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Benzotetramisole: A Remarkably Enantioselective Acyl Transfer Catalyst

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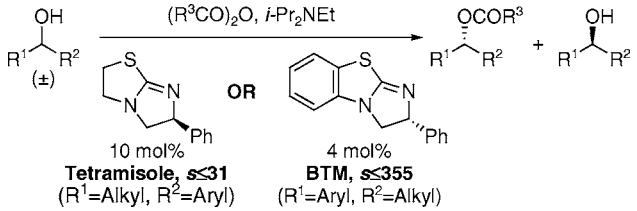
ABSTRACT



A commercially available pharmaceutical, tetramisole, was found to be a competent enantioselective acylation catalyst. Its benzannellated analogue, benzotetramisole (BTM), produced outstanding enantioselectivities in kinetic resolution of secondary benzylic alcohols.

Development of nonenzymatic catalysts capable of achieving high enantioselectivities in asymmetric acylation of alcohols remains a serious challenge. Although even moderate selectivity factors[1] ($s = 20$) are considered practically useful for preparing enantiopure alcohols by kinetic resolution (KR) of racemates,[2a] significantly higher levels of selectivity are needed to obtain esters with sufficient enantiomeric excess.[1,2a,3] However, after almost a decade of intensive research in this area,[2,4] selectivity factors exceeding 100 are still far from common.[5]

Recent reports from our laboratory have described a new class of enantioselective acyl transfer catalysts based on the 2,3-dihydroimidazo[1,2-*a*]pyridine core. Catalyst CF_3−PIP (**1**), the best in the original DHIP series,[6] proved to be effective in the KR of secondary benzylic ($s \leq 85$)[6a] and allylic ($s \leq 26$)[5g] alcohols. Its benzannellated analogue Cl−PIQ (**2**) displayed considerably enhanced catalytic activity and enantioselectivity with the above classes of substrates ($s \leq 117$ and $s \leq 57$, respectively).[5g] The structure-selectivity trends observed in the KR experiments suggested the involvement of $\pi-\pi$ and cation$-\pi$ interactions between the acylated intermediate and the substrate molecule (**3**). We became curious whether the presence of the aromatic pyridinium ring in the acylated intermediate was indeed a requirement of this catalyst design. An opportunity to answer this question experimentally presented itself in the form of the chiral bicyclic isothiourea **4** (Figure 1). Although its structure looks purposely designed for comparison with the DHIP catalysts, this compound is in fact commercially

(1) Selectivity factor s is defined as the ratio of reaction rates of the fast- and the slow-reacting enantiomers of a substrate. For calculation of s from the ee's of the product and the recovered starting material, as well as other theoretical aspects of kinetic resolution, see: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

(2) For recent reviews, see: (a) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (c) Jarvo, E. R.; Miller, S. J. Asymmetric Acylation. In *Comprehensive Asymmetric Catalysis, Supplement 1*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Heidelberg, 2004; Chapter 43. (d) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985. (e) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5.

(3) For example, $s = 200$ would allow preparation of an ester with 98% ee in 40% theoretical yield by KR or with 99% ee in quantitative theoretical yield by dynamic kinetic resolution (DKR). For $s = 100$, these values would drop to 96% ee and 98% ee, respectively (ref 2a).

(4) For a list of leading references, see: refs 2a and 5g.

(5) The following articles reported $s \geq 100$ in KR of alcohols via nonenzymatic acylation: (a) Oriyama, T.; Hori, Y.; Imai, K.; Sasaki, R. *Tetrahedron Lett.* **1996**, *37*, 8543. (b) Sano, T.; Imai, K.; Ohashi, K.; Oriyama, T. *Chem. Lett.* **1999**, 265. (c) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412. (d) Bellemin-Laponnaz, S.; Tweddell, J.; Ruble, J. C.; Breitling, F. M.; Fu, G. C. *Chem. Commun.* **2000**, 1009. (e) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813. (f) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **2003**, *125*, 4166. (g) Birman, V. B.; Jiang, H. *Org. Lett.* **2005**, *7*, 3445.

(6) (a) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 12226. (b) Birman, V. B.; Li, X.; Jiang, H.; Uffman, E. W. *Tetrahedron* **2006**, *62*, 285.

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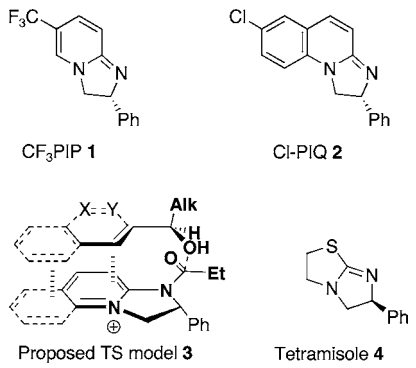


Figure 1. First- and second-generation catalysts and tetramisole.

