Kinetic Resolution

DOI: 10.1002/ange.201304281

Kinetic Resolution of Secondary Alcohols Catalyzed by Chiral Phosphoric Acids**

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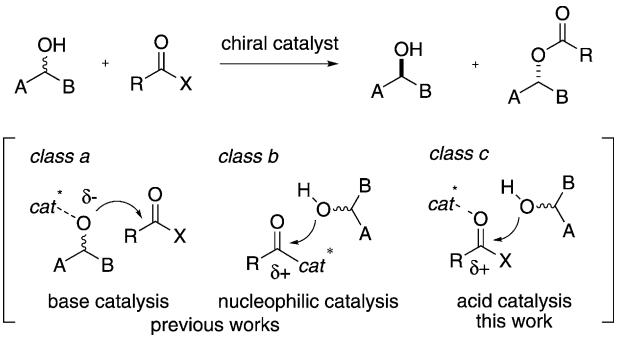
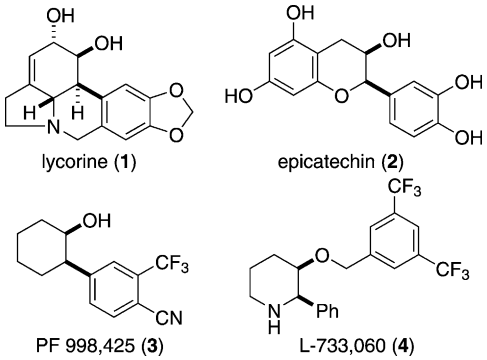
Of the many methods to separate enantiomeric constituents from racemic materials, kinetic resolution offers distinct advantages, especially when a chiral catalyst is involved. Kinetic resolution of racemic alcohols by esterification is an important process in synthetic chemistry, and many artificial catalysts as well as enzymatic methods have been developed for this purpose.[1] Their catalytic mechanisms are classified into two types: 1) Enhancement of the nucleophilicity of alcohols as a metal alkoxide bearing a chiral ligand[2] (Scheme 1, class a); and 2) in situ generation of chiral acylating reagents by nucleophilic chiral organocatalysts[3] (Scheme 1, class b).[4]



Scheme 1. Activation and enantiomer-discrimination modes in acylation-based kinetic resolution of secondary alcohols.

As a new mechanistic class, we expect that a chiral Brønsted acid will activate the acylating agent by hydrogen bonding and simultaneously discriminate the enantiomers of alcohols (Scheme 1, class c).[5] Herein we present the first kinetic resolution of secondary alcohols by chiral phosphoric acid catalyzed acylation.[6] This method provides effective access to optically pure 2-arylcycloalkanols,[7] which are structural motifs of biologically significant compounds, such as lycorine (**1**),[8] epicatechin (**2**),[9] PF-998,425 (**3**),[10] and L-733,060 (**4**)[11] (Scheme 2).



Scheme 2. *cis*-2-Arylcycloalkanol motifs in bioactive compounds.

Although Brønsted acids promote the acylation of alcohols with an acid anhydride,[12] a systematic study of their catalytic activity has not been reported. At the outset of this study, several Brønsted acids were tested in the acylation of *cis*-2-phenylcyclohexanol (**5a**) with isobutyric anhydride (**6a**).[13] Acylation did not occur in chloroform at ambient temperature after 24 h in the absence or presence of isobutyric acid. In contrast, stronger acids, such as phosphoric acid, accelerated acylation. With highly acidic triflic imide, acylation was complete within 0.5 h with only 0.5 mol% of the catalyst. These results show that isobutyric acid does not catalyze background acylation to give a racemic product, but an appropriately strong acid catalyzes acylation from **6a** in accordance to the acid strength of the catalyst.

