DOI: 10.1002/adsc.200900383

Effects of Methyl Substituents on the Activity and Enantioselectivity of Homobenzotetramisole-Based Catalysts in the Kinetic Resolution of Alcohols

Yuhua Zhang[a] and Vladimir B. Birman[a,*]

[a] Department of Chemistry, Washington University, Campus Box 1134, One Brookings Drive, St. Louis, Missouri 63130, USA
Fax: (+1)-314-935-4481; phone: (+1)-314-935-9188; e-mail: birman@wustl.edu

Received: June 2, 2009; Revised: July 27, 2009; Published online: October 1, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900383.

Abstract: Substitution of the tetrahydropyrimidine ring in the enantioselective acyl transfer catalyst homobenzotetramisole (HBTM) **6** with methyl groups exerts a dramatic influence on its performance in the kinetic resolution of secondary alcohols. The *syn*-3-methyl analogue of HBTM (**9a**) has proved to be superior to the parent compound in terms of catalytic activity, enantioselectivity, and synthetic accessibility.

Keywords: acylation; catalyst design; kinetic resolution; organocatalysis

Enantioselective acyl transfer catalysis has been successfully applied to a variety of synthetically useful asymmetric processes.[1] Therefore, there is a continued need to develop new catalysts that will be highly active, enantioselective, general, and, last but not least, easily obtainable. Our efforts in this area initially resulted in a series of imidazoline-based catalysts **1**–**4** illustrated in Figure 1. We demonstrated their utility in the kinetic resolution (KR)[2] of several classes of secondary alcohols[3] and 2-oxazolidinones[4] bearing a π-system α- to the nucleophilic atom. Several applications of catalysts **3** and **4** have been recently reported by other groups.[5]

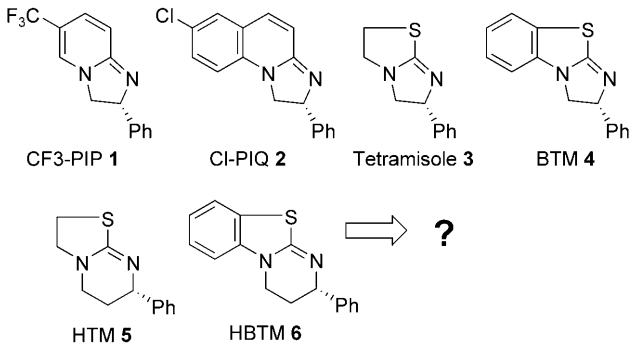
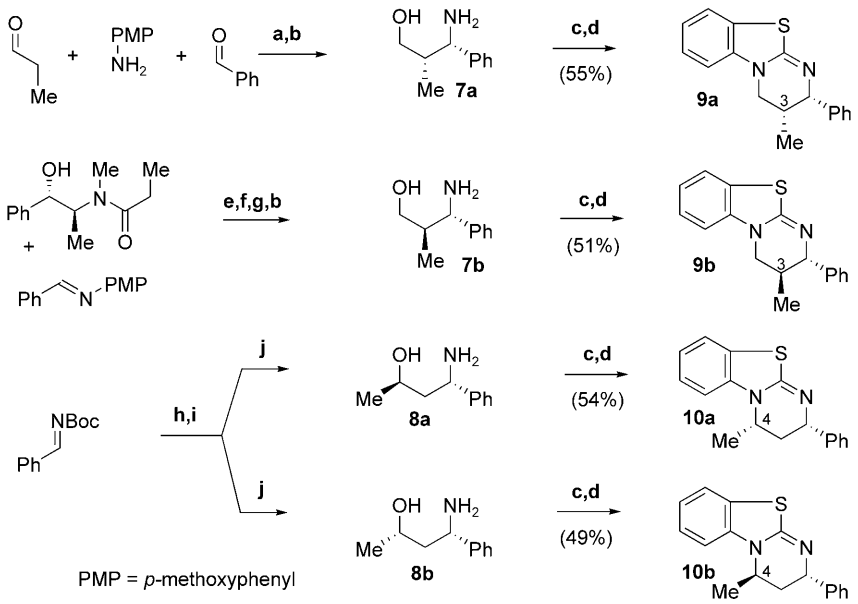


Figure 1. Amidine-based catalysts.

