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Asymmetric *O*-methylhalohydrin reaction of chiral *N*-enoyl-2-oxazolidinones: synthesis of N-protected *syn*-β-methoxyphenylalanine, an unusual amino acid component of cyclomarins

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Abstract—Asymmetric *O*-methylhalohydrin reactions of chiral *N*-enoyl-2-oxazolidinones were performed with halogens (Br_2/I_2) promoted by silver(I) in methanol with high regio- and *anti*-selectivity and moderate to good diastereoselectivity. Reagent-controlled opposite diastereoselectivity was observed especially for cinnamoyl and electron-deficient cinnamoyl substrates. This method was applied to the short enantioselective synthesis of N-protected *syn*-β-methoxyphenylalanine, an unusual amino acid component of cyclomarins.

β-Methoxy-α-amino acids are the unusual amino acid constituents of the recently discovered biologically active cyclic peptide and depsipeptide antibiotics such as callipeltines,[1] papuamides,[2] cyclomarins[3] and discokiolide.[4] Similar to the carboxyhalohydrins,[5] *O*-methylcarboxyhalohydrins, i.e. α-halo-β-methoxycarboxylic acid derivatives, would be an important direct precursor to the β-methoxyamino acids. Incidentally there have been no reports to date on the asymmetric synthesis of α-halo-β-methoxycarboxylic acids and their derivatives, although a number of stereoselective methods for accessing α-halo-β-hydroxycarboxylic acid derivatives exist.[6–8] A potentially straightforward method for the synthesis of *O*-methylcarboxyhalohydrins is the regio- and stereoselective *O*-methylhalohydrin reaction[9] of α,β-unsaturated carboxylic acid derivatives. Herein, we report our preliminary results on the asymmetric *O*-methylhalohydrin reaction of chiral *N*-enoyl-2-oxazolidinones **1** for the highly regio- and *anti*-selective synthesis of α-halo-β-methoxycarbonyls **2** and **3** and their application to the synthesis of N-protected *syn*-β-methoxyphenylalanine, an unusual amino acid component of cyclomarins.

Recently Hamada and co-workers[10] reported the diastereoselective synthesis of all the stereoisomers of β-methoxytyrosine by nucleophilic addition of arylmetal reagents to the Garner aldehyde followed by methylation and oxidation of the thus formed hydroxyamino compounds. Boukhris and Souizi reported[11] the reduction of β-alkoxy-α-oximino acid esters to β-alkoxy-α-amino esters by $NaBH_4$ in the presence of $TiCl_3$ and L-tartaric acid, but the configuration of the diastereomers and enantioselectivities were not determined.

There are only a few reports[12] of the *O*-methylhalohydrin reactions of α,β-unsaturated carbonyls. By screening those methods, we found that the combination of silver nitrate and halogen (Br_2/I_2) in MeOH is an effective system for the regio- and stereoselective *O*-methylhalohydrin reaction of chiral *N*-enoyl-2-oxazolidinones **1**. Initial results of the *O*-methylhalohydrin reactions of **1** with $AgNO_3$ and Br_2/I_2 are summarised in Table 1.

Towards the development of the asymmetric *O*-methylhalohydrin reaction of chiral *N*-enoyl-2-oxazolidinones, a methanolic solution of compound **1a** was treated

Keywords: Asymmetric; *O*-Methylhalohydrin; Silver(I); Halogen; *N*-Enoyl-2-oxazolidinones; α-Halo-β-methoxycarboxylic acid derivatives; *syn*-β-Methoxyphenylalanine.
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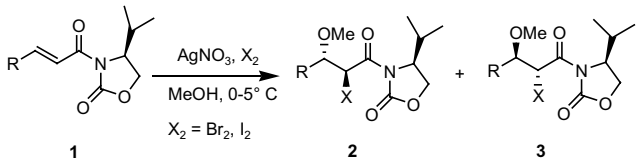
Table 1. $AgNO_3$-promoted *O*-methylhalohydrin reaction of **1**[a]



