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A Bioinspired Zn^{II}/Fe^{III} Heterobimetallic Catalyst for Thia-Michael Addition

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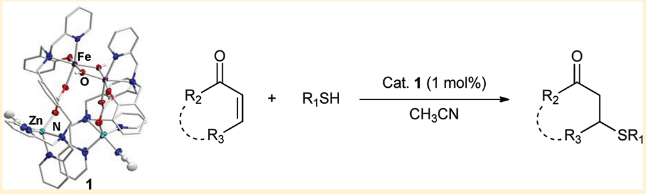
Supporting Information

ABSTRACT: A novel tetranuclear Zn^{II}/Fe^{III} heterobimetallic complex was synthesized, and the complex can efficiently catalyze the Michael addition of thiophenols to α,β-unsaturated enones, even for tertiary carbon−sulfur bond formation.



Organometallic catalysts, one of the most powerful synthetic tools in industry, have been developed for clean, fast, and efficient catalysis for several decades.[1] Recently, many studies have focused on discovering efficient catalytic processes which benefit from the synergistic effect between two adjacent active centers in multinuclear metal complexes.[2] Among the efficient examples, heterobimetallic catalysts have drawn intense attention over the past decade.[3] Several efficient catalysts, such as rare earth-alkali metal−BINOL complexes and bimetallic Schiff base complexes, have been reported in the literature.[4] However, many of those catalysts consist of heavy or rare metals and their toxicity and high cost are a great concern for large-scale manufacturing.[5] Therefore, the use of abundant, cheap, and environmentally friendly metal ions, such as iron and zinc, for developing efficient catalysts is essential for current and future industrial applications.[6] In addition to heterobimetallic catalysts, highly efficient catalysis can be cooperatively carried out by two different metal centers in several metalloenzymes, such as Cu/Zn superoxide dismutases, [NiFe] hydrogenases, cytochrome *c* oxidases, etc. Among those metalloenzymes, purple acid phosphatases (PAPs) possess a dinuclear active site composed of a zinc and an iron center[7] bridged by a monodentate aspartate and presumably a hydroxide.[8] With the structural inspiration of the active site of PAPs, we have designed and prepared a benzoate-based asymmetric polydentate ligand, 2-bis[(2-pyridylmethyl)-aminomethyl]-6-[(2-hydroxybenzyl)(2-pyridylmethyl)-aminomethyl]benzoate acid (H_2PHPB), in which one side arm has two pyridyl groups connected to a tertiary amine and the other has one pyridyl and one hydroxyphenyl group connected to a tertiary amine, for synthesizing novel heterobimetallic complexes (Figure 1). Encouragingly, the ester form of H_2PHPB could be prepared by a one-pot reaction of di-2-picolylamine, methyl 2,6-bis(bromomethyl)benzoate, and (2-hydroxybenzyl)-(2-picolyl)amine in THF in the presence of NEt_3. Further hydrolysis gives an off-white solid of H_2PHPB.

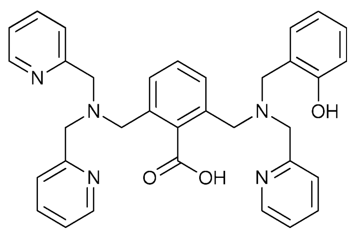


Figure 1. ChemDraw sketch of H_2PHPB.

In a previous work, we have reported a dinuclear complex, $[Ni_2(BBPAB)(CH_3CN)(THF)](ClO_4)_3$ (HBBPAB = 2,6-bis-((2-bis(2-pyridylmethyl)aminoethoxy))benzoic acid), which is a good catalyst for thia-Michael addition.[9] With the newly designed asymmetric polydentate ligand, a tetranuclear heterobimetallic complex, $[(PHPB)Zn(CH_3CN)Fe(\mu\text{-}OH)]_2(ClO_4)_4$ (**1**), was synthesized.[10] It is noteworthy that complex **1** was formed as $[Zn(H_2O)_6](ClO_4)_2$ and $[Fe(H_2O)_6](ClO_4)_3$ were simultaneously added into a methanol solution of the deprotonated $PHPB^{2-}$. The molecular structure of **1** determined by X-ray crystallography reveals two Zn^{II}/Fe^{III} dinuclear units bridged by two hydroxyl groups between two Fe^{III} ions, and the Zn^{II} and Fe^{III} centers of each unit are bridged by the central benzoate group of $PHPB^{2-}$ with a distance of 6.00 Å between the two metal ions (Figure 2). Therefore, the geometry of **1** can be described as a dimer of dimers. More interestingly, the Zn^{II} center is spontaneously bound to the neutral tridentate side arm of $PHPB^{2-}$ containing three N donors, and the Fe^{III} center resides at the anionic tridentate side arm composed of two N donors and one O^- donor. In addition, each Zn^{II} center is coordinated by an acetonitrile molecule. With a labile acetonitrile molecule, the Zn^{II} center of **1** can serve as a Lewis acid for substrate bonding. Meanwhile, the two bridging hydroxide ions on the Fe^{III} center adequately interact with the substrate. Two metal ions, Zn^{II} and Fe^{III}, supported by the asymmetric polydentate ligand of $PHPB^{2-}$ cooperatively function as a heterobimetallic catalyst.

