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Enantioselective Michael addition reactions of malononitrile catalyzed by chiral Lewis acid and achiral amine catalysts

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Abstract—Reactions of malononitrile with 3-(2-alkenoyl)-2-oxazolidinones or 1-(2-alkenoyl)-4-bromo-3,5-dimethylpyrazoles can be doubly activated by the use of catalytic amounts (10 mol% each) of both (*R*,*R*)-DBFOX/Ph·Ni$(ClO_4)_2$·3H_2O and amines, to give the Michael adducts in high chemical yields with satisfactory enantioselectivities.

Michael addition reactions represent one of the most important carbon–carbon bond forming reactions in modern synthetic organic chemistry.[1] Although catalyzed variants of enantioselective Michael additions are known, most are based on the activation of metallated donors modified by chiral ligands[2] and the activation of acceptors by chiral Lewis acid catalysts is quite rare.[3,4] Shibasaki's method using chiral heterobimetallic complexes is based on a different concept in which electrophiles and nucleophiles are both activated by a single catalyst.[5] We have recently achieved catalytic enantioselective Michael addition reactions of nitromethane by use of both catalytic amounts of chiral Lewis acid and amine catalysts.[6] This synthetic method, where donors and acceptors are both activated separately by catalytic amounts of Lewis base and Lewis acid catalysts, can be named 'a double catalytic activation method' using Lewis acid and amine catalysts. The correct choice of Lewis acid catalyst is essential for the success of double catalytic reactions.[6,7]

We report in this communication an enantioselective version of the double catalytic activation method in the Michael additions of malononitrile to 3-(2-alkenoyl)-2-oxazolidinones and 1-(2-alkenoyl)-4-bromo-3,5-dimethylpyrazoles. The reactions are activated by use of both catalytic amounts (10 mol% each) of amines and the aqua complex derived from (*R*,*R*)-DBFOX/Ph and nickel(II) perchlorate hexahydrate in either dichloromethane or tetrahydrofuran at room temperature to give the corresponding Michael adducts in high chemical yields with satisfactory enantioselectivities. Important factors operating in the reactions under the double catalytic activation conditions, such as the proper choice of chiral Lewis acid and amine catalysts, chelating auxiliaries, reaction solvents, and additives, have been discussed.

No reactions occur between 3-crotonoyl-2-oxazolidinone **1a** and malononitrile **2** without catalysts, and amines themselves do not work effectively either. However, a chiral Lewis acid (*R*,*R*)-DBFOX/Ph·Ni$(ClO_4)_2$·3H_2O[8] (**A**, 10 mol%) activated the same reaction giving the Michael adduct **3a** (rt, 72 h, 40%, 5% e.e., Scheme 1), and *R*,*R*-DBFOX/Ph·Mg$(ClO_4)_2$ showed even more effective activation (rt, 48 h, 45%, 86% e.e.).[9] When a catalytic amount of 2,6-lutidine (10 mol%) was added to the reaction catalyzed by **A**, adduct **3a** was given in 90% yield (rt, 4 h, 76% e.e.). Based on the rate enhancement and moderate enantioselectivity observed, the effective activation of acceptor **1a** by coordination to the chiral Lewis acid catalyst **A** was achieved even in the presence of amine catalyst. Thus, the suspected fatal deactivation of the Lewis acid

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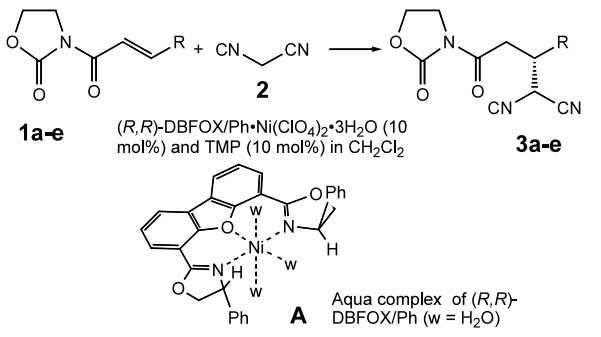


Scheme 1.

catalyst by strong binding of amine was a groundless anxiety in this case.

