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Kinetic Resolution of Allylic Alcohols Using a Chiral Phosphine Catalyst

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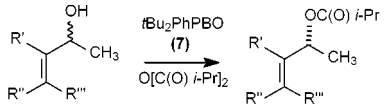
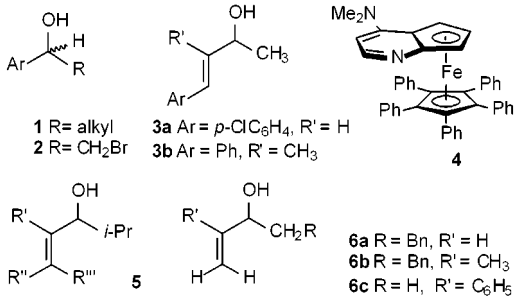
ABSTRACT



The kinetic resolution of racemic allylic alcohols 3, 6, and 12–17 has been explored using the PBO catalyst 7 for activation of isobutyric anhydride. Trisubstituted allylic alcohols (12–15; 17) are the best substrates and react with an enantioselectivity of $s = 32–82$ at –40 °C.

Several groups have recently reported effective nonenzymatic catalysts for the kinetic resolution of alcohols using chiral amine[1] or phosphine[2] catalysts. Most of the initial efforts were directed at aryl alkyl carbinols of general structure **1**, but considerable progress has been made with substrates containing more versatile functionality (Scheme 1).[1b,e,f]

Scheme 1



Oriyama et al. have demonstrated enantioselectivities above 100 for several bromohydrins **2** using a chiral diamine catalyst,[1b] while Fu et al. have reported good results with β-aryl-substituted substrates of general formula **3** using the planar-chiral DMAP derivative **4** as the catalyst (for **3a** and **3b**, $s = 14$ and $s = 22$ in ether at room temperature, or $s = 64$ and $s = 80$ in *tert*-amyl alcohol at 0 °C, respectively).[1d,e] Lower selectivities were found for a number of other allylic alcohols lacking the β-aryl group ($s = 4.7$ to 29; 11 examples), including eight isopropyl alkenyl carbinols **5**. Methyl analogues of **5** (replace *i*-Pr by CH_3), **6** (R = H), or cyclic allylic alcohols were not mentioned.

We have also explored the kinetic resolution of allylic alcohols. As in our earlier study of aryl alkyl carbinols **1**, acylations were performed at −40 °C in toluene or heptane with isobutyric anhydride and the di-*tert*-butylphenyl-PBO catalyst **7**, Scheme 2 (PBO = phospha-bicyclo[3.3.0]octane skeleton).[2b] In a preliminary survey,[3] unsaturated alcohols **8** ($n = 1$ or 2), containing the allylic double bond as well as the hydroxyl group within a ring, were found to be less than desirable substrates for the PBO catalysts ($s < 1.5$ at room temperature). In the current study, both diastereomers of the analogous cyclic allylic alcohol **9** were likewise acylated without significant enantioselectivity. The allylic alcohol **10** having an exocyclic double bond was also a poor substrate ($s = 1.6$), suggesting that low enantioselectivities may be associated with the presence of conformational constraints.

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(2) (a) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430. (b) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813.

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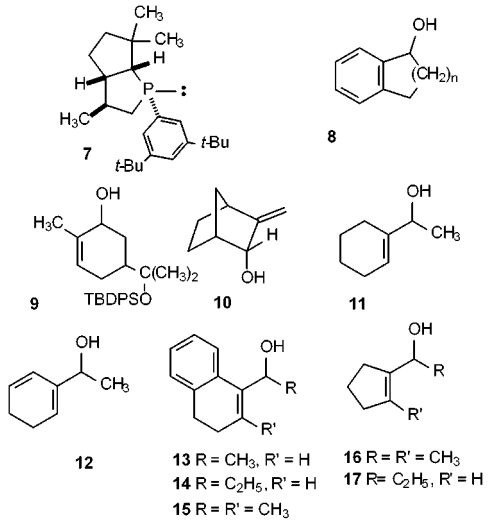
Scheme 2



Evidently, these alcohols have restricted access to the conformation required for enantiodiscrimination by the reactive (*P*-butyroyl-phosphonium carboxylate) form of the catalyst.

