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Dinuclear *versus* Mononuclear Pathways in Zinc Mediated Nucleophilic Addition: A Combined Experimental and DFT Study

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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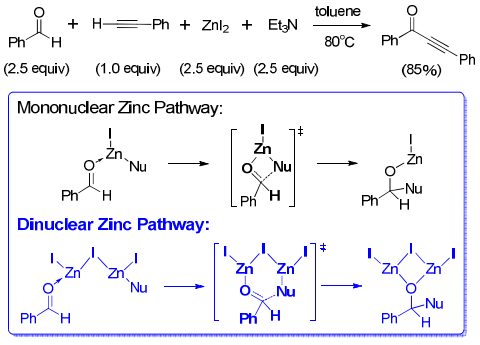
Employing the oxidative coupling of phenylacetylene with benzaldehyde as a model reaction, a density functional theory (DFT) study combined with extended X-ray absorption fine structure (EXAFS) experiment was carried out to reveal the difference between dinuclear and mononuclear zinc mediated nucleophilic addition. Newly reported DFT method M11-L computed results suggest that the mononuclear zinc mediated pathway, in which nucleophilic addition occurs via a four-membered ring transition state, is unfavourable both thermodynamically and kinetically. The dinuclear zinc mechanism, which properly explains the experimental observations, involves a six-membered ring transition state for nucleophilic addition. Subsequent *in situ* EXAFS experiment confirmed the existence of dinuclear zinc active species. Moreover, frontier molecular orbital (FMO) analysis and distortion-interaction energy analysis along the whole reaction pathways have provided interpretations for the advantage of dinuclear zinc mediated nucleophilic addition. Consequently, we believe this dinuclear zinc pathway will open up a general consideration of dinuclear zinc mechanism for nucleophilic additions.

Introduction

Owing to the inherent elemental characteristics, zinc (II) salts have been widely used as Lewis acids in nucleophilic addition reactions, for instance, the Aldol reaction,[1-4] the Henry reaction,[5-8] the Michael reaction[9-12] and Mannich reaction.[13-16] Plenty of efforts have been made to employ these strategies to construct new C—C bonds or carbon quaternary stereocenters.[17-21] Almost all of these transformations are considered to proceed through a mononuclear zinc (II) mediated pathway.[22-25] For example, many $ZnCl_2$,[3] $ZnBr_2$,[20] ZnI_2,[22] $Zn(OTf)_2$,[11-12] Et_2Zn,[26] and *in-situ* generated organozinc[2,17] promoted nucleophilic additions are proposed or proved to contain mononuclear zinc species as the key intermediates.

Dinuclear zinc pathways have always been neglected because chemists are far more familiar with mononuclear zinc pathway when considering the mechanism of zinc-involved organic transformations. Actually, it plays a vital role especially in enzyme chemistry.[27-29] Researches into zinc enzyme have shown that many enzymes involve a binuclear zinc centre as the active site.[30-32] In synthetic chemistry, however, seldom have dinuclear zinc pathways been proposed in zinc mediated organic reactions,[33-35] which is in contrast to other transition metals.[36-42] One example on dinuclear zinc promoted nucleophilic addition was reported by Trost and co-workers in 2000,[43] in which two oxygen-bridged dinuclear zinc catalysts were designed by employing crown compounds as the templates. This report showed a good example of dinuclear zinc mechanism in nucleophilic addition. Nevertheless, the special templates limited its utilization, and therefore it is difficult to shed light on the generality of simple zinc salt promoted organic transformations by this particular dinuclear zinc catalyst.[44-47]

Although zinc chemistry has been developed for several decades, little attention has been paid to the comparison between dinuclear and mononuclear zinc mediated nucleophilic addition, and no mechanistic study on the difference between these two pathways has been reported. Consequently, revealing the dinuclear versus mononuclear zinc pathway is of great importance for the understanding of zinc chemistry as well as the development of multinuclear zinc catalysts.



Scheme 1. Mono- and dinuclear zinc pathways for the nucleophilic addition of terminal alkynes with aldehydes.

