Catalytic Asymmetric 1,3-Dipolar Cycloaddition of a Nitrone Bearing a Bulky Amide Moiety to γ-Substituted Allylic Alcohols

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A catalytic asymmetric 1,3-dipolar cycloaddition reaction of a nitrone possessing diisopropyl amide moiety to γ-substituted allylic alcohols was achieved by using diisopropyl (*R*, *R*)-tartrate as a chiral auxiliary to afford the corresponding 3,4,5-trisubstituted isoxazolidines with excellent enantioselectivity up to over 99% ee.

1,3-Dipolar cycloaddition is one of the most important reactions for the construction of a variety of 5-membered heterocyclic compounds. In particular, asymmetric 1,3-dipolar cycloaddition reaction of nitrones to alkenes has received considerable attention in organic syntheses, since it can create three contiguous carbon stereocenters in a single step and the resulting isoxazolidine is a versatile chiral building block for numerous attractive chemicals.[1] In the course of our study on asymmetric 1,3-dipolar cycloaddition reactions,[2] we recently reported an efficient enantioselective 1,3-dipolar cycloaddition of nitrones bearing an amide moiety to a terminal olefin, 2-propen-1-ol, in the presence of a catalytic amount of diisopropyl (*R*, *R*)-tartrate [(*R*, *R*)-DIPT] as a chiral auxiliary to afford 3,5-*cis*-disubstituted isoxazolidines with excellent enantioselectivity.[2a] In this paper, we reveal that this catalytic strategy is also applicable to the cycloaddition of a nitrone possessing diisopropylamide moiety with a range of γ-substituted allylic alcohols to afford the corresponding 3,4,5-trisubstituted cycloadducts with high regio-, diastereo- and enantioselectivities.

The catalytic asymmetric 1,3-dipolar cycloaddition of nitrone **2** possessing diisopropylamide moiety to (*E*)-2-buten-1-ol (**1a**) was first investigated. As shown in Table 1, the predominant formation of 3,5-*cis*-cycloadduct **3a**[3] and the high enantioselectivity are comparable to the case of 2-propen-1-ol,[2a] while the chemical yield was rather low (Entry 1).[4] Formation of regio- and diastereoisomers of **3a** was not observed and no nitrone **2** was recovered due to the gradual decomposition during the reaction. When the amount of **1a** was increased together with the proper amounts of diethylzinc, iodine and pyridine *N*-oxide, the chemical yield based on the nitrone was improved (Entries 2,3,5,7,8). In order to achieve the reproducible higher chemical yield and enantioselectivity, slow addition of the nitrone was essential. By employing 2.9 molar amounts of **1a**, the chemical yield was improved to 57% with almost complete enantioselectivity (Entry 7). Furthermore, the concentration of the reaction was found to influence the reactivity. That is, while the reaction employing 1.9 molar amounts of **1a** on a 0.5 mmol scale in 9 ml of $CHCl_3$ afforded the corresponding cycloadduct **3a** in 51% yield (Entry 3), the reaction performed on 1.5 mmol scales in 12 ml of $CHCl_3$ improved the chemical yield up to 64% with complete enantioselectivity (Entry 4). In the case of the reaction using 2.4 molar amounts of **1a** under the high concentration conditions, precipitate was observed to give **3a** in lower chemical yield and enantioselectivity (Entry 6). When (*Z*)-2-buten-1-ol was subjected to the reaction under the same conditions as Entry 1, no cycloadduct was obtained.[4] However, the reaction appears general with respect to the (*E*)-γ-alkyl-substituted allylic alcohols. (*E*)-2-Hexen-1-ol (**1b**) afforded the corresponding cycloadduct **3b** with the enantioselectivity higher than 99% ee (Entries 9, 10).

