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Catalytic activation of nucleophile precursors with metal acetates in alcohol media and applications to enantioselective Michael addition reactions

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ABSTRACT

Nickel(II) acetate tetrahydrate works as catalyst to activate nucleophile precursors in Michael addition reactions. Use of alcohol media is essential for the high catalytic activation of nucleophile precursors. Catalytic enantioselective reactions using a chiral nickel(II) acetate tetrahydrate between dimedone and α,β-unsaturated amide acceptors provide a useful synthetic access to enantiomers of enol lactones through the carbon-carbon bond formation.

The 'double catalytic activation method (**A** to **B**)', using both catalytic amounts of amine and chiral Lewis acid catalysts, is now recognized as a powerful tool for the enantioselective carbon–carbon bond forming reaction.[1] The combined use of cationic nickel(II) aqua complexes of DBFOX/Ph ligand and 2,2,6,6-tetramethylpiperidine (TMP) in tetrahydrofuran (THF) was especially effective in the Michael addition reactions at room temperature using nucleophile precursors (Eq. 1 of Fig. 1).[2–4] High chemical yields and excellent enantioselectivities were successfully achieved, but the optimization work to find the best amine catalyst was rather time-consuming under the double catalytic conditions. Therefore, we needed a new effective catalytic activation method other than the reaction under the double catalytic activation conditions.

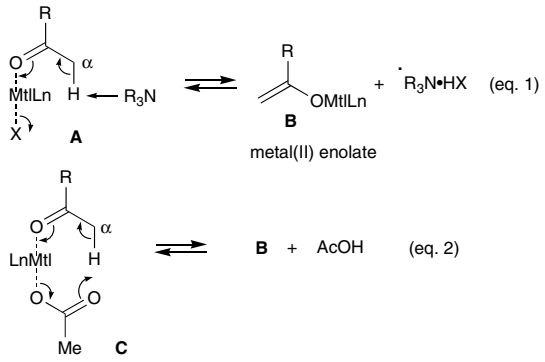

Figure 1. Double catalytic activation method and possible metal enolization through the coordination of a nucleophile precursor to a Lewis acid.

We expected that use of a metal salt catalyst having both Lewis acidic and basic properties would solve this problem. Commercially available metal acetates are the catalysts of our choice.[5] The possible function of metal acetate catalysts is given in Figure 1. When a nucleophile precursor, a methyl ketone as example, coordinates to a metal acetate as Lewis acid catalyst, the proton α to the electron-withdrawing substituent of nucleophile precursor, such as carbonyl or nitro group, becomes more acidic, and the acetoxyl anion contained in the Lewis acid catalyst becomes more basic in the resulting complex **C** so that the nucleophile precursor may be metalated by spontaneous elimination of acetic acid leading to the catalytic generation of metal enolate intermediate **B**, which should show enhanced nucleophilic reactivity in the following reactions (Eq. 2).[6] The acetic acid separated then works to protonate metal enolate **B**, making this process reversible under the absolutely neutral conditions. However, effective precedents are limited for the enantioselective reactions under catalytic conditions using metal acetates.[7] The use of an appropriate reaction solvent would be important for the success.

In this Letter, we will present the successful catalytic activation of nucleophile precursors by treatment with a catalytic amount of nickel(II) acetate tetrahydrate in an alcohol solvent. The resulting reactive nucleophiles catalytically generated can be applied to the highly effective enantioselective Michael addition reactions with α,β-unsaturated amide acceptors.

5,5-Dimethyl-1,3-cyclohexanedione (**1**), a readily enolizable cyclic 1,3-diketone,[6] was successfully activated with a catalytic amount of nickel(II) acetate tetrahydrate (10 mol %) in tetrahydrofuran (THF) at room temperature. However, the reactive nucleophile generated from **1** was trapped only with such a reactive electrophile as 1-crotonoyl-3,5-dimethylpyrazole (**2a**), no reaction having been observed when either 3-crotonoyl-2-oxazolidin- one (**4**) or 1-crotonoyl-3-isopropy-2-imidazolidinone (**5**) was used as acceptor molecule under the comparable reaction conditions (Scheme 1).