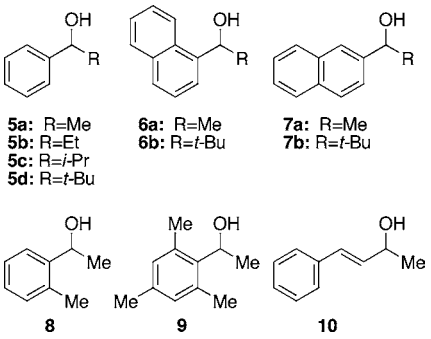


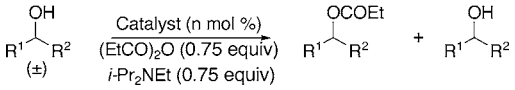
Figure 2. Substrates for KR.

available (as hydrochloride) in enantiomerically pure form under the name Tetramisole. It is rather inexpensive (thanks to its large-scale production for medicinal and veterinarian applications)[7] and would obviously be an attractive addition to the arsenal of chiral reagents. To the best of our knowledge, it has not been previously used in asymmetric synthesis.

The first catalytic activity test was carried out under the previously described set of conditions.[6b] Tetramisole base proved to be catalytically competent in this reaction, albeit less active than **1** and especially **2**. More intriguingly, its enantioselectivity turned out to be comparable to those of **1** and **2** (Table 1, entries 1−3). The absolute sense of enantioselection displayed by (*S*)-tetramisole (**4**) was the opposite of that obtained with (*R*)-**1** and (*R*)-**2**, which is consistent with a similar transition state. Three other substrates were tested using an increased catalyst loading of **4** (10 mol %) at 0 °C. Benzylic alcohols **5a** and **7a** produced results similar to those for **5b**, whereas cinnamyl alcohol **10** was resolved with only low selectivity (Table 1, entries 4−7; Figure 2). On one hand, these results indicated that an aromatic pyridinium ring was not necessary for either the catalytic activity or the enantioselectivity. On the other hand, the performance of tetramisole as a catalyst could obviously stand some improvement. On the basis of our earlier experience with catalysts **1** and **2**,[5g,6b] we expected that benzannellation of the structure of **4** would increase its enantioselectivity by extending the π-system available for the attractive interactions with the substrate and removing the hydrogens that might contribute to the steric repulsion (cf. **11**→**12**, Scheme 1). With this in mind, we synthesized compound **16** by a slight modification of our previously developed protocol.[5g,6,8]

The new catalyst **16**, dubbed "benzotetramisole" (BTM), was tested first at room temperature and displayed activity comparable to that of CF_3PIP (**1**). To our delight, the selectivity factor observed with **16** was more than twice as high as that obtained with **1** or **2** (Table 1, entries 1, 2, and 8). Encouraged by this finding, we set out to optimize the reaction conditions. Our attempts to lower the reaction temperature and thus achieve further enhancement of selectivity initially proved unsuccessful. The reaction completely stopped at low levels of conversion, suggesting loss of catalytic activity. It occurred to us that this effect might simply be due to the moisture sensitivity of the acylated

Table 1. KR Catalyzed by **1**, **2**, **4**, and **16**



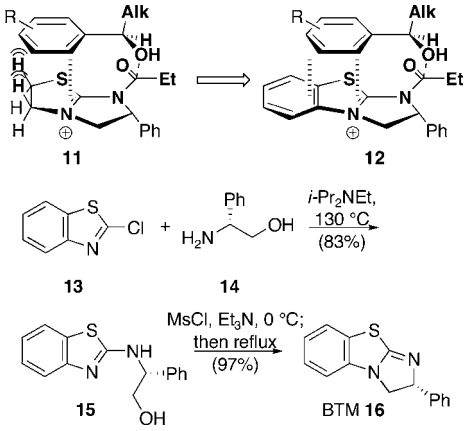
entry	catalyst	substrate	time	% conv	s^g
1[a,b]	(*R*)-**1**	**5b**	40 min	47	28
2[a,b]	(*R*)-**2**	**5b**	15 min	51	33
3[a]	(*S*)-**4**	**5b**	4 h	45	27(*S*)
4[c]	(*S*)-**4**	**5b**	6 h	53	31(*S*)
5[c]	(*S*)-**4**	**5a**	6 h	52	31(*S*)
6[c]	(*S*)-**4**	**7a**	3.75 h	56	25(*S*)
7[c]	(*S*)-**4**	**10**	8 h	45	4.9(*S*)
8[a]	(*R*)-**16**	**5b**	1 h	49	57
9[d]	(*R*)-**16**	**5b**	24 h	47	109
10[d]	(*R*)-**1**	**5b**	12 h	47	47
11[d]	(*R*)-**2**	**5b**	3.5 h	50	47
12[e]	(*S*)-**4**	**5b**	10.5 h	47	32(*S*)
13[d]	(*R*)-**16**	**5a**	33 h	49	80
14[d]	(*R*)-**16**	**5c**	36 h	48	111
15[d,f]	(*R*)-**16**	**5d**	48 h	51	166
16[d]	(*R*)-**16**	**6a**	8.5 h	49	128
17[d]	(*R*)-**16**	**7a**	10.5 h	50	108
18[d]	(*R*)-**16**	**8**	33 h	50	209
19[d,f]	(*R*)-**16**	**6b**	32 h	45	307
20[d]	(*R*)-**16**	**7b**	32 h	38	299
21[d]	(*R*)-**16**	**9**	24 h	20	2.5
22[d,f]	(*R*)-**16**	**10**	32 h	36	23

