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Chiral Phosphoric Acid Catalyzed Enantioselective Transfer Deuteration of Ketimines by Use of Benzothiazoline As a Deuterium Donor: Synthesis of Optically Active Deuterated Amines

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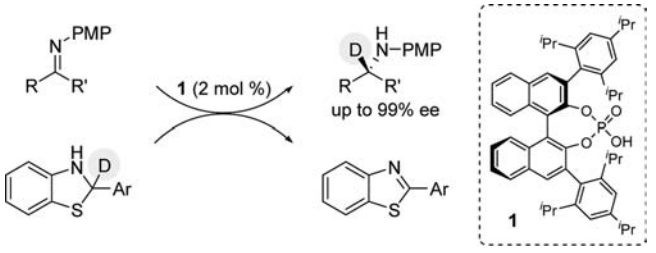
ABSTRACT



By use of 2-deuterated benzothiazoline as a deuterium donor in combination with a chiral phosphoric acid, the transfer deuteration of ketimine and α-iminoester took place smoothly to give α-deuterated amines in high yields with excellent enantioselectivities. The remarkable kinetic isotope effect suggests that carbon−deuterium bond cleavage is the rate-determining step.

Deuterated compounds are an important class of materials that are used in various areas, including the analysis of the metabolic pathways of bioactive compounds,[1a,b] the determination of the mechanisms of both chemical and enzymatic reactions,[1c,d] and NMR solvents.

Recently, 'heavy drugs' have emerged as novel drugs that exhibit better stability and/or bioavailability than their hydrogen analogs.[2] For instance, the deuterium substitution on the methylenedioxy moiety of deuterated paroxetine,[3] an antidepressant, altered the drug's metabolism and prolonged its activity *in vivo*. Telaprevir is generally acknowledged as an inhibitor of the hepatitis C virus; however, the chiral center next to α-ketoamide (*S*-configuration) in telaprevir tends to epimerize to furnish an (*R*)-diastereoisomer that has ∼30-fold lower activity. Through the deuteration of telaprevir, the epimerization of telaprevir-d_1 is retarded due to the presence of deuterium (Figure 1).[4] In both cases, the introduction of deuterium improved the bioavailability.

The significance of deuteration has been growing at a rapid pace. A number of practical methods for the

(1) (a) Nelson, S. D.; Trager, W. F. *Drug Metab. Dispos.* **2003**, *31*, 1481–1498. (b) Hall, L. R.; Hanzlik, R. P. *J. Biol. Chem.* **1990**, *265*, 12349–12355. (c) Haesler, J.; Schindelholz, I.; Riguet, E.; Bochet, C. G.; Hug, W. *Nature* **2007**, *446*, 526–529. (d) MacDonald, D.; Lu, P. *J. Am. Chem. Soc.* **2002**, *124*, 9722–9723.

(2) (a) Sanderson, K. *Nature* **2009**, *458*, 269. (b) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529–2591.

(3) For the press release of Concert Pharmaceuticals on September 14th, 2009, see: http://www.concertpharma.com/ACCPPresentation.htm.

(4) Maltais, F.; Jung, Y. C.; Chen, M.; Tanoury, J.; Perni, R. B.; Mani, N.; Laitinen, L.; Huang, H.; Liao, S.; Gao, H.; Tsao, H.; Block, E.; Ma, C.; Shawgo, R. S.; Town, C.; Brummel, C. L.; Howe, D.; Pazhanisamy, S.; Raybuck, S.; Namchuk, M.; Bennani, Y. L. *J. Med. Chem.* **2009**, *52*, 7993–8001.

