DFT Study of the Mechanisms of In Water Au(I)-Catalyzed Tandem [3,3]-Rearrangement/Nazarov Reaction/[1,2]-Hydrogen Shift of Enynyl Acetates: A Proton-Transport Catalysis Strategy in the Water-Catalyzed [1,2]-Hydrogen Shift

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Abstract: A computational study with the Becke3LYP density functional was carried out to elucidate the mechanisms of Au(I)-catalyzed reactions of enynyl acetates involving tandem [3,3]-rearrangement, Nazarov reaction, and [1,2]-hydrogen shift. Calculations indicate that the [3,3]-rearrangement is a two-step process with activation free energies below 10 kcal/mol for both steps. The following Nazarov-type 4π electrocyclic ring-closure reaction of a Au-containing dienyl cation is also easy with an activation free energy of 3.2 kcal/mol in CH_2Cl_2. The final step in the catalytic cycle is a [1,2]-hydride shift, and this step is the rate-limiting step (with a computed activation free energy of 20.2 kcal/mol) when dry CH_2Cl_2 is used as the solvent. When this tandem reaction was conducted in wet CH_2Cl_2, the [1,2]-hydride shift step in dry solution turned to a very efficient water-catalyzed [1,2]-hydrogen shift mechanism with an activation free energy of 16.4 kcal/mol. Because of this, the tandem reaction of enynyl acetates was found to be faster in wet CH_2Cl_2 as compared to the reaction in dry CH_2Cl_2. Calculations show that a water-catalyzed [1,2]-hydrogen shift adopts a proton-transport catalysis strategy, in which the acetoxy group in the substrate is critical because it acts as either a proton acceptor when one water molecule is involved in catalysis or a proton-relay stabilizer when a water cluster is involved in catalysis. Water is found to act as a proton shuttle in the proton-transport catalysis strategy. Theoretical discovery of the role of the acetoxy group in the water-catalyzed [1,2]-hydrogen shift process suggests that a transition metal-catalyzed reaction involving a similar hydrogen shift step can be accelerated in water or on water with only a marginal effect, unless a proton-accepting group such as an acetoxy group, which can form a hydrogen bond network with water, is present around this reaction's active site.

1. Introduction

In recent years, water has become the solvent of choice to perform many organic transformations for reasons of cost, safety, and environmental concerns.[1] Furthermore, in some cases, rate acceleration and higher selectivity have also been achieved in aqueous reaction media as compared to those in organic solvents.[2] Substantial rate acceleration was observed under on water conditions, as discovered by Breslow and Rideout and Sharpless et al., when the organic reactants were insoluble in the aqueous phase.[3] Many asymmetric amine catalysts utilizing enamine intermediates can also catalyze reactions in water,[4] although it was arguable that these reactions were not performed under truly aqueous conditions.[5] Now, these reactions that are not all wet are called in water (or in the presence of water) reactions.[5] Most reported on water or in water reactions are usually referred to as traditional organic ones without employing air- or moisture-sensitive transition metal catalysts. This situation has recently been changed because many


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(1) (a) Grieco, P. A. *Organic Synthesis in Water*; Blackie: London, 1998. (b) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751. (c) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095. (d) Lubineau, A.; Auge, J. *Top. Curr. Chem.* **1999**, *206*, 1. (e) Engberts, J. B. F. N.; Blandamer, M. J. *J. Chem. Soc., Chem. Commun.* **2001**, 1701. (f) Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *Org. Lett.* **2005**, *7*, 4411.

(2) For recent reported reactions carried out in water, see: (a) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958. (b) Azizi, N.; Aryanasab, F.; Torkiyan, L.; Ziyaei, A.; Saidi, M. R. *J. Org. Chem.* **2006**, *71*, 3634. (c) Kurahashi, T.; Shinokubo, H.; Osuka, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6336. (d) Carril, M.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Org. Lett.* **2006**, *8*, 1467. (e) Xing, D.; Guan, B.; Cai, G.; Fang, Z.; Yang, L.; Shi, Z. *Org. Lett.* **2006**, *8*, 693. (f) Tiwari, S.; Kumar, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4824. (g) Geletii, Y. V.; Hill, C. L.; Atalla, R. H.; Weinstock, I. A. *J. Am. Chem. Soc.* **2006**, *128*, 17033. (h) Pirrung, M. C. *Chem.—Eur. J.* **2006**, *12*, 1312.

(3) (a) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816. (b) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159. (c) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275.

(4) (a) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983. (b) Wu, Y. S.; Chen, Y.; Deng, D. S.; Cai, J. *Synlett* **2005**, 1627. (c) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 734. (d) Dziedzic, P.; Zou, W.; Háfren, J.; Córdova, A. *Org. Biomol. Chem.* **2006**, *4*, 38.

(5) (a) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 8100. (b) Hayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8103. (c) Blackmond, D. G.; Armstrong, A.; Coombe, V.; Wells, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3798.

Scheme 1
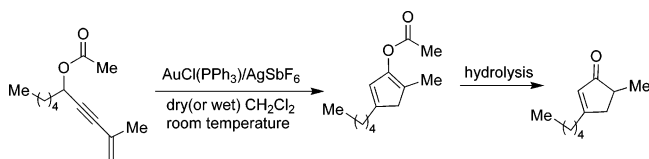
transformations catalyzed by metal catalysts can also be operated in the presence of water.[6] Despite the previously mentioned progress, little is known about the detailed mechanisms of how water assists or catalyzes these on water or in water reactions.[7]

Zhang and Wang recently discovered an efficient method to synthesize cyclopentenones through Au(I)-catalyzed tandem [3,3]-rearrangement/Nazarov reaction/[1,2]-hydrogen shift (Scheme 2) at room temperature, as exemplified by the reaction shown in Scheme 1.[8,9]

Three features of this reaction are worthy of emphasis. First, it was found that the reaction is faster when wet dichloromethane (CH_2Cl_2) was used as the solvent.[8] We are very interested in the detailed mechanism of this tandem reaction, particularly why this in water reaction of enynyl acetates in wet CH_2Cl_2 is faster than that operated in dry CH_2Cl_2. Second, the Nazarov substrates were generated in situ through Au(I)-catalyzed [3,3]-rearrangement of enynyl acetates, which are much easier to be synthesized as compared to the synthesis of dienones. Finally, this reaction can be carried out under remarkably mild conditions in either dry or wet CH_2Cl_2 at room temperature.

The originally proposed mechanism for the tandem reaction by Zhang and Wang is shown in Scheme 2.[8] In this mechanism, the cationic complex $[Au(PPh_3)]^+ PF_6^-$ first catalyzes a [3,3]-rearrangement of propargylic esters to form carboxyallenes, **B**, which can be activated later by the same Au catalyst to form a Au-containing pentadienylic cation, **D**; the pentadienylic cation subsequently undergoes a Nazarov-type 4π electrocyclic ring closure, yielding a gold carbenoid intermediate, **F**; finally, this carbenoid undergoes either a direct [1,2]-hydride shift or a two-step process involving the abstraction of H^+ by H_2O and the protonation of an alkenylgold intermediate in wet CH_2Cl_2 to regenerate the Au(I) catalyst and complete the catalytic cycle.

Most hydrogen shift reactions of carbocations are usually easy with activation barriers less than 10 kcal/mol,[10] and the hydride shift step in a multistep reaction is usually not the rate-limiting

step. On the basis of the proposed mechanism shown in Scheme 2, together with the fact that the reaction rate of Zhang and Wang's Au-catalyzed tandem reaction of enynyl acetates in the presence of water is accelerated,[8] we hypothesized that the direct [1,2]-hydride shift is the rate-limiting step of the tandem reaction in dry CH_2Cl_2. In wet CH_2Cl_2, we further hypothesized that an energetically more favored water-catalyzed proton-transfer process circumvents the direct [1,2]-hydride shift occurring in dry CH_2Cl_2, resulting in acceleration of the reaction rate.

But how do these Au(I)-catalyzed tandem reactions of enynyl acetates occur? More importantly, how does water affect the mechanisms of these tandem reactions? If the rate acceleration of the tandem rearrangement in water is due to the mechanistic change of the [1,2]-hydrogen shift process, we are very curious to know whether other transition metal-catalyzed reactions that involve a [1,2]-hydride shift step can also be facilitated in the presence of water or in water. For example, the cycloisomerization reactions of vinyl allenes, reported separately by Toste and Lee, and Iwasawa et al., have similar [1,2]-hydride shift processes (Scheme 3).[11] Can these reactions and others involving [1,2]-hydride shifts[11a,b] be accelerated in the presence of water? Even though Toste and Lee, and Iwasawa et al. did not run their reactions in the in water conditions, we believe that understanding the origin of the rate acceleration in Zhang and Wang's reaction in wet CH_2Cl_2 could provide insights that are helpful for understanding other transition metal-catalyzed reactions and for designing new in water reactions.