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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Recently, we reported a zinc iodide mediated oxidative coupling of terminal alkynes with aldehydes to construct ynones (Scheme 1), in which a dinuclear zinc intermediate was proven to be the active species.[48] This research sets a precedent for dinuclear zinc promoted organic transformations because of the utilization of simple zinc halide. Meanwhile, it provides us an opportunity to study both mononuclear and dinuclear zinc promoted nucleophilic addition by density functional theory (DFT) calculation. *In situ* EXAFS and *Operando* IR experiments are also employed to investigate the mechanism. As depicted in Scheme 1, in commonly considered mononuclear zinc pathway, the nucleophilic addition is supposed to occur via a typical four-membered-ring transition state. However, initial computational investigation towards mononuclear zinc mechanism suggests that the generation of dinuclear zinc complex is favourable. This novel finding further promoted us to study the possibility of dinuclear zinc pathway, which involves a six-membered-ring transition state for the nucleophilic addition (Scheme 1). Herein, we report a combined experimental and DFT study on this zinc mediated oxidative coupling reaction to reveal the difference between dinuclear and mononuclear zinc mediated nucleophilic addition. We hope this novel dinuclear zinc pathway will open up a general consideration of dinuclear zinc mechanism in zinc chemistry.

Computational Methods

All the DFT calculations were carried out with the GAUSSIAN 09 series of programs.[49] DFT method B3-LYP[50-53] with a standard 6-31G(d) basis set (SDD[54-56] basis set for Zn and I) was used for geometry optimizations. Harmonic frequency calculations were performed for all stationary points to confirm them as a local minima or transition structures and to derive the thermochemical corrections for the enthalpies and free energies. M11-L functional,[57-60] recently proposed by Truhlar group, which could give more accuracy energetic information, is used to calculate single point energies. Solvent effects were considered by single point calculations on the gas-phase stationary points with a SMD continuum solvation model.[61] The larger basis set 6-311+G(d) (LanL08[62] basis set for Zn and I) is used in the solvation single point calculations. The energies given in this work are the M11-L calculated Gibbs free energies in toluene solvent. The Frontier Molecular Orbital (FMO) are calculated at the B3LYP/6-31G(d) level of theory.

In this work, the intrinsic reaction coordinates (IRC)[63] of all aldehyde insertion transition states are employed to calculate the reaction pathway at B3LYP/6-31G(d) level of theory. Distortion energy is set to the energy difference between the energy of distorted aldehyde and alkynyl-zinc parts along the reaction pathway and the energy of fully optimized aldehyde

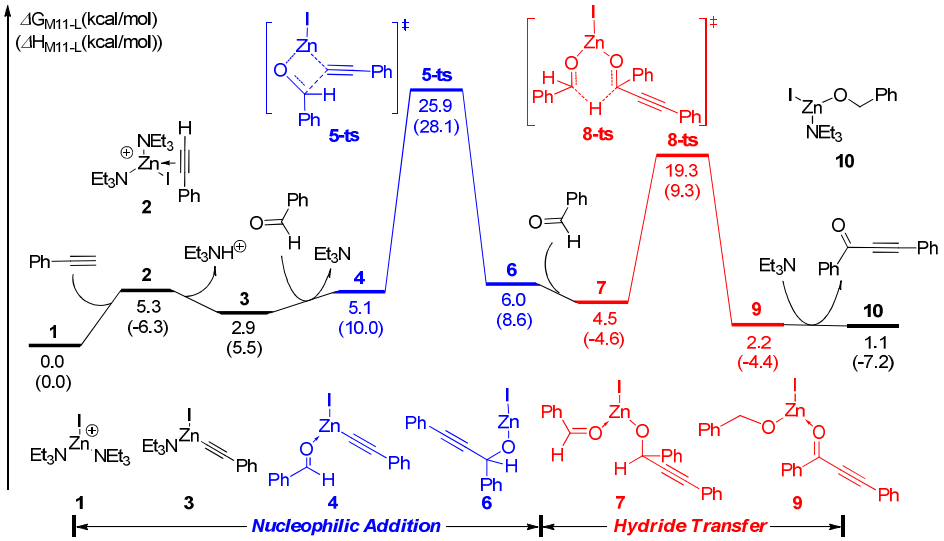

Figure 1. Free energy profile for mononuclear zinc mediated oxidative coupling of phenylacetylene with benzaldehyde.

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and alkynyl-zinc part by single point energy calculation at B3-LYP/6-31G(d) level of theory (SDD basis set for Zn and I). The interaction energy is set to the energy difference between the single point energy at B3-LYP/6-31G(d) level of theory (SDD basis set for Zn and I) of the geometry on the reaction coordinate and the energy of the relative distorted aldehyde and alkynyl-zinc parts.

