Asymmetric 1,3-Dipolar Cycloaddition Reaction of Azomethine Imines to Allyl Alcohol

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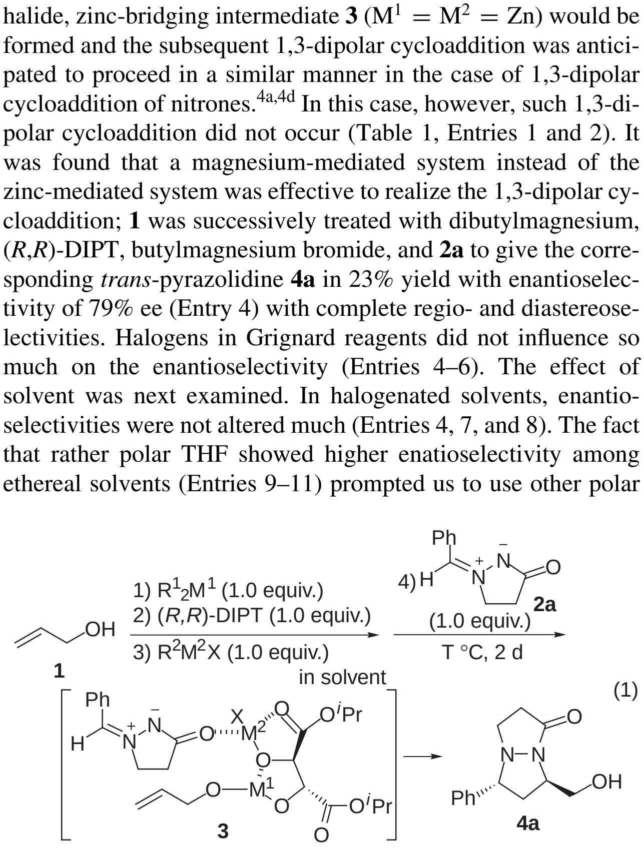
The asymmetric 1,3-dipolar cycloaddition of azomethine imines to allyl alcohol was achieved by utilizing diisopropyl (*R*,*R*)-tartrate as a chiral auxiliary to afford the corresponding optically active *trans*-pyrazolidines with excellent regio-, diastereo-, and enantioselectivities.

The development of 1,3-dipolar cycloaddition provided one of the most powerful strategies for the enantioselective construction of 5-membered heterocycles.[1] Considerable progress has been made in the asymmetric 1,3-dipolar cycloaddition of nitrones and nitrile oxides which contain oxygen, while the cycloaddition of 1,3-dipoles with two nitrogen atoms were still limited.[2] We have already reported asymmetric 1,3-dipolar cycloaddition of nitrile oxides and nitrones utilizing tartaric acid ester as a chiral auxiliary.[3,4] Herein, we wish to describe an asymmetric 1,3-dipolar cycloaddition of azomethine imines to allyl alcohol utilizing tartaric acid ester as a chiral auxiliary.

First the 1,3-dipolar cycloaddition of 1-benzylidene-3-oxopyrazolidin-1-ium-2-ide (**2a**) was examined in CH_2Cl_2 at rt. When allyl alcohol (**1**) was treated with equimolar amount of diethylzinc, diisopropyl (*R*,*R*)-tartrate [(*R*,*R*)-DIPT], and ethylzinc halide, zinc-bridging intermediate **3** ($M^1 = M^2 = Zn$) would be formed and the subsequent 1,3-dipolar cycloaddition was anticipated to proceed in a similar manner in the case of 1,3-dipolar cycloaddition of nitrones.[4a,4d] In this case, however, such 1,3-dipolar cycloaddition did not occur (Table 1, Entries 1 and 2). It was found that a magnesium-mediated system instead of the zinc-mediated system was effective to realize the 1,3-dipolar cycloaddition; **1** was successively treated with dibutylmagnesium, (*R*,*R*)-DIPT, butylmagnesium bromide, and **2a** to give the corresponding *trans*-pyrazolidine **4a** in 23% yield with enantioselectivity of 79% ee (Entry 4) with complete regio- and diastereoselectivities. Halogens in Grignard reagents did not influence so much on the enantioselectivity (Entries 4–6). The effect of solvent was next examined. In halogenated solvents, enantioselectivities were not altered much (Entries 4, 7, and 8). The fact that rather polar THF showed higher enatioselectivity among ethereal solvents (Entries 9–11) prompted us to use other polar solvents. Product **4a** was not obtained by using DMF and DMSO, while nitriles were found to be solvent of choice to realize excellent enantioselectivities (Entries 12 and 14). When the reaction temperature was raised to accelerate the cycloaddition, the chemical yields were improved without remarkable decrease of enantioselectivities (Entries 12–16). In CH_3CN, the cycloadduct was obtained in 66% yield with the enantioselectivity of 88% ee. The big difference was not observed in chemical yields and enantioselectivities when the reaction was carried out in CH_3CN and C_2H_5CN.