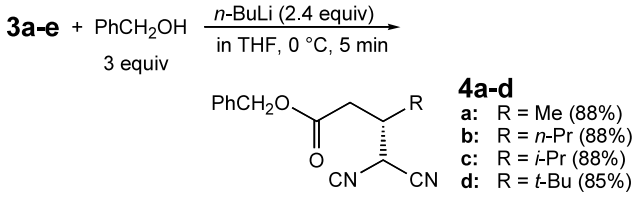
Therefore, a variety of amine catalysts (10 mol%) were examined in the reaction of **1a** with **2** in the presence of Lewis acid catalyst **A** (10 mol%). Some bulky amines were chosen with an expectation of minimized deactivation of the Lewis acid catalyst (Table 1). They include 1,8-bis(dimethylamino)naphthalene (proton sponge), ethyldiisopropylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), *N*,*N*-dibenzylamine, *N*,*N*-dicyclohexylamine, and 2,2,6,6-tetramethylpiperidine (TMP). These amines all worked well in the reactions performed at −20°C to enhance the reaction rates resulting in the satisfactory improvement of yields and enantioselectivities for adduct **3a**. Among these amines, TMP was selected in the enantioselective Michael additions of malononitrile **2** under the double catalytic activation conditions since this amine was best in terms of catalytic activity and enantioselectivity. The high basicity and bulkiness of TMP are synthetically advantageous in this case.[10]

In the reaction of **1a** with **2** under the double catalytic activation conditions, the nickel(II) aqua complex **A** derived from *R*,*R*-DBFOX/Ph and $Ni(ClO_4)_2 \cdot 6H_2O$ gave the highest catalytic activity for the formation of **3a**.[9] Although the magnesium complex (*R*,*R*)-DBFOX/Ph·$Mg(ClO_4)_2$ showed the highest catalytic activity in the reactions without amine catalyst, it was heavily deactivated in the presence of triethylamine (rt, 96 h, 26%, 26% e.e.). Binding of the amine to the magnesium ion is probably stronger than that to the hydrated nickel(II) ion.[11] At the end, the reactions of a variety of 3-(2-alkenoyl)-2-oxazolidinones **1a**–**e** with **2** were performed under the optimized double catalytic activation conditions[12] using Lewis acid **A** and TMP catalysts (10 mol% each) in dichloromethane, mostly at −20°C and in other cases at 0°C to rt, to provide enantiomers of Michael adducts **3a**–**e** (Table 2).[13]

Table 1. Effect of amines in the reaction of **1a** to **2** catalyzed by **A** (10 mol%)

Amine (10 mol%)	Temp. (°C)	Time (h)	Yield (%)	% e.e.
None	rt	72	40	5
Proton sponge	−20	18	92	85
i-Pr_2EtN	−20	24	Quant.	87
DBU	−20	96	70	87
N,*N*-Dibenzylamine	−20	32	Quant.	82
N,*N*-Dicyclohexylamine	−20	8	85	82
TMP	−20	6	90	85

Chiral HPLC analysis was not effective to determine the enantiomeric composition of adducts **3a**–**d**. Therefore, they were transformed into the corresponding benzyl esters **4a**–**d** in good yields by treatment with lithium benzyloxide (THF, 0°C, 5 min, Scheme 2), and the enantioselectivities of Michael adducts **3a**–**d** were found to be satisfactory on the basis of the chiral HPLC analysis of **4a**–**d** on a Daicel Chiral Cell OD-H (85–90% e.e., Table 2). Although the highest enantioselectivity of 94% e.e. was recorded when the β-substituent is bulky as **1d**, the reaction was too slow at −20°C, and therefore the reaction temperature was raised to 0°C. The aryl-substituted substrate **1e** is also less reactive, the reaction occurring at room temperature giving an enantioselectivity of 75% e.e.



Scheme 2.

Although dichloromethane was used effectively in the reaction of **1a** with **2**, some polar solvents could also be employed (Table 3). Thus, acetonitrile was a good solvent for the same reaction at room temperature, but

Table 2. Reactions of **1** with **2** catalyzed by **A** and TMP (10 mol% each) in dichloromethane

R	Alkene	Temp. (°C)	Time (h)	Adduct	Yield (%)	% e.e.
Me	**1a**	−20	6	**3a**	90	85
n-Pr	**1b**	−20	96	**3b**	Quant.	90
i-Pr	**1c**	−20	48	**3c**	90	87
t-Bu	**1d**	0	168	**3d**	58	90
t-Bu	**1e**	−20	168	**3e**	38	94
Ph	**1f**	rt	96	**3f**	95	75

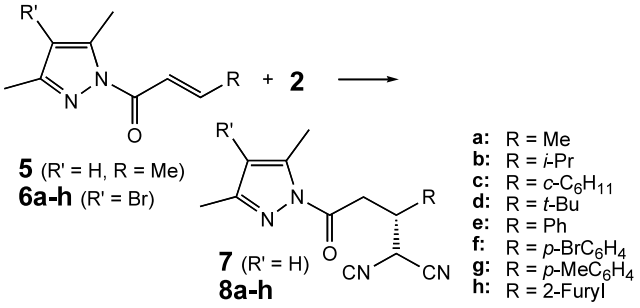
Table 3. Solvent effects in the reactions of **1a** to **2** catalyzed by **A** and TMP (10 mol% each)

Solvent	Temp. (°C)	Time (h)	Yield (%)	% e.e.
MeCN	rt	1.5	89	69
MeCN	−20	120	23	74
MeCN:THF = 1:1 v/v	rt	1.5	92	75
CH_2Cl_2:THF = 10:1 v/v	0	4	98	81
CH_2Cl_2:MeOH = 10:3 v/v	−20	24	Quant.	84

the reaction rate became unexpectedly slow at −20°C. A 1:1 v/v mixture of acetonitrile and THF was an even better solvent and an enantioselectivity of 75% e.e. was observed for **3a**. When dichloromethane was diluted with a small amount of THF (10:1 v/v) or methanol (10:3 v/v), the reaction rates remained high to give quantitative yields of **3a** with satisfactory enantioselectivities even at lower reaction temperatures.