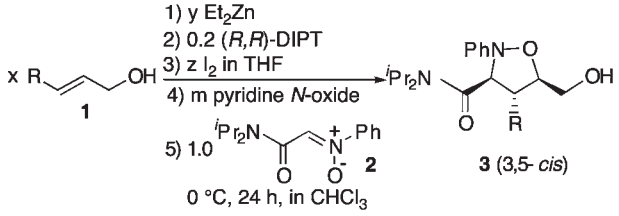


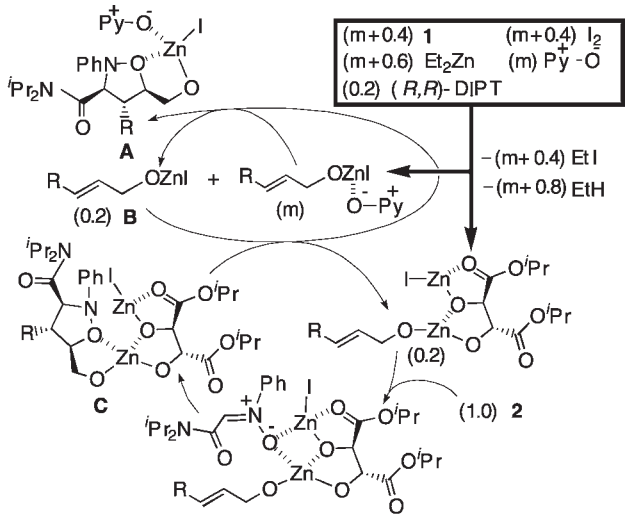
Table 1. The catalytic asymmetric 1,3-dipolar cycloaddition of the nitrone **2** to γ-alkyl-substituted allylic alcohols **1**

Entry	**1**	R	x	y	z	m	Yield of **3**/%	ee/%
1[a]	**a**	Me	1.0	1.6	1.4	1.0	24	99[b]
2[a]	**a**	Me	1.4	1.6	1.4	1.0	47	>99[b]
3[a]	**a**	Me	1.9	2.1	1.9	1.5	51	>99[b]
4[c]	**a**	Me	1.9	2.1	1.9	1.5	64	>99[b,d]
5[a]	**a**	Me	2.4	2.6	2.4	2.0	53	>99[b]
6[c]	**a**	Me	2.4	2.6	2.4	2.0	42	97[b]
7[a]	**a**	Me	2.9	3.1	2.9	2.5	57	99[b]
8[a]	**a**	Me	3.4	3.6	3.4	3.0	51	99[b]
9[c]	**b**	^{n}Pr	1.4	1.6	1.4	1.0	48	>99[e,f]
10[c]	**b**	^{n}Pr	1.8	2.0	1.8	1.4	45	>99[e]

[a]Reaction was carried out on a 0.5 mmol scale in 9 ml $CHCl_3$, and the solid nitrone **2** was added to the reaction mixture over a period of 2 h. [b]Enantioselectivity was determined by HPLC analysis (Daicel Chiralcel OD-H). [c]Reaction was carried out on 1.5 mmol scales in 12 ml $CHCl_3$, and the solid nitrone **2** was added to the reaction mixture over a period of 3 h. [d]$[\alpha]_D^{25}$-98 (c 3.02, EtOH). [e]The product was isolated as the corresponding acetate and its enantioselectivity was determined by HPLC analysis (Daicel Chiralcel OD-H). [f]The specific rotation of the corresponding acetate; $[\alpha]_D^{25}$-90 (c 2.91, EtOH).

Although the precise reaction mechanism is not yet clear, the plausible catalytic cycle is shown in Scheme 1 to rationalize the proper molar amounts of each reagent we found, x : y : z : m = (m + 0.4) : (m + 0.6) : (m + 0.4) : m. In order to realize the catalytic cycle, zinc-bridging chiral salt (**C**) must be replaced by the zinc salt of **1** (**B**) being free from pyridine *N*-oxide to afford (**A**).

To broaden the scope of the present method, the reaction of γ-



Scheme 1.

functionalized allylic alcohols was next examined. It was found that asymmetric 1,3-dipolar cycloaddition of nitrone **2** to (*E*)-4-hydroxy-2-butenoates **4** proceeded smoothly to give the corresponding trisubstituted isoxazolidine **5** with 3,5-*cis*-relationship in complete regio- and diastereoselective manner with high enantioselectivities as shown in Table 2. The use of excess amounts of methoxycarbonyl substituted allylic alcohol **4a** improved both chemical yield (63%) and enantioselectivity (97% ee) (Entry 3). In the reaction of allylic alcohol **4c** bearing a bulkier isopropyl ester, the chemical yield was decreased (Entry 6).[4]

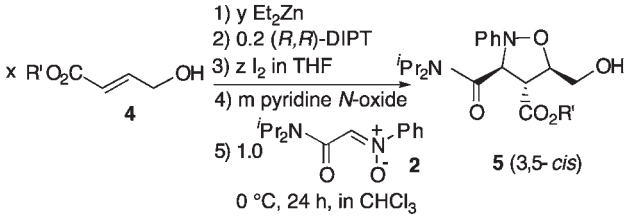


Table 2. The catalytic asymmetric 1,3-dipolar cycloaddition of the nitrone **2** to (*E*)-4-hydroxy-2-butenoates **4**[a]