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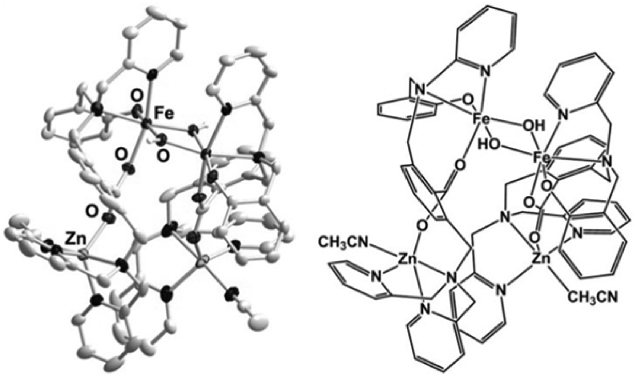
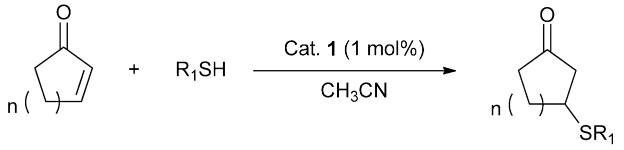
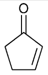
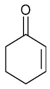
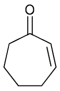


Figure 2. X-ray crystal structure (left) and a schematic drawing (right) of $[(PHPB)Zn(CH_3CN)Fe(\mu\text{-}OH)]_2(ClO_4)_4$ (**1**). Hydrogen atoms, solvent molecules, and the counteranions of **1** are omitted for clarity.

Conjugate addition of thiols to α,β-unsaturated enones is one of the most important synthetic strategies for carbon−sulfur bond formation.[11] Many reported metallocatalysts, including that in our previous study, a dinickel $[Ni_2(BBPAB)(CH_3CN)(THF)](ClO_4)_3$ catalyst, can facilitate the catalysis of thia-Michael addition.[9,12] Complex **1**, which contains bridging hydroxyl groups on Fe^{III} centers, is expected to be an effective catalyst for conjugate addition. 4-Methoxythiophenol was initially selected as a Michael donor to react with 2-cyclohexenone (**3**) by using 1 mol % of **1** in acetonitrile at room temperature for 2 h (Table 1, entry 6). The isolated yield of the product after column chromatography is almost quantitative (97%). To the best of our knowledge, only a few reported ferric organometallic complexes possessed catalytic ability toward Michael additions.[13] The optimized conditions were then applied for screening Michael acceptors and donors. Also, all catalytic reactions were terminated after 2 h for comparison. In fact, many reactions were complete within 10 min. First, a series of Michael acceptors, cycloenones with different ring size, and Michael donors, thiophenols with a methoxy substituent in different positions, were investigated (Table 1). When the methoxy substituent of thiophenol was changed from para to meta and ortho positions, the yield decreased from 97% to 88% and 80%, respectively (Table 1, entries 4−6). A logical speculation for the decrease in reaction yield would be the steric hindrance of the methoxy substituent of thiophenol at a meta or ortho position. The reaction yields for the 2-cyclopentenone (**2**) system were much lower than those for the system of 2-cyclohexanone, especially for 4-methoxythiophenol, but the yield did not follow the trend of bulkiness of methoxythiophenols. Interestingly, the yields for the system of 2-cycloheptenone (**4**) were even higher than those for the 2-cyclohexenone system. This result could be rationalized by the flexibility of the large ring size of cycloheptenone. To examine the catalytic ability of complex **1** for weak Michael donors, 4-nitrothiophenol was selected to react with 2-cyclohexenone. The yield apparently decreased to 64% (Table 2, entry 2) under the same reaction condition as for 4-methoxythiophenol (97%) and thiophenol (89%, Table 2, entry 1). Electronic effects did play a critical role in this heterobimetallic catalytic system. A less reactive Michael acceptor, *N*-crotyloxazolidinone (**6**), was also employed to react with different Michael donors, such as 4-methoxythiophenol, thiophenol, and 4-nitrothiophenol, and the

