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Kinetic Resolution of Secondary Alcohols by the Combination of a Chiral Brønsted Acid, DABCO, and Acetyl Chloride

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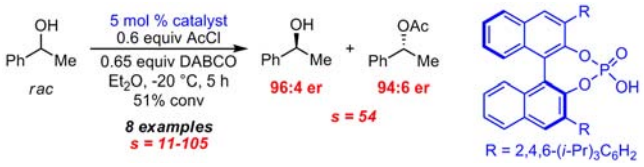
ABSTRACT



An efficient and simple protocol for the kinetic resolution of secondary alcohols is presented. The new system is based on a combination of chiral Brønsted acid, DABCO, and acetyl chloride and gives various enantioenriched alcohols with selectivity factors up to 105.

Over the past two decades, the kinetic resolution of secondary alcohols through the use of nonenzymatic methods has become an important transformation. Many researchers in this field have focused on the development of nucleophilic catalysts with high catalytic activity and enantioselectivity.[1] In such a reaction, the catalyst is evaluated in terms of the Kagan's equation, which gives the stereoselectivity factor (s).[2] In general, a catalyst with an s factor greater than 20 is considered to be synthetically useful.[3] Meanwhile, chiral Brønsted acids have been widely used in asymmetric reactions[4] since the pioneering studies by Akiyama[5] and Terada[6] in 2004. Although chiral Brønsted acids have been used in the dynamic kinetic resolution of azlactones through acyl transfer[7] and in the kinetic resolution of homoaldols through transacetalyzation,[8] to the best of our knowledge, there are no examples of the kinetic resolution of secondary alcohols through the use of a simple acetylating reagent in the presence of a chiral Brønsted acid. In this communication, we report the kinetic resolution of secondary alcohols by the combination of a chiral Brønsted acid, DABCO, and acetyl chloride.

First, we sought to identify reaction systems in which a chiral Brønsted acid increased the reaction rate and exhibited the selectivity. Acetyl chloride and acetic anhydride are commonly used as acylating reagents in combination with organic bases such as pyridine. Acetyl chloride is a less-reactive acylating reagent than acetic anhydride because of the difference in the structure of the ion pair as well

(1) For a recent review of nucleophilic catalysts in asymmetric transformations, see: (a) Taylor, J. E.; Bull, S. D.; Williams, J. M. J. *Chem. Soc. Rev.* **2012**, *41*, 2109. (b) Krasnov, V. P.; Gruzdev, D. A.; Levit, G. L. *Eur. J. Org. Chem.* **2012**, 1471. (c) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 1613. (d) Müller, C. E.; Schreiner, P. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 6012. (e) Wurz, R. P. *Chem. Rev.* **2007**, *107*, 5570.

(2) Kagan, H. B.; Fiaud, J. C. Kinetic resolution. In *Topics in Stereochemistry*; John Wiley & Sons, Inc.: 1988; p 249.

(3) For selected examples of the kinetic resolution of secondary alcohols by a nucleophilic catalyst with $s > 20$, see: (a) Li, X.; Jiang, H.; Uffman, E. W.; Guo, L.; Zhang, Y.; Yang, X.; Birman, V. B. *J. Org. Chem.* **2012**, *77*, 1722. (b) Birman, V. B.; Li, X. *Org. Lett.* **2008**, *10*, 1115. (c) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351. (d) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601. (e) Ishihara, K.; Kosugi, Y.; Akakura, M. *J. Am. Chem. Soc.* **2004**, *126*, 12212. (f) Bellemin-Laponnaz, S.; Tweddell, J.; Ruble, J. C.; Breitling, F. M.; Fu, G. C. *Chem. Commun.* **2000**, 1009. (g) Sano, T.; Imai, K.; Ohashi, K.; Oriyama, T. *Chem. Lett.* **1999**, *28*, 265. (h) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809. (i) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492.

(4) For a recent review of chiral Brønsted acid catalysts, see: (a) Terada, M. *Curr. Org. Chem.* **2011**, *15*, 2227. (b) Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W.; Atodiresei, I. *Angew. Chem., Int. Ed.* **2011**, *50*, 6706. (c) Terada, M. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 101. (d) Terada, M. *Synthesis* **2010**, 1929. (e) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395. (f) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (g) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (h) Terada, M. *Chem. Commun.* **2008**, 4097.

