

# Synergistic Effects between Lewis and Brønsted Acids: Application to the Prins Cyclization

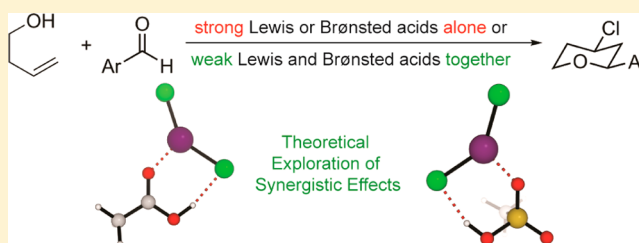
Martin Breugst,<sup>\*,†</sup> René Grée,<sup>‡</sup> and K. N. Houk<sup>\*,†</sup>

<sup>†</sup>Department of Chemistry and Biochemistry, University of California, Los Angeles, 607 Charles E. Young Drive East, Los Angeles, California 90095-1569, United States

<sup>‡</sup>Institut des Sciences Chimiques de Rennes UMR CNRS 6226, Université de Rennes 1, Avenue du Général Leclerc, 35042 Rennes Cedex, France

**S** Supporting Information

**ABSTRACT:** Brønsted and Lewis acids can catalyze the Prins cyclization, an efficient method for the synthesis of tetrahydropyrans from homoallylic alcohols and carbonyl compounds. Synergistic effects between weak Brønsted and Lewis acids in these reactions have been analyzed by density functional theory [M06-L/def2-QZVP/IEFPCM(CH<sub>2</sub>Cl<sub>2</sub>)/M06-L/6-311+G(2df,2p)]. In order to characterize the reactivities of the employed Lewis acids, methyl anion and hydroxide affinities were determined. On the basis of our calculations, we found that the coordination of Lewis acids to carboxylic and sulfonic acids results in a significant increase in the Brønsted acidities of the latter.

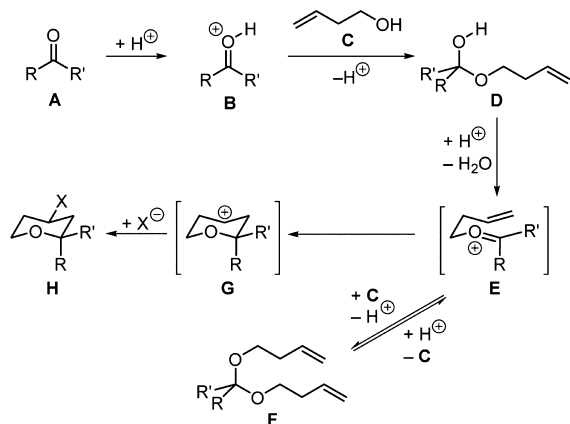


## INTRODUCTION

The acid-catalyzed addition of olefins to aldehydes, the Prins reaction,<sup>1</sup> is a powerful method for the formation of C–C bonds and can be employed for the synthesis of many natural products.<sup>2</sup> While the combination of olefins and aldehydes typically results in diols or allyl alcohols, Hanschke reported on the formation of tetrahydropyrans from 3-buten-1-ol and a variety of aldehydes and ketones **A** (Scheme 1).<sup>3</sup> It has been demonstrated that either strong Brønsted acids or strong Lewis acids can be employed as effective catalysts for the Prins cyclization.<sup>2a,c</sup> A strong Lewis acid such as SiMe<sub>3</sub>Cl, TiCl<sub>4</sub>, or InCl<sub>3</sub> can replace the Brønsted acid H<sup>+</sup> in Scheme 1 and

coordinate to the carbonyl group of **A**. Both Brønsted and Lewis acids lead to increased electrophilicity of the carbonyl (in **B**) and facilitate the subsequent attack of the alcohol **C** yielding the hemiacetal **D**. After elimination of water, the intermediate oxacarbenium ion **E** undergoes a 6-*endo-trig* cyclization to form a tetrahydropyranyl cation **G** that can easily be trapped by a nucleophile to give the experimentally isolated tetrahydropyran **H**. Different nucleophiles X<sup>−</sup> (e.g., halides, arenes, nitriles) have successfully been employed for the final transformation of **G** to **H**.<sup>4</sup> Both inter- and intramolecular modes of nucleophilic trapping have been explored in synthesis.<sup>2,4</sup> It has recently been shown that the acetal **F** can be formed as an intermediate under the reaction conditions as well and can be transformed to the tetrahydropyran **H** in the presence of weak Lewis acids.<sup>5</sup>