Entry	Substrate	R	X	Ratio[b] (**2**:**3**)	Yield[c] (%)
1	**1a**	Ph	Br	71:29	91
2	**1b**	2-$NO_2C_6H_4$	Br	65:35	84
3	**1c**	2-ClC_6H_4	Br	60:40	91
4	**1d**	4-$MeOC_6H_4$	I	62:38	94
5	**1e**	3,4-$MeOC_6H_3$	I	76:24	91
6	**1f**	3,4,5-$MeOC_6H_2$	I	74:26	93
7[d]	**1g**	2-Naphthyl	I	73:27	88
8	**1h**	CH_3	Br	86:14[e]	62[f]

[a] *O*-Methylhalohydrin reactions were performed using 1.2 equiv of $AgNO_3$ and 1.2 equiv of halogen (X_2) in MeOH at 0–5 °C for 30 min.
[b] Determined from the ^1H NMR spectrum of the crude reaction mixture.
[c] Combined isolated yields of **2** and **3** after column chromatography.
[d] 30% CH_2Cl_2 used due to poor solubility of the substrate **1g** in MeOH.
[e] Including 18% of the other regioisomers.
[f] Isolated yield of the major isomer **2h** only, minor isomer **3h** could not be separated from the other regioisomers.

with silver nitrate (1.2 equiv) and bromine (1.2 equiv) at 0–5 °C. Within 20–30 min, the α-bromo-β-methoxycarbonyls **2a** and **3a** were obtained in high yield (91%) with a diastereomeric ratio of 71:29. The *O*-methyliodohydrin reaction of **1a** under the same reaction conditions gave <5% of the desired compounds, and there was no improvement even with the use of excess reagents and under different reaction conditions. This *O*-methylhalohydrin reaction was studied on a variety of cinnamoyl substrates containing different electron-withdrawing and -donating substituents on the aromatic ring as well as alkenoyl substrates. It was found that the electron-deficient cinnamoyl substrates **1b** and **1c** smoothly underwent *O*-methylbromohydrin reactions (entries 2 and 3) but no *O*-methyliodohydrin reactions. The electron-rich cinnamoyl substrates **1d–g** preferred to undergo *O*-methyliodohydrin reactions (entries 4–7); *O*-methylbromohydrin reactions gave either a low yield of the desired compounds or complex reaction mixtures. The alkenoyl substrate **1h** responded to the *O*-methylbromohydrin reaction with a good diastereomeric ratio of 86:14 along with 18% of other regioisomers (entry 8).

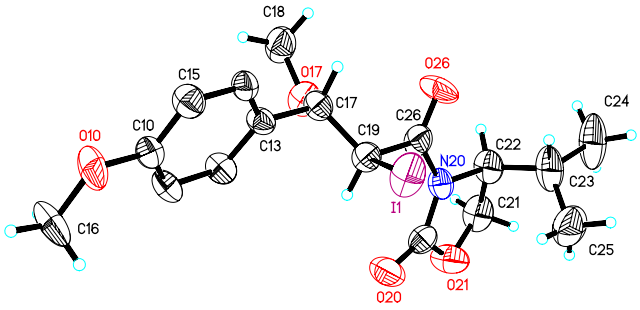


Figure 1. ORTEP diagram of **2d**.

The stereochemistry of **2** was confirmed from the single crystal X-ray analysis[13] of compound **2d** (Fig. 1).

When the *O*-methylhalohydrin reactions of **1** were performed in the presence of AgOAc instead of $AgNO_3$, similar results were also obtained, i.e. **2** was the major diastereomer (results are not included in Table 1). Since, the chiral auxiliary (3*S*)-3-(1-methylethyl)-2-oxazolidinone gave moderate to good diastereoselectivities, we have also examined other oxazolidinone chiral auxiliaries viz (3*S*)-3-phenyl- and (3*S*)-3-(diphenylmethyl)-2-oxazolidinones. The *O*-methylhalohydrin reaction of those substrates having different oxazolidinone chiral auxiliaries (Ph and Ph_2CH) using either Br_2 or I_2 gave complex mixtures of products.

