Carbonyl-Ene Reactions Catalyzed by Bis(oxazoline) Copper (II) Complexes Proceed by a Facile Stepwise Mechanism: DFT and ONIOM (DFT:PM3) Studies

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Ene reactions are additions of electrophilic π-bonds to alkenes with concomitant transfer of an allylic hydrogen (Scheme 1).[1] Hetero- and metallo-ene reactions have received considerable attention in recent years from an experimental and theoretical viewpoint given their synthetic importance.[2] While this process is relatively slow in the absence of acid catalysis, requiring high reaction temperatures, the use of transition-metal catalysts has provided a means for carrying out these additions under mild conditions with enhanced selectivity and a wider range of substrates.[3]

Scheme 1. Copper-Catalyzed Carbonyl-Ene Reaction
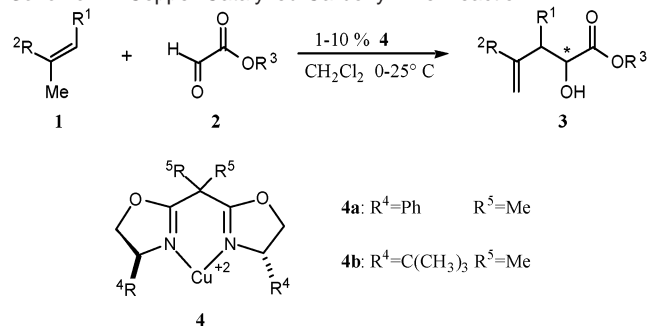
In particular, C2-symmetric bis(oxazoline) (BOX) ligands in the presence of copper salts **4a,b**, have been used for numerous catalytic asymmetric reactions because of their efficiency, selectivity, and broad substrate tolerance.[4,5] Of these, glyoxylate- and pyruvate-ene reactions afford α-hydroxy esters which show interesting biological properties and are versatile synthons in organic synthesis.[6] As a result, Lewis acid-catalyzed ene reactions of glyoxylate esters using bis(oxazoline) copper (II) complexes have been experimentally studied by several groups,[7] but the mechanism of these reactions remains unclear and is the subject of this communication. While KIE studies have shown that carbonyl enophile complexes follow stepwise reaction pathways,[8] concerted asynchronous transition state (TS) models have been proposed and argued to explain the stereochemical outcome.[7d]

As these calculations are computationally demanding, we here present both a conventional DFT study[9] (UB3LYP/6-31G*) and a two-layered ONIOM treatment[10] (UB3LYP/6-31G*:PM3[11]) which we show here provides a fast and reliable method for modeling d-metal catalyzed reactions.[12] To test the ONIOM approach we initially studied the structure of the catalyst **4a·2H₂O** and compared our results to crystallographic data.[13,14] The study of different ONIOM partitioning schemes showed that the cyclic framework of the ligand (methylene diimine moiety) must be considered in the high-level region to reproduce the full DFT and experimental results, whereas the remainder can be treated at a semiempirical level (Figure 1).[15-17] Both the full DFT and ONIOM treatments showed that the copper coordination is a distorted square planar rather than tetrahedral geometry with the methylene diimine-copper
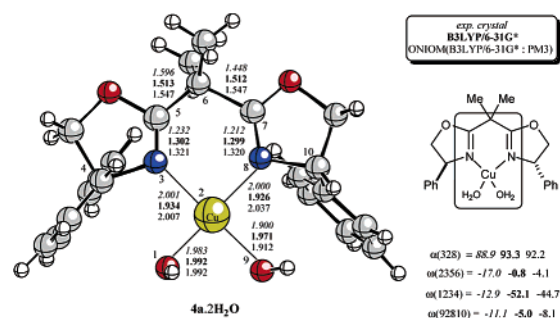
Figure 1. Main geometrical parameters for **4a·2H₂O**. Selected bond lengths (Å) and angles (deg). Atoms included in the high level region are within the box.
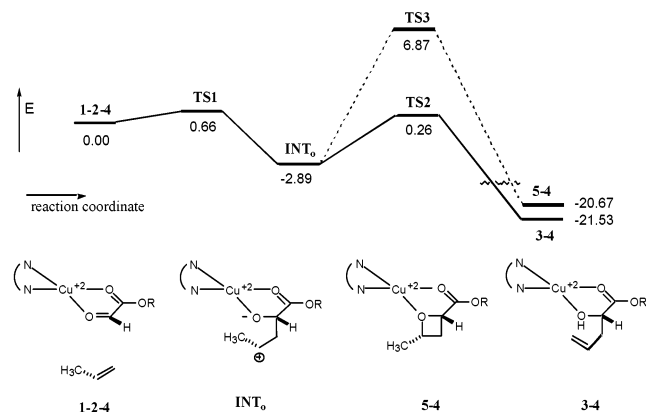
Figure 2. Relative free energies (in kcal/mol) on the pathway ($1 + 2 \rightarrow 3$) catalyzed by **4** (solid lines) at the UB3LYP(PCM)/6-311G**//UB3LYP/6-31G* level. Only one enantiomer has been drawn (*exo* approach) for clarity. Alternative pathways are indicated by hashed lines.