More recently, we investigated their tetrahydropyrimidine analogues, homotetramisole (HTM) **5** and homobenzotetramisole (HBTM) **6**.[6] HBTM proved to be effective in the KR of both α- and β-aryl-substituted alcohols[6a] and of α-substituted carboxylic acids.[6b] It was also considerably more active and more tolerant of reaction conditions than the previously developed imidazoline-based catalysts. Furthermore, compared to the latter, the structure of HBTM provides more opportunities for introducing additional substituents in the non-aromatic ring, which could alter its conformation and/or provide additional interactions with the substrate molecules, thus potentially enhancing its catalytic activity and enantioselectivity. With this in mind, we decided to synthesize methyl-substituted HBTM analogues **9a**, **9b**, **10a** and **10b** and evaluate their performance in acylation reactions. Thanks to recent advances in the stereo- and enantioselective Mannich reactions, the four requisite 1,3-amino alcohols are easily available in enantiopure form (Scheme 1), thus obviating the need for the classical resolution employed in the original synthesis of **6**.[6a]

Chiral 1,3-amino alcohol **7a** was prepared *via* the *syn*-selective proline-catalyzed asymmetric Mannich reaction according to the protocol described by Hayashi et al.[7] followed by removal of the *p*-methoxyphenyl group by periodate oxidation[8] (Scheme 1). Its diastereomer **7b** was synthesized from *N*-propionyl-*(S,S)*-pseudoephedrine *via* the highly *anti*-selective Mannich reaction disclosed by Badia et al.[9] Preparation of the diastereomeric amino alcohols **8a** and **8b** relied on the asymmetric Mannich reaction procedure



Scheme 1. Preparation of HBTM analogues. *Conditions:* (a) L-proline, DMF, −20 °C; then $NaBH_4$;[7] (b) HIO_4, H_2SO_4, MeCN-H_2O;[8] (c) 2-chlorobenzothiazole, $(i\text{-Pr})_2NEt$; (d) MsCl, NEt_3, CH_2Cl_2; (e) LDA; $ZnCl_2$;[9] (f) H_2SO_4, MeOH;[9] (g) LiCl, $NaBH_4$, THF, EtOH, 0 °C (96%); (h) L-proline, acetone;[10] (i) $NaBH_4$, MeOH, 0 °C (61% *anti*-, 38% *syn*-); (j) CF_3CO_2H, CH_2Cl_2 (quant.).

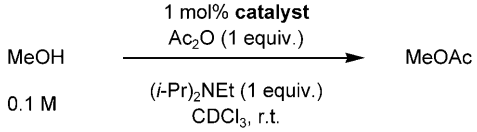
reported by List et al.[10] Reaction of amino alcohols **7a**, **7b**, **8a** and **8b** with 2-chlorobenzothiazole followed by cyclization delivered **9a**, **9b**, **10a**, and **10b**, respectively. With sufficient quantities of the four methyl-substituted HBTM analogues in hand, we undertook their systematic comparison with the parent catalyst (**6**). The first test reaction – acylation of methanol with acetic anhydride – revealed the significant influence of the substitution pattern on the catalytic activity (Table 1). Catalyst **9a** demonstrated the best performance, whereas **9b** and **10a** were somewhat less active than HBTM. In sharp contrast, **10b** proved to be far less active than the rest.

Even more remarkable differences were observed in the KR of secondary alcohols (±)-1-phenylpropanol **11** (Table 2) and (±)-*trans*-2-phenylcyclohexanol **12** (Table 3). Again, **9a** emerged as the most active of the five catalysts in both reactions. It was somewhat inferior in terms of selectivity to HBTM in the first test, but surpassed it in the second. Catalyst **10a**, albeit less active than HBTM, produced the highest selectivity factors in the acylation of both alcohols. On the other hand, catalysts **9b** and **10b** displayed drastically reduced activities in both tests, requiring 10-fold higher catalyst loadings to achieve acceptable reaction rates.

Catalyst **9b** produced dismal selectivities in the KR of both **11** and **12**, whereas **10b** was only effective in the case of the former substrate.