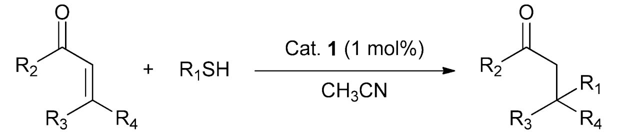
Table 1. Thia-Michael Addition of Thiophenols to Cycloenones[a]

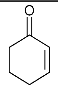
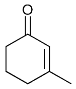
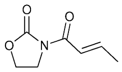


Entry	Michael acceptor	Michael donor	Yield (%)[b]
1	 **2**	2-$MeOC_6H_4SH$	65 (**2a**)
2	**2**	3-$MeOC_6H_4SH$	72 (**2b**)
3	**2**	4-$MeOC_6H_4SH$	69 (**2c**)
4	 **3**	2-$MeOC_6H_4SH$	80 (**3a**)
5	**3**	3-$MeOC_6H_4SH$	88 (**3b**)
6	**3**	4-$MeOC_6H_4SH$	97 (**3c**)
7	 **4**	2-$MeOC_6H_4SH$	99 (**4a**)
8	**4**	3-$MeOC_6H_4SH$	98 (**4b**)
9	**4**	4-$MeOC_6H_4SH$	99 (**4c**)

[a] The reaction was conducted on a 1 mmol scale in CH3CN (4 mL) at room temperature under N_2 for 2 h, and the ratio of enones and thiophenols is 1:1.1. [b] Yield of isolated product after column chromatography.

Table 2. Thia-Michael Addition of Thiophenols to α,β-Unsaturated Enones[a]



Entry	Michael acceptor	Michael Donor	Yield (%)[b]
1	 **3**	C_6H_4SH	89 (**3d**)
2	**3**	4-$NO_2C_6H_4SH$	64 (**3e**)
3	 **5**	4-$MeOC_6H_4SH$	78 (**5a**)[c]
4	 **6**	4-$MeOC_6H_4SH$	85 (**6a**)
5	**6**	C_6H_4SH	73 (**6b**)
6	**6**	4-$NO_2C_6H_4SH$	73 (**6c**)

[a] The reaction was conducted on a 1 mmol scale in CH_3CN (4 mL) at room temperature under N_2 for 2 h, and the ratio of enones and thiophenols is 1:1.1. [b] Yield of isolated product after column chromatography. [c] The catalyst loading of the reaction is 10 mol %, and the reaction is terminated after 2 days.

yields for those reactions were all above 73% for only 1 mol % of catalyst loading (Table 2, entries 4–6). In comparison with our previous dinickel catalyst, $[Ni_2(BBPAB)(CH_3CN)(THF)](ClO_4)_3$,[7] complex **1** is more active toward thia-Michael additions. Furthermore, we have also selected 3-methyl-2-cyclohexenone as a Michael acceptor, and the reaction yield could reach 78% when the catalyst loading was increased to 10 mol %. It is noteworthy that complex **1** can catalyze the formation of a tertiary carbon–sulfur bond.

