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Optical resolution of racemic norbornene aldehydes: kinetically controlled intramolecular haloetherification of ene acetals

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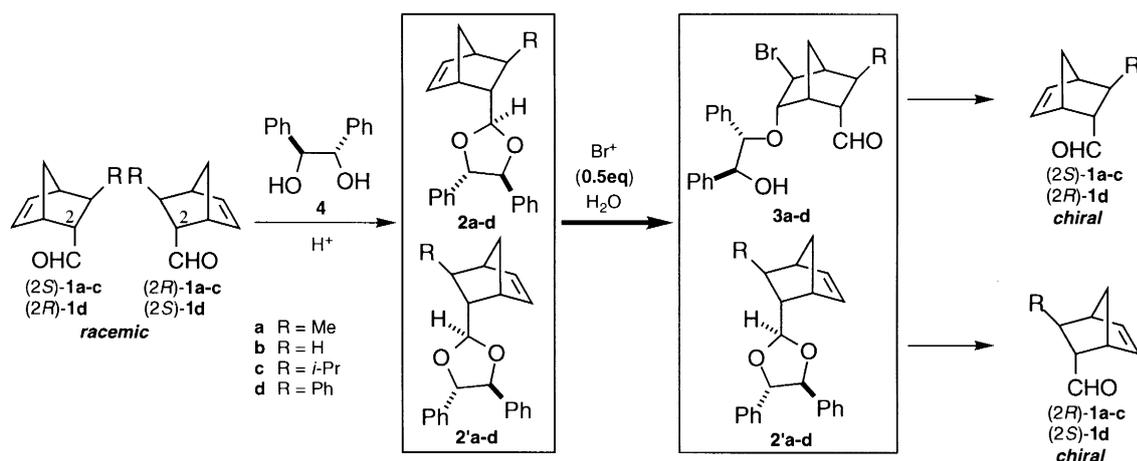
Abstract

Haloetherification reaction of a diastereomeric mixture of the ene acetals **2** and **2'**, derived from racemic norbornene aldehydes and chiral non-racemic (*S,S*)-hydrobenzoin, proceeded in a kinetically controlled manner to give the optically pure aldehydes **3** along with the intact ene acetals **2'**. Compounds **3** and **2'** were converted to the optically pure norbornene aldehydes in both enantiomeric forms. Then a new chiral auxiliary for asymmetric desymmetrization of *meso*-1,2-diols was found. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: optical resolution; kinetic control; norbornene aldehyde; intramolecular haloetherification; ene acetal; hydrobenzoin.

Recently, we developed a new asymmetric desymmetrization method of *meso*-1,2-diols using optically pure chiral non-racemic methylnorbornene aldehyde (*2R*)-**1a** as a chiral auxiliary. This method is quite useful because it forms an efficient desymmetrization reaction cycle and works well for not only cyclic *meso*-diols but also acyclic ones.¹ However, in the studies we prepared (*2R*)-**1a** through asymmetric Diels–Alder reaction using rather expensive Evans' reagent as a key reaction.² This preparation method is useful to get optically pure (*2R*)-**1a**, because the product (90% de) of asymmetric Diels–Alder reaction is recrystallized. Usually asymmetric Diels–Alder reactions are used for synthesizing optically active norbornene derivatives, but the methods make it hard to get optically pure compounds without the recrystallization process.³ So only the recrystallized compounds, which are very limited, are obtained in an optically pure state and this methodology does not have generality. We present here an alternative way of getting optically pure norbornene aldehyde derivatives by optical resolution via a kinetically controlled intramolecular haloetherification using easily obtained chiral non-racemic (*S,S*)-hydrobenzoin **4** for a chiral resolving auxiliary (Scheme 1). And we found that non-volatile compound **1d** became a better auxiliary for our desymmetrization cycle; in contrast to this, **1a** is volatile and its treatment needed a lot of care.

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Scheme 1.

First, we investigated the ability of chiral nonracemic diols, viz, (*S,S*)-hydrobenzoin **4**, (*2S,3S*)-1,4-dimethoxy-2,3-butanediol **5**, (*1R,2S,3R,4S*)-1,7,7-trimethylbicyclo-[2,2,1]-heptane-2,3-diol **6** and diethyl L-tartrate **7**, as chiral resolving auxiliaries using racemic norbornene aldehyde **1a** as a substrate (Fig. 1). Acetalization of (*2S*)- and (*2R*)-**1a** with chirals **4**, **5**, **6** and **7** proceeded without any problem to give corresponding diastereomixtures, **2a** and **2'a**, in a quantitative yield. The haloetherification reaction was carried out with NBS (0.5 equiv.) in the presence of H₂O (5 equiv.) at rt. The reaction of the mixture of **2a** and **2'a**, derived from racemic **1a**, a 1:1 mixture of (*2S*)- and (*2R*)-**1a**, and **4**, proceeded with very high selectivity and gave the pure product **3a** (44%), which was easily purified from the trace amount of the diastereomer of **3a** derived from **2'a** and the intact ene acetal **2'a** (50%, 96% de) by simple SiO₂ column chromatography separation (Scheme 2).⁴ Its stereochemistry was determined by conversion to the known compound.¹ On the other hand, **5–7** did not show enough ability as chiral-resolving auxiliaries (Fig. 1). This observation clearly shows that hydrobenzoin **4** is the auxiliary of choice for optical resolution. We rationalized these results due to the large steric repulsion in **2'a** between the norbornene aldehyde skeleton and the benzene ring which is bulky and sterically fixed. That is, the haloetherification reaction of **2'a** hardly proceeds and kinetic control occurred with high selectivity.

