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Kinetic Resolution of Secondary Alcohols Using Amidine-Based Catalysts

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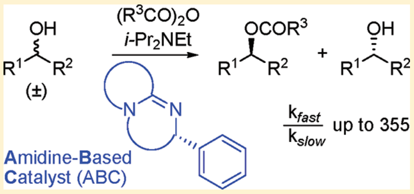
Supporting Information

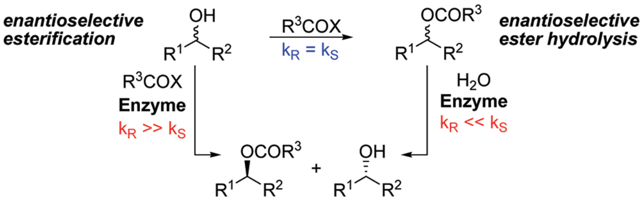
ABSTRACT: Kinetic resolution of racemic alcohols has been traditionally achieved via enzymatic enantioselective esterification and ester hydrolysis. However, there has long been considerable interest in devising nonenzymatic alternative methods for this transformation. Amidine-based catalysts (ABCs), a new class of enantioselective acyl transfer catalysts developed in our group, have demonstrated, inter alia, high efficacy in the kinetic resolution of benzylic, allylic, and propargylic secondary alcohols and 2-substituted cycloalkanols, and thus provide a viable alternative to enzymes.



INTRODUCTION

Chiral secondary alcohols can be encountered in virtually all areas of organic chemistry. They are especially broadly represented among natural products, pharmaceuticals, and synthetic intermediates. Despite great advances in their enantioselective synthesis,[1] kinetic resolution (KR) of racemates[2] remains a widely used method for their preparation in optically pure form. Traditionally, this transformation has been accomplished by using two enantioselective enzymatic methods: esterification and hydrolysis of the corresponding esters (Scheme 1).[3]

Scheme 1. Enzymatic Kinetic Resolution of Alcohols



Although both of these methods have been applied successfully to many structural classes of alcohols and often exhibit excellent enantioselectivity, enzymes are less than ideal as catalysts. One of their most obvious limitations is their availability in only one enantiomeric form, which requires identification of a different enzyme and reoptimization of reaction conditions whenever the enantioselectivity of a given enzymatic process needs to be reversed. Apart from purely practical considerations, exclusive dependence on enzymes for achieving a synthetic transformation is intellectually unsatisfying. As a result, over the last one and a half decades, many research groups have been engaged in the development of low molecular weight enantioselective acylation catalysts that would be able to serve, inter alia, as an alternative to enzymes in KR of alcohols.[4,5]

In 2003, our group initiated a research program aimed at developing a new class of easily accessible enantioselective acyl transfer catalysts. The most successful of these amidine-based catalysts (ABCs) developed thus far are shown in Figure 1.

KR of secondary alcohols provided both the initial impetus for the design of this class of catalysts and a convenient context for their development and exploration of their mechanism of action.[6] In addition to our own efforts in this area, several other groups have subsequently explored the use of ABCs in this transformation and made important contributions by broadening their known substrate scope, establishing new reaction protocols, and exploring additional variations of the catalyst design.[7−11] Furthermore, we and others have demonstrated the utility of ABCs in other types of transformations as well, such as desymmetrization of *meso*-diols,[6g] KR of oxazolidinones and *β*-lactams via enantioselective N-acylation,[12] intramolecular ketene [2 + 2] and [2 + 4] cycloadditions,[13] Steglich rearrangement,[14,15] KR and DKR of chiral acyl donors via enantioselective alcoholysis,[16,17] epoxide opening,[18] O-silylation,[19] and Michael addition.[20]

The primary objective of this paper is to provide an overview of ABC-catalyzed KR of the four main classes of secondary alcohols explored by our group to date: benzylic, allylic, propargylic, and *β*-substituted cycloalkanols. We shall focus on the key structure−selectivity trends noted in the course of our work and thereby hopefully give the reader an accurate idea of the currently known scope and limitations of this methodology. With this in mind, we have excluded the details of our studies on the optimization of catalyst design and reaction protocol and shall concentrate on the results obtained with the most successful and well-studied catalysts developed in our group (**1−5a**) under optimal reaction conditions.

RESULTS AND DISCUSSION

Benzylic Alcohols. Many nonenzymatic enantioselective acyl transfer catalysts have proved to be effective in the KR of secondary benzylic alcohols.[21] As a result, this transformation

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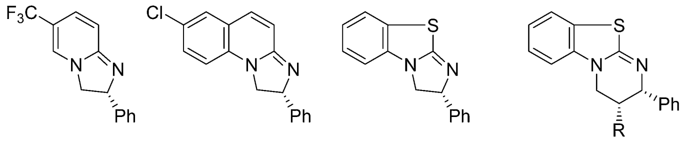
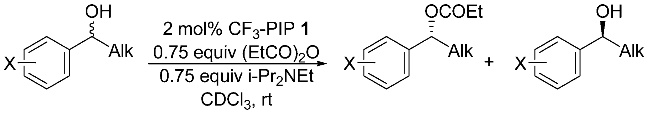


1, (*R*)-CF$_3$-PIP (2004)[6a]
2, (*R*)-Cl-PIQ (2005)[6b]
3, (*R*)-BTM (2006)[6d]
4, R = H: (*S*)-HBTM (2008)[6h]
5a, R = Me: (*S*)-HBTM-2 (2009)[6j]
5b, R = *i*-Pr: (*S*)-HBTM-2.1 (2009, Smith)[16b]

Figure 1. Most successful amidine-based catalysts.

has been widely used to test the enantioselectivity of newly designed catalysts. ABCs were no exception. The first successful catalyst of this class, CF$_3$-PIP **1**, demonstrated good to excellent levels of enantioselectivity with this type of substrates (Scheme 2).[6a]

Scheme 2. Kinetic Resolution of Benzylic Alcohols Using CF$_3$−PIP 1



The most significant structure−selectivity trends noted with this catalyst were as follows:

(a) increasing the steric bulk of the alkyl group resulted in higher selectivity factors[22] (cf. Table 1, entries 1a, 2a, 3a, and 4a)
(b) replacing the phenyl group with an aryl containing an extended π-system led to better enantioselectivities and higher reaction rates (entries 1a vs 5a and 7a)
(c) cyclic benzylic alcohol **14** reacted very slowly and without any detectable asymmetric induction (entry 9a)
(d) sterically similar, but fully saturated, substrate **15** failed to react under the standard conditions (entry 10a)

These observations led us to propose that in the transition state the benzene ring of the substrate is stacked above the pyridinium ring of the N-acylated catalyst due to $\pi-\pi$ and/or cation−π interactions. Subsequently, this simplistic transition state model was analyzed and refined by computational studies in collaboration with the Houk group[6i] (Figure 2).

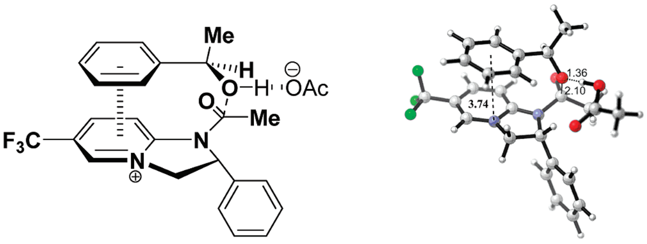


Figure 2. Proposed transition state. Predictive model and geometry optimized by DFT calculations.

Second-generation catalyst Cl-PIQ **2** developed in the course of our subsequent studies[6b] exhibits higher enantioselectivity and reaction rates than CF$_3$-PIP **1** (Table 1, entries 1−6, b vs a). The third-generation catalyst BTM **3**[6d] is even more enantioselective, although less active, than **2** (entries 1−6, c,d vs b). All three imidazoline-based catalysts **1**−**3**, however, usually display qualitatively similar trends in the KR of benzylic alcohols. Entries 7 and 8 (vs 5c,d and 6c,d) demonstrate that a combination of a bulky alkyl group and a polarizable aryl group leads to very high selectivity factors, suggesting that these two factors are more or less additive.[23] Tetrahydropyrimidine-based catalysts **4** and **5a** were less enantioselective than **2** or **3** when tested in KR of substrates **7** and **12** at room temperature (entries 2e and 6e). Fortunately, they are considerably more active than the latter at low temperatures, which allows them to achieve quite respectable results in these cases (entries 2f and 7f). Although we have not explored systematically the structure−selectivity trends exhibited by tetrahydropyrimidine-based catalysts **4** and **5a** for this class of substrates, recent studies by Smith et al.[9] using catalyst **5b** suggest that they should be largely similar to those noted above.