**Scheme 1. Mechanism of the Acid-Catalyzed Prins Cyclization Reaction**

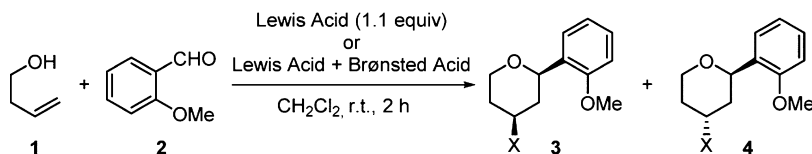


It has also been shown that strong Lewis acids (e.g., TiCl<sub>4</sub>, SiMe<sub>3</sub>Cl, InCl<sub>3</sub>) are able to catalyze the Prins cyclization of but-3-en-1-ol (**1**) and 2-methoxybenzaldehyde (**2**) (Scheme 2), while neither weak Lewis acids (e.g., LiCl, MgBr<sub>2</sub>) nor weak Brønsted acids (acetic acid, benzoic acid, *p*-toluenesulfonic acid) cause this transformation.<sup>5</sup> Surprisingly, a combination of weak Lewis acids (e.g., MgBr<sub>2</sub>) and weak Brønsted acids (e.g., *p*-toluenesulfonic acid) also resulted in efficient cyclization reactions with moderate to excellent yields (Scheme 2).<sup>5</sup> Following the seminal studies by Olah and others on superacids,<sup>6</sup> it has been proposed that the synergistic effects between weak Lewis acids and weak Brønsted acids might arise from an acidity increase of the latter by coordination of the Lewis acid.<sup>5</sup>

Received: July 26, 2013

Published: August 28, 2013

Scheme 2. Synergistic Effects between Weak Lewis and Brønsted Acids in Prins Cyclizations (from Ref 5)



Lewis Acid	Yield / %
TiCl <sub>4</sub> <sup>a</sup>	88
ZnCl <sub>2</sub>	25
MgBr <sub>2</sub>	–
MgBr <sub>2</sub> + HOAc	55
MgBr <sub>2</sub> + <i>p</i> TsOH	94

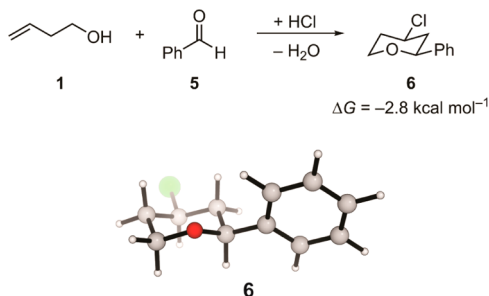
<sup>a</sup>: at –40 °C

In order to test this hypothesis, we examined the energetics of the acid-catalyzed Prins reaction and quantified the acidity change upon coordination of the Lewis acid by means of density functional theory. We now report on the calculated acidity changes in both acetic acid and methanesulfonic acids as model Brønsted acids and discuss how these affect the energy profile.

## RESULTS AND DISCUSSION

**Brønsted-Acid-Catalyzed Prins Cyclization.** We first calculated the free energy profile for an acid-catalyzed Prins reaction. These calculations were performed at the M06-L/def2-TZVPP/IEFPCM(CH<sub>2</sub>Cl<sub>2</sub>)//M06-L/6-31+G(d,p)/IEFPCM(CH<sub>2</sub>Cl<sub>2</sub>) level. We employed the slightly truncated model system in Scheme 3. The overall reaction leading to the experimentally preferred stereoisomer **6** was calculated to be slightly exergonic by 2.8 kcal mol<sup>–1</sup>.

Scheme 3. Model Prins Reaction Studied Computationally, Calculated Product Structure, and Reaction Free Energy [M06-L/def2TZVPP/IEFPCM(CH<sub>2</sub>Cl<sub>2</sub>)//M06-L/6-31+G(d,p)/IEFPCM(CH<sub>2</sub>Cl<sub>2</sub>)]



As the accurate computational description of proton transfer reactions in dichloromethane solution as well as the acetal formation is often problematic because of direct solvent participation, we did not attempt to calculate transition states for the acetal formation. From previous experiments in protic solvents, the formation of the (hemi)acetal can be estimated to occur with activation free energies of ca. 20 kcal mol<sup>–1</sup>.<sup>7</sup> Additionally, we base the discussion of the acid-catalyzed mechanism in Figure 1 on the protonated aldehyde **5–H<sup>+</sup>** and include only positively charged species in the free energy profile for reasons of simplicity.

The protonated benzaldehyde (**5–H<sup>+</sup>**) and but-3-en-1-ol (**1**) form oxacarbenium ion **7** in a slightly exergonic reaction

