Direct asymmetric bromination of aldehydes catalyzed by a binaphthyl-based secondary amine: highly enantio- and diastereoselective one-pot synthesis of bromohydrins†

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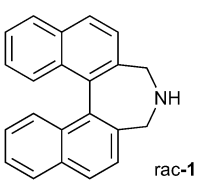
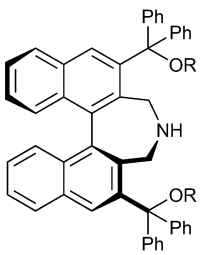
One-pot stereoselective synthesis of bromohydrins as a useful chiral building block was achieved by the reaction of Grignard reagents with optically active α-bromoaldehydes, which were *in situ* generated by direct asymmetric bromination of aldehydes catalyzed by a binaphthyl-based secondary amine (*S*)-3.

Asymmetric enamine catalysis is a powerful organocatalytic strategy for the stereoselective α-functionalization of carbonyl compounds.[1,2] In this area, catalytic asymmetric α-halogenations of carbonyl compounds have been investigated by several research groups,[3–5] since α-haloaldehydes and ketones can serve as versatile synthetic intermediates in the formation of carbon–carbon bonds as well as various carbon–heteroatom bonds.[6] However, optically active α-haloaldehydes except α-chloroaldehydes need to be converted to the corresponding alcohols prior to the isolation procedure due to their instability, thereby losing the apparent advantage of carbonyl functionality. Although α-bromo and α-iodoaldehydes would be useful building blocks because of their size and leaving group ability of bromine and iodine atoms, only a few *in situ* transformations using such characteristic features have been reported to date.[5c,7,8] In addition, among the direct asymmetric α-halogenations, the bromination of aldehydes requires a high catalyst loading (~20 mol%), probably due to the deactivation of the secondary amine catalyst by a brominating agent. In this context, we have been interested in the development of a general method for synthesis of optically active α-bromoaldehydes and utilization of their carbonyl moiety by *in situ* transformation. Herein we wish to report a direct asymmetric α-bromination of aldehydes using a novel binaphthyl-based secondary amine catalyst and highly stereoselective one-pot synthesis of bromohydrins.



rac-**1**



(*S*)-**2** (R = H)
(*S*)-**3** (R = TMS)

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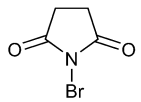
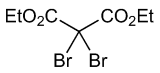


4a



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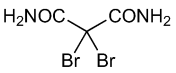

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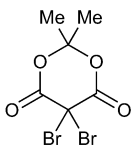

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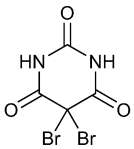
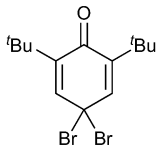
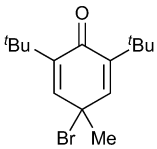


4e



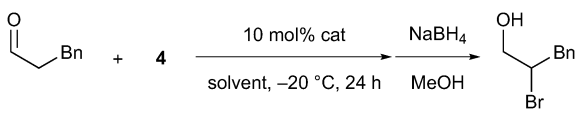
4f



4g

We first investigated α-bromination of 3-phenylpropanal with various brominating agents **4** in CH_2Cl_2 in the presence of 10 mol% of a secondary amine catalyst rac-**1** at −20 °C, and the results are shown in Table 1. Among the brominating agents tested, **4d** and **4f**[5a,b,9] gave the brominated product in moderate yield (entries 4 and 6). We then examined an axially

Table 1 Direct asymmetric bromination of 3-phenylpropanal with various brominating agents[a]



