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Preparation of optically active α-hydroxy oxime ether by diastereoselective imino 1,2-Wittig rearrangement of hydroximates and its application to synthesis of (+)-cytoxazone

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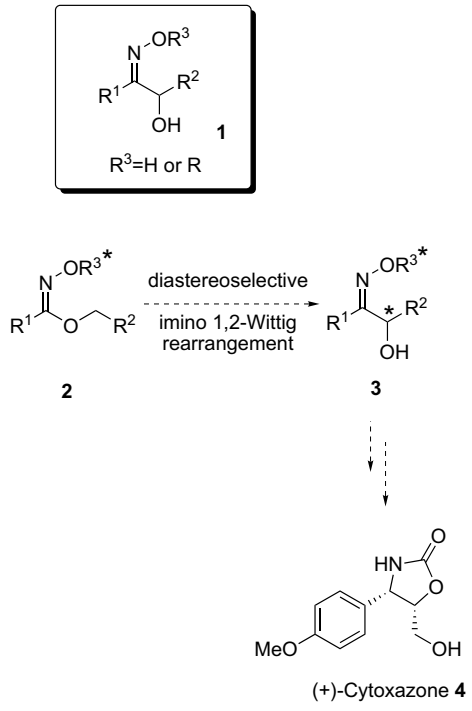
Abstract—The diastereoselective imino 1,2-Wittig rearrangement of hydroximates provides a novel method for the construction of optically active α-hydroxy oxime ethers. Upon treatment with LDA, allyl *p*-methoxyphenylhydroximate carrying a chiral auxiliary smoothly underwent diastereoselective rearrangement to give the (*R*)-α-hydroxy oxime ether which was effectively converted into (+)-cytoxazone.

The α-hydroxy oximes and oxime ethers **1** have recently received much attention as important precursors and intermediates for the preparation of a wide variety of natural products, drugs, and metal-binding ligands.[1] Furthermore, they can be easily converted into amino alcohols and hydroxy ketones which are one of the most important functional groups.[1] Therefore, the development of methodologies for the preparation of enantiomerically pure α-hydroxy oximes and oxime ethers is of considerable interest. Recently, we found that the imino 1,2-Wittig rearrangement of benzyl and allyl *Z*-hydroximates (*N*-alkoxyimidates) proceeded smoothly to give the (±)-2-hydroxy oxime ethers.[2] This method is suitable for the preparation of unsymmetrical α-hydroxy oxime ethers ($R^1 \neq R^2$). We now report the first example of diastereoselective imino 1,2-Wittig rearrangement of allyl hydroximates **2** for preparation of optically active α-hydroxy oxime ethers **3** and application of this method to the synthesis of (+)-cytoxazone **4** (Scheme 1). To our knowledge, there are a few papers published on diastereo- and enantioselective migration of the sp^2 carbon in 1,2-Wittig rearrangement.[3]

We first investigated the diastereoselective 1,2-Wittig rearrangement of allyl hydroximates **5**[4] carrying a chiral auxiliary on the oxime ether moiety (Scheme 2, Table 1). We chose an optically active (*S*)-(2-hydroxy-1-phenyl)ethyl group as a chiral auxiliary.[5,6] The



Scheme 1.

Keywords: Imino Wittig rearrangement; Hydroximate; Diastereoselective reaction; Oxime ether; Cytoxazone.
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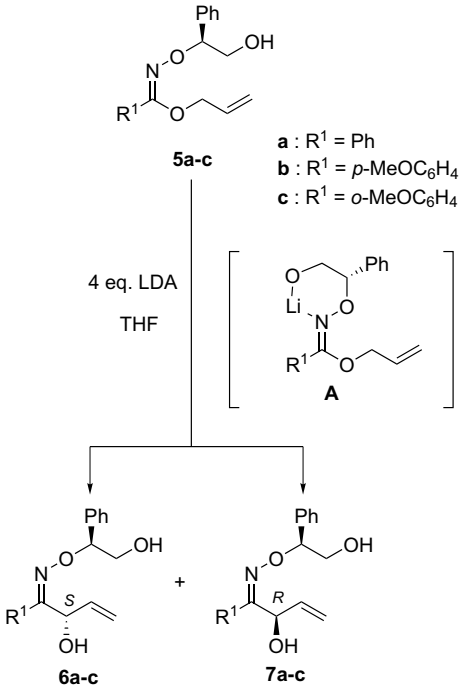


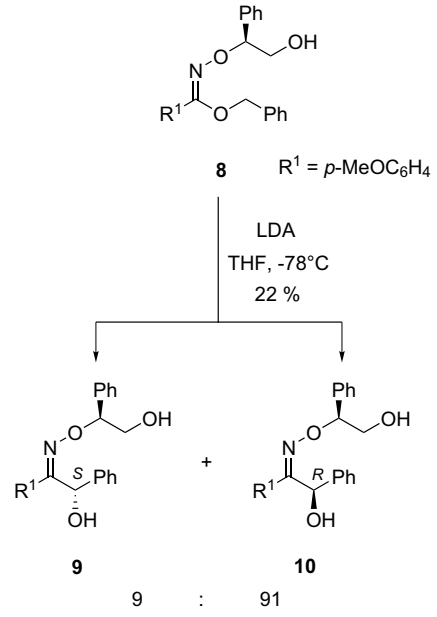
Scheme 2.

