Lanthanide Triflate-Catalyzed Three-Component Coupling Reactions of Aldehydes, Hydroxylamines, and Alkenes Leading to Isoxazolidine Derivatives

Shū Kobayashi,* Ryo Akiyama, Mikako Kawamura, and Haruro Ishitani
Department of Applied Chemistry, Faculty of Science, Science University of Tokyo (SUT), and CREST, Japan Science and Technology Corporation (JST), Kagurazaka, Shinjuku-ku, Tokyo 162

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Three-component coupling reactions of aldehydes, hydroxylamines, and alkenes proceeded smoothly in the presence of a catalytic amount of a lanthanide triflate, to afford isoxazolidine derivatives in high yields with high diastereoselectivities. The asymmetric 1,3-dipolar cycloaddition using a chiral lanthanide catalyst is also described.

The 1,3-dipolar cycloaddition of nitrones to alkenes provides a useful route to isoxazolidine derivatives, whose reductive cleavage gives a range of compounds such as β-hydroxy ketones and β-amino alcohols, etc.[1] Lewis acids are known to promote the cycloaddition,[1,2] however, some nitrones, especially α-aliphatic nitrones, are unstable under these conditions and lower yields are sometimes observed. It is desirable from a synthetic point of view that nitrones, which are prepared *in situ* from aldehydes and hydroxylamines, immediately react with alkenes (the one-pot preparation of isoxazolidine derivatives from aldehydes). In addition, three-component reactions provide a useful method for the preparation of isoxazolidine libraries.[3] In this paper, we report lanthanide triflate-catalyzed three-component reactions of aldehydes, hydroxylamines, and alkenes, which provide isoxazolidine derivatives in high yields with high diastereoselectivities. The asymmetric 1,3-dipolar cycloaddition using a chiral lanthanide catalyst is also described.

Recently, we have demonstrated that lanthanide triflates and related compounds are excellent catalysts for the activation of nitrogen-containing compounds (for example, aldimines).[4-9] While many Lewis acids are deactivated or sometimes decomposed by the nitrogen atoms and even when the desired reactions proceed, more than stoichiometric amounts of the Lewis acids are needed because the acids are trapped by the nitrogen atoms. On the other hand, it has been demonstrated that lanthanide triflates retain activity in the presence of nitrogen-containing compounds, and that Mannich-type reactions,[4,5] imino Diels-Alder reactions,[4,6] allylation[7] and cyanation reactions[8] of aldimines, etc.[9] proceed smoothly in the presence of catalytic amounts of lanthanide triflates. On the basis of these results and backgrounds, activation of nitrones by lanthanide triflates was examined, and it was found that cycloaddition of nitrones with alkenes proceeded smoothly in the presence of a catalytic amount of a lanthanide triflate.[10]

Furthermore, it was also found that the intended three-component reactions of aldehydes, hydroxylamines, and electron-defficient alkenes proceeded smoothly by using a lanthanide triflate as a catalyst, to afford the desired isoxazolidine derivatives. It should be noted that most Lewis acids can not be used in this reaction since they are decomposed or deactivated by the amines and water which exist at the stage of nitrone formation. In addition, it was revealed that nitrone formation was also accelerated by lanthanide triflates. The effect of solvents in the model reaction of benzaldehyde, *N*-benzylhydroxylamine, and 3-(2-butenoyl)-1,3-oxazolidin-2-one (**1**) using 20 mol% Yb(OTf)$_3$ is shown in Table 1. While toluene, benzene, hexane, and ether gave high yields of the isoxazolidine, a lower yield was observed in PE. High *endo* selectivities were observed in most cases. It is noteworthy that hexane gave a high chemical yield and diastereoselectivity while no product was obtained in acetonitrile. These results are contrary to the standard solvent effect in the lanthanide triflate-catalyzed reactions.[11] While a 70% yield of the adduct was still obtained using 10 mol% Yb(OTf)$_3$ (toluene, rt, 10 h), the yield decreased to 33% in the presence of 5 mol% Yb(OTf)$_3$ under the same reaction conditions. The oxazolidine derivative was obtained in a 77% yield (*endo*/*exo* = 96/4) when 20 mol% Sc(OTf)$_3$ was used (toluene, rt, 10 h).

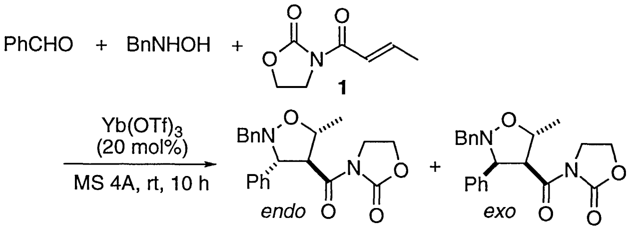


Table 1. Effect of solvents

Solvent	Yield/%	*endo*/*exo*[a]
CH_2Cl_2	42	88/12
Toluene	82	94/ 6
Benzene	80	96/ 4
Hexane	80	98/ 2
PE	31	94/ 6
Et_2O	74	97/ 3
CH_3CN	0	—
MeOH	0	—
DMF	0	—

[a] Determined by ^{1}H NMR.