Results and discussion

The oxidative coupling of terminal alkynes with aldehydes promoted by zinc iodide consists of two main steps: First, the nucleophilic addition of terminal alkynyl zinc to the aldehyde generates propargylic alcohol;[64-70] Second, the following oxidation of propargylic alcohol through hydride transfer could afford the product ynone.[71-73] The generally considered mononuclear zinc-mediated pathway is first put forward and calculated. As shown in Figure 1, monomeric zinc complex **1** is chosen as relative zero in the free energy profile. After coordination of one phenylacetylene, complex **2** is formed and is 5.3 kcal/mol endothermic. Subsequent deprotonation can afford complex **3**, which is 2.4 kcal/mol more stable than complex **2**. After ligand exchange, one benzaldehyde coordinates with zinc, generating complex **4**.

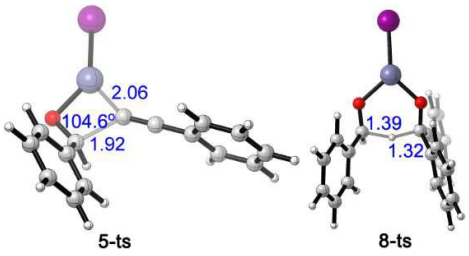


Figure 2. Geometry information of transition state **5-ts**, **8-ts**.

Subsequent nucleophilic addition of alkynyl zinc to the aldehyde carbonyl proceeds via a four-membered-ring transition state **5-ts** with a barrier of 20.8 kcal/mol, producing complex **6** reversibly. Coordination of an additional benzaldehyde towards complex **6** generates intermediate **7** with 1.5 kcal/mol free energy decrease. The following propargylic alcohol oxidation could take place reversibly through an intramolecular hydride transfer transition state **8-ts** with only a barrier of 14.8 kcal/mol, affording complex **9**, which is 2.3 kcal/mol more stable than complex **7**. The geometry information of transition state **8-ts** is shown in Figure 2. Two oxygen atoms from both benzaldehyde and propargyl alcohol groups are coordinated to one zinc centre. Hydride transfer then proceeds via a six-membered-ring transition state, in which the forming and breaking carbon-hydrogen bond lengths are 1.39 Å and 1.32 Å, respectively. The geometry of **8-ts** is close to the corresponding transition states of Oppenauer oxidation with aluminium or magnesium catalysts.[74-77]

It is noteworthy that the generation of complex **9** and **10** concomitant with product ynone is 2.2 and 1.1 kcal/mol endothermic, respectively, indicating that the mononuclear zinc mechanism is thermodynamically unfavourable. Furthermore, an IR peak was found to increase fast at first and then gradually faded away in the *operando* IR study,[48] suggesting that an active intermediate might be accumulated during the reaction. In the free energy profile of mononuclear zinc mediated pathway, however, the relative free energy of intermediate **6** or **7** is higher than that of intermediate **4**, which indicates that this nucleophilic addition process is thermodynamically unfavourable, and intermediate **6** or **7** cannot be observed. Meanwhile, the relative free energy of **8-ts** is 6.6 kcal/mol lower than that of **5-ts**, suggesting that the consumption rate of intermediate **6** or **7** to generate **9** beats their formation rate from **4**. All of these considerations reveal that intermediates **6** and **7** can only exist as transient intermediates both thermodynamically and kinetically. Therefore, the mononuclear zinc-mediated pathway is unreasonable and should be ruled out. Although this conclusion enhances the level of complexity for the reaction mechanism, it also implies some interesting insights in it, which further intrigues us to elucidate a new mechanistic scenario, i. e. the dinuclear zinc mediated pathway.

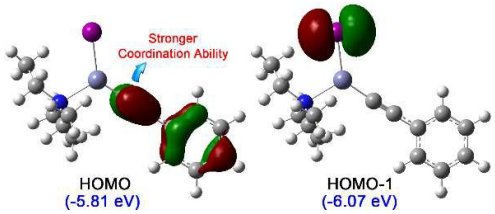
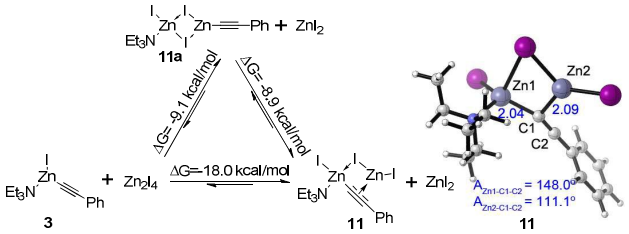


Figure 3. The frontier molecular orbital (FMO) of complex **3**.