(5) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566.

(6) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

(7) (a) Lu, G.; Birman, V. B. *Org. Lett.* **2011**, *13*, 356. (b) Wang, C.; Luo, H.-W.; Gong, L.-Z. *Synlett* **2011**, 992.

(8) Čorić, I.; Müller, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 17370.

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as the basicity of the counteranion (acetate vs chloride) in the *N*-acetylpyridinium salts (Figure 1).[9]

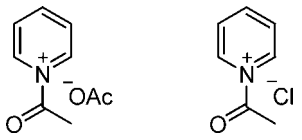


Figure 1. *N*-Acetylpyridinium salt intermediates.

We envisioned that it may be possible to activate the slow reaction system by the introduction of a chiral Brønsted acid, which would change the reactivity of the ion pair and also provide a chiral environment. Hence, we first examined the kinetic resolution of a racemic secondary alcohol (**1a**) with the use of 0.5 equiv of acetyl chloride and a variety of bases in the presence of a chiral phosphoric acid **3a** as a potential chiral Brønsted acid (Table 1).

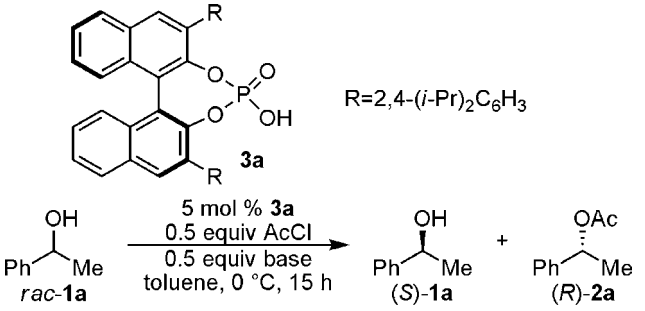
Pyridine derivatives, and other organic bases, showed very similar *s*-factors (s = 1.1−3.4, entries 1−8). Surprisingly, a fairly good result could be achieved when DABCO was used as a base (s = 9.4, entry 9).[10] Further explorations with DABCO-related structures were performed (entries 10−14). Quinuclidine, which has one less nitrogen than DABCO, gave a much lower *s*-factor (s = 1.6, entry 10). Disconnection of one bridgehead carbon in DABCO, 1,4-dimethyl piperazine, also resulted in a low *s*-factor (s = 2.1, entry 11). 1-Methyl piperidine and 1-methyl morpholine as well as the acyclic 1,2-diamine also gave results that were inferior to those with DABCO (s = 1.4−2.4, entries 12−14). Based on these results, two nitrogens and the rigid bicyclic framework are essential and should greatly contribute to the high *s*-factor.

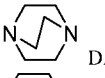
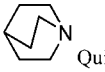
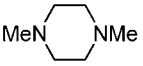
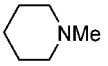
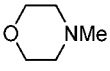
Next, a series of chiral phosphoric acids as a Brønsted acid catalyst were tested in an attempt to increase the *s*-factor. As shown in Table 2, a change in the catalyst from **3a** to **3b** or **3c** dramatically decreased the *s*-factor, indicating that the size of the *o*-substituent on the phenyl ring (R) significantly influenced the selectivity (entries 1−3). The catalysts bearing a 2,4,6-trisubstituted phenyl group **3d** and **3e** showed almost the same *s*-factor as the corresponding 2,4-disubstituted catalysts (entry 4 vs 3, entry 5 vs 1). The catalyst **3f**, 4-MeOC$_6$H$_4$- and 4-CF$_3$C$_6$H$_4$-substituted catalysts **3g** and **3h**, and 3,5-di-CF$_3$C$_6$H$_3$-substituted catalyst **3i** showed unsatisfactory results (s = 1.0−1.5, entries 6−9). The catalysts **3j** and **3k**, which are often used in various asymmetric transformations, were also inferior to **3e** (s = 1.1−3.2, entries 10 and 11). According to the results of catalyst screening, **3e** appeared to be the best catalyst for the kinetic resolution of *rac*-**1a**.

