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Remote chirality control based on the organocatalytic asymmetric Mannich reaction of α-thio acetaldehydes†

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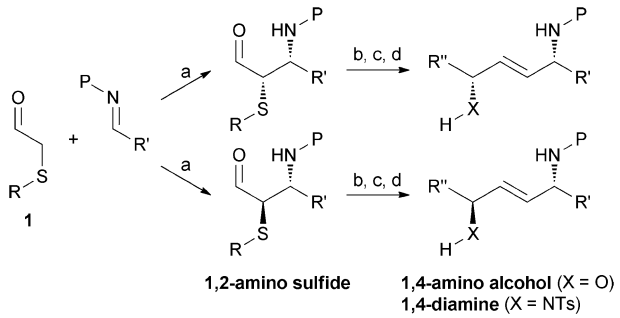
Remote chirality control leading to 1,4-difunctionalized compounds such as 1,4-amino alcohols and 1,4-diamines was achieved by both *syn*- and *anti*-selective asymmetric Mannich reactions of α-thio acetaldehydes, the subsequent olefination and the stereospecific 2,3-sigmatropic rearrangement.

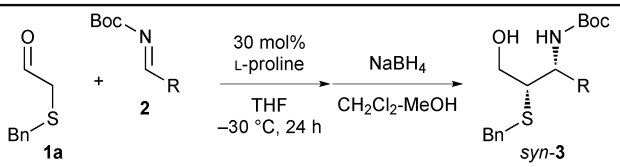
Remote chirality control such as 1,4-asymmetric induction is not an easy task in current asymmetric synthesis. In developing such a synthetic method for the preparation of chiral 1,4-difunctionalized compounds including 1,4-amino alcohols and 1,4-diamines, we focused on a new stereoselective approach to chiral 1,2-amino sulfides, which can be stereospecifically converted to chiral 1,4-amino alcohols and 1,4-diamines (Scheme 1). Chiral 1,2-amino sulfides (and 1,2-amino thiols) also constitute important structural motifs which are found in a broad variety of biologically active compounds[1–4] and chiral catalysts in various asymmetric reactions.[5,6] Some catalytic asymmetric methods, mostly based on the ring-opening of *meso*-aziridines with thiols and the conjugate addition of nitrogen or sulfur nucleophiles to α,β-unsaturated carbonyl compounds, have been developed for the synthesis of chiral 1,2-amino sulfides.[7–9] However, efficient methods for the enantio- and diastereoselective synthesis of both *syn*- and *anti*-1,2-amino sulfides from the same set of reactants are scarce, despite the high synthetic utility.[10] We then became interested in the use of α-thio acetaldehydes **1** (ref. 11) as nucleophiles in the amine-catalyzed asymmetric Mannich reaction, which can afford both diastereomers through C–C bond formation (Scheme 1).[10,12] The resulting chiral 1,2-amino sulfides would be applied to the stereoselective synthesis of chiral 1,4-amino alcohols and 1,4-diamines through olefination[13] and subsequent 2,3-sigmatropic rearrangement[14,15] by utilizing the unique property of the sulfide moiety. Here we wish to report our initial results on this subject.



Scheme 1 Diastereo- and enantioselective synthesis of 1,4-amino alcohols and 1,4-diamines based on the organocatalytic Mannich reaction of α-thio acetaldehydes **1**. (a) Organocatalytic asymmetric Mannich reaction. (b) Olefination. (c) Sulfoxidation or sulfimination. (d) 2,3-Sigmatropic rearrangement.

We first examined the Mannich reaction of (benzylthio)acetaldehyde (**1a**)[10] (2 equiv.) with an *N*-Boc-protected imine **2a** (R = Ph) derived from benzaldehyde in the presence of 30 mol% of L-proline. After optimization of the reaction conditions,[16] the desired *syn*-Mannich product *syn*-**3a** (R = Ph) was obtained as a major diastereomer in excellent enantioselectivity

Table 1 Mannich reaction of α-thio acetaldehyde **1a** with imine **2**[a]



Entry	R	Yield[b] (%)	*syn*/*anti*[c]	ee[d] (%)
1[e]	Ph	77	7.7/1	99
2	4-MeOC$_6$H$_4$	80	11/1	99
3	4-ClC$_6$H$_4$	70	13/1	99
4[e]	2-MeC$_6$H$_4$	68	14/1	98
5[e]	2-Naphthyl	64	8.2/1	99

[a] The reaction of **1a** (0.375 mmol) with **2** (0.125 mmol) was carried out in the presence of L-proline (0.0375 mmol) in THF (0.25 mL) at −30 °C for 24 h. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC using a chiral column. [e] Isolated as an aldehyde.