Taking into account its synthetic accessibility, catalyst **9a** (dubbed HBTM-2) was deemed to be the most

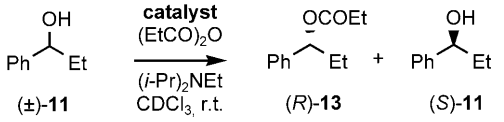
Table 1. Methanol test.



Entry	Catalyst	$t_{1/2}$[a]
1	HBTM **6**	6 min
2	*syn*-3-Me-HBTM **9a**	4.5 min
3	*anti*-3-Me-HBTM **9b**	13 min
4	*syn*-4-Me-HBTM **10a**	12 min
5	*anti*-4-Me-HBTM **10b**	7.5 h

[a] Time required to achieve 50% conversion was determined by monitoring the reactions by ^1H NMR.

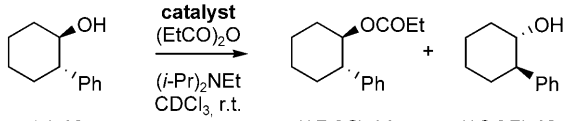
Table 2. KR of (±)-1-phenylpropanol **11**.[a]



Entry	Catalyst (mol%)	Time [h]	Conversion [%]	S
1	**6** (1)	1.5	48	26
2	**9a** (1)	0.90	50	22
3	**9b** (10)	4.0	49	4.4
4	**10a** (1)	4.1	49	40
5	**10b** (10)	24	48	29

[a] *Conditions:* 0.25 M **11**, 0.75 equiv. $(EtCO)_2O$, 0.75 equiv. $(i\text{-Pr})_2NEt$, $CDCl_3$, room temperature.

Table 3. KR of (±)-*trans*-2-phenylcyclohexanol **12**.[a]



(±)-**12** (1*R*,2*S*)-**14** (1*S*,2*R*)-**12**

Entry	Catalyst (mol%)	Time [h]	Conversion [%]	S
1	**6** (1)	3.0	49	31
2	**9a** (1)	1.0	49	38
3	**9b** (10)	13	54	1.2
4	**10a** (1)	7.0	47	44
5	**10b** (10)	40	19	2.9

[a] *Conditions:* 0.25 M **12**, 0.75 equiv. $(EtCO)_2O$, 0.75 equiv. $(i\text{-Pr})_2NEt$, $CDCl_3$, room temperature.

practical and thus was selected for further study. Investigation of solvent and temperature effects on the KR of **12** with HBTM-2 (Table 4) revealed qualitatively similar trends to those displayed by HBTM,[6a] except that the former performed equally well in pure toluene and in the toluene-*tert*-amyl alcohol mixture at −40 °C, which led to a more convenient experimental protocol (entries 9 and 13). It is also noteworthy that HBTM-2 typically produced higher selectivity factors in shorter times than HBTM *at half the catalyst loadings of the latter* (e.g., entries 9 *vs.* 14, 13 *vs.* 15.)

The substrate scope of **9a** was evaluated using 1% catalyst loadings in toluene at −40 °C (Table 5). The best results previously obtained with amidine-based catalysts **2**, **4** and **6** are listed in the right column for comparison. Several cyclohexanol derivatives with a π-system β to the hydroxy were resolved with equal or higher enantioselectivities than those previously achieved with HBTM (entries 1–5). In the case of the structurally similar, but fully saturated substrate menthol, HBTM-2 was found to be completely ineffective (entry 6). Useful levels of selectivity were also obtained with representative benzylic (**11**), propargylic (**20**) and cinnamyl (**21**) alcohols, although they fell short of those previously obtained with benzotetramisole (BTM) **4** and 7-chloro-2-phenyl-2,3-dihydroimidazo[1,2-*a*]quinoline (Cl-PIQ) **2** (entries 7–9). However, HBTM-2 proved to be clearly superior in the KR of benzylic amino alcohol **22**, which undergoes rapid background acylation and thus cannot be resolved efficiently with the less reactive BTM.[11] It is noteworthy that the acylation of **21** catalyzed by **9a** was quite rapid, whereas the structurally similar BTM was inhibited by this substrate.[3c]

Table 4. Optimization of reaction conditions for **9a**[a]