A dinuclear zinc mechanism is inspired by the frontier molecular orbital (FMO) analysis of an important intermediate **3**. As shown in Figure 3, the highest occupied molecular orbital (HOMO) of alkynyl zinc **3** is localized on the alkynyl group, and the HOMO-1, which is 0.26 eV lower than the HOMO, is localized on the coordinated iodide. FMO analysis suggests that alkynyl is a better electron donor compared with iodide. According to this clue we deduce that the combination of complex **3** with another zinc might be favourable. Subsequent computation was carried out to verify this speculation. As

expected, the alkynyl bridged bimetallic zinc species **11** could be generated and is 18.0 kcal/mol exothermic through the reaction between complex **3** and iodide bridged zinc dimer Zn_2I_4 (Scheme 2), while the formation of iodide bridged isomer **11a** is 9.1 kcal/mol exothermic, which is 8.9 kcal/mol higher. The bond lengths of C1—Zn1 and C1—Zn2 in complex **11** are 2.04 Å and 2.09 Å, respectively, and the bond angles of C2—C1—Zn1 and C2—C1—Zn2 are 148.0° and 111.1°, respectively. These results indicate that alkynyl group coordinates to Zn1 with the terminal lone pair electrons, and coordinates to Zn2 with polarized π bond electrons, which is consistent with FMO calculations.



Scheme 2. The balance between intermediate **3**, **11** and **11a**.

By choosing alkynyl bridged dinuclear zinc complex **11** as the starting point, the free energy profile of dinuclear zinc mediated nucleophilic addition is calculated and shown in Figure 4. After losing one triethylamine, intermediate **12** is generated, which is uphill by 11.7 kcal/mol. The following coordination of benzaldehyde forms complex **13** with 6.2 kcal/mol exothermic. Subsequent nucleophilic addition proceeds via a six-membered-ring transition state **14-ts** with a barrier of 19.2 kcal/mol, producing complex **15** irreversibly. In this pathway, the relative free energy of nucleophilic addition transition state **14-ts** is 16.3 kcal/mol lower than that of **5-ts** in mononuclear zinc-mediated pathway. Figure 5 shows the geometry information of transition state **14-ts**. The attacking angle of alkynyl to carbonyl (O—C3—C1) is 107.5°, which is 2.9° larger than that in **5-ts**. The O—C3—C1 bond angle in transition state **14-ts** is closer to a standard Bürgi-Dunitz angle,[78] which indicates that the ring strain in six-membered ring transition state **14-ts** is smaller than that in four-membered ring transition state **5-ts**.

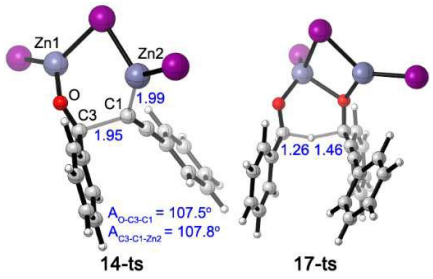


Figure 5. Geometry information of transition state **14-ts**, **17-ts**.

Subsequent alcohol oxidation could take place after the coordination of another molecule of benzaldehyde towards intermediate **15**. An intramolecular hydride transfer could occur via transition state **17-ts** with 27.7 kcal/mol barrier, and intermediate **18** is formed with 7.3 kcal/mol endothermic. The isomerization of intermediate **18** irreversibly leads to a more stable ynone coordinated complex **19**, the formation of which is 24.2 kcal/mol exothermic. As shown in Figure 4, the activation free energy of hydride transfer step is 27.7 kcal/mol, which is 8.5 kcal/mol higher than that of alkynyl nucleophilic addition step. This energy information suggests that the hydride transfer process is slower than the nucleophilic addition, and the thermodynamically stable propargylic alcohol intermediate **16** could accumulate during the reaction. Moreover, calculated vibration frequency of C-O single bond in complex **16** is 964 cm^{-1}, which is very close to the *Operando* IR results (peak at 972 cm^{-1}).[48] Therefore, the dinuclear zinc intermediate **16** is most likely to be the experimentally observed active species.

