



Molecular sieves 4A work to mediate the catalytic metal enolization of nucleophile precursors: application to catalyzed enantioselective Michael addition reactions

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ABSTRACT

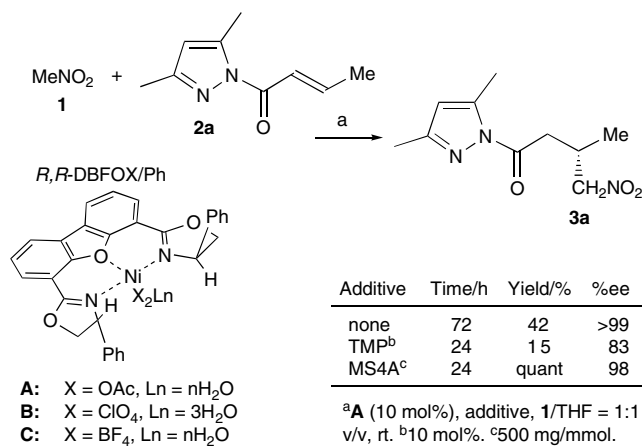
Molecular sieves 4A (MS4A) work effectively as base leading to catalytic generation of nickel(II) enolate or nitronate nucleophiles through deprotonation of the α -hydrogen atom of nucleophile precursors on treatment with a catalytic amount of chiral nickel(II) ions. The resulting reactive intermediates can be successfully trapped with α,β -unsaturated carbonyl electrophiles to produce the corresponding Michael adducts in good yields with high enantioselectivities.

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We have recently developed two catalytic activation methods of nucleophile precursors, such as cyclic 1,3-dicarbonyl compounds, malononitriles, and nitromethane: (1) the double catalytic activation method using both catalytic amounts of chiral cationic nickel(II) and amine catalysts¹ and (2) the catalysis with chiral nickel(II) acetate tetrahydrate in alcohol media.² These methods have been successfully applied to the enantioselective Michael addition reactions with α,β -unsaturated carbonyl acceptors. We believe that these processes involve the reversible generation of metal enolates and related reactive species.

However, nitromethane (**1**) was rather difficult to be activated through either of these methods due to its low enolization ability.³ Thus, the reactions of **1** with 1-crotonoyl-3,5-dimethylpyrazole (**2a**) at room temperature in the presence of a catalytic amount (10 mol %) of the chiral catalyst **A** derived from *R,R*-DBFOX/Ph ligand and nickel(II) acetate tetrahydrate in THF (**1**/THF = 1:1 v/v), either with or without 2,2,6,6-tetramethylpiperidine (TMP), produced the Michael adduct **3a** only in 15% and 42% yields after 24 and 72 h, respectively (Scheme 1). However, we have found during our preliminary works that the same reaction was highly accelerated in the presence of MS4A (500 mg/mmol of **2a**), and the excellent enantioselectivity of 98% ee was observed.

In the present Letter, we will report a new catalytic activation method of nitromethane as nucleophile precursor with the combined use of a Lewis acid and MS4A in alcohol media. The resulting reactive intermediate can be successfully employed in the enantioselective nitromethane Michael addition reactions.

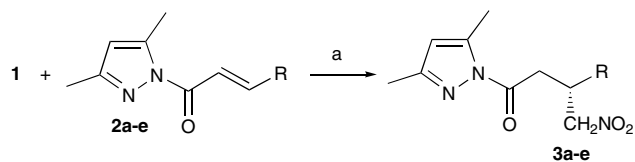


Scheme 1. MS4A mediated rate acceleration of nitromethane Michael addition reactions catalyzed with nickel(II) acetate complex **A**.

