doi:10.1246/cl.2010.382

Published on the web March 13, 2010

Efficient and Enantioselective Kinetic Resolution of Cyclic β-Hydroxy Sulfides by Chiral 1,2-Diamine Catalyzed Asymmetric Acylation

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Kinetic resolution of cyclic β-hydroxy sulfides has been achieved by reaction with benzoyl chloride in the presence of a catalytic amount (0.1 mol %) of a chiral 1,2-diamine combined with triethylamine. This reaction affords the corresponding benzoates and unreacted alcohols with excellent enantioselectivities.

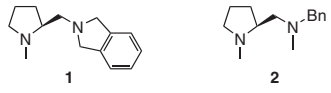
Optically active β-hydroxy sulfides are known to be versatile synthetic intermediates in organic synthesis.[1] For example, they can be converted to useful ligands for asymmetric synthesis.[2] They can generally be obtained by asymmetric ring-opening of *meso*-epoxides with thiols[3] or asymmetric reduction of β-keto sulfides.[4] Only a few reports describe the preparation of cyclic β-hydroxy sulfides with high enantioselectivities. In 1997, Shibasaki and co-workers developed a gallium–lithium–bis(binaphthoxide) complex, which is presently the most enantioselective catalyst (up to 98% ee) available for the asymmetric ring-opening reaction of cyclic *meso*-epoxides with thiols.[5] However, the nucleophile is limited to *t*-BuSH.

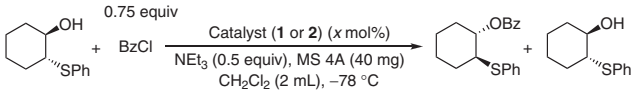
Kinetic resolution of β-hydroxy sulfides by asymmetric acylation is another prominent protocol for obtaining optically active β-hydroxy sulfide derivatives. However, only enzymatic methods for this purpose have been demonstrated.[6] We have developed highly enantioselective non-enzymatic methods for the organocatalytic asymmetric acylation of a variety of racemic alcohols[7] and *meso*-diols.[8] The reaction of alcohols with benzoyl chloride as an achiral acylating agent in the presence of a catalytic amount (0.3–0.5 mol %) of a chiral 1,2-diamine derived from (*S*)-proline produced excellent enantioselectivities. Overall, chiral 1,2-diamines having an isoindoline (**1**) or a benzylmethylamino group (**2**) were the most promising organocatalysts for the asymmetric acylation of various alcohols.

Herein, we report a kinetic resolution of cyclic β-hydroxy sulfides by highly efficient organocatalytic asymmetric acylation.

First, we attempted the reaction of racemic *trans*-2-phenylsulfanyl-1-cyclohexanol (0.3 mmol) as a model substrate with 0.75 equiv of benzoyl chloride in the presence of 0.3 mol % of chiral diamine **1** combined with 0.5 equiv of triethylamine and 40 mg of molecular sieves (MS) 4A[9] in dichloromethane at −78 °C. After stirring for 5 h, the reaction catalyzed by chiral diamine **1** afforded the corresponding benzoate, (+)-*trans*-1-benzoyloxy-2-phenylsulfanylcyclohexane (**3a**), in 49% yield with 97% ee and unreacted alcohol, (−)-*trans*-2-phenylsulfanyl-1-cyclohexanol (**4a**), in 47% yield with 99% ee (Table 1, Run 1). Chiral diamine **2** also catalyzed the acylation with excellent enantioselectivities. However the acylation proceeded slowly to give benzoate **3a** in lower yield in 24 h (Table 1, Run 2). When the chiral diamine **1** content was decreased to 0.1 mol % from 0.3 mol %, asymmetric acylation gave the benzoate **3a** in 49% yield with 98% ee ($s = 360$) in 12 h (Table 1, Run 3). Decreasing MS 4A from 40 mg to 30 mg also resulted in a similar yield of the benzoate **3a** with similar enantioselectivity ($s = 300$) (Table 1, Run 4). As a result, the optimal reaction conditions involved β-hydroxy sulfides (0.3 mmol) with benzoyl chloride (0.75 equiv) in the presence of chiral diamine **1** (0.1 mol %) combined with triethylamine (0.5 equiv) and MS 4A (30 mg) in dichloromethane (2 mL) at −78 °C.

Table 1. Catalytic asymmetric acylation of racemic *trans*-2-phenylsulfanyl-1-cyclohexanol





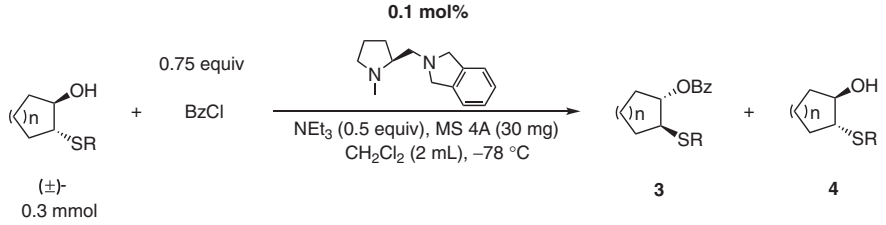
Run	Catalyst (x/mol %)	Time /h	3a Yield /%[a]	3a ee /%[b]	4a Yield /%[a]	4a ee /%[c,d]	s[e]
1	**1** (0.3)	5	49	97	47	99	220
2	**2** (0.3)	24	19	96	78	22	60
3	**1** (0.1)	12	49	98	47	97	360
4[f]	**1** (0.1)	12	50	97	49	96	300
5[g]	**1** (0.1)	12	44	98	51	85	290
6[h]	**1** (0.1)	24	15	99	82	16	170

