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Mechanism and Ligand-Transfer Selectivity of 1,2-Addition of Organozincate Complexes to Aldehyde

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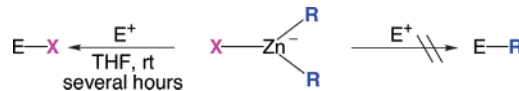
Abstract: Density functional theory (DFT) calculations have been performed to investigate the origin of the reactivity and ligand-transfer selectivity of organozincates in the 1,2-addition to carbonyl compounds. Examination of the addition of Me₃ZnLi to formaldehyde as compared with that of Me₂Zn showed that the addition reaction is facilitated by the push–pull synergy of the Lewis acidic Li atom and the negatively charged Me₃Zn moiety. This analysis then provided an answer to the mechanistic question about the experimentally established ligand-transfer selectivity in the 1,2-addition of heteroleptic organozincate Me₂-Zn(X)Li (X = H⁻, R₂N⁻, and R₃Si⁻). The addition of these heteroleptic zincate compounds results in selective transfer of H, R₂N, and R₃Si groups owing to the favorable orbital interaction between these groups and the carbonyl π-system. The addition reaction of the zincate compounds conforms to the mechanistic framework of the conventional nucleophilic reaction, such as the addition reaction of MeLi dimer, and is different from the reaction of organocuprates, where oxidation/reduction of the copper atom is involved.

Introduction

Lithium diorganocuprates R₂CuLi have long been known to be much more reactive than the corresponding neutral organo-copper compounds RCu.¹ Similarly, lithium triorganozincates R₃ZnLi¹ are more reactive than their neutral counterparts R₂Zn.^{2–6} Heteroleptic organocuprates RCu(X)Li often transfer selectively either R or X in carbonyl addition reactions,⁴ and so do heteroleptic organozincates R₂Zn(X)Li.^{7–9} For example, dialkylhydridezincates ([R₂Zn(H)]⁻M⁺),⁷ dialkylaminozincates ([R₂Zn(NR'₂)]⁻M⁺),⁸ and dialkylsilylzincates ([R₂Zn(SiR'₃)]⁻M⁺)⁹ transfer selectively the non-carbon ligand to electrophiles (Scheme 1).

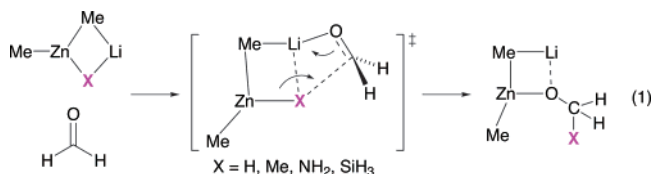
Such similarity notwithstanding, one naturally suspects that the similarity is only apparent since the Group 11 metal is a

Scheme 1. Selective Transfer of Ligand on Heteroleptic Zincate^a



^a X = H, R₂N, R₃Si > R = alkyl.

transition metal element and the Group 12 metal belongs to the main group. The enhanced reactivity of the diorganocuprates R₂CuLi is due to their high-lying Cu 3d orbital that can mix with the sp orbital of the R group,³ and the ligand-transfer selectivity for RCu(X)Li is largely due to the stabilization of a Cu(III) intermediate by Li–X ligation. The zinc atom does not have high-lying 3d orbitals, and hence there is no Zn(IV) state. Thus, the Cu/Zn similarity must indeed be superficial, and therefore one would be interested in finding the true reasons for the higher reactivity of triorganozincate compounds and the origin of the ligand-transfer selectivity for heteroleptic organozincate reagents. In this article, we report the results of the computational/theoretical studies on these reactivity and selectivity issues as studied for the 1,2-addition of Me₃ZnLi and Me₂Zn(X)Li (X = H⁻, R₂N⁻, and R₃Si⁻) to formaldehyde (eq 1).



The present results indicated that the reactivity and the selectivity issues can be explained in terms of an ordinary nucleophilic

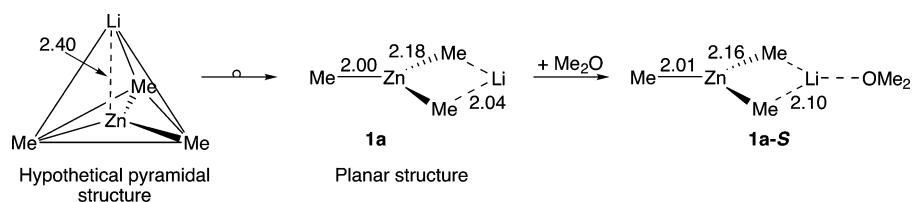
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Scheme 2



mechanism similar to the one invoked in the reaction of MeLi dimer, that is, the electrophilic activation of the carbonyl group with the Li cation and the nucleophilic attack of the Me group that takes place without an electron-transfer process between the organometallic reagent and the electrophile.