six-membered ring presenting a boatlike conformation having the methylene carbon and metal at the apexes, in line with crystallographic data.[13,14]

We have determined the potential energy surface for the copper-catalyzed reaction (R^{1-5} = H, Scheme 1) at both these levels of theory.[18,19] Although both approaches gave very similar geometries (bond lengths to within 0.15 Å), there were substantial discrepancies in relative energetics of the corresponding stationary points. Therefore, we recommend the evaluation of the energy at the full DFT level, using the computed ONIOM geometries.[20] Figure 2 shows the free energy profile of this reaction at the UB3LYP(PCM)/6-311G**//UB3LYP/6-31G* level, the dichloromethane solvent being simulated by means of the polarizable dielectric model (ϵ = 8.93).[21]

We first considered the possible combinations of the initial reactants. Thus, the naked catalyst **4** can be coordinated to either substrate ($1-4$, $2-4$) or both reactants ($1-2-4$, $1-4-2$). The catalyst–olefin π-complex $1-4$ presents a T-shaped planar struc-

ture,[22] and the catalyst–glyoxylate **2**–**4** chelate, a distorted square planar geometry similar to that of bis(aquo) analogues. Our calculations show a strong preference for the binding of the *O,O*-bidentate compound **2** as reflected in short Cu–O bond distances (2.0 Å). Interaction between **2**–**4** and **1** yields two different ternary complexes, **1**–**4**–**2** and **1**–**2**–**4**, depending on the coordination of the alkene to the chelate. The **1**–**4**–**2** complex, in which propene is coordinated to the copper atom in a bent square pyramidal geometry,[23] is the more stable by 1 kcal/mol, but all attempts to find a corresponding transition state were fruitless. However, IRC calculations showed that the **1**–**2**–**4** complex (Figure 2) does lead to C–C bond formation via both *exo* and *endo* alkene approach orientations to the aldehyde face.[24] The *endo* attack is sterically disfavored, and a slight *exo* preference is conserved along the reaction coordinate (solid-line pathway in Figure 2), which may thus be sensitive to bulky substituents. An open zwitterionic intermediate (INTo) is obtained after the transition structure (TS1) of the first step, namely C–C bond formation. A 1,5-hydrogen shift of this intermediate, via TS2, affords the observed final product **3**. Alternative ring closure of this intermediate to form an oxetane-like compound **5**–**4** of slightly higher energy than **3**–**4** proceeds via TS3, which is also higher in energy than TS2. Therefore, the four-membered ring product **5**, which is not experimentally observed, is neither kinetically nor thermodynamically favored. The potential energy surface was found to be quite flat, and at the UB3LYP/6-311G** level, **1**–**2**–**4**, TS1, INTo, and TS2 are within 3 kcal/mol. The transition structure for rotation between *exo-* and *endo*-INTo is less stable than both corresponding TS2s, which is consistent with the selectivity of the reaction even in a stepwise mechanism.