The details of the mechanism of the tandem reaction and the hydrogen shift process in the presence of water are not easily accessible by experiment.[8] Therefore, we present our theoretical studies of the Au(I)-catalyzed tandem reactions of enynyl acetates in both gas phase and solution, aiming to understand the details of the energy surfaces, the structures of intermediates, and the transition states involved in these transformations. Our theoretical results can satisfactorily explain the details of the reaction at a molecular level. More importantly, we uncovered a very interesting proton-transfer catalysis strategy[12] for the water-catalyzed [1,2]-hydrogen shift in the present reaction,

(6) (a) Wender, P. A.; Love, J. A.; Williams, T. J. *Synlett* **2003**, 1295. (b) Yao, X.; Li, C.-J. *Org. Lett.* **2006**, *8*, 1953. (c) Botar, B.; Geletii, Y. V.; Kogerler, P.; Musaev, D. G.; Morokuma, K.; Weinstock, I. A.; Hill, C. L. *J. Am. Chem. Soc.* **2006**, *128*, 11268. (d) Estevan, F.; Lloret, J.; Sanau, M.; Ubeda, M. A. *Organometallics* **2006**, *25*, 4977. (e) Candeias, N. R.; Gois, P. M. P.; Afonso, C. A. M. *J. Org. Chem.* **2006**, *71*, 5489. (f) Ogo, S.; Takebe, Y.; Uehara, K.; Yamazaki, T.; Nakai, H.; Watanabe, Y.; Fukuzumi, S. *Organometallics* **2006**, *25*, 331. (g) Shirakawa, S.; Kobayashi, S. *Synlett* **2006**, 1410. (h) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584.

(7) For mechanistic studies concerning how water affects reactions, see: (a) Chandrasekhar, J.; Shariffskul, S.; Jorgensen, W. L. *J. Phys. Chem. B* **2002**, *106*, 8078. (b) Butler, R. N.; Cunningham, W. J.; Coyne, A. G.; Burke, L. A. *J. Am. Chem. Soc.* **2004**, *126*, 11923. (c) Blake, J. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 7430. (d) Blake, J. F.; Lim, D.; Jorgensen, W. L. *J. Org. Chem.* **1994**, *59*, 803. (e) Kong, S.; Evanseck, J. D. *J. Am. Chem. Soc.* **2000**, *122*, 10418. (f) Otto, S.; Engberts, J. B. F. N. *Pure Appl. Chem.* **2000**, *72*, 1365. (g) Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492.

(8) (a) For the initial study, see: Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442. (b) The authors observed later that the reactions were faster in wet CH_2Cl_2 than in dry CH_2Cl_2.

(9) For other Au-catalyzed reactions from Zhang's group: (a) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804. (b) Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, *128*, 14274. (c) Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, *128*, 8414. (d) Wang, S.; Zhang, L. *Org. Lett.* **2006**, *8*, 4585.

(10) (a) Shaler, T. A.; Borchardt, D.; Morton, T. H. *J. Am. Chem. Soc.* **1999**, *121*, 7907. (b) Vrćek, I. V.; Vrćek, V.; Siehl, H.-U. *J. Phys. Chem. A* **2002**, *106*, 1604. (c) Kraka, E.; Cremer, D. *J. Phys. Org. Chem.* **2002**, *15*, 431. (d) Nishizawa, M.; Yadav, A.; Iwamoto, Y.; Imagawa, H. *Tetrahedron* **2004**, *60*, 9223. (e) Hayase, S.; Hrovat, D. A.; Borden, W. T. *J. Am. Chem. Soc.* **2004**, *126*, 10028. (f) Vrćek, V.; Vrćek, I. V.; Siehl, H.-U. *J. Phys. Chem. A* **2006**, *110*, 1868. (g) Lemière, G.; Gandon, V.; Agenet, N.; Goddard, J. P.; de Kozak, A.; Aubert, C.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 7596. (h) Hess, B. A., Jr.; Baldwin, J. E. *J. Org. Chem.* **2002**, *67*, 6025.

(11) (a) Lee, J. H.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 912. (b) Funami, H.; Kusama, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 909. For other recent examples of organometallic reactions involving [1,2]-hydrogen shifts, see: (c) Fürstner, A.; Aïssa, C. *J. Am. Chem. Soc.* **2006**, *128*, 6306. (d) Shi, M.; Liu, L.-P.; Tang, J. *J. Am. Chem. Soc.* **2006**, *128*, 7430.

(12) (a) Mourgues, P.; Audier, H. E.; Leblanc, D.; Hammerum, S. *Org. Mass Spectrom.* **1993**, *28*, 1098. (b) Audier, H. E.; Leblanc, D.; Mourgues, P.; McMahon, T. B.; Hammerum, S. *J. Chem. Soc., Chem. Commun.* **1994**, 2329. (c) Bohme, D. K. *Int. J. Mass Spectrom. Ion Process.* **1992**, *115*, 95. (d) Gauld, J. W.; Radom, L. *J. Am. Chem. Soc.* **1987**, *119*, 9831. (e) Gauld, J. W.; Audier, H.; Fossey, J.; Radom, L. *J. Am. Chem. Soc.* **1996**, *118*, 6299. (f) Chalk, A. J.; Radom, L. *J. Am. Chem. Soc.* **1997**, *119*, 7573. (g) East, A. L. L.; Smith, B. J.; Radom, L. *J. Am. Chem. Soc.* **1997**, *119*, 9014. (h) Smith, D. M.; Golding, B. T.; Radom, L. *J. Am. Chem. Soc.* **1999**, *121*, 5700. (i) Smith, D. M.; Golding, B. T.; Radom, L. *J. Am. Chem. Soc.* **1999**, *121*, 1383. (j) Trikoupis, M. A.; Terlouw, J. K.; Burgers, P. C. *J. Am. Chem. Soc.* **1998**, *120*, 12131. (k) Ruttink, P. J. A.; Burgers, P. C.; Fell, L. M.; Terlouw, J. K. *J. Phys. Chem. A* **1998**, *102*, 2976. For recent discussion of water as a single molecule catalyst, see: (l) Vöhringer-Martinez, E.; Hansmann, B.; Hernandez, H.; Francisco, J. S.; Troe, J.; Abel, B. *Science (Washington, DC, U.S.)* **2007**, *315*, 497. (m) Smith, I. *Science (Washington, DC, U.S.)* **2007**, *315*, 470.

Scheme 2
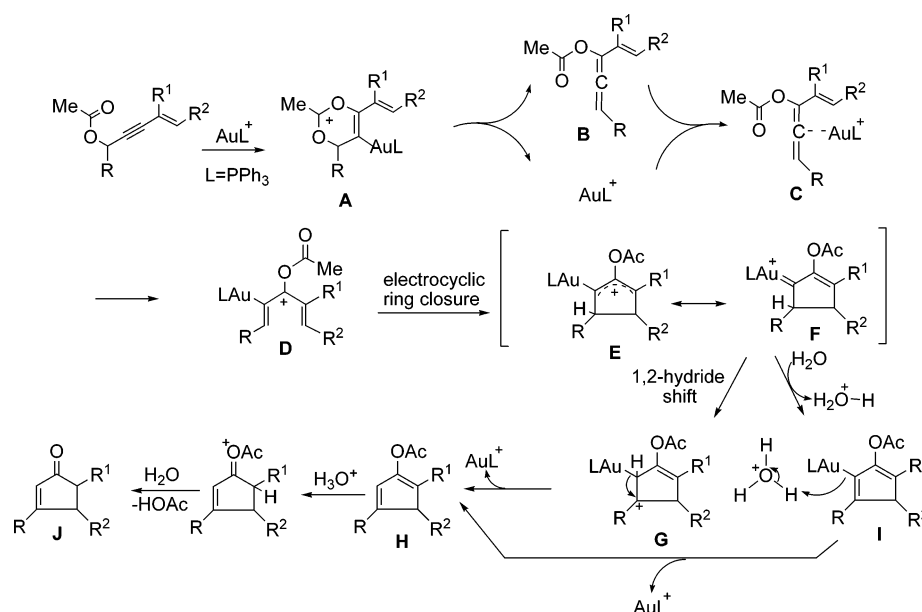
Scheme 3
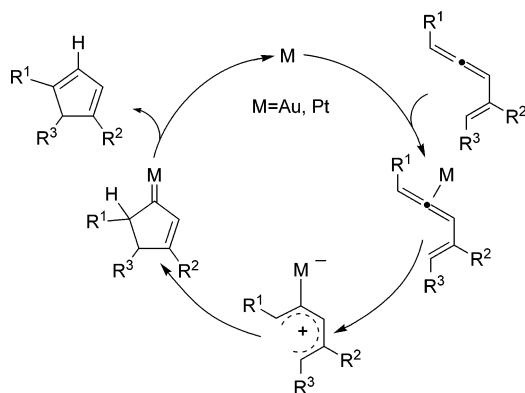
which is similar to those enzymatic reactions involving general acid/general base catalysis and organic reactions as well.[13–15] We also found that the acetoxy group, which acts as a proton acceptor or a proton-relay stabilizer in the proton-transfer process, is critical for the rate acceleration of the title reaction in wet CH$_2$Cl$_2$. Water is found to act as a proton shuttle in the present hydrogen shift process. These theoretical discoveries are expected to bring new insight into many other in water

organic and transition metal-catalyzed reactions involving hydrogen shift processes.[11] On the other hand, theoretical studies of the mechanisms of the present tandem reaction will also be helpful in understanding other Au-catalyzed reactions[16] and to give guidance for future design of new catalysts and new reactions.[17,18]