Computational Methods and Chemical Models

All calculations were carried with a Gaussian 98 program package.¹⁰ The molecular structures and harmonic vibrational frequencies were obtained using the hybrid density functional method based on Becke's three-parameter exchange function and the Lee–Yang–Parr nonlocal correlation functional (B3LYP).¹¹ We used Ahlrichs' SVP^{4,12} all-electron basis set for the zinc atom and 6-31+G* for the other atoms (denoted as 631SVP in the text). Geometry optimization and vibrational analysis were performed at the same level. All stationary points were optimized without any symmetry assumptions and characterized by normal coordinate analysis at the same level of the theory (the number of imaginary frequency, NIMAG, 0 for minima and 1 for transition states (TSs)).

We employed Me₂Zn, Me₃ZnLi, and Me₂Zn(X)Li (X = H, NH₂, SiH₃) as chemical models for the zinc compounds with and without a molecule of Me₂O coordinated either to the zinc or to the lithium atom. The neutral diorganozinc compounds in crystals⁵ exist with a linear C–Zn–C geometry, and so does the calculated structure of Me₂Zn.⁶ The gas-phase calculations indicated that MeLi and Me₂Zn react to form a trigonal planar complex **1a** with large exothermicity (24.2 kcal/mol; B3LYP/631SVP), and dissociation of Me₃ZnLi into an ion pair, [Me₃Zn][−] and Li⁺, occurs with 147.5 kcal/mol endothermicity (Scheme 2). This structure [Me₃Zn][−]Li⁺ is essentially the same as the crystallographic structure of Me₃ZnK,¹³ and the average of the calculated Zn–C bond lengths of [Me₃Zn][−]Li⁺ (2.074 Å) is in good agreement with the experimental data for [Me₃Zn][−]K⁺ (2.071 Å).¹³ Solvation of the lithium atom with a Me₂O molecule does not alter much this planar geometry (Scheme 2).

We confirmed that the planar geometry is the global minimum by making an artificial pyramidal geometry of Me₃ZnLi by first placing the lithium cation 2.40 Å above the zinc atom in an ideal trigonal structure (Scheme 2). Geometry optimization then caused smooth migration of the lithium atom without an energy barrier to form the planar structure **1a**. In light of the experimentally known fractionality of the organozincate structures,¹³ however, we must keep in mind the fact that the gas-phase calculations and the crystallographic structures

exaggerate the electrostatic interactions, the stability of the metal–carbon bond, and hence the planarity of the complex. Nonetheless, these structures provide a valuable starting point for our considerations of the reactivity of the organozincate intermediates.

Though there has been little structure and reactivity information available for the heteroleptic zincate compounds, we assumed that their behavior is essentially the same as that of Me₃ZnLi.¹⁴ The formation process and the structure of Me₂Zn(H)Li will be discussed in detail in the Results and Discussion section.

Formaldehyde was used as a model of a carbonyl compound. Lacking substituents, the TS of the 1,2-addition with a nucleophile tends to be quite early, yet it has been proved, in a number of previous studies,¹⁵ to serve as a useful general model of aldehydes and ketones.

Results and Discussion

I. Pathway of 1,2-Addition of Me₂Zn and Me₃ZnLi to Formaldehyde. The addition of Me₂Zn to formaldehyde is discussed first (Figure 1). An association complex **CPi** forms without much energy gain (3.6 kcal/mol) and with little change of the geometry. The C–Zn–C angle (169.3°) is bent by only 10.7°, and the C=O bond length (1.21 Å) is elongated by only 3% as compared with those in the reactants. C–C bond formation occurs as the carbonyl carbon approaches one of the methyl groups with an activation energy of 19.9 kcal/mol. This large energy loss is a result of the cleavage of the stable C–Zn bond (bond dissociation energy of 44.46 kcal/mol)¹⁶ and of the rather small energy gain to form an O–Zn bond in the expense of the C–Zn bond cleavage. The overall gain to form the addition product **CPii** is rather small (29.1 kcal/mol). The calculated result is consistent with the experimental fact that dialkylzinc compounds are inert in the carbonyl addition reaction in a nonpolar medium.¹⁷

We can expect a priori that Me₃ZnLi is more reactive toward an aldehyde than Me₂Zn, because of the higher electron density of the [Me₃Zn][−] moiety, and so it was found (Figure 2). Me₃ZnLi and formaldehyde first form a Lewis acid/Lewis base complex **CPi-1** with a reasonably large stabilization energy (15.9 kcal/mol). The Li coordination takes place on the plane of the carbonyl group as in the MeLi dimer/formaldehyde complex.^{15b} There are two nonequivalent Me groups in **CPi-1**. One of the two methyl groups bound to the lithium can migrate very smoothly, along the intrinsic reaction coordinate,¹⁸ to the