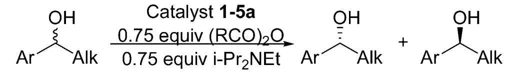
Electronic effects of substitution on the aromatic ring have been explored most systematically using CF$_3$-PIP **1** (Table 2, entries 1−5). Electron-rich *meta*-substituents lead to increased enantioselectivities, while electron-withdrawing groups have the opposite effect, which is consistent with the expected enhancement of cation−π interactions. Apart from this study, 3,5-disubstituted alcohol **21**, which is valuable as a precursor to antiemetic drug aprepitant (Emend, Merck & Co.), was resolved with BTM **3**. The lower enantioselectivity obtained in this case, relative to the unsubstituted alcohol **6** (Table 2, entry 6 vs Table 1, entry 1c), is also in accord with the trend noted above.

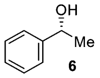
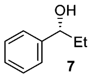
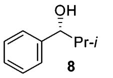
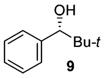
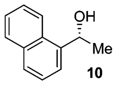
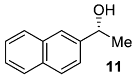
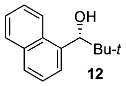
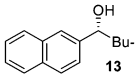
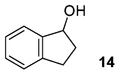
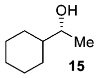
Ortho-substitution has a more dramatic effect on the outcome of KR. Thus, 1-(*o*-tolyl)ethanol **22** is resolved with 2−3-fold higher selectivity factors than the unsubstituted alcohol **6** using catalysts **1**−**3** (Table 3, entry 1, vs Table 1, entry 1). Other groups have also reported that this substrate produces superior results with other classes of catalysts.[24] Increased enantioselectivity is also observed when the *ortho*-substituent is a methoxy group, especially when using catalyst **2** (entry 2a). Consistent with this trend, another *ortho*-substituted alcohol, 1-(1-naphthyl)ethanol **10**, is also resolved with higher enantioselectivities than **6**, as observed in our studies (Table 1, entries 5 vs 1) and those by others.[24]

In sharp contrast to **22**, substitution of *both ortho*-positions with methyl groups is highly detrimental: 1-mesitylethanol **24** is resolved with rather low enantioselectivities by all ABCs tested, particularly BTM **3** (Table 3, entry 3). It is noteworthy that the very same substrate was resolved with a record selectivity factor (s = 390) with Vedejs' phosphine-based asymmetric acylation catalyst.[5n] Furthermore, 1-(2,6-dimethoxyphenyl)ethanol **25** *cannot be acylated at all* using catalysts **2** and **3** (entry 4). Nevertheless, 1-(9-anthryl)ethanol **26**, in which both *ortho*-positions are occupied by fused benzene rings, turns out to be an excellent substrate for both Cl-PIQ **2** and BTM **3** (entry 5). In fact, the latter result is twice as high as the only one previously obtained for this compound.[5i,26] Its trifluoromethyl analog **27**, developed by Pirkle et al. as a chiral NMR shift reagent,[27] is also resolved with outstanding enantioselectivity and unusually short reaction time (entry 6).

Although the effects of polar substituents in the alkyl chain have not been studied systematically in our group, several examples provided in Table 4 illustrate that these too can have a profound influence on reactivity and enantioselectivity. KR of chlorinated alcohol **28**, the key intermediate en route to

Table 1. KR of Secondary Benzylic Alcohols: Basic Variations



entry[a]	(±)-substrate[b]	catalyst (mol%)	temp °C	time h	% conv	s
1a	 **6**	**1** (2)	0	8	32	26 [6a]
1b		**2** (2)	0	8	55	33 [6b]
1c		**3** (4)	0	33	49	80 [6d]
1d [c]		**3** (4)	0	33	46	104 [6d]
2a	 **7**	**1** (2)	0	8	39	36 [6a]
2b		**2** (2)	0	8	51	41 [6b]
2c		**3** (4)	0	24	47	109 [6d]
2d [c]		**3** (4)	0	36	45	145 [6d]
2e		**4** (2)	23	1	47	27 [6h]
2f [d]		**4** (4)	-40	10	39	55 [6h]
2g [e]		**5a** (2)	-40	11	49	54 [6j]
3a	 **8**	**1** (2)	0	8	43	50 [6b]
3b		**2** (2)	0	4	50	59 [6b]
3c		**3** (4)	0	36	48	111 [6d]
4a	 **9**	**1** (2)	0	52	48	85 [6a]
4b		**2** (2)	0	8	42	117 [6b]
4c		**3** (4+4)	0	48	51	166 [6d]
4d [c]		**3** (4+4)	0	48	31	192 [6d]
5a	 **10**	**1** (2)	0	8	51	56 [6a]
5b		**2** (2)	0	8	56	55 [6b]
5c		**3** (4)	0	9	49	128 [6d]
5d [c]		**3** (4)	0	9	49	184 [6d]
6a	 **11**	**1** (2)	0	8	50	42 [6b]
6b		**2** (2)	0	2	51	74 [6b]
6c		**3** (4)	0	11	50	108 [6d]
6d [c]		**3** (4)	0	11	46	226 [6d]
6e		**4** (2)	23	0.4	48	25 [6h]
6f [d]		**4** (4)	-40	5	37	49 [6h]
7a	 **12**	**3** (4+4)	0	32	45	307 [6d]
7b [c]		**3** (4+4)	0	48	33	207 [6d]
8	 **13**	**3** (4)	0	32	38	299 [6d]
9a	 **14**	**1** (2)	0	50	16	≈1 [6a]
9b		**3** (8)	23	22	14	1.3
9c		**4** (2)	23	1.7	62	1.1
10a	 **15**	**1** (2)	0	52	0	ND[6a]
10b		**2** (20)	0	53	39	1.8
10c		**3** (20)	0	52	59	2.2

[a] Conditions: 1.0 equiv of (±)-substrate, 0.75 equiv of $(EtCO)_2O$, 0.75 equiv of i-Pr_2NEt, catalyst, $CDCl_3$, unless specified otherwise. [b] Absolute configuration shown refers to the fast-reacting enantiomer of the substrate in reactions catalyzed by (*R*)-**1**, **2**, **3**, or (*S*)-**4** and **5a**. [c] $(i$-$PrCO)_2O$ was used instead of $(EtCO)_2O$. [d] The reaction was carried out in toluene. [e] The reaction was carried out in *tert*-amyl alcohol/toluene mixture.

fluoxetine (Prozac, Eli Lilly & Co.) proceeds with lower enantioselectivity (Table 3, entry 1) than that of the des-chloro compound **7** (Table 1, entry 2d). Not entirely unexpectedly, a problem was encountered in the KR of 3-amino alcohols, which we investigated in the context of a model study leading up to an asymmetric synthesis of (+) and (−)-lobeline.[6g] The simplest member of this series, **29**, turned out to undergo rather rapid uncatalyzed reaction even at 0 °C (Table 4, entry 2a), which, obviously, reduced the efficacy of BTM, even at a high catalyst loading (entry 2b). Diastereomeric substrates (±)-sedamine **30** and (±)-*allo*-sedamine **31**, in which the tertiary amino group forms part of a piperidine ring, also underwent significant background acylation (entries 3a and 4a). Most intriguingly, however, a synthetically useful selectivity factor was obtained in the former case (entry 3b), but not the latter (entry 4b), despite the fact that the background reaction was, in fact, faster for **30** than for **31**. We attribute these observations to the presence of a hydrogen bond between the tertiary nitrogen and the hydroxyl group, which increases the nucleophilicity of the latter. The geometry of this interaction is obviously important in both the catalyzed and the uncatalyzed acylations, as suggested by the significant differences between **29** and its two constrained analogs **30** and **31**. (Figure 3). Substrate **32** is resolved with

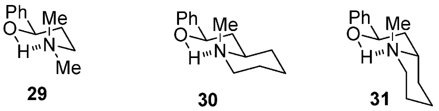
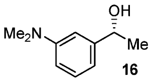
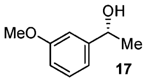
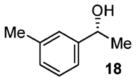
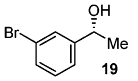
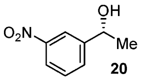
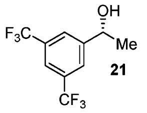


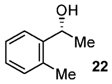
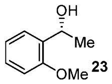
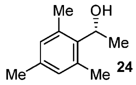
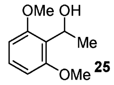
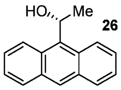
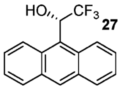
Figure 3. Hydrogen bonding in 3-amino alcohols **29**−**31**.