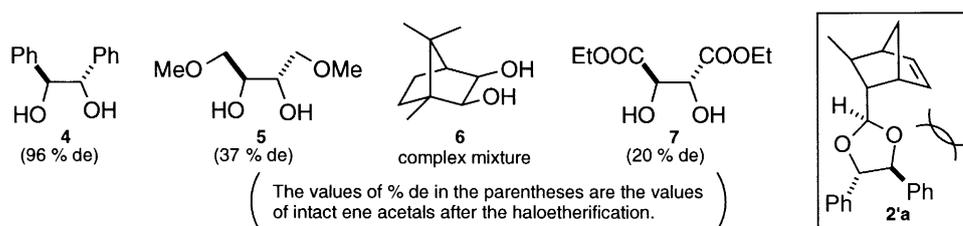
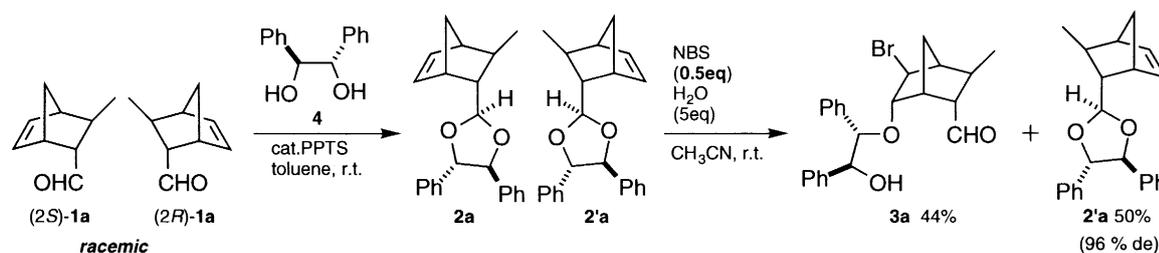


Fig. 1.

Applicability of this method to other racemic norbornene aldehydes, prepared in the usual way using the Diels–Alder reaction of unsaturated aldehydes and cyclopentadiene, was then examined. The results are shown in Table 1, including those for **2a** and **2'a** for comparison. Treatment of **2a–d** and **2'a–d** with NBS (0.5 equiv.) afforded the pure aldehydes and the intact ene acetals with high diastereoselectivities (Entries 1, 4 and 5). In the case of **2c** and **2'c**, optically pure **2'c** was obtained (Entry 4). Slight excess use of NBS was effective in increasing the diastereomeric excess of **2'** (Entries 3 and 6).

Having successfully accomplished the kinetic control, we then focused our attention on the conversion

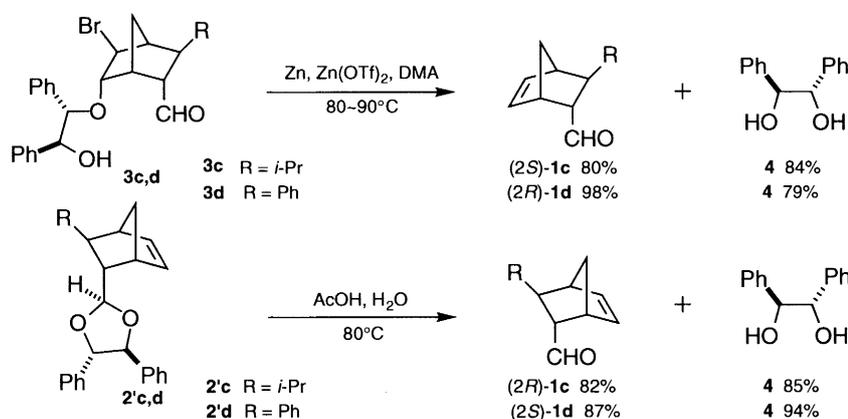


Scheme 2.

