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Nitrone cycloaddition reactions to α,β-unsaturated carbonyl acceptors catalyzed by a pinhole Lewis acid catalyst. Dramatic rate acceleration and improvement of regioselectivity and diastereoselectivity

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Abstract—A catalytic amount of aluminum tris(2,6-diphenylphenoxide), designated as ATPH, catalyzes nitrone cycloaddition reactions between *N*-benzylideneaniline *N*-oxide and α,β-unsaturated carbonyl acceptors and induces a dramatic rate enhancement showing high to exclusive control of regioselectivity in favor of the formation of isoxazolidine-4-carboxaldehydes. Such high regioselectivities leading to electronically controlled cycloadducts provides a striking contrast to the selectivities generally observed for the uncatalyzed reactions in which regioselectivities result from a competition between steric and electronic factors. Thus, the use of a pinhole catalyst is effective for a selective activation of electrophiles in the catalyzed reactions using strongly coordinating bulky nucleophiles.

Effective activation of 1,3-dipolar cycloaddition reactions by use of a Lewis acid catalyst has remained unsolved for a long period of time, and to date has remained a challenging subject in modern synthetic organic chemistry. After our fundamental researches on reaction control of nitrone[1] and nitrile oxide cycloaddition reactions[2] by the influence of a Lewis acid catalyst, Jørgensen and co-workers were successful to report the first example of catalyzed asymmetric nitrone cycloadditions in 1994.[3] Since then, quite a number of examples have been reported for the catalyzed asymmetric nitrone cycloaddition including cycloadditions with electron-deficient alkenes[4] and electron-rich alkenes.[5]

One serious problem is the strong coordination of the nitrone 1,3-dipoles to the catalyst since this undesired coordination leads to a fatal decrease of catalytic activity.[6] Although the use of Lewis acid catalysts, which can undergo rapid ligand exchange for strongly coordinating 1,3-dipoles, is effective to solve the problem, activation of the reaction has to depend upon the disappointingly small contribution of the dipolarophile/catalyst complex. Even when highly coordinating chelating dipolarophiles such as 3-alkenoyl-2-oxazolidinones or 1-alkenoyl-2-imidazolidinones are employed, the binding of the nitrones to the catalyst is still much more favored. An idea to change the equilibrium in favor of the dipolarophile/catalyst complex is required for a more fundamental solution.

When the metal center of a Lewis acid is surrounded by bulky ligand(s), it can be expected that the resulting complex has a small opening in the ligand sphere. Such Lewis acid catalysts whose metal center is open to the outside through a small opening could be called '*pinhole catalyst*'. It should be difficult for relatively bulky 1,3-dipoles to coordinate to the metal center of the pinhole catalyst due to serious steric congestion. Accordingly, it is expected that deactivation of the catalyst by strong binding of the 1,3-dipoles can be effectively avoided. On the other hand, less bulky electrophilic dipolarophiles such as α,β-unsaturated aldehydes or methyl ketones should be able to coordinate more readily to the metal center via the opening in the ligand sphere of the catalyst.

Keywords: nitrones; 1,3-dipolar cycloaddition; pinhole catalyst; ATPH, regiocontrol; unsaturated aldehydes and ketones; electronic control; isoxazolidine-5-carbaldehydes.

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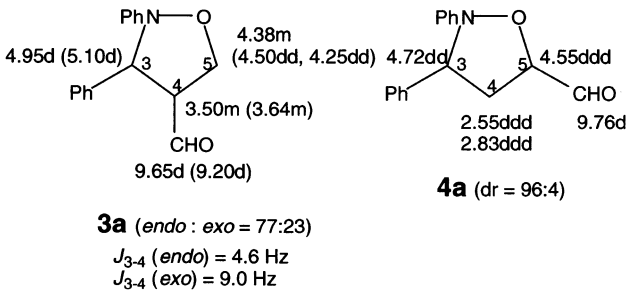
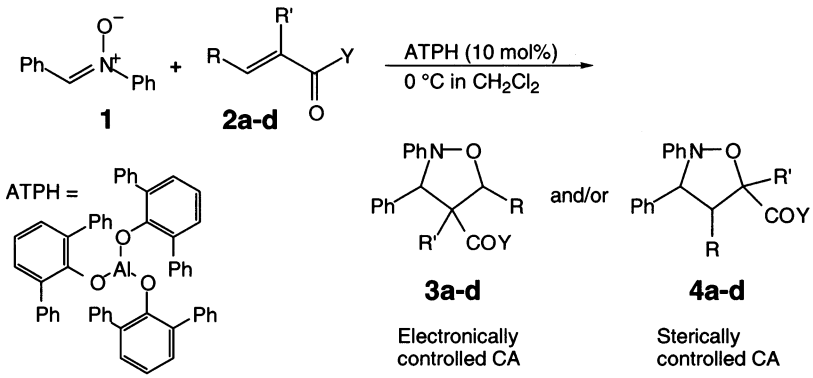
Here we report an effective activation of 1,3-dipolar cycloadditions by use of a pinhole catalyst. Aluminum tris(2,6-diphenylphenoxide) [ATPH], the preparation of which was reported by H. Yamamoto et al.,[7] is the pinhole catalyst chosen for the present work. ATPH is known to give stable complexes with carbonyl compounds, and therefore complexes of this type have been utilized as useful carbonyl protecting reagents.[7] A pinhole exists in ligand sphere, and this hole is used for the tight complexation of the metal with the carbonyl group. Only a limited number of reports have appeared describing the catalytic use of ATPH.[8] However, it could be anticipated that ATPH would work well as a Lewis acid catalyst in nitrone cycloadditions, since the cycloaddition reaction of nitrones to activated carbon–carbon double bonds leads to the formation of bulky isoxazolidines.