Entry	4	Cat	Solvent	Yield[b] (%)	ee[c] (%)
1	**4a**	rac-**1**	CH_2Cl_2	<5	—
2	**4b**	rac-**1**	CH_2Cl_2	<5	—
3	**4c**	rac-**1**	CH_2Cl_2	<5	—
4	**4d**	rac-**1**	CH_2Cl_2	40	—
5	**4e**	rac-**1**	CH_2Cl_2	<5	—
6	**4f**	rac-**1**	CH_2Cl_2	30	—
7	**4g**	rac-**1**	CH_2Cl_2	<5	—
8	**4d**	(*S*)-**2**	CH_2Cl_2	17	87
9	**4f**	(*S*)-**2**	CH_2Cl_2	10	96
10	**4d**	(*S*)-**3**	CH_2Cl_2	69	91
11	**4f**	(*S*)-**3**	CH_2Cl_2	94	97
12[d]	**4f**	(*S*)-**3**	CH_2Cl_2	76	97
13[e]	**4f**	(*S*)-**3**	CH_2Cl_2	97	92
14	**4f**	(*S*)-**3**	THF	64	3
15	**4f**	(*S*)-**3**	Et_2O	64	16
16	**4f**	(*S*)-**3**	Toluene	29	7
17	**4f**	(*S*)-**3**	Hexane	<5	—
18	**4f**	(*S*)-**3**	$CF_3C_6H_5$	79	87

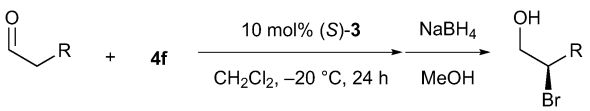
[a] Unless otherwise specified, the reaction between 3-phenylpropanal (0.1 mmol) and brominating agent **4** (0.1 mmol) was carried out in a solvent (2.0 mL) in the presence of a secondary amine catalyst (0.01 mmol) at −20 °C. [b] Isolated yield. [c] Enantiomeric excess determined by HPLC analysis using chiral column. [d] 5 mol% of (*S*)-**3**. [e] 3 mol% of (*S*)-**3** for 72 h.

chiral amino alcohol catalyst (*S*)-**2**[10] with the expectation of activating the brominating agent through hydrogen bonding with hydroxydiphenylmethyl groups at 3,3′-positions. Although excellent enantioselection was observed in the reaction with **4f**, the product yield was drastically decreased (entry 9). An NMR study revealed that the deactivation rate of catalyst (*S*)-**2** with **4f** was faster than that of rac-**1** despite the sterically more congested secondary amine moiety of (*S*)-**2**. This observation suggested that the hydroxy groups of (*S*)-**2** accelerated the undesired reaction between (*S*)-**2** and **4f**. Thus, a hydroxy-protected secondary amine catalyst (*S*)-**3**[11] having bulky substituents at 3,3′-positions was synthesized by the introduction of trimethylsilyl groups into (*S*)-**2** with the aim of circumventing the catalyst deactivation. As a result of the protection of hydroxyl group and the introduction of steric bulkiness into the catalyst, the bromination catalyzed by (*S*)-**3** proceeded smoothly in excellent yield and enantioselectivity (entry 11). The catalyst loading could be reduced to 5 mol% without loss of enantioselectivity (entry 12). Both yield and enantioselectivity in the present bromination showed a strong solvent dependence (entries 14–18), and consequently, CH_2Cl_2 was determined to be the solvent of choice.

With the axially chiral secondary amine catalyst (*S*)-**3** in hand, the direct asymmetric α-bromination of several other aldehydes with **4f** was examined, and selected results are shown in Table 2. In most cases examined, the direct asymmetric α-bromination of aldehydes proceeded to give the corresponding α-bromoaldehydes in good to excellent yields and enantioselectivities (entries 1–7), while the use of sterically demanding 3,3-dimethylbutanal was unsatisfactory (entry 8).

The absolute configuration of the product in this reaction catalyzed by (*S*)-**3** was determined to be *R* by comparison of the optical rotation with the literature data.[5a] Based on the observed stereochemistry, a transition state model can be proposed as shown in Fig. 1.[12] One face of the enamine intermediate is effectively shielded by the bulky substituent of (*S*)-**3**, and consequently, the reaction of an aldehyde with **4f** catalyzed by (*S*)-**3** provides the *R* isomer predominantly.

Table 2 Direct asymmetric bromination of various aldehydes with **4f** catalyzed by (*S*)-**3**[a]



Entry	R	Yield[b] (%)	ee[c] (%)
1[d]	Bu	80	93
2	Hex	92	92
3	Bn	94	97
4	CH_2Cy	82	96
5	CH_2OBn	92	99
6	*i*-Pr	71	96
7	Cy	73	99
8	*t*-Bu	<5	—

[a] Unless otherwise specified, the reaction between an aldehyde (0.1 mmol) and **4f** (0.1 mmol) was carried out in a solvent (2.0 mL) in the presence of (*S*)-**3** (0.01 mmol) at −20 °C. [b] Isolated yield. [c] Enantiomeric excess determined by HPLC and GC analysis using chiral column. [d] 2 equiv. of **4f**.