We thus predict that the reaction proceeds via a stepwise mechanism with very low barriers. All attempts to find a concerted pathway were unsuccessful. We have elucidated the role of the catalytic metal center in this important reaction. In contrast to typical metathesis and oxidative addition processes, we find that the β-hydrogen is transferred without direct participation of the metal. Thus, the metal can be viewed as a simple enophile activator.

Supporting Information Available: Total energies, balls-and-stick representations, and Cartesian coordinates at both levels of theory for all copper-bound calculations (PDF). This material is available free of charge via the Internet at http://www.pubs.acs.org

References

(1) (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556–577. (b) Snieckus, V.; Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476–486.

(2) (a) Sturla, S. J.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 1976–1977. (b) Matlin, A. R.; Lahti, P. M.; Appella, D.; Straumanis, A.; Lin, S.; Patel, H.; Schrieber, K. P.; Pauls, J.; Rauterson, P. *J. Am. Chem. Soc.* **1999**, *121*, 2164–2173. (c) Takayama, Y.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 3559–3560. (d) Cheng, D.; Zhu, S.; Liu, X.; Norton, S. L.; Cohen, T. *J. Am. Chem. Soc.* **1999**, *121*, 10241–10242. (e) Deiters, A.; Hoppe, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 546–548. (f) Vassilikogiannakis, G.; Elemes, Y.; Orfanopoulos, M. *J. Am. Chem. Soc.* **2000**, *122*, 9540–9541. (g) Hirai, A., Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 11791–11798. (h) Adam, W.; Bottke, N.; Engels, B.; Krebs, O. *J. Am. Chem. Soc.* **2001**, *123*, 5542–5548. (i) Drury, W. J.; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67–77.

(3) (a) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, pp 527–561 and Vol. 5, pp 1–27. (b) Mikami, K.; Terada, M.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021–1050.

(4) The combination of chiral BOX ligands–Lewis acids has been used for catalytic asymmetric reactions such as aldol, Diels–Alder, 1,3-dipolar cycloadditions, cyclopropanation, allylic substitution, allylation and ad-

(5) dition, aziridination, hetero-Diels–Alder, carbonyl-ene, Friedel–Crafts, Mannich, aza-Henry, Claisen rearrangement, and Kharasch–Sosnovsky reactions. For details, see reviews, ref 5.

(5) (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1–45. (b) Jorgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thurhauge, J. *Acc. Chem. Res.* **1999**, *32*, 605–613. (c) Evans, D. A.; Rovis, T.; Johnson, J. S. *Pure Appl. Chem.* **1999**, *71*, 1407–1415. (d) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325–335. (e) Thorhauge, J.; Roberson, M.; Hazell, R. G.; Jorgensen, K. A. *Chem. Eur. J.* **2002**, *8*, 1888–1898.

(6) Coppola, G. M.; Schuster, H. F. α-*Hydroxy Acids in Enantioselective Synthesis*; Wiley-VCH: Weinheim, 1997.

(7) (a) Gao, Y.; Lane-Bell, P.; Vederas, J. C. *J. Org. Chem.* **1998**, *63*, 2133–2143. (b) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824–5825. (c) Gethergood, N.; Jorgensen, K. A. *J. Chem. Soc., Chem. Commun.* **1999**, 1869–1870. (d) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936–7943.

(8) Singleton, D. A.; Hang, C. *J. Org. Chem.* **2000**, *65*, 895–899 and references therein.

(9) This DFT method has proved to be a reliable tool for the description of ene-reaction paths (a–c) and transition-metal complexes (d): (a) Pranata, J. *Int. J. Quantum Chem.* **1997**, *62*, 509–514. (b) Deng, Q.; Thomas, B. E. N.; Houk, K. N.; Dowd, P. *J. Am. Chem. Soc.* **1997**, *119*, 6902–6908. (c) Engels, B.; Musch, P. N. *J. Am. Chem. Soc.* **2001**, *123*, 5557–5562. (d) Niu, S.; Hall, M. B. *Chem. Rev.* **2000**, *100*, 353–405.

