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Development of chiral dinitrones as modular Lewis base catalysts: asymmetric allylation of aldehydes with allyltrichlorosilanes

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ABSTRACT

Chiral dinitrones were synthesized by the condensation of a C_2-symmetrical chiral dihydroxylamine with various aldehydes. The electronic and steric properties of the dinitrones can be modified by changing the aldehyde component. The activity of dinitrones as Lewis base catalysts was examined for the asymmetric allylation of aldehydes with allyltrichlorosilanes. Using DMPU as an additive in chloroform, the reaction proceeded at room temperature to afford allylated products in good yields and good enantioselectivities.

1. Introduction

The effectiveness of a given catalyst generally depends on the reaction, the substrates, and the conditions. Therefore, modification of the catalyst structure is an important factor for catalyst design.[1] We have previously reported that chiral bisquinoline or bisisoquinoline *N,N′*-dioxides or diphosphine dioxides serve as effective Lewis base catalysts for reactions including the allylation of aldehydes with allyltrichlorosilanes or aldol reaction with trichlorosilyl enol ethers.[2] The polar N–O or P–O bond enables these catalysts to nucleophilically activate chlorosilane reagents to promote these enantioselective transformations.[3] However, a low ability to modify the catalyst structure has been a drawback. In order to address this issue, we herein propose the use of chiral dinitrones as new and readily modifiable Lewis base catalysts.

Nitrones are imine *N*-oxides possessing a negatively charged oxygen similar to that of pyridine *N*-oxides. Although nitrones have been successfully utilized as electrophiles or 1,3-dipoles in organic synthesis,[4] their use as Lewis base catalysts has not yet been exploited.[5] We envisaged that chiral dinitrones **1** derived readily from C_2-symmetrical dihydroxylamine and various aldehydes would be effective asymmetric Lewis base catalysts (Fig. 1).[6]

2. Results and discussion

Dihydroxylamine dihydrochloride was prepared from (*S,S*)-1,2-cyclohaxanediamine according to the procedure reported by Yamamoto et al.[7] Condensation of the dihydrochloride salt with various aromatic aldehydes was conducted in the presence of sodium bicarbonate in dichloromethane at reflux for 6 h (Table 1).[8] After purification by silica gel column chromatography, dinitrones **1a**–**1g** were obtained in high yield as stable and crystalline compounds having high specific rotations.

To examine the activity of dinitrone **1a** as a Lewis base catalyst, the asymmetric allylation of benzaldehyde (**2a**) with allytrichlorosilane was investigated under various conditions (Table 2).[9] When **1a** and the reactants were mixed in dichloromethane at rt, both the yield and enantioselectivity were low (entry 1). To improve the reactivity, several additives were next examined (entries

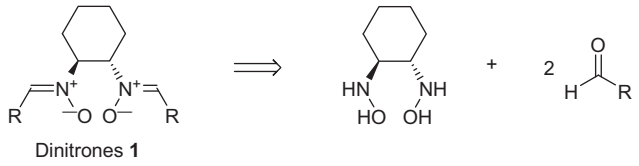

Figure 1. Design of chiral dinitrones **1**.

Table 1
Preparation and properties of chiral dinitrones **1**[a]

Entry	R in dinitrone **1**	Yield (%)	Mp (°C)	$[\alpha]_D$
1	Ph **1a**	98	207–208	+279.8
2	1-Naphthyl **1b**	83	249–250	−56.6
3	2-Naphthyl **1c**	93	203–204	+578.6
4	*p*-ClC_6H_4 **1d**	95	179–180	+223.6
5	*p*-$NO_2C_6H_4$ **1e**	Quant	213–214	+418.4
6	*p*-$MeOC_6H_4$ **1f**	91	215–216	+185.8
7	3,4,5-$(MeO)_3C_6H_2$ **1g**	99	240–241	+111.9

[a] All reactions were performed using the dihydroxylamine dihydrochloride (0.5 mmol), an aldehyde (3 equiv), and sodium bicarbonate (6 equiv) in dichloromethane at reflux for 6 h.

