



Molecular sieve 4 Å generates nitrile oxides from hydroximoyl chlorides. Development of catalyzed enantioselective nitrile oxide cycloadditions to monosubstituted alkenes

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ABSTRACT

The effective generation of nitrile oxide 1,3-dipoles from hydroximoyl chlorides can be achieved with powdered molecular sieves 3 Å and 4 Å as mild solid bases. Rate of nitrile oxide generation depends upon the choice of reaction solvents, among which alcohols are the best media. A catalytic process is achieved by use of a catalytic amount of amine in the presence of MS 4 Å leading to the amine-catalytic generation of nitrile oxides. This new synthetic method can be applied to the catalytic enantioselective nitrile oxide 1,3-dipolar cycloaddition reactions with monosubstituted alkenes.

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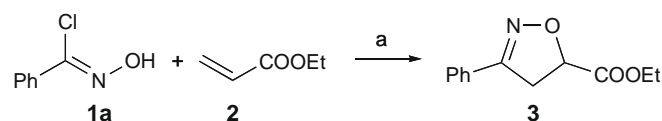
We have recently reported the new synthetic application of molecular sieves, designated MSs hereafter, in the effective catalytic generation of metalated nucleophiles. Combined use of nucleophile precursors with a catalytic amount of chiral Lewis acid in the presence of MS 4 Å as base results in the smooth generation of metal enolates or related nucleophilic species; alcohols are by far the most appropriate reaction solvents.¹ We believe that MS 4 Å (Na) acts as strong base through ion exchange with the protonic acid produced in the catalytic enolization reaction, and that this ion exchange reaction should be more favored in alcohol media. With such a success, we paid attention to investigate the MS-mediated dehydrohalogenation reactions under nearly neutral reaction conditions without amine bases. The target reaction that we aimed to demonstrate was the MS-mediated 1,3-dipolar cycloaddition reaction using hydroximoyl chlorides known as nitrile oxide 1,3-dipole precursors.²

In this Letter, we will present that powdered MSs 3 Å and 4 Å work as mild solid bases to react with hydroximoyl chlorides generating nitrile oxides. The rate of nitrile oxide generation depends upon the choice of reaction solvent and alcohols are the best choice. This new synthetic method can be successfully applied to the first successful catalytic enantioselective nitrile oxide cycloaddition reactions with monosubstituted alkenes.

A solution of benzohydroximoyl chloride (**1a**, 0.22 M), ethyl acrylate (**2**, 1.5 equiv) as dipolarophile and fluorene as internal reference (0.2 equiv of **1a**) in several deuterated reaction solvents, such as dimethyl sulfoxide-*d*₆, acetonitrile-*d*₃, methanol-*d*₄, dichlo-

romethane-*d*₂, and toluene-*d*₈, in the presence of powdered molecular sieve 4 Å (MS 4 Å, 500 mg/mmol of **1a**) at room temperature.³ The reaction was monitored after 2 and 5 h by sampling part of it. The MS 4 Å used was removed by filtration through membrane filter.⁴ The filtrate was submitted to ¹H NMR spectroscopic analysis to determine the yield of cycloadduct **3** between nitrile oxide **4** and dipolarophile **2** on the basis of relative ratio to the internal reference. The results are listed out in the table of Scheme 1.

Both for the reaction times of 2 and 5 h, methanol was the most effective solvent and acetonitrile was the second. On the other hand, dichloromethane and toluene were poor solvents providing only low yields of **3**. Thus, MS 4 Å worked as effective base in the



Solvent	Yield/% of 3	
	2 h	5 h
DMSO- <i>d</i> ₆	42	57
CD ₃ CN	68	80
CD ₃ OD	77	94
CD ₂ Cl ₂	13	36
Toluene- <i>d</i> ₈	12	26

^aMS 4 Å (500 mg/mmol), solvent (0.22 M), rt

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Scheme 1.

generation of nitrile oxide **4** from hydroximoyl chloride **1a** in methanol. However, the MS 4 Å-mediated generation of nitrile oxide **4** from **1a** is much slower than the reaction with triethylamine, and it should be even more important to notice that the rate of generation can be easily controlled by the choice of reaction solvents.

A variety of MSs were examined as solid base for the generation of **4** in methanol as shown in the upper table of Scheme 2. Among MSs 3 Å, 4 Å, and 5 Å which have the same aluminosilicate framework structure and Si/Al ratio of 1, MS 4 Å was found to be most effective, and MS 3 Å was the next. MS 13X having higher aluminum content (Si/Al = 1.4) worked as stronger base than MS 13Y (Si/Al = 20).