2. Computational Methods

All calculations were carried out with the Gaussian 03 programs.[19] The geometrical optimizations of all the intermediates and transition states were performed using Becke's three-parameter exchange func-

(13) (a) For a recent thematic issue on the studies of enzymatic reaction mechanisms, see: Schramm, V. L. *Chem. Rev.* **2006**, *106*, 3029 and references therein. (b) Gao, J.; Ma, S.; Major, D. T.; Nam, K.; Pu, J.; Truhlar, D. G. *Chem. Rev.* **2006**, *106*, 3188. (c) Ragsdale, S. W. *Chem. Rev.* **2006**, *106*, 3317. (d) Zhang, X.; Houk, K. N. *Acc. Chem. Res.* **2005**, *38*, 379.

(14) Perrin, C. L.; Ohta, B. K. *J. Am. Chem. Soc.* **2001**, *123*, 6520. (b) George, P.; Glusker, J. P.; Bock, C. W. *J. Am. Chem. Soc.* **1997**, *119*, 7065. (c) de Visser, S. P.; Shaik, S. *J. Am. Chem. Soc.* **2003**, *125*, 7413. (d) Widersten, M.; Bjornestedt, R.; Mannervik, B. *Biochemistry* **1996**, *35*, 7731. (e) Hong, Y. J.; Tantillo, D. J. *Org. Lett.* **2006**, *8*, 4601. (f) Hollfelder, F.; Kirby, A. J.; Tawfik, D. S.; Kikuchi, K.; Hilvert, D. *J. Am. Chem. Soc.* **2000**, *122*, 1022.

(15) (a) Li, L.; Marsh, E. N. G. *J. Am. Chem. Soc.* **2006**, *128*, 16056. (b) Francisco, W. A.; Knapp, M. J.; Blackburn, N. J.; Klinman, J. P. *J. Am. Chem. Soc.* **2002**, *124*, 8194. (c) Cheek, J.; Broderick, J. B. *J. Am. Chem. Soc.* **2002**, *124*, 2860. (d) Davydov, R.; Matsui, T.; Fujii, H.; Ikeda-Saito, M.; Hoffman, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 16208. (e) Hong, B.; Haddad, M.; Maley, F.; Jensen, J. H.; Kohen, A. *J. Am. Chem. Soc.* **2006**, *128*, 5636. (f) Spies, M. A.; Toney, M. D. *Biochemistry* **2003**, *42*, 5099. (g) De Vivo, M.; Ensing, B.; Dal Peraro, M.; Gomez, G. A.; Christianson, D. W.; Klein, M. L. *J. Am. Chem. Soc.* **2007**, *129*, 387. (h) Qian, M.; Tu, C.; Earnhardt, J. N.; Laipis, P. J.; Silverman, D. N. *Biochemistry* **1997**, *36*, 15758.

(16) For recent reviews of Au-catalyzed reactions, see: (a) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (b) Jiménez-Núñez, E.; Echavarren, A. M. *J. Chem. Soc., Chem. Commun.* **2007**, 333. (c) Gorin, D. J.; Toste, F. D. *Nature (London, U.K.)* **2007**, *446*, 395. For other recent Au-catalyzed reactions, see: (d) Brouwer, C.; He, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1744. (e) Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2006**, *348*, 691. (f) Han, X.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747. (g) Hashmi, A. S. K.; Blanco, M. C.; Fischer, D.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, *1387*. (h) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200. (i) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genet, J.-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112. (j) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473. (k) Reich, N. W.; Yang, C.-G.; Shi, Z.; He, C. *Synlett* **2006**, *8*, 1278. (l) Liu, Z.; Wasmuth, A. S.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 10352. (m) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798. (n) Sun, J.; Conley, M. P.; Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 9705. (o) Skouta, R.; Li, C.-J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1117. (p) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1141. (q) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802. (r) Peng, L.; Zhang, X.; Zhang, S.; Wang, J. *J. Org. Chem.* **2007**, *72*, 1192. (s) Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5452.

(17) For recent theoretical studies of Au-catalyzed reactions, see: (a) Faza, O. N.; Lopez, C. S.; Alvarez, R.; de Lera, A. R. *J. Am. Chem. Soc.* **2006**, *128*, 2434. (b) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402. (c) Roithová, J.; Hrušák, J.; Schröder, D.; Schwarz, H. *Inorg. Chim. Acta* **2005**, *358*, 4287. (d) Joshi, A. M.; Delgass, W. N.; Thomson, K. T. *J. Phys. Chem. B* **2006**, *110*, 2572. (e) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem.–Eur. J.* **2006**, *12*, 5916. (f) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6146. For early studies of transition metal–carbene complexes, see: (g) Heinemann, C.; Hertwig, R. H.; Wesendrup, R.; Koch, W.; Schwarz, H. *J. Am. Chem. Soc.* **1995**, *117*, 495. (h) Irikura, K. K.; Goddard, W. A., III. *J. Am. Chem. Soc.* **1994**, *116*, 8733. For an excellent review about using DFT to study organometallic reaction mechanisms, see: (i) Niu, S.; Hall, M. B. *Chem. Rev.* **2000**, *100*, 353.

(18) For our recent theoretical studies of transition metal-catalyzed reactions, see: (a) Wu, Y.-D.; Yu, Z.-X. *J. Am. Chem. Soc.* **2001**, *123*, 5777. (b) Yu, Z.-X.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 13825. (c) Yu, Z.-X.; Wender, P. A.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 9154.
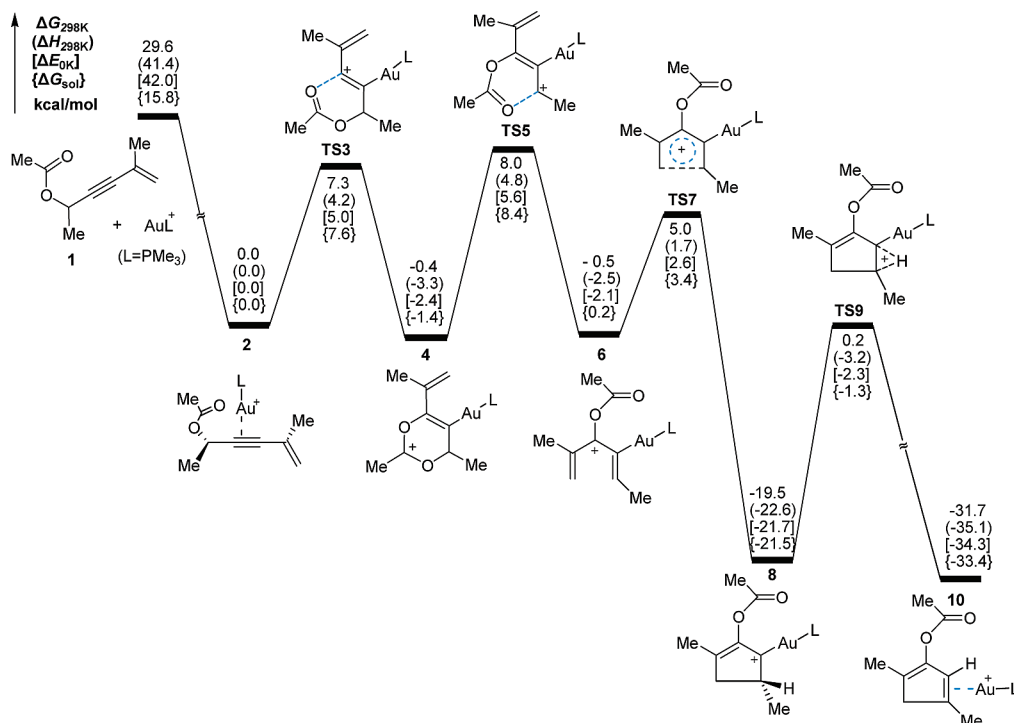
Figure 1. DFT computed energy surface for the Au(I)-catalyzed tandem reaction of enynyl acetate.