(5) (a) Martins, A.; Lautens, M. *Org. Lett.* **2008**, *10*, 4351–4353. (b) Erdogan, G.; Grotjahn, D. B. *J. Am. Chem. Soc.* **2009**, *131*, 10354–10355. (c) Atzrodt, J.; Derdau, V.; Fey, T.; Zimmermann, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7744–7765. (d) Campos, J.; Esqueda, A. C.; López-Serrano, J.; Sánchez, L.; Cossio, F. P.; de Cozar, A.; Álvarez, E.; Maya, C.; Carmona, E. *J. Am. Chem. Soc.* **2010**, *132*, 16765–16767. (e) Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 17096–17098. (f) Mohrig, J. R.; Reiter, N. J.; Kirk, R.; Zawadski, M. R.; Lamarre-Vincent, N. *J. Am. Chem. Soc.* **2011**, *133*, 5124–5128. (g) Imada, Y.; Iida, H.; Kitagawa, T.; Naota, T. *Chem.—Eur. J.* **2011**, *17*, 5908–5920.

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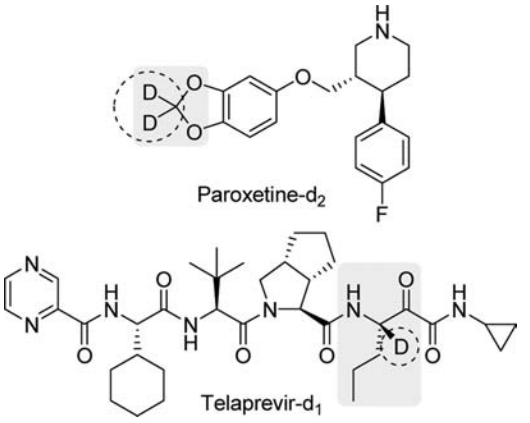


Figure 1. Deuterated pharmaceuticals.

deuteration, such as catalytic deuteration, conventional deuteride reduction, and a H−D exchange reaction, have been reported.[5] Although Yamada and co-workers reported the enantioselective reduction of aldimine with $NaBD_4$,[6] asymmetric deuteration is underexplored. We focused on the deuteride reduction of imine[6,7] as a versatile reaction for the preparation of chiral α-deuterated amine.[8]

The enantioselective transfer hydrogenation of ketimines by the combined use of Hantzsch ester and chiral phosphoric acid has emerged as a useful method for the preparation of chiral amines.[9] On the other hand, we demonstrated that benzothiazoline[10] functioned as a novel hydrogen donor for the asymmetric transfer hydrogenation of ketimines[11] by means of chiral phosphoric acid.[12,13] The advantages of benzothiazoline are twofold: (1) benzothiazoline can be easily synthesized by mixing 2-aminothiophenol and aldehyde; and (2) the ease of tuning the reactivity and enantioselectivity by changing the substituent at the 2-position of benzothiazoline (Figure 2).[14]

We hypothesized that the use of deuterated benzothiazoline, which is readily accessible from D_1-aldehyde, would enable efficient access to optically active deuterated amines (Scheme 1).

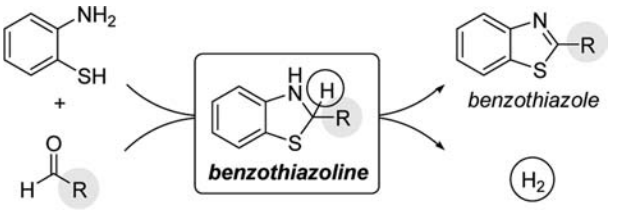
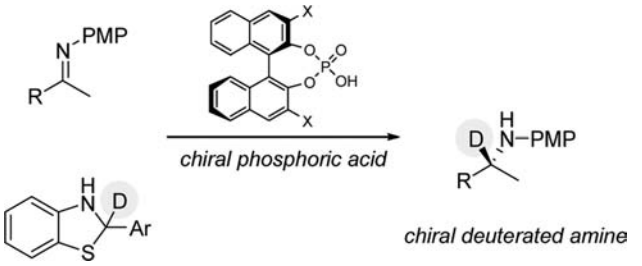


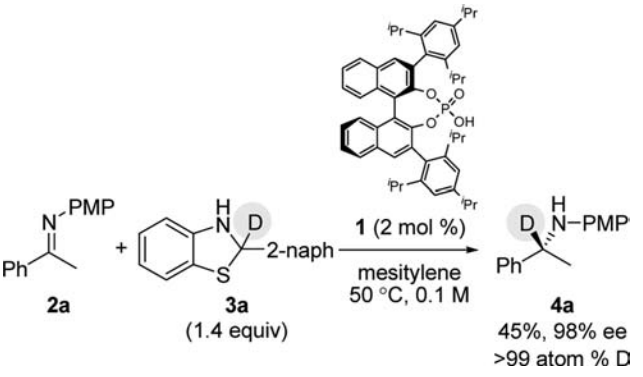
Figure 2. Benzothiazoline.