In order to catch a glimpse of the reaction mechanism of thia-Michael addition catalyzed by complex **1** (*m*/*z* 762.0), excess 4-methoxythiophenol was added into the acetonitrile solution of **1**. A dominant peak at *m*/*z* 835.1 for $[(PHPB)Zn(4\text{-}SC_6H_4OCH_3)Fe(\mu\text{-}OH)]_2^{2+}$ was observed in the ESI-MS spectrum of the reaction mixture, even with the presence of excess 2-cyclohexenone (Figure 3). This result suggested that the thiol group of the Michael donor first coordinates to the Zn^{II} center of the heterobimetallic catalyst **1**, and the thiol proton was dissociated (Figure 4). The enone substrate then had a hydrogen interaction with the bridging hydroxyl group of **1** to form an enolate. The deprotonated thiolate subsequently attacked the *β*-carbon cation of the enolate to form the carbon–sulfur bond. The produced enolate picked up a proton from the surrounding acetonitrile to give the thia-Michael product and to regenerate the catalyst **1** to complete the catalytic cycle. Similar mechanisms catalyzed by mononuclear metallic catalysts have also been proposed.[12j]

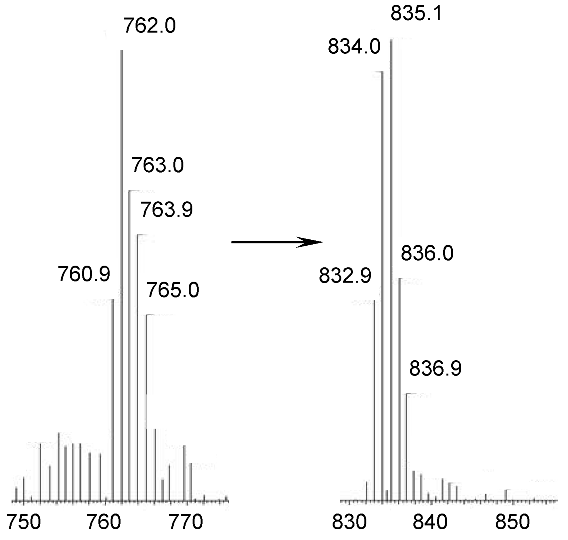


Figure 3. ESI-MS spectra of complex **1** in acetonitrile (left) and **1** with excess 4-methoxythiophenol in acetonitrile (right).

In conclusion, we have prepared the asymmetric benzoate-based dinucleating ligand, H_2PHPB, through a one-pot reaction. The tetranuclear heterobimetallic catalyst $[(PHPB)Zn(CH_3CN)Fe(\mu\text{-}OH)]_2(ClO_4)_4$ (**1**) was synthesized, and Zn^{II} and Fe^{III} ions were spontaneously bound to their prospective coordination site. This heterobimetallic catalyst possesses effective catalytic ability toward the conjugate additions of thiophenols to *α*,*β*-unsaturated enones. The efficient catalytic ability of complex **1** suggests the existence of a synergistic effect between the Zn^{II} and Fe^{III} centers. Further investigations into developing multinuclear ferric asymmetric catalysts are currently being carried out.

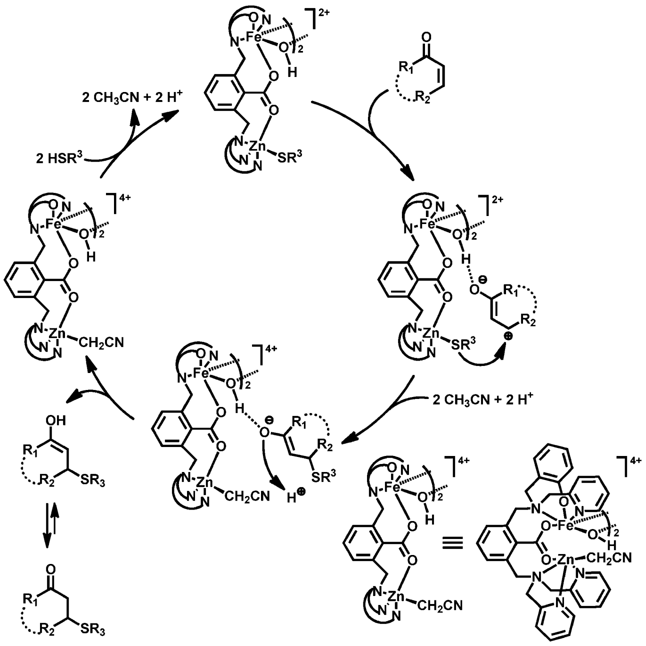


Figure 4. Proposed mechanism for the thia-Michael addition reactions catalyzed by heterobimetallic catalyst **1**.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

A CIF file giving X-ray crystallographic data for complex **1** and text, tables, and figures giving details of the syntheses, characterization data, and ^1H and ^{13}C NMR spectra of the Michael addition products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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