Several examples of the present three-component coupling reactions are summarized in Table 2. 3-(2-Propenoyl)-1,3-oxazolidin-2-one also worked well, and the corresponding isoxazolidine derivative was obtained in a high yield with perfect *endo* selectivity. Not only aromatic, but also aliphatic and heterocyclic aldehydes reacted smoothly under these conditions. As for alkenes, *N*-phenylmaleimide and an enone were also found to be good substrates in these reactions. In all cases, good to excellent *endo* selectivities were observed. It is noted that lanthanide triflates are excellent catalysts in these three-component coupling reactions, and that the catalysts could be recovered quantitatively after the reactions were completed and could be reused.[12,13]

Finally, a catalytic asymmetric 1,3-dipolar cycloaddition was carried out using a chiral ytterbium catalyst.[14] The chiral catalyst, which was effective in asymmetric Diels-Alder reactions,[15] was prepared from Yb(OTf)$_3$, (R)-(+)-1,1'-bi-naphthol, and 1,2,6-trimethylpiperidine according to our

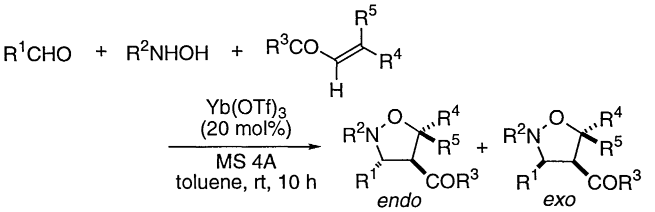
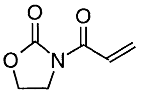
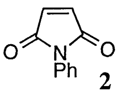
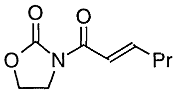
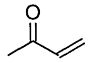
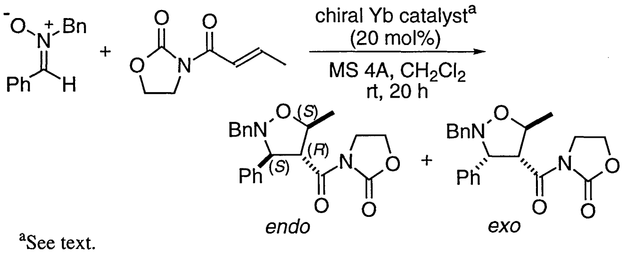


Table 2. Synthesis of isoxazolidine derivatives

R^1	R^2	Dipolarophile	Yield/%	*endo*/*exo*[a]
Ph	Bn	**1**	82	94/ 6
$Ph(CH_2)_2$	Bn	**1**	93	98/ 2
Ph	Bn		90	>99/ 1
Ph	Bn	 **2**	53 (52	>99/ 1 >99/ 1)[b]
Ph	Ph	**1**	88 (quant.	85/15 91/ 9)[c]
Ph	Ph		87	80/20[c]
Ph	Ph		75	77/23[c]
1-naphthyl	Ph	**1**	68 (quant.	88/12 83/17)[c]
2-furyl	Ph	**1**	99	89/11[c]
$Ph(CH_2)_2$	Bn	**2**	79	nd[d]

[a]Determined by ^{1}H NMR. [b]$Sc(OTf)_3$ was used in dichloro-methane at rt. [c]$Sc(OTf)_3$ was used in dichloromethane at 0 °C. [d]Diastereomer ratio = >99/1 (determined by ^{1}H and ^{13}C NMR). Relative stereochemical assignment was not made.

previous report,[15] and the reaction of benzylbenzylideneamine *N*-oxide with 3-(2-butenoyl)-1,3-oxazolidin-2-one (**1**) was performed in the presence of the chiral catalyst (20 mol%). The reaction proceeded smoothly in dichloromethane at rt, and the desired isoxazolidine was obtained in a 72% yield with perfect diastereoselectivity (*endo*/*exo* = >99/1), and the enantiomeric excess of the *endo* adduct was 78% as determined by HPLC analysis.[16]



[a]See text.

72% yield, *endo*/*exo* = >99/1, 78% ee (*endo*)

Further studies to modify these three-component reactions to a method for the synthesis of isoxazolidine and amino alcohol libraries as well as to develop more efficient chiral catalyst systems are now in progress.

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16 We have found that reverse enantioselectivity was observed when a chiral scandium catalyst was used in stead of the chiral ytterbium catalyst (the same chiral source). Further investigations are under way and will be reported in due course.

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