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Diastereoselective reduction and carbon–carbon bond formation of α-keto esters/amides with SmI_2

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Abstract—The stereoselective reduction of α-keto esters/α-keto amides, which have various chiral auxiliaries using SmI_2, is examined. 2(*S*)-Methoxymethylpyrrolidine, 1,1,2(*S*)- and 1,1,2(*R*)-triphenylethanediol were found to be suitable chiral auxiliaries that produced the corresponding α-hydroxy ester and amide in good diastereoselectivity with satisfactory yields. Allylation, the Reformatsky-type reaction, and the ketyl-alkene coupling reaction with the 1,1,2(*R*)-triphenylethanediol and 2(*S*)-methoxymethylpyrrolidine, derivative of the α-keto ester/amide proceeded smoothly with high diastereoselectivity.

We have succeeded in the SmI_2-mediated asymmetric coupling reaction of carbonyl compounds with chiral α,β-unsaturated esters[1] and with chiral α-bromocarboximides[2] with excellent selectivities. Based on our and other research group studies,[3] the use of SmI_2 should produce high stereoselectivity for asymmetric reactions with chiral molecules by choosing an appropriate chiral auxiliary due to the chelation control. Optically active α-hydroxy acids are synthetically useful intermediates, in addition to being commonly used building blocks for organic synthesis.[4] Their main synthetic applications are as chiral synthons, stereo directing groups for the enantioselective synthesis of natural products, and the synthesis of phosphine ligands for use in transition-metal complex catalysts. The diastereoselective reduction of chiral α-keto esters/amides is one of the convenient methods for the synthesis of α-hydroxy acids.[5] The reduction of the chiral α-keto ester by SmI_2 may be the simplest and most promising way to access optically active α-hydroxyl acids with high stereoselectivity. In this report, we describe the diastereoselective reduction of chiral α-keto esters/amides, which have several classes of chiral auxiliaries by SmI_2. Highly diastereoselective carbon–carbon bond formation, i.e. allylation and the Reformatsky-type reaction will also be described.

We first investigated the reduction of benzoylformic acid esters and amides (**1**), which are derived from various chiral auxiliaries with SmI_2; 1,1,2(*S*)-, (*R*)-triphenylethanediol (**1a**, **1b**), (−)-borneol (**1c**), (−)-8-phenylmenthol (**1d**), 2(*S*)-methoxymethylpyrrolildine (**1e**), 1(*S*)-phenylethylamine (**1f**) and (*S*)-valinol (**1g**) were examined with respect to the level of asymmetric induction during the reduction (Scheme 1).

All the chiral auxiliaries employed here were readily prepared from inexpensive optically active compounds such as amino acids. The results are summarized in Table 1. The reaction was usually carried out at −78°C for 2 h in tetrahydrofuran (THF), and the α-hydroxyl esters/amides were isolated by PTLC after the usual work-up. The diastereomeric excess (% de) was determined by ^{1}H NMR (400 MHz) and/or GC/MS as esters of trifluoroacetic acid. The use of water as a proton source was essential for obtaining a high yield and selectivity. Methanol, *t*-butanol and tetrahydrofurylmethyl alcohol may be used as a proton source but gave less selectivity; 40–50% de using **1a** as a chiral auxiliary (entries 2–5).[6] The reduction product was only slightly formed in the absence of a proton source. Chiral auxiliaries **1a**, **1b** and **1e**, were found to be efficient to produce the reduction product with good de values, 63, 60 and 75% de, respectively (entries 1, 6, 9). It is interesting that this reaction proceeded with a good selectivity by using a simple chiral auxiliary and non-sterically demanding SmI_2, while good stereoselectivity could usually be achieved by using a combination of a steric hindered hydride agent and a more bulky chiral auxiliary for the reduction of the chiral α-keto ester/amide.[5] The addition of HMPA (1 equiv. to SmI_2)

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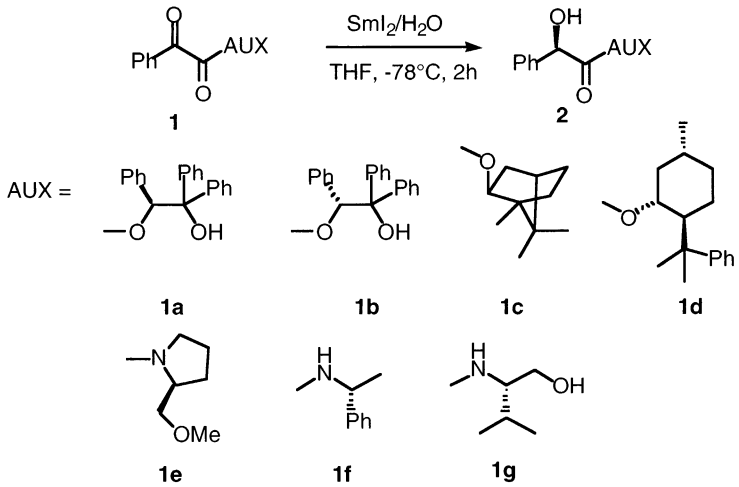


Scheme 1.