Table 2. KR of Secondary Benzylic Alcohols: Effects of *Meta*-Substituents

entry[a]	(±)-substrate[b]	catalyst (mol%)	temp °C	time h	% conv	s
1	 16	**1** (2)	0	8	43	38
2	 17	**1** (2)	0	8	40	34 [25]
3	 18	**1** (2)	0	8	36	27 [25]
4	 19	**1** (2)	0	8	44	32 [25]
5	 20	**1** (2)	0	6	32	11
6 [c]	 21	**3** (4)	0	24	45	47

[a,b]See Table 1.

Table 3. KR of Secondary Benzylic Alcohols: Effects of *Ortho*-Substituents

entry[a]	(±)-substrate[b]	catalyst (mol%)	temp °C	time h	% conv	s
1a	 22	**1** (2)	0	8	34	55 [25]
1b		**2** (2)	0	6	48	60
1c		**3** (4)	0	33	50	209 [6d]
1d [c]		**3** (4)	0	33	48	355 [6d]
2a	 23	**2** (5)	0	5	49	112
2b		**3** (5)	0	20	52	102
3a	 24	**1** (2)	0	25	49	8.8 [25]
3b		**2** (2)	0	7	48	12
3c		**3** (4)	0	24	20	2.5 [6d]
4a	 25	**2** (5)	0	47	0	ND
4b		**3** (5)	0	47	0	ND
5a	 26	**2** (2)	0	5	54	45
5b		**3** (4)	0	24	46	202
6	 27	**3** (4)	0	1	49	210

[a,b]See Table 1.

only modest enantioselectivity (entry 5) despite the absence of a significant background reaction.[28] Of course, the limitations posed by the presence of a tertiary amino group may often be circumvented synthetically, i.e., by keeping the nitrogen in the form of amide. Both diastereomeric carbamates **33** and **34** underwent fairly effective KR at room temperature (entries 6 and 7) and could be subsequently reduced to sedamine and *allo*-sedamine, respectively.[6g] However, a more straightforward solution to this problem would also be desirable. As we demonstrated recently, the use of HBTM-2 **5a** is advantageous in the KR of amino alcohol **29** simply because the low temperature at which this highly active catalyst can operate allows the uncatalyzed acylation to be effectively suppressed (entries 2c vs 2b).

The KR of heteroaryl alcohols **35** and **36** was investigated only briefly. The results obtained with Cl-PIQ **2** and BTM **3** were rather modest (entries 8 and 9). While we have made no attempt at optimization in these cases, a recent study by Shiina et al.[7c] has demonstrated that good to excellent enantioselectivities can be obtained in BTM-catalyzed KR of similar substrates using mixed diphenylacetic−pivalic anhydride as the acylating agent.

Allylic Alcohols. Enantioselective acylation of allylic alcohols has received much less attention than that of the benzylic alcohols discussed above.[29] Prior to our work, only two systematic studies in this area were published by Fu[30] and by Vedejs.[31,32] Our interest in this class of substrates stemmed from the realization that π-interactions likely played the key role in the chiral recognition of benzylic alcohols by CF_3-PIP **1**. We were curious whether a double bond adjacent to the hydroxyl group would also be able to direct chiral recognition. However, our attempt to achieve KR of the simplest *trans*-cinnamyl alcohol **37** using CF_3-PIP **1** was only moderately successful. The lower rate and enantioselectivity observed in this case (Table 5, entry 1a), compared with the analogous reaction of its benzylic analogue **6** (Table 1, entry 1a), was not surprising. We speculated that, although the new substrate featured an extended π-system, in the proposed transition state, most of it was too far away from the pyridinium ring to contribute much to the π-interaction. In an effort to improve the enantioselectivity in the KR of this class of substrates, we decided to extend the π-system of the catalyst itself and developed the second-generation catalyst, Cl-PIQ **2** (Figure 4).

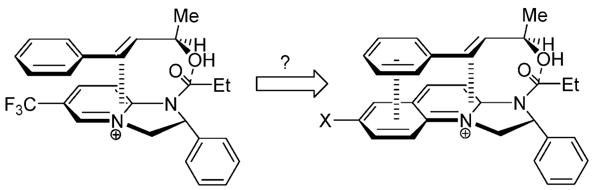
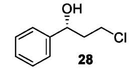
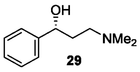
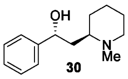
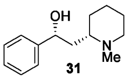
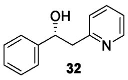
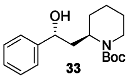
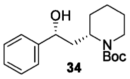
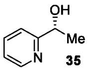
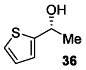


Figure 4. Rationale for the second-generation catalyst design.

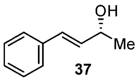
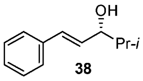
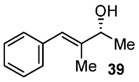
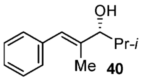
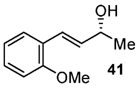
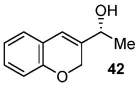
As we had hoped, the new catalyst achieved uniformly higher reaction rates and enantioselectivities, compared to CF_3-PIP **1**, in the KR of all *trans*-cinnamyl alcohols examined (Table 5). Available data suggest that increasing the steric bulk of the alkyl substituent in this category of substrates is not as clearly beneficial for the enantioselectivity as it was in the benzylic series,

Table 4. KR of Secondary Benzylic Alcohols: Effect of Heteroatoms in the Ring and on the Alkyl Chain

entry[a]	(±)-substrate[b]	catalyst (mol%)	temp °C	time h	% conv	s
1[c]	 **28**	**3** (4)	0	24	49	66
2a	 **29**	none	23	2.9	50	NA [6g]
2b		**3** (8)	0	6	44	8.2 [6g]
2c		**5a** (2)	-40	11	48	19 [6j]
3a	 **30**	none	23	0.73	50	NA [6g]
3b		**3** (8)	-20	3.5	54	50 [6g]
4a	 **31**	none	23	3.7	50	NA [6g]
4b		**3** (8)	0	7	49	4.6 [6g]
5a	 **32**	**3** (8)	0	10	56	15
5b[c]		**3** (8+8)	0	22	45	26
6a	 **33**	**3** (8)	23	14	47	50
6b [c]		**3** (8)	23	18	47	78
7a	 **34**	**3** (8+8)	23	24	48	43
8a	 **35**	**2** (5)	0	14	47	13
8b		**3** (10)	0	30	43	21
9a	 **36**	**2** (2)	0	6	45	15
9b		**3** (10)	0	30	38	19

[a-c]See Table 1.

Table 5. KR of Secondary *trans*-Cinnamyl Alcohols

entry[a]	(±)-substrate[b]	catalyst (mol%)	temp °C	time h	% conv	s
1a	 **37**	**1** (2)	0	8	14	11[6b]
1b		**2** (2)	0	8	44	27[6b]
1c		**3** (4+4)	0	32	36	23 [6d]
1d [c]		**5a** (2)	-40	11	54	23 [6j]
2a	 **38**	**1** (2)	0	8	30	21[6b]
2b		**2** (2)	0	8	53	24[6b]
3a	 **39**	**1** (2)	0	8	14	9[6b]
3b		**2** (2)	0	8	38	17[6b]
4a	 **40**	**1** (2)	0	8	9	13[6b]
4b		**2** (2)	0	8	32	22[6b]
5a	 **41**	**1** (2)	0	8	27	6.5[6b]
5b		**2** (2)	0	8	56	31[6b]
6a	 **42**	**1** (2)	0	8	50	26[6b]
6b		**2** (2)	0	4	55	57[6b]

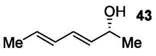
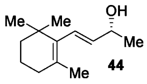
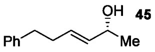
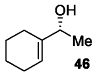
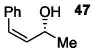
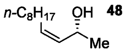
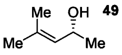
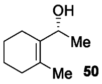
[a,b]See Table 1. [c]The reaction was carried out in toluene.

and may depend on the substitution on the double bond (entries 2 vs 1 and 4 vs 3). Overall, it appears that coplanarity of the benzene ring and the double bond plays an important role. This is particularly evident in the comparison of selectivity factors achieved for substrate **41** and its conformationally restricted analogue **42** (entries 5 and 6). The lower rates and/or enantioselectivities obtained with alcohols bearing a methyl group *cis*- to the phenyl (cf. entries 3 vs 1 and 4 vs 2) may also be attributed to the same factor.

