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Catalytic Enantioselective Conjugate Addition of Nitromethane to α′-Hydroxy Enones as Surrogates of α,β-Unsaturated Carboxylic Acids and Aldehydes

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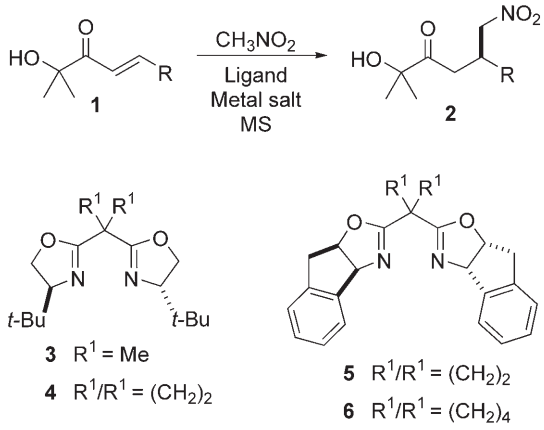
Abstract: No base is required for the Mg(II)-catalyzed conjugate addition of nitromethane to α′-hydroxy enones in the presence of molecular sieves. Good enantioselectivities are attained using 3 or 4 Å MS and about 10 mol% of $Mg(OTf)_2$-chiral bisoxazoline complexes. Elaboration of the adducts through oxidative cleavage of the ketol moiety provides an entry to enantioenriched γ-nitro carboxylic acids, while a sequential carbonyl reduction-diol oxidation yields the corresponding aldehydes.

Keywords: conjugate addition; enantioselective; hydroxy ketones; Michael reaction; nitromethane

The conjugate addition of nitroalkanes to α,β-unsaturated carbonyl substrates[1] is a meaningful tool for remote functionalization in organic synthesis because of the pivotal importance of the nitro group as precursor to amines, through reduction,[2] and to other functionalities.[1a,3] The development of catalytic asymmetric variants is therefore a desirable objective and considerable effort has been devoted in recent years using complementary approaches, namely, metal catalysis,[4] organocatalysis,[5] and PTC conditions.[6] Suitable Michael acceptors with almost no exception are restricted to enones (chalcones, linear aryl enones, and cycloalkenones). While the availability of practical and highly selective methods that are also applicable to unsaturated carboxylic acid derivatives will considerably expand the potential of this remote functionalization strategy in organic synthesis, its implementation is apparently difficult. So far, the only available approaches are due to Kanemasa,[4e] who described a highly enantioselective addition of nitromethane to alkenoylpyrazoles triggered by a combination of a nickel complex and an amine base, and Maruoka,[6e] who showed the addition of nitropropane and other higher nitroalkanes to alkylidenemalonates with good *anti* selectivity and high enantioselectivity under PTC conditions and stoichiometric Cs_2CO_3. Given our recent finding that α′-hydroxy enones act as efficient unsaturated carboxylic acid equivalents in the Cu(II)-catalyzed conjugate addition reactions of certain weak nucleophiles,[7] the assessment of their suitability in the context of the conjugate addition of nitroalkanes was undertaken. In this communication the Mg(II)-bisoxazoline-catalyzed enantioselective conjugate addition of nitromethane to α′-hydroxy enones (Scheme 1) is described.

At the outset, the reaction of nitromethane with enone **1a** in the presence of an amine base[8] and a metal-bisoxazoline[9] complex as catalyst was examined, assuming that preactivation of both the Michael acceptor and the nucleophile was a requirement. In initial experiments using copper(II) as the metal, no



Scheme 1. Conjugate addition of nitromethane to α′-hydroxy enones **1** under Lewis acid catalysis.

Table 1. Effect of ligands and metal salts on the reaction of nitromethane with α′-hydroxy enone **1a** [R = $PhCH_2CH_2$].[a]

Entry	MLn	Ligand	*T* [°C]	*t* [days]	Conv. [%]	*ee*[b] [%]
1[c]	$Cu(OTf)_2$	**3**	−20	11	< 15	0
2	$Cu(OTf)_2$	**5**	20	2	0	–
3[c]	$Zn(OTf)_2$	**3**	−20	11	79	36
4	$Zn(OTf)_2$	**5**	−20	6	< 10	–
5	$Mg(OTf)_2$	**3**	10	1	< 15	0
6	$Mg(OTf)_2$	**4**	10	2	78	0
7	$Mg(OTf)_2$	**5**	10	1	> **99**	**74**
8[c]	$Mg(OTf)_2$	**5**	−20	6	> **99**	**94**
9[d]	$Mg(OTf)_2$	**5**	10	2	93	40
10[e]	$Mg(OTf)_2$	**5**	20	1	96	60
11	$Mg(OTf)_2$	**6**	−20	6	< 10	–