Table 1. Imino 1,2-Wittig rearrangement of allyl hydroximates **5a–c**

Entry	Substrate	Solvent	Temp (°C)	Yield (%)[a] **6**+**7**	Ratio (**6**:**7**)
1	**5a**	THF	−40	65 (6)	25:75
2	**5a**	THF	−78	25 (60)	24:76
3	**5a**	Et_2O	−40	25 (46)	25:75
4	**5a**	Toluene	−78	22 (42)	26:74
5	**5b**	THF	−40	55 (14)	31:69
6	**5b**	THF	−78	63 (29)	10:90
7	**5c**	THF	−40	61 (9)	33:67
8	**5c**	THF	−78	23 (49)	27:73

[a] Yields in parentheses are for recovered starting materials.

diastereoselective reaction of **5** would proceed smoothly under the basic conditions because the conformation of the chiral auxiliary part could be easily fixed even in the absence of Lewis acid as shown in intermediate **A**. The results are summarized in Table 1. The chiral allyl phenylhydroximate **5a** was treated with 4 equiv of LDA in THF at −40 °C. The imino 1,2-Wittig rearrangement proceeded smoothly to give a mixture of (*S*)-**6a**[7] and (*R*)-**7a**[7] with a ratio of 25:75 (entry 1). In order to improve diastereoselectivity, the reaction was carried out at −78 °C. However, **6a** and **7a** were obtained in low yield with almost the same selectivity (entry 2). When Et_2O and toluene were used as the solvent, no increased selectivity was observed (entries 3 and 4). Previously, we found that an electron-donating group on the benzene ring accelerated the rearrangement.[2d] Therefore, we next examined the rearrangement of hydroximates **5b** and **5c** having *p*- and *o*-methoxyphenyl groups (entries 5–8). As shown in entry 6, the rearrangement of hydroximate **5b** with a *p*-methoxylphenyl group proceeded smoothly even at −78 °C to give (*R*)-**7b**[7] with high diastereoselectivity which was readily isolated by column chromatography.



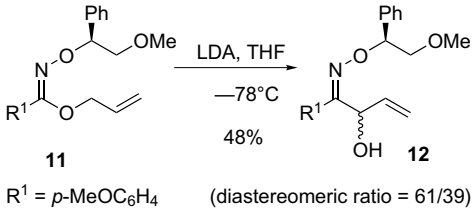
Scheme 3.

Similarly, benzyl hydroximate **8** was subjected to diastereoselective rearrangement to afford (*R*)-**10**[7] in low yield, but with high diastereoselectivity (Scheme 3).

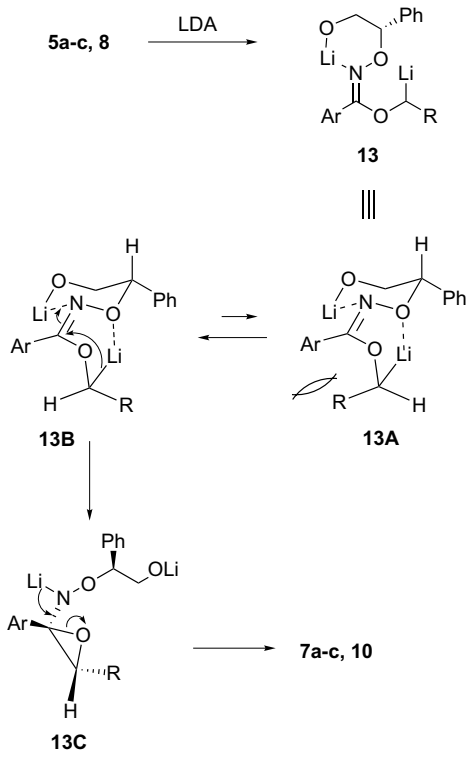
In order to examine the influence of a hydroxyl group on a chiral auxiliary, we investigated the rearrangement of hydroximate **11** carrying an (*S*)-(2-methoxy-1-phenyl)ethyl group and found that under the same conditions, **11** afforded two diastereomers **12** with low diastereoselectivity (Scheme 4).