tional[20] and the nonlocal correlation functional of Lee, Yang, and Parr[21] (B3LYP) with the 6-31G(d) basis set for all atoms except for gold, which has been described by the Stuttgart/Dresden (SDD) ECP valence basis set.[22] This computational method has been successfully applied in the mechanistic studies of transition metal-catalyzed reactions.[17,18] Frequency calculations at the same level were performed to confirm each stationary point to be either a minimum or a transition structure (TS). In several cases where TS are not easily confirmed by animation of their vibrations, intrinsic reaction coordinate (IRC)[23] calculations were performed to confirm the connection of each TS to its corresponding reactant and product. The free energies of solvation in this study were calculated based on the gas phase optimized structures with the conductor-like polarizable continuum model (CPCM) using UAKS radii.[24] The dielectric constant in the CPCM calculations was set to $\epsilon = 8.93$ to simulate dichloromethane (CH_2Cl_2), the solvent medium in the experiments.[8] The single point energies were also computed using the MP2 method (6-31+G(d,p) for C, H, O, and P and SDD for Au), showing that the potential energy surface at the MP2 level is quite similar to that at the B3LYP level (see the Supporting Information for details). This further demonstrates that the DFT method is quite suitable to investigate Au-catalyzed reactions.[17] All reported charges are electrostatic potential (ESP) charges.[25] Wiberg bond indices (WBI) were evaluated with Weinhold's natural bond orbital method.[26] Topological analysis of the electron densities at bond critical points was performed

with the AIM 2000 program to confirm the weak interactions.[27] The catalytic species in the present investigated reaction is believed to be cationic $[Au(PPh_3)]^+$, which is generated in situ by extracting the Cl^- from $AuCl(PPh_3)$ using $AgSbF_6$. To keep the computational study efficient, the experimentally used ligand PPh_3 was replaced by PMe_3, and we believe that such a simplification is not expected to change the conclusions in this study because our testing studies have established that the steric and electronic effects of the phenyls in triphenylphosphine have little effect on the potential energy surface (details are given in the Supporting Information). In what follows, the discussed energies are relative Gibbs free energies (ΔG_{298K}). The relative enthalpies (ΔH_{298K}) and ZPE corrected electronic energies (ΔE_{0K}) as well as free energies in CH_2Cl_2 (ΔG_{sol}) are also provided for reference.

3. Results and Discussion

In this section, we will first present the computational study of the Au(I)-catalyzed tandem [3,3]-rearrangement/Nazarov reaction/[1,2]-hydrogen shift of enynyl acetates in the gas phase and dry dichloromethane solution, and then a detailed study of the water-catalyzed [1,2]-hydrogen shift is presented to understand the role of water in the rate acceleration of this tandem reaction.

3.1. Mechanism of the Tandem Reaction of Enynyl Acetates in Gas Phase and Dry Dichloromethane. The DFT computed energy surface in the gas phase and CH_2Cl_2 for the tandem [3,3]-rearrangement/Nazarov reaction/[1,2]-hydrogen shift of enynyl acetates is given in Figure 1. The optimized structures of key stationary points along the reaction pathway are collected in Figure 2.

The tandem reaction begins with coordination of the cationic catalyst, $[Au(PMe_3)]^+$, to the substrate, enynyl acetate **1**. In

(19) Frisch, M. J. et al. Gaussian 03, revision C.02; Gaussian, Inc.: Pittsburgh, PA, 2004.
(20) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
(21) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
(22) (a) Szentpaly, L. V.; Fuentealba, P.; Preuss, H.; Stoll, H. *Chem. Phys. Lett.* **1982**, *93*, 555. (b) Dolg, M.; Wedig, U.; Stoll, H.; Preuss, H. *J. Chem. Phys.* **1987**, *86*, 866. (c) Schwerdtfeger, P.; Dolg, M.; Schwarz, W. H. E.; Bowmaker, G. A.; Boyd, P. D. W. *J. Chem. Phys.* **1989**, *91*, 1762.
(23) (a) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154. (b) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523.
(24) (a) Barone, V.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* **1998**, *19*, 404. (b) Takano, Y.; Houk, K. N. *J. Chem. Theory Comput.* **2005**, *1*, 70.
(25) (a) Besler, B. H.; Merz, K. M., Jr.; Kollman, P. A. *J. Comput. Chem.* **1990**, *11*, 431. (b) Singh, U. C.; Kollman, P. A. *J. Comput. Chem.* **1984**, *5*, 129.
(26) (a) Wiberg, K. B. *Tetrahedron* **1968**, *24*, 1083. (b) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.

(27) (a) Bader, R. F. W. *Atoms in Molecules: A Quantum Theory*; Oxford University Press: Oxford, 1990. (b) Biegler-König, F.; Schönbohm, J.; Bayles, D. J. *J. Comput. Chem.* **2001**, *22*, 545. (c) Biegler-König, F.; Schönbohm, J.; Bayles, D. J. *AIM 2000*; http://gauss.fh-bielefeld.de/aim2000.
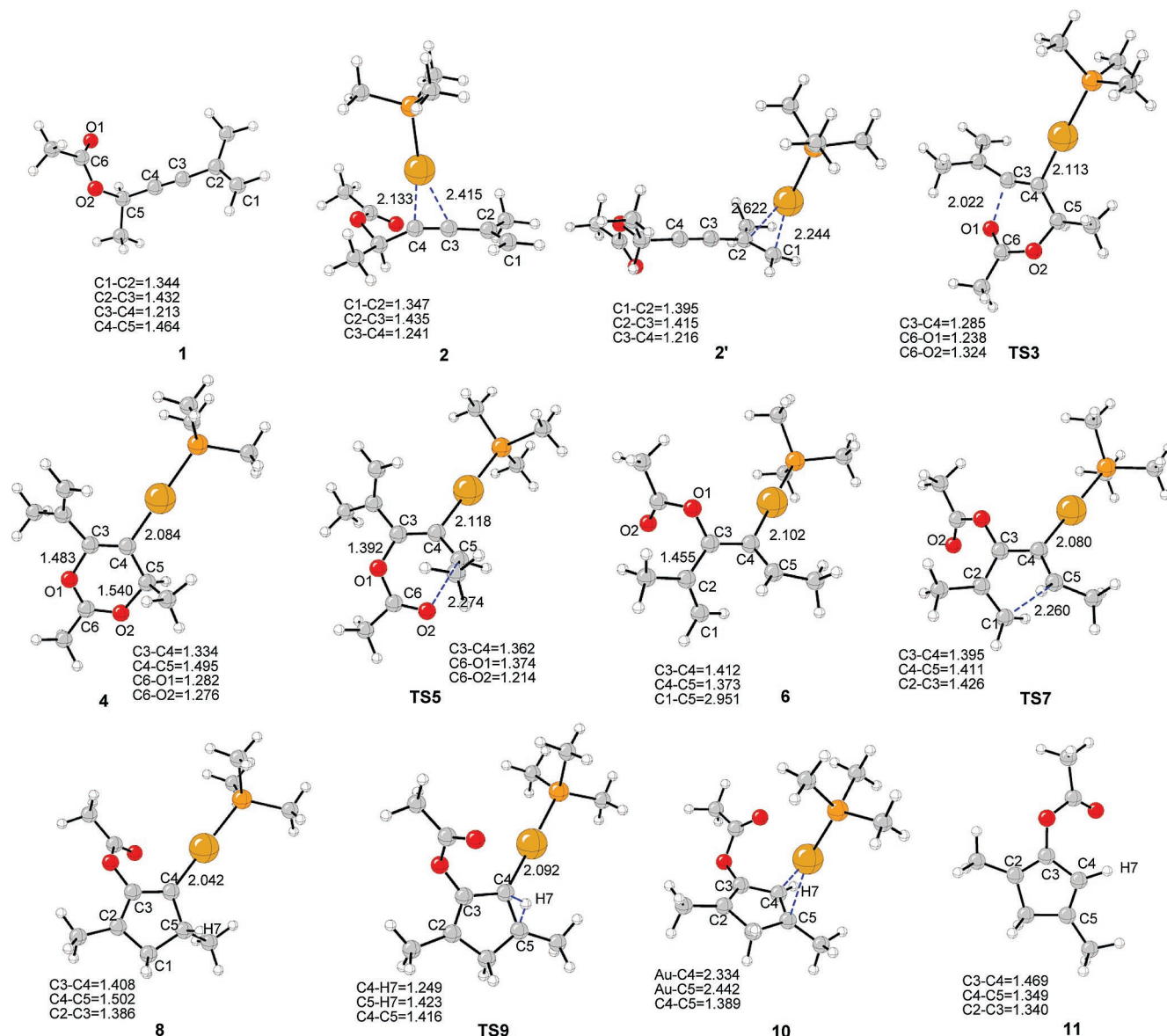
Figure 2. DFT optimized key structures for the Au(I)-catalyzed tandem reaction of enynyl acetate (distances in Å).