Since the pioneering work of Akiyama and Terada,[14] chiral phosphoric acids have emerged as powerful Brønsted acid catalysts for various organic transformations.[15] However, acylation reactions catalyzed by this type of catalyst have rarely been reported.[6] Nevertheless, in the presence of chiral phosphoric acid (*R*)-TRIP (**7a**)[16,17] (5 mol%), a solution of (±)-**5a** and **6a** (1.5 equiv) in chloroform was stirred at ambient temperature. Acylation proceeded slowly, and reached 47% conversion after 48 h to give (+)-**8aa** with good enantioselectivity ($s = 24$;[18] Table 1, entry 1). Although the reaction was greatly accelerated (41–64% conversion after 0.5–5 h) using more acidic **7b**–**7d**, the selectivity decreased ($s = 1$–17; entries 2–4). TRIP-based phosphoric acid **7e**,[19] which bore bromine atoms at the 6,6′-positions, enhanced the selectivity as well as the reaction rate ($s = 45$, 50% conversion after 24 h; entry 5). Finally, a new catalyst **7f**, which had nitro groups at the 6,6′-positions, was the best catalyst, exhibiting a sufficient s value and reaction rate ($s =$ 110, 32% conversion after 5 h; entry 6). Even with a decreased amount of **6a** (0.7 equiv), the reaction with catalyst **7f** proceeded with a similar selectivity ($s = 113$) and reached 51% conversion after 24 h (entry 7).[13]

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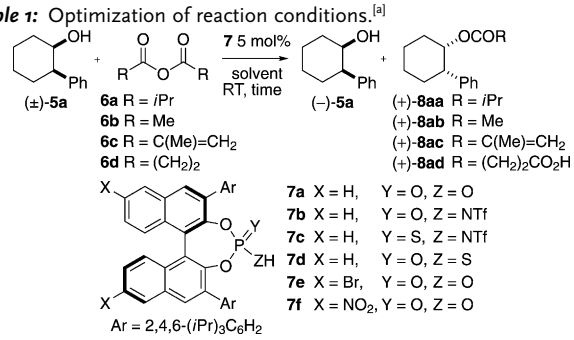
[**] We thank MEXT (Japan) for financial support (Grants-in-Aid for Scientific Research and Platform for Drug Design, Discovery, and Development).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201304281.

Table 1: Optimization of reaction conditions.[a]



Entry	6	7	Solvent	Time [h]	Conversion [%]	*s*
1	**6a**	**7a**	$CHCl_3$	48	47 (48)[b]	24
2	**6a**	**7b**	$CHCl_3$	1	52	2
3	**6a**	**7c**	$CHCl_3$	5	41	17
4	**6a**	**7d**	$CHCl_3$	0.5	64	1
5	**6a**	**7e**	$CHCl_3$	24	50	45
6	**6a**	**7f**	$CHCl_3$	5	32	110
7[c]	**6a**	**7f**[d]	$CHCl_3$	24	51	113
8	**6b**	**7f**	$CHCl_3$	5	37	6
9	**6c**	**7f**	$CHCl_3$	96	25	30
10	**6d**	**7f**	$CHCl_3$	5	48	35
11[c]	**6a**	**7f**	$MeNO_2$	24	44	68
12[c]	**6a**	**7f**	MeCN	24	27	43
13[c]	**6a**	**7f**	Et_2O	24	15	22

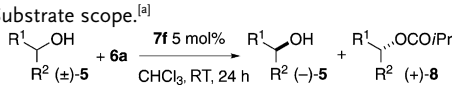
[a] With **5a** (0.1 mmol) and **6** (1.5 equiv) in $CHCl_3$ (0.2 mL). Absolute configuration was determined based on the specific rotation. [b] Yield of isolated product in parentheses. [c] With **6a** (0.7 equiv) in solvent (0.1 mL). [d] Recovered **7f** was used.