A question arose as to how much of MS 4 Å would be enough for the complete generation of nitrile oxide **4** from the hydroximoyl chloride precursor **1a** in methanol. If MS 4 Å works as base through ion exchange between proton and sodium cations, MS 4 Å of ca. 182.5 mg is equivalent to 1 mmol of **1a**.⁵ When 500 mg of MS 4 Å was used for 1 mmol of **1a** (ca. 2.74 equiv to **1a**), nitrile oxide **4** was generated at least in 94% yield after 5 h in methanol at room temperature (the lower table of Scheme 2). With a small excess amount (1.37 equiv to **1a**) of MS 4 Å, the reaction generating **4** remained incomplete even after 5 h.

It is interesting to find that the generation of nitrile oxide **4** from hydroximoyl chloride **1a** becomes catalytic in terms of amine in the presence of MS 4 Å (Scheme 3). Thus, the reaction between **1a** and **2** was much more accelerated with a catalytic amount (5 mol %) of triethylamine even in toluene in the presence of MS 4 Å (500 mg/mmol of **1a**) giving cycloadduct **3** in 94% yield after 5 h at room temperature. Triethylamine is known to react with hydroximoyl chloride **1a** to undergo smooth generation to nitrile oxide **4**, and the resulting triethylammonium chloride then undergoes ion exchange with MS 4 Å to regenerate free triethylamine catalyst. This catalytic cycle is probably repeated in the amine-catalyzed reaction. It is likely that the rate of ion exchange reaction of triethylammonium ion with MS 4 Å is much faster in toluene than the direct deprotonation of **1a** with MS 4 Å. Even 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a much stronger base than triethylamine, worked as amine catalyst in the presence of MS 4 Å, indicating that MS 4 Å works as stronger base than DBU.

Thus, a generation method of nitrile oxide **4** was developed by use of MS 4 Å and hydroximoyl chloride **1a**. Alcohols were the best choice as reaction solvent.

1a + **2** \xrightarrow{a} **3**
1.5 equiv

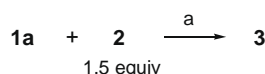
Type	Si/Al Ratio	MS	Yield/% of 3	
			2 h	5 h
3A:	1	3Å	50	70
4A:	1	4Å	77	94
5A:	1	5Å	39	54
13X:	1.4	13X	68	81
13Y:	ca 20	13Y	16	20

^aMS (500 mg/mmol), CD₃OD (0.22 M), rt

MS 4Å		Yield/% of 3	
mg/mmol	equiv/Na ⁺	2 h	5 h
250	1.37	60	66
500	2.74	77	94
750	4.11	86	98

^aMS 4Å, CD₃OD (0.22 M), rt

Scheme 2.



^aAmine catalyst (5 mol%), MS 4Å (500 mg/mmol), solvent (0.22 M), rt

Solvent	Catalyst	Yield/%	
		2 h	5 h
Toluene- <i>d</i> ₈	none	12	26
"	Et ₃ N	76	94
"	DBU	46	78
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CD ₃ OD	none	77	94

Scheme 3.

Nitrile oxides are 1,3-dipoles showing extremely high reactivity to monosubstituted alkenes regardless of the electronic nature of the substituent.⁶ Accordingly, catalysts working effectively in nitrile oxide cycloaddition reactions are not available,⁷ indicating that effective chirality induction with a catalytic amount of chiral catalyst⁸ is extremely difficult since a catalytic amount of the chiral dipolarophile complex can hardly predominate over the uncatalyzed cycloaddition reactions producing racemic product. We challenged to apply our new generation method of 1,3-dipoles in the aid of MS 4 Å to the catalytic enantioselective versions of nitrile oxide 1,3-dipolar cycloaddition reactions.

Our idea includes a procedure in which an equimolar mixture of nitrile oxide precursor **1a** and dipolarophile **5** is slowly added to a mixture of MS 4 Å and chiral catalyst (Fig. 1). With this procedure, one can expect the quick formation of chiral dipolarophile complex **6** and the relatively slow generation of nitrile oxide **4**. By adjusting the proper rate of slow addition of the both substrates, dipolarophile **5** becomes chiral as soon as it is exposed to the catalyst, and less amount of nitrile oxide **4** is gradually generated. Thus, the reactive 1,3-dipole **4** quickly reacts with the chiral dipolarophile complex **6** providing the cycloadduct in high selectivities. Therefore, our procedure should work well. This can be called 'a synthetic method for the production of highly enantioenriched product