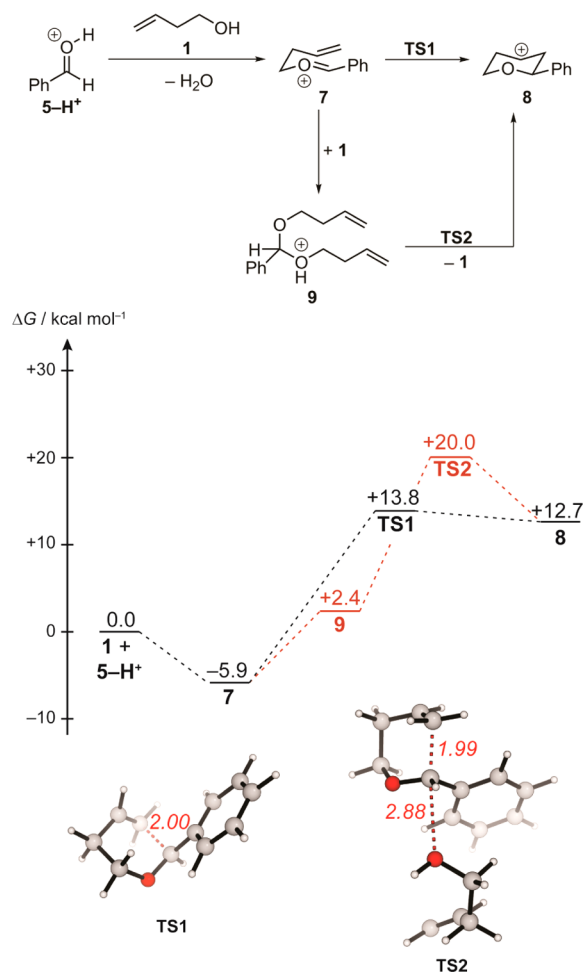
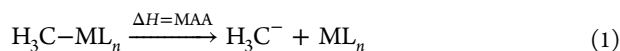


Figure 1. Calculated Gibbs free energy profile [M06-L/def2-TZVPP/IEFPCM(CH<sub>2</sub>Cl<sub>2</sub>)//M06-L/6-31+G(d,p)/IEFPCM(CH<sub>2</sub>Cl<sub>2</sub>)] for the formation of the tetrahydropyran cation **8** from the protonated aldehyde **5–H<sup>+</sup>** and homoallyl alcohol **1**.

(Figure 1). The subsequent cyclization reaction occurs through transition state **TS1** ( $\Delta G^\ddagger = 13.8$  kcal mol<sup>–1</sup>) and yields the thermodynamically less stable tetrahydropyran cation **8** ( $\Delta G = 12.7$  kcal mol<sup>–1</sup>). These calculations are in perfect agreement with previous computational data [B3LYP/6-31G(d)] by Alder and co-workers on a smaller model system.<sup>8</sup> Carbocation **8** is subsequently trapped by a chloride ion, yielding the experimentally observed major stereoisomer **6** (Scheme 1) in a highly exothermic charge recombination reaction.

As acetals are obtained as side products in these reactions and can be transformed to the final Prins product under the reaction conditions, we also analyzed a direct  $S_N2$ -like intramolecular displacement of protonated acetal **9** to give carbocation **8**. The transition state for that transformation was found to be 6.2 kcal mol<sup>-1</sup> less favorable than **TS1** (red pathway in Figure 1). Therefore, the isolated acetals should be formed reversibly and undergo dissociation to form oxocarbenium ion **7** prior to product formation.

As most of the steps in Figure 1 are acid-catalyzed, we subsequently analyzed whether the combination of weak Brønsted and Lewis acids leads to an increase in Brønsted acidity. For that purpose, we first characterized the experimentally employed Lewis acids according to their reactivities. Lewis acids are typically divided into different classes according to their reactivity toward a nucleophile.<sup>9</sup> However, not all of the Lewis acids employed in the experimental investigation have previously been studied under the same conditions. Therefore, we first calculated their reactivities toward carbanions [methyl anion affinities (MAAs), eq 1] and alkoxides [hydroxide affinities (HAs), eq 2]. These reactions were chosen for their computational simplicity to quantify the Lewis acidities of these acids. The results are shown in Table 1.



**Table 1.** Calculated Methyl Anion Affinities (MAAs, eq 1) and Hydroxide Affinities (HAs, eq 2) for Different Lewis Acids [in kcal mol<sup>-1</sup>; M06-L/def2-QZVP/IEFPCM (CH<sub>2</sub>Cl<sub>2</sub>)/M06-L/6-311+G(2df,2p) Using the SDD Pseudopotential for Sn and In]

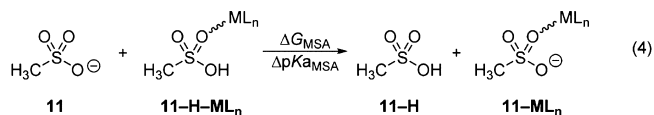
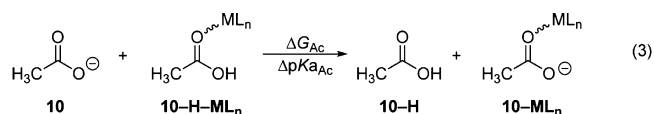
Lewis acid	MAA	HA
LiCl	19.6	25.7
LiBr	20.6	26.6
MgCl <sub>2</sub>	47.3	50.0
MgBr <sub>2</sub>	50.0	52.4
Me <sub>3</sub> Si	55.7	47.7
TiCl <sub>4</sub>	58.7	66.5
ZnCl <sub>2</sub>	61.3	47.1
ZnBr <sub>2</sub>	61.5	46.7
NiBr <sub>2</sub>	69.7	57.2
NiCl <sub>2</sub>	70.3	57.6
SnCl <sub>2</sub>	74.4	64.4
SnCl <sub>4</sub>	85.2	63.5
InBr <sub>3</sub>	88.6	76.1
InCl <sub>3</sub>	91.2	78.8
FeCl <sub>3</sub>	95.7	66.2