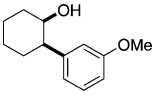
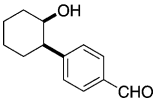
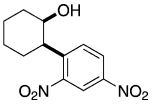
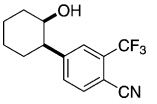
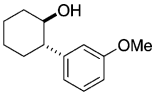
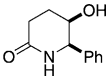
Next, we tested other anhydrides and solvents. With acetic anhydride (**6b**), the selectivity significantly decreased ($s = 6$; entry 8). Notably, methacrylic anhydride (**6c**) was applicable to this reaction, and (+)-**8ac** was obtained in a lower but acceptable selectivity ($s = 30$; entry 9). Acylation with succinic anhydride (**6d**) also proceeded with good selectivity ($s = 35$) to yield (+)-**8ad**, which bore a carboxylic acid moiety and was easily separated from (−)-**5a** by alkaline extraction (entry 10).

Replacing chloroform with nitromethane, acetonitrile, or diethyl ether decreased the enantioselectivity and the reaction rate (entries 11–13). The observed selectivity ($s = 113$, 68, 43, and 22 for $CHCl_3$, $MeNO_2$, MeCN, and Et_2O, respectively) and the reaction rate (51%, 44%, 27%, and 15% conversion after 24 h) seem to be correlated with the basicity of the solvents (donor numbers = 0, 2.7, 14, and 19),[20] suggesting that hydrogen bonding plays a critical role in the transition state.

With the optimal conditions (Table 1, entry 7), the scope of alcohols was investigated (Table 2). *cis*-Alcohol (±)-**5b**, which possessed an electron-rich aryl group, was successfully resolved ($s = 215$) at ambient temperature to give (−)-**5b** (51%, 97:3 *er*) and ester (+)-**8b** (49%, 98:2 *er*; entry 2). Alcohols (±)-**5c**, **5d**, and **3** with an electron-deficient aryl group were also good substrates, affording a high selectivity ($s = 120$–135; entries 3–5). PF-998,425 (**3**)[10] was obtained with a high optical purity in an almost ideal yield (entry 5). *cis*-Arylcycloalkanols with different ring sizes, such as (±)-**5f** and (±)-**5g**, were also resolved with a high selectivity ($s = 55$ and 151; entries 6 and 7, respectively). *trans*-Isomers as well as acyclic alcohol were also resolved in a practical level of selectivity ($s = 23$–39; entries 8 and 9).[13] Importantly, **7f** was quantitatively recovered and recycled.

Table 2: Substrate scope.[a]



Entry	Recovered **5**	**5** Yield [%],[b] *er*	**8** Yield [%],[b] *er*	*s*
1[c]		(−)-**5a** 48%, >99:1	(+)-**8aa** 52%, 95:5	116
2		(−)-**5b** 51%, 97:3	(+)-**8b** 49%, 98:2	215
3		(−)-**5c** 48%, 95:5	(+)-**8c** 47%, 98:2	135
4		(+)-**5d** 48%, 98:2	(−)-**8d** 50%, 97:3	120
5		(−)-**3** (=**5e**) 48%, >99:1	(+)-**8e** 52%, 96:4	126
6		(−)-**5f** 49%, 96:4	(+)-**8f** 51%, 94:6	55
7		(−)-**5g** 48%, >99:1	(+)-**8g** 50%, 96:4	151
8		(−)-**5i** 45%, 99:1	(+)-**8i** 55%, 90:10	39
9		(+)-**5l** 44%, 92:8	(−)-**8l** 47%, 90:10	23
10		(−)-**5m** 46%, >99:1	(+)-**8m** 52%, 94:6	128
11[d]		(−)-**5n** 55%, 85:15	(+)-**8n** 43%, 95:5	39

[a] With **5** (0.25 mmol) and **6a** (0.7 equiv) in $CHCl_3$ (0.25 mL). The absolute configurations were determined based on specific rotation, except for entries 2–4, 7, and 8, which were assigned by analogy. [b] Yield of isolated product. [c] With **5a** (1 mmol) in $CHCl_3$ (0.1 mL) for 15 h. [d] With **6a** (1.5 equiv) in $MeNO_2$ (0.1 mL).

