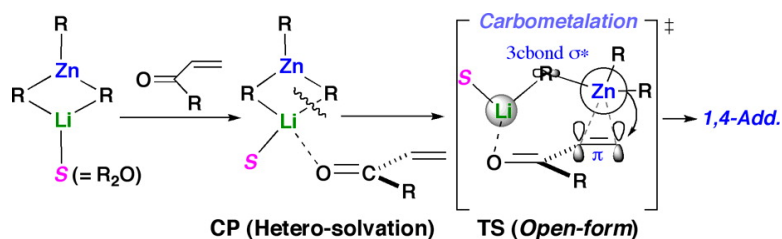


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J. Am. Chem. Soc., **2007**, 129 (44), 13360-13361 • DOI: 10.1021/ja070123k • Publication Date (Web): 17 October 2007

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Reaction Pathway of Conjugate Addition of Lithium Organozincates to *s-trans*-Enones

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Zinc and copper are neighbors in the periodic table, so that Zn(II) and Cu(I) have isoelectronic states, and consequently, their organometallic complexes have many similarities in reactivity. For instance, their ate complexes, lithium triorganozincates $R_3Zn(II)-Li^1$ and lithium diorganocuprates $R_2Cu(I)Li$,² react smoothly and selectively with α,β -unsaturated carbonyl compounds to undergo 1,4-addition reactions, and hence both can be classified as “soft” reagents (Figure 1).³ However, this similarity is essentially superficial because the group 11 metal is a transition metal element and the group 12 metal belongs to the main group.⁴ Thus, it is of interest to investigate the true reason for the origin of the 1,4-addition selectivity (“soft” nucleophilicity) of organozincate reagents.⁵ Here, we report a theoretical/computational study, using density functional theory, of the pathway and mechanism of the selectivity of 1,4-addition of Me_3ZnLi to α,β -unsaturated carbonyl compounds, using *s-trans* methyl vinyl ketone (MVK) (**1**) as the simplest model for acyclic and cyclic enones.⁶

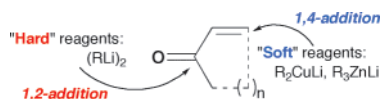


Figure 1. HSAB classification of organometallic reagents.

The reaction pathway of Me_3ZnLi addition to **1**, as shown in Figure 2, is completely different from that of the addition of cuprates.⁵ The reactants (**RT**) first form an association complex (**CPI**) with a large energy gain (11.8 kcal/mol). On the basis of X-ray crystallographic and theoretical studies, the central zinc atom in a zincate, unlike the lithium atom in alkyllithium dimer, is never solvated.⁷ This is because the LUMO components are localized completely on the Li atom in the case of zincates (heterobimetals).⁶ The formation of this intermediate, **CPI**, causes the C–Li–C angle (106.5°) to be deformed by 7.4° and the C–Li bond length (2.26 Å) to be elongated by more than 7% as compared with those in the reactants (**RT**). To reach the TS for the 1,4-addition, the (hetero)-bimetallic rhombic structure of the zincate opens, so that the CH_3 can interact with the π^* -orbital of the C=C bond of MVK, and the CH_3-Li electrostatic bond is cleaved with an overall energy loss of 16.8 kcal/mol. The CH_3 transfer from the central Zn through an “open form” transition state ($TS_{1,4-add}(MVK)$) generates an enolate–zincate cyclic complex ($CPIi_{1,4-add}$), which is –53.0 kcal/mol lower in energy than $TS_{1,4-add}(MVK)$. We also identified another TS for 1,2-addition, $TS_{1,2-add}(MVK)$, which is a four-centered “closed form” TS, analogous to the 1,2-addition TS for

formaldehyde.^{6b} However, $TS_{1,4-add}(MVK)$ is energetically more favorable than $TS_{1,2-add}(MVK)$ by $\Delta\Delta E^\ddagger = 2.0$ kcal/mol.⁸ These results are in accordance with the experimental finding that the zincates show high 1,4-addition selectivity toward enones.