Scheme 1. Synthesis of Chiral Deuterated Amine



At the outset, we tried to perform the deuteride reduction of ketimine.[11a] On treatment of ketimine **2a** with 2-deuterio-2-(2-naphthyl)benzothiazoline (**3a**) in the presence of a catalytic amount of chiral phosphoric acid **1** in mesitylene at 50 °C, the transfer deuteration proceeded to give corresponding α-deuterated amine **4a** with excellent enantioselectivity. Deuterium was incorporated at the α-position of nitrogen (Scheme 2).

Scheme 2. Transfer Deuteration of Ketimine by Use of D-Benzothiazoline



(6) For an example of enantioselective deuteration by use of $NaBD_4$, see: Miyazaki, D.; Nomura, K.; Yamashita, T.; Iwakura, I.; Ikeno, T.; Yamada, T. *Org. Lett.* **2003**, *5*, 3555–3558.

(7) For the use of deuterated Hantzsch ester in the nonasymmetric reaction, see: Fujii, M.; Aida, T.; Yoshihara, M.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3845–3847.

(8) (a) Meyers, A. I.; Dickman, D. A. *J. Am. Chem. Soc.* **1987**, *109*, 1263–1265. (b) Lown, J. W.; Akhtar, M. H. *J. Chem. Soc., Chem. Commun.* **1973**, 511–513. (c) Battersby, A. R.; Staunton, J.; Summers, M. C. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1052–1056.

(9) For reviews, see: (a) Zheng, C.; You, S.-L. *Chem. Soc. Rev.* **2012**, *41*, 2498–2518. (b) Rueping, M.; Sugiono, E.; Schoepke, F. R. *Synlett* **2010**, 852–865. (c) Rueping, M.; Dufour, J.; Schoepke, F. R. *Green Chem.* **2011**, *13*, 1084–1105.

(10) Chikashita, H.; Miyazaki, M.; Itoh, K. *J. Chem. Soc., Perkin Trans. 1* **1987**, 699–706.

(11) (a) Zhu, C.; Akiyama, T. *Org. Lett.* **2009**, *11*, 4180–4183. (b) Zhu, C.; Akiyama, T. *Adv. Synth. Catal.* **2010**, *352*, 1846–1850. (c) Henseler, A.; Kato, M.; Mori, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 8180–8183. (d) Saito, K.; Akiyama, T. *Chem. Commun.* **2012**, *48*, 4573–4575. See also: (e) Zhu, C.; Falck, J. R. *ChemCatChem* **2011**, *3*, 1850–1851.

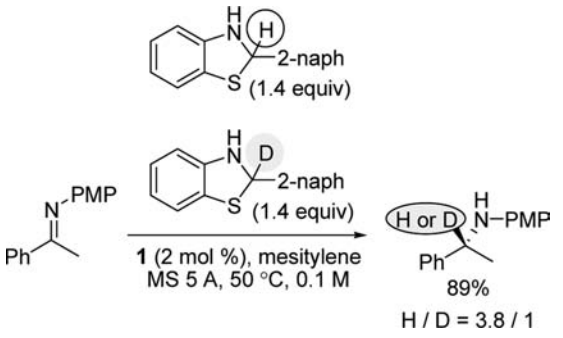
(12) For seminal work, see: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566–1568. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357.

(13) For selected reviews, see: (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999–1010. (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744–5758. (c) Terada, M. *Synthesis* **2010**, 1929–1982. (d) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539–4549. (e) Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, *44*, 1156–1171.

(14) Zhu, C.; Akiyama, T. *Synlett* **2011**, 1251–1254.

