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Bimetallic Zinc Complex --- Active Species in Coupling of Terminal Alkynes with Aldehydes via Nucleophilic Addition/Oppenauer Oxidation

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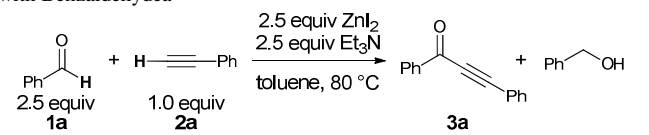
A mechanistic study on the zinc-promoted coupling between aldehydes and terminal alkynes via nucleophilic addition/Oppenauer oxidation using operando IR, XANES/EXAFS and DFT calculations techniques was demonstrated. A bimetallic zinc complex was determined to be the active species.

Zinc salts have long been utilized in synthetic community, such as in Adol reactions,¹ Mannich-type reactions² and Michael reactions.³ Various types of organic transformations could be achieved in the presence of zinc salts.⁴ Due to the nature of zinc element, Zn(II) usually acts as Lewis acid in all those reactions, which makes its rules clear to organic chemists.^{1a, 2c, 5} However, very few attentions have been paid to the real structure of Zn intermediates in organic transformations.^{1e, 6} Since the first demonstration by Trost group,⁷ bimetallic zinc complexes have been used to promote C-C bond formations involving enolates in chemical synthesis.⁷⁻⁸ Meanwhile, due to the remarkable efficiency and stereoselectivity, bimetallic zinc complexes have also been successfully applied in Henry reactions,⁹ CO₂/epoxide copolymerization,¹⁰ desymmetrization of meso 1,3-diols,¹¹ and alkynylation reactions.¹² In most of those transformations, the bimetallic zinc complexes were supported by utilizing special organic ligands.^{7, 8c, 13} Revealing bimetallic zinc complex as the reactive species in simple zinc salt (such as zinc halide) might open up a common phenomenon in zinc involved organic transformations, but it has not been discovered up to date. Herein, by using Zn-promoted coupling between aldehyde and terminal alkyne as the model, we report a bimetallic zinc complex as the active species by direct utilizing ZnI₂ as the promoter through operando IR, XAS analysis and DFT calculation studies.

The addition of terminal alkynes to aldehydes has been previously studied.¹⁴ In the presence of zinc salts, propargylic alcohols could be smoothly generated. However, to the best of our knowledge, using ZnI₂ as the catalyst to promote the Oppenauer oxidation is rare,¹⁵ and the one-pot direct synthesis of ynones from aldehydes and terminal alkynes has not been reported up to date. Herein, we demonstrated a discovery and mechanistic investigation of a ZnI₂ promoted generation of

ynones directly from the reaction between aldehydes and terminal alkynes (Table 1).

Table 1. Impact of Reaction Parameters on the Coupling of Phenylacetylene with Benzaldehyde^a



Entry	Variation from "standard conditions"	Yield of 3a (%) ^b
1	none	85
2	ZnCl ₂ , instead of ZnI ₂	20
3	ZnBr ₂ , instead of ZnI ₂	36
4	ZnI ₂ , 1.5 equiv instead of 2.5 equiv	61
5	ZnI ₂ , 1.0 equiv instead of 2.5 equiv	n.d. ^c
6	ZnI ₂ , 0.5 equiv instead of 2.5 equiv	n.d. ^c
7	Et ₃ N, 1.0 equiv instead of 2.5 equiv	25

^a Standard reaction conditions: 0.5 mmol terminal alkynes, 1.25 mmol benzaldehyde, 1.25 mmol ZnI₂, 1.25 mmol TEA, 2.0 mL toluene, 80 °C, N₂, overnight. ^b Determined by GC with biphenyl as the internal standard. ^c Propargylic alcohol was obtained.