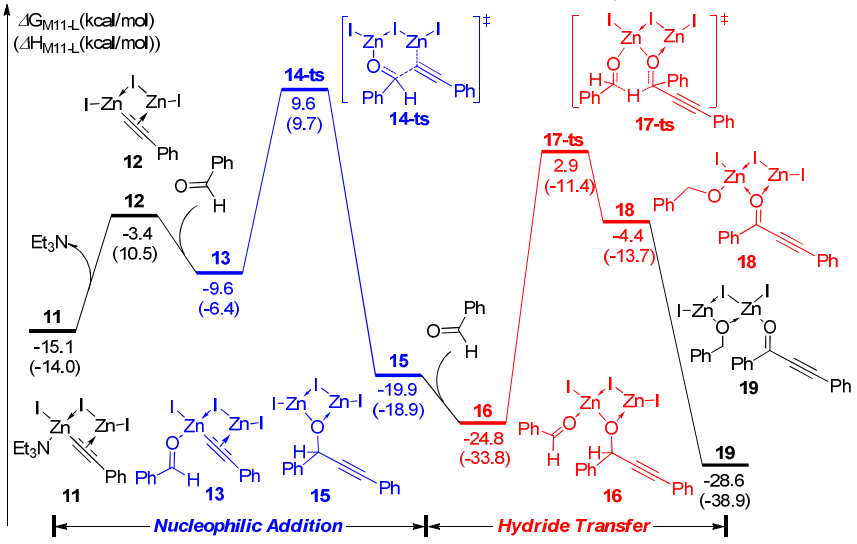


Figure 4. Free energy profile for dinuclear zinc mediated oxidative coupling of phenylacetylene with benzaldehyde.

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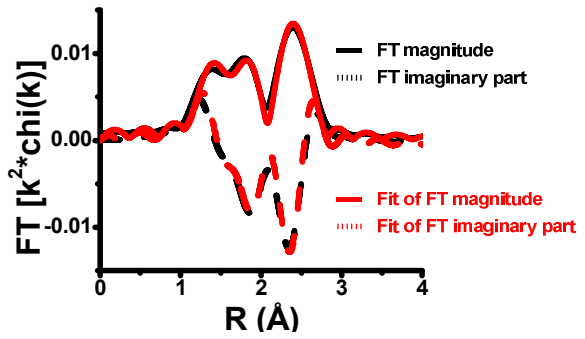

Figure 6. Fitting results of the R-space EXAFS spectrum. FT: Fourier transform. (2.86 Å-1 < k < 10.85 Å-1, 1.16 Å < R < 2.81 Å)

Besides *Operando* IR, subsequent *in situ* EXAFS experiments also correspond well with the dinuclear zinc mechanism. X-ray absorption spectroscopy (XAS) is known as a unique and powerful technique for probing local geometric and electronic structure of metal ions in noncrystalline systems.[79-82] Thus, we conducted the extended X-ray absorption fine structure (EXAFS) experiments to reveal the structural information of *Operando* IR observed species. The fitting results show that each Zn in the active species is bonded to two iodide anions (Figure. 6), which indicates the observed species is a dinuclear zinc complex,[48] thereby validating the dinuclear zinc pathway.

To further clarify the difference in dinuclear and mononuclear zinc mechanism, distortion, interaction, and total reaction energy analysis along the reaction pathways, which has been frequently used to explain the reactivity of bimolecular reactions,[83-88] is employed to investigate the nucleophilic addition step. Herein, the relative energies (ΔE) along the reaction pathways are decomposed into the sum of distortion energies (ΔE_{dist}) and interaction energies (ΔE_{int}) between distorted reactants. As shown in Figure 7, the distance of the forming C—C bond is utilized as the reaction coordinate along the reaction pathway. With the decrease of reaction coordinate, the distortion energy of mononuclear and dinuclear zinc mediated pathways increase simultaneously, while the latter energy is always higher along the whole pathway. However, the trend of interaction energy is different. In dinuclear zinc mediated nucleophilic addition, the interaction energy decreases smoothly when the forming C—C bond length is longer than 2.1 Å, and it decreases quickly when that length is shorter than 2.1 Å, which indicates a withdrawing effect between nucleophile and aldehyde moiety. In another case of mononuclear zinc mediated reaction pathway, the interaction energy increases alongwith the reaction coordinate when the forming C—C bond length is longer than 2.3 Å. This result indicates a repulsion effect between nucleophile and aldehyde moiety, which can be attributed to the small Bürgi-Dunitz angle in **5-ts**. Therefore, the activation energy of mononuclear zinc mediated nucleophilic addition is higher than that in dinuclear zinc pathway.