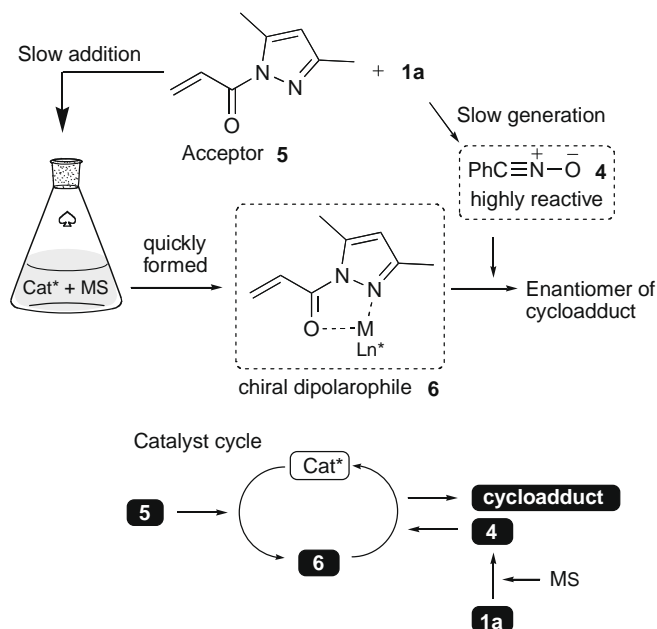


Figure 1. A possibility of enantiomer synthesis through repeated stoichiometric enantioselective reactions.

with repeated stoichiometric reactions' as shown in the lower catalyst cycle in Figure 1.

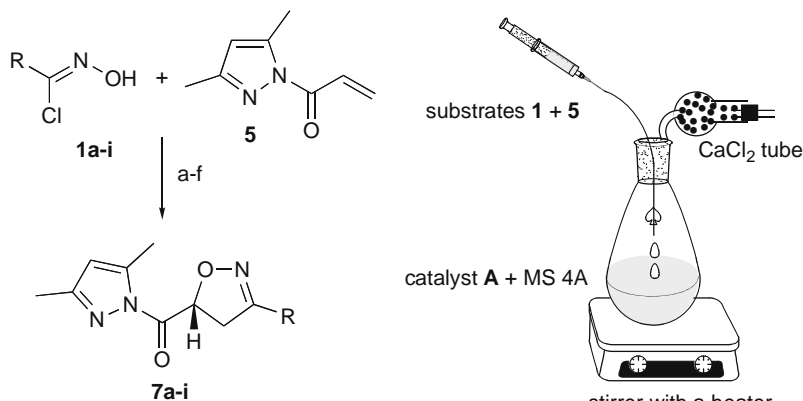
We used the nickel(II) aqua complex⁹ of *R,R*-DBFOX/Ph ligand **A** ($X = \text{ClO}_4$) as chiral Lewis acid catalyst and 1-acryloyl-3,5-dimethylpyrazole (**5**) as dipolarophile, since the substrate **5** is known to form a strong coordination structure with the chiral catalyst **A**.¹⁰ In the preliminary experiment, to a mixture of commercially available MS 4 Å (120 mg) and catalyst **A** ($X = \text{ClO}_4$, 0.024 mmol) in 2-propanol/dichloromethane (1/5 v/v, 0.5 mL)¹¹ was added slowly at room temperature a solution of **1a** and **5** in dichloromethane (0.24 mmol each, 0.2 mL) by use of a syringe.¹² This procedure took 30 min. After the addition was complete, stirring was continued for additional 30 min at room temperature. The MS 4 Å was filtered off through Celite. Purification of the crude product through silica-gel column chromatography gave **7a** in 81% yield with the enantioselectivity of 81% ee.

With such success of the preliminary experiment in hand, the reaction conditions were optimized in terms of the chiral catalyst **A** ($X = \text{ClO}_4$ and BF_4) under dry argon, the preactivation of MS 4 Å by heating with a heat gun under vacuum, use of the dry mixed solvent of 2-propanol/1,2-dichloroethane (1/5 v/v, 0.5 mL), the reaction temperature at 30 or 40 °C, and the spontaneous removal of low-boiling solvent such as dichloromethane. Consequently, better yield (95%) and enantioselectivity (96% ee) were observed for **7a** under the optimized reaction conditions (conditions shown in Scheme 4).

