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Enantioselective Direct Aldol-Type Reaction of Azlactone via Protonation of Vinyl Ethers by a Chiral Brønsted Acid Catalyst

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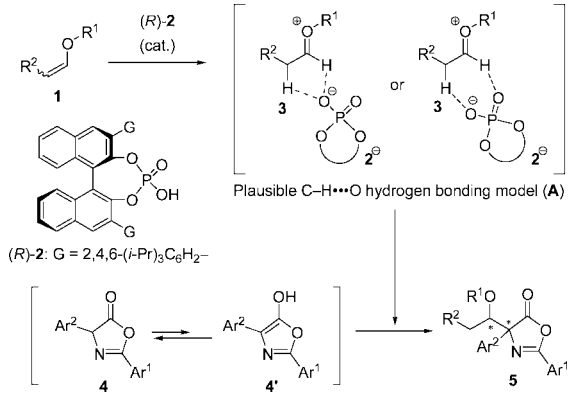
Chiral Brønsted acids have emerged as efficient enantioselective catalysts for a variety of organic transformations.[1] A critical factor in achieving high stereoselectivities in these transformations is the hydrogen bond formed between the donor site of the acid catalyst and the acceptor (basic) site of the electrophilic component, X−H···Y (heteroatom−hydrogen···heteroatom).[2] In this regard, C−H···X (carbon−hydrogen···heteroatom (X = O or N)) hydrogen bonding interactions have recently been identified as important factors in some stereoselective transformations.[3−5]

Activation of vinyl ethers by a Brønsted acid catalyst is an extensively utilized and fundamental method in synthetic organic chemistry and is used in the protection of alcohols and the formation of carbon−carbon bonds among other processes. In this activation mode, the use of chiral Brønsted acids, instead of achiral acids, would give rise to ion pairs of a chiral conjugate base and an oxocarbenium ion via protonation of the vinyl ether. In this case, the acidic proton(s) of the oxocarbenium ion would interact with the anionic site(s) of the chiral conjugate base. The interaction, namely C−H···X hydrogen bond formation, would allow the reaction to proceed under a chiral environment regulated by the chiral conjugate base,[6] since the C−H···X hydrogen bond(s) would specify the relative configuration between the chiral conjugate base and the oxocarbenium ion. To ascertain the feasibility of this hypothesis, we aimed to develop chiral conjugate base-controlled enantioselective transformations involving oxocarbenium ions as the reactive intermediate.[7] For this purpose, we adopted the activation of vinyl ethers (**1**) by chiral phosphoric acid catalysts (**2**)[8,9] to generate the oxocarbenium ion (**3**) and applied the intermediary **3** to a direct aldol-type reaction of azlactones (**4**) via their oxazole tautomer (**4′**) (Scheme 1).[10] In this communication,

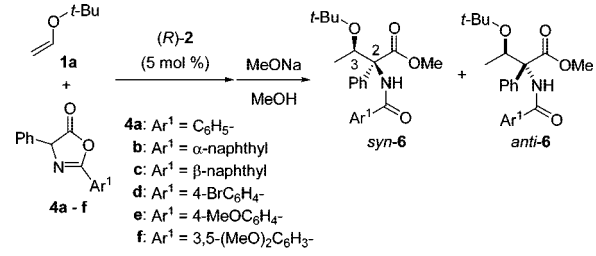
Scheme 1. Direct Aldol-Type Reaction of Azlactone (**4**) with Oxocarbenium Ion (**3**) Generated by Protonation of Vinyl Ether (**1**)



we report the successful demonstration of the proposed enantioselective transformation, which afforded aldol type products (**5**) in excellent enantio- and diastereoselectivities. The method enables efficient access to biologically and pharmaceutically intriguing β-hydroxy-α-amino acid derivatives having a quaternary stereogenic center at the α-carbon atom.