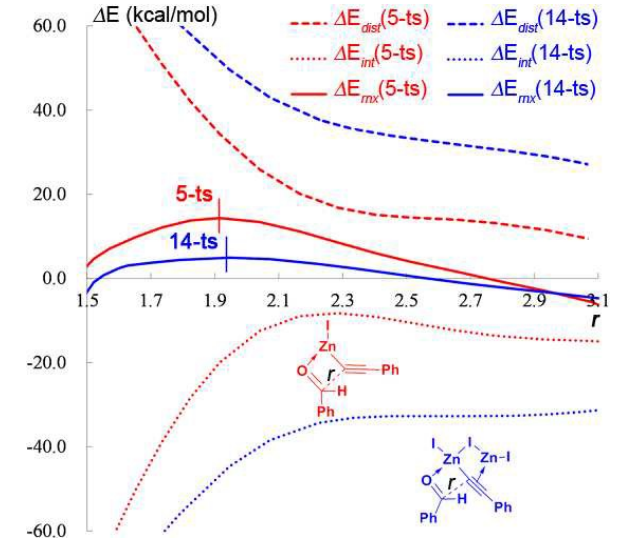

Figure 7. Distortion, interaction, and total reaction energies analysis along the reaction pathways of the nucleophilic addition step mediated by monometallic zinc and bimetallic zinc. The solid lines are the reaction energies. The dashed lines are the distortion energies. The dotted lines are the interaction energies. The reaction pathways for mononuclear zinc and dinuclear zinc mediated nucleophilic additions are represented by red and blue lines, respectively.

Conclusions

Using the oxidative coupling of phenylacetylene with benzaldehyde as a model reaction, a DFT study combined with *in situ* EXAFS and *Operando* IR was carried out to reveal the difference between dinuclear and mononuclear zinc mediated nucleophilic addition. Newly reported density functional theory method M11-L is employed to calculate the detailed mechanism of two different reaction pathways. The typical mononuclear zinc mediated pathway, which involves a four-membered ring transition state for nucleophilic addition, is demonstrated to be unfavourable both thermodynamically and kinetically. The dinuclear zinc pathway, in which the nucleophilic addition proceeds through a six-membered-ring transition state, is proved to be favourable and corresponds well with the experimental observations. Moreover, *in situ*

EXAFS experiments confirmed the existence of dinuclear zinc active species, further validating the DFT calculation. Besides, distortion-interaction analysis along the nucleophilic addition pathway reveals the repulsion between nucleophile and aldehyde moiety in mononuclear zinc pathway, which is not exist in dinuclear zinc pathway. Consequently, because of the rationality and novelty, we believe the dinuclear zinc pathway will provide new insights for chemists to understand zinc involved nucleophilic additions and will promote the development of multinuclear zinc catalysts.

Acknowledgements

This project was supported by the National Science Foundation of China (Grants 21372266, 21372268, 51302327, 21302148, 21390400, and 21025206), the 973 Program (2012CB725302), and the Foundation of 100YOUNG Chongqing University (project 0903005203191). We are also thankful for the project (No.106112015CDJZR228806) supported by the Fundamental Research Funds for the Central Universities (Chongqing University).

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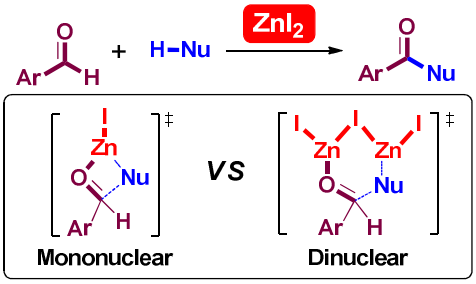

A combined experimental and DFT study was conducted to reveal the difference between dinuclear and mononuclear zinc mediated nucleophilic addition.