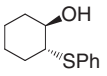
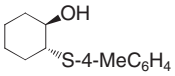
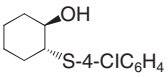
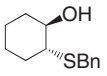
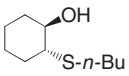
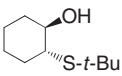
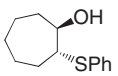
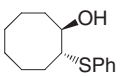
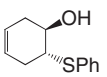
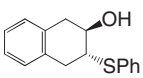
[a]Isolated yields. [b]Determined by HPLC analysis using a Daicel Chiralpak AD-H column. [c]Determined by HPLC analysis using a Daicel Chiralcel OD column. [d]Absolute configuration was determined by the comparison of optical rotation of **4a** (Ref. 3a). [e]Calculated from the conversion (isolated yield) and ee of the acylated product (Ref. 10). [f]30 mg of MS 4A were used. [g]20 mg of MS 4A were used. [h]Without MS 4A.

Table 2 summarizes the successful results of the substrate scope of this reaction.[11] The asymmetric acylation of six-membered cyclic β-hydroxy sulfides afforded the corresponding benzoates **3** and unreacted alcohols **4** with high to excellent enantioselectivities except for the unreacted alcohol of Run 6 (Runs 1–6, 10, and 11). The five-membered cyclic β-hydroxy sulfide was acylated with moderate enantioselectivity (Run 7). The asymmetric synthesis of seven- and eight-membered cyclic β-hydroxy sulfides with excellent enantioselectivities is difficult; however, the asymmetric acylation of seven- and eight-membered cyclic β-hydroxy sulfides proceeded smoothly with excellent enantioselectivities (Runs 8 and 9).

In conclusion, we have succeeded in developing the first non-enzymatic method for the asymmetric acylation of β-

Table 2. Catalytic asymmetric acylation of various racemic cyclic β-hydroxy sulfides



Run	Substrate	Time/h	3		4		s[d]
			Yield/%[a]	ee/%[b]	Yield/%[a]	ee/%[c]	
1		12	50	97	49	96[e]	280
2		13	49	96	47	97[e]	160
3		13	49	98[f]	49	94[e,g]	360
4		12	49	96	48	99[e]	160
5		12	46	92	43	93[e,g]	57
6		48[h]	42	98	44	73[e,g]	210
7		12	48	68[i]	48	69[e]	10
8		5[j]	48	97	47	97	200
9		5[j]	49	95[i]	48	99[e]	160
10		16	50	94	47	93	120
11		3[j]	49	86	49	81[e]	34

[a]Isolated yields. [b]Unless otherwise mentioned, determined by HPLC analysis using a Daicel Chiralpak AD-H column. [c]Determined by HPLC analysis using a Daicel Chiralcel OD column. [d]Calculated from the conversion (isolated yield) and ee of the acylated product (Ref. 10). [e]Absolute configurations were determined by the comparison of optical rotations of **4** (Refs. 3a, 3h, and 5). [f]Determined by HPLC analysis using a Daicel Chiralcel OJ-H column. [g]Determined by HPLC analysis using a chiral column after conversion to the corresponding benzoate. [h]3 mol % of the chiral diamine was used. [i]Determined by HPLC analysis using a chiral column after conversion to the corresponding alcohol. [j]0.5 mol % of the chiral diamine was used.

hydroxy sulfides catalyzed by a chiral 1,2-diamine derived from (*S*)-proline. This reaction has striking advantages such as high efficiency, excellent enantioselectivities, and very low catalyst loadings (0.1 mol %). Additionally this reaction is very attractive from the standpoint of green chemistry; the organocatalytic reaction does not require metallic compounds. Further investigations to broaden the scope and synthetic applications of asymmetric acylation are under way.

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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9 Powdered MS 4A (purchased from Wako Chemical Co., Inc.) was dried at 120 °C for 8 h under reduced pressure before use.

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11 Typical experimental procedure is as follows: Triethylamine (21 µL, 0.15 mmol) was added to a mixture of (*S*)-1-methyl-2-[(dihydroisoindole-2-yl)methyl]pyrrolidine (**1**) (0.065 mg, 0.30 µmol) and racemic *trans*-2-phenylsulfanyl-1-cyclohexanol (62.5 mg, 0.30 mmol) in CH_2Cl_2 (2 mL) in the presence of MS 4A (30 mg) at room temperature. Benzoyl chloride (26 µL, 0.22 mmol) was added at −78 °C. After stirring for 12 h at −78 °C, the reaction mixture was quenched with a phosphate buffer (pH 7) and the organic materials were extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude products were purified by thin-layer chromatography on silica gel to give (+)-*trans*-1-benzoyloxy-2-phenylsulfanylcyclohexane (46.9 mg, 50% yield with 97% ee) and (−)-*trans*-2-phenylsulfanyl-1-cyclohexanol (30.6 mg, 49% yield with 96% ee).