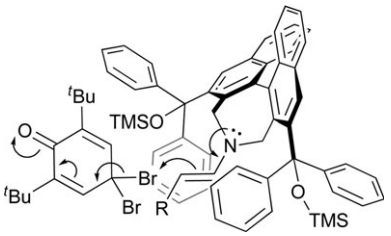
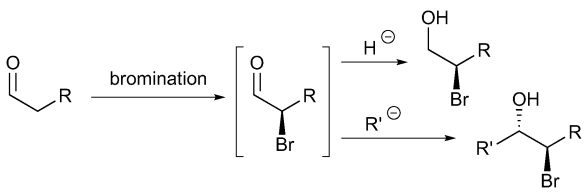


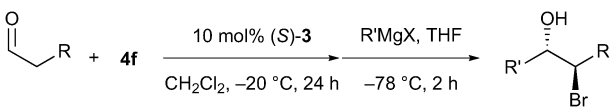
Fig. 1 Plausible transition state model.

The optically enriched α-bromoaldehydes should be reduced *in situ* with $NaBH_4$ to the corresponding alcohol due to the inherent instability of α-haloaldehydes. If a certain carbon anion species could be used instead of the hydride anion under the influence of the large bromine atom, an additional stereocenter could be constructed stereoselectively through the carbon–carbon bond formation (Scheme 1).[4d,13] Hence, we then examined the one-pot synthesis of bromohydrins using Grignard reagents as one of the most versatile organometallic reagents. The reaction of the *in situ* generated optically enriched α-bromoaldehyde with methyl Grignard reagents in THF at −78 °C proceeded to give the corresponding *anti*-bromohydrin in good to excellent diastereoselectivity (Table 3, entries 1–3), and the best result was attained with methylmagnesium chloride (entry 1). The observed diastereoselectivity is well explained by the non-chelation control, which might be attributable to the large bromine atom.[14] The product yield could be improved by addition of Et_2O as cosolvent (entry 4)



Scheme 1 One-pot synthesis of bromohydrins.

Table 3 Enantio- and diastereoselective one-pot synthesis of bromohydrins[a]



Entry	R	R′MgX	Equiv.	Yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	Bn	MeMgCl	3.0	55	>20/1	97
2	Bn	MeMgBr	3.0	26	>20/1	77
3	Bn	MeMgI	3.0	53	10/1	91
4[e]	Bn	MeMgCl	3.0	69	16/1	97
5[e]	Bn	MeMgCl	5.0	82	>20/1	96
6[e]	Bn	PhMgCl	5.0	83	>20/1	99
7[e]	*i*-Pr	PhMgCl	5.0	73	>20/1	99

[a] Unless otherwise specified, the reaction between an aldehyde (0.1 mmol) and **4f** (0.1 mmol) was carried out in a solvent (2.0 mL) in the presence of (*S*)-**3** (0.01 mmol) at −20 °C, and was followed by addition of a THF solution of Grignard reagent at −78 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy. [d] Enantiomeric excess determined by HPLC analysis using chiral column. [e] After the bromination, Et_2O (2.0 mL) was added.

and increasing the amount of the Grignard reagent (entry 5). In the reaction of phenylmagnesium chloride, the optical purity of the obtained bromohydrin slightly exceeded that observed in the standard bromination–reduction procedure (Table 3, entry 6 *vs.* Table 2, entry 3; Table 3, entry 7 *vs.* Table 2, entry 6). This observation might indicate the partial degradation of the optical purity during reduction of α-bromoaldehydes.

In summary, we have developed a direct asymmetric bromination of aldehydes catalyzed by the binaphthyl-based secondary amine (*S*)-**3** and the one-pot procedure for the highly stereoselective synthesis of bromohydrins. This method represents a rare example of the organocatalytic asymmetric bromination and the *in situ* transformation of the resulting α-bromoaldehydes.

Notes and references

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