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Kinetic Resolution of Propargylic Alcohols Catalyzed by Benzotetramisole

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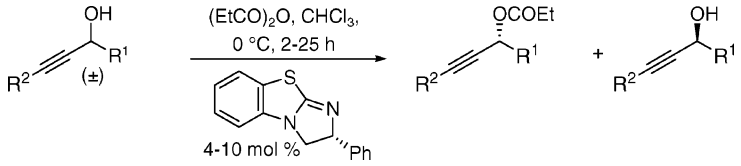
ABSTRACT



Kinetic resolution of variously substituted secondary propargylic alcohols catalyzed by benzotetramisole (BTM) proceeds with selectivity factors up to 32, the highest ever achieved with nonenzymatic catalysts for this class of substrates.

Several of the nonenzymatic asymmetric acylation catalysts developed to date[1] achieve their highest enantioselectivities in kinetic resolution (KR) of benzylic alcohols.[2a,3a,c,4,5a−c,6,7] Some of them have also been found to be suitable for KR of allylic alcohols.[2b,3b,5b,6] The only nonenzymatic catalyst that has proved competent in KR of propargylic alcohols is Fu's planar-chiral DMAP derivative **1** (Figure 1).[2c,8,9,10]

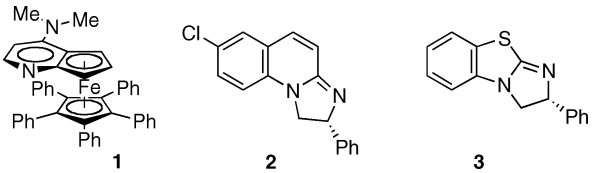


Figure 1. Fu's catalyst (**1**), Cl-PIQ (**2**), and BTM (**3**).

However, the selectivities in this case were found to be highly dependent on the structure of the substrate. Thus, whereas substrate **4a** (Figure 2) was resolved with a respectable selectivity factor[11] $s = 20$, replacing the methyl with bulkier alkyl groups (**4b**−**d**), or the phenyl ring with a substituted phenyl, alkenyl, alkynyl, acyl, and especially *n*-alkyl groups led to lower enantioselectivities. In addition, many of the reactions required very long reaction times (up to 3 weeks).

We were curious whether our recently developed catalysts Cl-PIQ (**2**)[5b] and BTM (**3**)[5c] could overcome these limitations. Our study began by subjecting racemic substrate **4a** to the KR protocol that we had previously utilized for benzylic alcohols[5c] (Table 1, entries 1 and 2). The reactions proceeded

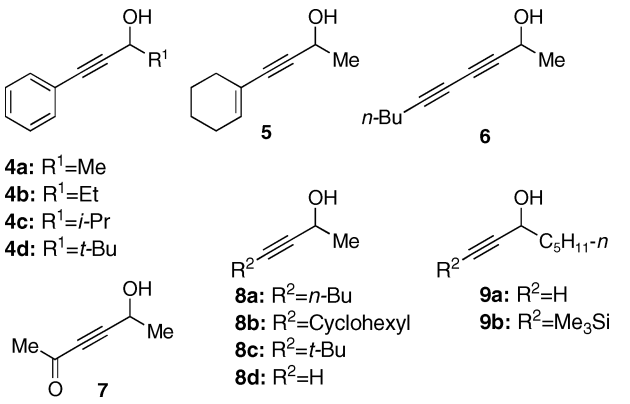


Figure 2. Propargylic alcohol substrates.

(1) 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*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Heidelberg, 2004; Supplement 1, Chapter 43.

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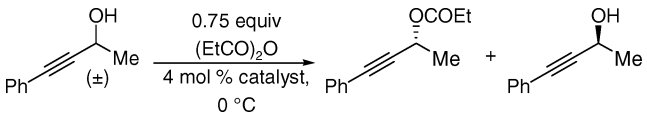
Table 1. Optimization of Reaction Conditions[a]



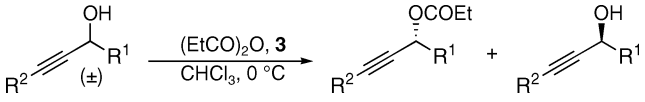
entry	catalyst	solvent	base	time, h	% convn	*s*
1	**2**	$CHCl_3$	*i*-Pr_2NEt	1	52	19
2	**3**	$CHCl_3$	*i*-Pr_2NEt	5	52	28
3	**2**	$CHCl_3$	none	45.5	41	18
4	**3**	$CHCl_3$	none	10.5	59	31
5[b]	**2**	$CHCl_3$	none	92	34	10
6[c]	**3**	$CHCl_3$	none	21.5	47	21
7	**2**	THF	none	6.5	46	15
8	**3**	THF	none	24	0	-[b])
9	**2**	$EtCMe_2OH$	none	7	37	14
10	**3**	$EtCMe_2OH$	none	7	47	17