principle, [Au(PMe$_3$)]$^+$ can coordinate to either the carbon–carbon double bond or the carbon–carbon triple bond of the substrate. Coordination of the catalyst to the triple bond in **1** leads to the formation of complex **2**, which is a polarized complex with distances between Au and two sp-hybridized carbon atoms of 2.13 and 2.42 Å, respectively. This complex can then enter the subsequent catalytic cycle of the tandem reaction. Alternatively, coordination of the catalyst to the double bond in **1** leads to the formation of another complex **2′**, an isomer of **2**. This coordination path is a dead-end one because **2′** cannot undergo subsequent reactions. Calculations indicate that coordination of the catalyst to the C–C triple bond as compared to the C–C double bond in **1** is energetically favored by 2.6 kcal/mol. Such a preference of the C–C triple bond over the C–C double bond for the coordination of [Au(PMe$_3$)]$^+$ was also found in the reactions of Au(I)-catalyzed skeletal rearrangement and cycloadditions of enynes.[16a,17f] The coordination process is exergonic by 29.6 kcal/mol in the gas phase. The unsymmetrical mode of coordination in **2** is to maximize the delocalization of the positive charge in C1–C2–C3.

The conversion of complex **2** to the dialkene intermediate **6** via two six-membered ring transition structures is a two-step process. In **TS3**, nucleophilic attack of O1 (−0.44 e) on the positively charged C3 (+0.10 e) occurs, generating a six-membered intermediate **4**. This transformation only requires an activation free energy of 7.3 kcal/mol in the gas phase and is a thermodynamically neutral process (exergonic by only 0.4 kcal/mol). Intermediate **4** is an oxonium ion, in which both the C3–O1 and the C5–O2 bonds are weaker than that of a normal C–O single bond (1.43 Å), as demonstrated by their long bond lengths of 1.48 and 1.54 Å, respectively (their bond orders are 0.77 and 0.72, respectively). Intermediate **4** is then converted to the dialkene **6** via a four-electron rearrangement transition structure **TS5**. In **TS5**, the breaking C5–O2 bond is 2.27 Å. The activation free energy of the second step is 8.4 kcal/mol, and the formation of **6** is also a thermodynamically neutral process. IRC calculations show that **TS5** first leads to a structure with the Au and acetate moiety in a trans-configuration; however, this structure is not a minimum and will automatically

Scheme 4
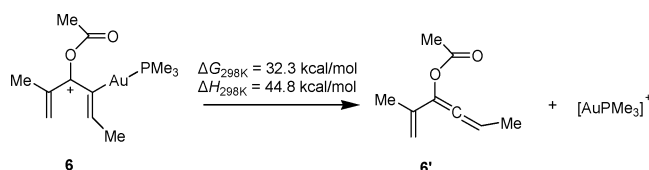
rotate to give the *cis*-dialkene cation **6**.[28] Intermediate **6** can also be regarded as a π-complex between Au(I) and carboxyallene **6′** (Scheme 4). However, the dissociation of [Au(PMe₃)]⁺ from **6** to liberate carboxyallene **6′** is not energetically feasible because this is endergonic by 32.3 kcal/mol. The tandem Au-catalyzed rearrangements have activation free energies below 10 kcal/mol; this is dramatically easier than the uncatalyzed [3,3]-rearrangement of **1** to **6′**, which has an activation free energy of 39.7 kcal/mol calculated at the B3LYP/6-31G(d) level.

Intermediate **6** can be also regarded as a pentadienyl cation, which can undergo a Nazarov-type electrocyclic reaction to give intermediate **8**. The 4π electrocyclic ring closure via **TS7** requires only an activation free energy of 5.5 kcal/mol in the gas phase. **TS7** has a conrotation mode,[29] and the length of the forming C1−C5 bond is 2.26 Å. Similar to the Nazarov reaction of O-heterocyclic compounds,[30a] the formation of **8** from **6** is dramatically exergonic (25.2 kcal/mol) due to the formation of a new C−C bond.

The final step of the tandem reaction is a [1,2]-hydride shift process. The traditional [1,2]-hydride shift in carbocations is very easy with activation barriers less than 10 kcal/mol.[10] This is because hydride shifts of carbocations are intimately coupled with internal charge stabilization by increasing the coordination through forming three-centered two electron (3c-2e) bonds. Calculations indicate that the C4 in **8** only possesses a charge of +0.04 e, whereas C3 is more positive (+0.13 e). The low charge density of C4 in **8** is mainly due to the delocalization of the positive charge. In the hydride shift transition state, **TS9**, the distance of C4−H7 is shorter than that of C5−H7 (1.25 vs 1.42 Å). An unsymmetrical three-membered ring structure characterizes **TS9** with an imaginary vibration frequency (822 *i* cm⁻¹). Hydride shift through **TS9** leads to the formation of **10**, a complex between [Au(PMe₃)]⁺ and product **11**. The hydride shift step is exergonic by 12.2 kcal/mol and requires an activation free energy of 19.7 kcal/mol in the gas phase.

The overall potential energy surface in the gas phase shows that the hydride shift is the rate-limiting step of the tandem reaction. Therefore, the activation free energy for the tandem reaction is 19.7 kcal/mol in the gas phase. In addition, the whole catalytic cycle is highly exergonic by 61.3 kcal/mol. Since the cationic gold complex, [Au(PMe₃)]⁺, has the preference of coordination to the triple bond over the double bond, the alkyne complex **2** is readily regenerated from **10** via a ligand exchange reaction shown in Scheme 5. Calculations indicate that such a
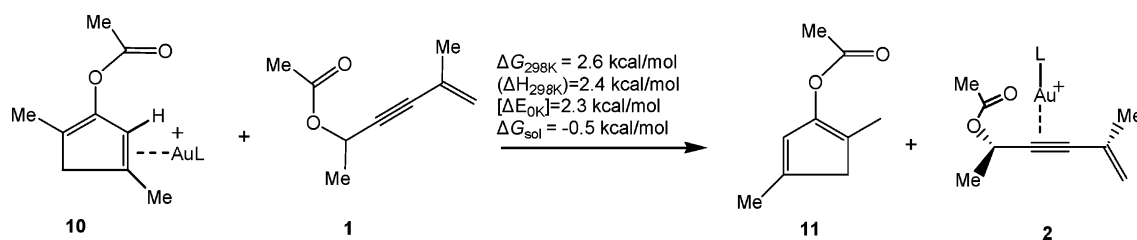
ligand exchange process to regenerate complex **2** is endergonic by 2.6 kcal/mol in the gas phase and is slightly exergonic in CH₂Cl₂ solvent.

The solvent effects of the present reaction have been studied using the CPCM model with CH₂Cl₂ as the solvent. The potential energy surface in solution is similar to that obtained in the gas phase, and the [1,2]-hydride shift is still the rate-limiting step in CH₂Cl₂ (see ΔG_{sol} values in Figure 1). Calculations show that the tandem reaction has a very close reaction rate in CH₂Cl₂ to that in the gas phase because the overall activation free energy is only increased by 0.5 kcal/mol in CH₂Cl₂ as compared to that in the gas phase.

3.2. How Does Water Catalyze the [1,2]-Hydride Shift? The previous calculations indicate that the Au(I)-catalyzed tandem reaction of enynyl acetates is easy in both gas phase and dry CH₂Cl₂, with activation free energies of ca. 20 kcal/mol. In this section, we focus on how water molecules affect the reaction rate of the tandem reaction. In wet CH₂Cl₂, water could theoretically affect all steps of the tandem reaction. Calculations indicate that the effect of water molecules on the [3,3]-rearrangement and the Nazarov reaction is negligible. It is found that the energy surface in the presence of one water molecule is very similar to that without a water molecule. Calculations indicate that in wet CH₂Cl₂, the water molecule acts as a ligand coordinated to the Au(I) catalyst, and this coordination does not alter the reaction mechanisms of the tandem [3,3]-rearrangement and the Nazarov reaction (see Figure S3 in the Supporting Information). However, calculations show that the presence of water changes the direct [1,2]-hydride shift to a stepwise proton-transfer process that is quite similar to the proton-transfer processes in proton-transport catalysis and many enzyme-catalyzed reactions.[12-15] This water-assisted proton-transfer process can also explain the experimentally observed incorporation of deuterium in the 2-position of the final product. Therefore, in this section, we mainly focus our study on how water molecules affect the [1,2]-hydride shift process.