Benzaldehyde **1a** and phenylacetylene **2a** were initially utilized in optimization of reaction conditions. After considerable efforts, ZnI₂ (2.5 equiv.), triethylamine (2.5 equiv.) in toluene at 80 °C with the ratio of **1a:2a** = 2.5:1 were found to be optimal and the desired ynone **3a** was obtained in 85% yield (Table 1, entry 1). Variation from the standard conditions showed that ZnCl₂ afforded **3a** in a 20% GC yield along with the observation of 1 equivalent of benzyl alcohol (Table 1, Entry 2). When ZnBr₂ was applied instead of ZnI₂, a 36% yield of **3a** was obtained (Table 1, Entry 3), indicating that stronger Lewis acid leads to better yield of **3a**. The equivalence of ZnI₂ is essential for the ynone generation. Decreasing the amount of ZnI₂ results in lower yield of **3a** along with the observation of the corresponding propargylic alcohol. No desired product **3a** was detected when the amount of ZnI₂ was decreased to 1 equivalent, while only the corresponding propargylic alcohol was obtained (Table 1, Entries 5-6), indicating that propargylic alcohol might be the intermediate for the synthesis of the final

ynone. Decreasing the amount of Et₃N also results in a low yield of the ynone **3a**, while in this case, the main issue is due to the low conversion of **1a** and **2a**.

This method is general for a variety of terminal alkynes and aldehydes (See ESI Scheme S1). However, the mechanistic insight is still less known. Especially, the role of ZnI₂ is indistinct, as excess amount of ZnI₂ has to be utilized to generate ynone in good yield. Thus, it is highly desirable to carefully investigate the mechanism for this transformation.

It has been shown that Zn-salt is able to promote the addition of terminal alkynes to aldehydes.¹⁴ The observation of the addition product propargylic alcohols inspired us to believe that the first step of this transformation was also the addition of terminal alkyne to aldehyde. Then, the *in-situ* Oppenauer oxidation of the generated propargylic alcohol led to the ynone product.

To gain insights into this transformation, the reaction between **1a** and **2a** was initially monitored by operando IR¹⁶ to see the kinetic profile of the whole reaction course (Figure 1). It is interesting to note that a peak at around 972 cm⁻¹ increased very fast in the beginning and then gradually faded away. This phenomenon suggests this peak might represent an active intermediate, component **I**. Besides component **I**, another component **II** was also detected. By comparing the ConcIRT spectrum with the authentic sample, the component **II** was assigned to be the product ynone **3a** (See ESI, Figure S1). As shown in Figure 1, the peak height of component **I** decreased readily along with the simultaneous formation of **3a**, indicating that component **I** was initially generated from **1a** and **2a**, then gradually consumed to afford the final product **3a**.

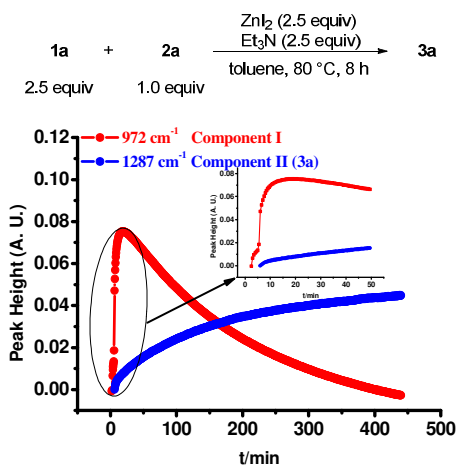
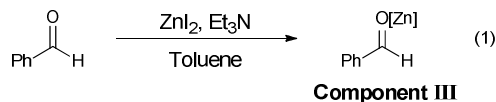


Figure 1. ^a Kinetic profiles of component **I** and **II**. ^b Amplification of kinetic profiles

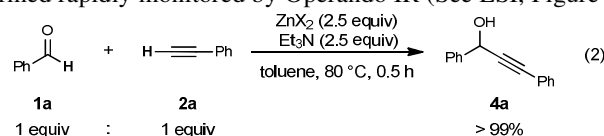
We deduced that component **I** was the terminal alkyne addition product with the oxygen coordinated to a [Zn] center and the peak at 972 cm⁻¹ was speculated to be ν(C-O) stretching mode for component **I**. Furthermore, the spectrum of component **I** has obvious absorption peaks in the range from 1550 to 1800 cm⁻¹ (See Figure S2 in ESI). Normally, the absorption in the 1600-1800 cm⁻¹ region are usually generated from the ν(C=O) stretching. As excess aldehyde was utilized, we speculated that component **I** might have aldehyde carbonyl coordinated to the [Zn] center.

To further assess the structure of component **I**, the stoichiometric reaction between benzaldehyde **1a**, Et₃N, and ZnI₂ was carried out (eqn. (1)), and monitored by operando IR. The reaction vessel was first charged with Et₃N, and ZnI₂ in toluene. After the addition of benzaldehyde, a new component

III appeared immediately along with benzaldehyde decreasing (Figure S3 in ESI). We speculated the structure of the component **III** as an aldehyde carbonyl coordinated Zn complex. By comparing the ConcIRT spectrum of component **I** and **III**, it is obvious to find that they are similar in the range of 1600-1800 cm⁻¹ (Figure 2). The result further confirmed that the component **I** might contain a Zn-coordinated carbonyl unit.