The proposed enantioselective aldol-type reaction was initially performed using *tert*-butyl vinyl ether (**1a**), azlactone (**4a**), and 5 mol% of (*R*)-**2** at room temperature in toluene. The enantio- and diastereoselectivity were determined after transformation to the corresponding methyl ester (**6**) by treatment of **5** with sodium methoxide in methanol. Delightfully, the corresponding product (**6aa**) was obtained in good yield, albeit with moderate enantio- and diastereoselectivity (Table 1, entry 1). To enhance stereoselectivity, we investigated the effects of the substituent (Ar^1) at the C2 position of azlactone (**4**). As shown in Table 1, the naphthyl substituents exhibited a similar level of stereoselectivity (entries 2,3); however, the electronic manipulation of Ar^1 substituents made a significant impact not only on the reactivity of **4** but also on the stereochemical outcome in terms of both enantio- and diastereoselectivities (entries 4−6). Most notably, when electron-donating methoxy substituents were introduced to the 3,5-positions of the phenyl ring (entry 6), the corresponding product (**6af**) was obtained in high enantio- and diastereoselectivity. Further optimization of the reaction conditions with changing solvent and temperature (entries 7−10) revealed that dichloromethane was the best in terms

Table 1. Enantioselective Direct Aldol-Type Reaction between Azlactone (**4**) and Vinyl Ether (**1a**) Catalyzed by (*R*)-**2**[a]



entry	4	solvent	conditions	6	yield (%)[b]	syn:anti	ee (%)[c] (syn/anti)
1	**4a**	toluene	rt, 20 h	**6aa**	81	78:22	67/60
2	**4b**	toluene	rt, 20 h	**6ab**	96	68:32	63/70
3	**4c**	toluene	rt, 20 h	**6ac**	99	75:25	74/65
4	**4d**	toluene	rt, 20 h	**6ad**	60	69:31	39/35
5	**4e**	toluene	rt, 20 h	**6ae**	88	81:19	82/61
6	**4f**	toluene	rt, 9 h	**6af**	90	94:6	97/46
7	**4f**	$CF_3C_6H_5$	rt, 6 h	**6af**	99	94:6	96/35
8	**4f**	CH_3CN	rt, 6 h	**6af**	30	92:8	86/25
9	**4f**	CH_2Cl_2	rt, 4 h	**6af**	99	95:5	96/5
10	**4f**	CH_2Cl_2	0 °C, 20 h	**6af**	99	98:2	98/8

[a] All reactions were carried out using 0.01 mmol of (*R*)-**2** (5 mol %), 0.4 mmol of **1a** (2.0 equiv), and 0.2 mmol of **4** in 0.4 mL of the indicated solvent. [b] Combined yield of *syn*/*anti*-**6**. [c] Determined by chiral HPLC analysis. Absolute stereochemistry of *syn*-**6af** was determined to be 2*S*,3*R*. See Supporting Information for details.

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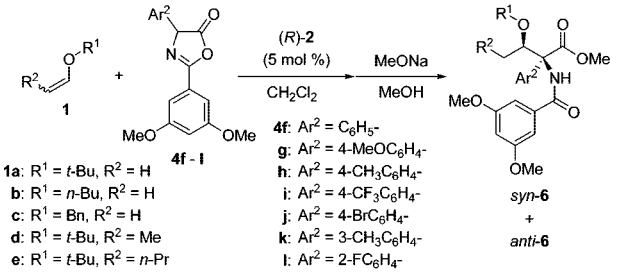
of reactivity while maintaining a high level of stereoselectivity (entry 6 vs 9). The selectivity was increased with a decrease in reaction temperature, reaching 98% *syn* along with 98% ee at 0 °C (entry 10).[11]

Having identified suitable substituents (Ar^1 = 3,5-$(MeO)_2C_6H_3$−) of azlactone (**4**) and optimal reaction conditions, we began to further explore the substrate scope of this reaction (Table 2). Investigation

Table 2. Substrate Scope of Enantioselective Direct Aldol-Type Reaction Catalyzed by (*R*)-**2**[a]



entry	1	4	conditions	6	yield (%)[b]	syn:anti	ee (%)[c] (syn)
1	**1b**	**4f**	rt, 10 h	**6bf**	94	82:18	96
2	**1c**	**4f**	rt, 30 h	**6cf**	62	80:20	93
3	**1d**[d]	**4f**	rt, 20 h	**6df**	99	96:4	97
4	**1e**[e]	**4f**	rt, 20 h	**6ef**	66	88:12	94
5	**1a**	**4g**	rt, 20 h	**6ag**	67	95:5	95
6	**1a**	**4h**	0 °C, 30 h	**6ah**	86	97:3	96
7	**1a**	**4i**	0 °C, 12 h	**6ai**	97	94:6	91
8	**1a**	**4j**	0 °C, 12 h	**6aj**	99	98:2	95
9	**1a**	**4k**	0 °C, 20 h	**6ak**	67	96:4	97
10	**1a**	**4l**	rt, 48 h	**6al**	45	70:30	37