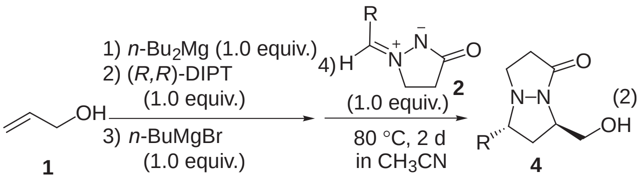
(1)

Table 1. The asymmetric 1,3-dipolar cycloaddition of azomethine imine **2a** to allyl alcohol (**1**)

Entry	$R^1{}_2M^1$	R^2M^2X	Solvent	T/°C	Yield/%[a]	ee/%[b]
1	Et_2Zn	EtZnCl	CH_2Cl_2	25	—	—
2	Et_2Zn	EtZnI	CH_2Cl_2	25	—	—
3	Et_2Zn	*n*-BuMgBr	CH_2Cl_2	25[c]	3	61
4	*n*-Bu_2Mg	*n*-BuMgBr	CH_2Cl_2	25	23	79
5	*n*-Bu_2Mg	*n*-BuMgCl	CH_2Cl_2	25	15	81
6	*n*-Bu_2Mg	*n*-BuMgI	CH_2Cl_2	25	15	62
7	*n*-Bu_2Mg	*n*-BuMgBr	$CHCl_3$	25	20	84
8	*n*-Bu_2Mg	*n*-BuMgBr	$Cl(CH_2)_2Cl$	25	28	77
9	*n*-Bu_2Mg	*n*-BuMgBr	Et_2O	25	5	47
10	*n*-Bu_2Mg	*n*-BuMgBr	THF	25	10	77
11	*n*-Bu_2Mg	*n*-BuMgBr	DME	25	5	62
12	*n*-Bu_2Mg	*n*-BuMgBr	CH_3CN	25	15	90
13				80	66	88
14	*n*-Bu_2Mg	*n*-BuMgBr	C_2H_5CN	25	23	92
15				80	64	88
16				97	53	90

[a] Isolated yields. [b] Enantioselectivities were determined by HPLC analysis (Daicel Chiralcel OD-H). [c] The reaction time was 3 d.

The asymmetric cycloaddition of several azomethine imines **2** to allyl alcohol (**1**) was performed in CH_3CN at 80 °C (eq 2) as shown in Table 2. Aryl-substituted azomethine imines **2a**–**2f** realized high enantioselectivities (Entries 1–6). The cycloaddition of pentyl- and cyclohexyl-substituted azomethine imines **2g** and **2h** proceeded in moderate stereoselective manners (Entries 7 and 8), while *t*-butyl-substituted azomethine imine **2i** resulted in high enantioselectivity (Entry 9).



(2)

Next, in order to make the procedure simpler, only the Grignard reagent was used as a magnesium source instead of dibutylmagnesium. It is well known that dibutylmagnesium could be generated from 2 equivalents of butylmagnesium bromide accompanied by generation of $MgBr_2$. To a mixture of allyl alcohol (**1**) and (*R*,*R*)-DIPT were added 3 equivalents of butylmagnesium bromide and azomethine imine **2a** successively (eq 3). Sur-

Table 2. The asymmetric 1,3-dipolar cycloaddition of azomethine imines **2**

Entry	R		Yield/%[a]	ee/%
1	Ph	**a**	66	88[b]
2	p-EtC_6H_4	**b**	57	92[b]
3	p-$MeOC_6H_4$	**c**	49	92[b]
4	p-ClC_6H_4	**d**	67	91[b]
5	p-$O_2NC_6H_4$	**e**	53	88[b]
6	2-Furyl	**f**	42	82[c]
7	n-C_5H_{11}	**g**	7[d]	72[c]
8	c-C_6H_{11}	**h**	17	54[b]
9	t-Bu	**i**	36	89[b]

[a] Isolated yields. [b] Enantioselectivity was determined by HPLC analysis (Daicel Chiralcel OD-H). [c] Enantioselectivity was determined by HPLC analysis (Daicel Chiralcel IA). [d] Yield was determined by ^1H NMR analysis due to difficulty separating from a by-product **5**.