The MAAs for different Lewis acids were found to fall in a large range between 20 (LiCl) and 95 kcal mol<sup>-1</sup> (FeCl<sub>3</sub>), and the HAs range from 25 to 80 kcal mol<sup>-1</sup>. Exchanging the counterion from chloride to bromide has only a little influence on the calculated affinities (<2.7 kcal mol<sup>-1</sup>). In general, there is no correlation between the affinity toward carbon (MAA) and that toward oxygen (HA). TiCl<sub>4</sub>, which is 10th in carbon basicity, has the third highest affinity toward oxygen, while FeCl<sub>3</sub> displays a much higher carbon affinity in comparison with its affinity toward oxygen. On the basis of an analysis of

Table 1, compounds with small carbon affinities (Li, Mg, and Ti salts) have considerably larger affinities for oxygen, whereas compounds with high carbon affinities prefer reactions with the carbon Lewis base over the oxygen Lewis base.

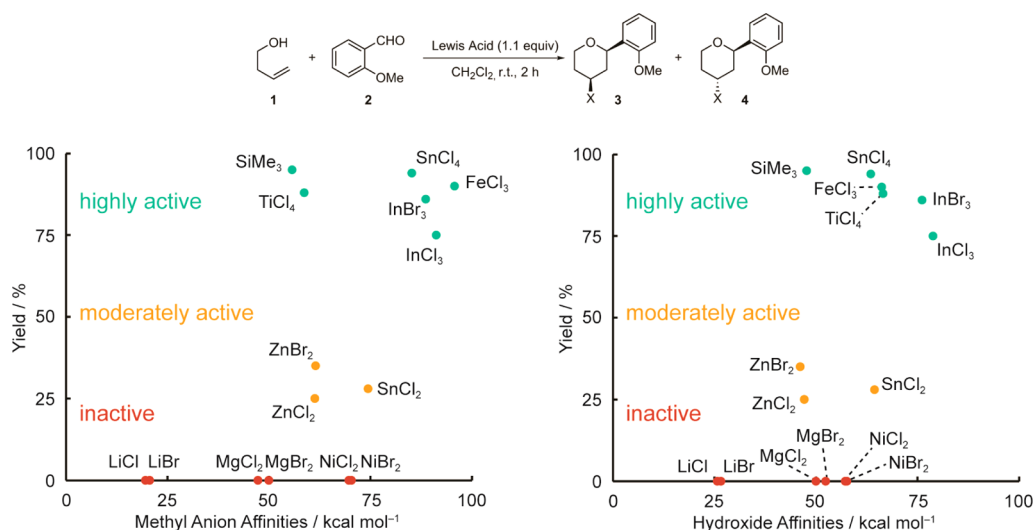
As shown in Figure 2, there is no simple correlation between the isolated yields in Prins cyclizations and the calculated MAAs or HAs. However, with a few exceptions (e.g., the low yields observed for the Ni salt series), our calculations predict the same qualitative ranking of Lewis acidities as previously determined experimentally for the Prins reaction.<sup>5</sup> Lithium and magnesium salts (less reactive Lewis acids in the Prins cyclization) display smaller MAAs and HAs than moderately reactive Lewis acids (Zn salts, SnCl<sub>2</sub>) or highly reactive Lewis acids, in which the metal displays a high valence number (InCl<sub>3</sub>, InBr<sub>3</sub>, FeCl<sub>3</sub>). Our predictions are also in line with previously reported activities in benzylation reactions. Among the Lewis acids under investigation in this study, Olah and co-workers classified InCl<sub>3</sub> and FeCl<sub>3</sub> as moderately active, SnCl<sub>4</sub> and TiCl<sub>4</sub> as weakly active, and MgBr<sub>2</sub> as inactive,<sup>9a</sup> which also corresponds to the calculated MAAs.

In order to analyze the influence of coordination of a Lewis acid on the Brønsted acidity, we chose acetic acid (**10-H**) and methanesulfonic acid (**11-H**) as model systems for the carboxylic and sulfonic acids employed in the experimental studies. We further chose the isodesmic proton transfer reactions (eqs 3 and 4) for this purpose, since the calculation of absolute acidities is difficult. The similar structures of the reactants and the products in eqs 3 and 4 reduce further errors. While all of the experimentally employed Lewis acids were tested for acetic acid (**10-H**), only the weaker Lewis acids were considered for the methanesulfonic acid (**11-H**) for comparisons.