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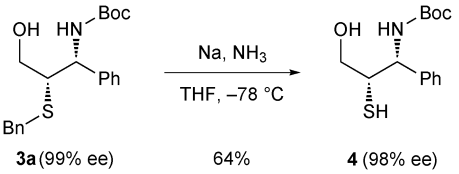


3a (99% ee) 64% **4** (98% ee)

Scheme 2 Deprotection of benzyl thioether **3a**.

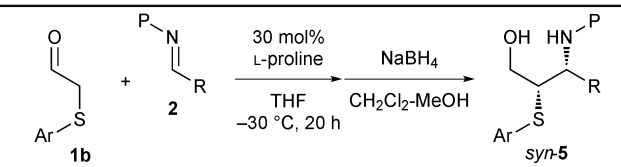
(Table 1, entry 1). Other imines generally afforded the corresponding *syn*-Mannich products in similar yield and stereoselectivity (entries 2–5). The benzyl group on the benzylthio group of Mannich product **3a** (*syn*/*anti* = >20/1) could be removed under Birch conditions, thus leading to the corresponding thiol **4** (*syn*/*anti* = >20/1) (Scheme 2).

The present method was then applied to the reactions of (4-methoxyphenylthio)acetaldehyde (**1b**) and synthetically more important chiral 1,2-amino sulfides *syn*-**5**, which are more suitable for further transformations, were obtained with high stereoselectivities (Table 2). The relative and absolute configuration of *syn*-**5** (P = Cbz, R = Ph) was determined by conversion to the known compound and comparing the optical rotation with the literature value.[16]

We then studied the stereoselective synthesis of chiral 1,4-amino alcohols and 1,4-diamines by using the Mannich product **6** (Scheme 3).[17,18] Thus, the Mannich product **6** (*syn*/*anti* = >20/1) was converted to the allyl sulfides **7a** (*syn*/*anti* = 15/1) and **7b** (*syn*/*anti* = 16/1) by Takai olefination.[13] Subsequent sulfoxidation with mCPBA and treatment with trimethyl phosphite gave 1,4-amino alcohols **8a** (*syn*/*anti* = 15/1) and **8b** (*syn*/*anti* = 16/1), respectively.[14] On the other hand, sulfimination of **7c** (*syn*/*anti* = 16/1) with chloramine-T[19] and treatment with trimethyl phosphite afforded 1,4-diamine **9** (*syn*/*anti* = 16/1) in good yield.[15] In these transformations, neither formation of *Z*-isomers nor loss of optical purity was observed.[16]

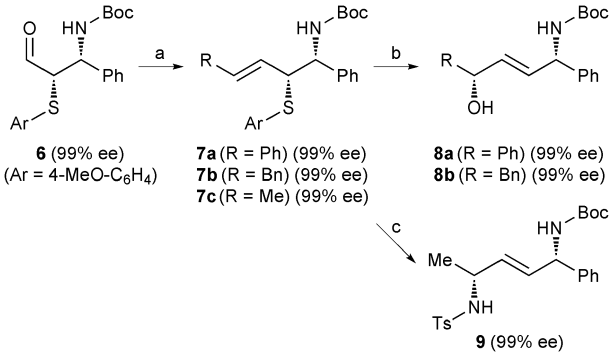
When we employed a binaphthyl-based amino sulfonamide (*S*)-**10** (ref. 20) instead of L-proline as the catalyst, *anti*-Mannich product **11** was obtained as a major diastereomer in virtually perfect enantioselectivity, albeit with moderate yield (Scheme 4). The observed diastereoselectivity was contrasted sharply with the *syn*-selective Mannich reaction catalyzed by proline. The

Table 2 Mannich reaction of α-thio acetaldehyde **1b** with imine **2**[a]