Contrary to our expectations, the third-generation catalyst BTM **3**, which had displayed far better selectivity factors in the KR of most types of benzylic alcohols, turned out to be less suitable for KR of allylic alcohols than Cl-PIQ **2**. Not only did it produce a somewhat lower selectivity factor in the KR of **37** (Table 5, entries 1c vs 1b) but also required extended reaction time and additional catalyst loading due to the apparent catalyst deactivation by this substrate (vide infra). Results obtained with other allylic alcohols are consistent with these observations (Table 6, entries 1–8, b). On the other hand, the analogous ring-expanded catalyst HBTM-2 **5a** is quite active in the KR of alcohol **37** and able to afford the same enantioselectivity at −40 °C (Table 5, entry 1d).

Later studies also demonstrated that the phenyl substituent can be replaced with an additional double bond without significant loss of enantioselectivity provided that effective conjugation is maintained. Thus, the results obtained in the Cl-PIQ-catalyzed KR of dienyl alcohol **43** are comparable to those achieved with its cinnamyl analogue **37** (Table 6, entry 1a vs Table 5, entry 1b), whereas in the case of β-ionol **44** the enantioselectivity is drastically reduced (Table 6, entry 2a). Presumably, the steric interactions imposed by the three methyl groups in **44** force the cyclohexene ring to twist out of conjugation with the $\beta-\gamma$ double bond and interfere with its approach to the N-acylated catalyst. Unconjugated allylic alcohols **45** and **46** can also be resolved using Cl-PIQ, although the selectivity factors are only modest and larger catalyst loadings are required due to reduced reaction rates (entries 3a and 4b). Still, π-interactions between the single double bond and the catalyst evidently play a critical role in the chiral recognition of these substrates because the fully saturated alcohol **15** (Table 1, entries 10b and c) reacts much more slowly than **46** and displays greatly reduced enantioselectivity. Interestingly, the beneficial influence of a β-phenyl substituent is observed in the KR of *cis*-cinnamyl alcohol **47**, even though it can hardly attain coplanarity with the double bond. In fact, the selectivity factors obtained with *cis*-alcohols **47** and **48** (Table 6, entries 5 and 6) are comparable with those obtained with their *trans*-counterparts **37** (Table 5, entries 1b and c) and **45** (Table 6, entry 3). The presence of a *cis*-methyl group in substrates **49** and **50** apparently slows their acylation, but does

Table 6. KR of Miscellaneous Secondary Allylic Alcohols

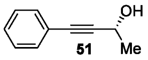
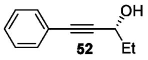
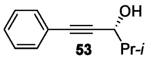
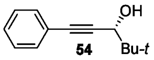
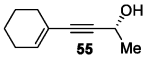
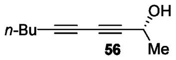
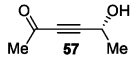
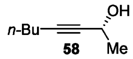
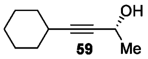
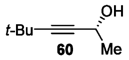
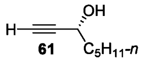
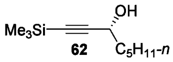
entry[a]	(±)-substrate[b]	catalyst (mol%)	temp °C	time h	% conv	s
1a	 43	**2** (5)	0	7	52	21
1b		**3** (10)	0	120	34	11
2a	 44	**2** (5)	0	23	47	2.4
2b		**3** (10)	0	47	29	2.3
3a	 45	**2** (10)	0	12	42	8.3
3b		**3** (10)	0	30	32	5.9
4a	 46	**1** (10)	0	32	40	11[6b]
4b		**2** (10)	0	11	47	17[6b]
4c		**3** (10)	0	47	25	10
5a	 47	**2** (5)	0	23	44	22
5b		**3** (10)	0	35	14	4.1
6a	 48	**2** (10)	0	6	47	9.6
6b		**3** (10)	0	24	43	4.9
7a	 49	**2** (10)	0	24	46	9.4
7b		**3** (10)	0	35	38	2.4
8a	 50	**2** (10)	0	45	36	13
8b		**3** (10)	0	35	21	1.8

[a,b]See Table 1.

not have much effect on the enantioselectivity (cf. entries 7 vs 3 and 8 vs 4).

Propargylic Alcohols. Apart from Fu's seminal study,[33] the nonenzymatic KR of propargylic alcohols had not been explored in detail. In 2006, we examined this class of substrates with the aim of testing the ability of ABCs to "recognize" a triple bond. BTM proved to be superior to Cl-PIQ and was adopted for the systematic study of the structure−selectivity trends. In sharp contrast to the benzylic series (Table 1), increasing the size of the alkyl group α- to the hydroxyl leads to a *decrease* in enantioselectivity (Table 7, entries 1−4). Conjugated propargylic alcohols wherein the alkyne moiety is substituted with an aryl, alkenyl, alkynyl, or acyl group are acylated with higher enantioselectivity than their unconjugated counterparts (cf. entries 1b and 5−7 vs entries 8−10; entry 2 vs entries 11 and 12). Within the latter category, the enantioselectivity drops off with increased steric bulk of the alkyl (or silyl) substituent, presumably because the latter interferes with the π-interaction between the substrate and the N-acylated catalyst in the transition state. All these trends are qualitatively in line with Fu's earlier observations. However, the selectivity factors are uniformly higher than those obtained in his study. Tetrahydropyrimidine-based catalyst **5a** produced a respectable first result (entry 1c). Its isopropyl analogue **5b** was recently reported by Smith et al. to exhibit even higher enantioselectivity in the KR of the same substrate.[9]

Table 7. KR of Propargylic Alcohols

entry[a]	(±)-substrate[b]	catalyst (mol%)	temp °C	time h	%conv	s
1a	 51	**2** (4)	0	1	52	19[6e]
1b		**3** (4)	0	11	59	31[6e]
1c[c]		**5a** (2)	-40	11	53	21[6j]
2	 52	**3** (4)	0	11	56	27[6e]
3	 53	**3** (4)	0	11	56	18[6e]
4	 54	**3** (4)	0	11	43	9.5[6e]
5	 55	**3** (10)	0	18	62	27[6e]
6	 56	**3** (4)	0	2	52	32[6e]
7	 57	**3** (4)	0	1.5	55	26[6e]
8	 58	**3** (10)	0	25	42	13[6e]
9	 59	**3** (10)	0	23	60	11[6e]
10	 60	**3** (10)	0	19	48	6.8[6e]
11	 61	**3** (10)	0	6	55	11[6e]
12	 62	**3** (10)	0	2.5	57	5.4[6e]

[a,b]See Table 1, except that the reaction was carried out without adding i-Pr_2NEt. [c]The reaction was carried out in toluene.

2-Substituted Cycloalkanols. The structures of the first three series of substrates examined in this study share a common pattern: all of them bear an unsaturated moiety, such as an aryl, alkenyl, or alkynyl group, α- to the hydroxyl group. Although some structure−selectivity trends and relative performance of ABCs varied from series to series, we had every reason to believe that in all these cases the mechanism of chiral recognition remained substantially the same and in accord with our π-interaction hypothesis (Figure 2). Naturally, we wished to explore the efficacy of ABCs in the KR of structurally different substrates. With this in mind, we examined the KR of (±)-*trans*-2-phenylcyclohexanol **63**,[34] hoping that the aryl ring at the β-position relative to the hydroxyl might still serve as a viable recognition element. Imidazoline-based catalysts **2** and especially **3** produced encouraging selectivity factors in the first trial, although the reactions were rather slow and required high catalyst loadings (Table 8, entries 1a and 1b). Under the same conditions, tetrahydropyrimidine-based HBTM **4** displayed much higher reaction rate and somewhat better enantioselectivity (entry 1c). Thankfully, its catalytic activity decreased only moderately at low temperatures, while the enantioselectivity increased manifold (entry 1d). Ultimately, this catalyst and its more active analogue **5a** proved to be particularly suitable for substrate **63** and other 2-arylcycloalkanols (entries 2−5). They also display modest enantioselectivities in the KR of cyclohexanols bearing an ester or azide moiety at the β-position (entries 6−8) but are virtually ineffective when the substituent is an isopropyl group (entry 9). This evidence suggests that π-interactions are critical for chiral recognition of 2-substituted cycloalkanols,[35] although the geometry of such interactions would be somewhat different from that of the previously studied substrates (Figure 5). In addition, rigidity of the substrate appears to play an important role, since acyclic alcohol **72** is resolved with much lower enantioselectivity (entry 10b) than either diastereomer of 2-phenylcyclohexanol (entries 1d and 4).