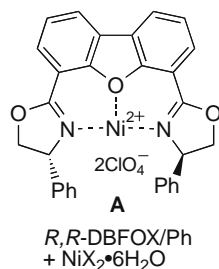
When the pyrazole amide dipolarophile **5** was used together with aqua complex catalyst **A** in a water-soluble solvent such as alcohol, the amide linkage of both **5** and **7a** tends to be hydrolyzed so that the yield of cycloadduct **7a** was significantly lowered. However, the drying procedure of alcoholic solution of catalyst **A** by

stirring with the preactivated MS 4 Å, under dry argon at room temperature for 30 min, was found to be effective to minimize water content in the reaction mixture. With an expectation of shortening the reaction time, the mixed solvent of 2-propanol/dichloromethane was replaced with 2-propanol/1,2-dichloroethane (1/5 v/v, 0.5 mL), and the reaction temperature was raised to either 30 or 40 °C. With this procedure, dichloromethane as a low-boiling solvent was mostly removed by spontaneous evaporation through the drying tube attached to the reaction vessel.¹³ As a result, the solvent contained in the reaction vessel could be kept to be constant in volume so the rate of catalytic reaction was mostly steady.

Under the optimized reaction conditions of 'synthetic method for the generation of highly enantioenriched product with repeated stoichiometric reactions', reaction was performed as follows: An equimolar solution of 2-propanol and 1,2-dichloroethane (1/5 v/v, 2 mL/mmol) containing a catalytic amount of chiral catalyst **A** ($X = \text{BF}_4$, 10 mol%) was allowed to stir with the preactivated MS 4 Å powder (500 mg/mmol) at room temperature under dry argon for 30 min. Then, a dichloromethane solution (2 mL/mmol) of hydroximoyl chlorides **1b–i** and pyrazole dipolarophile **5** was slowly added in the period of 30 min, at 40 °C in some cases using less reactive 1,3-dipoles. After the addition of both substrates **1b–i** and **5** was complete, the resulting mixture was stirred at the same temperature for 30 min. Purification of the crude product through silica gel column chromatography with dichloromethane/ethyl acetate (4/1 v/v) gave isoxazoline cycloadducts **7b–i** in excellent yields with perfect regioselectivities and enantioselectivities. As shown in the table of Scheme 4, the highest yield of **7** was 94% and the maximized enantioselectivity was up to 97% ee.



a: Preactivation of MS 4 Å (120 mg). b: *R,R*-DBFOX/Ph + $\text{Ni}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ (0.024 mmol each) in *i*-PrOH/ CH_2Cl_2 (1/5 v/v, 0.5 mL). c: stirring at rt, 0.5 h. d: **1** + **5** (0.24 mmol each) in CH_2Cl_2 (0.5 mL) is slowly added (0.5 mL/h) at 30 or 40 °C. e: stirring for 0.5 h. f: filtration through Celite, short column (CH_2Cl_2 /ethyl acetate = 4/1 v/v).



1	R	temp/°C	7	yield/%	% ee
1a	Ph	40	7a	94	96
1b	<i>p</i> -MeC ₆ H ₄	30	7b	92	97
1c	<i>p</i> -MeOC ₆ H ₄	30	7c	88	95
1d	<i>p</i> -BrC ₆ H ₄	30	7d	94	93
1e	<i>p</i> -NO ₂ C ₆ H ₄	40	7e	74	90
1f	<i>o</i> -ClC ₆ H ₄	40	7f	65	93
1g	<i>m</i> -ClC ₆ H ₄	40	7g	88	92
1h	<i>p</i> -C ₆ H ₄	40	7h	81	92
1i	<i>t</i> -Bu	30	7i	67	90

Scheme 4.

One of the cycloaddition products **7a** was treated with sodium borohydride in methanol to give a quantitative yield of (5*R*)-3-phenylisoxazoline-5-methanol whose absolute structure was assigned by comparison with the authentic sample.¹⁴ Other isoxazoline derivatives **7b–i** were determined to be 5*R*-enantiomers on the basis of the absolute stereochemistry of **7a**. The stereochemistry observed in the present catalytic cycloaddition reactions producing **7** involves the selective attack of nitrile oxides at the *Re*-face of dipolarophile **5**. This is consistent with the mode of enantioselectivity observed in our previous reactions using chelating acceptor molecules.^{9a,15}

In conclusion, we have developed the effective use of molecular sieve 4 Å for the rate-controlled slow generation of nitrile oxide 1,3-dipoles from hydroximoyl chlorides in alcohol media. Less than 3 equiv of MS 4 Å was sufficient enough for the quantitative generation of nitrile oxides in a few hours. This MS 4 Å-mediated generation method of nitrile oxide can be effectively applied to the catalytic enantioselective nitrile oxide cycloadditions with mono-substituted alkene dipolarophiles. Such highly enantioselective synthesis of isoxazoline enantiomers is otherwise difficult to attain.

Ongoing work in our laboratory will address the application of our newly developed methodology using MS 4 Å to other enantioselective transformations. The results will be presented soon.

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