More flexible allylic alcohols **3** and **6** were investigated (Table 1). Modest to good enantioselectivities were found,

Table 1. Kinetic Resolution of Allylic Alcohols with Isobutyric Anhydride and **7** (Scheme 2)[a]

alcohol	time (h)	convn (%)	ee[b]	ee′[c]	*s*
3a	12	55.1	77.7	63.3	10
3b	27	45.1	67.3	82.0	21
6a	41	47.9	41.7	45.4	4
6b	19	48.1	66.4	71.7	12
6c	19	38.1	45.7	74.3	11
11	14	50.4	89.8	88.2	52[d,e]
12	7	53.0	90.0	81.4	34[d]
13	72	52.6	96.1	86.7	55
14	128	34	48.9	94.8	61
15	25	40.3	64.2	95.3	82[d]
16	46	67.2	99.9	48.8	25[d]
17	46	37.7	56.4	93.5	52

[a] Reactions were performed at −40 °C using 0.1 M substrate, 2.5 equiv of isobutyric anhydride, and 5 mol % of **7** in toluene unless noted. [b] Unreacted alcohol ee. [c] Product ee′ (measured on alcohol obtained by ester saponification). [d] Reaction in heptane solution. [e] Data from ref 2b.

and increased alkene substitution (**3b** vs **3a**; **6b** vs **6a**) resulted in better selectivity. Further improvements were observed when the double bond was placed within a carbocyclic ring (**11**−**17**), and the best selectivities were found with substrates having larger alkene substituents.

The absolute configuration of the more reactive enantiomers of **3a** and **3b** was established by comparison with literature data.[1d,4] For **12** and **13**,[5] absolute configurations were assigned after aromatization (Pd/C with norbornadiene in refluxing toluene)[6] to the corresponding **1** (Ar = phenyl or 1-naphthyl, respectively),[2b] while the enantioselectivity for **11** had already been established in our earlier report.[2b] All of these alcohols, as well as the analogous aryl carbinols **1** studied previously,[2b] reacted with a preference for the *R*-enantiomer using the PBO catalyst **7**. The more reactive enantiomer for the remaining examples (**14**, **15**)[7] was therefore assigned the same *R*-configuration by analogy.

Good substrates for kinetic resolution via enantioselective *iso*-butyroylation using the PBO catalyst **7** have a conformationally flexible allylic hydroxyl-bearing carbon (Table 1). The best selectivities are obtained with alcohols **13**−**15**. The drop in selectivity from **11** to **12**, from **11** to **16**, or from **13** to **12** suggests that the alkene substituent effect may have a steric origin. One likely role of this effect would be to keep the R-substituent in **13**−**15** turned away from the plane of the double bond to minimize $A_{1,2}$-strain. Lower selectivities result when the size and number of alkene substituents decreases or when the C═C−C−O subunit is constrained, as in **8**−**10**. The latter structures can be taken to represent geometries that do not match catalyst preferences for enantioselective isobutyroyl transfer.

In contrast to the results of Fu et al. using catalyst **4**,[1e] *β*-aryl substitution (as in **6c**) does not enhance enantioselectivity in the PBO experiments. This was somewhat unexpected because catalysts **4** and **7** have a qualitatively similar selectivity profile with typical aryl carbinol substrates **1**.[1c,d,2b] The reactive intermediates in phosphine-catalyzed or DMAP-catalyzed acyl transfer are believed to be *P*-acyl phosphonium or *N*-acylpyridinium carboxylates, respectively.[1c,d,2b] However, important mechanistic features that would play a role in determining transition state preferences remain unknown in both series, including the location of the crucial carboxylate anion that is probably involved as a general base in the proton-transfer process. It would therefore be premature to speculate further about transition state geometries.

In summary, some promising structural types for kinetic resolution of allylic alcohols have been identified. The dienyl alcohol examples **12**−**15** represent a new category of good substrates for chiral, nucleophilic acylation catalysts.

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Supporting Information Available: Assay and characterization data; representative procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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