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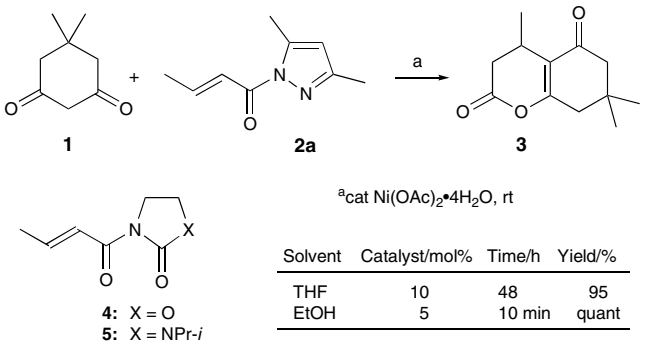
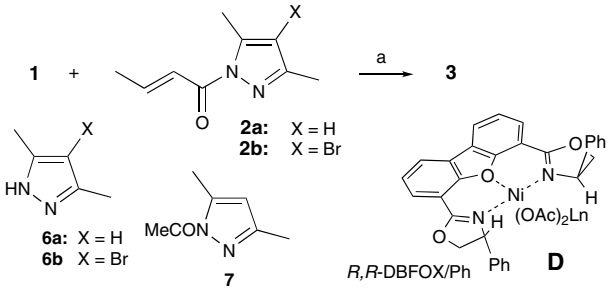


Solvent	Catalyst/mol%	Time/h	Yield/%
THF	10	48	95
EtOH	5	10 min	quant

Scheme 1. Enol lactonization reactions of dimedone (**1**) with 1-crotonoyl-3,5-dimethylpyrazole (**2a**) catalyzed with nickel(II) acetate tetrahydrate.

The reaction in THF took two days to complete and 4,7,7-trimethyl-3,4,5,6,7,8-hexahydrobenzopyran-2(*H*),5-dione (**3**)[4b] was produced in 95% yield. Although the slow reaction rate observed was rather disappointing, this reaction was found to show an extensive rate acceleration in an alcohol solvent. Thus, the reaction in ethanol was complete only in 10 min at room temperature even in the presence of 5 mol % of the catalyst to give enol lactone **3** in a quantitative yield, indicating that the reaction rate was more than 300 times faster in ethanol. We believe that the corresponding nickel(II) enolate was catalytically generated as highly reactive nucleophile.[8,10] This will be mentioned below.

An enantioselective reaction was demonstrated by use of the chiral nickel(II) catalyst **D** derived from (*R,R*)-4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline), DBFOX/Ph, and nickel(II) acetate tetrahydrate. Thus, the reaction of dimedone (**1**) with 1-crotonoyl-3,5-dimethylpyrazole (**2a**) in ethanol at room temperature in the presence of a catalytic amount (2 mol %) of chiral catalyst **D** produced the *S*-enantiomer of enol lactone **3** in a quantitative yield with a moderate enantioselectivity of 75% ee (Scheme 2, entry 4). However, optimization of this reaction was not so difficult. Since enol lactone **3** is formed through cyclization of the 1:1 Michael adduct between **1** and **2a** with the elimination



Entry[a]	Acceptor	Solvent	Cat/mol%	Additive	Time/h	Yield/%	% ee
1	**2a**	THF	10	–	3	36	34
2	**2a**	THF	10	Ac_2O	3	64	71
3	**2a**	THF	10	**6a**	3	14	10
4	**2a**	EtOH	2	–	3	100	75
5	**2a**	EtOH	10	Ac_2O	0.5	80	76
6	**2b**	THF	10	-	3	100	58
7	**2b**	THF	10	Ac_2O	3	100	92
8	**2b**	EtOH	10	Ac_2O	0.5	100	87
9	**2b**	*i*-PrOH	10	Ac_2O	0.5	100	95
10	**2b**	*i*-PrOH	0.5	Ac_2O	16	100	94

[a]DBFOX/Ph + $Ni(OAc)_2•4H_2O$ (10 mol% each unless otherwise stated), additive (1 equiv to **1**), rt.

Scheme 2. Enantioselective enol lactonization reactions of **1** with 1-crotonoyl-3,5-dimethylpyrazoles **2a**,**b**.

of 3,5-dimethylpyrazole (**6a**) as chelating auxiliary, we decided to examine the effect of 3,5-dimethylpyrazole as additive. When 3,5-dimethyl- pyrazole (**6a**, 1 equiv to **1**) was added to the reaction mixture, the yield and selectivity of **3** were both dramatically decreased, indicating that the 3,5-dimethylpyrazole seriously disturbs the reaction (entry 3). Trapping of the pyrazole **6a** with acetic anhydride (1 equiv to **1**) through *N*-acetylation was found to be effective to improve both the yield and enantioselectivity (entries 1 vs 2; 4 vs 5). However, a little more improvement of enantioselectivity was needed.