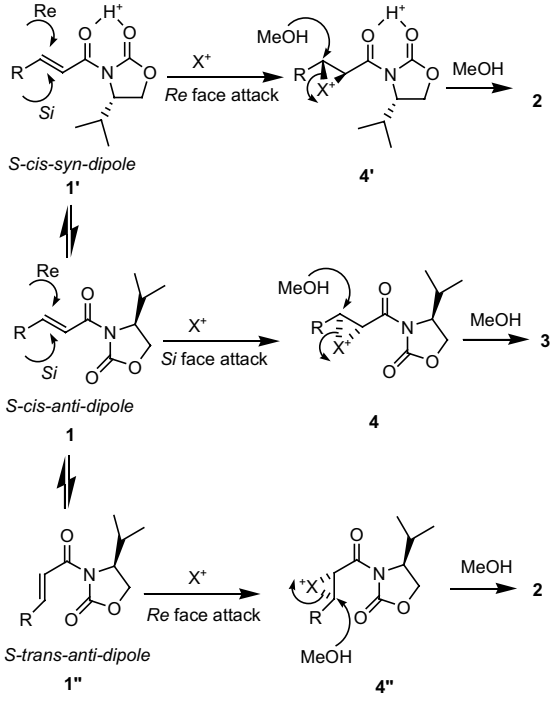
To assess whether the counterion of the Ag(I) salt affects the diastereoselectivity of the *O*-methylhalodrin reactions, product studies were carried out employing the electronically different cinnamoyl substrates **1a–b** and

Table 2. Ag_2O-promoted *O*-methylhalohydrin reaction of **1**[a]

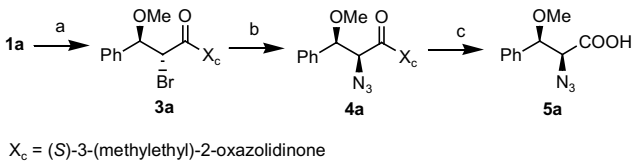
Entry	Substrate	Additive	X	Ratio[b] (**2**:**3**)
1	**1a**	None	Br	27:73
2	**1b**	None	Br	35:65
3	**1d**	None	I	48:52
4	**1e**	None	I	47:53
5	**1a**	HNO_3	Br	72:28 (70:30)
6	**1b**	HNO_3	Br	64:36 (67:33)
7	**1d**	HNO_3	I	61:39 (62:38)
8	**1e**	HNO_3	I	75:25 (73:27)

[a] *O*-Methylhalohydrin reactions were performed using 0.7 equiv of Ag_2O and 1.2 equiv of halogen (X_2) in MeOH at 0–5 °C for 30 min.
[b] Determined from the ^1H NMR spectrum of the crude reaction mixture. Ratios in parentheses refer to reactions in the presence of AcOH.