[a] Conditions: 1.0 M substrate, 5 mol % of catalyst, room temperature. [b] Data from previous work.[6b] [c] Conditions: 1.0 M substrate, 10 mol % of catalyst, 0 °C. [d] Conditions: 0.25 M substrate, 4 mol % of catalyst, Na_2SO_4, 0 °C. [e] Conditions: 0.25 M substrate, 10 mol % of catalyst, Na_2SO_4, 0 °C. [f] 4 mol % of catalyst **16** added after 12 h. [g] (*R*)-Enantiomer of the product was obtained, unless specified otherwise.

(7) Tetramisole hydrochloride [CAS# 16595−80−5]: $39.50/10 g, Aldrich catalog 2005, p. 2229; Merck 13, 5480.

(8) The racemate of **16** [CAS# 78291−80−2] had been previously prepared via a different route: Amarouch, H.; Loiseau, P. R.; Bonnafous, M.; Caujolle, R.; Payard, M.; Loiseau, P. M.; Bories, C.; Gayral, P. *Farm. Ed. Sci.* **1988**, *43*, 421.

Scheme 1. Design and Synthesis of BTM



intermediate and the increased air humidity in the ice bath where these experiments were performed. To test this hypothesis, we purposely added a small amount of water to the reaction mixture at room temperature and observed a similar loss of activity.[9] Careful exclusion of external moisture and addition of sodium sulfate to the reaction mixture allowed us to prolong the catalyst's life at 0 °C and thus achieve the anticipated improvement. We were pleased to observe that the selectivity factor in the KR of **5b** exceeded 100 (Table 1, entry 9). To provide fair comparison with the previously used catalysts, we repeated the experiment with **1**, **2**, and **4** under the modified set of conditions and obtained only slight improvement of selectivity over the previously reported results. Use of the new catalyst allowed resolution of substrates **5a**−**d**, **6a**, **7a**, and **8** with enantioselectivities higher than, or at least equal to, those ever obtained for these substrates using nonenzymatic catalysts[10,11] (Table 1, entries 9 and 13−18). Substrates **6b** and **7b** combining two structural features known to lead to high enantioselectivity, the 1- and 2-naphthyl aryl moieties and the bulky *tert*-butyl alkyl groups, were both resolved with selectivity factors of about 300 (Table 1, entries 19 and 20). Interestingly, *o*-tolylmethyl carbinol **8** was acylated with much higher enantioselectivity (s = 209) than its unsubstituted phenyl analogue **5a** (s = 80) (cf. Table 1, entries 13 and 18). Qualitatively similar observations were made by Fu (s = 71 and 43)[12] and Vedejs (s = 188 and 45)[5f] with their respective catalysts, whereas our first-generation catalyst **1** produced the same selectivity (s = 26) with both of these substrates.[6a] By contrast, mesitylmethyl carbinol **9** (Table 1, entry 21) was acylated with very poor selectivity (s = 2.5), much lower than that obtained with CF_3−PIP (**1**) (s = 20).[6a] Curiously, this very substrate produced the highest selectivity ever observed (s = 390) with Vedejs' catalyst.[5f] We have also found that BTM-catalyzed KR of cinnamyl alcohols, e.g., **10** (Table 1, entry 22), produces moderate selectivities and slow reaction rates.[13]

Table 2. Variation of the Solvent[a]

entry	solvent	time (h)	% conv	s
1	CH_2Cl_2	7	45	45
2	*tert*-amyl alcohol	24	11	35
3	PhMe	24	31	32
4	THF	24	0	
5	Et_2O	24	2	

[a] Conditions: 0.25 M **5b**, 4 mol % of (*R*)-**16**, 0.75 equiv of $(EtCO)_2O$, 0.75 equiv of *i*-Pr_2NEt, solvent, Na_2SO_4, room temperature.