Polar solvents should prevent the coordination of acceptor **1a** to the chiral catalyst **A** resulting in deceleration of reaction, but at the same time such solvents should work to suppress the undesired coordination of amine to the catalyst **A**. These two counterbalancing interactions always compensate each other. This is a pattern usually observed in enantioselective reactions under the double catalytic activation conditions. A good balance of the activating and deactivating factors is important.

We next utilized 1-crotonoyl-3,5-dimethylpyrazole **5** as a Michael acceptor in the reaction of malononitrile **2** as shown in Scheme 3. No reactions took place between **2** and **5** in the absence of a catalyst, and the reaction in the presence of amine catalyst was unworkably slow (TMP, 10 mol%, rt, 96 h, 17% of **7**). Although the complex **A** was an active catalyst and enhanced the reaction between **2** and **5**, the catalytic activity and enantioselectivity were unacceptably low in both dichloromethane (rt, 24 h, 57%, 51% e.e.) and in THF (rt, 96 h, 67%, 75% e.e.). However, the use of TMP as an amine catalyst together with **A** (10 mol% each) was again effective.



Scheme 3.

In the reaction of **2** to pyrazole substrate **5** under double catalytic activation conditions, the presence of a catalytic amount of acetic anhydride (10 mol%) worked to improve the chemical yields and enantioselectivities of **7** where THF was a good solvent (Table 4). The acceptors **6a–h** derived from 4-bromo-3,5-dimethylpyrazole were found to be more reactive than **5** and higher enantioselectivities were given for **8a–h**. Thus, the Michael addition reactions of **2** to bromopyrazole substrates **6a–h** were performed in THF at room temperature in the presence of acetic anhydride (10 mol%) under double catalytic activation conditions using chiral Lewis acid **A** and TMP (10 mol% each). Not only acceptors with β-alkyl substituents **6a–d** but also those with β-aryl substituents **6e**,**f** showed satisfactory enantioselectivities for the reactions performed at room temperature to give Michael adducts **8a–f** (Table 5). Poor reactivity and lower enantioselectivities were observed for the acceptors **6g**,**h** with electron-rich aryl and furyl substituents.

Table 4. Role of acetic anhydride in the reactions of **5** to **2** catalyzed by **A** and TMP (10 mol% each)

Ac_2O (equiv.)	Temp. (°C)	Time (h)	Yield (%)	% e.e.
None	rt	5	86	23
1	rt	6	89	81
0.1	rt	6	82	81

Table 5. Reactions of **5** or **6** with **2** catalyzed by **A** and TMP (10 mol% each)[a]

R	Alkene	Time (h)	Adduct	Yield (%)	% e.e.
Me	**5**	5	**7**	94	81
Me	**6a**	6	**8a**	92	88
Me[b]	**6a**	5	**8a**	89	86
i-Pr	**6b**	7	**8b**	94	93
c-C_6H_{11}	**6c**	24	**8c**	88	90
t-Bu	**6d**	120	**8d**	82	91
Ph	**6e**	12	**8e**	87	88
p-BrC_6H_4	**6f**	12	**8f**	94	85
p-MeC_6H_4	**6g**	24	**8g**	91	78
2-Furyl	**6h**	48	**8h**	78	55

[a] At rt in THF, Ac_2O (10 mol%).
[b] In 2-nitropropane.

The absolute configuration of the Michael adduct **8d** was determined to be *S* on the basis of X-ray crystallographic analysis (Fig. 1), indicating that the *Re*-face of **6d** was involved in the attack of malononitrile **2**. The other adducts **8a**–**h**, as well as **3a**–**e**, were similarly assigned on the basis of the assumed reaction mechanism.