Piperidinol (±)-**5m** was an appropriate substrate ($s = 128$), and (−)-**5m**, a known intermediate for L-733,060 (**4**),[11] with 99:1 *er* was recovered in 46% yield (entry 10). For lactam alcohol (±)-**5n**, which had a poor solubility in chloroform, nitromethane was a substitute solvent, although the selectivity was lower ($s = 39$, entry 11). An α,β-unsaturated ester (Table 1, entry 9), a formyl group (Table 2, entry 3), nitromethane (Table 2, entry 9), carboxylic acid, aryl acetate, and 1,3-dione,[13] which are potentially sensitive to nucleophilic catalysts providing side reactions, were inert under these conditions.

Chiral phosphoric acid would catalyze acylation not only as a Brønsted acid to activate acid anhydride as an electro-

phile by protonation, but also as a general base[21] to enhance the nucleophilicity of alcohol. However, another possibility was that nucleophilic catalysis occurred. Namely, phosphoric acid might react with acid anhydride to form the corresponding acyl phosphate (mixed anhydride), which then acylates alcohols.

To exclude this possibility, equimolar mixtures of **6a** with **7a** or **7f** in deuterochloroform were monitored by ^{1}H and ^{31}P NMR. Only signals of **6a** and **7a** or **7f** appeared, respectively, and no formation of acyl phosphates was observed for 48 h.[22] Therefore, the high performances of **7e** and **7f** can be explained by the stronger acidity, which allows stronger hydrogen bonds, increasing the reaction rate and selectivity (Table 1, entry 1 vs. entries 5 and 6).

The geometry of the proposed transition state was calculated at the B3LYP/6-31G** level of theory (Figure 1). The distances of P=O···H, P–O···H, and H···O=C were 1.41, 1.26, and 1.15 Å, respectively, clearly indicating that the expected hydrogen-bond network was operative. The activation energy was reasonably low (22.6 kcal mol^{-1}), supporting the plausibility of the model. The decreased selectivity with **7b–d** (Table 1, entries 2–4) and the above-mentioned solvent effect (Table 1, entries 11–13) also suggest the importance of hydrogen bonding in the transition state.

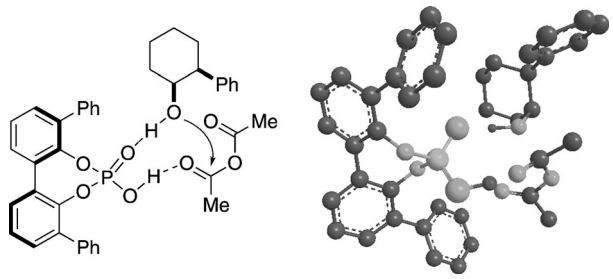


Figure 1. Perspective view of the calculated transition-state model (the H atoms of the C–H bonds are omitted for clarity).

In conclusion, we have developed the kinetic resolution of secondary alcohols by chiral phosphoric acid-catalyzed acylation. New electronically tuned binaphthyl-based phosphoric acid **7f** was developed by installing nitro groups at the 6,6′-positions of TRIP, enabling the resolution of *cis*-2-arylcycloalkanols with a high selectivity even at ambient temperature. Hydrogen bonding most likely plays a crucial role in the selectivity and acceleration of the acylation. Facile access to biologically significant compounds highlights the utility of this reaction. The reaction procedure is simple and does not require additives, such as a stoichiometric amount of base, which was required for the conventional methods. This acid-catalyzed reaction provides complementary functional group compatibility to already-known methods.

Received: May 18, 2013
Revised: June 27, 2013
Published online: August 12, 2013

Keywords: asymmetric acylation · chiral alcohols · kinetic resolution · organocatalysis

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material. In simple first-order kinetics, $s = k_{fast}/k_{slow} = \ln[(1-C)(1-ee')]/\ln[(1-C)(1+ee')] = \ln[1-C(1+ee)]/\ln[1-C(1-ee)]$ and $C = ee'/(ee'+ee)$, where C is conversion, and ee and ee' are enantiomeric excesses of the product, and the recovered starting material, respectively: H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249.

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