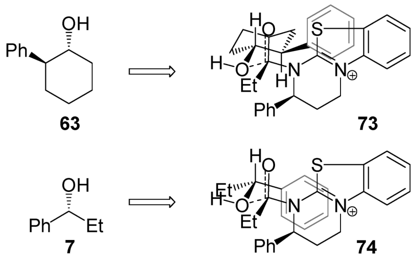
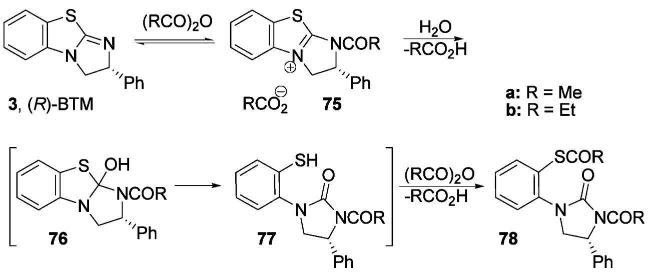


Figure 5. Transition-state models of the HBTM-catalyzed KR of alcohols **63** and **7**.

Deactivation of BTM.

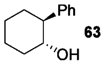
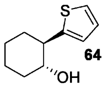
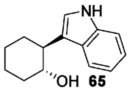
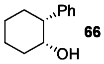
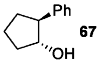
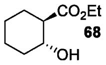
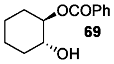
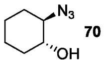
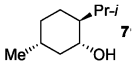
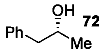
Shortly after discovering the remarkable enantioselectivity of BTM in the KR of benzylic alcohols, we became aware of its sensitivity to the presence of moisture during the reaction. When BTM-catalyzed acylations were carried out in an ice bath, we often observed that the reaction slowed or stopped at low conversions until additional catalyst was introduced. A control experiment revealed the origin of the problem: when a solution of BTM and excess acetic anhydride in $CDCl_3$ was kept for several days at room temperature, a new compound was gradually formed (Scheme 3).

Scheme 3. Deactivation of BTM 3 in the Presence of Moisture



Its formation was accelerated considerably when small amounts of water were added intentionally to the solution. The structure of this degradation product, **78a**, indicated that it probably arose from the attack of water on the isothiouronium carbon of the N-acylated intermediate **75a** followed by the opening of the thiazole ring and, finally, acylation of the thiol group. Fortunately, the formation of **78** could be effectively suppressed by utilizing dry chloroform as the reaction media and adding a drying agent, such as anhydrous sodium sulfate or carbonate.

Table 8. KR of 2-Substituted Cycloalkanols

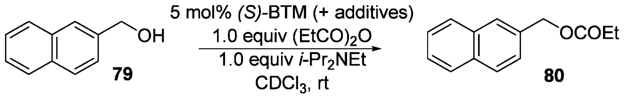
entry[a]	(±)-substrate[b]	catalyst (mol%)	temp °C	time h	%conv	s
1a		**2** (8)	23	12	45	11[6h]
1b		**3** (8)	23	6	48	25[6h]
1c		**4** (2)	23	1.4	47	29[6h]
1d[c]		**4** (4)	-40	10	51	107[6h]
1e[d]		**5a** (2)	-40	11	52	112[6j]
2a[c]		**4** (4)	-40	10	44	44[6h]
2b[d]		**5a** (2)	-40	11	51	66[6j]
3		**4** (2)	23	26	41	49[6h]
4[c]		**4** (4)	-10	12	46	28[6h]
5[c]		**4** (4)	-40	7	51	66[6h]
6a[e]		**4** (4)	-10	12	55	10[6h]
6b[d]		**5a** (2)	-40	11	40	16[6j]
7a[c]		**4** (4)	-40	10	28	5.6[6h]
7b[d]		**5a** (2)	-40	11	43	5.7[6j]
8a[c]		**4** (4)	-40	10	26	10[6h]
8b[d]		**5a** (2)	-40	11	52	10[6j]
9a[e]		**4** (4)	-10	10	33	3.2[6h]
9b[d]		**5a** (2)	-40	11	55	1.2[6j]
10a		**3** (8)	23	8	15	9.9
10b[c]		**4** (4)	-40	10	34	7.9[6h]

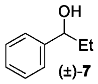
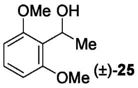
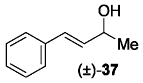
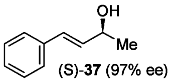
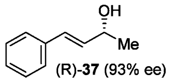
[a,b] See Table 1. [c] The reaction was carried out in *tert*-amyl alcohol/toluene mixture. [d] The reaction was carried out in toluene. [e] The reaction was carried out in *tert*-amyl alcohol.

Later, we also observed seemingly similar behavior in BTM-catalyzed KR of allylic alcohols, despite the usual precautions to exclude and absorb moisture. However, the catalyst was largely recovered unchanged by chromatography, and no appreciable amounts of **78b** or any other degradation product could be isolated. We surmised that the catalyst in this case might be inhibited by the alcohol substrate itself via formation of a hypothetical inactive species that later reverts to BTM during chromatography. To test this possibility, we devised the following experiment.

As expected, BTM-catalyzed acylation of the primary benzylic alcohol (2-naphthyl)methanol **79** was found to occur at a much faster rate than that of typical secondary alcohols. We reasoned that replacing pure BTM in this reaction with an aliquot of a KR reaction mixture containing an equivalent amount of the catalyst should result in significantly reduced reaction rates only if the KR substrate has already inhibited it. The results obtained with several representative secondary alcohols are summarized in Table 9.

Table 9. Substrate Inhibition Test



entry	effective catalyst loading	additive	$t_{1/2}$ (additive conversion)	
			1.5 min	2 h
1	0 mol%	None	n/a	n/a[a]
2	5 mol%	None	28 min	n/a
3	5 mol%	 (±)-**7**	45 min (49%)	51 min (82%)
4	5 mol%	 (±)-**25**	35 min (0%)	258 min (0%)
5	5 mol%	 (±)-**37**	119 min (46%)	282 min (60%)
6	5 mol%	 (S)-**37** (97% ee)	53 min (79%)	42 min (98%)
7	5 mol%	 (R)-**37** (93% ee)	260 min (15%)	309 min (18%)

[a] 0% after 4 h.

(±)-1-Phenylpropanol **7** was chosen as a typical "non-problematic" substrate. When its KR was carried out in the presence of 20 mol % of (*S*)-BTM, the conversion reached 49% after only 1.5 min (entry 3, column 4). An aliquot withdrawn at this point and added to a solution of **79** produced only slightly lower catalytic effect than the same amount of pure BTM ($t_{1/2}$ = 45 vs 28 min, respectively, cf. entries 3 and 2), indicating that the catalyst inhibition was not significant. Repetition of the same experiment after 2 h, when the conversion of **7** reached over 80%, produced essentially the same results.

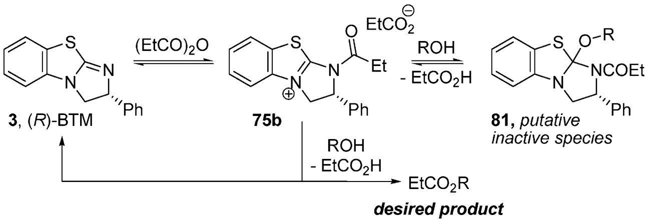
On the other hand, benzylic alcohol **25**, notable for its total lack of reactivity under BTM catalysis, produced a strikingly different outcome under identical conditions. An aliquot of its reaction mixture taken shortly after mixing (entry 4, column 4) catalyzed acylation of **79** to essentially the same extent as did pure BTM (entry 2, column 4). After 2 h, however, the same mixture, despite the absence of any observable reaction of **25**, produced a markedly lower catalytic effect (columns 5 and 6), indicating that the inhibition had already taken place.

Racemic allylic alcohol **37** displayed an interesting combination of these two modes of behavior. The first aliquot, in which the conversion had already reached nearly the same level as in the case of (±)-**7**, nevertheless produced clear signs of catalyst inhibition (entry 5, column 4). After 2 h, the conversion of **37** had reached a plateau at 60% (column 5). The inhibitory activity was comparable to that of **25**, which accounted for the lack of further reaction progress.

