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Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Imines to Homoallylic Alcohols

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The asymmetric 1,3-dipolar cycloaddition of azomethine imines to homoallylic alcohols was achieved by utilizing diisopropyl (*R*,*R*)-tartrate as a chiral auxiliary to give the corresponding optically active *trans*-pyrazolidines with excellent regio-, diastereo-, and enantioselectivities. The catalytic use of diisopropyl (*R*,*R*)-tartrate was also effective in the presence of $MgBr_2$.

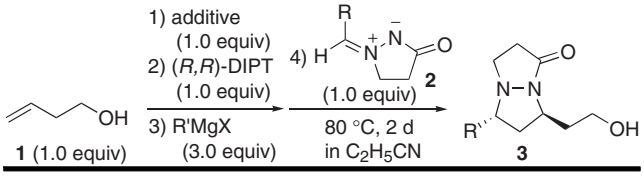
1,3-Dipolar cycloaddition of azomethine imines to olefins is a useful method for the synthesis of pyrazolidines, which have biological activities[1] and are versatile synthetic intermediates for nitrogen containing chemicals such as 1,3-diamines.[2] Compared with progress of asymmetric 1,3-dipolar cycloaddition of nitrones, that of azomethine imines is still limited.[3] Recently we have developed an asymmetric 1,3-dipolar cycloaddition of azomethine imines to allyl alcohol utilizing a stoichiometric and a catalytic amount of diisopropyl (*R*,*R*)-tartrate [(*R*,*R*)-DIPT].[4] In order to synthesize optically active nitrogen containing chemicals with oxygen functionalities, it would be ideal to employ various types of unsaturated alcohols as 1,3-dipolarophiles. Herein, we wish to describe a stoichiometric and a catalytic asymmetric 1,3-dipolar cycloaddition of azomethine imines to homoallylic alcohols utilizing (*R*,*R*)-DIPT as a chiral auxiliary.

First the 1,3-dipolar cycloaddition of 1-benzylidene-3-oxopyrazolidin-1-ium-2-ide (**2a**) to homoallyl alcohol, 3-buten-1-ol (**1**), was examined. To a mixture of 1.0 equiv of **1** and 1.0 equiv of (*R*,*R*)-DIPT were added 3.0 equiv of MeMgBr and 1.0 equiv of azomethine imine **2a** successively in CH_3CN and the reaction mixture was heated at 80 °C for 2 d.[4a] To our surprise, the corresponding pyrazolidine **3a** was obtained in an excellent enantioselective manner with complete regio- and diastereoselectivities (Table 1, Entry 1).[5] By the use of C_2H_5CN as a solvent, the chemical yield was enhanced (Entry 2). Halogens in Grignard reagents slightly influenced the reaction. When *n*-BuMgCl was used, the cycloadduct **3a** was obtained in 97% ee (Entry 3). By addition of $MgBr_2$, chemical yields tended to decrease (Entries 4 and 5).

The asymmetric cycloaddition of several azomethine imines **2** to homoallyl alcohol (**1**) was performed in C_2H_5CN at 80 °C. Aryl-substituted azomethine imines **2b** and **2c** realized excellent enantioselectivities (Entries 6 and 7). The cycloaddition of a pentyl-substituted azomethine imine **2d** proceeded in an enantioselective manner, while a by-product **4** was obtained in 52% yield (Entry 8). The cycloaddition of a cyclohexyl-substituted azomethine imine **2e** afforded **3e** with enantioselectivity over 90% ee by the use of CH_3CN (Entry 10) instead of C_2H_5CN (Entry 9) as a solvent. A *t*-butyl-substituted azomethine imine **2f** also resulted in excellent enantioselectivity (Entry 11).

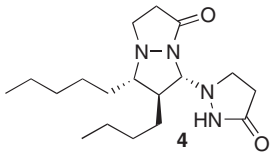
Next, in order to make the procedure more efficient, a catalytic amount of (*R*,*R*)-DIPT was used as a chiral auxiliary.