N-Benzylideneaniline *N*-oxide (**1**), as a typical acyclic nitrone, shows only a poor reactivity towards acrolein (**2a**) at room temperature in the absence of a catalyst. When **1** is allowed to react with **2a** at room temperature in dichloromethane for 8 h in the absence of a catalyst, a 20:80 mixture of regioisomeric cycloadducts, 2,3-diphenylisoxazolidine-4-carbaldehyde (**3a**) and -5-carbaldehyde (**4a**), is obtained in only 5% total yield. The starting materials can be mostly recovered unchanged (Scheme 1). On the other hand, when the same reaction is performed at 0°C in the presence of a catalytic amount of ATPH (10 mol%), isoxazolidine-4-carbaldehyde derivative **3a** is produced after 8 h in quantitative yield as a single regioisomer (**3a**:**4a**>99:1), albeit in a poor diastereoselectivity (*ds* = 77:23). Thus, the use of ATPH catalyst is effective both in rate enhancement and in improving the regioselectivity. Especially, the exclusive formation of the regioisomer **3a** as the electronically controlled product is surprising. Nitrone cycloadditions with alkenes having an electron-withdrawing substituent show a regioselectivity in favor of the isoxazolidine-5-carbaldehydes, as shown in the reaction between **1** and **2a**. An almost exclusive control of regioselectivity leading to the electronically favored 4-substituted isoxazolidines is rare even in Lewis acid catalyzed reactions. The effective catalytic use of ATPH should also be emphasized. All these points will be discussed below.



Chemical shifts and coupling paterns for the major (minor) diastereomers

Although only a fair diastereoselectivity (*ds* = 77:23) could be observed in the ATPH-catalyzed reaction between **1** and **2a**, the major diastereomer **3a** formed was characterized to be the *endo*-cycloadduct on the basis of ^{1}H NMR spectrum as shown above.[9] The major *endo*-diastereomer of **3a** shows 3-methine and



a: R = H, R' = H, Y = H
b: R = H, R' = H, Y = Me
c: R = H, R' = Me, Y = H
d: R = Me, R' = H, Y = H

Dipolarophile	R	R'	Y	Catalyst	Time/h	Yield/%	**3 : 4**
Acrolein (**2a**)	H	H	H	None	8	5	20:80
				ATPH	8	quant	>99:1
3-Buten-2-one (**2b**)	H	H	Me	None	24	7	8:92
				ATPH	24	82	100:0
Methacrolein (**2c**)	H	Me	H	None	22	5	0:100
				ATPH	22	quant	91:9
Crotonaldehyde (**2d**)	Me	H	H	None	24	2	100:0
				ATPH	24	quant	100:0

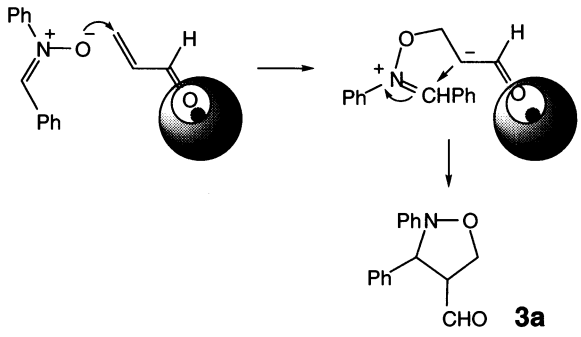
Scheme 1.