These results led us to hypothesize that the inhibitory activity of substrate **37** might reside primarily in the (*R*)-enantiomer, which undergoes O-acylation only slowly in the presence of (*S*)-BTM and therefore continues to be available for the putative side reaction diverting BTM from the catalytic cycle. Indeed, the fast-reacting (*S*)-**37** produced little catalyst inhibition and, accordingly, was completely acylated within 2 h (entry 6). At the same time, enantioenriched (R)-**37** inhibited acylation of **79** even more strongly than did its racemate (entry 7 vs 5).

Taken together, these results provide evidence that the slow-reacting enantiomer of the allylic alcohol substrate in BTM-catalyzed KR is not an innocent bystander but, often, an unwelcome source of interference. The same may be true for other classes of alcohols, albeit to a lesser extent. The correlation between an alcohol's structure and inhibitory activity remains unclear at this point, as does the nature of the putative inactive form of the catalyst. We surmise, however, by analogy with the water-induced catalyst degradation discussed above, that alcohols in general may react with the isothiouronium carbon of N-acylated BTM (**75b**) to produce a species like **81** (Scheme 4). The rate of its formation relative to the desired attack at the acyl carbonyl and the ease of the reverse reaction likely determine the degree of inhibition. This hypothesis, if correct, would also account for the surprisingly low catalytic activity of BTM (and tetramisole) in acetylation of methanol noted in our earlier work.[6f]

Scheme 4. Proposed Mechanism of Substrate Inhibition of BTM



■ CONCLUSION

As we have seen, the five generations of ABCs developed thus far do not simply differ in their overall activity and enantioselectivity but exhibit different enantioselectivity profiles toward various classes of substrates and thus can be subdivided into three groups, which are somewhat complementary to one another in their practical utility. Although the details of our optimization studies are beyond the scope of this article, some general recommendation regarding their use are provided below, as they would be of interest to the synthetic practitioner.

(1) CF$_3$-PIP **1** and Cl-PIQ **2**. These catalysts work best in chloroform at 0 °C, at least in the context of KR of alcohols. Propionic anhydride is the optimal acylating agent, while acetic and isobutyric anhydrides produce lower enantioselectivities. For all substrates examined, **1** and **2** produce qualitatively similar results, with the latter being uniformly superior to the former in terms of both enantioselectivity and reaction rates. Therefore, apart from its sentimental value as the first effective ABC, there appears to be little to recommend CF$_3$-PIP **1** for future studies, while Cl-PIQ **2** still remains our catalyst of choice for the KR of allylic alcohols.

(2) BTM **3**. This catalyst is less active than Cl-PIQ **2** and, therefore, is typically used in higher catalyst loadings. In addition, it is relatively more prone to deactivation in the presence of moisture, as discussed above. Therefore, it is advisible to protect the reaction mixture from atmospheric moisture and to add a drying agent, such as anhydrous sodium sulfate or carbonate. Chloroform is the preferred reaction medium. In contrast to the other ABCs, BTM **3** often produces higher enantioselectivities when used in combination with isobutyric rather than propionic anhydride. More elaborate acylating agents have not been studied systematically in our group due to their higher cost. However, recent studies by Shiina[7b,c] indicate that the use of diphenylacetic-pivalic anhydride often results in dramatically increased selectivity factors. Overall, BTM **3** is the most enantioselective of all ABCs developed to date in the KR of benzylic and propargylic alcohols, as well as several other applications described elsewhere.[12a,17b,e]

(3) HBTM **4**, HBTM-2 **5a**, and HBTM-2.1 **5b**. Tetrahydropyrimidine-based catalysts **4** and **5a** are considerably more active than imidazoline-based catalysts **1**−**3** and have been typically used at −40 °C, which produces greatly improved selectivity factors compared to 0 °C while allowing reaction times to be kept reasonably short. In addition, **4** and **5a** are more tolerant of solvent variation than **1**−**3** and demonstrate good performance in toluene, *tert*-amyl alcohol, and chloroform, the former currently being our first choice. HBTM **4** and HBTM-2 **5a** are both more active and more enantioselective than Cl-PIQ **2** and BTM **3** in the KR of cycloalkanols, as well as some other applications.[13,15b,17a,c,d] Although they are less enantioselective than the latter two toward benzylic, allylic, and propargylic alcohols at room temperature, they can still be quite useful in their KR of these substrates at low temperatures. The higher catalytic activity and easier synthesis of HBTM-2 **5a** lead us to favor it relative to the parent catalyst **4**. As might be expected, its isopropyl homologue HBTM-2.1 **5b** is even more active and enantioselective than **5a**,[9] although its synthesis is somewhat more involved.[15b]

In summary, we have demonstrated that ABCs exhibit good to excellent performance in the KR of several classes of alcohols bearing a π-system adjacent to the hydroxyl group. Their broad substrate scope, coupled with easy availability in both enantiomeric forms and generally high enantioselectivity, suggest that they can indeed provide a practical alternative to enzymes. The absolute configurations of the products observed in all cases studied are consistent with our proposed general TS model,[6a,i] which underscores its value as a predictive tool and a guide to further development of new applications of ABCs.

■ EXPERIMENTAL SECTION

1. General Methods. All reagents were obtained commercially and used as received unless otherwise specified. Catalysts **1**−**4** were prepared as previously described.[6a,b,d,h] Substrate alcohols were either obtained commercially or synthesized using known procedures.

Solvents used for chromatography were ACS or HPLC grade, as appropriate. Reactions were monitored by thin-layer chromatography (TLC) and by ^{1}H NMR. EM Science 60F silica gel plates were used for TLC analyses. Flash column chromatography was performed over ICN Ecochrom silica gel (32−63 mm). HPLC analyses were performed using Chiralcel OD-H and Chiralpak AS-H analytical chiral stationary-phase columns (4.6 × 250 mm, Chiral Technologies, Inc.) at 1 mL/min flow rate, unless specified otherwise. ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer. The chemical shifts are reported as δ values (ppm) relative to TMS using residual CHCl$_3$ peak (7.26 ppm) as the reference. High-resolution mass spectral analyses were performed on using the electrospray ionization (ESI) method.

2. Kinetic Resolution Data. Tables 10−13 summarize previously unpublished data grouped by the catalyst used. Detailed descriptions of experimental conditions can be found in the previous publications (CF3-PIP **1**,[6a] Cl-PIQ **2**,[6b] BTM **3**,[6d] and HBTM **4**,[6h] respectively). Selectivity factors and conversions were calculated from the enantiomeric excess values of the ester products and the recovered unreacted alcohol substrates according to Kagan's equations.[2,22] The ee's of alcohols were determined by chiral stationary-phase HPLC either directly or after appropriate derivatization, as specified in section 3. All esters were hydrolyzed to the corresponding alcohols prior to HPLC analysis.

3. HPLC Properties and Characterization Data. Unless specified otherwise, absolute configurations were determined by comparing the sign of optical rotation with the literature data. In those cases when the method of establishing the absolute configuration is not specified, the assignment of HPLC peaks is by analogy.

*Indan-1-ol (**14**). Alcohol:* Commercially available. HPLC (OD-H, 3% *i*-PrOH/hexane): 17.8 min, 20.8 min. **Propionate ester:** Previously reported.[36]

*1-cyclohexylethan-1-ol (**15**). Alcohol:* Commercially available. (−)-(*R*)-enantiomer[37] recovered after KR using (*S*)-**2** and -**3**. HPLC: Separation achieved using the corresponding benzoate (see below). *Propionate ester:* Previously reported.[36] *Benzoate ester:* Previously reported.[38] HPLC (OD-H, 100% hexane): 10.6 min (*R*), 11.5 min (*S*).

*1-[3-(Dimethylamino)phenyl]ethan-1-ol (**16**). Alcohol:* Commercially available. HPLC (OD-H, 10% *i*-PrOH/hexane): 9.4 min (*R*), 16.0 min (*S*). *Propionate ester:* ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.25 (t, J = 8.1 Hz, 1H), 6.75−6.65 (m, 3H), 5.86 (q, J = 6.6 Hz, 1H), 2.98 (s, 6H), 2.36 (q, J = 7.5 Hz, 1H), 1.54 (d, J = 6.6 Hz, 3H), 1.14 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 174.0, 150.9, 143.0, 129.4, 114.4, 112.2, 110.5, 72.9, 40.8, 28.2, 22.6, 9.4; IR: 2980, 2939, 1735, 1606, 1502, 1355, 1187, 1064, 994, 776, 697. MS HR-ESI: calcd for $C_{13}H_{20}NO_2^+$ (M + H$^+$) 222.1489, found 222.1487.