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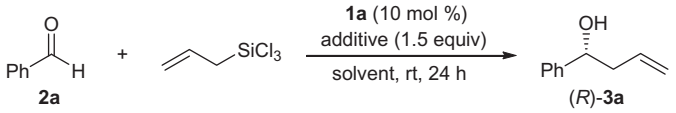
Table 2
Allylation of benzaldehyde using **1a**[a]



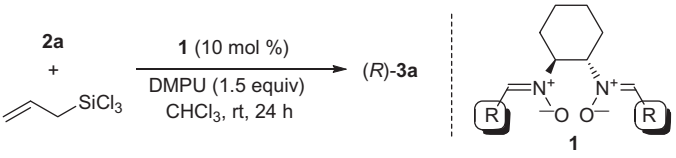
Entry	Additive[b]	Solvent	Yield (%)	ee (%)
1	None	CH_2Cl_2	6	26
2	$^iPr_2NEt$	CH_2Cl_2	13	11
3	NMP	CH_2Cl_2	27	31
4	DMI	CH_2Cl_2	7	19
5	DMPU	CH_2Cl_2	36	35
6	DMPU	THF	13	10
7	DMPU	EtCN	19	18
8	DMPU	$CHCl_3$	41	44
9[c]	DMPU	$CHCl_3$	46	45
10[d]	DMPU	CH_2Cl_2	17	—

[a] Unless otherwise noted, reactions were performed using **1a** (10 mol %), an additive (1.5 equiv), benzaldehyde (0.4 mmol), and allyltrichlorosilane (1.2 equiv) in a solvent at rt for 24 h.
[b] NMP, *N*-methyl-2-piperidone; DMI, 1,3-dimethyl-2-imidazolidinone; DMPU, *N*,*N*′ -dimethylpropyleneurea.
[c] With allyltrichlorosilane (1.5 equiv).
[d] Without **1a**.

2–5), and *N*,*N*′-dimethylpropyleneurea (DMPU) emerged as the most effective additive (entry 5).[10,11] Interestingly, the combined use of **1a** and DMPU gave higher enantioselectivity than did **1a** alone (entries 1 vs 5), although DMPU itself was found to promote the reaction (entry 10). Screening of solvents identified chloroform as the optimal solvent (entries 6–8). The use of 1.5 equiv of allyltrichlorosilane resulted in the further improvement of the yield (entry 9).

Under the conditions optimized for catalyst **1a** (see Table 2, entry 9), the activity of the other nitrones **1b–g** was investigated (Table 3). Dinitrone **1b** having a 1-naphthyl group lowered the selectivity, whereas dinitrone **1c** bearing a 2-naphthyl group provided good selectivity (entries 2 and 3). Electron-deficient benzene rings significantly decreased both the yield and selectivity (entries 4 and 5). Presumably because of the low Lewis basicity of the catalyst, the reaction with **1e** was promoted by only DMPU to give the racemic product (see Table 2, entry 10). In contrast, the electron-rich *p*-$MeOC_6H_4$ group (dinitrone **1f**) significantly improved the catalyst performance (entry 6). However, increasing steric hindrance as well as the electron-donating ability (dinitrone **1g**) provided inferior results (entry 7). Varying the reaction temperature (35 or 0 °C) did not affect the yield and selectivity of the reaction using dinitrone **1f** (entries 8 and 9). Finally, the use of 20 mol % of **1f** provided an improved result (entry 10). It should be noted that dinitrones **1a–g** were stable under the reaction and work-up conditions and could be recovered by silica gel column chromatography after isolation of the product.[12]

Table 3
Catalyst screening for allylation of **2a**[a]



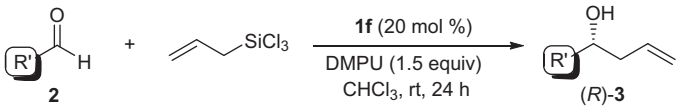
Entry	R in dinitrone **1**	Yield (%)	ee (%)
1	Ph **1a**	46	45
2	1-Naphthyl **1b**	62	35
3	2-Naphthyl **1c**	57	60
4	*p*-ClC_6H_4 **1d**	28	32
5	*p*-$NO_2C_6H_4$ **1e**	27	0
6	*p*-$MeOC_6H_4$ **1f**	66	71
7	3,4,5-$(MeO)_3C_6H_2$ **1g**	39	37
8[b]	**1f**	61	71
9[c]	**1f**	59	70
10[d]	**1f**	78	74

[a] All reactions were performed using **1** (10 mol %), DMPU (1.5 equiv), benzaldehyde (0.4 mmol), and allyltrichlorosilane (1.5 equiv) in $CHCl_3$ at rt for 24 h.
[b] At 35 °C.
[c] At 0 °C.
[d] With 20 mol % of catalyst.