Table 1. The stoichiometric asymmetric 1,3-dipolar cycloaddition of azomethine imines **2** to homoallyl alcohol (**1**)



Entry	Additive	R′MgX	R	3	Yield/%	ee/%
1[a]	—	MeMgBr	Ph	**a**	80	95[b]
2	—	MeMgBr			90	93[b]
3	—	*n*-BuMgCl			82	97[b]
4	$MgBr_2$	MeMgBr			65	93[b]
5	$MgBr_2$	*n*-BuMgCl			76	98[b]
6	—	*n*-BuMgCl	*p*-$MeOC_6H_4$	**b**	76	99[c]
7	—	*n*-BuMgCl	*p*-ClC_6H_4	**c**	85	97[b]
8	—	*n*-BuMgCl	*n*-C_5H_{11}	**d**	24[d]	95[c]
9	—	*n*-BuMgCl	*c*-C_6H_{11}	**e**	96	85[b]
10[a]	—	*n*-BuMgCl			71	91[b]
11[e]	—	*n*-BuMgCl	*t*-Bu	**f**	79	94[b]

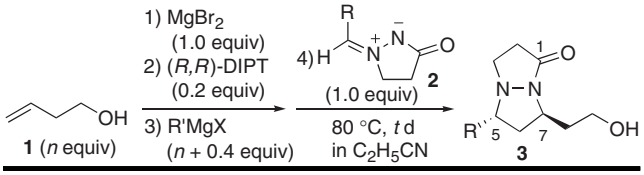
[a]Solvent was CH_3CN instead of C_2H_5CN. [b]Enantioselectivity was determined by HPLC analysis (Daicel CHIRALCEL OD-H). [c]Enantioselectivity was determined by HPLC analysis (Daicel CHIRALPAK IA). [d]By-product **4**, produced via rearrangement of **2d** to an enamine intermediate, was obtained in 52% yield. [e]The reaction time was 4 d.



To a mixture of **1** and 0.2 equiv of (*R*,*R*)-DIPT were added 1.4 equiv of MeMgBr and azomethine imine **2a** successively in C_2H_5CN and the reaction mixture was heated at 80 °C for 2 d (Table 2): Delightedly the corresponding pyrazolidine **3a** was obtained with high enantioselectivity (Entry 1). When *n*-BuMgCl was used instead of MeMgBr, the enantioselectivity was increased (Entry 2). As previously reported,[4b] the addition of magnesium salt was expected to enhance the enantioselectivity. By the addition of $MgBr_2$, enantioselectivity went up to 93% ee (Entry 3). When a slightly excess amount of homoallyl alcohol (**1**) was employed, chemical yield was further improved (Entry 4).

The catalytic asymmetric cycloaddition of several azomethine imines **2** to homoallyl alcohol (**1**) was performed in C_2H_5CN at 80 °C. Aryl-substituted azomethine imines **2b** and **2c** realized excellent enantioselectivities (Entries 5 and 6). The cycloaddition of pentyl- and cyclohexyl-substituted azomethine imines **2d** and **2e** proceeded with moderate enantioselectivities (Entries 7 and 8), while the *t*-butyl-substituted azomethine imine **2f** still resulted in high enantioselection (Entry 9).

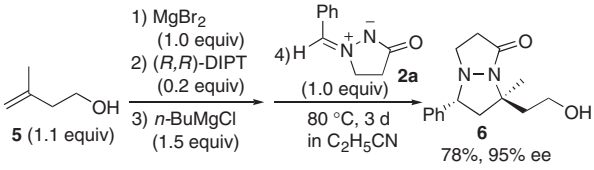
Table 2. The catalytic asymmetric 1,3-dipolar cycloaddition of azomethine imines **2** to homoallyl alcohol (**1**)



Entry	R′MgX	*n*	R	**3**	*t*/d	Yield/%	ee/%
1[a]	MeMgBr	1.0	Ph	**a**	2	77	83[b]
2[a]	*n*-BuMgCl	1.0			2	50	88[b]
3	*n*-BuMgCl	1.0			2	76	93[b]
4	*n*-BuMgCl	1.1			2	90	94[b]
5	*n*-BuMgCl	1.1	*p*-$MeOC_6H_4$	**b**	2	72	93[c]
6	*n*-BuMgCl	1.1	*p*-ClC_6H_4	**c**	2	87	93[b]
7	*n*-BuMgCl	1.1	*n*-C_5H_{11}	**d**	2	23[d]	65[c]
8	*n*-BuMgCl	1.1	*c*-C_6H_{11}	**e**	3	93	63[b]
9	*n*-BuMgCl	1.1	*t*-Bu	**f**	4	80	83[b]

[a]The $MgBr_2$ was not added as an additive in step 1. [b]Enantioselectivity was determined by HPLC analysis (Daicel CHIRALCEL OD-H). [c]Enantioselectivity was determined by HPLC analysis (Daicel CHIRALPAK IA). [d]By-product **4** was obtained in 53% yield.

