CHEMCOMM
Communication
www.rsc.org/chemcomm

Nonenzymatic kinetic resolution of β-amino alcohols: chiral BINAP mediated S_N2 displacement of hydroxy groups by halogens through formation of an aziridinium ion intermediate

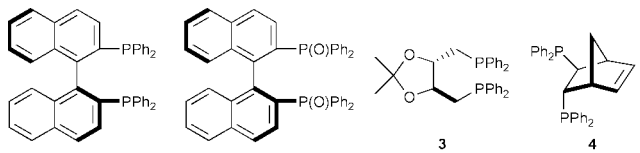
Govindasamy Sekar and Hisao Nishiyama*

School of Materials Science, Toyohashi University of Technology, Tempaku-cho, Toyohashi, Aichi 441-8580, Japan. E-mail: hnishi@tutms.tut.ac.jp

Received (in Cambridge, UK) 15th March 2001, Accepted 6th June 2001
First published as an Advance Article on the web 27th June 2001

A series of optically active cyclic *trans*-β-amino alcohols were obtained (up to 97% ee) from nonenzymatic kinetic resolution of corresponding racemic amino alcohols using commercially available (*S*)-BINAP and NCS by halogenation of hydroxy groups through formation of a *meso*-aziridinium ion intermediate.

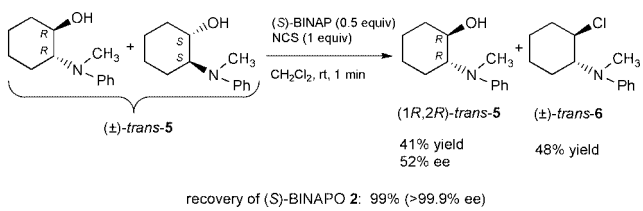
Enantiopure β-amino alcohols are an important class of organic compounds that have found much use in asymmetric synthesis[1] and medicinal chemistry,[2] and can be produced by reduction of optically active α-amino acids.[3] Kinetic resolution of β-amino alcohols through enzyme-catalysed acylation or deacylation is also one of the most efficient methods for the synthesis of chiral β-amino alcohols.[4] Nonenzymatic kinetic resolution (NKR) is the alternative for the enzymatic process, which is considered to be a challenging issue in organic synthesis.[5,6] Very recently, we reported the NKR of secondary alcohols by S_N2 displacement of the hydroxy groups by halogens using chiral BINAP (**1**).[7] In



1 **2** **3** **4**

this communication, we report highly enantioselective NKR of racemic *trans*-β-amino alcohols by halogenation of the hydroxy groups through an aziridinium ion intermediate.

First, we have chosen racemic *trans*-2-(*N*-methyl-*N*-phenylamino)cyclohexanol, (±)-*trans*-**5**, as a model substrate, which was subjected to kinetic resolution with NCS (1 equiv. compared to (±)-*trans*-**5**) and (*S*)-BINAP (0.5 equiv.) in CH_2Cl_2 at room temperature [eqn. (1)]. The reaction was found



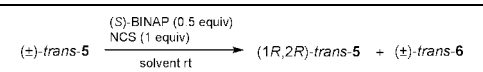
(1)

to be extremely fast with moderate selectivity. After 1 min, 41% of optically active amino alcohol (1*R*,2*R*)-*trans*-**5**[8] (52% ee) and 48% of racemic *trans*-β-amino chloride (±)-*trans*-**6** were isolated. BINAP was recovered as BINAP dioxide **2** in quantitative yield without any racemization (> 99.9% ee),[9] which can be reused after reduction.[10] In this reaction, the hydroxy group of the (1*S*,2*S*)-enantiomer of the racemic amino alcohol was selectively replaced by chloride ion through double S_N2 reactions (intramolecular S_N2 displacement of hydroxy group by amine followed by intermolecular S_N2 attack by chloride ion) to produce racemic *trans*-β-amino chloride **6**.