[a] Reactions conducted on a 0.25 mmol scale using CH_3NO_2 (1.5 mL), ligand (12 mol%), metal salt (10 mol%), and molecular sieves (MS) 4 Å (150–250 mg), unless otherwise noted.
[b] Determined by HPLC.
[c] Using 3 Å MS.
[d] Using CH_2Cl_2 as solvent.
[e] Using THF as solvent.

reaction was observed at all, regardless of the bisoxazoline ligand and amine base employed. Using as catalyst the complexes of $Mg(OTf)_2$[10] with ligands **4** or **5**, respectively, the reactions proceeded to variable extents depending on the amine employed (conversions with ligand **5**: DIPEA 65%/10 °C/2 days; 2,2,6,6-tetramethylpiperidine 64%/10 °C/1 day; 2,6-di-*tert*-butylpyridine 18%/−20 °C/8 days), but essentially racemic products were obtained. The results changed drastically when the above reactions were carried out in the presence of molecular sieves. For example, the reaction catalyzed by the $Mg(OTf)_2$-**5** complex and 2,6-di-*tert*-butylpyridine in the presence of 4 Å MS at −20 °C gave an 86% conversion and led to product of 76% enantioselectivity. In subsequent experiments with molecular sieves as additive, it was eventually observed that no amine base was neccesary to achieve reproducible reactivity and selectivity.

Accordingly, a series of Lewis acid-chiral bisoxazoline complexes were tested as catalysts for the reaction of **1a** and nitromethane in the presence of 4 Å MS and the absence of base (Table 1). Of the metals examined, copper (entries 1 and 2) was unable to promote the reaction within a reasonable time-frame regardless of the chiral ligand employed. The complexes of $Zn(OTf)_2$ and ligand **3** or $Mg(OTf)_2$ and ligand **4** did promote the reaction, although long reaction times were needed and selectivities were unsatisfactory (entries 3 and 6). The best performances were attained with the $Mg(OTf)_2$-**5** complex in neat nitromethane (entries 7 and 8) at temperatures from −20 to 10 °C; lower and higher temperatures being accompanied with too low conversions and limited selectivities, respectively. The same systems but with CH_2Cl_2 or THF as solvent (entries 9 and 10) led to diminished enantioselectivities.

The scope of the reaction was examined next. As the results summarized in Table 2 show, the higher reactivity of β-alkyl-substituted substrates with linear alkyl chains (α′-hydroxy enones **1a–c**) allowed their reaction to be performed at the lowest practical temperature (−20 °C) for optimum enantioselectivity (typically, 90–94% *ee*). While quantitatively small, there was an effect of the size of the sieves used on both the reactivity and selectivity, with the following order of increasing performance 5 Å < 4 Å < 3 Å. With enones bearing branched chain acyclic or cyclic alkyl substituents (**1d–f**), room temperature was needed for reasonable reaction times, but still enantioselectivities were around 90%. Modest enantioselectivities were attained with aryl-substituted enones (**1g–i**).

While some examples of base-free activation of the pronucleophile in related reaction systems are described,[11] the precise mechanisms of such activation processes have not been elucidated yet. In our system, the equilibrium concentrations of the tautomeric nitronic acid (or nitronate) species under the reaction conditions are apparently high enough to initiate the catalytic cycle. Molecular sieves, which are attributed to possess both acidic and basic properties,[12] might play a key role in facilitating the tautomerization of nitromethane. On the other hand, in test experiments carried out with other typical Michael acceptors, such as **7–9**, under the base-free conditions reported above, the respective nitromethane addition adducts were obtained in racemic form (Figure 1), an observation that reinforces the critical importance of the α′-hydroxy enone moiety and its ability for strong 1,4-metal binding.

We next studied how structural modification of the ketol auxiliary might influence, and possibly improve, the chemical and stereochemical efficiency of the ad-

Table 2. Enantioselective conjugate addition of nitromethane to α′-hydroxy enones **1** catalyzed by ligand **5**-$Mg(OTf)_2$ complex.[a]

α′-Hydroxy enone **1** Comp.	R	MS	T [°C]	t [days]	Product **2** Yield [%]	ee[b] [%]
a	$PhCH_2CH_2$	4 Å	−20	10	74	90
		3 Å	−20	6	76	94
b	$CH_3(CH_2)_5$	5 Å	−20	9	20	88
		4 Å	−20	9	62	90
		3 Å	−20	6	60	92
c	CH_3CH_2	3 Å	−20	11	60	88
d	$(CH_3)_2CHCH_2$	4 Å	−20	10	74	90[c]
e	*c*-C_6H_{11}	4 Å	r.t.	3	74	86
f	$(CH_3)_3C$	3 Å	r.t.	10	56	90
g	Ph	4 Å	r.t.	9	93	74
h	4-ClC_6H_4	4 Å	r.t.	3	77	78
i	2-MeC_6H_4	3 Å	r.t.	3	75	70

[a] Reactions conducted on a 1 mmol scale using CH_3NO_2 (55.56 mmol, 3 mL), ligand **5** (12 mol%), $Mg(OTf)_2$ (10 mol%) and molecular sieves (1.0 g).
[b] Determined by HPLC.
[c] Determined by ^1H NMR using $Eu(fod)_3$.