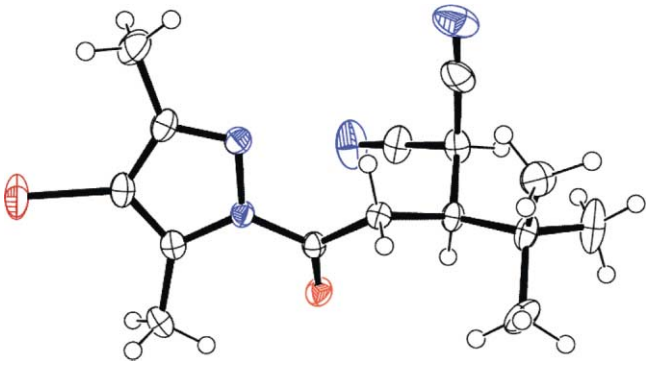


Figure 1. X-Ray determined structure of **8d**.

The enantioselective Michael additions of malononitrile under the double catalytic activation conditions are most likely to proceed through the catalytic cycle shown in Fig. 2. Amine catalyst **D** undergoes deprotonation of malononitrile **C** to generate malononitrile anion **E** which then undergoes enantioselective Michael addition to the reactive complex between electron-deficient alkene **B** and chiral catalyst **A** to give the enantiomer of adduct anion **F**. The resulting metal bound enolate **F** should be a stronger base than the dicyano-stabilized carbanion **G** so that intramolecular protonation of **F** takes place easily leading to anion **G**. Probably, intermolecular anion exchange between **G** and malononitrile **C** occurs to produce the Michael adducts **H** with the concurrent liberation of chiral Lewis acid catalyst **A** and malononitrile anion **E**, which are then involved in the next catalytic cycle shown in Fig. 2.[14] When the stabilized anion **G** is trapped with another molecule of acceptor **B**, the 2:1 adduct is formed. This is a possible side reaction. Actually, the formation of the 2:1 adduct has happened albeit in a poor yield. Especially, when the β-position of acceptors

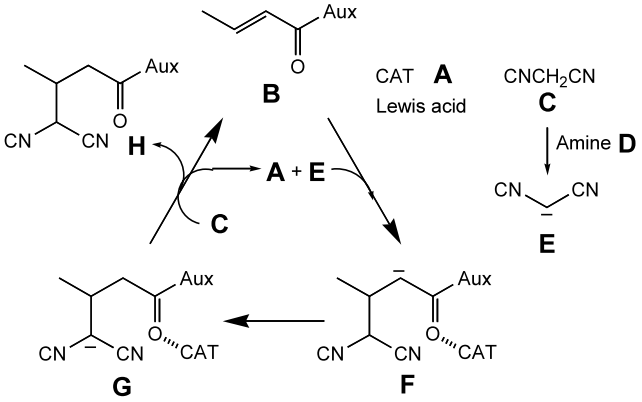


Figure 2. Michael additions under CDAM conditions.

is unsubstituted, formation of the 2:1 adduct predominates.

In conclusion, the double catalytic activation method has worked successfully in the enantioselective Michael additions of malononitrile either to 3-(2-alkenoyl)-2-oxazolidinones or 1-(2-alkenoyl)-4-bromo-3,5-dimethylpyrazoles in the presence of catalytic amounts (10 mol% each) of (*R*,*R*)-DBFOX/Ph·Ni$(ClO_4)_2$·$3H_2O$ as chiral Lewis acid and TMP as amine catalyst. The corresponding Michael adducts have been produced in high chemical yields with satisfactory enantioselectivities. Applications of the double catalytic activation method as a new synthetic methodology for the effective construction of enantiomers through other reactions are now under way[14] and the results will be reported elsewhere soon.

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9. Among the Lewis acid catalysts examined in the reactions under the double catalytic activation conditions, the *R,R*-DBFOX/Ph complexes derived from $Ni(ClO_4)_2{\cdot}6H_2O$ showed much higher catalytic activity and enantioselectivity than other *R,R*-DBFOX/Ph complexes derived from $Zn(ClO_4)_2{\cdot}6H_2O$, $Cu(ClO_4)_2{\cdot}6H_2O$, and $Fe(ClO_4)_3{\cdot}nH_2O$. The achiral titanium catalyst such as $TiCl_2(O^iPr)_2$ did not show any catalytic activity either.
10. Bulky amines such as TMP should be less coordinating to the metallic center of *R,R*-DBFOX/Ph complexes so that deactivation of the Lewis acid catalyst is relatively avoided.
11. The nickel(II) aqua complexes derived from *R,R*-DBFOX/Ph have been demonstrated as tolerant Lewis acid catalysts toward a variety of strongly coordinating nucleophiles.[8b]
12. When the catalytic amounts of amines were reduced, both catalytic activity and enantioselectivities were much decreased.
13. Sometimes, when reactions are performed under a lower temperature such as −40 to −78°C, unexpectedly low enantioselectivities result. The reason has remained unsolved.
14. Such intramolecular protonation has been involved in an enantioselective sequence of Michael addition/cyclization reactions of cyclic 1,3-diketones producing enol lactones under the double catalytic activation conditions. See: Ito, K.; Kanemasa, S., unpublished results.