Nonenzymatic Kinetic Resolution of Secondary Alcohols: Enantioselective S_N2 Displacement of Hydroxy Groups by Halogens in the Presence of Chiral BINAP

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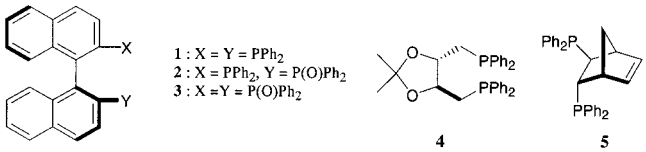
Enantiopure alcohols are very important structural units for the synthesis of a wide range of natural products, chiral ligands, and biologically active compounds[1] that can be available by kinetic resolution of racemic and *meso* secondary alcohols through acylation or deacylation catalyzed by enzymes.[2] Nonenzymatic



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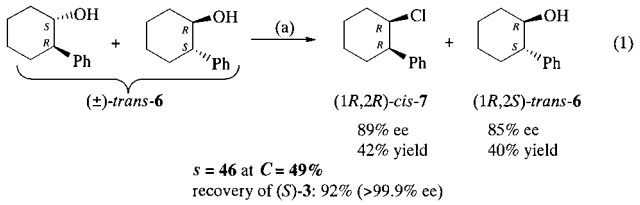
kinetic resolution (NKR) of racemic alcohol is the alternative for the enzymatic process, which is considered to be a challenging issue in organic synthesis. Recently, significant progress has been made in the literature for NKR of racemic and *meso* secondary alcohols using chiral or achiral acylating agents.[3] However, most of the methods suffered from the multistep synthesis of chiral auxiliaries and often provided only moderate enentioselectivities (s = selectivity factor[4] < 20). In this communication, for the first time we report high enantioselective nonenzymatic kinetic resolution of secondary alcohols through S_N2 displacement of the hydroxy group by halogen ions with halogenating agents in the presence of commercially available chiral diphosphine BINAP **1**.[5]

At the outset, we have chosen commercially available (±)-*trans*-2-phenylcyclohexan-1-ol **6** (TPCH)[6] as a model substrate, which was subjected to the kinetic resolution with *N*-chlorosuccinimide (NCS, 1.0 equiv to TPCH) in the presence of (*S*)-BINAP (0.3 equiv, stoichiometric amount of phosphorus) in THF at ambient temperature (eq 1). The reaction was found to be very



(1)

Reagents and conditions: (a) (±)-TPCH (0.25 mmol, 1 equiv), NCS (0.25 mmol, 1 equiv), (*S*)-BINAP **1** (0.075 mmol, 0.3 equiv), THF (2 mL), room temperature, 6 min.

fast and highly enantioselective (s = 46 and conversion (C) = 49%). After 6 min, 42% of alkyl chloride (1*R*,2*R*)-*cis*-**7** (89% ee) and 40% of alcohol (1*R*,2*S*)-*trans*-**6** (85% ee) were isolated. BINAP was recovered as BINAP bisoxide **3** in 92% yield without any racemization (>99.9% ee),[7] which can be reused after reduction.[8] In this reaction, the hydroxy group of (1*S*,2*R*)-enantiomer of the racemic alcohol was selectively replaced by chloride ion through S_N2 reaction to produce *cis*-alkyl chloride.[9]

A wide-ranging solvent study showed that both the conversion and enantioselectivity (s) of the NKR of (±)-TPCH are highly dependent on solvent (Table 1). Although we have not yet been able to correlate enantioselectivity with any single solvent parameter, it is clear that THF is the solvent of choice as it gave highest selectivity and conversion (entry 7). Several halogenating agents such as *N*,*N*-dichlorourethane (DCU), *N*-bromosuccinimide (NBS), and *N*-bromoacetamide (NBA) were tested for the kinetic resolution of (±)-TPCH with (*S*)-BINAP. Although all of the reactions proceeded smoothly to give corresponding products, NCS was found to be superior to all in the view of enantioselectivity (Table 1, entries 7−10).