When the reaction of **1** with **2a** was carried out in *t*-butyl alcohol (**1**/*t*-BuOH = 1:1 v/v) at room temperature in the presence of a catalytic amount (10 mol %) of the chiral catalyst **A** derived from *R,R*-DBFOX/Ph ligand and nickel(II) acetate tetrahydrate, this reaction was complete in 24 h to give the Michael adduct **3a** in 95% yield with the enantioselectivity of 98% ee (Scheme 2, entry 1), but a little more rate enhancement was needed. Although a catalytic amount of TMP (10 mol %) was added to the above reaction, no significant rate enhancement was observed (entry 2). The presence of acetic acid lowered the reactivity, and trifluoroacetic acid as stronger acid inhibited the reaction (entries 4 and 5). This

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Entry	R	Additive	mol%	Time/h	3	Yield/%	%ee
1	Me	—	—	24	a	95	98
2		TMP	10	22		quant	>99
3		CH ₃ COOH	40	24		46	>99
4		CF ₃ COOH	50	48		—	—
5		MS4A	b	3		quant	>99
6		MS5A	b	24		66	96
7	Ph	MS4A	b	12	b	77	>99
8	<i>i</i> -Pr	MS4A	b	72	c	71	96
9	<i>t</i> -Bu	MS4A	b	72	d	25	98
10	EtOOC	MS4A	b	2	e	90	98

^aA (10 mol%), additive, **1**/*t*-BuOH = 1:1 v/v, rt. ^b500 mg/mmol.

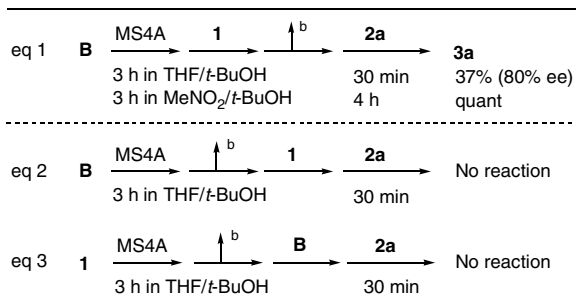
Scheme 2. MS4A mediated nitromethane Michael addition reactions catalyzed with the chiral nickel(II) acetate complex **A**.

indicates that the reversible process for catalytic generation of basic intermediate may be involved in the reaction, and the reacting species reversibly generated is quenched through protonation with acidic additives. To our delight, the reaction was finished in a short time of 3 h in the presence of MS4A to give a quantitative yield of **3a** with an absolute enantioselectivity (entry 5), while MS5A was less effective (entry 6).^{4,5} The catalytic reactions of **1** with a variety of Michael acceptors **2b–e** under the catalysis of **A** were also efficiently mediated by MS4A (entries 7–10).

One possibility for the highly enhanced rate acceleration observed in the above reactions would be based upon the effective catalytic generation of intermediary nickel(II) enolate in high concentration by the aid of MS4A. If this is the case, the cationic nickel(II) catalyst **B** should be the catalyst of choice since **B** is a stronger Lewis acid than nickel(II) acetate complex **A**.⁶ Actually, adduct **3a** was produced quantitatively in 4 h at room temperature under the catalysis of the DBFOX/Ph complex **B** derived from nickel(II) perchlorate hexahydrate in the reaction of **1** with **2a** in *t*-butyl alcohol in the presence of MS4A (Eq. 1 of Scheme 3).

In order to confirm the role of MS4A in the catalytic activation of nitromethane (**1**), we examined three experimental procedures shown in Scheme 3. A mixture of catalyst **B** and MS4A was treated with or without **1** for 3 h, MS4A was filtered off, and then the filtrate was allowed to react with **2a** for 30 min in Eq. 1 or allowed

Catalyst: **B** (10 mol%), MS4A (500 mg/mmol).



^bMS4A was filtered off, and the filtrate was used for the following procedure.

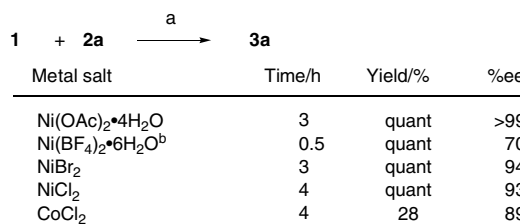
Scheme 3. Experimental procedures for the catalytic activation of nitromethane with **B** by the aid of MS4A.

to react with a mixture of **1** and **2a** in Eq. 2. MS4A was treated with **1** for 3 h and MS4A was filtered off, and the filtrate was allowed to react with a mixture of **B** and **2a** in Eq. 3. It was found that the effective catalytic activation was observed only when MS4A was treated with a mixture of nitromethane (**1**) and the catalyst **B** (Eq. 1). Other two procedures (Eqs. 2 and 3) were totally ineffective. This indicates that nucleophile precursor **1** was activated with MS4A only in the presence of catalyst **B**. MS4A may have worked to increase the concentration of a reactive intermediate, probably the corresponding nickel(II) enolate.⁷ This will be discussed later.

