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

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Abstract

Substitution of the tetrahydropyrimidine ring in enantioselective acyl transfer catalyst homobenzotetramisole (HBTM) **6** with methyl groups exerts a dramatic influence on its performance in the kinetic resolution of secondary alcohols. *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^[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]

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 reaction, 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 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 ($\pm$)-1-phenylpropanol **11** (Table 2) and ($\pm$)-*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 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 hydroxyl 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 benzetramisole (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]

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. (2S,3S)-3-[(2-benzothiazolyl)amino]-2-methyl-3-phenyl-propanol-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*-Pr₂NEt (0.70 mL, 4.0 mmol) and a stir bar was flushed with N₂ several times, stoppered and heated at 135±5°C for 24hr. After cooling the tube to 30-40°C, the viscous reaction mixture was treated with 2 mL of CH₂Cl₂ 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 0.459 g of the title compound as a white solid (77% yield). ¹H NMR (300 MHz, CDCl₃) δ 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); ¹³C NMR (75 MHz, CDCl₃) δ 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, cm⁻¹) 3270, 1599, 1538, 1446; HRESI calculated for C₁₇H₁₉N₂S⁺ (M+H⁺) *m/z*: 299.1213, found 299.1212. [α]₂₀ = -116.0° (c=0.1, MeOH). mp 149-150°C.

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

A solution of **23a** (0.459 g, 1.54 mmol) in anhydrous CH₂Cl₂ (40 mL) was cooled to 0°C under N₂ and treated with NEt₃ (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. NEt₃ (1.5 mL) was added and the mixture was refluxed for 5 hrs. After cooling, the mixture was washed with a small amount of water, dried over MgSO₄ and rotary evaporated. The crude product was purified by chromatography (5% isopropanol, 1% NEt₃ in hexanes) to give 0.311 g of **9a** as light yellow solid (72 % yield). ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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, cm⁻¹) 1619, 1580, 1477, 1462; HRESI calculated for C₁₇H₁₇N₂S⁺ (M+H⁺) *m/z*: 281.1107, found 281.1105. [α]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*-Pr₂NEt (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 Na₂SO₄, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Amidine- based catalysts

Scheme 1.

Preparation of HBTM analogues. *Conditions:* (a) L-proline, DMF, -20 °C; then NaBH₄^[7] (b) HIO₄, H₂SO₄, MeCN-H₂O^[8] (c) 2-chlorobenzothiazole, *i*-Pr₂NEt (d) MsCl, NEt₃, CH₂Cl₂ (e) LDA; ZnCl₂, [Ref. 9] (f) H₂SO₄, MeOH;^[9] (g) LiCl, NaBH₄, THF, EtOH, 0 °C (96%) (h) L-proline, acetone [Ref. 10] (i) NaBH₄, MeOH, 0 °C (61% *anti*-, 38% *syn*-) (j) CF₃CO₂H, CH₂Cl₂ (quant)

Table 1

Methanol test.

Entry	Catalyst	$t_{1/2}$ [a]
1	HBTM 6	6 min
2	<i>syn</i> -3-Me-HBTM 9a	4.5 min
3	<i>anti</i> -3-Me-HBTM 9b	13 min
4	<i>syn</i> -4-Me-HBTM 10a	12 min
5	<i>anti</i> -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	% conv	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*-Pr₂NEt, CDCl₃, rt

Table 3

KR of ($\pm$)-*trans*-2-phenylcyclohexanol **12**.^[a]

Entry	Catalyst (mol %)	time, h	% conv	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 $(\text{EtCO})_2\text{O}$, 0.75 equiv $i\text{-Pr}_2\text{NEt}$, CDCl_3 , rt

Table 4

Optimization of reaction conditions for **9a**^[a]

Entry	Catalyst (mol%)	Solvent, t (°C)	Time h	% Conv	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 ₂ Cl 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*-Pr₂NEt.^[b] Data from Ref. 6; TA = *tert*-amyl alcohol TAT = *tert*-amyl alcohol/toluene 1:1 mixture

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*-Pr₂NEt, 2 mol% HBTM-2, PhMe, -40 °C.