1d–e using Ag_2O, which does not produce any acid on reacting with a halogen in MeOH (Eq. 3), as a promoter under a variety of reaction conditions (Table 2). The results showed that the diastereoselectivities for the Ag_2O-mediated reactions were in favour of the diastereomer **3** (Table 2, entries 1–4) and more interestingly, that **1a** and the electron-deficient **1b** show opposite diastereoselectivities (Table 2, entries 1 and 2) compared to the $AgNO_3$-mediated reactions (Table 1, entries 1 and 2). When the Ag_2O-promoted *O*-methylhalohydrin reactions of **1** were performed in the presence of either HNO_3 or AcOH as an additive, these showed diastereoselectivities (entries 5–8) similar to either $AgNO_3$– or AgOAc-promoted reactions (Table 1, entries 1, 2, 4 and 5). Reaction of either $AgNO_3$ or AgOAc with halogens in MeOH generated acid (Eqs. 1 and 2), so it might be concluded here that in either $AgNO_3$– or AgOAc-promoted reactions, the H^+-chelated *S-cis-syn-dipole* conformation **1′** might be involved in the *O*-methylhalohydrin reaction. The preferred attack of X^+ from the *Re-face* of conformation **1′** and subsequent opening of the halonium intermediate **4′** by *anti*-nucleophilic attack of MeOH at the β-position yielded **2** as the major diastereomer (Scheme 1). In the Ag_2O-promoted reaction, the *Si-face* of the unchelated *S-cis-anti-dipole* conformation **1** might be involved giving **3** as the major diastereomer. This is supported by the Ag_2O-mediated reactions performed in the presence of either HNO_3 or AcOH as an additive (Table 2, entries 5–8). The poor diastereoselectivities of the electron-rich substrates **1d–e** in Ag_2O-promoted reactions (Table 2, entries 3 and 4), might be accounted for by the involvement of both the equilibrated *S-cis-* and *S-trans-anti-dipole* conformations **1** and **1″**, due to the extensive conjugation of the electron-donating substituent at the *p*-position with the α,β-unsaturated carbonyls.



Scheme 1.



Scheme 2. Reagents and conditions: (a) Ag_2O, Br_2, MeOH, 0–5 °C, 30 min, 64%; (b) NaN_3, DMF, 60 °C, 3 h, 84%; (c) LiOH, H_2O_2, THF, 0–5 °C, 2 h, 77%.

$$AgNO_3 + X_2 + MeOH \rightarrow AgX\downarrow + MeOX + HNO_3 \quad (1)$$

$$AgOAc + X_2 + MeOH \rightarrow AgX\downarrow + MeOX + AcOH \quad (2)$$

$$Ag_2O + 2MeOH + 2X_2 \rightarrow 2AgX\downarrow + 2MeOX + H_2O \quad (3)$$

After achieving the reagent-controlled reverse diastereoselectivity of the *O*-methylhalohydrin reaction, especially for cinnamoyl and electron-deficient cinnamoyl systems, the usefulness of the new process was exemplified in a short synthesis of N-protected *syn*-β-methoxyphenylalanine (Scheme 2), an unusual amino acid component of the biologically active cyclic peptides, cyclomarins. Ag_2O-mediated *O*-methylbromohydrin reaction of chiral *N*-cinnamoyl-2-oxazolidinone **1a** gave α-bromo-β-methoxycarboxylic acid derivative **3a** as the major diastereomer in 68% yield along with a minor amount of **2a** (25%). Reaction of **3a** with NaN_3 in DMF at 60 °C gave the *syn*-α-azido-β-methoxycarboxylic acid derivative **4a** (84%). Subsequent removal of the chiral auxiliary by treatment with LiOH and H_2O_2 in THF at 0 °C yielded the *syn*-α-azido-β-methoxycarboxylic acid **5a** (77%). Azido-carboxylic acids serve as N-protected amino acids in peptide antibiotic syntheses.[5a] Thus compound **5a** can be directly used as an N-protected β-methoxyphenylalanine for the synthesis of cyclomarins.

In summary, we have described the Ag(I)-promoted asymmetric *O*-methylhalohydrin reaction of chiral *N*-enoyl-2-oxazolidinones **1** with high regio- and *anti*-selectivity and moderate to good diastereoselectivity with good yields. More interestingly the use of Ag_2O reverses the diastereoselectivity, especially for cinnamoyl and electron-deficient cinnamoyl substrates. This new process has been applied to the synthesis of N-protected *syn*-β-methoxyphenylalanine, an unusual amino acid component of cyclomarins. This methodology offers an asymmetric synthesis of β-methoxy amino acids. We are currently attempting to improve the diastereoselectivity of this process and are also applying this concept to other halo-nucleophilic (X^+Nu^-) addition reactions for the asymmetric hetero-bifunctionalisation of alkenes.

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