ORGANIC LETTERS

2008
Vol. 10, No. 6
1115−1118

Homobenzotetramisole: An Effective Catalyst for Kinetic Resolution of Aryl-Cycloalkanols

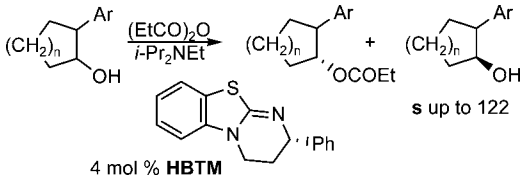
Vladimir B. Birman* and Ximin Li

Department of Chemistry, Washington University, Campus Box 1134, One Brookings Drive, St. Louis, Missouri 63130

birman@wustl.edu

Received December 28, 2007

ABSTRACT



Homobenzotetramisole (HBTM), a ring-expanded analogue of the previously reported catalyst BTM, displays higher catalytic activity and a different structure-selectivity profile. It displays good enantioselectivities in kinetic resolution of secondary benzylic alcohols but is particularly effective for 2-aryl-substituted cycloalkanols.

Over the past several years, we have developed a new class of enantioselective acyl transfer catalysts **1**−**4** represented in Figure 1.[1] These compounds have proved to be effective in kinetic resolution (KR)[2,3] of secondary benzylic, allylic and propargylic alcohols, and 4-aryl-substituted oxazolidinones (**5**−**8**) (Figure 2). Throughout our structure optimization studies, we have kept constant one structural feature:

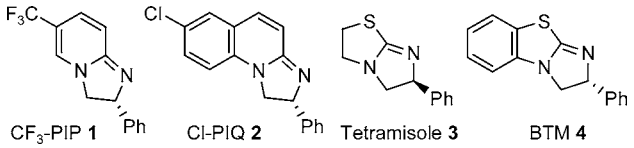


Figure 1. Previously developed catalysts.

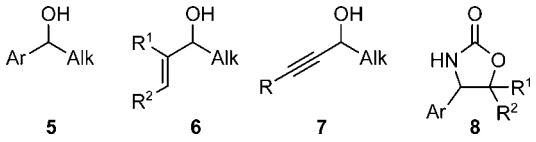


Figure 2. Previously resolved classes of substrates.

the chiral imidazoline moiety (**9**) (Figure 3). Likewise, all of the substrates investigated so far have shared the same general pattern—a π-system located α- to a nucleophilic atom (**10**)—and displayed the same absolute sense of enantioselection in kinetic resolutions. These observations lend support to our supposition that their chiral recognition occurs via a common mechanism involving $\pi-\pi$ and/or cation$-\pi$ interactions, as illustrated by structure **11**.

Having achieved good to excellent selectivities in the aforementioned cases, we became interested in exploring further structural variations of our catalysts, as well as

(1) (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.; Jiang, H. *Org. Lett.* **2005**, *7*, 3445. (c) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351. (d) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536. (e) Birman, V. B.; Guo, L. *Org. Lett.* **2006**, *8*, 4859.

(2) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

(3) For review of nonenzymatic kinetic resolution of alcohols and alternative catalyst designs, see: Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974.

10.1021/ol703119n CCC: $40.75
Published on Web 02/16/2008

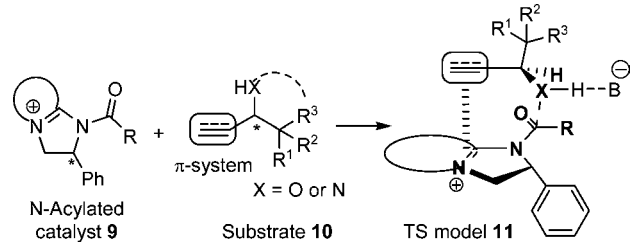


Figure 3. Proposed general mode of chiral recognition.

identifying new types of substrates. In this communication, we report the synthesis of a new type of enantioselective acyl transfer catalyst and its use in kinetic resolution of cyclic alcohols.

We have recently examined a new class of achiral acylation catalysts, **12**−**14**, containing a tetrahydropyrimidine, rather than imidazoline, moiety[4] (Figure 4). The highly