The experimental procedure including the removal of MS4A through filtration after the catalytic preactivation of nucleophile precursors, followed by treatment with acceptor **2a**, resulted in even faster reaction. Thus, the Michael addition reaction of **1** with **2a**, catalyzed by the cationic nickel(II) complex **C**, was complete in 30 min at room temperature, but the enantioselectivity observed in this reaction was unfortunately lower (70% ee, Scheme 4) than the reaction catalyzed by the nickel(II) acetate complex **A** (>99% ee, Scheme 2).⁸ Other metal complex catalysts derived from nickel(II) bromide and chloride showed high catalytic activity and satisfactory selectivity. However, cobalt(II) chloride complex showed a rather low reactivity.

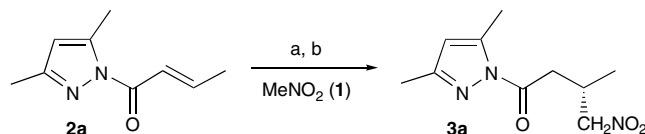
By the way, how quickly does the preactivation including catalytic generation of the reactive intermediate take place by the aid of MS4A? In order to answer this question, we performed the reaction monitoring experiments under various preactivation times as described below in Scheme 5.

A mixture of chiral and cationic complex catalyst **B** and nitromethane (**1**) in *t*-butyl alcohol (**1**/*t*-butyl alcohol = 1:1 v/v) was allowed to interact with MS4A at room temperature for a fixed



^aDBFOX/Ph + metal salt (10 mol% each), MS4A (500 mg/mmol), **1**/*t*-BuOH = 1:1 v/v, rt. ^bMS4A was filtered off after stirring for 3 h, then the filtrate was used in the reaction.

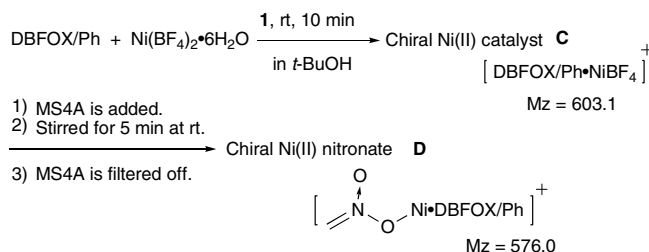
Scheme 4. Use of a variety of metal salts.



^a**B** (10 mol% each), MS4A (500 mg/mmol), **1**/*t*-BuOH = 1:1 v/v, rt, x h.
^bMS4A was filtered off, and then the filtrate was treated with **2a** at room temperature for 0.5 h.

Activation (x h)	Yield/%	% ee
5 min	52	86
0.5	80	74
1	98	79
2	97	79
3	quant	76
26	18	71

Scheme 5. How quick is the Ni(II) nitronate generation?



Scheme 6. Ion spray TOF mass spectral analysis of the preactivation process.

period of time (\times h as preactivation time), and then the MS4A used was removed off through filtration. The filtrate was then allowed to react with the acceptor molecule **2a** at room temperature for 30 min. After the usual workup including chromatographic purification, the yield and enantioselectivity of adduct **3a** were recorded. This procedure was repeated for several preactivation times, and the results obtained are summarized in **Scheme 5**.

After 5 min of preactivation time, adduct **3a** was produced in 52% yield, and 80% after 30 min of preactivation. The yield of adduct **3a** became quantitative after 1 h, indicating that MS4A could act as a strong mediator under the catalysis of cationic nickel(II) catalyst **B**. In addition, the preactivation of nitromethane (**1**) needed only a short period of time. However, when the preactivation of **1** was performed at room temperature for a time longer than 1 day, the catalytic activation almost disappeared. This means that the reacting intermediate catalytically generated is rather unstable under the reaction conditions. The intermediate undergoes partial decomposition to reduce the concentration of nickel(II) enolate as reactive transient species.