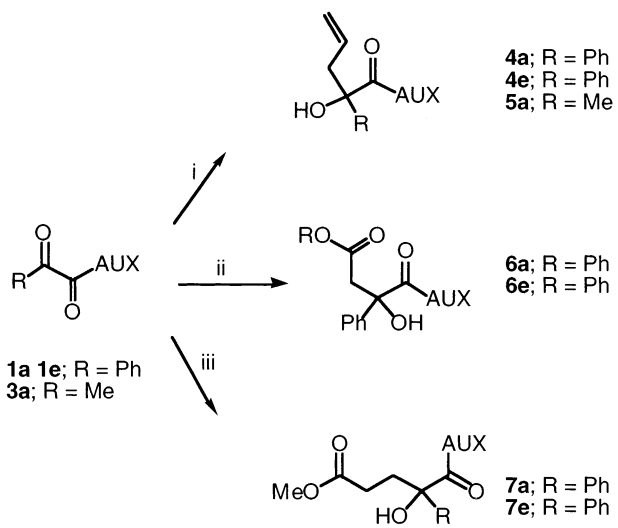
Table 1. Asymmetric reduction of α-keto esters and amides by SmI_2[a]

Entry	AUX in **1**	ROH	Yield (%) of **2**	de (%)[b]	Config.
1	**1a**	H_2O	70	63	*R*
2	**1a**	MeOH	88	45	*R*
3	**1a**	*t*-BuOH	82	44	*R*
4	**1a**	2-THFCH_2OH	59	46	*R*
5	**1a**	AcOH	50	51	*R*
6	**1b**	H_2O	70	60	*S*
7	**1c**	H_2O	48	13	*R*
8	**1d**	H_2O	80	12	*R*
9	**1e**	H_2O	92	75	*S*
10	**1f**	H_2O	57	32	–
11	**1g**	H_2O	45	8	*S*

[a] SmI_2 (1.5 mmol), ROH (5.5 mmol), **1** (0.5 mmol).
[b] Determined by GC or HPLC.

to the reaction solution resulted in a decrease of the diastereoselectivity; a 65% de in the reaction with the **1e** derivative of the amide. The absolute configurations of the newly formed alcoholic carbon were determined after hydrolysis of the esters/amides and comparison of the sign of the specific rotations of the α-hydroxyl acid, i.e. mandelic acid. Starting from the benzoylformate isomers of **1a** and **1b**, (*S*)- and (*R*)-mandelic acid were produced, respectively. Reduction of the pyruvate of **3a** with SmI_2 similarly proceeded to yield the corresponding α-hydroxyl ester but with poor selectivity (5% de).[7]

We next examined the SmI_2 induced reductive coupling reaction of benzoylformate and pyruvate of **1a** with the allyl iodide,[8] the α-bromo ester[2] and the α,β-unsaturated ester[1] (Scheme 2). The allylation of the **1a**, and **3a** proceeded smoothly at −78°C for 2 h quantitatively to give the corresponding 2-hydroxy-4-pentenoic acid esters, **4a** and **5a** in 57 and 54% de, respectively. The allylation with **1e** proceeded at 0°C only in THP to give **4e** in 70% yield with 35% de. It is noteworthy that the reaction with allyllithium and allylmagnesium bromide hardly gave the homoallyl alcohol.[9] The Reformatsky-type reaction of **1a** and **1e** with methyl α-bromoacetate afforded the corresponding 1,4-diesters, **6a** and **6e**, in 80–90% yields with 72 and 60% de, respectively. The de value was improved



Scheme 2. (i) Allyl iodide/SmI_2/THP. (ii) Methyl- or *t*-butyl α-bromoacetate/SmI_2/THF. (iii) Methyl acrylate/*t*-butanol/SmI_2/THF.

up to 89% by the use of the *t*-butyl ester in the reaction with **1a**. The coupling reaction of methyl acrylate with **1a** proceeded smoothly to yield the corresponding 1,5-diester **7a**, in a 91% yield with 78% de, while the reaction with **1e** resulted in a low yield (47%) with 86% de.

The following description provides a typical experimental procedure for the reduction of 2(*S*)-methoxymethylpyrrolidine benzoylamide (**1e**). The SmI_2 solution (0.1 M, 15 mL, 1.5 mmol) in a Schlenk tube was cooled in a dry ice–methanol bath. Water (0.1 mL, 5.5 mmol) was first added and then **1e** (125 mg, 0.5 mmol) was added. The resulting solution was stirred at −78°C for 2 h during which time the deep green color of the solution faded. The solution was hydrolyzed with 15 mL of 0.1 mol/L HCl and the aqueous phase was extracted with three 20 mL portions of ethyl acetate. The organic phase was washed with aqueous $Na_2S_2O_3$ to remove liberated iodine, brine and then dried over $MgSO_4$. The solvent was removed under reduced pressure, and the yellow residue was subjected to PTLC on silica gel (hexane/ethyl acetate = 4:1 as eluent) to afford a mixture of the diastereomers of 2-methoxymethylpyrrolidinyl mandelamide (**2**) as a colorless liquid (112 mg, 0.46 mmol; 92% yield). The diastereomeric excess (75% de) of the product was determined by GC/MS analysis after trifluoroacetylation with trifluoroacetic anhydride (HP INNOWAX, 30m, oven temperature = 160°C; retention time; first fraction, 9.19 min; second fraction, 9.72 min). The absolute configuration of the alcoholic carbon was determined by hydrolysis leading to the mandelic acid $[\alpha]_D^{20} = +117.0$ ($c = 0.46$, MeOH).

Acknowledgements

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