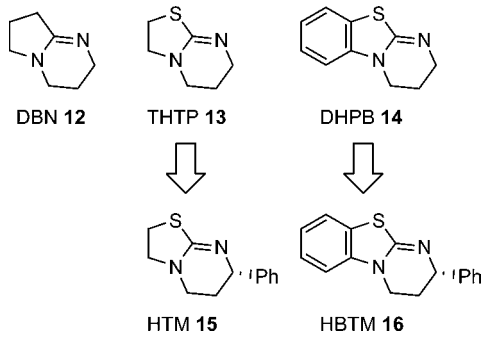
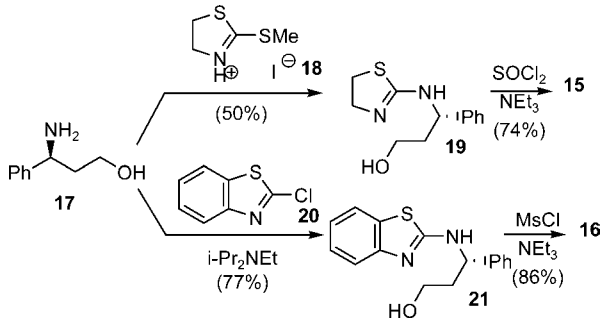


Figure 4. Design of HTM and HBTM.

active catalyst **13** developed by our group and **14** discovered at the same time by Okamoto and Kobayashi[5] appeared to be especially suitable as leads for designing their chiral analogues. We were especially interested in examining their 2-phenyl-substituted derivatives, **15** and **16** (Scheme 1), which might be viewed as ring-expanded versions of catalysts **3** and **4**. Accordingly, the new structures were dubbed HTM (for HomoTetraMisole) and HBTM (for HomoBenzoTetraMisole), respectively.

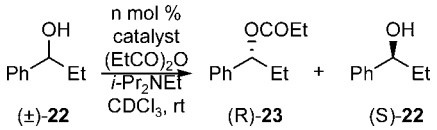
Chiral γ-aminoalcohol **17** was prepared in enantiopure form according to a literature procedure.[6] Its condensation with **18** afforded a moderate yield of aminothiazoline derivative **19**,[7] which was cyclized with thionyl chloride to produce HTM **15**. Preparation of HBTM **16** was accomplished using the protocol previously developed for BTM **4**.[1c]

Scheme 1. Preparation of **15** and **16**



The efficacy of the new catalysts was first examined in KR of (±)-1-phenylpropanol **22**, employed as the test substrate in our previous studies (Table 1). As anticipated,

Table 1. KR of 1-phenylpropanol[a]



entry	catalyst (mol %)	time, h	% convn	*s*
1	**3** (10)	3	31	28
2[b]	**4** (4)	2.2	49	72
3	**15** (1)	1.7	47	30
4	**16** (1)	1.5	48	26

[a] Conditions: 0.25 M **23**, 0.75 equiv of $(EtCO)_2O$, 0.75 equiv of *i*-Pr_2NEt, $CDCl_3$, Na_2SO_4, rt. [b] Data from previous work.[1c]

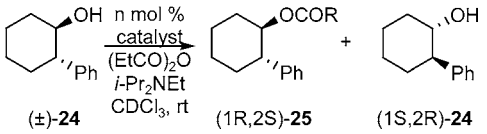
15 and **16** proved to be substantially more catalytically active than **3** and **4** (entries 3 and 4 vs 1 and 2). Surprisingly, HTM **15** displayed essentially the same catalytic activity as HBTM **16**, despite the fact that in the achiral series, THTP **13** was several times less active than its benzannulated analogue DHPB **14**.[4] The enantioselectivity of both **15** and **16**, however, was only moderate, especially by comparison with BTM **4**. We turned our attention to enantioselective acylation of other classes of chiral alcohols. Keeping in mind that π-interactions with aromatic rings were beneficial for chiral recognition of the previously investigated classes of substrates, we decided to examine kinetic resolution of *trans*-phenylcyclohexanol **24**, in which the phenyl group is two carbon atoms away from the hydroxyl (Table 2).[8,9]

Tetramisole **3** produced only modest enantioselectivity and apparently underwent deactivation, so that low conversion

(4) Birman, V. B.; Li, X.; Han, Z. *Org. Lett.* **2007**, *9*, 37.
(5) Kobayashi, M.; Okamoto, S. *Tetrahedron Lett.* **2006**, *47*, 4347.
(6) Liu, S.; Müller, J. F. K.; Neuburger, M.; Schaffner, S.; Zehnder, M. *Helv. Chim. Acta.* **2000**, *83*, 1256.
(7) McKay, A. F.; Whittingham, D. J.; Kreling, M.-E. *J. Am. Chem. Soc.* **1958**, *80*, 3339.

(8) For enzymatic kinetic resolution of **24** and its utility as a chiral auxiliary, see: Whitesell, J. K.; Chen, H.-H.; Lawrence, R. M. *J. Org. Chem.* **1985**, *50*, 4663.
(9) Efficient nonenzymatic kinetic resolution of **24** has been previously reported by: (a) Oriyama, T.; Hori, Y.; Imai, K.; Sasaki, R. *Tetrahedron Lett.* **1996**, *37*, 8543 ($s = 200$). (b) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496 ($s > 50$). (c) Jeong, K.-S.; Kim, S.-H.; Park, H.-J.; Chang, K.-J.; Kim, K. S. *Chem. Lett.* **2002**, 1114 ($s = 21$).