[a] General conditions: 0.25 M **4a**, 0.010 M (*R*)-**2** or (*R*)-**3**, 0.19 M (0.75 equiv) anhydride, 0.19 M (0.75 equiv) base (if any), 0 °C. [b] (*i*-$PrCO)_2O$ was used instead of $(EtCO)_2O$ in these two cases. [c] Not determined.

much faster than with any classes of substrates we had previously tested. The initial results were encouraging enough with both catalysts, **2** being more reactive and **3** more selective, as had been the case with benzylic alcohols[5c] (Table 1, entries 1 and 2). On the basis of Fu's pioneering study,[2c] we expected to observe improved selectivities and decreased reaction rates in the absence of a stoichiometric base. Remarkably, the base-free conditions led to differentiation between catalysts **2** and **3**. The selectivities in each case remained at similar levels; however, the catalytic activity of **2** decreased dramatically, whereas that of **3** was not affected to a significant extent (Table 1, entries 3 and 4). Substituting isobutyric anhydride for propionic, which had sometimes proved beneficial in the past,[5c,d] led to lower selectivities and reaction rates with both catalysts (Table 1, entries 5 and 6). Replacing chloroform with THF or *tert*-amyl alcohol led to significant rate accelerations in the case of **2**, although the selectivities diminished somewhat (Table 1, entries 7 and 9). As in the earlier study of benzylic alcohol substrates,[5c] the reaction with catalyst **3** did not proceed at all when THF was used as a solvent (Table 1, entry 8), whereas the use of *tert*-amyl alcohol resulted in a comparable reaction rate but lower selectivity (Table 1, entry 10). Overall, **3** was judged to be superior to **2**, and chloroform was once again confirmed to be the solvent of choice. Although diisopropylethylamine was not particularly detrimental to the performance of **3**, it did not offer any significant advantages, either, and therefore, all subsequent reactions were carried out in its absence.

Investigation of the influence of the structure of the substrate on the enantioselectivity of KR began with variation of the steric bulk of the alkyl group R^1. In contrast to our earlier observations with secondary benzylic alcohols, the selectivities decreased in the series Me → Et → *i*-Pr → *t*-Bu (Table 2, entries 1−4). The same trend was found by Fu et al.[2c] Quantitative comparison, however, was clearly in favor of catalyst **3**, in terms of both the selectivity and the time scale of KR experiments. Replacement of the phenyl group with other unsaturated substituents was examined next. Gratifyingly, the selectivities in all the cases examined remained at similar levels (Table 2, entries 5−8). 1-Cyclohexenyl derivative reacted rather slowly, which necessitated higher catalyst and anhydride loadings (Table 2, entries 5

Table 2. Variation of the Substrate[a]



entry	substrate	R^2	R^1	time, h	% convn	*s*
1[b]	**4a**	Ph	Me	10.5	59	31
2[b]	**4b**	Ph	Et	10.5	56	27
3[b]	**4c**	Ph	*i*-Pr	10.5	56	18
4[b]	**4d**	Ph	*t*-Bu	10.5	43	9.5
5[b]	**5**	1-cyclohexenyl	Me	24	13	27
6[c]	**5**	1-cyclohexenyl	Me	18	62	27
7[b]	**6**	1-hexynyl	Me	2	52	32
8[b]	**7**	acetyl	Me	1.5	55	26
9[b]	**8a**	*n*-butyl	Me	24	24	11
10[d]	**8a**	*n*-butyl	Me	25	42	13
11[d]	**8b**	cyclohexyl	Me	23	60	11
12[d]	**8c**	*tert*-butyl	Me	19	48	6.8
13[d]	**9a**	H	*n*-C_5H_{11}	6	55	11
14[d]	**9b**	TMS	*n*-C_5H_{11}	2.5	57	5.4

[a] General conditions: 0.25 M substrate, $CHCl_3$, 0 °C. [b] 0.010 M (4 mol %) (*R*)-**3**, 0.19 M (0.75 equiv) $(EtCO)_2O$. [c] 0.025 M (10 mol %) (*R*)-**3**, 0.38 M (1.5 equiv) $(EtCO)_2O$. [d] 0.025 M (10 mol %) (*R*)-**3**, 0.19 M (0.75 equiv) $(EtCO)_2O$.