To explore the validity of our hypothesis for the coordination of component **I**, the reaction between **1a** and **2a** with a 1:1 ratio under the standard condition was investigated and monitored by operando IR. The data collection started from blank toluene solvent, followed by sequential addition of phenylacetylene, triethylamine and benzaldehyde. Operando IR spectra were recorded over the course of the reaction. The product was propargylic alcohol **4a** and a quantitative isolated yield was obtained (eqn. (2)). Meanwhile, a new component **IV** was formed rapidly monitored by Operando IR (See ESI, Figure S5).



The comparison between the ConcIRT spectrum of component **I**, **III** and **IV** is shown in Figure 2(a). By comparing the 1600-1800 cm⁻¹ region (Figure 2(b)), we found that component **IV** did not have remarkable absorption in the region of 1600-1800 cm⁻¹. However, there are similar peaks with components **I** and **III** in the 1600-1800 cm⁻¹ region. The result once again indicated that component **I** might contain carbonyl group from benzaldehyde.

Furthermore, *in situ* XANES/EXAFS experiments¹⁷ were conducted to reveal the structural information of component **I** (Figure 3). The data provided direct evidence to validate the above results. As shown in the XANES spectra in Figure 3a, during the course of the reaction, the oxidation state of Zn remains unchanged and the structure of the Zn-species changes slightly. The edge energy of 9661.6 eV, which was determined by the inflection point of the first peak, is in the typical range of Zn(II) species (See ESI for detailed information). The FT magnitudes of ZnI₂ and the observed Zn species under the reaction conditions are shown in Figure 3b. Zn-I peaks were still observed, indicating that the iodide anion is still bound to Zn(II). Besides the iodide peaks, a peak with a shorter bond distance was also observed, suggesting the presence of O/N coordination to Zn(II).

In order to get detailed structural information, the R-space spectrum was fitted using experimental phase shift and amplitude. **The fitting results suggest that each Zn is bonded to two iodide anions at a distance of 2.60 Å. Two light scattering atoms (N/O) were de-termined at an averaged distance of 2.01 Å (Figure 4).** Combining the results from operando IR and *in situ* XANES/EXAFS, we could conclude that each Zinc has two iodides, one aldehyde oxygen and one more O or N ligands.

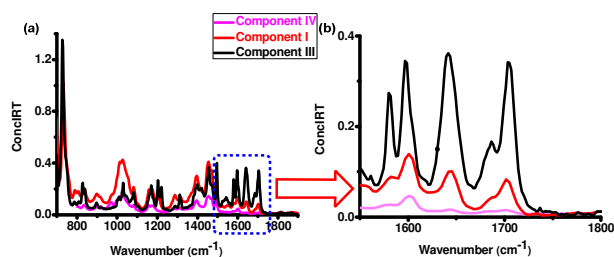


Figure 2. *a* The ConcIRT spectrum of component I, III, IV. *b* Expanded view of the ConcIRT spectrum

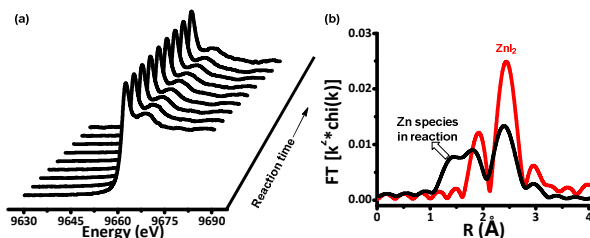


Figure 3. *a* Operando XANES spectra *b* Magnitude of Fourier Transforms of k^2 -weighted EXAFS data (Fourier Transform: Zn species in the reaction: $2.86 \text{ \AA}^{-1} < k < 10.85 \text{ \AA}^{-1}$; ZnI_2 : $2.53 \text{ \AA}^{-1} < k < 11.57 \text{ \AA}^{-1}$)

According to those structural information that the component **I** contains aldehyde carbonyl and each Zn is bonded to two iodide anions and two light scattering atoms (N/O), three possible structures of component **I** were speculated, including two bimetallic zinc complexes **Ia**, **Ib** and one monometallic zinc complex **Ic** (Scheme 2). Component **Ia** and **Ib** are bimetallic zinc complexes with iodide and oxygen as the bridging atoms. **Ia** has two zinc center with different coordination environment and **Ib** has equal coordination environment. For the monomer **Ic**, to fit the structural information obtained from IR and XANES/EXAFS experiments, only one ate-complex structure might be possible with the coordination of two iodides, one aldehyde oxygen and one alcoholic oxygen.