The kinetic isotope effect (k_H/k_D = 3.8) was observed in the competitive reaction between H- and D-benzothiazolines, which clearly implies that cleavage of the C−H bond is the rate-limiting step (Scheme 3).

Scheme 3. Competition Experiment between H- and D-Benzothiazolines



We propose the reaction mechanism shown in Figure 3. Phosphoric acid activates ketimine as a Brønsted acid, and phosphoryl oxygen forms a hydrogen bond with N−H of benzothiazoline. Then, the D-atom attacks ketimine as a deuteride.

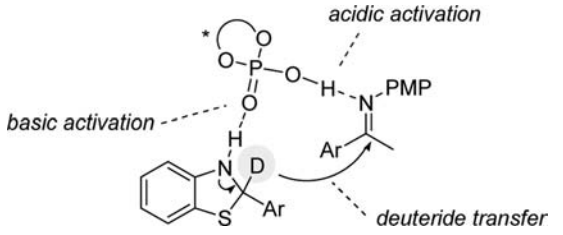


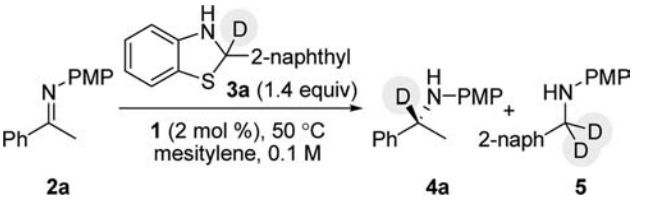
Figure 3. Proposed reaction mechanism.

An acetal exchange between ketimine and D-benzothiazoline and a subsequent deuteride reduction proceeded to give **5** as the byproduct. We investigated this deuteride reduction in an effort to improve the yield of α-deuterated amine **4a** by suppressing the exchange reaction (Table 1). Although the addition of a dehydrating reagent and the increase in temperature were not effective in improving the yields (entries 2 and 3), the addition of MS 5 A had a beneficial effect, furnishing **4a** quantitatively (entry 4).

With the optimized reaction conditions in hand, we investigated the substrate scope of the reaction (Table 2). We could obtain optically active α-deuterated amines in high yields and with excellent enantioselectivities in all the cases examined.

The deuteride reduction was successfully applied to α-iminoesters (Table 3). 2-Deuterio-2-phenylbenzothiazoline proved to be the most effective hydrogen donor to give corresponding α-amino α-aryl acetates with excellent enantioselectivities.

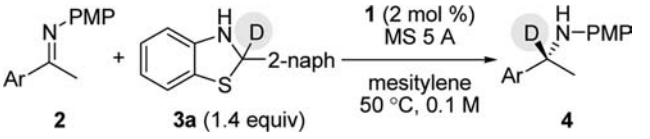
Table 1. Optimization of Conditions for Asymmetric Deuteration of Ketimine by Use of D-Benzothiazoline



entry	time/h	yield of **4a**/%[a]	ee of **4a**/%[b]	yield of **5**/%[a]
1	32	45	98	21
2[c]	28	50	97	15
3[d]	42	44	97	22
4[e]	26	quant	98	0

[a] Isolated yield. [b] Determined by HPLC analysis on a chiral stationary phase using Daicel Chiralcel OD-H column. [c] $MgSO_4$ was added. [d] At 70 °C. [e] MS 5 A was added.

Table 2. Asymmetric Deuteration of Ketimines **2** by Use of D-Benzothiazoline **3a**



entry	Ar	time/h	yield/%[a]	ee/%[b]
1	Ph	26	quant	98
2	2-naphthyl	24	90	98
3	*p*-tolyl	24	93	98
4	*p*-$MeOC_6H_4$	24	91	97
5	*p*-FC_6H_4	20	71	98
6	*p*-ClC_6H_4	26	97	97
7[c]	*p*-$NO_2C_6H_4$	25	77	95
8	*m*-$NO_2C_6H_4$	20	84	97

[a] Isolated yield. [b] Determined by HPLC analysis on a chiral stationary phase using Daicel Chiralcel OD-H column and Daicel Chiralpak AD-H column. [c] MS 13 X was employed instead of MS 5 A.