4-methine protons in higher fields and formyl proton in a lower field than those of the minor *exo*-cycloadduct of **3a** whose formyl group is magnetically shielded by the adjacent *cis*-phenyl group. The regiochemistry of **3a** was easily characterized by lower chemical shifts of the 5-methylene protons than those of **4a**.

The reaction of nitrone **1** with 3-buten-2-one (**2b**) shows a more dramatic change of regioselectivity between the catalyzed and uncatalyzed reactions. Without catalyst, the sterically controlled cycloadduct **4b** is produced as the by far major regioisomer after 24 h at room temperature, albeit only in a poor yield (7%, **3b**:**4b** = 92:8). However, under catalyzed conditions, by use of a catalytic amount of ATPH, the isoxazolidine-4-carbaldehyde derivative **3b** is produced as a single regioisomer and diastereomer. Thus, not only the formyl group but also the rather bulkier methyl keto-group can coordinate to the aluminum ion of the ATPH catalyst and can be activated.

Methacrolein (**2c**) is a 1,1-disubstituted alkene and its uncatalyzed reaction with nitrone **1** gives 5,5-disubstituted isoxazolidine **4c** as the exclusive and sterically controlled regioisomer (5% yield). Under ATPH-catalysis, however, this reaction is accelerated at 0°C to give a 91:9 mixture of regioisomeric cycloadducts **3c** and **4c**. In this case, an exclusive reversal of regioselectivity in favor of the electronically controlled regioisomer **3c** can not be achieved. On the other hand, crotonaldehyde as a 1,2-disubstituted alkene reacts with nitrone **1** in an exclusively regioselective manner under both noncatalyzed and ATPH-catalyzed conditions to give the isoxazolidine-4-carbaldehyde **3d** as the electronically controlled product. Methyl acrylate is not reactive both under non-catalyzed and ATPH-catalyzed conditions. Although the coordination of methyl esters to ATPH is known,[7h] a sufficient activation for nitrone cycloadditions was not observed.

In conclusion, the following new findings have been obtained: (1) ATPH acts effectively as pinhole catalyst in 1,3-dipolar cycloaddition reactions of nitrones leading to reaction rate acceleration and an improvement of regioselectivity, (2) ATPH selectively activates the alkene dipolarophiles with a relatively small electron-withdrawing substituent such as a formyl or acetyl group, (3) α,β-unsaturated esters cannot be activated effectively by ATPH, probably due to the steric bulk of the ester group,



(endo and exo mixture)

(4) the electronically controlled regioisomers are produced as the major regioisomers in the ATPH-catalyzed nitrone cycloadditions.

The above effective catalytic cycle of ATPH should be noteworthy. Participation of betaine intermediates is likely to effect the catalytic cycle: 1,3-dipolar cycloadditions possibly proceed stepwise when catalyzed by a strong Lewis acid catalyst.[6] Especially in the catalyzed reactions via the ATPH/dipolarophile complex, the α-position of dipolarophiles is sterically so hindered that the concerted bond formation in the 1,3-dipolar cycloadditions becomes rather difficult since it contains bond a formation at the congested α-position. The betaine intermediate formed through the stepwise reaction is followed by cyclization which results in serious steric hindrance. Then, the free cycloadducts are liberated from the ATPH/cycloadduct complexes. If this is the case, ATPH would work as effective catalyst in 1,3-dipolar cycloaddition reactions using other 1,3-dipoles and α,β-unsaturated aldehydes. Research along this line is now under way.

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9. A 77:23 diastereomer mixture of **3a** was obtained in the ATPH-catalyzed reaction, but a further separation by column chromatography failed: colorless liquid, ^{1}H NMR ($CDCl_3$) major diastereomer: $\delta=3.50$ (1H, m, H4), 4.38 (2H, m, H5), 4.95 (1H, d, $J=4.6$ Hz, H3), 6.9–7.8 (10H, m, Ph), and 9.65 (1H, d, $J=1.7$ Hz, CHO); minor isomer: $\delta=3.64$ (1H, m, H4), 4.25 (1H, dd, $J=8.5$ and 8.7 Hz, one of H5), 4.50 (1H, dd, $J=4.8$ and 8.7 Hz, the other of H5), 5.10 (1H, d, 8.9 Hz, H3), 6.9–7.8 (10H, m, Ph), and 9.65 (1H, d, $J=2.0$ Hz, CHO), ^{13}C NMR ($CDCl_3$) major isomer: $\delta=65.42$, 66.20, 69.90, and 198.04; minor isomer: $\delta=59.06$, 71.29, and 198.73, MS: m/z (rel. intensity,%) 253 (M^+, base peak), 181 (13), 180 (18), 117 (48), 115 (12), 91 (92), and 77 (32). Anal. calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 76.05; H, 6.01; N, 5.53.