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Catalytic Efficiency, Ligand Acceleration, and Concentration Effect in Magnesium Ion Mediated 1,3-Dipolar Cycloadditions of Mesitonitrile Oxide to Allylic Alcohols

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Abstract: Magnesium ion catalysis in nitrile oxide cycloadditions to allylic alcohols has been studied by use of stable mesitonitrile oxide. Moderate catalytic efficiency, ligand acceleration effect, and concentration effect have been observed to provide a promising access to a catalytic version of 1,3-dipolar cycloaddition reactions. © 1997 Elsevier Science Ltd.

We have recently reported that the nitrile oxide cycloadditions to allylic alcohols are highly accelerated in the presence of magnesium ion leading to the dramatic improvement of regio- and stereoselectivity.[1] The chelation transition state arising from the coordination of both 1,3-dipole and dipolarophile on the same magnesium ion should be responsible for the high rate enhancement. Although this was the first successful example for the metal ion catalyzed 1,3-dipolar cycloadditions, it is difficult to achieve an effective catalytic cycle in the above magnesium ion catalyzed reactions. The isoxazoline-5-methanols obtained by the cycloaddition of nitrile oxides to allylic alcohols are a bidentate ligand, which is extremely disfavored in the release of magnesium ion incorporated. This should be observed in most of the metal ion catalyzed 1,3-dipolar cycloadditions with hetero substituted dipolarophiles such as allylic alcohols. To the best of our knowledge, no catalytic efficiency in the magnesium ion catalyzed cycloadditions of simple nitrile oxides such as benzonitrile oxide is available because there are no effective quenching agents better than the magnesium alkoxides of allylic alcohols.[3] Hence, use of stable derivatives of nitrile oxide like mesitonitrile oxide may solve this problem.

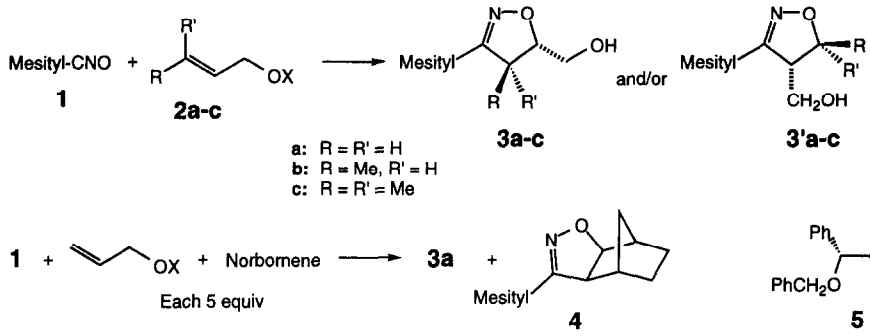
In the present communication, we report the magnesium ion mediated 1,3-dipolar cycloadditions of mesitonitrile oxide to allylic alcohols. Based on the competitive reaction method, moderate levels of catalytic efficiency, ligand acceleration effect, and concentration effect have been observed. These results should be important to analyze the possibility of a catalytic version of 1,3-dipolar cycloaddition reactions.

Although mesitonitrile oxide (**1**) shows a moderate reactivity to 2-propen-1-ol (**2a**) at room temperature (6% after 5 h), higher temperatures are needed for the completion of reactions with bulkier dipolarophiles such as (*E*)-2-buten-1-ol (**2b**) and 3-methyl-2-buten-1-ol (**2c**) (Table 1, entries 1-3). Because of bulkiness of the mesityl substituent of dipole **1**, regioselectivities of these reactions are mainly dependent upon the steric size of substituents attached on the unsaturated moiety of **2**.