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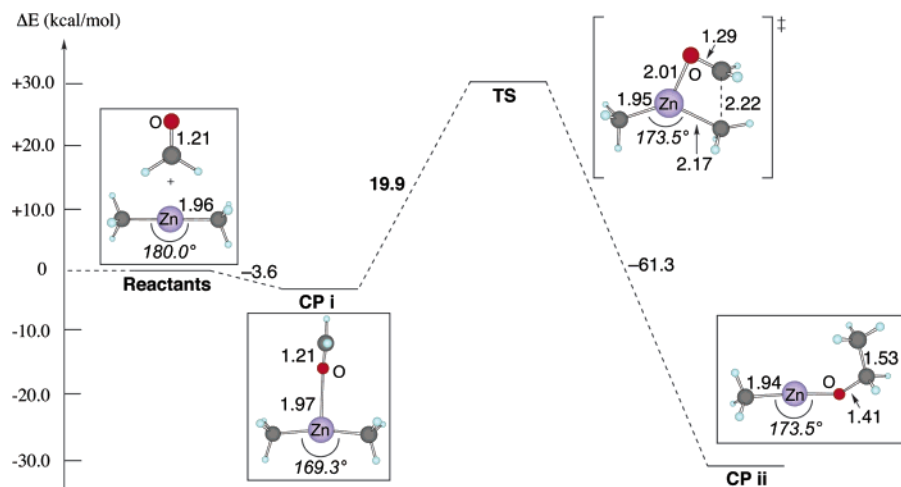


Figure 1. Energy diagram of the Me_2Zn addition of H_2CO (B3LYP/631SVP). Energy changes at the B3LYP/631SVP level are shown in kilocalories per mole and bond lengths in angstroms.

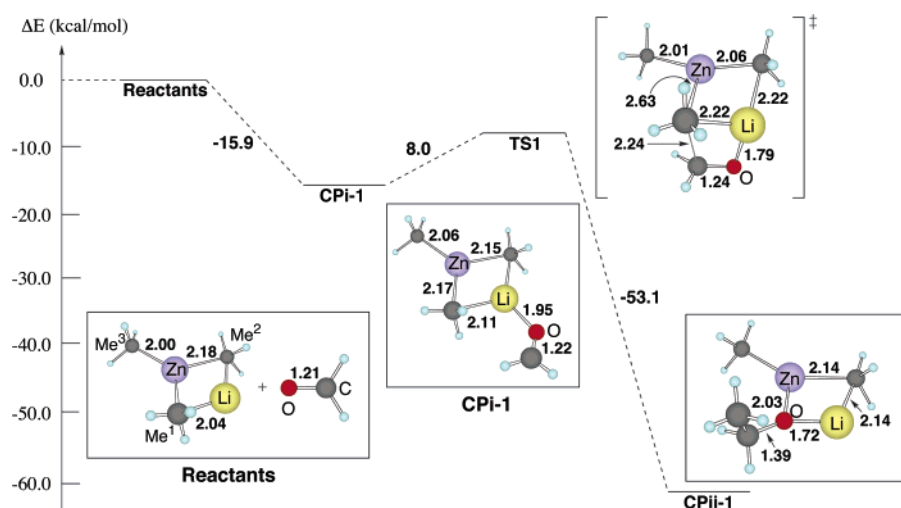


Figure 2. Energy diagram of the Me_3ZnLi addition of H_2CO (B3LYP/631SVP). Energy changes at the B3LYP/631SVP level are shown in kilocalories per mole and bond lengths in angstroms.

carbonyl carbon atom with a small activation energy (8.0 kcal/mol from **CPi-1**). As judged by the degree of elongation of the $\text{Me}-\text{Zn}$, $\text{Me}-\text{Li}$, and $\text{C}=\text{O}$ bond lengths in the TS (2%, 9%, and 2%, respectively), as well as the short forming $\text{Me}-\text{C}$ bond (2.24 Å), we consider this TS to be rather late. As the Me group migrates to the carbonyl carbon atom, the alkoxide group becomes attached to the zinc atom to produce the adduct, $\text{Me}_2\text{Zn}(\text{OCH}_2\text{CH}_3)\text{Li}$ (**CPii-1**). The stabilization energy is very large (−53.1 kcal/mol) because of the formation of $\text{Li}-\text{O}$ and $\text{Zn}-\text{O}$ bonds, and provides a driving force of the addition reaction. It is probable, as discussed later for the reaction of $\text{Me}_2\text{Zn}(\text{H})\text{Li}$, that the product $\text{Me}_2\text{Zn}(\text{OCH}_2\text{CH}_3)\text{Li}$ may disproportionate into Me_2Zn and $\text{CH}_3\text{CH}_2\text{OLi}$ tetramer to gain further stabilization.

All attempts to locate a TS in which the Me^3 group in **CPi-1** undergoes $\text{C}-\text{C}$ bond formation with the aldehyde carbon atom (while keeping the $\text{Li}-\text{O}$ coordination) resulted in a sudden change of the geometry to generate **TS1** through migration of the Li atom to the Me^3 group.