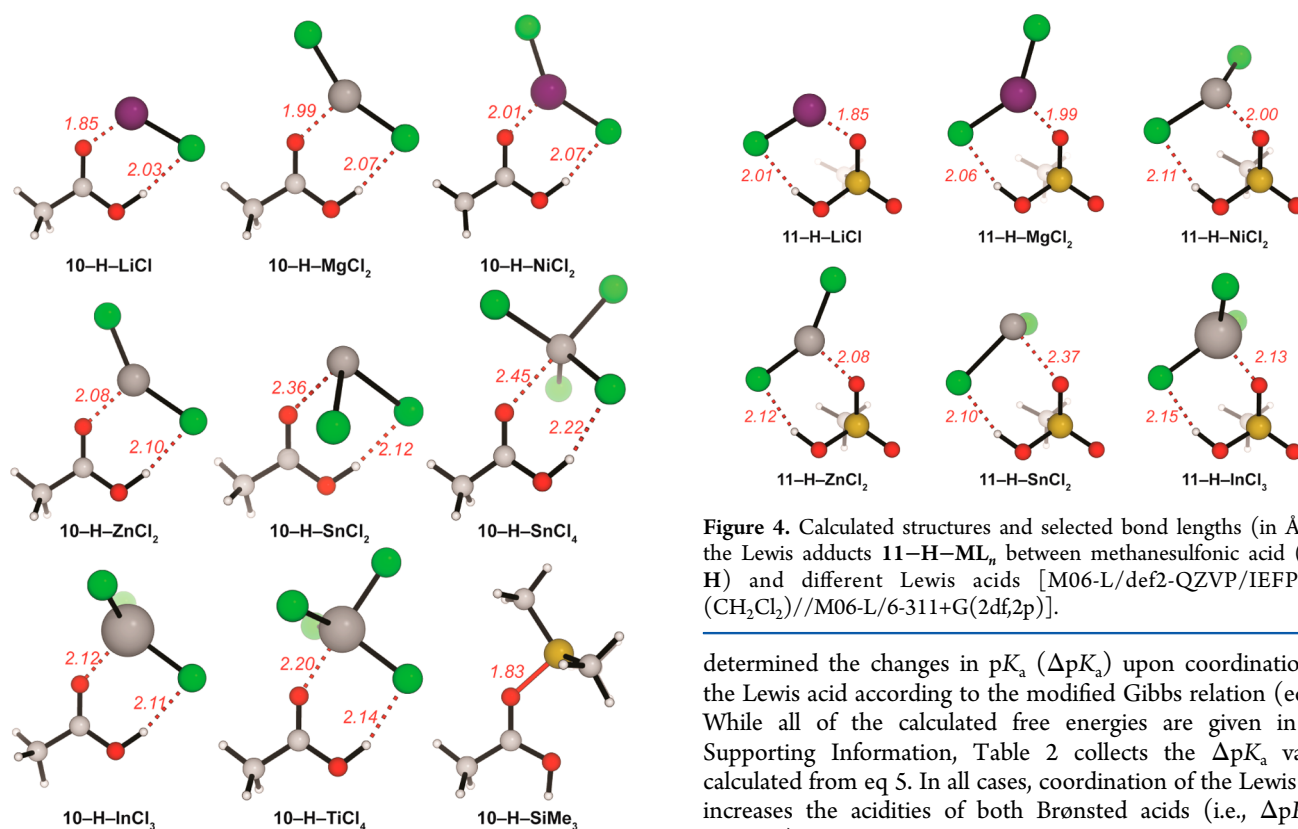


The Lewis adducts **10-H-ML<sub>n</sub>** of acetic acid (**10-H**) and the different Lewis acids ML<sub>n</sub> (Figure 3) adopt *cis-cis* configurations (with respect to the M-O-C-O and the O-C-O-H dihedrals) to minimize steric repulsions. An additional O-H...Cl interaction further stabilizes the Lewis adducts in these conformations. The extent of stabilization through hydrogen bonding could vary, as it is known that the strength of these interactions strongly depends on the solvent.<sup>10</sup> While the oxygen-(transition-)metal bond length strongly depends on the Lewis acid, the hydrogen bond length changes only to a smaller extent (2.03–2.22 Å). The trimethylsilylated acetic acid, which cannot profit from a hydrogen bond, prefers the *trans-cis* conformation over the *cis-cis* conformation (ΔG = 2.6 kcal mol<sup>-1</sup>) because of the higher steric demand of the bulkier trimethylsilyl substituent.