The reactive intermediate catalytically generated by the aid of MS4A was characterized as the nickel(II) nitronate of nitromethane (**1**) on the basis of ion spray TOF massspectral analysis (**Scheme 6**). When an alcohol solution of 1:1 catalytic mixture of DBFOX/Ph chiral ligand and nickel(II) fluoroborate hexahydrate was treated with an excess amount of **1** at room temperature in 10 min, an ion peak corresponding to the chiral complex **C** only appeared at $m/z = 603.1$, but no ion peak being observed for the nickel(II) nitronate of **1**. However, a new ion peak appeared at $m/z = 576.0$, assignable as the chiral nickel(II) nitronate **D**, immediately after MS4A was added to the above solution; this ion peak finally grew up as the far major peak after 1 h at room temperature. It is now clear that MS4A is essential for the catalytic generation of nickel(II) nitronate intermediate **D**, and that the concentration of **D** becomes maximized in the reaction mixture.

Thus, MS4A effectively worked as base to induce the catalytic process as described in the experiments shown in **Schemes 3, 5,**

and 6. The authors believe that the nickel(II) enolate **D** of nitromethane has been catalytically generated as reactive nucleophiles in the presence of a catalytic amount of nickel(II) ion catalyst and MS4A.

When nickel(II) acetate is used as catalyst in the reaction with nucleophile precursors, acetic acid is formed together with the nickel(II) enolates. Since acetic acid is a rather weak acid, the resulting nickel(II) enolates can survive in alcohol media not to cause serious deactivation of the enolate by protonation (Eq. 1 of **Fig. 1**). On the other hand, when catalyzed with cationic nickel(II) ions MX (X = ClO₄ or BF₄) instead, the highly strong acid HX is formed as a result of the reversible metal enolization, and the resulting protonic acid works to protonate the nickel(II) enolates.

Nevertheless, cationic nickel(II) catalysts **B** and **C** showed higher catalytic activity than nickel(II) acetate **A** in the presence of MS4A. This indicates that MS4A has worked as effective proton scavenger.⁸ Thus, MS4A(Na) underwent ion exchange reaction with the strong acid HX (X = ClO₄ or BF₄) produced in the catalytic enolization reaction so that a mixture of the protonated Molecular sieves MS4A(H) and neutral sodium salt NaX could be produced.⁹ This ion exchange reaction¹⁰ should be more favored in alcohol media.

In conclusion, we have succeeded to find an effective synthetic method for the catalytic generation of metal enolates or related reactive intermediates from nucleophile precursors by the aid of a mixture of Lewis acid catalyst and MS4A in alcohol media. Use of strong Lewis acid catalyst is more favored for the generation of catalytic species in high concentration. This catalytic method should be widely applied to a variety of synthetic reactions.

References and notes

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- pK_a Values measured in DMSO of the following nucleophile precursors: dimedone: 11.16 (a) Arnett, E. M.; Harrelson, J. A., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 809–812; malononitrile: 11.1 and nitromethane: 17.2 (b) Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006–7014.
- MS3A was similarly effective as well.
- Commercially available MS4A powder was used without further preactivation procedure in the present reactions.
- A strong Lewis acid catalyst should be kinetically favored for the catalytic generation of metal enolates as the forward transformation, but the ready proton quenching with the resulting strong acid is even more favored thermodynamically. If MS4A works as effective proton scavenger, the combined use of a strong Lewis acid and MS4A should result in the effective generation of metal enolates in high concentration.

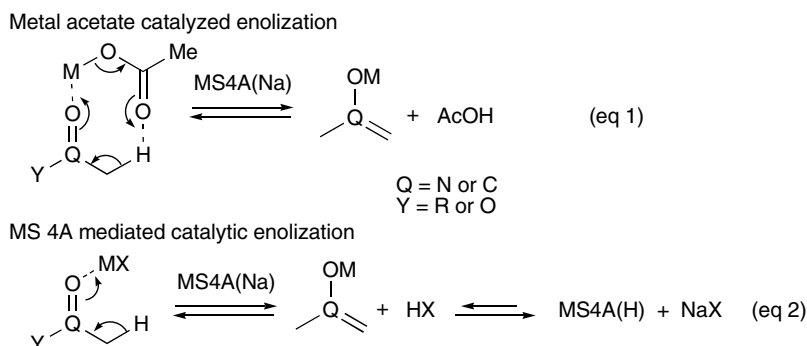


Figure 1. Nickel(II) enolates as reacting intermediates catalytically generated.

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