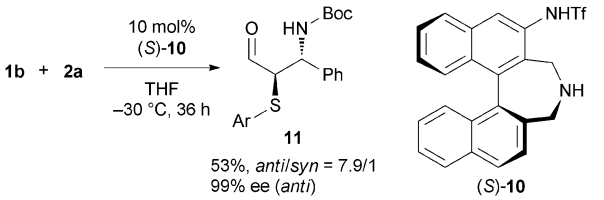


Entry	P	R	Yield[b] (%)	*syn*/*anti*[c]	ee[d] (%)
1[e]	Boc	Ph	78	>20/1	99
2	Boc	4-$MeOC_6H_4$	67	>20/1	99
3	Boc	4-BrC_6H_4	81	16/1	99
4	Cbz	Ph	83	>20/1	98

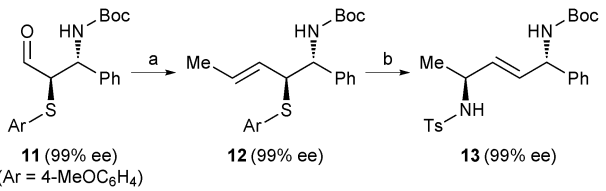
[a] The reaction of **1b** (0.375 mmol) with **2** (0.125 mmol) was carried out in the presence of L-proline (0.0375 mmol) in THF (0.25 mL) at −30 °C for 20 h. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC using a chiral column. [e] The reaction was performed for 22 h.



Scheme 3 Synthesis of 1,4-amino alcohols **8** and 1,4-diamine **9**. Reagents and conditions: (a) $RCHX_2$, $CrCl_2$, DMF, THF, 76% (R = Ph, X = Br), 65% (R = Bn, X = I), 54% (R = Me, X = I); (b) mCPBA, CH_2Cl_2; $P(OMe)_3$, MeOH, 70% (R = Ph), 75% (R = Bn); (c) chloramine-T, MeCN; $P(OMe)_3$, MeOH, 95%.



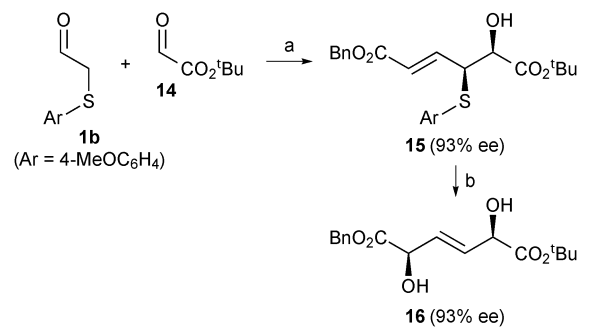
Scheme 4 *anti*-Selective Mannich reaction of **1b** with **2a**.



Scheme 5 Synthesis of 1,4-diamine **13**. Reagents and conditions: (a) $MeCHI_2$, $CrCl_2$, DMF, THF, 65%; (b) chloramine-T, MeCN; $P(OMe)_3$, MeOH, 81%.

Mannich product **11** (*anti*/*syn* = 7.9/1) could also be converted to the corresponding 1,4-diamine **13** (*anti*/*syn* = 4.7/1) through allyl sulfide **12** (*anti*/*syn* = 5.2/1) without loss of optical purity (Scheme 5).

When we examined the aldol reaction of **1b** (3 equiv.) with *tert*-butyl glyoxylate (**14**) in the presence of 5 mol% of (*S*)-**10** in



Scheme 6 Synthesis of 1,4-diol **16**. Reagents and conditions: (a) (*S*)-**10** (5 mol%), NMP; Ph_3P = $CHCO_2Bn$, $CHCl_3$, 74% (*syn*/*anti* = 4.6/1), 93% ee (*syn*); (b) mCPBA, CH_2Cl_2; $P(OMe)_3$, MeOH, 73% (*syn*/*anti* = 4.6/1).

N-methylpyrrolidone (NMP) at −20 °C, the desired *syn*-aldol product was obtained as a major diastereomer with good enantioselectivity (Scheme 6). The obtained aldol product could be converted to the corresponding α,β-unsaturated ester **15** (*syn*/*anti* = 4.6/1).[21] Subsequent sulfoxidation of **15** with mCPBA and treatment with trimethyl phosphite gave 1,4-diol **16** (*syn*/*anti* = 4.6/1) without loss of diastereo- and enantioselectivity.

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21 This aldol reaction–olefination procedure led to a higher diastereo- and enantioselectivity (*syn*/*anti* = 5.7 : 1, 98% ee) but lower yield (36%) when performed in one pot as compared to the stepwise method.