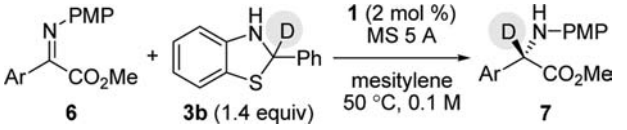
Enantiomerically pure deuterated amine **4b** could be obtained by a single recrystallization from hexane. The *p*-methoxyphenyl group of **4b** was oxidatively cleaved by trichloroisocyanuric acid (TCCA),[15] and the adduct was isolated as *N*-Boc amine **8** in good yield and in optically pure form (Scheme 4).

The absolute configuration of deuterated α-aminoester **7a** was determined to be (*S*) by X-ray crystallographic analysis of 4-bromobenzoate **9** (Scheme 5).

As an application of the present methodology, deuterated oxazolidinone **11** was prepared starting from **7a** by

(15) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Alsters, P. L.; van Delft, F. L.; Rutjes, F. P. J. T. *Tetrahedron Lett.* **2006**, *47*, 8109–8113.

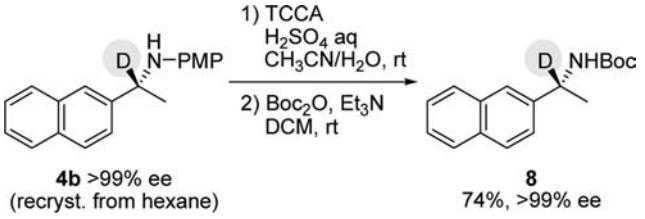
Table 3. Asymmetric Deuteration of Iminoesters **6** by Use of D-Benzothiazoline **3b**



entry	Ar	time/h	yield/%[a]	ee/%[b]
1	Ph	4	94	97
2	2-naphthyl	13	quant	97
3	*p*-tolyl	13	91	96
4	*p*-$MeOC_6H_4$	9	96	94
5	*o*-FC_6H_4	4	96	99
6	*m*-FC_6H_4	5	77	97
7[c]	*p*-FC_6H_4	15	81	93
8[d]	*p*-$NO_2C_6H_4$	3	99	92
9	2-thienyl	15	95	90

[a] Isolated yield. [b] Determined by HPLC analysis on a chiral stationary phase using Daicel Chiralcel OJ-H column and Daicel Chiralpak AS-H, AD-H column. [c] Imine was generated *in situ*. [d] At 30 °C.

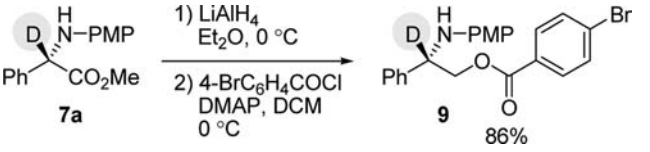
Scheme 4. Deprotection of *p*-Methoxyphenyl Group on Nitrogen Atom



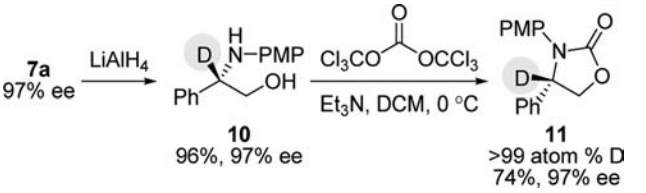
$LiAlH_4$ reduction followed by exposure to triphosgene (Scheme 6).

In summary, we developed a novel method for the transfer deuteration of ketimines with excellent enantioselectivities by use of benzothiazoline as the deuterium donor in combination with chiral phosphoric acid. The large kinetic isotope effect (k_H/k_D = 3.8) indicates that cleavage of the carbon−deuterium bond is the rate-determining step.

Scheme 5. Preparation of 4-Bromobenzoate **9**



Scheme 6. Transformation to Oxazolidinone Bearing Deuterium Atom



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Supporting Information Available. Experimental procedures, characterization data, cif file of compound **9**, and copies of NMR and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.