Entry	Catalyst (mol%)	Solvent, *t* [°C]	Time [h]	Conversion [%]	S
1	**9a** (1)	$CDCl_3$, 23	1.4	49	38
2	**9a** (1)	$CDCl_3$, 0	1.5	51	49
3	**9a** (2)	$CDCl_3$, −20	1.7	54	66
4	**9a** (2)	$CDCl_3$, −40	2.0	53	75
5	**9a** (1)	MeCN, 23	1.5	51	20
6	**9a** (1)	CH_2Cl_2, 23	1.1	48	30
7	**9a** (1)	THF, 23	1.0	51	33
8	**9a** (1)	PhMe, 23	0.67	54	44
9	**9a** (2)	PhMe, −40	2.3	52	131
10	**9a** (2)	PhMe, −63	4.0	25	127
11	**9a** (1)	TA, 23	0.35	54	53
12	**9a** (2)	TA, −8	0.42	47	87
13	**9a** (2)	TAT, −40	2.3	50	132
14	**6** (4)	PhMe, −40	2.5	45	67
15[b]	**6** (4)	TAT, −40	3.0	46	101

[a] *Conditions:* 0.25 M **12**, 0.75 equiv. $(EtCO)_2O$, 0.75 equiv. $(i\text{-Pr})_2NEt$.

[b] Data from Ref.[6]; TA = *tert*-amyl alcohol; TAT = *tert*-amyl alcohol/toluene 1:1 mixture.

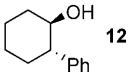
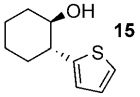
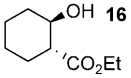
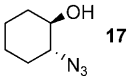
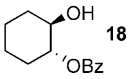
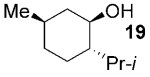
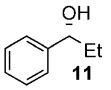
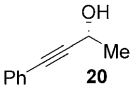
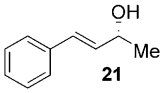
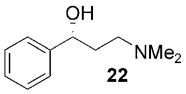
In conclusion, we have developed HBTM-2, a highly active and versatile enantioselective acylation catalyst obtainable from inexpensive starting materials in four steps. The asymmetric route used to prepare it can be easily adapted for the synthesis of variously substituted HBTM analogues. We have also demonstrated that the substitution pattern of HBTM analogues exerts a profound influence on their catalytic activity and enantioselectivity. Theoretical studies linking these effects with the conformational and steric changes induced by the methyl substituents are ongoing and will be reported in due course.

Experimental Section

A: (2*S*,3*S*)-3-[(2-Benzothiazolyl)amino]-2-methyl-3-phenylpropanol-1 (23a)

Amino alcohol **7a** was prepared in enantio- and diastereomerically pure form (>99% *ee* and *de* by HPLC) *via* a combination of two literature procedures[7,8] and repeated recrystallization of the *N*-PMP derivative from ethyl acetate. A 25-mL pressure tube charged with 2-chlorobenzothiazole (0.378 g, 2.2 mmol), **7a** (0.348 g, 2.0 mmol), $(i\text{-Pr})_2NEt$ (0.70 mL, 4.0 mmol) and a stir bar was flushed with N_2 several times, stoppered and heated at 135 ± 5 °C for 24 h. After cooling the tube to 30–40 °C, the viscous reaction mixture was treated with 2 mL of CH_2Cl_2 and left at room temperature to dissolve. The diluted mixture was applied directly to a chromatographic column and eluted with EtOAc/hexanes/ (1:2) to afford the title compound as a white solid; yield: 0.459 g (77%). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.52–7.22$ (m, 8H), 7.07–7.02 (m, 1H), 5.58 (br, 1H), 5.08–4.98 (m, 1H), 3.70–3.52 (m, 2H), 2.58–2.40 (m, 1H), 0.82 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168.3$, 151.6, 139.3, 130.3, 128.7, 127.7, 126.2, 121.8, 121.1, 118.8, 64.5, 62.1, 40.6, 12.5; IR (film): $\nu = 3270$, 1599, 1538, 1446 cm^{-1}; HR-ESI-MS: $m/z = 299.1212$, calcd. for $C_{17}H_{19}N_2S^+$ ($M+H^+$): 299.1213; $[\alpha]_D^{20}$: −116.0° (*c* 0.1, MeOH); mp 149–150 °C.