(2) (a) Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794. (b) Bellemin-Laponnaz, S.; Tweddell, J.; Ruble, J. C.; Breitling, F. M.; Fu, G. C. *Chem. Commun.* **2000**, 1009. (c) Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 5091. (d) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542.

(3) (a) Vedejs, E.; Daugulis, O.; *J. Am. Chem. Soc.* **1999**, *121*, 5813. (b) Vedejs, E.; MacKay J. A. *Org. Lett.* **2001**, *3*, 535. (c) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **2003**, *125*, 4166.

(4) Spivey, A. C.; Fekner, T.; Spey, S. E. *J. Org. Chem.* **2000**, *65*, 3154.

(5) (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.

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

(7) Yamada, S.; Misono, T.; Iwai, Y. *Tetrahedron Lett.* **2005**, *46*, 2239.

(8) A single example (substrate **4a**) reported in ref 7 proceeded with low selectivity ($s = 6.6$).

(9) Efficient KR of propargylic alcohols can be achieved using enzymes. See, e.g.: (a) Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 6129. (b) Xu, D.; Li, Z.; Ma, S. *Tetrahedron Lett.* **2003,** *44*, 6343.

(10) Enantioenriched propargylic alcohols are also prepared via asymmetric synthesis. For enantioselective alkynylation of aldehydes, see: (a) Pu, L. *Tetrahedron* **2003**, *59*, 9873 (review). (b) Wolf, C.; Liu, S. *J. Am. Chem. Soc.* **2006**, *128*, 10996 (up-to-date list of references). For enantioselective reduction of α,β-acetylenic ketones, see: (c) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867. (d) Brown, H. C.; Ramachandran, P. V.; Weissman, S. A.; Swaminathan, S. *J. Org. Chem.* **1990**, *55*, 6328. (e) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.

(11) Selectivity factor is defined as $s = k$(fast-reacting enantiomer)/k(slow-reacting enantiomer). See: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

and 6). On the other hand, acylation of the 1-hexynyl- (**6**) and the acetyl-substituted (**7**) substrates required much shorter reaction times, compared to that of the phenyl analogue (Table 2, cf. entries 1 vs 7 and 8).

Finally, we turned our attention to unconjugated propargylic alcohols. *n*-Butyl derivative **8a**, the least successful substrate in Fu's study ($s = 3.9$), was tested first. Increased catalyst loadings had to be employed in this case to achieve respectable conversion levels. We were pleased to observe the 3-fold higher selectivity using our catalyst (Table 2, entries 9 and 10), even though it fell short of those obtained with the conjugated substrates. Resolution of the cyclohexyl- and the *tert*-butyl-substituted analogues **8b** and **8c** proceeded with lower selectivities (Table 2, entries 11 and 12). Since the corresponding unsubstituted analogue, 1-butyn-3-ol (**8e**), was too volatile (bp 111 °C), 1-octyn-3-ol (**9a**) was chosen instead for the sake of experimental convenience. This alcohol reacted considerably faster than the alkyl-substituted substrates **8a**−**c** and with comparable enantioselectivity (Table 2, entry 13). Finally, its silylated analogue **9b** was found to react with the lowest selectivity and, unexpectedly, the highest reaction rate among all the unconjugated alcohols tested (Table 2, entry 14).

The structure−selectivity trends noted above are generally consistent with our $\pi-\pi$/cation$-\pi$ model proposed previously for benzylic and allylic alcohols. The absolute sense of enantioselection observed with propargylic alcohols is the same as with all of the previously tested classes of substrates.[5] Extended π-systems are beneficial for the enantioselectivity; very bulky R^2 substituents on the acetylene, such as *tert*-butyl and trimethylsilyl, are detrimental, presumably because they interfere with the π-interactions. The opposite effect of the steric bulk of the α-substituent R^1 on the enantioselectivity in the case of propargylic and benzylic alcohols constitutes the most intriguing, albeit precedented,[2c] observation. Although detailed analysis of this phenomenon must await future computational studies, the difference probably stems from the much less significant steric interaction of R^1 with the acetylenic moiety than with an aromatic ring.

In summary, we have demonstrated the effectiveness of BTM (**3**) in KR of propargylic alcohols. Although the selectivity factors observed in this study are not very high, they are the highest ever obtained for this class of substrates using nonenzymatic catalysts. Most importantly, our results indicate that, in addition to the aryl and the alkenyl moieties, the alkynyl can also serve as an effective "recognition element" in enantioselective acylation using our catalysts. KR of other classes of alkynyl-substituted substrates, such as oxazolidinones,[5d] is under investigation and will be reported in due course.

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Supporting Information Available: Experimental procedures and ^1H 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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