The corresponding adducts from methanesulfonic acid (**11-H**) and the different Lewis acids are depicted in Figure 4. In all cases, coordination to only one sulfinyl group was preferred over coordination to two sulfinyl groups because of the additional O-H...Cl interactions present in the former. Our



**Figure 2.** Plots of the experimentally isolated yields versus the calculated methyl anion and hydroxide affinities of different Lewis acids [M06-L/def2-QZVP/IEFPCM(CH<sub>2</sub>Cl<sub>2</sub>)/M06-L/6-311+G(2df,2p) using the SDD pseudopotential for Sn and In].



**Figure 3.** Calculated structures and selected bond lengths (in Å) for the Lewis adducts **10-H-ML<sub>n</sub>** between acetic acid (**10-H**) and different Lewis acids [M06-L/def2-QZVP/IEFPCM(CH<sub>2</sub>Cl<sub>2</sub>)/M06-L/6-311+G(2df,2p) using the SDD pseudopotential for Sn and In].

calculations predicted almost identical bond lengths between the oxygen atoms and the (transition) metals for both Brønsted acids (Figures 3 and 4). In contrast, slightly longer oxygen–metal bond lengths (by ca. 0.03 Å) were determined for the metal complexes of the corresponding acetate anion compared with the sulfonate anion (see the Supporting Information).

Next, we calculated the reaction free energies for the isodesmic proton transfer reactions (eqs 3 and 4) and

**Figure 4.** Calculated structures and selected bond lengths (in Å) for the Lewis adducts **11-H-ML<sub>n</sub>** between methanesulfonic acid (**11-H**) and different Lewis acids [M06-L/def2-QZVP/IEFPCM(CH<sub>2</sub>Cl<sub>2</sub>)/M06-L/6-311+G(2df,2p)].

determined the changes in  $pK_a$  ( $\Delta pK_a$ ) upon coordination of the Lewis acid according to the modified Gibbs relation (eq 5). While all of the calculated free energies are given in the Supporting Information, Table 2 collects the  $\Delta pK_a$  values calculated from eq 5. In all cases, coordination of the Lewis acid increases the acidities of both Brønsted acids (i.e.,  $\Delta pK_a$  is negative). While substantial acidity changes were calculated for the adducts of different Lewis acids with acetic acid ( $-35 < \Delta pK_a < -6$  for **10-H**), smaller changes ( $\Delta \Delta pK_a \approx 5$ ) were determined for complexes with the stronger methanesulfonic acid **11-H**. As the acidity changes for eqs 3 and 4 are linearly correlated with each other, similar underlying factors can be assumed for the two Brønsted acids (Figure 5).

$$\Delta G = 2.303RT \Delta pK_a \quad (5)$$

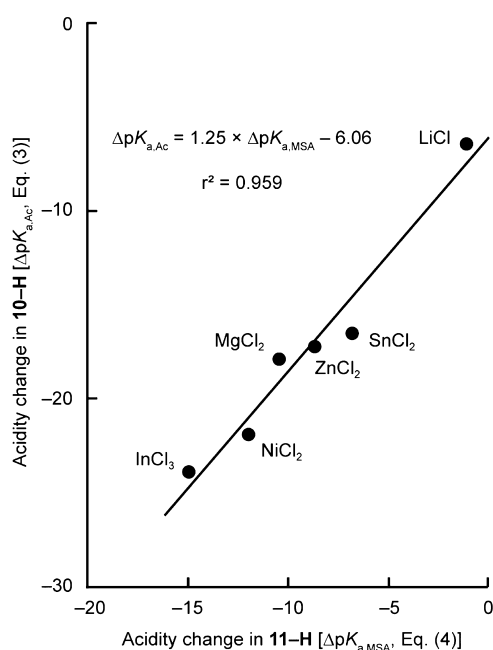
In general, weaker Lewis acids such as LiCl or MgCl<sub>2</sub> resulted in smaller acidity changes than stronger Lewis acids such as SnCl<sub>4</sub> or TiCl<sub>4</sub>. Since the Prins reaction depicted in Scheme 2 depends on the protonation of aldehyde **2** (or the intermediate acetal), an increase in the Brønsted acidity above a



**Table 2.** Calculated Changes in Acidity upon Coordination of Different Lewis Acids to Acetic Acid ( $\Delta pK_{a,Ac}$ ) and Methanesulfonic Acid ( $\Delta pK_{a,MSA}$ ) and Isolated Product Yields [M06-L/def2-QZVP/IEFPCM(CH<sub>2</sub>Cl<sub>2</sub>)/M06-L/6-311+G(2df,2p) Using the SDD Pseudopotential for Sn and In]