(9) (a) Kattnig, E.; Albert, M. *Org. Lett.* **2004**, *6*, 945. (b) Spivey, A. C.; Arseniyadis, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5436. (c) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

(10) The combination of acetyl chloride and DABCO for the non enantioselective esterification reaction under a solvent-free system has been reported; see: Hajipour, A. R.; Mazloumi, G. *Synth. Commun.* **2002**, *32*, 23.

Table 1. Screening of Various Amines[a]

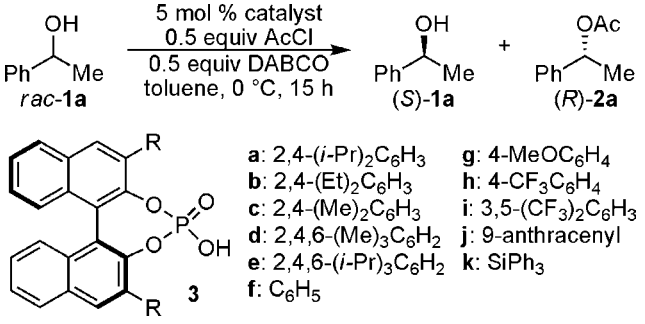


entry	base	conv [%][b]	s[c]
1	Pyridine	40	3.4[d]
2	DMAP	21	1.5[d]
3	2,6-Lutidine	38	1.7
4	2,6-Di-*t*-Bu-pyridine	29	1.7
5	DBU	20	1.1
6	*N*-Methyl imidazole	31	1.1
7	Et_3N	30	1.5
8	$EtN(i\text{-}Pr)_2$	27	1.2
9	 DABCO	24	9.4
10	 Quinuclidine	18	1.6
11		53	2.1
12		31	1.4
13		31	2.4
14	TMEDA	40	1.5

[a] The reactions were performed on 0.2 mmol scale under Ar. [b] Conversions were determined by ^{1}H NMR analysis of the unpurified reaction mixture. [c] Determined by HPLC; see the Supporting Information. [d] The absolute configurations were assigned to be (*R*)-**1a** and (*S*)-**2a**.

The effects of the solvent and the concentration of the substrate were also investigated (Table 3). The reaction in toluene, CH_2Cl_2, MeCN, and THF gave moderate to high selectivity (s = 5.5−10, entries 1−4). In contrast, the reactions in various acyclic ethers as solvents more efficiently promoted the kinetic resolution of *rac*-**1a** with high selectivities (s = 8.5−14, entries 5−7). The conversion was improved when 0.6 equiv of acetyl chloride and 0.65 equiv of DABCO were used (45% conv.; s = 18; entry 8). In all cases, the reaction mixture became heterogeneous when acetyl chloride was added to a mixture[11] of 5 mol % of **3e** and DABCO before the addition of the *rac*-alcohol. According to this observation, we thought that it might be important to increase the amount of solvent so that any insoluble material could be effectively dissolved. As expected, a lower concentration of substrate improved the *s*-factor (s = 29, entry 9). At the same concentration, the

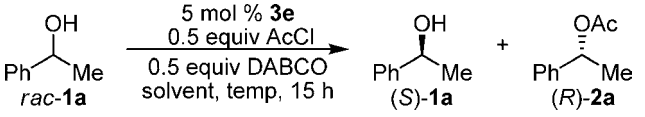
Table 2. Screening of Various Brønsted Acids[a]



entry	catalyst	conv (%)[b]	s[c]
1	**3a**	24	9.4
2	**3b**	26	3.4
3	**3c**	25	2.8
4	**3d**	28	2.4
5	**3e**	21	10
6	**3f**	29	1.3
7	**3g**	16	1.5
8	**3h**	19	1.5
9	**3i**	21	1.0
10	**3j**	14	3.2
11	**3k**	31	1.1

[a] See footnote a of Table 1. [b] See footnote b of Table 1. [c] See footnote c of Table 1.