This 1,4-addition of the Me group from Me_3ZnLi to MVK takes place as a single event, as is clear from the smooth charge changes during the reaction (see Supporting Information). The charges of the Li and the Zn atoms remain essentially constant during the reaction. This is the signature of the absence of any oxidation/reduction process during the reaction and is distinctly different from the changes that occur in the addition reactions of cuprates to an α,β -unsaturated carbonyl compound, where the positive charge of the Cu atom increases then decreases as it goes from Cu(I) to Cu(III) and then back to Cu(I).^{2,4} Our finding is consistent with previous reports that the 3d orbital is very low-lying in both neutral and anionic zinc compounds⁴ and therefore would be incapable of directly interacting with any organic electrophile.

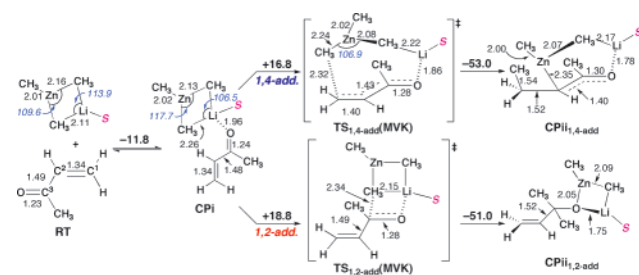


Figure 2. Possible reaction pathways of addition of Me_3ZnLi to MVK. Energy changes at the B3LYP/631SVP level are shown in kcal/mol on the arrows; S = Me_2O .

The origin of this 1,4-addition selectivity was then investigated based on NBO analysis.⁹ Second-order perturbation analysis (see Table 1) of $TS_{1,4-add}(MVK)$ indicated a large stabilization energy (8.4 kcal/mol) due to the donor–acceptor interaction, corresponding to the secondary orbital interaction (defined as INT iv) between the vinyl π -system ($C^1=C^2$: donor NBO) and the unoccupied σ -orbital of zinc in the bimetal three-center, two-electron bond (Zn– CH_3-Li : acceptor NBO). Reaction pathway analysis of $(MeLi)_2$, which generally prefers 1,2-addition over 1,4-addition, revealed that the activation energies of $(MeLi)_2$ for 1,4-addition (open form TS) and for 1,2-addition (closed form TS) are 10.5 and 10.3 kcal/mol, respectively (Table 1). The donor–acceptor interaction (INT iv) energy at the TS for 1,4-addition is only 0.2 kcal/mol, being smaller than that of the zincate. The bond lengths between the central metal and the vinyl group at each TS also support the interaction; the

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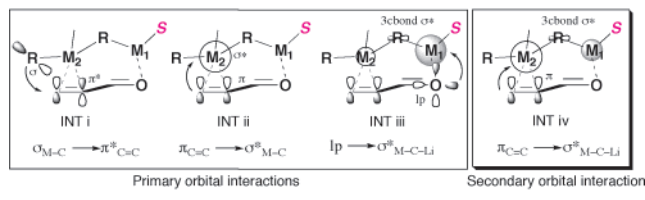
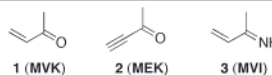
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[¶] Emory University.

Table 1. Comparison of Activation Energies and Energetic Analysis of NBO Donor–Acceptor Interactions for 1,4-/1,2-Addition