In order to improve the enantioselectivity of the kinetic resolution, the reaction was carried out in a wide range of solvents and the effect of other commercially available C_2-symmetric diphospine ligands were also examined (Table 1). Comparatively the reaction was very much faster and higher enantiomeric excess was obtained for recovered (1*R*,2*R*)-*trans*-**5** when the reaction was carried out in polar solvents than in non-polar solvents. THF turned out to be the solvent of choice among the solvents examined as it provided (1*R*,2*R*)-*trans*-**5** in 87% ee (entry 5). When the NKR was carried out with other commercially available C_2-symmetric diphospine ligands such as (+)-DIOP **3** and (+)-Norphos **4** the ee of (1*S*,2*S*)-*trans*-**5** dropped to 52 and 40%, respectively (entries 8 and 9). Lowering the reaction temperature to −10 °C–rt slightly improved the ee to 89% but longer reaction times discouraged us from doing the reaction at that temperature (entry 10). Surprisingly, the ee of (1*R*,2*R*)-*trans*-**5** dropped to 82% when the reaction was carried out at −74 °C–rt (entry 11). We next studied the effect of other halogenating agents such as *N,N*-dichlorocarbamic acid ethyl ester, NBS, *N*-bromosuccinimide, and *N*-bromoacetamide for the kinetic resolution of (±)-*trans*-**5** with (*S*)-BINAP in THF at room temperature. Although all the reactions proceeded smoothly to give corresponding products, a very poor ee was obtained for recovered (1*R*,2*R*)-*trans*-**5** (5–12%).

Using the optimized conditions, a series of racemic cyclic *trans*-β-amino alcohols[11] were resolved and the results are summarized in Table 2. When the kinetic resolution was allowed for 60–70% conversion, excellent enantiomeric excess was obtained for all the six- and seven-membered cyclic β-

Table 1 Effect of solvents, temperature and various diphosphine ligands in NKR of (±)-*trans*-**5**

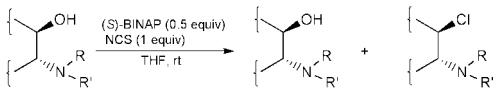


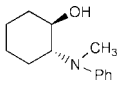
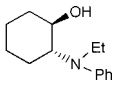
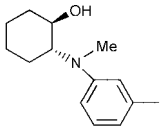
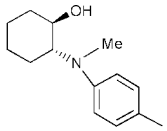
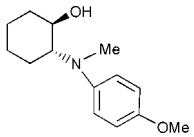
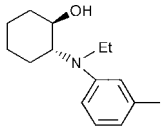
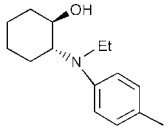
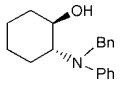
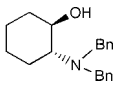
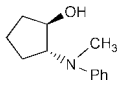
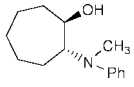
Entry	Diphosphine	Solvent	Time	Yield of **6** (%)[a]	Recovery of **5** (%)[a]	Ee of recovered **5** (%)[b]
1	**1**	Hexane	1 day	11	68	7
2	**1**	Benzene	30 min	47	43	38
3	**1**	Toluene	5 h	25	49	19
4	**1**	Ether	1 day	36	49	5
5	**1**	THF	20 min	61	27	87
6	**1**	CH_2Cl_2	1 min	48	41	52
7	**1**	CH_3CN	1 min	57	39	55
8	**3**	THF	3.5 h	54	29	52[c]
9	**4**	THF	4 h	63	27	40[c]
10[d]	**1**	THF	10 h	60	31	89
11[e]	**1**	THF	10 h	60	33	82

[a] Isolated yield. [b] Determined by HPLC analysis using Chiralcel OD column. [c] (1*S*,2*S*)-*trans*-**5** was the major enantiomer. [d] Reaction temperature was −10 °C–rt. [e] Reaction temperature was −74 °C–rt.

 DOI: 10.1039/b102460b

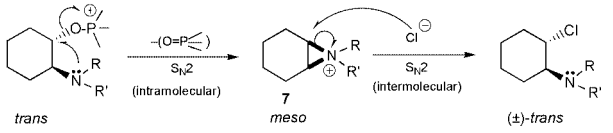
Table 2 NKR of variety of cyclic β-amino alcohols with (*S*)-BINAP and NCS[a]



Entry	β-Amino alcohol	Time	Recovery of β-amino alcohol (%)[b]	Ee of recovered β-amino alcohol (%)[c]
1		20 min	27	87
2		30 min	29	80
3		20 min	27	94
4		25 min	26	89
5		25 min	26	97
6		2 h	33	73
7		30 min	38	72
8		2 h	33	76
9[d]		25 min	38	72
10		15 min	25	59
11		10 min	35	86

[a] To a mixture of (*S*)-BINAP (0.125 mmol) and NCS (0.25 mmol) was added β-amino alcohol (0.25 mmol) in THF (2 mL) at room temperature. The white turbid reaction mixture turning to a colorless or slightly brown homogeneous solution shows the completion of the reaction. In all the reactions (±)-*trans*-β-amino chlorides were obtained in 42–69% isolated yield. [b] Isolated yield (the theoretical maximum yield in a kinetic resolution is 50%). [c] Determined by HPLC using chiral columns. [d] 2 equiv. of NCS were used.