From the above result, we propose a possible reaction pathway in the rearrangement of **5a–c** and **8** (Scheme 5). Low diastereoselectivity in the rearrangement of **11** having the methoxy group suggests that the formation of the lithium alkoxide is crucial for promoting the diastereoseletive rearrangement of **5** and **8**. Intermediates **13A** and **13B**, which have a bicyclic chelated structure, are formed by the treatment of **5** and **8** with LDA. Intermediate **13B** is more stable than **13A** because steric repulsion between the Ar and R groups exists in intermediate **13A**. Therefore, the rearrangement of **5** and **8** proceeds via intermediates **13B** and **13C** to afford (*R*)-**7** and **10** as a major product.

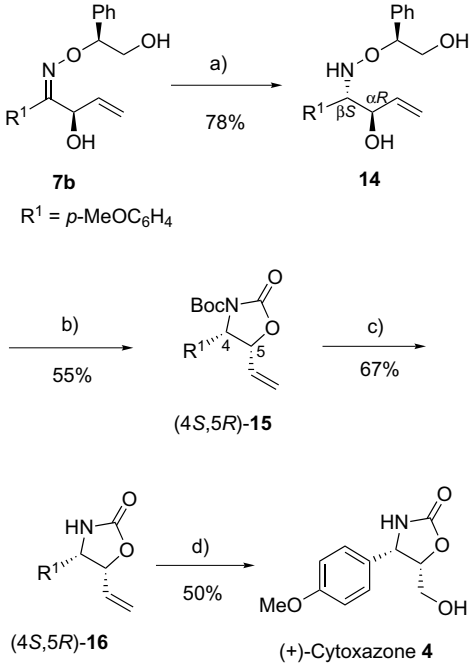
With (*R*)-α-hydroxy oxime ether **7b** in hand, we next investigated its conversion into (+)-Cytoxazone **4** (Scheme 6). Cytoxazone has shown cytokine-modulat-



Scheme 4.



Scheme 5.



Scheme 6. Reagents and conditions: (a) $NaBH_3CN$, 0 °C; (b) (1) $LiAlH_4$, 35 °C, (2) $(Boc)_2O$, DMAP; (c) TFA; (d) (1) O_3, −78 °C, (2) $NaBH_4$, −78 to 0 °C.

ing activity by inhibiting the signaling pathway of Th2 cells.[8] Inhibitors of Th2-dependent cytokine production would be potent chemotherapeutic agents in the field of immunotherapy. Therefore, Cytoxazone and its analogs have been a new subject of synthetic studies for the development of a cytokine modulator.[9] Previously, we have synthesized (−)-cytoxazone from racemic (±)-α-hydroxy oxime ether via optical resolution. According to the reported method,[2d] we examined the conversion of **7b** into oxazolidinone **15** via reduction with $LiAlH_4$ and subsequent acylation with $(Boc)_2O$. However, an undesired diastereomer (4*R*,5*R*)-**15** was obtained in low yield and the desired (4*S*,5*R*)-**15** was not isolated. The reduction of the oxime ether part with other reducing agents was reexamined. As a result, the diastereoselective reduction of **7b** with $NaBH_3CN$ proceeded smoothly to give the desired (α*R*,β*S*)-alkoxyamino alcohol **14** in 78% yield, in addition to 15% yield of a diastereomer. The reductive cleavage of the N–O bond followed by acylation of the resulting amino alcohol gave (4*S*,5*R*)-oxazolidinone **15**. Treatment of **15** with TFA gave the desired oxazolidinone **16** in 67% yield, which was smoothly converted into (+)-cytoxazone **4**[10] via oxidation of **16** with O_3 and subsequent reduction of the ozonide with $NaBH_4$. The physical and spectral data of the synthetic (+)-cytoxazone **4** were identical with those of the authentic sample.

In conclusion, we have now developed a new strategy for preparation of optically active α-hydroxy oxime ethers via diastereoselective imino 1,2-Wittig rearrangement of allyl hydroximates. Furthermore, this method has been successfully applied to the asymmetric synthesis of (+)-cytoxazone.

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10. (+)-Cytoxazone **4**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.00 (1H, br s), 7.11 (2H, br d, J = 9 Hz), 6.89 (2H, br d, J = 9 Hz), 4.87 (1H, d, J = 8.5 Hz), 4.76 (1H, t, J = 5 Hz), 4.66 (1H, br td, J = 8.5, 5 Hz), 3.71 (3H, s), 2.93 (2H, m). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 159.0, 158.7, 129.3, 128.0, 113.7, 80.0, 61.0, 56.2, 55.1. HRMS *m/z*: Calcd for $C_{11}H_{13}NO_4$ (M^+) 223.0844. Found: 223.0846. $[\alpha]_D^{30}$ +74.4 (*c* 0.86, MeOH). [lit.[2d] $[\alpha]_D^{29}$ +75.0 (*c* 0.51, MeOH)].