*1-(3-Methoxyphenyl)ethan-1-ol (**17**). Alcohol:* Synthesized by borohydride reduction of the corresponding ketone. ^{1}H NMR data (see the Supporting Information) are in agreement with those previously reported.[39] HPLC (OD-H, 5% *i*-PrOH/hexane): 9.4 min (*R*), 11.5 min (*S*). *Propionate ester:* ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.26 (t, J = 7.8 Hz, 1H), 6.59−6.81 (m, 4H), 5.87 (q, J = 6.6 Hz, 1H), 2.40−2.32 (m, 2H), 1.52 (d, J = 6.6 Hz, 3H), 1.15 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 173.8, 159.9, 143.8, 129.8, 118.5, 113.2, 112.0, 72.2, 55.4, 28.1, 22.5, 9.3. IR (KBr, cm^{-1}) 2981, 1736, 1186, 699; MS HR-ESI:: calcd for $C_{12}H_{16}NaO_3^+$ (M + Na$^+$) 231.0992, found 231.0993.

*1-(3-Methylphenyl)ethan-1-ol (**18**). Alcohol:* Synthesized by borohydride reduction of the corresponding ketone. ^{1}H NMR data (see the Supporting Information) are in agreement with those previously reported.[39,40] HPLC (OD-H, 5% *i*-PrOH/hexane): 16.7 min (*R*), 20.0 min (*S*). *Propionate ester:* ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.15−6.98 (m, 4H), 5.75 (q, J = 6.6 Hz, 1H), 2.28−2.20 (m, 5H), 1.41 (d, J = 6.6 Hz, 3H), 1.03 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 173.8, 141.9, 138.2, 128.7, 128.5, 126.9, 123.2, 72.2, 28.0, 22.4, 21.6, 9.2. IR (KBr, cm^{-1}) 3027, 2981, 1737, 1188, 1065, 786, 703.

Table 10. KR Catalyzed by CF$_3$-PIP (1)[a]

entry	substrate	time (h)	no.	ee$_{PR}$ (%)	ee$_{SM}$ (%)	C$_{HPLC}$ (%)	*s*	C$_{AVG}$ (%)	*s*$_{AVG}$
1	**16**	8	1	90.0	65.7	42.2	37.4	43	38
			2	89.7	69.7	43.7	38.5		
2	**17**	8	1	90.3	50.1	35.7	32.1	41	34
			2	88.3	74.3	46.3	36.7		
3	**18**	8	1	90.2	21.9	19.5	24.1	21	24
			2	90.1	24.7	21.5	24.3		
			3	89.6	27.2	23.3	23.7		
4[b]	**19**	8	1	78.6	67.1	46.1	16.7	48	17
			2	79.7	72.3	47.5	19.0		
			3	75.2	72.5	49.1	15.2		
5	**20**	8	1	78.1	38.8	33.2	11.8	32	11
			2	32.3	77.0	30.0	10.5		
6[c]	**22**	8	1	94.2	48.0	33.8	53.9	34	56
			2	94.4	50.3	34.8	57.1		
7[b,d]	**24**	25	1	64.7	62.0	48.9	8.6	49	8.8
			2	65.0	64.0	49.6	9.0		

[a] General conditions: 1.0 M substrate, 0.75 M $(EtCO)_2O$, 0.75 M *i*-Pr$_2$NEt, 2 mol % (*S*)-CF$_3$-PIP, CDCl$_3$, 0 °C. (*S*)-Enantiomer of the product is favored. [b] The selectivity factor is lower than previously reported (ref 6a. [c] The selectivity factor is higher than previously reported (ref 6a). [d] (*R*)-CF$_3$-PIP was used.

Table 11. KR Catalyzed by Cl-PIQ (2)[a]

entry	substrate	catalyst (mol %)	time (h)	no.	ee$_{PR}$ (%)	ee$_{SM}$ (%)	C$_{HPLC}$ (%)	*s*	C$_{AVG}$ (%)	*s*$_{AVG}$
1	**15**	20	53	1	21.4	13.6	38.9	1.8	39	1.8
				2	21.5	13.9	39.2	1.8		
2	**22**	2	6	1	91.6	84.8	48.1	61.3	48	60
				2	91.3	84.7	48.1	59.3		
3	**23**	5	5	1	94.1	92.2	49.5	109	49	112
				2	94.4	92.3	49.4	115		
4	**24**	2	6.5	1	74.0	66.8	47.5	13.3	48	12
				2	70.1	67.2	48.7	11.6		
5	**25**	5	47	1			0		0	
				2			0			
6[b]	**26**	2	5	1	83.4	97.3	53.8	46.8	54	45
				2	82.3	97.1	54.1	43.0		
7	**35**	5	35	1	72.7	62.0	46.0	11.8	47	13
				2	74.4	66.6	47.2	13.5		
8	**36**	2	6	1	78.2	63.1	44.6	15.5	45	15
				2	78.0	62.4	44.5	15.3		
9	**43**	5	7	1	78.2	82.5	51.4	20.7	52	21
				2	77.8	83.7	51.8	20.8		
10	**44**	5	23	1	29.2	26.6	47.7	2.3	47	2.4
				2	31.8	27.7	46.6	2.5		
11	**45**	10	12	1	67.6	46.6	40.8	8.1	42	8.3
				2	67.6	51.7	43.3	8.6		
12	**47**	5	23	1	83.4	65.5	44.0	21.7	44	22
				2	83.3	65.4	44.0	21.5		
13	**48**	10	6	1	68.4	60.6	47.0	9.8	47	9.6
				2	67.6	59.9	47.0	9.4		
14	**49**	10	24	1	69.1	58.8	46.0	9.8	46	9.4
				2	67.8	56.1	45.3	9.0		
15	**50**	10	45	1	78.5	45.5	36.7	13.0	36	13
				2	79.8	42.6	34.8	13.5		

[a] General conditions: 1.0 M substrate, 0.75 M $(EtCO)_2O$, 0.75 M *i*-Pr$_2$NEt, 2 mol % of (*S*)-Cl-PIQ, CDCl$_3$, 0 °C, anhydrous Na$_2$CO$_3$. (*S*)-enantiomer of the product is favored. [b] (*R*)-Cl-PIQ was used.

MS HR-ESI: calcd for $C_{12}H_{16}NaO_2^+$ $(M + Na^+)$ 215.1043, found 215.1043.

*1-(3-Bromophenyl)ethan-1-ol (**19**)*. *Alcohol:* Synthesized by borohydride reduction of the corresponding ketone. ^{1}H NMR data (see the Supporting Information) are in agreement with those previously reported.[40] HPLC (OD-H, 5% *i*-PrOH/hexane): 8.9 min (*S*), 9.8 min (*R*). *Propionate ester:* ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.49 (s, 1H), 7.40 (d, $J = 7.8$ Hz, 1H), 7.28–7.17 (m, 2H), 5.83 (q, $J = 6.6$ Hz, 1H), 2.35 (q, $J = 7.8$ Hz, 2H), 1.50 (d, $J = 6.6$ Hz, 3H), 1.14 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 173.7, 144.4, 131.1, 130.3, 129.3, 124.9, 122.8,