Table 3. Screening of Various Solvents and Concentrations of Substrate[a]



entry	solvent	concn (M)	time (h)	temp (°C)	conv (%)[b]	s[c]
1	toluene	0.20	15	0	21	10
2	CH_2Cl_2	0.20	15	0	21	6.4
3	MeCN	0.20	15	0	31	5.8
4	THF	0.20	15	0	5	5.5
5	TBME	0.20	15	0	16	13
6	i-Pr_2O	0.20	15	0	7	8.5
7	Et_2O	0.20	15	0	22	14
8[d]	Et_2O	0.20	15	0	45[e]	18
9[d]	Et_2O	0.07	15	0	40[e]	29
10[d]	Et_2O	0.07	15	−20	56[e]	43
11[d,f]	Et_2O	0.07	15	−20	11[e]	–
12[d]	Et_2O	0.07	5	−20	51[e]	54
13[d]	Et_2O	0.07	1	−20	49[e]	52

[a] See footnote a of Table 1. [b] See footnote b of Table 1. [c] See footnote c of Table 1. [d] 0.6 equiv of AcCl and 0.65 equiv of DABCO were used. [e] Conversions were determined by HPLC using following equation [conversion = $ee_{alcohol}/(ee_{alcohol} + ee_{ester})$]. [f] The reaction was carried out in the absence of **3e**.

reaction at a lower reaction temperature (−20 °C, 15 h) showed s = 43 (entry 10). Without the Brønsted acid catalyst **3e**, the reaction with acetyl chloride and DABCO afforded the ester in only 11% conversion after 15 h (uncatalyzed reaction, entry 11). The s-factor improved with a shorter reaction time because of the competing uncatalyzed reaction was suppressed. The reaction for 5 h showed s = 54 with 51% conversion, and that for 1 h showed s = 52 with 49% conversion (entries 12 and 13). These experiments clearly indicate that Brønsted acid **3e** drastically accelerated the acetylation reaction with the use of DABCO and acetyl chloride, which is otherwise very slow.

The chiral Brønsted acid catalyzed kinetic resolution could be performed with various racemic alcohols (Figure 2). Phenyl- and naphthyl-based carbinols **1a**, **1b**, and **1c** could be efficiently resolved within 5 h with s = 30−54. The propargylic alcohols **1d** and **1e** could also be used in the kinetic resolution with s = 19−27, which is still a good selectivity factor. In addition, the new system is compatible with various functionalities. For example, the reaction of the vinyl alcohol **1f**, which possesses a silyl ether, and which is an important intermediate for the synthesis of a stagonolide series,[12] proceeded with acceptable selectivity (s = 11). The Morita−Baylis−Hillman adduct **1g** could be used in the reaction to give alcohol **1g** and the ester **2g** with good selectivity (s = 19). Cyclic *cis*-alcohols bearing a benzoate functionality could be used in the reaction and gave the alcohol **1h** and the diester **2h** (s = 105) without the migration and/or loss of benzoate. Our method gives various enantioenriched alcohols within 5 h.

The mechanism of the chiral Brønsted acid catalyzed kinetic resolution of racemic secondary alcohols is not yet clear. As mentioned above, the reaction mixtures are heterogeneous and there are some insoluble species that might be in a complex equilibrium. Since a preliminary spectroscopic investigation indicated that there are no appreciable quantities of intermediates in the solution phase, a small quantity of reactive species with high acyl-transfer ability may be generated in the solution. According to the pK_a value of the conjugate acid of DABCO,[13] one of the two protons (pK_a 2.97) is enormously dissociable (Figure 3). We presume that such a dicationic intermediate (**4** or **5**) involving chiral phosphate ion(s)[14] would be generated in the solution, and the characteristics of the conjugate acid of DABCO suggest that intermediates **4**

(11) We thought that the salt of **3e** and DABCO would form initially. For pioneering studies on the use of a Brønsted acid and amine salt in enantioselective transformation, see: (a) Wang, X.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6070. (b) Wang, X.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 1119. (c) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368. (d) Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193.