Using catalyst **1f** (20 mol %), the allylation of various aldehydes was investigated (Table 4).[13] The reaction of hydrocinnamaldehyde, a non-conjugated aldehyde, afforded the desired product **3b** in moderate yield with diminished selectivity (entry 2) compared with benzaldehyde (entry 1).[14] In contrast, conjugated aromatic aldehydes showed good reactivities (entries 3–11). The reaction tolerated relatively bulky aromatic aldehydes to provide good yields and selectivities (entries 3–5). Benzaldehyde derivatives having electron-withdrawing groups increased the yield, but tended to decrease the selectivity (entries 6 and 7). *p*-Anisaldehyde bearing an electron-donating methoxy substituent decreased both the yield and selectivity (entry 8), whereas *m*-anisaldehyde gave a comparable result with benzaldehyde (entry 9). Further substitution at the 3,5- or 3,4,5-positions of benzaldehyde with methoxy groups was found to improve the selectivity (entries 10 and 11), and the latter aldehyde **2k** provided the highest enantioselectivity among the aldehydes tested (entry 11).

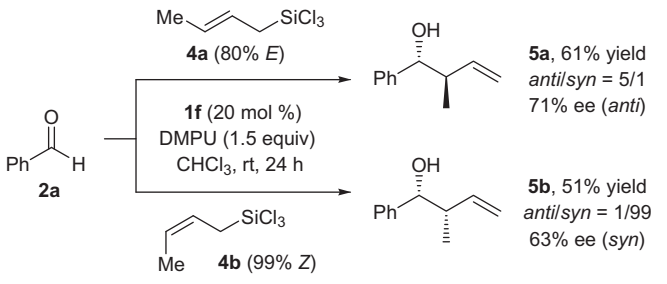
The combination of catalyst **1f** and DMPU was also applied to the crotylation of benzaldehyde with (*E*)- and (*Z*)-trichlorocrotylsilanes **4a** and **4b** (Scheme 1). Branched *anti*- and *syn*-crotylated

Table 4
Allylation of various aldehydes[a]



Entry	R′ in aldehyde **2**	**3**	Yield (%)	ee (%)
1	Ph **2a**	**3a**	78	74
2	$Ph(CH_2)_2$ **2b**	**3b**	42	8
3	3,5-$Me_2C_6H_3$ **2c**	**3c**	75	75
4	1-Naphthyl **2d**	**3d**	69	71
5	2-Naphthyl **2e**	**3e**	81	77
6	*p*-BrC_6H_4 **2f**	**3f**	84	74
7	*p*-$NO_2C_6H_4$ **2g**	**3g**	93	64
8	*p*-$MeOC_6H_4$ **2h**	**3h**	68	63
9	*m*-$MeOC_6H_4$ **2i**	**3i**	76	74
10	3,5-$(MeO)_2C_6H_3$ **2j**	**3j**	71	77
11	3,4,5-$(MeO)_3C_6H_2$ **2k**	**3k**	82	87

[a] All reactions were performed using **1f** (20 mol %), DMPU (1.5 equiv), an aldehyde (0.4 mmol), and allyltrichlorosilane (1.5 equiv) in $CHCl_3$ at rt for 24 h.



Scheme 1. Crotylation of **2a**.

products **5a** and **5b** were obtained from **4a** and **4b** with moderate yields and enantioselectivities, respectively. The observed high stereospecificity suggests a mechanism involving a chair-like cyclic transition state with the aryl group of the aldehyde in the equatorial orientation. Further studies are needed to elucidate the detailed mechanism involving the role of the DMPU additive.

3. Conclusion

In summary, we have proposed the use of chiral dinitrones as new and modular Lewis base catalysts. With DMPU as an additive in chloroform, chiral dinitrones effectively catalyzed the asymmetric allylation of aldehydes with allyltrichlorosilanes to give good yields and good enantioselectivities. Further improvement of the catalytic activity and selectivity as well as application to other reactions utilizing the concept of modularity of dinitrone catalysts are currently in progress.

Acknowledgment

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12. Catalyst **1a** (Table 3, entry 1) and **1f** (entry 10) were recovered in 99% and 93%, respectively.
13. *General procedure for allylation of aldehydes with allyltrichlorosilanes*: to a solution of dinitrone **1f** (20 mol %), an aldehyde **2** (0.4 mmol), and DMPU (1.5 equiv) in chloroform (1 mL) was added allyltrichlorosilane (1.5 equiv) under argon at room temperature. After being stirred at that temperature for 24 h, the reaction was quenched with satd aqueous $NaHCO_3$ (10 mL), and the slurry was stirred for 1 h. The mixture was filtered through cotton wool and extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with brine (1×30 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate) to give the product **3**. The enantiomeric excess was determined by HPLC analysis.
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