Table 1

Entry	2 and 2'	NBS (eq)	3	2'	%de of 2'
1	a R=Me	0.5	44	50	96
2	b R=H	0.5	38	47	82
3	b R=H	0.6	45	37	98
4	c R= <i>i</i> -Pr	0.5	45	48	>99
5	d R=Ph	0.5	44	49	96
6	d R=Ph	0.55	43	42	>99

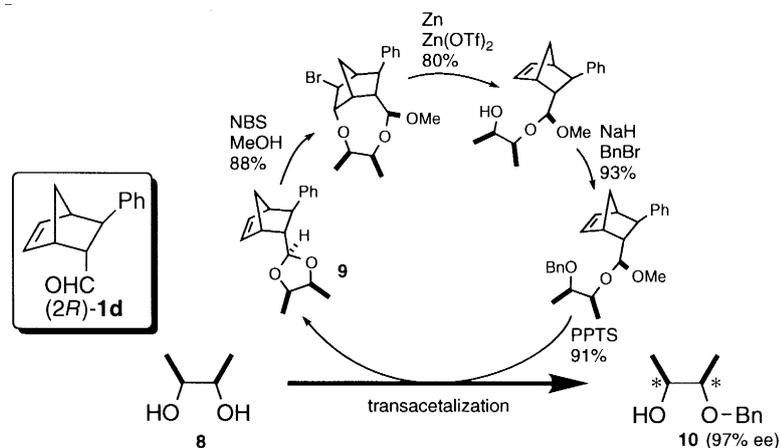
of **3** and **2'** to the corresponding aldehydes (*2S*)- and (*2R*)-**1**. Although the yields of (*2S*)- and (*2R*)-**1a**, and (*2S*)- and (*2R*)-**1b** were low because of their volatility, other non-volatile norbornene aldehydes (*2S*)- and (*2R*)-**1c**, and (*2S*)- and (*2R*)-**1d** were obtained in sufficient yields. The transformation is shown in Scheme 3. That is, debromoetherification of **3c** and **3d** with Zn/Zn(OTf)₂ afforded (*2S*)-**1c** (80%) and (*2R*)-**1d** (98%) along with chiral hydrobenzoin **4** respectively.⁵ Stereochemistries of the aldehydes were determined by comparison with the authentic samples¹ and these results made the stereochemistries of the hydroxy aldehydes **3** and the ene acetals (*2R*)-**2** clear. The conversion of the intact ene acetals **2'c** and **2'd** to the enantiomers of (*2S*)-**1c** and (*2R*)-**1d**, (*2R*)-**1c** (82%) and (*2S*)-**1d** (87%), with **4** was attained by AcOH treatment.



Scheme 3.

Having both the enantiomers of norbornene aldehyde derivatives in hand, we examined the ability of norbornene aldehyde (*2R*)-**1d**, which is non-volatile, as a chiral auxiliary for asymmetric desymmetrization of *meso*-1,2-diols. Acetalization of (*2R*)-**1d** with *meso*-2,3-butanediol **8** afforded *cis*-ene acetal **9** stereospecifically in quantitative yield. Intramolecular haloetherification, debromoetherification

with $\text{Zn}/\text{Zn}(\text{OTf})_2$, protection of the hydroxyl group as a benzyl ether, then transacetalization using **8**, proceeded highly stereoselectively without any problem and gave the optically active **10**.¹ From this it was proved that (2*R*)-**1d** is a good chiral auxiliary in the place of (2*S*)-**1a** (Scheme 4).



Scheme 4.

In conclusion, we disclosed the optical resolution method of norbornene aldehyde derivatives via an extremely highly kinetically controlled intramolecular haloetherification and found a good chiral auxiliary for our desymmetrization cycle. Since the method shown here could open the way to achieving both enantiomers of the norbornene aldehydes in an optically pure state by an easy procedure, this work will provide a useful tool for many studies using optically active norbornene aldehydes.

Acknowledgements

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- Experimental procedure for haloetherification: To a stirred solution of **2a** and **2'a** (0.1 mmol) in CH_3CN (1 ml) were added H_2O (5 equiv.) and NBS (0.5 equiv.) at rt under N_2 . After completion of the reaction (TLC check), aqueous saturated $\text{Na}_2\text{S}_2\text{O}_3$ was added to the mixture. Extraction with EtOAc, the usual workup and purification by silica gel column chromatography (hexane:EtOAc) afforded **3a** and **2'a**.
- Typical experimental procedure for debromoetherification: To a stirred solution of **3c** (0.1 mmol) in $\text{CH}_3\text{CON}(\text{CH}_3)_2$ (DMA) (1 ml) were added $\text{Zn}(\text{OTf})_2$ (10 equiv.) and Zn (30 equiv.) under N_2 . The mixture was stirred at around 80°C . After completion of the reaction (TLC check), the mixture was diluted with ether and filtered through a Celite pad. The filtrate was evaporated in vacuo and purified by silica gel column chromatography (hexane:EtOAc) to afford (2*S*)-**1c** and **4**.