The 1,3-dipolar cycloaddition of **2a** to other homoallylic alcohols was examined. Although the reaction with (*E*)-3-penten-1-ol did not proceed, 3-methyl-3-buten-1-ol (**5**) worked as a dipolarophile to afford a cycloadduct **6** with excellent enantioselectivity of 95% ee.



(1)

The absolute configuration of **3a** was determined to be *R*,*R* as follows: The enantiomerically rich **3a** (94% ee) was treated with (1*S*)-camphanic chloride and Et_3N in the presence of a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine in CH_2Cl_2 to give the corresponding ester **7** (98%). Recrystallization gave the diastereomerically pure ester **7**. The absolute stereochemistry of pyrazolidine skeleton in **7** was determined to be *R*,*R* by X-ray crystallographic analysis of a single crystal (Figure 1).[6] Based on the absolute configuration of **3a**, the azomethine imine **2a** was revealed to attack from the *re*-face of olefinic moiety of homoallyl alcohol (**1**), that is the same as that in the case of allyl alcohol.[4a,4b] The absolute configurations of other products were tentatively determined to be *R*,*R* for **3b**, **3c**, **3e**, **3f**, and **6**, and 5*S*,7*R* (configurational arrangement of the substituents at the 5- and 7-positions is the same as other products) for **3d**, respectively.[7]

Although the precise mechanism is not yet clear, the generation of chloromagnesium salt of homoallyl alcohol was crucial because a 1,3-dipolar cycloaddition of **2a** to the benzyl homoallyl ether did not proceed at all in the presence of bis(chloromagnesium) salt of (*R*,*R*)-DIPT in C_2H_5CN at 80 °C for 2 d. At the transition state, not imine nitrogen but carbonyl oxygen of **2** might coordinate to magnesium salt of DIPT

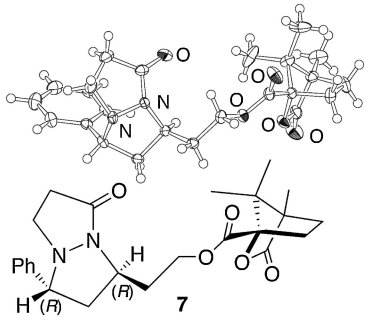


Figure 1.

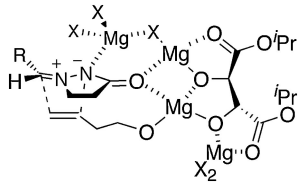


Figure 2.

(Figure 2) and the azomethine imine moiety is located more away from DIPT moiety than the case of other 1,3-dipoles such as nitrile oxides or nitrones, in which allyl alcohol was suitable as a 1,3-dipolarophile.[5,8] Therefore, higher enantioselectivity was realized especially in the catalytic reaction of aromatic azomethine imines.[4b]

As described above, an attractive and unique asymmetric cycloaddition of azomethine imines to homoallylic alcohols has been developed. The present method would be useful for the preparation of optically active nitrogen and oxygen containing chemicals.

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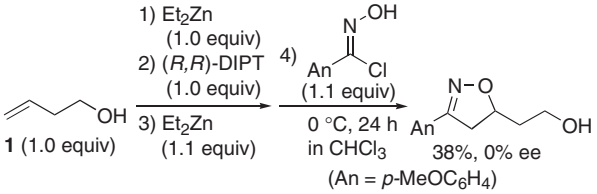
5 Although the asymmetric 1,3-dipolar cycloaddition of a nitrile oxide generated in situ to homoallyl alcohol (**1**) was tried, no chiral induction was observed, that is different from the case of a similar 1,3-dipolar cycloaddition to allyl alcohol.[8]



6 Single crystals of **7** were obtained by recrystallization from Et_2O/hexane. Crystal data: $C_{24}H_{30}N_2O_5$, $M_r = 426.51$, monoclinic, $P2_1$, $a = 6.749(1)$, $b = 11.182(2)$, $c = 14.898(2)$ Å, $V = 1101.4(3)$ Å^3, $\beta = 101.625(1)°$, $Z = 2$. $D_{calcd} = 1.286$ g cm^{-3}. $R = 0.035$ ($R_w = 0.047$) for 4154 reflections with $I > 3.00\sigma(I)$ and 281 variable parameters. Crystallographic data for **7** have been deposited with Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-785029. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.

7 Specific rotations ($[\alpha]_D^{25}$ (EtOH)) of **3a**, **3b**, **3c**, and **6** were +54 (98% ee), +44 (99% ee), +61 (97% ee), and +34 (95% ee), respectively, which support the presumed structure of **3b**, **3c**, and **6**.

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