We next studied the effect of the ratio of chiral BINAP and NCS in the NKR of (±)-TPCH at room temperature; the approach proved to be fruitful. We were surprised to observe that the selectivity and conversion were highly dependent on the amount of BINAP and NCS used. Even by only changing the amount of NCS, the selectivity and conversion of the reaction can be controlled to some extent. Usage of 2−3-fold excess NCS (with respect to BINAP) dramatically increased the enantioselectivity. For example, in the presence of 1 equiv of NCS, 0.3 equiv of (*S*)-BINAP gave highest selectivity (s = 46 and C = 49%). In the same way, considerably good selectivity was obtained when 0.4 equiv of (*S*)-BINAP and 0.9 equiv of NCS were used (s = 35 and C = 55.1%). When we used more than 0.4 equiv of BINAP, the reaction proceeded with poor enantioselectivity. For example, in the presence of 0.5 equiv of BINAP and 1.1 equiv of NCS the selectivity was dropped to 6 (C = 76%). In the same way, s is 12 (C = 69.7%) when 1.1 equiv of BINAP and NCS were used.

When the NKR of (±)-TPCH was carried out with other commercially available C_2-symmetric chiral diphosphines such as (+)-DIOP **4** and (+)-Norphos **5** with NCS, the enantioselectivities were dramatically dropped to 1 and 3, respectively (Table 2). These results clearly show that the bulkiness of naphthyl moiety of BINAP plays an important role in the transition state to provide very high enantioselectivity. We also found that the

(1) For the synthesis and application of enantiopure alcohols, see: (a) Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley-VCH: NewYork, 2000. (b) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer-Verlag: Berlin, 1999; Vol. 1−3. (c) Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953.

(2) Reviews: (a) Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: New York, 1994. (b) Johnson, C. R. *Acc. Chem. Res.* **1998**, *31*, 333.

(3) For selected papers on NKR of alcohols using chiral or achiral acylating agents, see: (a) Spivey, A. C.; Fekner, T.; Spey, S. E. *J. Org. Chem.* **2000**, *65*, 3154. (b) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629. (c) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169. (d) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492. (e) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809. (f) Spivey, A. C.; Maddaford, A.; Redgrave, A. J. *Org. Prep. Proced. Int.* **2000**, *32*, 333 and references therein.

(4) Selectivity factor (s) = (rate of fast reacting enantiomer)/(rate of slow reacting enantiomer). For more information, see: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

(5) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144 and references therein.

(6) For the application of chiral TPCH, see: (a) Schwartz, A.; Madan, P. B.; Mohasci, E.; O'Brien, J. P.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem.* **1992**, *57*, 851. (b) Whitesell, J. K..; Carpenter, J. F. *J. Am. Chem. Soc.* **1987**, *109*, 2839. (c) Greene, A. E.; Charbonnier, F.; Luche, M.-J.; Moyano, A. *J. Am. Chem. Soc.* **1987**, *109*, 4752. (d) Whitesell, J. K.; Chen, H.-H.; Lawrence, R. M. *J. Org. Chem.* **1985**, *50*, 4663, and ref 1c.

(7) (*S*)-BINAP bisoxide **3** was quantitatively recovered when the crude reaction mixture was kept overnight before the column chromatography purification. The ee of **3** was determined by HPLC analysis with Chiralpak AD column (hexane/2-propanol = 75:25).

(8) For the deoxygenation of chiral BINAP bisoxide to BINAP without loss of enantiomeric excess, see: (a) Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth.* **1988**, *67*, 20. (b) Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.

(9) *trans*-Alkyl chloride was not observed in the reaction. The stereochemistry of the *cis*-alkyl chloride was deduced from coupling constant (dt, J = 12.6, 3.0 Hz) of peak at 2.89 ppm (C*H*-Ph) in the ^{1}H NMR spectrum.