Table 2. KR of (±)-*trans*-2-Phenylcyclohexanol **25**[a]



entry	catalyst (mol %)	anhydride	time, h	% convn	*s*
1	**3** (20)	$(EtCO)_2O$	3	19	5.5
2	**4** (8)	$(EtCO)_2O$	6	48	25
3	**2** (8)	$(EtCO)_2O$	12	45	11
4	**15** (2)	$(EtCO)_2O$	1.8	43	14
5	**16** (2)	$(EtCO)_2O$	1.4	47	29
6	**16** (2)	$(MeCO)_2O$	0.5	59	19
7	**16** (2)	$(i\text{-}PrCO)_2O$	48	39	26

[a] Conditions: 0.25 M substrate, 0.75 equiv of $(EtCO)_2O$, 0.75 equiv of *i*-Pr_2NEt, $CDCl_3$, rt.

was obtained even at a 20 mol % catalyst loading (entry 1). BTM **4** produced a synthetically useful selectivity factor with this substrate; however, the reaction was quite slow, necessitating a high catalyst loading (entry 2). Cl-PIQ **2**, our most active catalyst for asymmetric acylation of benzylic alcohols, turned out to be rather slow in the case of substrate **24** and displayed only moderate levels of enantioselectivity (entry 3). In contrast, acylations of **24** catalyzed by both HTM **15** and HBTM **16** proceeded rapidly at 2 mol % loadings (entries 4 and 5). In addition, HBTM produced the highest selectivity factor and thus was selected for further optimization. We tested the suitability of acetic and isobutyric anhydrides as achiral acyl donors (entries 5 and 6), only to confirm that propionic anhydride was indeed the best. Variation of the reaction temperature was examined next (Table 3, entries

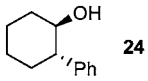
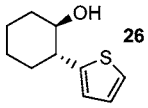
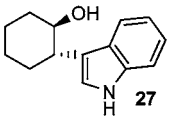
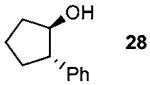
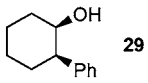
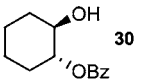
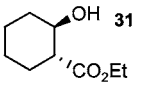
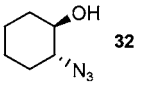
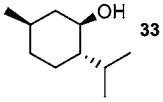
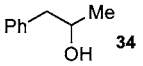
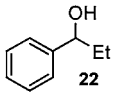
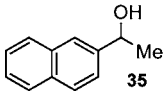
Table 3. Optimization of Reaction Conditions[a]

entry	mol % of **16**	solvent	temp, °C	time, h	% convn	*s*
1	2	$CDCl_3$	23	1.4	47	29
2	2	$CDCl_3$	0	2.3	52	43
3	2	$CDCl_3$	−20	3	53	53
4	4	$CDCl_3$	−40	4	53	86
5	4	$CDCl_3$	−55	4	46	122
6	2	MeCN	23	2.5	48	15
7	2	CH_2Cl_2	23	1.8	47	23
8	2	THF	23	1.8	50	25
9	2	PhMe	23	1	54	30
10	2	TA	23	0.7	56	41
11	2	TA	−10	1.7	54	72
12	4	TA-PhMe	−40	3	46	101

[a] Conditions: 0.25 M substrate, 0.75 equiv of $(EtCO)_2O$, 0.75 equiv of *i*-Pr_2NEt.

1−5). We were pleased to find that, in contrast to BTM, which was rarely effective below 0 °C, HBTM produced convenient reaction rates at temperatures as low as −55 °C, which allowed us to obtain a 4-fold increase in the enantioselectivity (entries 5 vs 1). Interestingly, the decrease in the

Table 4. Kinetic Resolutions with HBTM **16**

entry	(±)-substrate[a]	KR at room temperature[b]	KR at low temperature
1	 **24**	**s = 29** (47%/1.4 h)	**s = 107**[c] (51%/10 h)
2	 **26**	**s = 16** (42%/1.7 h)	**s = 44**[c] (44%/10 h)
3	 **27**	**s = 49** (41%/26 h)[e]	ND[f]
4	 **28**	**s = 28** (58%/1.2 h)	**s = 66**[c] (51%/7 h)
5	 **29**	**s = 15** (37%/24 h)	**s = 28**[c] (46%/12 h)
6	 **30**	**s = 4.7** (50%/1.8 h)	**s = 5.6**[c] (28%/10 h)
7	 **31**	**s =5.6** (39%/12 h)	**s = 10**[d] (55%/12 h)
8	 **32**	**s = 7.8** (48%/1.3 h)	**s = 10**[c] (26%/10 h)
9	 **33**	**s = 2.3** (40%/22 h)	**s = 3.2**[d] (33%/10 h)
10	 **34**	**s = 5.6** (47%/1.3 h)	**s = 7.9**[c] (34%/10 h)
11	 **22**	**s = 26**[g] (47%/1 h)	**s = 55**[c] (39%/10 h)
12	 **35**	**s = 25**[g] (48%/0.4 h)	**s = 49**[c] (37%/5 h)