[a] All reactions were carried out using 0.01 mmol of (*R*)-**2** (5 mol %), 0.4 mmol of **1** (2.0 equiv), and 0.2 mmol of **4** in 0.4 mL of CH_2Cl_2. [b] Combined yield of *syn*/*anti*-**6**. [c] For major *syn*-**6**. Determined by chiral HPLC analysis. [d] *Z*/*E* = 79:21 for **1d**. [e] *Z*/*E* = 75:25 for **1e**.

of the substituent effect of vinyl ethers (**1**) showed that the sterically demanding *t*-butyl ether is important in achieving the high diastereoselectivity. Thus, the sterically less hindered *n*-butyl (**1b**) and benzyl (**1c**) substituents exhibited lower diastereoselectivity (entries 1,2), while the enantioselectivity of the major *syn* isomers was maintained in equally high levels (see: Table 1, entries 9,10). In addition, the kind of alkyl substituent is also critical in obtaining the product in high yield. In the reaction of benzyl ether (**1c**), the desired product (**6cf**) was obtained in modest yield, accompanied by a significant amount of byproducts, presumably formed from oligomerization of **1c** (entry 2). Vinyl ethers (**1d**, **e**) substituted by an alkyl group at the terminal position were also applicable, affording the desired product in high enantioselectivity (entries 3,4),[12] albeit with a slight decrease in diastereoselectivity for the vinyl ether (**1e**) having an *n*-propyl group (entry 4). Further investigation of the substrate scope of azlactones (**4**) having a series of aromatic groups (Ar^2) revealed uniformly high enantio- and diastereoselectivities for *para*- and *meta*-substituted aromatic rings (Ar^2), irrespective of their electronic properties (entries 5−9).[13] However, *ortho*-substitution led to a marked reduction of selectivity and chemical yield (entry 10), presumably due to retardation in tautomerization of **4l**.[14]

In conclusion, we have demonstrated the direct aldol-type reaction of azlactone with an oxocarbenium ion via protonation of a vinyl ether by a chiral phosphoric acid catalyst, which provides β-hydroxy-α-amino acid derivatives having a quaternary stereogenic center at the α-carbon atom in a highly enantio- and diastereoselective manner. The approach opens a new avenue for utilization of chiral Brønsted acids toward advanced enantioselective catalysis. Further application of the present method, namely generation of an oxocarbenium ion paired with a chiral conjugate base, is in progress with the aim of developing efficient enantioselective organic transformations.

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Supporting Information Available: Representative experimental procedure, spectroscopic data for azlactones (**3**) and products (**6**), determination of relative and absolute stereochemistry of **6**, and mechanistic considerations of the aldol-type reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) During the course of our studies, Tepe et al. reported the reaction of azlactone (Ar^2 = methoxycarbonyl) with vinyl ethers catalyzed by a chiral phosphoric acid (*G* = H), but no asymmetric induction was detected; see: Mosey, R. A.; Fisk, J. S.; Friebe, T. L.; Tepe, J. J. *Org. Lett.* **2008**, *10*, 825–828. Also see: Fisk, J. S.; Tepe, J. J. *J. Am. Chem. Soc.* **2007**, *129*, 3058–3059.

(11) The high stereoselectivity observed would be attributed to the formation of contact ion pairs between the oxocarbenium ion (**3**) and conjugate base of the chiral phosphoric acid (**2**) through a C−H···O hydrogen bonding interaction, as illustrated in the plausible structures (**A**) of hydrogen bonding in Scheme 1. See Supporting Information for details.

(12) The reactions of vinyl ethers (**1f**: R^1 = *n*-Bu, R^2 = Me), (*Z*)-**1f** (86% *Z*) and (*E*)-**1f** (97% *E*), exhibited identical diastereo- and enantioselectivities. See Supporting Information for details.

(13) The reaction of alkyl-substituted azlactone (Ar^2 = Me) did not provide any desired product, and it was recovered in >80% yield.

(14) The reaction of *ortho*-chloro substituted azlactone gave the corresponding product in <10% yield.

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