Lewis acid	$\Delta pK_{a,Ac}$	$\Delta pK_{a,MSA}$	yield/% (t/h) <sup>a</sup>
LiCl	-6.4	-1.2	30 (0.5); 52 (2)
LiBr	-7.6	-2.4	75 (2)
NiBr <sub>2</sub>	-14.8	-12.4	96 (2)
SnCl <sub>2</sub>	-16.5	-6.8	88 (0.5); 96 (1)
ZnCl <sub>2</sub>	-17.2	-8.7	90 (0.5); 98 (1)
ZnBr <sub>2</sub>	-17.7	-8.7	99 (1)
MgCl <sub>2</sub>	-18.0	-10.4	45 (0.5); 68 (2); 86 (4)
NiCl <sub>2</sub>	-18.1	-12.0	34 (0.5); 64 (2)
MgBr <sub>2</sub>	-19.2	-11.5	94 (0.5); 96 (2)
InBr <sub>3</sub>	-23.8	-14.6	99 (1)
InCl <sub>3</sub>	-23.9	-15.0	95 (0.5); 99 (1)
FeCl <sub>3</sub>	-26.1	-	-
TiCl <sub>4</sub>	-26.4	-	-
SnCl <sub>4</sub>	-28.0	-	-
Me <sub>3</sub> Si	-34.7	-	-

<sup>a</sup>Isolated yields after reaction time *t*.



**Figure 5.** Correlation between the calculated changes in the acidities of acetic acid (10-H) ( $\Delta pK_{a,Ac}$ ) and methanesulfonic acid (11-H) ( $\Delta pK_{a,MSA}$ ) upon coordination of Lewis acids  $MCl_n$  [M06-L/def2-QZVP/IEFPCM(CH<sub>2</sub>Cl<sub>2</sub>)/M06-L/6-311+G(2df,2p)].

certain threshold is required for the reaction to proceed. Both the formation of the (hemi)acetal or the Prins cyclization could be the rate-determining step in these reactions, and both alternatives will be greatly accelerated by Brønsted acids. Therefore, the rate of product formation will depend on the protonation equilibrium, as the rate depends on the concentration of  $5-H^+$ . This is also reflected in the time dependence of the isolated yield in Table 2. While product formation is almost complete after 30 min for strongly activating Lewis acids such as the indium salts, it takes

significantly longer for weaker activating analogues such as the lithium series. On the basis of the information collected in Table 2, even a small acidity increase is obviously enough to sufficiently increase the Brønsted acidities of carboxylic and sulfonic acids to make them suitable catalysts for Prins cyclization reactions.

## CONCLUSIONS

We have analyzed the synergistic effects between weak Brønsted and Lewis acids in Prins cyclizations employing density functional theory [M06-L/def2-QZVP/IEFPCM(CH<sub>2</sub>Cl<sub>2</sub>)/M06-L/6-311+G(2df,2p)]. On the basis of these calculations, we found that combining Lewis acids with carboxylic and sulfonic acids leads to a significant increase in the Brønsted acidities, which facilitates the Prins reaction. We consider that such synergistic effects between Brønsted and Lewis acids could also be effective in other acid-catalyzed reactions.

## COMPUTATIONAL DETAILS

**General.** All of the computations were performed using Gaussian 09.<sup>11</sup> The calculations used tight convergence criteria and an extremely fine grid with 99 radial shells per atom and 974 angular points per shell for numerical integration of the density. Entropic contributions to the reported free energies were calculated from partition functions evaluated using Truhlar's quasiharmonic approximation.<sup>12</sup> This method uses the same approximations as the usual harmonic one except that all vibrational frequencies lower than 100 cm<sup>-1</sup> are set equal to 100 cm<sup>-1</sup>.

**Prins Cyclization.** The conformational space of each intermediate for the Prins cyclization depicted in Figure 1 was explored using the OPLS\_2005 force field<sup>13</sup> and a modified Monte Carlo search routine implemented in MacroModel 9.9.<sup>14</sup> All of the structures were subsequently optimized using the dispersion-corrected M06-L functional<sup>15</sup> with the double- $\zeta$  6-31+G(d,p) basis. Electronic energies were subsequently obtained using the large triple- $\zeta$  def2-TZVPP basis set.<sup>16</sup> Solvation by dichloromethane was taken into account by using the IEFPCM continuum solvation model in all of the calculations.<sup>17</sup>

**Methyl and Hydroxide Affinities and Acidity Changes.** All of the structures were characterized in the gas phase employing the dispersion-corrected M06-L functional<sup>15</sup> with the triple- $\zeta$  6-311+G(2df,2p) basis set and the SDD pseudopotential<sup>18</sup> (for In and Sn) for the optimizations and the thermal corrections. Electronic energies were subsequently obtained using the large quadruple- $\zeta$  def2-QZVP basis set<sup>16</sup> and the SDD pseudopotential<sup>18</sup> (for In and Sn), and solvation by dichloromethane was taken into account by using the IEFPCM continuum solvation model.<sup>17</sup>

## ASSOCIATED CONTENT

### Supporting Information

Cartesian coordinates and energies of all reported structures and details of computational methods. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## AUTHOR INFORMATION

### Corresponding Authors

\*E-mail: mbreugst@chem.ucla.edu.