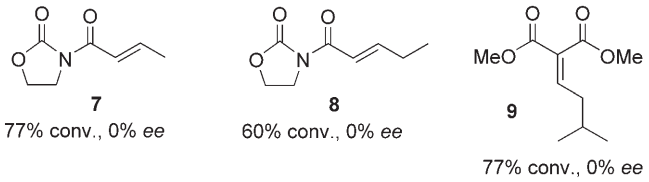
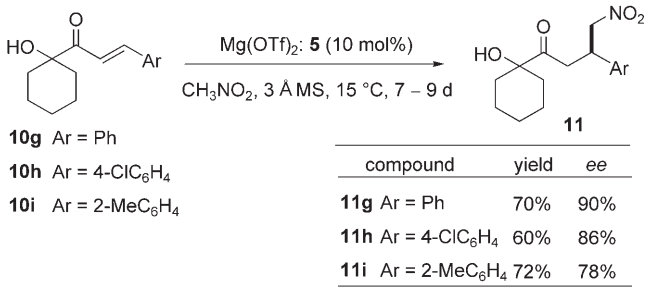


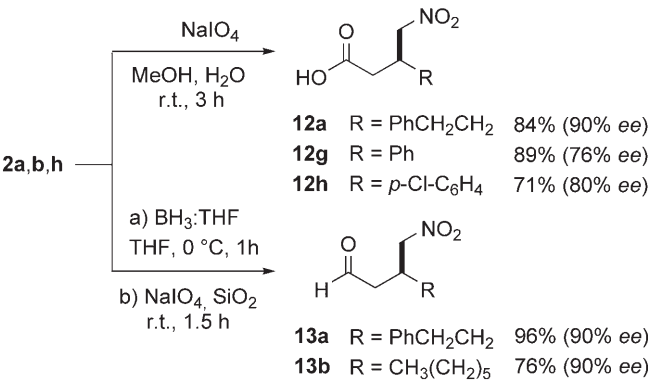
Figure 1. α,β-Unsaturated carboxylic acid surrogates examined for the base-free reaction with nitromethane. Conditions: ligand **5**:$Mg(OTf)_2$ (10 mol%), 4 Å MS, room temperature, 4–5 days.



Scheme 2. Improved results with structurally modified α′-hydroxy enone **10**.

dition reaction. After some examination, it was found that the new family of α′-hydroxy enones **10**, which bear a cyclohexyl ring instead of two methyl groups, led to significantly improved enantioselectivities. For instance (Scheme 2), for the difficult aryl-substituted substrates, enantioselectivities with these templates go from 74% to 90%, from 78% to 86%, and from 70% to 78% for the phenyl-, 4-chlorophenyl- and 2-methylphenyl-substituted enones, respectively.

The synthetic interest of the method is demonstrated by the subsequent elaboration of adducts into functionally diverse building blocks, such as γ-nitro carboxylic acids and aldehydes. For instance (Scheme 3), the treatment of adducts **2** with sodium periodate in methanol-water smoothly afforded the corresponding carboxylic acids **12a**, **12g**, and **12h**. On the other hand, the one-pot, two-step transformation of adducts **2** into the aldehydes **13** is feasible through carbonyl reduction and subsequent oxidative cleavage of the resulting diol with silica-supported sodium periodate. Both type of products **12** and **13** could be obtained[13] without appreciable racemization during the scission, and acetone is the only organic by-product formed along the process.



Scheme 3. Elaboration of adducts into γ-nitro carboxylic acids and aldehydes.

In summary, it has been shown that the base-free, catalytic asymmetric conjugate addition of nitromethane is possible when using α′-hydroxy enone templates under Mg(II):bisoxazoline catalysis in the presence of molecular sieves. The practical interest comes

from smooth elaboration of the adducts into enantioenriched γ-nitro carboxylic acids and aldehydes.

Experimental Section

General Procedure for the Conjugate Addition of Nitromethane to α′-Hydroxy Enones

Magnesium(II) triflate (32.2 mg, 0.10 mmol) and bisoxazoline **5** (42.8 mg, 0.12 mmol) were combined under a nitrogen atmosphere and, after addition of nitromethane (3 mL, 55.56 mmol), the solution was stirred for 1 h at room temperature. To this solution, molecular sieves (1.00 g, 4 Å or 3 Å) were added and the resulting mixture was stirred for an additional 1 h at the same temperature. The corresponding α′-hydroxy enone (1 mmol) was then added at −20 °C or room temperature and the resulting reaction mixture was stirred at the given temperature for the time specified in Table 2. The mixture was quenched with 1 M HCl (3 mL), diluted with CH_2Cl_2 and filtered through a glass filter funnel. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×4 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure, and the residue was purified by chromatography (silica gel; eluent: ethyl acetate/hexane, 1:4).

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