This transfer of the Me group from Me_3ZnLi to the carbonyl carbon takes place as a single event, as can be seen in the smooth charge changes during the reaction (Figure 3). Thus, the negative charge of the carbonyl oxygen increases monotonically from

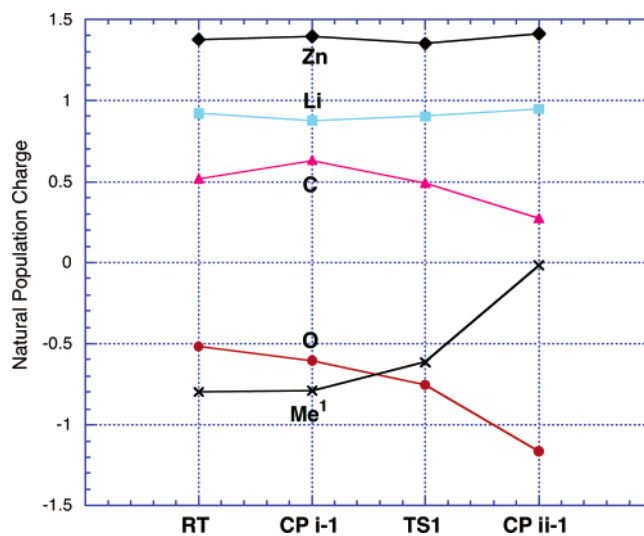
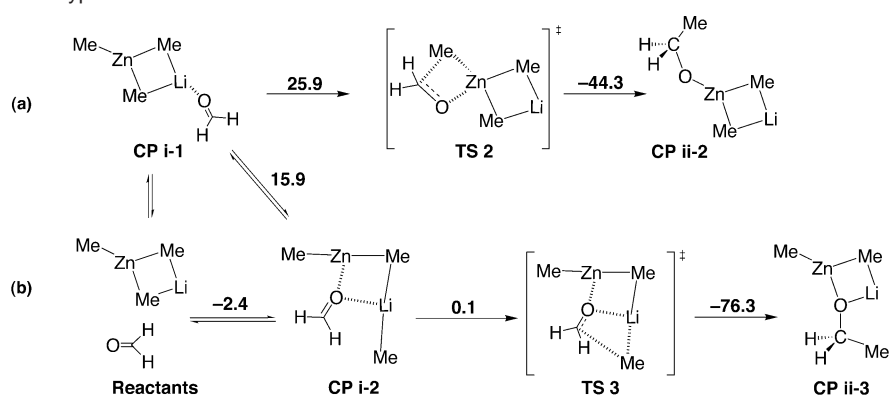


Figure 3. Charge change in the 1,2-addition of Me_3ZnLi to H_2CO .

the reactant to the product, and the negative charge of the transferred Me^1 group decreased monotonically toward zero in the product. The exchange of the electrons occurs exclusively between the Me anion and the carbonyl oxygen, and the charges

Scheme 3. Two Alternative Hypothetical Possibilities of Me Transfer

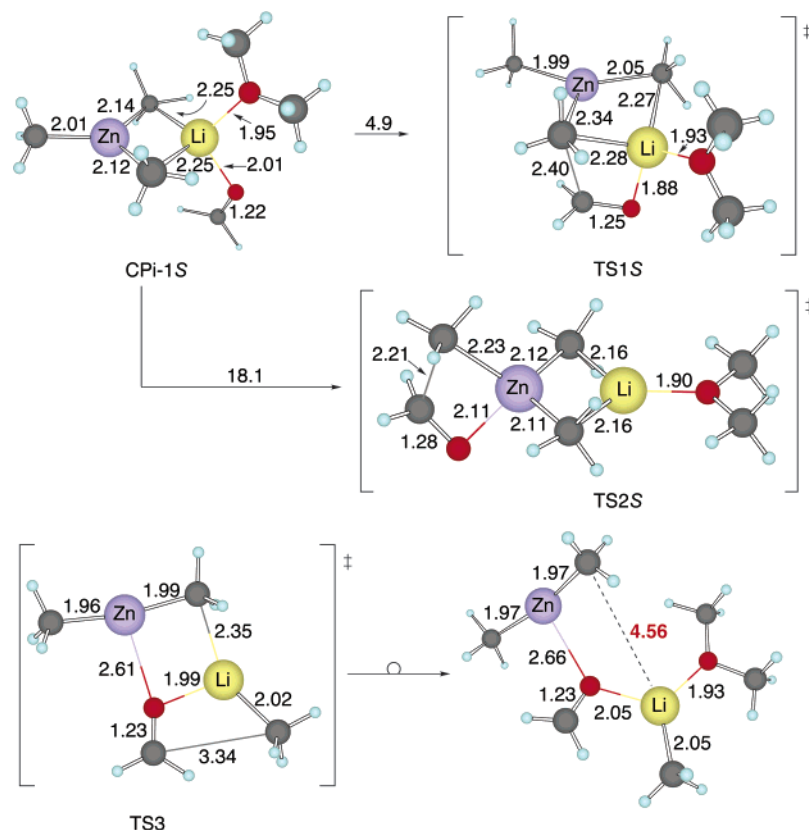
of the Li and the Zn atoms remain essentially constant during the reaction. This is a signature of the absence of any oxidation/reduction process in this reaction, and is markedly different from the addition reactions of Me₂CuLi to an α,β -unsaturated carbonyl compound, where the positive charge of the Cu atom first increases and then decreases as it goes from Cu(I) to Cu(III) and then back to Cu(I).^{2–4} Note that attempts failed to let the zinc atom interact directly with the formaldehyde π -system as in the cuprate reaction, where the copper(I) directly interacts with the organic electrophile.