A rate enhancement was observed in the reactions between **1** and **2a** when catalyzed by magnesium ion, one equivalent to the dipole **1** (entries 4-10). Competitive cycloadditions of **1** between **2a** and norbornene, both excess amounts (5 equiv each), were performed at room temperature to estimate the rate enhancement. The relative rates between **2a** and norbornene were estimated on the basis of the product ratio **3a/4**, and then each relative rate was compared with the ratio of **3a/4** observed in the uncatalyzed competitive reaction. The reaction in the presence of $MgBr_2 \cdot Et_2O$ (1 equiv) gave a moderate rate enhancement (entry 5), while use of

zinc bromide was found to be totally ineffective (entry 8).[4]

Table 1. Cycloadditions of Mesitonitrile Oxide (1) to Allylic Alcohols 2a-c[a]



Entry	2	X	Solvent[b]	Additive	M[c]	Temp (°C)	Time (h)	Product	Yield[d] (%)	Ratio[e,f]	
1	**2a**	H	TL	-	0.05	rt	62	**3a+3'a**	100	100:0	
2	**2b**	H	TL	-	0.05	65	17	**3b+3'b**	83	57:43	
3	**2c**	H	TL	-	0.05	80	10	**3c+3'c**	51	0:100	
4[g]	**2a**	H	DCM	-	0.05	rt	5	**3a+4**	97	1:5.9	(1)
5[g]	**2a**	H	DCM	$MgBr_2 \cdot Et_2O$ (1)	0.05	rt	5	**3a+4**	100	3.1:1	(18)
6[g]	**2a**	H	DCM	$MgBr_2 \cdot Et_2O$ (1)	0.005	rt	5	**3a+4**	95	12.2:1	(72)
7[g,h]	**2a**	MgBr (1)/H	DCM	-	0.005	rt	5	**3a+4**	99	71:1	(419)
8[g]	**2a**	H	DCM	$ZnBr_2$ (1)	0.05	rt	5	**3a+4**	87	1:6	(1)
9[g]	**2a**	H	DCM	$MgBr_2 \cdot Et_2O$ (1) + **5**[i]	0.05	rt	5	**3a+4**	92	8.5:1	(50)
10[g,h]	**2a**	MgBr (1)/H	DCM	**5**[i]	0.005	rt	5	**3a+4**	100	116:1	(684)

[a]All reactions were performed at room temperature. [b]TL: toluene, DCM: dichloromethane. [c]Molar concentration of the nitrile oxide **1**. [d]Yield of isolated products. [e]Calculated on the basis of the relative reaction rate between **2a** and norbornene (by ^1H NMR). [f]Relative ratio is in parenthesis. [g]Five equivalents each of **2a** and norbornene were used in the competitive cycloadditions. [h]One equivalent of the magnesium alkoxide was employed together with free alcohol (4 equiv). [i]Ligand **5** was equivalent to the magnesium ion.

Dilution with dichloromethane (0.05 M to 0.005 M solution) resulted in the enhancement of rate (entry 6, from 18 to 72 times faster than the uncatalyzed reaction, and hence 4 fold acceleration vs entry 5), confirming the chelation transition state previously proposed[5] for the observed rate enhancement. A better reaction rate (418 times) was observed in the reaction using the magnesium alkoxide of dipolarophile **2a** (1 equiv, entry 7). On the other hand, in the cycloaddition to **2b** as 1,2-disubstituted alkene, the rate acceleration should result in the improvement of regioselectivity between isomeric cycloadducts **3b** and **3'b**, since the uncatalyzed reaction is very poor in regioselectivity (**3b**:**3'b** = 57:43). Thus, the reaction of **1** with **2b** in the presence of $MgBr_2 \cdot Et_2O$ (1 equiv) gave the cycloadduct **3b** as an almost single regioisomer (Table 2, entry 9). However, no evidence for rate acceleration was observed in the magnesium mediated reactions using bulkier alcohol **2c**.