(12) (a) Giri, A. G.; Mondal, M. A.; Puranik, V. G.; Ramana, C. V. *Org. Biomol. Chem.* **2010**, *8*, 398. (b) Jana, N.; Mahapatra, T.; Nanda, S. *Tetrahedron: Asymmetry* **2009**, *20*, 2622.

(13) Benoit, R. L.; Lefebvre, D.; Fréchette, M. *Can. J. Chem.* **1987**, *65*, 996.

(14) For an example of a chiral anion-directed approach to kinetic resolution of secondary amines, see: De, C. K.; Klauber, E. G.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 17060.

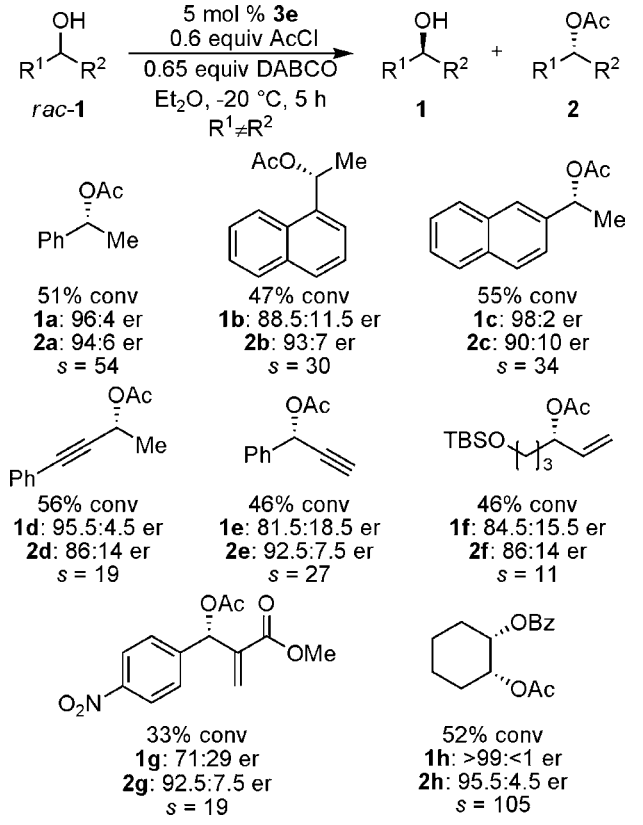


Figure 2. Substrate scope of the kinetic resolution of *rac*-alcohols.

and/or **5** are highly reactive. Very recently, Toste and coworkers reported the enantioselective fluorination of olefins with the combination of a Selectfluor and a chiral phosphate catalyst.[15] They also proposed that the reactive species should be a dicationic fluorinating reagent possessing bis chiral phosphates as counteranions related to **4** and **5**.

(15) (a) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681. (b) Phipps, R. J.; Hiramatsu, K.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 8376.

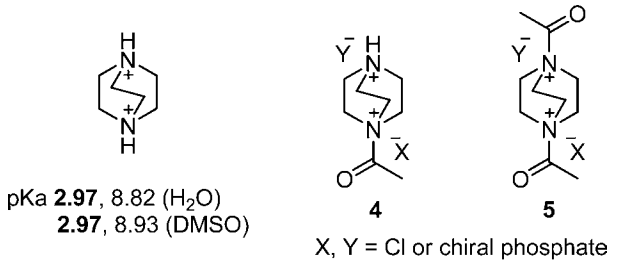


Figure 3. Plausible intermediates in the kinetic resolution.

In conclusion, we have presented an efficient method for the kinetic resolution of a wide range of alcohols involving aromatic carbinols, propargyl alcohols, vinyl alcohol, a Morita–Baylis–Hillman adduct, and a cyclic *cis*-alcohol. This process involves a practical procedure and proceeds efficiently (33–56% conversion) and with exceptional selectivity (s = 11–105). The present observations shed light on a new aspect of both acylation chemistry and chiral Brønsted acid catalyzed reaction. Further investigations on the mechanism of the kinetic resolution of secondary alcohols by a combination of chiral Brønsted acid, DABCO, and acetyl chloride are underway.

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Supporting Information Available. Experimental procedures and spectral data for substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.