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Table 1. Effect of Solvents and Various Halogenating Agents in the NKR of (±)-TPCH with (*S*)-BINAP[a]

entry	solvent	halogenating agent	time	*C* (%)[b]	*s*[b]
1	hexane	NCS	2.0 h	40.0	3
2	CH_2Cl_2	NCS	<10 min	42.6	17
3	ether	NCS	7.5 h	38.6	9
4	CH_3CN	NCS	7.0 h	38.8	14
5	$CHCl_3$	NCS	7.0 h	7.7	7
6	benzene	NCS	<10 min	31.0	7
7	THF	NCS	<10 min	48.2	32
8	THF	DCU[c]	<10 min	34.4	18
9	THF	NBS	7.0 h	38.8	14
10	THF	NBA	<10 min	20.2	19

[a] Molar ratio of TPCH/BINAP/halogenating agent = 1.0: 0.8: 0.8 in 2 mL of solvent. [b] For the calculation of *C* and *s* values, see the Supporting Information. [c] 0.4 equiv of DCU was used.

Table 2. NKR of (±)-TPCH with Various C_2-Symmetric Diphosphine Ligands and NCS, and Effect of Temperature[a]

entry	diphosphine	temperature	time	*C* (%)	*s*
1	**1**	rt	6 min	49.0	46
2	**4**	rt	3.5 h	91.7	1[b]
3	**5**	rt	10 min	46.3	3[b]
4	**1**	−10 °C−rt	12 h	36.7	66
5	**1**	−74 °C−rt	12 h	35.8	253

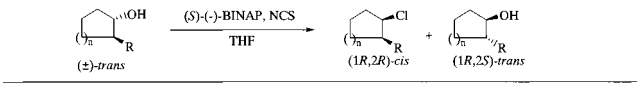
[a] Molar ratio of TPCH/diphosphine/NCS = 1.0: 0.3: 1.0 in THF. [b] (1*S*,2*S*)-*cis*-**7** and (1*S*,2*R*)-*trans*-**6** are the major enantiomers.

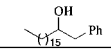
enantioselectivity of NKR is highly temperature-dependent. The enantioselectivity was increased as the temperature decreased. For example, the selectivity was drastically increased to 66 and 253 from 46 when the reaction temperature was reduced to −10 °C and −74 °C, respectively (Table 2, entries 1, 4, and 5).

Using the optimized reaction conditions, a wide range of β-aryl- and alkyl-substituted cyclic secondary alcohols were resolved with very high enantioselectivities. When the reactions were allowed for more than 50% conversion, excellent enantiomeric excesses were obtained for the recovered alcohols (Table 3). All of the β-aryl-substituted cyclohexanols are recovered in 95−99% enantiomeric excess with excellent enantioselectivities (*s* = 13−118, entries 1−8). (+)-2-Phenylcyclooctan-1-ol was recovered with 88% ee (*s* = 13, entry 10). β-Alkyl-substituted cyclohexanol gave moderate selectivity (*s* = 15, entry 9). As expected, acyclic secondary alcohol gave poor enantioselectivity (*s* = 2, entry 11). This could be because of the less steric hindrance, which occurs in the transition state. In the same way, excellent enantiomeric excess were observed for alkyl chlorides when the conversion of the NKR was controlled to be less than 50%.[10] *Importantly, to obtain comparatively very high ee for both the recovered alcohol and alkyl chloride (exactly 50% conversion), the reaction conditions should be thoroughly optimized for each particular racemic alcohol.*

Although at this movement 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 chloride ion attacks the alkoxide in S_N2 fashion to provide *cis*-alkyl chloride and bisoxide **3**. This was supported as **3** was recovered after the reaction. When the reaction 1 was carried out with monoxide **2**,[11] the reaction was much faster than the BINAP-mediated reaction with moderate enantioselectivity.[12] These observation suggests that the formation