In wet CH₂Cl₂, **8** and water can form cationic complex **12**, and this complexation process in the gas phase is exothermic by 9.9 kcal/mol and exergonic by 1.2 kcal/mol. Complex **12** is stabilized by two kinds of hydrogen bonding interactions. One is the O3−H8···O2 hydrogen bonding, which is formed between water's O−H bond and oxygen atom of the acetoxy moiety. The other is a weak C5−H7···O3 bonding,[31,32] which is formed between water's oxygen atom and H7−C5 bond. The distances of H8···O2 and H7···O3 in complex **12** are 1.96 and 2.46 Å, respectively.

The following steps are water-catalyzed two-step proton-transfer processes, including the deprotonation of the hydrogen H7 from C5 and protonation of the carbon atom C4, which is directly connected by the Au atom. In the deprotonation
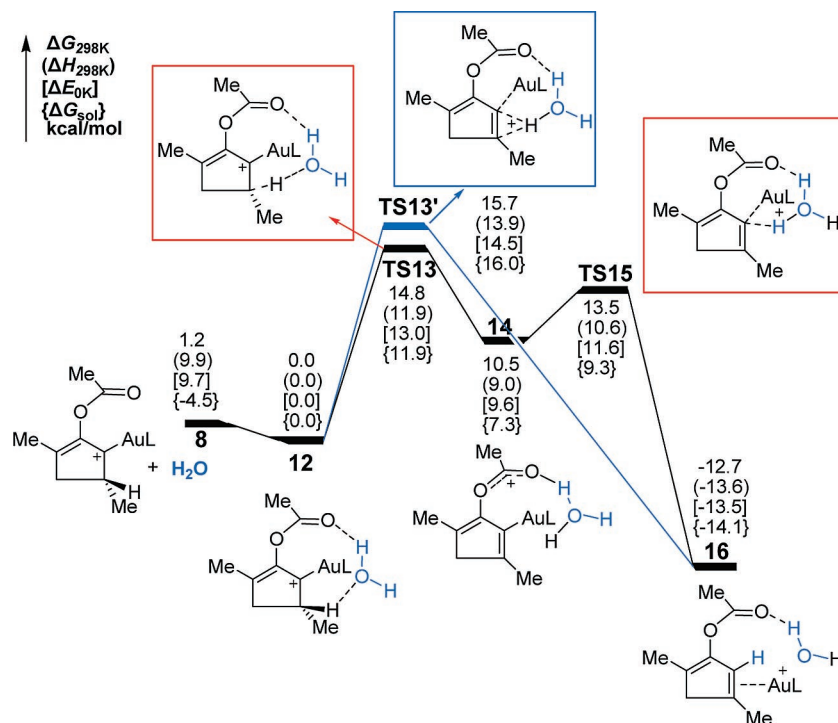
Scheme 5

Figure 3. DFT computed energy surface for the water-catalyzed proton transfer and water-assisted hydride shift processes.

transition structure **TS13**, the H7 atom connected with C5 is transferred to water's oxygen atom, and concurrently, water's hydrogen atom H8 is also transferred to the oxygen atom of the acetoxy group. The net result of this one-step two-proton-transfer process is to generate intermediate **14**. This step includes the breakage of two bonds and the formation of two new bonds, as reflected by the bond lengths of H7−C5 (2.36 Å), H8−O3 (1.39 Å), H7−O3 (0.99 Å), and H8−O2 (1.09 Å) in **14**. In the transformation of **12** to **14**, the acetoxy group acts as a proton acceptor, and the water molecule acts as a proton shuttle that transports a proton from C5 to O2. The strategy adopted in the deprotonation and protonation reactions is proton-transport catalysis, which is very similar to that used in some enzymatic reactions involving general acid/general base catalysis.[12−15]

The following protonation step from **14** to **16** via proton-relay transition state **TS15** also adopts an enzymatic proton-transport strategy. In **TS15**, the protonated acetoxy group acts as a general acid catalyst to transfer a proton to the water molecule. Simultaneously, the water molecule acting as a proton shuttle donates a proton to protonate the C4 atom.

Calculations indicate that the present proton-transport catalysis involving deprotonation/protonation is easy in the gas phase with activation free energies of 14.8 and 3.0 kcal/mol, respectively. Both steps are easier than the direct [1,2]-hydride shift process in anhydrous solvent. In solution calculations by CPCM, intermediate **8** and water are stabilized by the solvent CH_2Cl_2 more than their complex **12** by 4.5 kcal/mol, suggesting that the activation free energy for the water-catalyzed deprotonation/protonation is 16.4 kcal/mol (from **8** + H_2O to **TS13**). This indicates that the water-catalyzed [1,2]-hydrogen shift is also rate-limiting. As compared to the activation energy of 19.7 kcal/mol required in dry CH_2Cl_2, the tandem reaction in wet CH_2Cl_2 is much easier.

There is another possibility that water can directly assist the [1,2]-hydride shift.[33] Calculations indicate that such a process via **TS13′** directly gives complex **16**. **TS13′** is also stabilized by hydrogen bonding with water. This one-step water-assisted [1,2]-hydride shift requires an activation free energy of 15.7 kcal/mol, which is only 0.9 kcal/mol higher than the two-step water-catalyzed deprotonation/protonation process in the gas phase. However, in CH_2Cl_2 solution, the one-step water-assisted [1,2]-hydride is disfavored in terms of activation energy by 4.1 kcal/mol as compared to the water-catalyzed [1,2]-hydrogen shift processes, suggesting that in solution, water catalyzes the hydrogen shift through the two-step deprotonation/protonation proton-transport catalysis mechanism instead of **TS13′**.

After uncovering the origin of rate acceleration of the tandem reaction in wet CH_2Cl_2, we then turned our attention to explain

(29) (a) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed.* **1969**, *8*, 781. (b) For discussions of ring-closure reactions of 4-π systems, see: Dolbier, W. R., Jr.; Koroniak, H.; Houk, K. N.; Sheu, C. *Acc. Chem. Res.* **1996**, *29*, 471.

(30) (a) Cavalli, A.; Masetti, M.; Recanatini, M.; Prandi, C.; Guarna, A.; Occhiato, E. G. *Chem.—Eur. J.* **2006**, *12*, 2836. For early theoretical studies of Nazarov reaction, see: (b) Smith, D. A.; Ulmer, C. W. *Tetrahedron Lett.* **1991**, *32*, 725. (c) Smith, D. A.; Ulmer, C. W. *J. Org. Chem.* **1991**, *56*, 4444. (d) Smith, D. A.; Ulmer, C. W. *J. Org. Chem.* **1993**, *58*, 4118.

(31) Topological analysis of the electron densities at the bond critical points indicates that their electron densities and Laplacian are within the proper range required for hydrogen bonds (see details in the Supporting Information).

(32) For experimental and computational discussions on the C−H···O interactions, see: (a) Washington, I.; Houk, K. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 4485. (b) Raymo, F. M.; Bartberger, M. D.; Houk, K. N.; Stoddard, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 9264. (c) Arbely, E.; Arkin, I. T. *J. Am. Chem. Soc.* **2004**, *126*, 5362. (d) Matsuura, H.; Yoshida, H.; Hieda, M.; Yamanaka, S.-y.; Harada, T.; Shin-ya, K.; Ohno, K. *J. Am. Chem. Soc.* **2003**, *125*, 13910. (e) Vargas, R.; Garza, J.; Dixon, D. A.; Hay, B. P. *J. Am. Chem. Soc.* **2000**, *122*, 4750. (f) Scheiner, S.; Kar, T.; Gu, Y. *J. Biol. Chem.* **2001**, *276*, 9832.