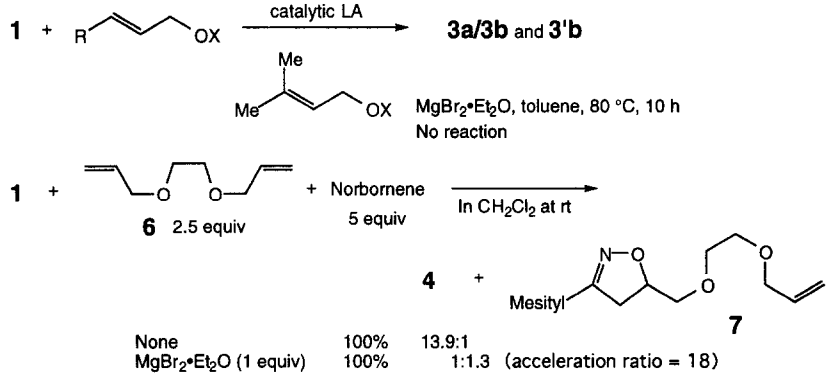
It is interesting to note that the addition of a 1,2-diether chelating ligand such as *rac*-1,2-bis(benzyloxy)-1,2-diphenylethane (**5**) in the magnesium ion catalyzed reactions did not reduce the reaction rate of the ligand-free reactions but the relative rate was even increased (Table 1, entries 5 vs 9, 7 vs 10). When magnesium ion is coordinated by the 1,2-diether ligand **5**,[6] the former should become sterically more hindered. Neverthless, the enhancement of reaction rate was observed. Thus, the rate deceleration by the

increased steric hindrance is compensated with the entropy-based rate acceleration. In the present cases, the entropy-based rate acceleration was more favored. This shows a possibility for the ligand acceleration methodology in metal ion catalyzed asymmetric 1,3-dipolar cycloaddition reactions, which is now in progress.[7]

Table 2. Catalytic Cycle in Magnesium Catalyzed Nitrile Oxide Cycloadditions between 1 and Allylic Alcohols 2a,b[a]

Entry	2	X	Solvent[b]	Additive	M[c]	Time (h)	Product	Yield (%)	Ratio	TON[d]
1	**2a**	H	DCM	-	0.05	5	**3a**	6		
2	**2a**	H	DCM	$MgBr_2 \cdot Et_2O$ (0.1)	0.05	5	**3a**	37		3.1
3	**2a**	H	DCM	$MgBr_2 \cdot Et_2O$ (0.3)	0.05	5	**3a**	68		2.1
4	**2a**	MgBr (0.1)/H	DCM	-	0.05	5	**3a**	89		8.3
5[e]	**2a**	MgBr (0.1)/H	DCM	-	0.05	5	**3a**	100		>9.4
6	**2a**	MgBr (0.05)/H	DCM	-	0.05	5	**3a**	50		8.8
7	**2a**	MgBr (0.01)/H	DCM	-	0.05	5	**3a**	40		34
8	**2a**	H	DCM	$MgBr_2 \cdot Et_2O$ (0.1) + **5** (0.1)	0.05	5	**3a**	39		3.3
9	**2b**	H	TL	$MgBr_2 \cdot Et_2O$ (1)	0.1	70	**3b+3'b**	36	99:1	3.6[f]
10	**2b**	MgBr (0.1)/H	DCM	-	0.003	72	**3b+3'b**	45	96:4	4.5
11[g]	**2b**	MgBr (0.1)/H	DCM	-	0.003	72	**3b+3'b**	14	70:30	1.4

[a,b,c]See Table 1. [d]Turn over number calculated by deducting the contribution of uncatalyzed reaction. [e]To the mixture of **1** and the catalyst, was added **2a** slowly by the aid of a syringe pump (1 h). [f]No cycloadducts were formed in the uncatalyzed reaction at room temperature. [g]Three equivalents of **2b** were used.



Scheme 1.