(10) (a) Dapprich, S.; Komiromi, I.; Byun, K. S.; Morokuma, K.; Frisch, M. J *J. Mol. Struct. (THEOCHEM)* **1999**, *461–462*, 1–21. (b) For an application in biochemistry: Torrent, M.; Vreven, T.; Musaev, D. G.; Morokuma, K.; Farkas, O.; Schlegel, H. B. *J. Am. Chem. Soc.* **2002**, *124*, 192–193. (c) For an application in catalysis: Liu, Z.; Torrent, M.; Morokuma, K. *Organometallics* **2002**, *21*, 1056–1071.

(11) (a) Thiel, W.; Voityuk, A. A. *Theor. Chim. Acta* **1992**, *81*, 391–404. (b) Thiel, W.; Voityuk, A. A. *Theor. Chim. Acta* **1996**, *93*, 315. (c) *HyperChem,* Hypercube, Inc.: Gainesville, FL.

(12) Standard calculations were carried out by means of *Gaussian 98*, revision A.7: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998. See computational details in Supporting Information.

(13) Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett.* **1999**, *40*, 2879–2882. [Cu (*S,S*)-(Ph-box)(H₂O)₂](SbF₆)₂ (cugzaf, CSD code).

(14) Calculations of Cu(ᵗBu-box)–alkylidene malonate complex (see Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134–9142) also gave good agreement with crystallographic data.

(15) For theoretical studies of other **4**-catalyzed reactions see: (a) Brandt, P.; Sodergren, M. J.; Andersson, P. G.; Norrby, P.-O. *J. Am. Chem. Soc.* **2000**, *122*, 8013–8020. (b) Fraile, J. M.; Garcia, J. I.; Martinez-Merino, V.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **2001**, *123*, 7616–7625.

(16) A QM/MM study of other **4**-catalyzed reaction have been recently performed, see: Rasmussen, T.; Jensen, J. F.; Ostergaard, N.; Tanner, D.; Ziegler, T.; Norrby, P.-O. *Chem. Eur. J.* **2002**, *8*, 177–184.

(17) For a QM/MM study of the role of bulky substituents in catalysis using diimine-based catalyst in QM region, see: Deng, L.; Woo, T. K.; Cavallo, L.; Margl, P. M.; Ziegler, T. *J. Am. Chem. Soc.* **1997**, *119*, 6177–6186.

(18) For all total energies, ball-and-stick structures, and Cartesian coordinates (*endo* and *exo* approaches) at both levels of theory see Supporting Information. The uncatalyzed reaction mechanism is a concerted pericyclic pathway with no energetic preference between *endo* and *exo* approaches (see Supporting Information).

(19) The two specific water molecules coordinating the catalytic complex **4a·2H₂O** were omitted in our study of the potential energy surface as the bis(aquo) catalyst yields the same efficiency and stereochemical results as the anhydrous catalyst (see ref 7).

(20) (a) Kwon, O.; Mckee, M. L. *J. Phys. Chem. A* **2001**, *105*, 10133–10138. (b) Irle, S.; Rubin, Y.; Morokuma, K. *J. Phys. Chem. A* **2002**, *106*, 680–688.

(21) (a) Miertus, S.; Scrocco, E.; Tomasi, J. *J. Chem. Phys.* **1981**, *55*, 117–129. (b) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027–2094.

(22) Froese, R. D. J.; Musaev, D. G.; Morokuma, K. *J. Am. Chem. Soc.* **1998**, *120*, 1581–1587.

(23) Martinez, A.; Salcedo, R.; Sansores, L. E.; Medina, G.; Gasque, L. *Inorg. Chem.* **2001**, *40*, 301–306.

(24) We denote *endo* and *exo* approaches as those in which the substituent of the reactive carbonyl group and the central carbon of the allyl group are in a *cis* and *trans* relationship, respectively.

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