(33) We also calculated the reaction mechanism in which the water molecules first carry out an autoionization process proposed in Scheme 2. Then, one hydrogen atom in the hydronium shifts to the C4 atom (see **8** in Figure 2 for atom labeling). Finally, the H7 atom is abstracted by water. The free energy needed for a H shift at room temperature is more than 30 kcal/mol, indicating that this reaction path is not favorable. For the discussion of autoionization process, see: Zhang, X.; Houk, K. N. *J. Org. Chem.* **2005**, *70*, 9712.
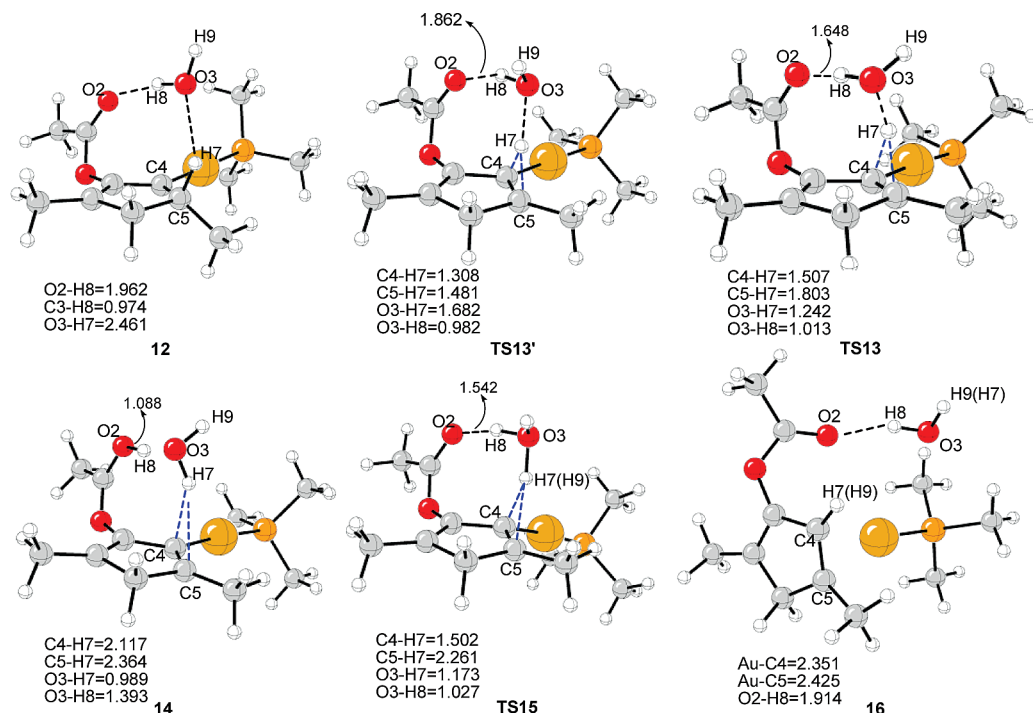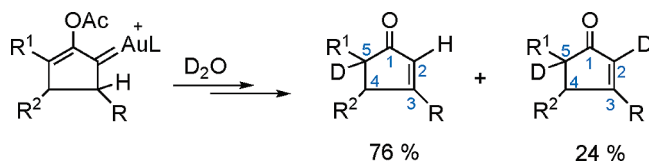
(28) The intermediate **6** has been re-optimized in CH_2Cl_2, and the resulting structures are similar to the one optimized in the gas phase.

Figure 4. DFT optimized structures for the water-catalyzed proton transfer and water-assisted hydride shift processes (distances in Å).

Scheme 6

the experimentally observed deuterium incorporation (Scheme 6).[8,34] The deuterium incorporation must come from the water-catalyzed proton-transport catalysis strategy. In the water-catalyzed proton-transport catalysis process, the incorporated atoms in the 2-position of the final cyclic enones can be either from the original hydrogen atoms of the substrates or from the water molecules. This can be understood by examining the intermediate **14**. In the water-catalyzed deprotonation/protonation process, the shifting H7 atom in **14** together with an original H atom (i.e., H9) gives a new water molecule H7−O3−H9 (see Figure 4). H7 and H9 can readily rotate along the H8−O3 axis. Therefore, the abstracted H7 atom from the original substrate and the H9 atom from the water catalyst can both be incorporated in the 2-position of the final cyclic enones. This means that, when the tandem reaction was run in CH_2Cl_2 saturated with D_2O, the 2-position of the final enones could be either hydrogen (from H7 of the original substrate) or deuterium (from the D_2O catalyst). In the D_2O-catalyzed process shown in Scheme 6, we thought that incorporation of hydrogen was preferred over deuterium. This is attributed to factors such as the kinetic isotopic effect of hydrogen versus deuterium, together with the possibility that incorporation of deuterium will require additional energy to break the hydrogen bond network of external D_2O molecules in intermediate **14**.[8,35−36]

It was thought that water molecules could form clusters in the reaction system and that water could act as a reactive

medium by supplying the protons via a hydrogen bond network.[37] Therefore, the [1,2]-hydrogen shift could also be catalyzed by a water cluster instead of a single water molecule to those substrates with water molecules in their neighborhood. It was found that a three-water cluster can be efficiently used to simulate how water clusters affect organometallic reactions.[37b] Therefore, we investigated the [1,2]-hydrogen shift catalyzed by a three-water cluster, and the computed potential energy surface is shown in Figure 5.[38] The three-water cluster-catalyzed [1,2]-hydrogen shift also involves deprotonation and protonation, and the acetoxy group is very critical to support the hydrogen network in these processes. In the gas phase, the three-water cluster is more efficient in catalyzing the [1,2]-hydrogen shift than a single water molecule (activation free energies of 4.8 and 14.8 kcal/mol, respectively). However, in solution, the computed activation free energy is 13.0 cal/mol (from **8** + $(H_2O)_3$ to **TS18**). This suggests that in this case, the rate-limiting step of the tandem reaction of enynyl acetates is still a water-catalyzed [1,2]-hydrogen shift via **TS18** since the Au(I)-catalyzed [3,3]-rearrangement or the Nazarov step has an

(34) In experiment, the cyclopentadienyl acetates were not isolated. The finally isolated cyclopentenones have deuterium incorporation of about 100% at its 5-position and 24% at its 2-position.[8]

(35) If the direct [1,2]-hydride shift in the tandem reaction is very difficult with a high activation barrier, and the tandem reaction cannot be achieved at room temperature, all the tandem reactions in wet solution must occur through the water-catalyzed [1,2]-proton shift pathway exclusively.[36] In the present Au(I)-catalyzed tandem reaction of enynyl acetates in wet CH_2-Cl_2, the direct [1,2]-hydride shift could act as a background reaction to compete with the water-catalyzed [1,2]-proton shift process since the [1,2]-hydride shift in dry solution is not difficult. This also means that the background [1,2]-hydride shift could compete with the deuterium incorporation shown in Scheme 6.

(36) In the Lu (3 + 2) cycloaddition between allenoates and activated alkenes catalyzed by P(Ph)₃, the direct [1,2]-hydrogen shift has a computed activation energy of about 40 kcal/mol. Because of this, the direct [1,2]-hydrogen shift does not occur. Instead, a water-catalyzed [1,2]-hydrogen shift takes place exclusively. For details, see: Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 3470.

(37) (a) Chu, H. S.; Xu, Z.; Ng, S. M.; Lau, C. P.; Lin, Z. *Eur. J. Inorg. Chem.* **2000**, 993. (b) Kovács, G.; Schubert, G.; Joó, F.; Pápai, I. *Organometallics* **2005**, *24*, 3059.