Next, catalytic cycle in the magnesium ion mediated nitrile oxide cycloadditions to allylic alcohols was investigated. The reactivity of **1** to **2a** in the absence of catalyst is very low as mentioned above (**3a**: 6% at rt for 5 h) so that this reaction can be utilized for the examination of catalytic efficiency (Scheme 1 and Table 2, entry 1). Although a moderate catalytic efficiency was observed in the case of reactions using 10 mol% of $MgBr_2 \cdot Et_2O$ catalyst (TONs = 3.1, 2.1, entries 2, 3), as expected, the reaction catalyzed by the magnesium alkoxide of **2a** was more effective. For example, use of 10 mol% of the alkoxide resulted in the formation of **3a** in 89% yield, and slow addition of dipolarophile **2a** was even more effective (entries 4, 5). The maximum turn over number observed was 34 (entry 7).

When (*E*)-2-buten-1-ol (**2b**) was used in the presence of the magnesium alkoxide of **2b** (10 mol%), a regioisomeric cycloadduct mixture was obtained in 45% yield (**3b**:**3b'** = 96:4, entry 10). Use of a large

excess of free alcohol **2b**, 30 times excess to the magnesium alkoxide of **2b**, led to the decreased reaction rate as well as the poor regioselectivity (entry 11). This contrasts with the result observed in the reaction run in entry 7. On the basis of these results, we conclude that allylic alcohols **2a,b** should be better ligands than nitrile oxide **1** to magnesium ion. The presence of a large excess of dipolarophile **2a,b** prevents the effective coordination of dipole **1** to the magnesium ion causing the decrease of reaction rate. In the case of less reactive **2b** such a rate decrease affected the yields of products, while more reactive **2a** maintained the reaction rate with better catalytic cycle.

As mentioned above, the ligand acceleration effect was observed in the magnesium ion (1 equiv) mediated reaction in the presence of ligand **5**. In the reaction using a catalytic amount of magnesium ion, the efficiency of catalytic cycle was not affected considerably either by the addition of the same diether ligand **5** (entries 2 vs 8). On the basis of the following experimental result, it is certain that the 1,2-diether ligand **5** is coordinating with the magnesium ion as effective chelating ligand: The reaction of **1** with 1,2-bis(2-propenyloxy)ethane (**6**), a dipolarophile of the 1,2-diether type, was significantly accelerated in the presence of $MgBr_2 \bullet Et_2O$, where rate of the catalyzed reaction was 18 times faster than the uncatalyzed reaction. The level of rate acceleration observed here was comparable to that recorded in the reaction between **1** and 2-propen-1-ol (**2a**) in the presence of $MgBr_2 \cdot Et_2O$ (Table 1, entry 5). This fact also suggests that the allylic 1,2-diether **6** can be used as effective dipolarophile in the magnesium ion mediated nitrile oxide cycloadditions.

Magnesium ion catalyzed asymmetric 1,3-dipolar cycloadditions by application of the ligand acceleration methodology is now being in progress. Details of the results will be soon reported elsewhere.[8]

References and Note

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2 Zinc ion catalyzed stereocontrol of nitrile oxide cycloadditions are known: Ukaji, Y.; Sada, K.; Inomata, K. *Chemistry Lett.* **1993**, 1847-1850.

3 Kanemasa, S.; Nishiuchi, M. *Tetrahedron Lett.* **1993**, 34, 4011-4014.

4 No rate acceleration of cycloadditions of benzonitrile oxide with allylic alcohols has been reported in our previous work (Ref. 1a).

5 This concentration effect is based on the quick equilibrating formation of three component complex between **1**, magnesium ion, and **2a**. Although the concentration of complex becomes lower in a diluted solution, the rate of cycloaddition should hold its inherent rate.

6 Coordination of ligand **5** to the magnesium ion can be confirmed by the rate acceleration observed in the reaction of **1** with **6** and norbornene in the presence of magnesium ion.

7 Preliminary study including the reaction of **1** with the magnesium alkoxide of **2a** in the presence of nonracemic **5** (1 equiv) has shown only a poor chiral induction. Structural design of ligand accelerators is needed.

8 Zinc catalyzed asymmetric nitrile oxide cycloaddition was reported recently: Shimizu, M.; Ukaji, Y.; Inomata, K. *Chemistry Lett.* **1996**, 455-456.

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