Variation of the reaction medium was studied next (Table 2). As in the case of CF_3−PIP (**1**),[6a] chloroform was confirmed to be the optimal solvent, whereas dichloromethane, toluene, and especially *tert*-amyl alcohol gave lower selectivities and reaction rates. Surprisingly, no appreciable reaction was observed in diethyl ether or THF. Because the geometry of BTM (**16**) was sufficiently different from that of CF_3−PIP (**1**) and Cl−PIQ (**2**), we also decided to reexamine other carboxylic anhydrides (Table 3). Although

Table 3. Variation of the Anhydride[a]

entry	anhydride	time (h)	% conv	s
1	$(MeCO)_2O$	4	51	36
2	$(EtCO)_2O$	2.75	49	72
3	$(i\text{-}PrCO)_2O$	18	42	101
4	$(PhCO)_2O$	24	7	−1.5

[a] Conditions: 0.25 M **5b**, 4 mol % of (*R*)-**16**, 0.75 equiv of anhydride, 0.75 equiv of *i*-Pr_2NEt, $CDCl_3$, Na_2SO_4, room temperature.

the use of acetic anhydride, as expected, led to reduced selectivity, the bulkier isobutyric anhydride resulted in notable improvement. This latter finding is in contrast to what we had observed with CF_3−PIP (**1**).[6a,14] Despite the markedly lower reaction rate at room temperature, compared with propionic anhydride, it proved feasible to reach similar levels of conversion at 0 °C at comparable reaction times (Table 4). Significantly increased selectivity factors were observed in the case of substrates **5a**, **5b**, **6a**, **7a**, and **8** (Table 4, entries 1−5), whereas the reactions with the sterically hindered carbinols **5d** and **6b** were too sluggish to reach respectable conversions in 2 days (Table 4, entries 6 and 7). Both propionic and isobutyric anhydrides can be recommended for practical use: whereas the former is more general and

(9) See Supporting Information.

(10) The highest selectivities previously reported for these substrates are: **5a**, s = 80 (ref 11); **5b**, s = 41 (ref 5g); **5c**, s = 99, corrected value s = 117 (ref 5f); **5d**, s = 117 (ref 5g); **6a**, s = 99, corrected value s = 116 (ref 5f); **7a**, s = 74 (ref 5g); **8**, s = 188 (ref 5f). It should be noted that high selectivity factors are difficult to determine precisely, and therefore, these values should be treated as approximate.

(11) Kano, T.; Sasaki, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 1347.

(12) Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794.

(13) Preliminary experiments suggest that rapid catalyst deactivation is responsible for the observed results. A more detailed study is currently underway.

(14) Selectivity factor s = 11 at 44% conversion was obtained with substrate **5b** using isobutyric anhydride in the presence of 2 mol % of CF_3−PIP (**1**), whereas propionic anhydride under identical conditions gave s = 36 at 42% conversion.

Table 4. Use of Isobutyric Anhydride[a]

entry	substrate	time (h)	% conv	*s*
1	**5a**	33	46	104
2	**5b**	36	45	145
3	**6a**	8.75	49	184
4	**7a**	10.5	46	226
5	**8**	33	48	355
6[b]	**5d**	48	31	192
7[b]	**6b**	48	33	207

[a] Conditions: 0.25 M substrate, 4 mol % of (*R*)-**16**, 0.75 equiv of (*i*-PrCO)$_2$O, 0.75 equiv of *i*-Pr$_2$NEt, $CHCl_3$, Na_2SO_4, 0 °C. [b] 4 mol % of catalyst added after 12 h.

works somewhat faster, the latter often leads to higher enantioselectivities. It should also be noted that, although most KR experiments in the present study have been carried out at 0 °C, selectivities obtained at room temperature would be sufficient for many applications.

In conclusion, we have developed an easily accessible and remarkably enantioselective acyl transfer catalyst. KR of secondary benzylic alcohols catalyzed by BTM (**16**) has been achieved with selectivity factors in the 100−350 range in all but one of the cases examined. Comparison of tetramisole (**4**) and BTM (**16**) suggests that an extended π-system in the structure of the catalyst is not necessary, but certainly beneficial, for the chiral recognition of this class of substrates. Exploration of new applications of BTM is in progress in our laboratory.[15]

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. Manuscript in preparation.