(38) When a three-water cluster acts as a catalyst, no direct [1,2]-H shift transition structure (similar to **TS13′**) can be located.
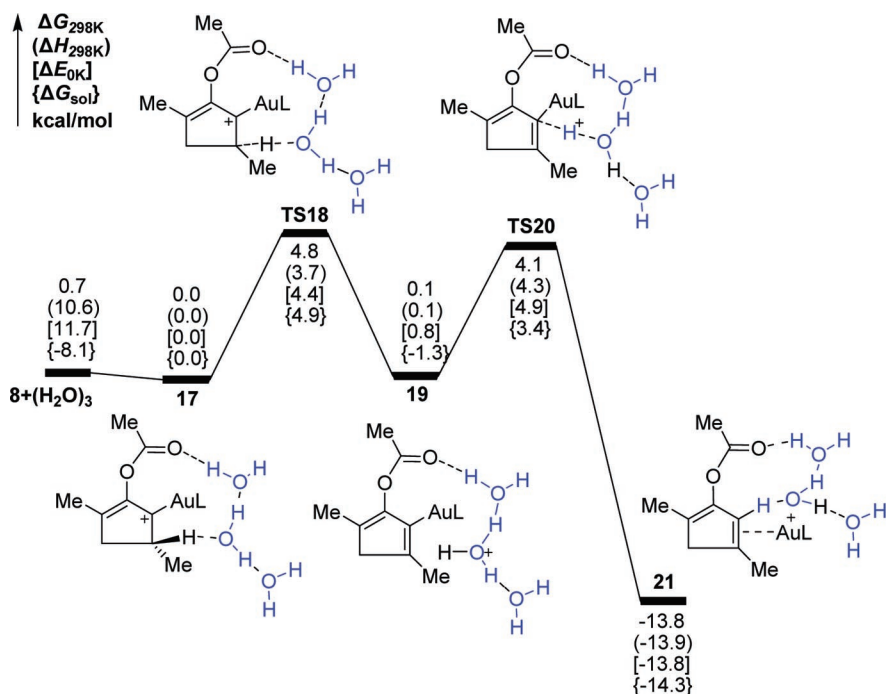
Figure 5. DFT computed energy surface for the [1,2]-hydrogen shift process catalyzed by a three-water cluster (L = PMe₃).
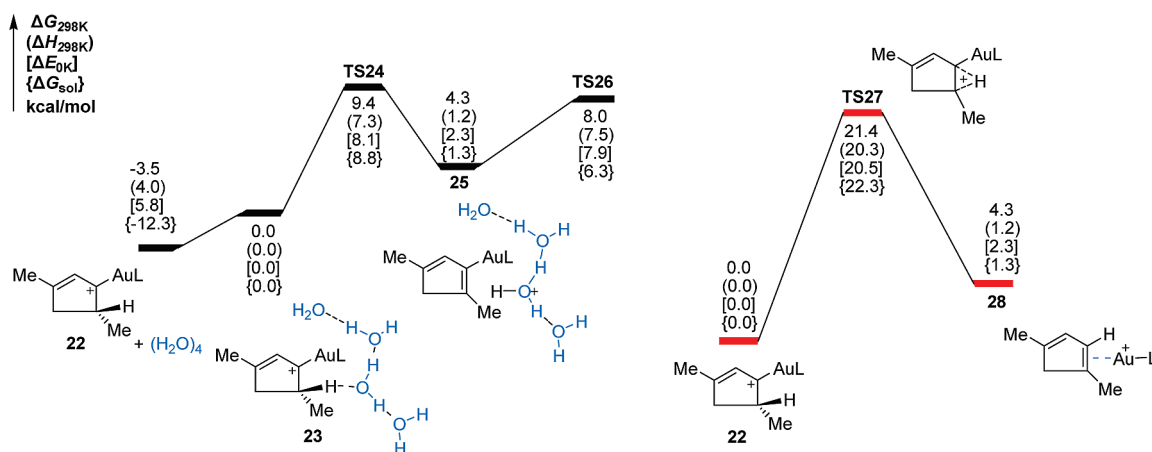

Figure 6. DFT computed energy surfaces for the four-water cluster-catalyzed [1,2]-proton transfer and direct [1,2]-hydride shift of **22** without an acetoxy group as the proton-relay stabilizer (L = PH₃).

activation energy of less than 10 kcal/mol (see Supporting Information). Therefore, the tandem reaction in wet solution is faster than in dry solution. Deuterium incorporation in Scheme 6 can also be explained in a similar way as that discussed for the one-water-catalyzed tandem reaction.

In the previous deprotonation and protonation processes, the acetoxy group is very important for rate acceleration. In the one-water-catalyzed [1,2]-hydrogen shift case, the acetoxy group acts as a proton acceptor that accepts a proton in the deprotonation step and donates a proton in the protonation step. Water acts as a proton shuttle in both processes. In the water cluster-catalyzed [1,2]-hydrogen shift case, the acetoxy group is also critical to support the proton relay for the deprotonation/ protonation. The water cluster acts as a proton shuttle in both deprotonation and protonation processes. The importance of the acetoxy group in the previous enzyme-like proton-transport catalysis is further manifested. Without the acetoxy group, no single water-catalyzed proton-transport catalysis process could be found by calculations. But, a water cluster can still facilitate

a [1,2]-hydrogen shift for a substrate without an acetoxy group, as indicated by the [1,2]-hydrogen shift of **22**, which does not have an acetoxy group for a hydrogen bonding interaction with solvent (Figure 6). The four-water cluster-catalyzed [1,2]-proton shift has an activation free energy of 21.1 kcal/mol in solution, 1.2 kcal/mol lower than the direct [1,2]-hydride shift via **TS27**. It is well-known that the activation entropy is overestimated for bi- and tri-molecular reactions.[39] Therefore, the water cluster-catalyzed [1,2]-proton shift shown in Figure 6 should be much faster than the direct [1,2]-hydride shift. Apparently, the water cluster-catalyzed [1,2]-proton shift for **22** has an activation free energy dramatically higher than the water-catalyzed proton shift of **8** shown in Figure 5 (21.1 vs 13.0 kcal/mol), indicating that

(39) For discussions of entropy overestimation in bimolecular reactions in aqueous solution, see: (a) Strajbl, M.; Sham, Y. Y.; Villa, J.; Chu, Z.-T.; Warshel, A. *J. Phys. Chem. B* **2000**, *104*, 4578. (b) Hermans, J.; Wang, L. *J. Am. Chem. Soc.* **1997**, *119*, 2707. (c) Amzel, L. M. *Proteins* **1997**, *28*, 144. (d) Yu, Z.-X.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 13825. (e) Chen, Y.; Ye, S.; Jiao, L.; Liang, Y.; Sinha-Mahapatra, D. K.; Herndon, J. W.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 10773.

the presence of an acetoxy group can dramatically assist water cluster-catalyzed [1,2]-hydrogen shift. On the basis of the theoretical insights shown in Figure 3, we conjectured that the reactions shown in Scheme 3 would have a marginal rate acceleration in water unless there is an acetoxy group or a carbonyl group that acts as a proton acceptor or a proton-relay stabilizer in these reaction substrates. We predicted that the acetoxy group could also be replaced by other groups (such as a CF_3 group) that can form hydrogen bond(s) with water. Calculations predict that the CF_3 group can also facilitate the [1,2]-hydrogen shift reaction with a high efficiency via the same proton-transport catalysis mechanism (only 2.8 kcal/mol in the gas phase is required to overcome the energy barrier of deprotonation, see Supporting Information for details).

In summary, the overall potential energy surface in the gas phase and dry solution shows that hydrogen abstraction is the rate-limiting step of the tandem reaction. In wet CH_2Cl_2, the [1,2]-hydride shift in dry solution is turned into a two-step water-catalyzed proton-transfer process with an activation free energy of 16.4 kcal/mol. This two-step water-catalyzed proton-transfer mechanism adopts a proton-transport catalysis strategy, in which the acetoxy group plays a critical role as either a proton acceptor or a proton-relay stabilizer and water acts as a proton shuttle. This mechanism can also explain the observed deuterium incorporation experiment shown in Scheme 6.

4. Conclusion

The mechanisms of the tandem Au(I)-catalyzed [3,3]-rearrangement/Nazarov reaction/[1,2]-hydrogen shift of enynyl acetates have been computationally addressed using DFT (B3LYP/6-31G*, SDD for Au). Calculations indicate that the [3,3]-rearrangement is a two-step process with activation free energies below 10 kcal/mol. Subsequent Nazarov cyclization only requires an activation free energy of 5.5 kcal/mol in the gas phase. The [1,2]-hydride shift process is the final step of the catalytic cycle and is the rate-limiting step with activation free energies of 19.7 and 20.2 kcal/mol in the gas phase and CH_2Cl_2 solution, respectively. In the wet CH_2Cl_2 solution, the

[1,2]-hydride step of the tandem reaction in dry solution is turned into a proton-transport catalysis strategy involving a two-step water-catalyzed deprotonation/protonation process. The water-catalyzed [1,2]-hydrogen shift is very efficient with activation free energies of 16.4 kcal/mol (with one water as the catalyst) and 13.0 kcal/mol (with a three-water cluster as the catalyst). Because of this, the tandem reaction in the wet CH_2Cl_2 solution is faster than that in the dry CH_2Cl_2 solution. Calculations indicate that in the present proton-transport catalysis, the acetoxy group plays a critical role as either a proton acceptor or a proton-relay stabilizer, and water acts as a proton shuttle. The theoretical insights presented in the present work are expected to help us understand other transition metal-catalyzed reactions involving hydrogen shift steps,[11] predict whether those transition metal-catalyzed reactions involving hydrogen shift steps can be facilitated or not when they are operated in water, and rationalize and design other new in water reactions.[5,11,40]

Supporting Information Available: Energies and Cartesian coordinates of all stationary points, discussions of ligand effects and computational methods, and full citation of computational methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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(40) Water-catalyzed [1,2]-hydrogen shift reactions could also occur in organocatalytic reactions. For recent examples, see: (a) ref 36. (b) Li, J.; Brill, T. B. *J. Phys. Chem. A* **2003**, *107*, 5993. (c) Chou, P.-T.; Yu, W.-S.; Wei, C.-Y.; Cheng, Y.-M.; Yang, C.-Y. *J. Am. Chem. Soc.* **2001**, *123*, 3599.