The role of pyrazole chelating auxiliary of acceptor **2a** determines the reactivity of **2a** not only as electrophile but also as leaving group. Accordingly, we next examined another acceptor **2b**, 4-bromo-1-crotonoyl-3,5-di- methylpyrazole, which is expected to be more reactive than **2a** because of the less basic property of 4-bromo-3,5-dimethylpyrazole (**6b**) as chelating auxiliary. It was our delight to find that 4-bromo-1-crotonoyl-3,5-dimethylpyrazole (**2b**) was actually better acceptor than **2a** (entries 1 vs 6; 2 vs 7; 5 vs 8). Thus, the reaction of **1** with **2b** in isopropyl alcohol in the presence of acetic anhydride (1 equiv) was finished in 30 min at room temperature giving enol lactone **3** in a quantitative yield with the satisfactory enantioselectivity of 95% ee (entry 9). The catalytic loading could be reduced to 0.5 mol % without decrease of the yield and selectivity, while the reaction needed a little longer period of time of 16 h (entry 10).

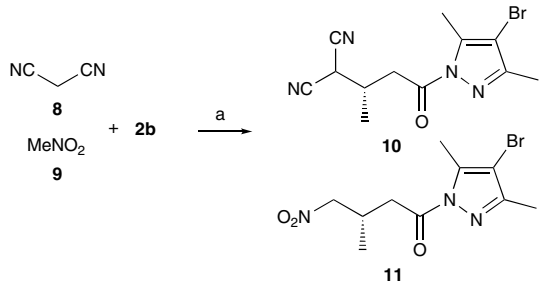
Some other catalysts cobalt(II) acetate tetrahydrate, copper(II) acetate hydrate, and nickel(II) acetylacetonate tetrahydrate[11] also showed high catalytic activity in the reaction between **1** and **2b** in isopropyl alcohol (0.5 M) in the presence of 10 mol % of the catalyst for 1 h at room temperature producing quantitative yields of enol lactone **3**. However, acetate or acetylacetonate salts of iron(II), zinc(II), and palladium(II) ions did not show catalytic activity at all.

Malononitrile (**8**)[6] could also be well activated with nickel(II) acetate in the enantioselective Michael addition reaction. Thus, the reaction of **8** with acceptor **2b** in the mixed solvent of *t*-butyl alcohol and THF (2:1 v/v) in the presence of a catalytic amount (10 mol %) of the *R,R*-DBFOX/Ph complex of nickel(II) acetate tetrahydrate for 4 h at room temperature produced the *S*-enantiomer of the 1:1 adduct **10** in 98% yield with the enantioselectivity of 92% ee (Scheme 2, entry 1). The catalytic loading could be minimized to 0.5 mol % without decrease of the yield of **10**, but the selectivity was lowered to 81% ee (entry 2).

However, the catalytic activation of nitromethane (**9**)[6] with the *R,R*-DBFOX/Ph complex of nickel(II) acetate tetrahydrate even by using excess amount of **9** in *t*-butyl alcohol was rather difficult. A 1:1 v/v mixture of **9** and *t*-butyl alcohol was allowed to react with **2b** in the presence of a catalytic amount (10 mol %) of the chiral nickel catalyst at room temperature for 24 h and the (S)-enantiomer of 1:1 adduct **11** was given in 95% yield with the excellent enantioselectivity of 98% ee (entry 3). The *R,R*-DBFOX/Ph complex of cobalt(II) acetate tetrahydrate also worked as catalyst, but the reaction was relatively slow. Use of *R,R*-DBFOX/Ph chiral ligand is often essential, especially in the reactions of nitromethane (**9**) with **2b**.[12]

Alcohols used as solvent can also be activated by action with nickel(II) acetate to cause the alcoholysis of pyrazole acceptors **2a,b**, and this undesired solvolysis reaction becomes competitive to the carbon-carbon bond forming reaction when the Michael addition reaction is rather sluggish either due to the difficult catalytic activation of nucleophile precursors or due to the low reactivity of metal enolates. In order to avoid such an undesired solvolysis, bulky *t*-butyl and isopropyl alcohols can be safely used (see Scheme 3).