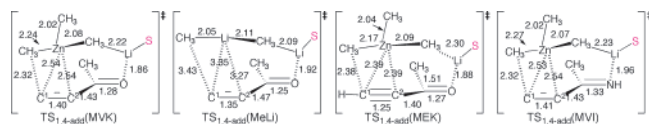
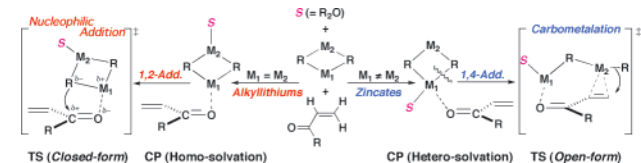
Substrate	Reagent	TS for 1,4-add.	$\pi_{C=C} \rightarrow \sigma^*_{M-C-Li}$		ΔE^{\ddagger} (kcal/mol)
			INT iv (kcal/mol)	1,4-add	
1	Me ₃ ZnLi	TS _{1,4-add} (MVK)	8.4	16.8	18.7
1	(MeLi) ₂	TS _{1,4-add} (MeLi)	0.2	10.5	10.3
2	Me ₃ ZnLi	TS _{1,4-add} (MEK)	8.6	10.0	15.1
3	Me ₃ ZnLi	TS _{1,4-add} (MVI)	8.4	23.8	32.7



Zn–C¹ and Zn–C² lengths are both 2.54 Å, which are much shorter than those of (MeLi)₂: 3.35 Å for Li–C¹ and 3.27 Å for Li–C² (Figure 3).

The reactions of Me₃ZnLi with methylethynylketone (MEK) **2** and methylvinylimine (MVI) **3** were next examined to assess substrate generality (Table 1 and Figure 3). On the basis of the B3LYP-calculated activation barriers, both reactions favor 1,4-addition over 1,2-addition kinetically, and this is fully consistent with the experimental observations.¹⁰ The values of the NBO donor–acceptor interaction (INT iv) energy for 1,4-addition were sufficiently large, being nearly equal to that of MVK **1**. These results strongly suggest that the secondary orbital interaction between zinc and the π -system plays an important role in the 1,4-addition selectivity regardless of substrate and reagent. It is worth mentioning that the second intermediate of 1,4-addition of zincate **CPii**_{1,4-add} has the characters of both α -zincio ketone and lithium enolate because of the short C³–O length and long C²–C³ length (1.30 and 1.40 Å, respectively). In other words, Me₃ZnLi reacts with α,β -unsaturated carbonyl compounds (and imines) in the carbometalation manner, while (MeLi)₂ reacts in the nucleophilic addition manner.¹¹

In summary, we have shown that the 1,4-addition of triorganozincate complexes to *s-trans* α,β -unsaturated carbonyl compounds takes place through an open form TS without any oxidation/reduction process (Figure 4). Heterobimetallic systems such as zincates prefer heterogeneous solvation over homosolvation, that is, enone and Me₂O both coordinate only to M₁(Li), and therefore the lithium ion coordinates four ligands (Figure 4, right). This heterosolvation decreases the Li–C(alkyl) bond strength, and the bond breaks more easily to form an open form TS for the 1,4-

**Figure 3.** Four TSs in the 1,4-addition reactions of Me₃ZnLi or (MeLi)₂ with MVK, MEK, and MVI. See Figure 2 for details.**Figure 4.** Summary of reaction pathways of homo- and heterobimetallic reagents to MVK.

addition of the zincate to the enone. The Lewis acid–Lewis base interaction between the olefin moiety of enones and the zinc center plays a critical role both for stabilization of **TS**_{1,4-add} and for activation of the migration ability of the R ligand. The present work underpins the idea that the combination of metals in bimetallic reagents and their electronegativities/Lewis acidities provide tunable functionality in the TSs.¹² We intend to investigate the nature of other standard synthetic reactions of organozincate species, including halogen–metal exchange and transmetalation.

Acknowledgment. We gratefully acknowledge financial support from KAKENHI ((S) (to E.N.), Young Scientist (A), Houga, and Priority Area (Nos. 452 and 459) (to M.U.)), JSPS Research Fellowship for Young Scientists (to S.N. and T.F.), and The 21st Century COE Program in Fundamental Chemistry from MEXT (to E.N.). M.U. is the recipient of a Visiting Fellowship at the Cherry L. Emerson Center of Emory University. The calculations were performed on the RIKEN Super Combined Cluster (RSCC).

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

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- NBO analysis was performed using 3CBOND and CHOOSE keywords in order to standardize the resonance structure representations of each TS. The descriptions are given in detail in the Supporting Information.
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JA070123K