tertiary amino alcohols (72–97% ee, 25–38% yield). Moderate enantiomeric excess was obtained for the five-membered β-amino alcohol (59% ee, entry 10). When the reaction was carried out with an acyclic amino alcohol such as racemic 1-(*N*-methyl-*N*-phenylamino)octadecan-2-ol, the (+)-amino alcohol was recovered in 34% yield with poor ee (15%).[12]



Scheme 1

Although at this moment the mechanism of the present reaction is not very clear, we assume that the reaction proceeds through an ionic phosphonium alkoxide intermediate (quaternary phosphonium salt) in which the amino group attacks the alkoxide by an intramolecular S_N2 reaction (neighboring group participation) to provide *meso*-aziridinium ion **7**. This is followed by an intermolecular S_N2 attack of *meso*-aziridinium ion **7** by chloride ion to provide racemic *trans*-β-amino chloride and dioxide **2** (Scheme 1). This phenomenon was supported as the dioxide **2** was recovered after the reaction and the product β-amino chloride was racemic with *trans* stereochemistry rather than optically active with *cis* stereochemistry. Formation of optically active β-amino chloride from the kinetic resolution of acyclic amino alcohol confirms the formation of an aziridinium ion intermediate. However, detailed mechanistic studies are under progress.

In conclusion, we have demonstrated highly enantioselective nonenzymatic kinetic resolution of racemic *trans*-β-amino alcohols using commercially available chiral BINAP and NCS. When the reaction was allowed for 60–70% conversion, excellent enantiomeric excess was obtained for all cyclic β-tertiary amino alcohols (up to 97% ee).

Notes and references

1 *Catalytic Asymmetric Synthesis 2nd edn.*, ed. I. Ojima, Wiley-VCH, NewYork, 2000; *Comprehensive Asymmetric Catalysis I-III*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer-Verlag, Berlin, 1999.

2 C. I. Fincham, M. Higginbottom, D. R. Hill, D. C. Horwell, J. C. O'Toole, G. S. Ratcliffe, D. C. Rees and E. Roberts, *J. Med. Chem.*, 1992, **35**, 1472; C. Auvin-Guette, S. Rebuffat, Y. Prigent and B. Bodo, *J. Am. Chem. Soc.*, 1992, **114**, 2170.

3 For a recent method for reduction of α-amino acids to β-amino alcohols, see: M. J. McKennon, A. I. Meyers, K. Drauz and M. Schwarm, *J. Org. Chem.*, 1993, **58**, 3568 and references cited therein.

4 G. Sekar, R. M. Kamble and V. K. Singh, *Tetrahedron: Asymmetry*, 1999, **10**, 3663 and references cited therein.

5 Nonenzymatic kinetic resolution of β-tertiary amino alcohols by enantioselective *N*-oxide formation using a stoichiometric chiral complex (1.2 equiv. of titanium tartrate complex was used) and *tert*-butyl hydroperoxide, see: S. Miyano, L. D.-L. Lu, S. M. Viti and K. B. Sharpless, *J. Org. Chem.*, 1985, **50**, 4350.

6 For a recent review on NKR of alcohols using chiral or achiral acylating agents, see: A. C. Spivey, A. Maddaford and A. J. Redgrave, *Org. Prep. Proced. Int.*, 2000, **32**, 331 and references cited therein.

7 G. Sekar and H. Nishiyama, *J. Am. Chem. Soc.*, 2001, **123**, 3603.

8 Absolute configuration was determined by the comparison of the sign of its optical rotation with that in literature. H. Yamashita, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 1213; H. Yamashita, *Chem. Lett.*, 1987, 525.

9 The ee of **2** was determined by HPLC analysis with a Chiralpak AD column (hexane–propan-2-ol = 75:25).

10 For the deoxygenation of chiral BINAP dioxide **2** to BINAP without loss of enantiomeric excess, see: H. Takaya, S. Akutagawa and R. Noyori, *Org. Synth.*, 1988, **67**, 20.

11 For the synthesis (±)-β-amino alcohols see: G. Sekar and V. K. Singh, *J. Org. Chem.*, 1999, **64**, 287; M. Chini, P. Critti and F. Macchia, *J. Org. Chem.*, 1991, **56**, 5939; J. Iqbal and A. Pandey, *Tetrahedron Lett.*, 1990, **31**, 575.

12 The product β-amino chloride was a mixture of two products (86.5:13.5) due to the attack of chloride ion on terminal and internal carbon atoms of the aziridinum ion intermediate. The ee of the major isomer (terminal-attacked product) was 16% which was determined by HPLC using a Chiralcel OD column (hexane–propan-2-ol = 1000:6).