Entry	**4**	R′	x	y	z	m	Yield of **5**/%	ee/%
1	**a**	Me	1.0	1.6	1.4	1.0	50	92[b]
2	**a**	Me	1.8	2.0	1.8	1.4	63	96[b]
3	**a**	Me	2.0	2.2	2.0	1.6	63	97[b]
4	**a**	Me	2.2	2.4	2.2	1.8	53	95[b]
5	**b**	Et	2.0	2.2	2.0	1.6	61	92[b,c]
6	**c**	*i*Pr	2.0	2.2	2.0	1.6	37	94[d,e]

[a]Reactions were carried out on 1.5 mmol scales in 12 ml $CHCl_3$, and the solid nitrone **2** was added to the reaction mixture over a period of 3 h. [b]Enantioselectivity was determined by HPLC analysis (Daicel Chiralcel OJ-H). [c]$[\alpha]_D^{25}$-117 (c 3.48, EtOH). [d]Enantioselectivity was determined by HPLC analysis (Daicel Chiralcel OD-H). [e]$[\alpha]_D^{25}$ -106 (c 2.16, EtOH).

The absolute configuration of **5a** was determined to be *3S,4R,5R* as follows: The enantiomerically pure **5a** (100% ee, $[\alpha]_D^{25}$-153 (c 0.96, EtOH)), obtained by recrystallization from AcOEt, was treated with (*R*)-1-(1-naphthyl)ethyl isocyanate in the presence of a catalytic amount of 4-(*N*,*N*-dimethylamino)-pyridine in CH_2Cl_2 to give the corresponding adduct **6** (79%). The absolute stereochemistry of **6** was determined to be *3S,4R,5R* by X-ray crystallographic analysis of its single crystal as shown in Figure 1.[5] The absolute configurations of products **3a,b** and **5b,c** were tentatively determined to be also *3S,4R,5R*.

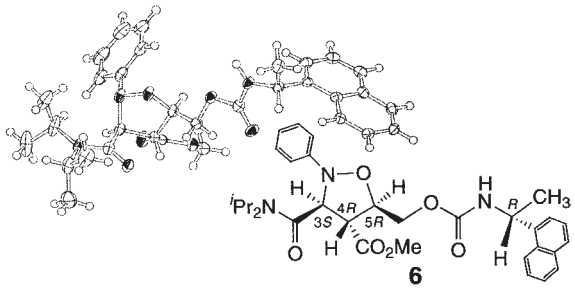


Figure 1.

In conclusion, we could establish an efficient regio-, diastereo-, and enantioselective 1,3-dipolar cycloaddition of nitrone **2** to γ-substituted allylic alcohols by using a catalytic amount of (*R*,*R*)-DIPT as a chiral auxiliary. This reaction thus provides a simple and attractive approach to highly functionalized isoxazolidines with almost complete enantioselectivity.

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Dedicated to Professor Teruaki Mukaiyama on the occasion of his 75th birthday.

References and Notes

1 K. V. Gothelf and K. A. Jørgensen, *J. Chem. Soc., Chem. Commun.*, **2000**, 1449; K. V. Gothelf and K. A. Jørgensen, *Chem. Rev.*, **98**, 863 (1998).

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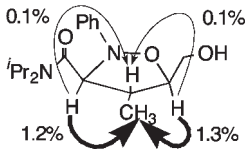
3 The relative stereochemistry of the cycloadduct **3a** was determined by NOE measurement.



4 Steric congestion between substituents at the transition state might retard the expected cycloaddition, especially in the formation of 3,4-*cis*-4,5-*cis*-adduct from (*Z*)-2-buten-1-ol.

5 Single crystal of **6** was obtained by recrystallization from AcOEt. Mp: 152.2–153.8 °C. Found: C, 68.28; H, 7.01; N, 7.33%. Calcd for $C_{32}H_{39}N_3O_6$: C, 68.43; H, 7.00; N, 7.48%. Crystal data: $C_{32}H_{39}N_3O_6$, *FW* 561.68, monoclinic, $P2_1$, $a = 10.851(1)$ Å, $b = 7.030(1)$ Å, $c = 20.246(1)$ Å, $\beta = 103.751(1)°$, $V = 1500.2(3)$ Å^3, $Z = 2$. $D_{calc} = 1.243$ g/cm^3. $R = 0.034$ ($R_w = 0.033$) for 3628 reflections with $I > 3.00\sigma(I)$ and 371 variable parameters.