Table 5. Substrate scope of HBTM-2 **9a**.

Entry	(±)-Substrate[a]	Result with HBTM-2 **9a**[b]	Best previous result
1	 **12**	S = 112 (52%/11 h)	HBTM,[6] S = 107 (51%/10 h)
2	 **15**	S = 66 (51%/11 h)	HBTM,[6] S = 44 (44%/10 h)
3	 **16**	S = 16 (40%/11 h)	HBTM,[6] S = 10 (55%/12 h)
4	 **17**	S = 10 (52%/11 h)	HBTM,[6] S = 10 (26%/10 h)
5	 **18**	S = 5.7 (43%/11 h)	HBTM,[6] S = 5.6 (28%/10 h)
6	 **19**	S = 1.2 (55%/11 h)	HBTM,[6] S = 3.2 (33%/10 h)
7	 **11**	S = 54 (49%/11 h)	BTM,[3c] S = 145 (45%/36 h)
8	 **20**	S = 21 (53%/11 h)	BTM,[3d] S = 31 (59%/11 h)
9	 **21**	S = 23 (54%/11 h)	Cl-PIQ,[3b] S = 27 (44%/8 h)
10	 **22**	S = 19 (48%/11 h)	BTM,[11] S = 8.2 (44%/5.5 h)

[a] Absolute configuration of the fast-reacting enantiomer is shown.
[b] *Conditions:* 0.25 M substrate, 0.55 equiv. $(EtCO)_2O$, 0.55 equiv. $(i\text{-}Pr)_2NEt$, 2 mol% HBTM-2, PhMe, −40 °C.

B: (2*S*,3*R*)-3,4-Dihydro-3-methyl-2-phenyl-2*H*-pyrimido-[2,1-*b*]benzothiazole (9a)

A solution of **23a** (0.459 g, 1.54 mmol) in anhydrous CH_2Cl_2 (40 mL) was cooled to 0 °C under N_2 and treated with NEt_3 (0.66 mL, 4.7 mmol) followed by MsCl (0.24 mL, 3.1 mmol). The mixture was stirred at 0 °C for 1 h and then warmed to room temperature. Methanol (0.2 mL) was added to quench the excess MsCl. NEt_3 (1.5 mL) was added and the mixture was refluxed for 5 h. After cooling, the mixture was washed with a small amount of water, dried over $MgSO_4$ and rotary evaporated. The crude product was purified by chromatography (5% isopropyl alcohol, 1% NEt_3 in hexanes) to give **9a** as light yellow solid; yield: 0.311 g (72%). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.15 (m, 7H), 7.01–6.95 (m, 1H), 6.73 (d, J = 7.8 Hz, 1H), 4.71 (d, J = 4.2 Hz, 1H), 3.79 (dd, J = 11.1, 5.1 Hz, 1H), 3.33 (dd, J = 11.1, 7.5 Hz, 1H), 2.44–2.32 (m, 1H), 0.78 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.8, 141.3, 141.0, 128.3, 128.0, 127.1, 126.1, 123.0, 122.1, 122.0, 107.7, 63.1, 46.6, 29.5, 14.1; IR (film): ν = 1619, 1580, 1477, 1462 cm^{-1}; HR-ESI-MS: m/z = 281.1105, calcd. for $C_{17}H_{17}N_2S^+$ ($M+H^+$): 281.1107; $[\alpha]_D^{20}$: +212.0° (c 0.1, MeOH); mp 88–89 °C.

C: Kinetic Resolution using HBTM-2 (9a); General Procedure

A stock solution was prepared by dissolving catalyst **9a** (3 mg, 0.01 mmol) and $(i\text{-}Pr)_2NEt$ (95 μL, 0.55 mmol) in PhMe in a 2.0-mL volumetric test tube and bringing the volume to the mark. Each KR experiment was performed in duplicate. A one-dram vial was charged with 0.25 mmol of a substrate, 100 mg of Na_2SO_4, 0.50 mL of PhMe and 0.50 mL of the stock catalyst solution and stirred at −40 °C for 15 min followed by addition of propionic anhydride (18 μL, 0.14 mmol). After 11 h, the reaction mixture was quenched by addition of methanol, worked up and analyzed as described previously.[3,6a] The results are presented in Table 5 above.