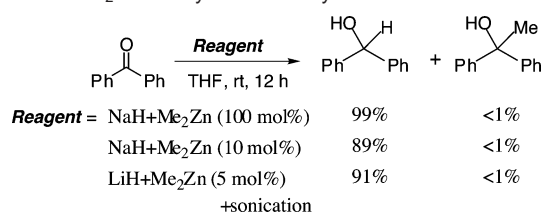
Of several other possibilities of Me transfer from Me₃ZnLi to formaldehyde, we could determine two TSs, **TS2** and **TS3** (Scheme 3). **TS2** (Scheme 3a) is a four-centered TS. The lack of the Li/carbonyl oxygen interaction makes this TS much less stable than **TS1**. **TS3** (Scheme 3b) is energetically more favorable than **TS2** by 10 kcal/mol because of double activation

of the carbonyl oxygen by the zinc and the lithium atoms. This pathway, however, first needs the formation of an open complex **CPi-2**, during which Me₃ZnLi dissociates into Me₂Zn and MeLi—a process leading the 24.2 kcal/mol loss of energy (vide supra). Both pathways (a and b) are therefore much less likely to take place than the pathway shown in Figure 2.

Solvation of Me₃ZnLi does not change the conclusion of the above analysis (Figure 4). Solvation does not change much the geometries of **TS1** and **TS2** and their energy relative to solvated **CPi-1** (**CPi-1S**) (Scheme 3a). Solvation of the lithium atom of **TS3** with one molecule of Me₂O led to collapse of **TS3** (Scheme 3b).

II. Ligand Transfer Selectivity of Heteroleptic Zincate Me₂Zn(X)Li. **A. Catalytic Reduction of Formaldehyde by Me₂Zn(H)Li.** The issue of ligand-transfer selectivity was studied first for the reaction of Me₂Zn(H)Li with formaldehyde. This

**Figure 4.** TSs of 1,2-addition with Me₂O coordinated to Li. Energy changes at the B3LYP/631SVP level are shown on the arrows in kilocalories per mole and bond lengths in angstroms.

Scheme 4. Me₂Zn-Catalyzed Metal Hydride Reduction

is the reactive species that has been assumed in the Me₂Zn-catalyzed reduction of a ketone with LiH or NaH (Scheme 4).⁷ A catalytic mechanism involving the heteroleptic zincate Me₂Zn(H)Li or Na (Figure 5) has been proposed on the basis of the inertness of LiH and NaH as reducing agents, IR detection of a metal hydride species ascribable to a zinc hydride (vide infra), the lack of Me transfer, and the diastereoselectivity of the reaction.

Two structures are a priori possible for Me₂Zn(H)Li, the unsymmetrical one **2a** and the symmetrical one **2b** (Figure 6). The coordination environments of the hydrogen atom in the two complexes are very different from each other, and hence the Zn–H stretching IR frequency must be different too. Indeed, the calculated IR frequency (not scaled) of **2a** is 1085 cm⁻¹ ($\delta_{\text{Zn-H}}$), while the Zn–H stretching frequency of **2b** is calculated to be 1787 cm⁻¹, and no IR bands exist between 650 and 1200 cm⁻¹. Experimentally, the FTIR (ATR) spectra of a THF solution of Me₂Zn(H)Li, freshly prepared from Me₂Zn and LiH, exhibits a single strong band at 1055 cm⁻¹, in good agreement with the calculated value.

The feasibility of the formation of Me₂Zn(H)Li by the reaction LiH and Me₂Zn was then probed. As Me₃ZnLi forms smoothly by the reaction of Me₂Zn and MeLi, the planar heteroleptic zincate **2a** forms with 27.3 kcal/mol stabilization. Although the assumption of monomeric LiH, which is polymeric in reality, therefore must overestimate the stabilization energy, this overwhelmingly large stabilization strongly suggest that Me₂Zn can assist depolymerization of LiH (or NaH) by the formation of the hydridezincate (Figure 7).

Having obtained the structure of Me₂Zn(H)Li that is likely involved in experiments, we examined the hydride-transfer reaction from the zincate to formaldehyde. The reaction pathway of the reduction, as shown in Figure 8, is similar to the reaction pathway of the Me₃ZnLi addition to formaldehyde, but the activation energy of the H transfer is much smaller than that of the Me transfer: Initial electrostatic coordination of Li to carbonyl oxygen results in the formation of a complex (C*P*i-H). The hydride transfer from the central Zn through TS1-H generates an alkoxide complex (C*P*ii-H). The key interaction in C*P*i-H being the one between the carbonyl lone-pair electrons and the Li cation, all heavy atoms and the lithium atom are located in a plane. To reach the TS of H-transfer (TS1-H), the orientation of the carbonyl group changes so that the π^* -orbital can interact with the hydride nucleophile, and the Li–H electrostatic bond cleaves with an overall energy loss of only 3.1 kcal/mol. The H-transfer product (C*P*ii-H) is a mixed zincate possessing a methoxide ligand and –45.3 kcal/mol lower in energy than TS1-H.