[a] Absolute configuration of the fast-reacting enantiomer is shown [b] Conditions: 0.25 M substrate, 0.75 equiv of $(EtCO)_2O$, 0.75 equiv of *i*-Pr_2NEt, 2 mol % HBTM, Na_2SO_4, $CDCl_3$, room temp [c] Conditions: 0.25 M substrate, 0.55 equiv of $(EtCO)_2O$, 0.55 equiv of *i*-Pr_2NEt, 4 mol % HBTM, Na_2SO_4, 1:1 tert-amyl alcohol/toluene, −40 °C [d] Conditions: 0.25 M substrate, 0.75 equiv of $(EtCO)_2O$, 0.75 equiv of *i*-Pr_2NEt, 4 mol % HBTM, Na_2SO_4, tert-amyl alcohol, −10 °C [e] Only 0.1 M of the substrate was used due to its poor solubility [f] Not Determined due to the poor solubility of the substrate [g] Two molar percent of the catalyst was used.

reaction rate was not as significant as we had anticipated. Similar observations were previously made by Vedejs et al.[10]

Screening various solvents (entries 6−10) revealed that, unlike all our previous catalysts, which were usually successful only in chloroform, HBTM was more tolerant of the reaction medium. In fact, tert-amyl alcohol (TA) proved to be clearly superior to chloroform at room temperature.[11]

Because of its high freezing point (−12 °C), however, it could not be used at temperatures below −10 °C. Therefore, a 1:1 mixture of toluene and tert-amyl alcohol, which could be cooled without freezing to −40 °C (acetonitrile−dry ice bath), was selected as a compromise.

Kinetic resolution of several structurally different substrates was studied next at room temperature in deuterated chloroform. On the basis of the enantioselectivities and reaction rates observed during this initial screening, we subsequently repeated some of these reactions at lower temperatures in tert-amyl alcohol or its mixture with toluene and obtained improved selectivity factors. Cyclohexanols bearing a *trans*-aryl or -heteroaryl group at C2 displayed good to excellent levels of enantioselectivity in HBTM-catalyzed acylations (Table 4, entries 1−3). The analogous *trans*-phenylcyclopentanol was also resolved with high selectivity (entry 4). Cis-isomer of phenylcyclohexanol **29** reacted rather slowly, but also reached a respectable selectivity factor of 28 (entry 5). On the other hand, cyclohexanols containing nonaromatic substituents produced only moderate selectivity factors (entries 6−9). In particular, menthol **33** reacted slowly and with very low selectivity (entry 9). These results suggested that the presence of a π-system is necessary for effective chiral recognition. The rigidity of the substrate molecule also appears to be important, as suggested by the modest selectivity factor achieved in KR of acyclic alcohol **34**, a conformationally flexible analogue of *trans*- and *cis*-phenylcyclohexanols (entry 10).[12] As expected, conducting KR of benzylic alcohols **22** and **35** at low temperatures produced high selectivities (entries 11 and 12), although these results were still below those achieved with BTM in our earlier work.[1c]

In conclusion, we have demonstrated that 2-aryl-cycloalkanols can be efficiently resolved using our new catalyst, HBTM. A seemingly straightforward modification in the structure of BTM—expansion of the imidazoline ring by one carbon—has led not only to an increased catalytic activity, but also to a significantly altered structure-selectivity profile. HBTM affords useful levels of selectivity in KR of benzylic alcohols but is particularly effective in KR of aryl-cycloalkanols, whereas BTM displays the opposite trend. Further investigation of the new type of enantioselective acylation catalysts and their applications is underway.

Acknowledgment. We thank NIGMS (NIH R01 GM072682) for financial support of this work. Mass spectrometry was provided by the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant No. P41RR0954).

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

OL703119N

(10) Vedejs, E.; and Daugulis, O. *J. Am. Chem. Soc.* **2003**, *125*, 4166.

(11) For use of tert-amyl alcohol as a solvent for KR, see, e.g.: Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794.

(12) Interestingly, BTM produced higher enantioselectivity in this case, although the reaction was quite slow ($s = 9.9$ at 15% conversion after 8 h at rt; 8 mol % catalyst loading).