Acknowledgements

This study was supported in part by NIGMS (NIH R01 GM072682). Mass spectrometry was provided by the Wash-

ington University Mass Spectrometry Resource, an NIH Research Resource (Grant No. P41RR0954).

References

[1] For a recent review, see: S. E. Denmark, G. L. Beutner *Angew. Chem.* **2008**, *120*, 1584; *Angew. Chem. Int. Ed.* **2008**, *47*, 1560.

[2] For principles of kinetic resolution, see: a) H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249. For a review of non-enzymatic kinetic resolution, see: b) E. Vedejs, M. Jure, *Angew. Chem.* **2005**, *117*, 4040; *Angew. Chem. Int. Ed.* **2005**, *44*, 3974 and Ref.[1] For leading references to selected contributions by other groups, see: c) E. Vedejs, O. Daugulis, *J. Am. Chem. Soc.* **2003**, *125*, 4166; d) G. C. Fu, *Acc. Chem. Res.* **2004**, *37*, 542; e) S. J. Miller, *Acc. Chem. Res.* **2004**, *37*, 601; f) T. Kano, K. Sasaki, K. Maruoka, *Org. Lett.* **2005**, *7*, 1347; g) D. Terakado, H, Koutaka, T. Oriyama, *Tetrahedron: Asymmetry* **2005**, *16*, 1157; h) Y. Kosugi, M. Akakura, K. Ishihara, *Tetrahedron* **2007**, *63*, 6191.

[3] a) V. B. Birman, E. W. Uffman, H. Jiang, X. Li, C. J. Kilbane, *J. Am. Chem. Soc.* **2004**, *126*, 12226; b) V. B. Birman, H. Jiang, *Org. Lett.* **2005**, *7*, 3445; c) V. B. Birman, X. Li, *Org. Lett.* **2006**, *8*, 1351; d) V. B. Birman, L. Guo, *Org. Lett.* **2006**, *8*, 4859.

[4] V. B. Birman, H. Jiang, X. Li, L. Guo, E. W. Uffman, *J. Am. Chem. Soc.* **2006**, *128*, 6536.

[5] See, e.g.: a) F. R. Dietz, H. Gröger, *Synlett* **2008**, 663; b) I. Shiina, K. Nakata, Y. S. Onda, *Eur. J. Org. Chem.* **2008**, *35*, 5887; c) V. C. Purohit, A. S. Matla, D. Romo, *J. Am. Chem. Soc.* **2008**, *130*, 10478; d) Q. Xu, H. Zhou, X. Geng, P. Chen, *Tetrahedron* **2009**, *65*, 2232.

[6] a) V. B. Birman, X. Li, *Org. Lett.* **2008**, *10*, 1115; b) X. Yang, V. B. Birman, *Adv. Synth. Catal.* **2009**, *351*, 2301.

[7] Y. Hayashi, W. Tsubo, I. Ashimine, T. Urushima, M. Shoji, K. Sakai, *Angew. Chem.* **2003**, *115*, 3805; *Angew. Chem. Int. Ed.* **2003**, *42*, 3677.

[8] J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg, P. L. Alsters, F. L. van Delft, F. P. J. T. Rutjes, *Tetrahedron Lett.* **2006**, *47*, 8109.

[9] J. L. Vicario, D. Badía, L. Carrillo, *Org. Lett.* **2001**, *3*, 773.

[10] a) J. W. Yang, M. Stadler, B. List, *Angew. Chem.* **2007**, *119*, 615; *Angew. Chem. Int. Ed.* **2007**, *46*, 609; b) This variant of the asymmetric Mannich reaction is also applicable to the synthesis of HBTM **6** and HBTM-2 **9a**. See also: J. W. Yang, C. Chandler, M. Stadler, D. Kampen, B. List, *Nature* **2008**, *452*, 453.

[11] V. B. Birman, H. Jiang, X. Li, *Org. Lett.* **2007**, *9*, 3237.