The alkoxide complex C*P*ii-H is further stabilized by the formation of Me₂Zn and a MeOLi homodimer with 22.5 kcal/mol stabilization or much better by the formation of a tetramer with 34.7 kcal/mol stabilization. Since the lithium alkoxide tetramer is an experimental minimum in solution,¹⁴ this process

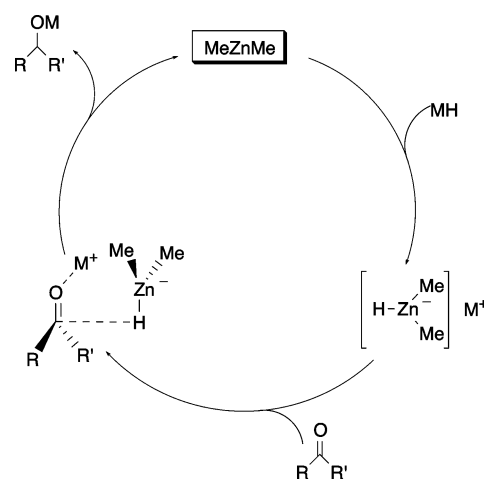


Figure 5. Proposed catalytic cycle of Me₂Zn-catalyzed reaction of carbonyl compound with MH (M = Li or Na).

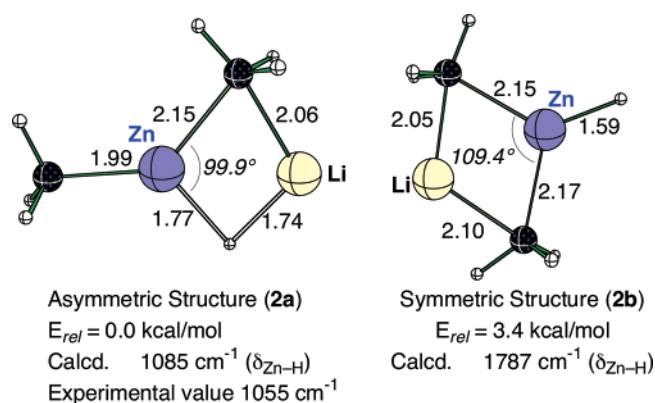


Figure 6. Asymmetric and symmetric structures of Me₂Zn(H)Li (B3LYP/631SVP), relative energies, and calculated and experimental IR spectra.

of Me₂Zn regeneration accounts for the catalytic role of Me₂Zn in the carbonyl reduction with LiH (or NaH) in Figure 8.

The hydride complex C*P*i-H can transfer its Me group to formaldehyde, but the activation energy of this process (10.8 kcal/mol) is comparable to the one for Me₃ZnLi (8.0 kcal/mol, Figure 2), and hence is much higher than the one of the H-transfer (3.1 kcal/mol). The 7.7 kcal/mol difference in energy between the H and the Me transfers translates into over a 10⁷-fold difference in the reaction rates at room temperature, and hence is consistent with the experiment where carbonyl reduction was observed exclusively in the Me₂Zn-catalyzed reaction of LiH with a ketone (Scheme 4).

B. Ligand-Transfer Selectivity for Me₂Zn(X)Li (X = NH₂ or SiH₃). It is experimentally established that mixed zincate compounds transfer selectively their nitrogen and silicon substituents to an electrophile, and hence the Me group, which may be less precious than the transferred group, acts a “dummy” ligand.^{7–9} Transfer selectivity of H \cong NR₂ > SiR₃ > alkyl (Me) has been reported.

To examine the ligand-transfer selectivity in question, we examined the reactions of [Me₂Zn(NH₂)Li] and [Me₂Zn(SiH₃)Li] with formaldehyde. The transition structures of the nitrogen and the silicon group transfer are shown and compared with those of the Me (TS1-Me) and the H transfers (TS1-H) in Figure 9. The activation energies for the transfer of NH₂ and SiH₃ in Me₂Zn(X)Li (X = NH₂ or SiH₃) are 2.7 and 6.1 kcal/mol,