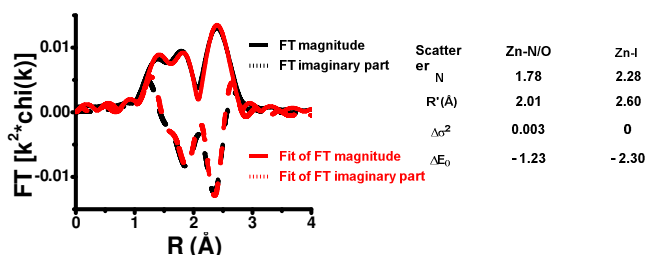
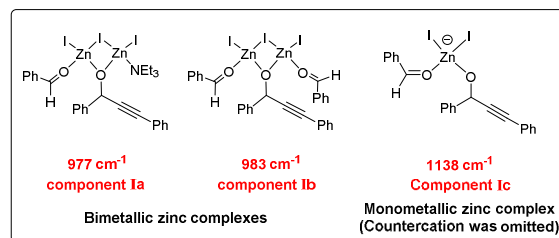


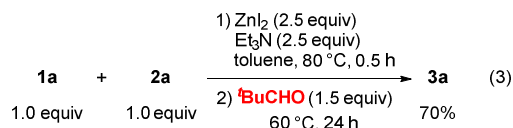
Figure 4. Fitting results of the R-space EXAFS spectrum. FT: Fourier transform; N: coordination number; R¹: bond distance; $\Delta\sigma^2$: Debye-Waller factor; E₀: threshold energy. ($2.86 \text{ \AA}^{-1} < k < 10.85 \text{ \AA}^{-1}$, $1.16 \text{ \AA} < R < 2.81 \text{ \AA}$)

To further elucidate the structure of component **I**, we computed the wavenumbers¹⁸ of component **Ia**, **Ib** and **Ic**. As shown in Scheme 1, DFT calculated wavenumbers of the C-O bond vibration in bimetallic zinc complexes were 977 cm⁻¹ and 983 cm⁻¹, respectively. However, the corresponding wavenumbers in monometallic zinc is 1138 cm⁻¹. DFT calculated C-O bond vibration of bimetallic zinc complexes were in better agreement with the experimental result shown in Figure 1 (peak at 972 cm⁻¹). Therefore, the bimetallic zinc complex is most likely to be the active species in this ynone synthesis.



Scheme 1. DFT calculation of the potential structure of component **I** and the wavenumbers.

At current stage, the requirement of 2.5 equivalents of aldehyde as the substrate is still a drawback for the application of aldehyde in this transformation. The mechanistic studies exhibited that it might be possible to reduce the amount of the starting aldehyde with the use of another simple aldehyde as the oxidant to obtain the final ynone product. It is reasonable to utilize readily available pivalaldehyde as the oxidant, since it does not contain any α -H, which would eliminate the competing aldol reaction. One example was selected and designed to test this approach. First, benzaldehyde **1a** and phenylacetylene **2a** with a 1:1 ratio was heated up to 80 °C in the presence of ZnI₂ (2.5 equiv) and NEt₃ (2.5 equiv) in toluene. After 30 min, 1.5 equiv of pivalaldehyde was added as the oxidant and the reaction was then heated at 60 °C. To our delight, the desired ynone was obtained in a 70% isolated yield (eqn. (3)). This promising model result increase the usefulness of this ynone synthesis approach.



Conclusions

In summary, we have demonstrated a mechanistic study on the zinc-promoted coupling between aldehydes and terminal alkynes via operando IR, XANES/EXAFS and DFT calculation techniques. A bimetallic zinc complex was determined to be the active species. Each zinc has two iodides, one aldehyde oxygen and one more O or N ligands. Operando IR study showed that the addition of terminal alkyne to aldehyde occurred quickly to generate a propargylic alcohol zinc complex followed by a relatively slow oxidation by another aldehyde to afford the final ynone.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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