\*E-mail: houk@chem.ucla.edu.

### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

We are grateful to the Alexander von Humboldt Foundation (Feodor Lynen scholarship to M.B.) and the National Science Foundation (CHE-0548209 to K.N.H.) for financial support of

this research. This work used the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by National Science Foundation Grant OCI-1053575, and resources from the UCLA Institute for Digital Research and Education (IDRE). We thank Professor van der Weghe, Dr. Arne Dieckmann, Dr. B. V. Subba Reddy, and P. Borkar for fruitful discussions.

## REFERENCES

- (1) (a) Prins, H. J. *Chem. Weekbl.* **1919**, *16*, 1510–1526. (b) Prins, H. J. *Chem. Weekbl.* **1919**, *16*, 1072–1073.
- (2) (a) Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, *51*, 505–555. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186. (c) Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. *Tetrahedron* **2010**, *66*, 413–445. (d) Crane, E. A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 8316–8326.
- (3) Hanschke, E. *Chem. Ber.* **1955**, *88*, 1053–1061.
- (4) For selected examples, see: (a) Yadav, J. S.; Reddy, B. V. S.; Ramesh, K.; Kumar, G. G. K. S. N.; Grée, R. *Tetrahedron Lett.* **2010**, *51*, 1578–1581. (b) Reddy, B. V. S.; Borkar, P.; Yadav, J. S.; Sridhar, B.; Grée, R. *J. Org. Chem.* **2011**, *76*, 7677–7690. (c) Reddy, B. V. S.; Ramesh, K.; Ganesh, A. V.; Kumar, G. G. K. S. N.; Yadav, J. S.; Grée, R. *Tetrahedron Lett.* **2011**, *52*, 495–498. (d) Reddy, B. V. S.; Borkar, P.; Yadav, J. S.; Reddy, P. P.; Kunwar, A. C.; Sridhar, B.; Grée, R. *Org. Biomol. Chem.* **2012**, *10*, 1349–1358.
- (5) Borkar, P.; van de Weghe, P.; Reddy, B. V. S.; Yadav, J. S.; Grée, R. *Chem. Commun.* **2012**, *48*, 9316–9318.
- (6) (a) Olah, G. A.; Prakash, G. K. S.; Sommer, J. *Science* **1979**, *206*, 13–20. (b) Kim, D.; Klein, M. L. *J. Phys. Chem. B* **2000**, *104*, 10074–10079. (c) Olah, G. A.; Surya Prakash, G. K.; Molnár, Á.; Sommer, J. *Superacid Chemistry*, 2nd ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2008.
- (7) (a) Davis, T. S.; Feil, P. D.; Kubler, D. G.; Wells, D. J. *J. Org. Chem.* **1975**, *40*, 1478–1482. (b) Daw, G.; Regan, A. C.; Watt, C. I. F.; Wood, E. J. *Phys. Org. Chem.* **2013**, DOI: 10.1002/poc.3138.
- (8) Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4960–4961.
- (9) (a) Olah, G. A.; Kobayashi, S.; Tashiro, M. *J. Am. Chem. Soc.* **1972**, *94*, 7448–7461. (b) Childs, R. F.; Mulholland, D. L.; Nixon, A. *Can. J. Chem.* **1982**, *60*, 809–812. (c) Laszlo, P.; Teston, M. *J. Am. Chem. Soc.* **1990**, *112*, 8750–8754.
- (10) *Hydrogen Bonding in Organic Synthesis*; Pihko, P. M., Ed.; Wiley-VCH: Weinheim, Germany, 2009.
- (11) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*; Gaussian, Inc.: Wallingford CT, 2009.
- (12) Ribeiro, R. F.; Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2011**, *115*, 14556–14562.
- (13) Banks, J. L.; Beard, H. S.; Cao, Y.; Cho, A. E.; Damm, W.; Farid, R.; Felts, A. K.; Halgren, T. A.; Mainz, D. T.; Maple, J. R.; Murphy, R.; Philipp, D. M.; Repasky, M. P.; Zhang, L. Y.; Berne, B. J.; Friesner, R. A.; Gallicchio, E.; Levy, R. M. *J. Comput. Chem.* **2005**, *26*, 1752–1780.
- (14) *MacroModel*, version 9.9; Schrödinger, LLC: New York, 2012.
- (15) Zhao, Y.; Truhlar, D. G. *J. Chem. Phys.* **2006**, *125*, No. 194101.
- (16) Weigend, F.; Ahlrichs, R. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297–3305.
- (17) Cancès, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032–3041.
- (18) (a) Bergner, A.; Dolg, M.; Küchle, W.; Stoll, H.; Preuß, H. *Mol. Phys.* **1993**, *80*, 1431–1441. (b) Leininger, T.; Berning, A.; Nicklass, A.; Stoll, H.; Werner, H.-J.; Flad, H.-J. *Chem. Phys.* **1997**, *217*, 19–27.