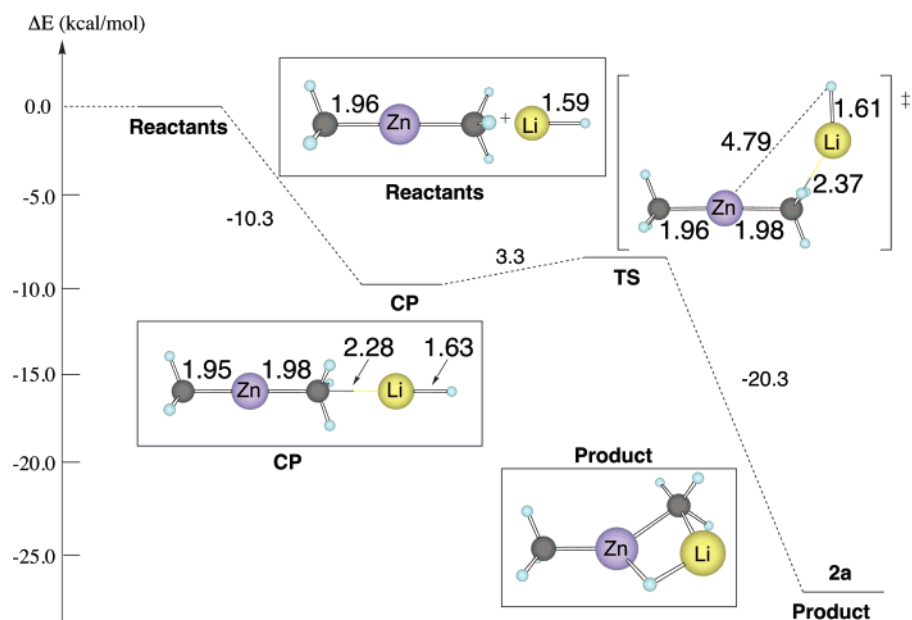


Figure 7. Representative reactants, complexes, and TS structures in ate complexation of Me_2Zn and LiH addition of H_2CO . Energy changes at the B3LYP/631SVP level are shown in kilocalories per mole and bond lengths in angstroms.

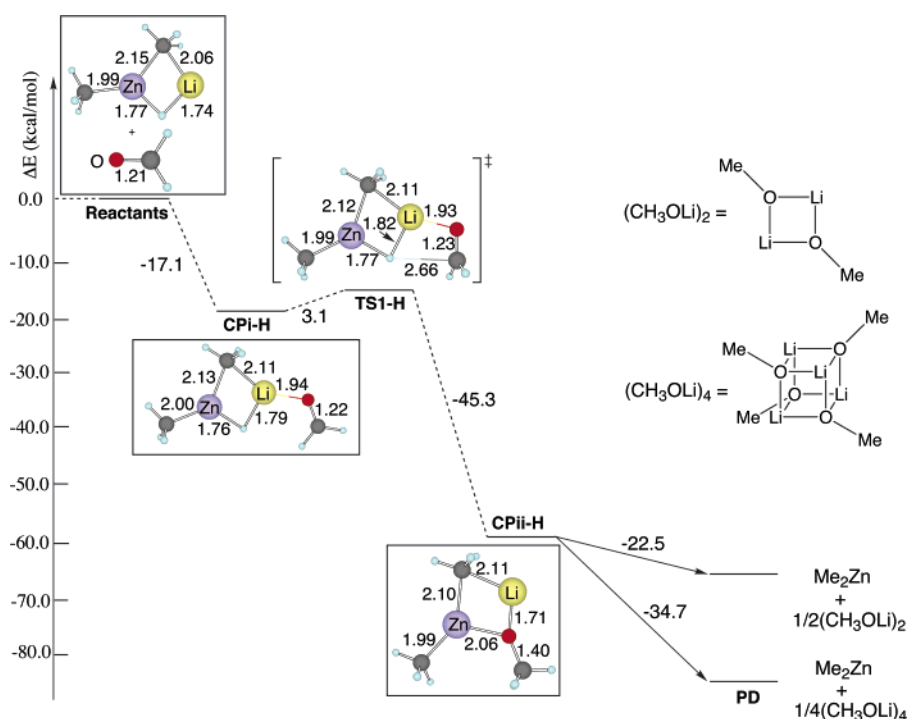


Figure 8. Energy diagram in reduction of H_2CO using $\text{Me}_2\text{Zn}(\text{H})\text{Li}$. Energy changes at the B3LYP/631SVP level are shown on the arrows in kilocalories per mole and bond lengths in angstroms.

respectively, and, being consistent with the experimental facts, are much lower than the barrier of the Me transfer.¹⁹ We also carried out calculations employing the self-consistent reaction field (SCRf) method.²⁰ In this model, the solvent effect is represented by a dielectric continuum characterized by its relative static dielectric permittivity, ϵ .²¹ The typical and

experimentally used solvent, THF ($\epsilon = 7.58$), was chosen for the calculations. Although the individual SCRf activation energies (**TS1-Me**, 15.3 kcal/mol; **TS1-H**, 4.8 kcal/mol; **TS1-NH₂**, 6.7 kcal/mol; and **TS1-SiH₃**, 10.3 kcal/mol, respectively) show a tendency to increase in comparison with those of the gas-phase calculation, the solvent effect does not change the conclusion of the above analysis.