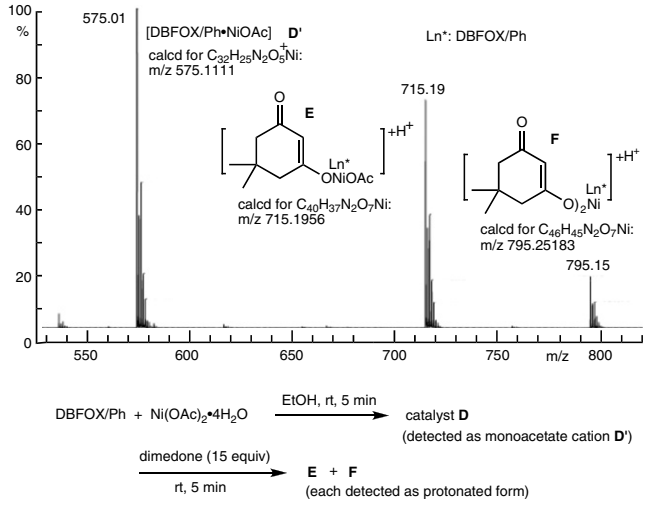
The reactive intermediate catalytically generated from dimedone (**1**) with the DBFOX/Ph complex **D** of nickel acetate tetrahydrate was characterized as the nickel(II) enolates of **1** on the



Entry	Precursor	Solvent	Cat/mol%	Time/h	Yield/%	% ee
1	**8**	*t*-BuOH/THF[b]	10	4	98	92
2	**8**	*t*-BuOH/THF[c]	0.5	12	quant	81
3	**9**	*t*-BuOH/$MeNO_2$[d]	10	24	95	98

[a]Cat **D** at rt. [b]2:1 v/v (0.5 M). [c]10:1 v/v (1 M). [d]1:1 v/v (0.5 M).

Scheme 3. Enantioselective Michael addition reactions of **8** or **9** with **2a** catalyzed with *R,R*-DBFOX/Ph–Ni$(OAc)_2{\cdot}4H_2O$ complex **D**.



Scheme 4. Ion spray TOF mass spectrum confirming the generation of nickel(II) enolates **E** and **F** from dimedone (**1**) and the chiral catalyst **D**.

basis of ion spray TOF mass spectral analysis (Scheme 4). Two intermediates **E** and **F** were generated immediately after **1** was treated with an excess amount of **D** in ethanol at room temperature, which were characterized as nickel(II) monoenolate and dienolate of **1** on the basis of the molecular weights newly appeared at m/z = 715.19 and 795.15, respectively (Scheme 4). We believe that these nickel(II) enolates are involved in the catalytic process of production of enol lactone **3** or other related adducts **10** and **11** under the catalytic conditions.

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8. The acetic acid formed during the reaction can be detected by its characteristic odor.[9]
9. Equimolar amounts of nickel(II) acetate tetrahydrate and dimedone (**1**) were stirred in ethanol, and the solvent was evaporated in vacuo to give a pale green solid with strong odor of acetic acid. This solid, highly soluble in ethanol, showed high catalytic activity in the reaction of **1** with **2a**, but slowly decomposed on treatment with acetone, ethyl acetate, and hot ethanol. Therefore, we could not identify this solid.
10. Enantioselective Michael additions catalyzed with nickel(II) acetate (stoichiometric reaction) are known: (a) Christoffers, J.; Rössler, U.; Werner, T. *Eur. J. Org. Chem.* **2000**, 701–705 and references cited therein; (b) for enantioselective aldol reactions catalyzed by copper(II) acetate: Ref. 5c.
11. Nickel(II) acetylacetonate (10 mol %), which is a commercially available stable salt, showed high catalytic activity in the reactions of dimedone (**1**) or malononitrile (**8**) with 4-bromo-1-crotonoyl-3,5-di-methylpyrazole (**2b**) in isopropyl alcohol at room temperature for 1 h producing quantitative yields of the corresponding Michael adduct or enol lactones, respectively.
12. Even nickel(II) acetate tetrahydrate or cobalt(II) acetate tetrahydrate did not show any catalytic activity without the DBFOX/Ph ligand in the reaction of nitromethane (**9**) with **2b** in *t*-butyl alcohol (**9**/*t*-butyl alcohol = 1:1 v/v) at room temperature.