its leaving-group ability in the displacement reaction.

Complex **10** was synthesized independently by reaction of **8** with NaH. Reaction of isolated **10** with linear carbonate **2** or either enantiomer of branched carbonate **1** cleanly generates π-allyl complex **9** in quantitative yield according to ^{1}H NMR spectroscopy. The gross features of the overall catalytic scheme have now been delineated and are shown in Scheme 1. Precatalyst **8** reacts with carbonate **2** to generate π-allyl complex **9** according to eq 2. Complex **9** reacts with malonate in the presence of a CO source (e.g., $Mo(CO)_6$) to form product **4** and molybdate complex **10**. Complex **10** reacts with carbonate **2** to regenerate complex **9** and release CO. A typical synthetic experiment using catalytic molybdenum was followed by NMR, and both complexes **9** and **10** were the only Mo-containing species observed, with high mass balance in Mo conserved throughout the reaction. This confirms that **9** and **10** are the catalyst resting states under actual catalytic synthetic conditions.

In light of the observed stereochemistry of allyl complex **9** and the crucial role played by CO transfer in its activation toward nucleophilic attack, questions remain as to the structure of the true catalytic species and how that species transfers chiral information from the ligand to the substrate. In addition, a number of features of this reaction, such as the observed kinetic resolution and memory effects and the high branched regioselectivity, remain to be explained.[14] Current work is focused on answering these questions via kinetic and synthetic studies.

Acknowledgment. We thank Dr. Richard Ball and Professor Guy Lloyd-Jones for helpful discussions.

Supporting Information Available: Synthetic procedures and NMR characterization for **6, 9**, and **10**, and the crystal structure for complex **9** are provided (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) The ^{15}N resonances of the pyridine and one of the amide nitrogens were shifted in complex **8** (δ 273, 133, respectively) relative to their values in free ligand **6** (δ 304, 118, respectively). The resonance of the unbound amide remained relatively unchanged (δ 123 in **8**, vs 119 in **6**).
(7) Crystallographic data for **9**·THF: $C_{38}H_{45}MoN_3O_6$, orange prisms, monoclinic, space group $P2(1)$, a = 10.4824(9) Å, b = 25.322(2) Å, c = 13.7540(12) Å, α = 90°, β = 104.515(2)°, γ = 90°, V = 3534.3(5) Å^3, Z = 4, ρ_{calcd} = 1.383 g cm^{-3}, T = 223(2) K, $R(F_0)$ = 0.0627, $wR(F_0^2)$ = 0.1555, GOF = 1.050. The THF solvent molecules were disordered.
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(9) The X-ray crystal structure of a monomeric Mo allyl complex of **7** (Mo:**7** = 2:1) has been reported: Morales, D.; Pérez, J.; Riera, L.; Riera, V.; Corzo-Suárez, R.; García-Granda, S.; Miguel, D. *Organometallics* **2002**, *21*, 1540−1545.
(10) Complex **9** can exist in any of four possible isomers wherein the ligand binds in a facial, tridentate fashion in one of two geometries (defined by either Δ or Λ stereochemistry between the skew lines formed by the two CO ligands and the two bound N atoms of the chiral ligand) and the π-allyl fragment binds via its *re* or *si* face.
(11) NMR characterization data for **9** were originally discussed in ref 5 and are included in the Supporting Information. The NOE data are consistent either with the structure shown in Figure 1 or with the diastereomeric structure formed by inversion of stereochemistry at both the metal center and the π-allyl fragment (cf. compound **20** in ref 5).
(12) Deprotonation of ligand **7** is precedented in metal complexes: Mulqi, M.; Stephens, F. S.; Vag, R. S. *Inorg. Chim. Acta* **1981**, *53*, L91−L93; Adolfsson, H.; Moberg, C. *Tetrahedron: Asymmetry* **1995**, *6*, 2023−2031.
(13) This result is in agreement with previous reactivity studies (ref 5) which showed that deprotonating ligand **7** before catalyst formation gives typical yields and enantioselectivities in the allylic alklyation reaction.
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(15) Intramolecular attack via a ligated malonate would provide the observed stereochemistry. However, since complex **9** is coordinatively saturated, precomplexation of malonate seems unlikely.

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