(19) The Gibbs energies of activation (298.15 K) are as follows: **TS1-Me**, 16.1 kcal/mol; **TS1-H**, 3.5 kcal/mol; **TS1-NH₂**, 3.4 kcal/mol; and **TS1-SiH₃**, 9.3 kcal/mol, respectively. Nearly similar tendencies were obtained.
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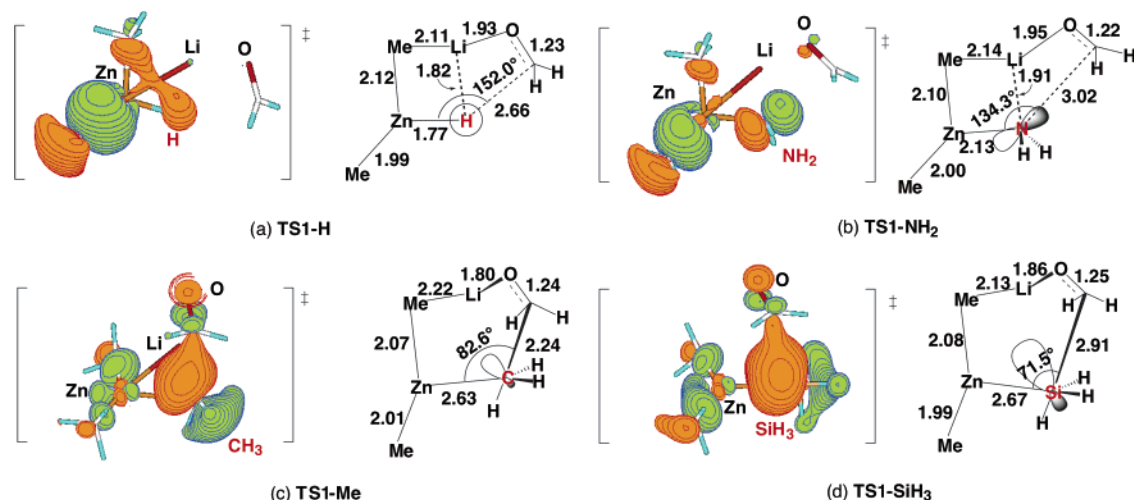


Figure 9. Kohn–Sham MOs of the TSs of Me, SiH₃, H, and NH₂ transfer.

While it is difficult to provide hard theoretical evidence that accounts for the energy difference of only several kilocalories per mole among the four TSs, orbital analysis lends some support to the selective transfer of the hydrogen, nitrogen, and silicon groups in preference to the Me transfer. The Kohn–Sham orbitals¹⁶ of **TS1-Me**, **TS1-H**, **TS1-NH₂**, and **TS1-SiH₃** involved in the bond alternation of the ligand transfer are shown in Figure 9.

As is generally known as an asset of hydride transfer,²² the lack of orientation of the 1s orbital of hydride generally makes the H-transfer facile, allowing the hydrogen atom to undergo smooth bond switching from Zn to the carbonyl carbon (though this is not obvious in Figure 9a). The nitrogen group transfer exhibits a special character (Figure 9b): As we view the zincate complex as a zinc amide, one can identify a p-orbital corresponding to the lone-pair orbital of the nitrogen atom that interacts with the carbonyl carbon. The orientation of this orbital appears to be ideal in **TS1-NH₂**.

No unexpectedly, the orbital pictures of the Me and the silicon group transfers are very similar to each other (Figure 9c,d). With this similarity, we understand that the more polarizable silicon atom can be transferred more easily than the less polarizable carbon atom.

Conclusion

In summary, the 1,2-addition of lithium triorganozincate to an aldehyde takes place in a manner similar to the addition of MeLi, taking place in a four-centered TS. The electron flow from the organometallic reagent to the aldehyde occurs unidirectionally and monotonically, without much change of the charge on the metal atoms. This mechanism is different from that of the reactions of lithium diorganocuprates that involves direct interaction between the Cu(I) atom and the organic electrophile and therefore involves two-electron oxidation/reduction during the reaction. This observation is consistent with the previous reports that the 3d orbital is very low lying with

both neutral and anionic zinc compounds,³ and therefore would be incapable of directly interacting with any organic electrophile.

The origin of the ligand-transfer selectivity for the heteroleptic zincate compounds is therefore entirely different from that for the heteroleptic organocuprate, where the stabilization of Cu(III) intermediates through Li atom ligation plays the major role. The selectivity for the heteroleptic zincate reagent, on the other hand, is controlled by the kinetic facility of the Zn(II)–X bond cleavage without change of the oxidation state of the metal.

In this first study, we have shown the viability of the simple model systems in the study of the nucleophilic reactivity of triorganozincate compounds. Studies will continue to investigate the nature of other standard synthetic reactions of organozincate species, including conjugate addition and transmetalation.

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Note Added after ASAP Posting. After this article was posted ASAP on August 6, 2004, two wording changes were made in the Figure 9 caption and the third paragraph under section II.B of the Results and Discussion section. The corrected version was posted August 12, 2004.

Supporting Information Available: Cartesian coordinates and total electron energies for the optimized stationary points at each level of theory. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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