Table 3. NKR of Various β-Aryl- and Alkyl-Substituted Secondary Alcohols with (*S*)-BINAP and NCS[a]



entry	R	n	temperature	*C* (%)	*s*	recovered alcohol: isolated yield[b] (%)	recovered alcohol: ee (%)[c]	recovered alcohol: absolute configuration[d]
1	Ph	2	rt	55.1	35	90	97	(1*R*,2*S*)
2	Ph	2	-10 °C - rt	52.5	79	85	98	(1*R*,2*S*)
3	C_6H_5-*o*-CH_3	2	rt	58.2	30	96	99[e]	(1*R*,2*S*)
4	C_6H_5-*m*-CH_3	2	-10 °C - rt	50.3	118	91	95	(1*R*,2*S*)
5	C_6H_5-*p*-CH_3	2	-10 °C - rt	53.8	40	93	96	(1*R*,2*S*)
6[f]	C_6H_5-*p*-OCH_3	2	-10 °C - rt	63.2	13	82	96	(1*R*,2*S*)
7	α-naphthyl	2	-10 °C - rt	59.5	20	96	97	(1*R*,2*S*)
8	β-naphthyl	2	-10 °C - rt	57.1	25	83	97	g[h]
9[f]	cyclohexyl	2	-10 °C - rt	47.6	15	95	69[e]	g[h]
10[f]	Ph	4	-10 °C - rt	57.9	13	89	88	g[h]
11			-74 °C - rt	70.4	2	97	38	g

[a] Molar ratio of alcohol/NCS/BINAP = 1.0:0.9:0.4 unless noted; room-temperature reactions were stirred for 10 min, and lower-temperature reactions were allowed to stir overnight. For the reactions illustrated in this table, the enantiomeric excess of *cis* cyclic alkyl chloride ranges from 56−94%. [b] Calculated from conversion. [c] Determined by HPLC analysis using chiral columns unless otherwise noted. [d] Determined by comparison of the sign of its optical rotation with literature values; see Supporting Information for more details. [e] Ee was determined by GC analysis using Supelco β-DEX 120 chiral capillary column. [f] 1.5 equiv of NCS was used. [g] Not determined. [h] Expected to be (1*R*,2*S*) based on the same analogy.

of monoalkoxide-phosphonium ion intermediate gives BINAP monoxide **2**, which might be immediately getting conversion to bisoxide **3** through the same alkoxide-phosphonium ion intermediate (stepwise mechanism). However, the detailed studies on the mechanism are under progress.

In conclusion, we have demonstrated highly enantioselective, novel nonenzymatic kinetic resolution of cyclic secondary alcohols by using chiral BINAP. To the best of our knowledge, this is the first report in the literature for kinetic resolution of secondary alcohols through selective S_N2 displacement of hydroxy groups by halogen ions (*s* = up to 253). Further investigations to broaden the scope and synthetic application of this new enantioselective NKR and to detail the mechanistic study are under progress. It is hoped that due to its economic and very high enantioselectivity, the NKR described herein will enjoy many new applications in the enantioselective organic synthesis.[13]

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Supporting Information Available: Experimental procedures, characterization data for new compounds, ee assay data, determination of absolute stereochemistry, and a table for alkyl chlorides (PDF). This material is available free of charge via the Internet at http:/pubs.acs.org.

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(10) In all the reactions, only *cis*-alkyl chlorides were selectively obtained through S_N2 displacement with excellent enantioselectivites. See the Table 4 in Supporting Information.

(11) For the synthesis of BINAP monoxide **2**, see: Grushin, V. V. *J. Am. Chem. Soc.* **1999**, *121*, 5831.

(12) When the (*S*)-BINAP mediated reaction 1 was carefully monitored by TLC, no spot was observed for BINAP monoxide (R_f 0.45, 40% EtOAc in hexane). This also suggested that the BINAP monoxide **2** should be much more reactive than BINAP, which might be immediately getting conversion to **3**.

(13) Importantly, the optically active alkyl halides are valuable intermediates that can be easily converted to variety of useful ligands such as chiral amines and phosphines. Larock, R. C. *Comprehensive Organic Transformations*; Wiley-VCH: New York, 1999 and refs 1a, b.