prisingly, the pyrazolidine **4a** was obtained in an enhanced chemical yield with the excellent enantioselectivity (Table 3, Entry 1).[5] In this procedure, it is not yet clear whether the intermediate **3** was produced along with the generation of $MgBr_2$ or a different intermediate was formed.[6] When the reaction was carried out longer time, the chemical yield was slightly enhanced (Entry 2). The 1,3-dipolar cycloaddition of several other azomethine imines **2** also realized excellent enantioselectivities as listed in Table 3, even in the case of pentyl- and cyclohexyl-substituted ones **2g** and **2h** (Entries 8 and 9).[7]

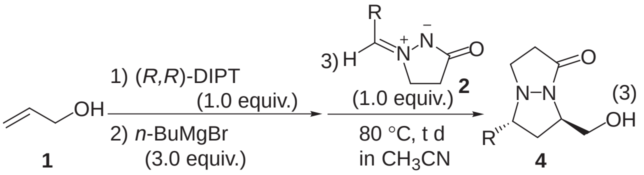
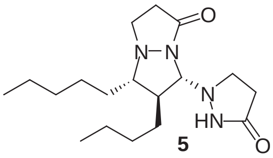


Table 3. The asymmetric 1,3-dipolar cycloaddition of azomethine imines **2** by the use of only the Grignard reagent as a magnesium source

Entry	R		t/d	Yield/%[a]	ee/%
1	Ph	**a**	2	74	95[b]
2			4	81	94[b]
3[c]	p-EtC_6H_4	**b**	4	57	96[b]
4	p-$MeOC_6H_4$	**c**	2	75	94[b]
5	p-ClC_6H_4	**d**	2	75	94[b]
6[c]	p-$O_2NC_6H_4$	**e**	4	66	94[b]
7[c]	2-Furyl	**f**	2	60	88[d]
8[c]	n-C_5H_{11}	**g**	3	51[e]	96[d]
9[c]	c-C_6H_{11}	**h**	4	78	94[b]
10[c]	t-Bu	**i**	4	50	96[b]

[a] Isolated yields. [b] Enantioselectivity was determined by HPLC analysis (Daicel Chiralcel OD-H). [c] MeMgBr was used instead of n-BuMgBr. [d] Enantioselectivity was determined by HPLC analysis (Daicel Chiralcel IA). [e] Yield was determined by ^1H NMR analysis due to difficulty separating from the by-product **5**.

The absolute configuration of **4a** was determined to be R,R as follows: The enantiomerically rich **4a** (80% ee) was treated with (S)-1-phenylethyl isocyanate in the presence of a catalytic amount of 4-(N,N-dimethylamino)pyridine in CH_2Cl_2 to give the corresponding urethane **6** (79%). Twice recrystallization from hexane gave diastereomerically pure **6**. The absolute stereochemistry of pyrazolidine skeleton in **6** was determined to be R,R by X-ray crystallographic analysis of its single crystal (Figure 1).[8] The absolute configurations of other products **4b**–**4i** were tentatively determined to be also R,R.



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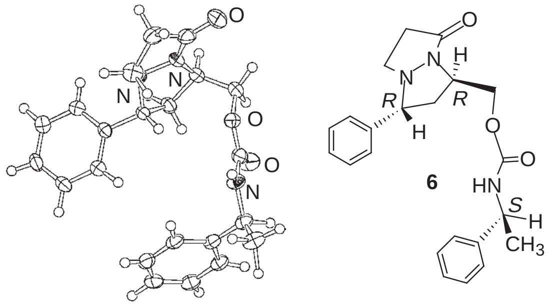

Figure 1.

As described above, an attractive asymmetric cycloaddition of azomethine imines to allyl alcohol has been developed.

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5 Enantioselectivity also increased in other solvents than CH_3CN by this procedure: Solvent/temperature/reaction time/yield of **4a**/ee; THF/66 °C/2 d/53%/84% ee; $Cl(CH_2)_2Cl$/80 °C/2 d/57%/90% ee.

6 When $MgBr_2$ was added in the reaction in Table 2, Entry 1, **4a** was obtained in 78% yield with 84% ee.

7 Although the 1,3-dipolar cycloaddition of **2a** to (E)-2-buten-1-ol was carried out under similar conditions in Table 3, Entry 1 for 7 d, the corresponding cycloadduct was not obtained.

8 Single crystals of **6**, obtained by recrystallization from toluene/hexane, contain hexane (hexane/**6** = 1/4) in disorder. Crystal data: $C_{23.5}H_{28.5}N_3O_3$, fw 401.00, monoclinic, $P2_1$, $a = 12.713(8)$, $b = 6.994(4)$, $c = 13.958(9)$ Å, $V = 1154(1)$ Å^3, $\beta = 111.469(5)°$, $Z = 2$. $D_{calcd} = 1.153$ g/cm^3. $R = 0.070$ ($R_w = 0.105$) for 4539 reflections with $I > 3.00\sigma(I)$ and 265 variable parameters. Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett.

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