Table 12. KR Catalyzed by BTM (3)[a]

entry	substrate	catalyst mol %	time (h)	no.	ee_{PR} (%)	ee_{SM} (%)	C_{HPLC} (%)	*s*	C_{AVG} (%)	s_{AVG}
1[b]	**14**	8	22	1	9.96	1.7	14.9	1.2	14	1.3
				2	11.6	1.6	12.3	1.3		
2[b]	**15**	20	52	1	23.3	33.5	59.0	2.2	59	2.2
				2	23.1	33.9	59.4	2.2		
3[c]	**21**	4	24	1	91.0	74.7	45.1	47.8	45	47
				2	90.8	75.2	45.3	47.1		
4	**23**	5	19.5	1	90.4	98.7	52.2	98.3	52	102
				2	90.8	98.8	52.1	105		
5	**25**	5	47	1			0		0	
				2			0			
6[d]	**26**	4	24	1	97.4	83.4	46.1	197.0	46	202
				2	97.5	82.6	45.9	206.7		
7[d]	**27**	4	1.0	1	97.2	93.5	49.0	243.0	48	210
				2	96.7	88.9	47.9	176.7		
8[c]	**28**	4	24	1	91.5	88.0	49.0	65.8	49	66
				2	92.0	85.5	48.2	65.6		
9	**32**	8	10	1	68.4	87.0	56.0	14.7	56	15
				2	67.6	87.2	56.3	14.3		
10[c]	**32**	8 + 8	22	1	85.0	71.0	45.5	26.1	45	26
				2	85.5	70.3	45.1	26.8		
11[b]	**33**	8	14	1	90.7	81.3	47.3	51.8	47	50
				2	90.1	80.1	47.1	47.4		
12[b,c]	**33**	8	18	1	93.7	82.4	46.8	79.2	47	78
				2	93.6	81.5	46.5	76.5		
13[b]	**34**	8 + 8	24	1	87.9	84.9	49.1	41.8	48	43
				2	89.4	80.6	47.4	44.3		
14	**35**	10	30	1	83.1	63.6	43.4	20.7	43	21
				2	83.9	61.3	42.2	21.3		
15	**36**	10	30	1	83.7	52.0	38.3	18.8	38	19
				2	83.9	50.1	37.5	18.5		
16	**43**	10	120	1	75.7	36.2	32.4	10.3	34	11
				2	77.0	42.1	35.4	11.6		
17	**44**	10	47	1	34.4	14.8	30.0	2.4	29	2.3
				2	33.7	13.6	28.7	2.3		
18[b]	**45**	10	30	1	62.9	30.3	32.5	5.9	32	5.9
				2	63.1	29.3	31.7	5.9		
19	**46**	10	47	1	78.2	25.4	24.5	10.5	25	10
				2	77.6	25.9	25.0	10.2		
20[b]	**47**	10	35	1	58.1	9.9	14.6	4.2	14	4.1
				2	57.4	9.2	13.8	4.1		
21[b]	**48**	10	24	1	51.8	38.7	42.8	4.5	43	4.9
				2	56.5	41.4	42.3	5.3		
22[b]	**49**	10	35	1	31.7	18.3	36.6	2.3	38	2.4
				2	33.9	22.1	39.5	2.5		
23[b]	**50**	10	35	1	24.7	7.6	23.4	1.8	21	1.8
				2	26.5	6.2	19.0	1.8		
24	**72**	8	8	1	79.3	14.3	15.3	9.9	15	9.9
				2	79.2	13.5	14.6	9.8		

[a] General conditions: 0.25 M substrate, 0.75 M $(EtCO)_2O$, 0.75 M *i*-Pr_2NEt, 4 mol % of (*S*)-BTM, $CDCl_3$, 0 °C, anhydrous Na_2SO_4. (*S*)-enantiomer of the product is favored. [b] Reaction performed at room temperature. [c] $(i\text{-}PrCO)_2O$ is used instead of $(EtCO)_2O$. [d] (*R*)-BTM was used.

Table 13. KR Catalyzed by HBTM (4)[a]

entry	substrate	catalyst	time (h)	no.	ee_{PR} (%)	ee_{SM} (%)	C_{HPLC} (%)	*s*	C_{AVG} (%)	s_{AVG}
1	**14**	2	1.7	1	3.1	5.4	63.7	1.1	62	1.1
				2	3.1	4.7	60.5	1.1		

[a] Conditions: 0.25 M (±)-**14**, 0.75 M $(EtCO)_2O$, 0.75 M *i*-Pr_2NEt, 2 mol % of (*S*)-HBTM, $CDCl_3$, rt, anhydrous Na_2SO_4.

71.5, 28.0, 22.5, 9.3. IR (KBr, cm^{-1}) 3063, 2981, 1739, 1182, 784, 695. MS HR-ESI: calcd for $C_{11}H_{13}BrNaO_2^+$ $(M + Na^+)$ 278.9991, found 278.9993.

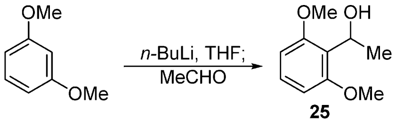
1-(3-Nitrophenyl)ethan-1-ol (**20**). *Alcohol:* Synthesized by borohydride reduction of the corresponding ketone. ^1H NMR data (see the Supporting Information) are in agreement with those previously reported.[39] HPLC (OD-H, 1% *i*-PrOH/hexane): 54.7 min (*S*), 58.4 min (*R*). *Propionate ester:* ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.22 (s, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 5.93 (q, *J* = 6.6 Hz, 1H), 2.43–2.34(m, 1H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 173.8, 148.7, 144.3, 132.5, 129.8, 123.0, 121.2, 71.1, 28.0, 9.2; IR: 2983, 2941, 1739, 1532, 1351, 1182, 1082, 1065, 738, 688. MS HR-ESI: calcd for $C_{11}H_{13}NNaO_4^+$ (M + Na$^+$) 246.0737, found 246.0736.

*1-[3,5-Bis(trifluoromethyl)phenyl]ethan-1-ol (**21**). Alcohol:* Commercially available. HPLC (OD-H, 2% *i*-PrOH/hexane): 9.2 min (*R*); 10.4 min (*S*). *Propionate ester:* ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.81 (s, 1H), 7.79 (s, 2H), 5.96 (q, *J* = 6.6 Hz, 1H), 2.41 (q, *J* = 7.8 Hz, 2H), 1.57 (d, *J* = 6.6 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 173.6, 144.8, 132.4, 131.9, 126.4, 122.0, 70.9, 27.9, 22.5, 9.2. IR (KBr, cm^{-1}) 2988, 1745, 1280, 1175, 1134, 899, 683; MS HR-ESI: calcd for $C_{13}H_{12}F_6NaO_2^+$ (M + Na$^+$) 337.0633, found 337.0649.

*1-(2-Methoxyphenyl)ethan-1-ol (**23**). Alcohol:* Synthesized by borohydride reduction of the corresponding ketone. ^{1}H NMR data (see the Supporting Information) are in agreement with those previously reported.[40] (+)-(*R*) enantiomer[37] recovered after KR using (*S*)-**2** and -**3**. HPLC (OD-H, 2% *i*-PrOH/hexane): 18.3 min (*S*), 19.8 min (*R*).

Propionate Ester. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.36 (dd; J_1 = 7.4 Hz, J_2 = 1.6 Hz; 1H), 7.26 (td; J_1 = 7.4 Hz, J_2 = 1.6 Hz; 1H), 6.96 (td; J_1 = 7.4 Hz, J_2 = 0.8 Hz; 1H), 6.87 (dd; J_1 = 7.4 Hz, J_2 = 0.8 Hz; 1H), 6.26 (q; *J* = 6.5 Hz; 1H), 3.84 (s; 3H), 2.37 (q; *J* = 7.7 Hz; 2H), 1.48 (d; *J* = 6.5 Hz; 3H), 1.16 (t; *J* = 7.7 Hz; 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.5, 156.0, 130.6, 128.5, 125.7, 120.6, 110.5, 66.9, 55.4, 27.9, 21.2, 9.2. IR (KBr, cm^{-1}): 2981.8, 2940.5, 1737.9, 1187.3. MS HR-ESI: calcd for $C_{12}H_{16}O_3Na$ (M + Na$^+$) *m*/*z* 231.0997, found 231.0986;

1-(2,6-Dimethoxyphenyl)ethan-1-ol (**25**). Previously reported[41] without characterization. Synthesized as described below.



A solution of 1,3-dimethoxybenzene (786 mg, 5.69 mmol) in 20 mL of THF was cooled to −78 °C and treated with 1.96 M *n*-BuLi in hexanes (3.8 mL, 7.5 mmol). The reaction mixture was allowed to warm to rt, stirred for 2 h, and then cooled to −78 °C and treated with acetaldehyde (0.5 mL, 9 mmol). The mixture was allowed to warm to rt and worked up as usual with water and Et$_2$O. The organic phase was dried over MgSO$_4$, concentrated, and subjected to flash chromatography (15→20% EtOAc/hexanes) to afford a pale-yellow solid (608 mg, 59% yield). Mp: 54–55 °C (from hexanes). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.26 (t, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 8.1 Hz, 2H), 5.38–5.27 (m, 1H), 3.88 (br, 1H), 3.84 (s, 3H), 1.49 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 157.4, 128.1, 120.9, 104.3, 64.0, 55.7, 23.6. IR: 2967, 1596, 1477, 1234, 1108. MS HR-ESI: calcd for $C_{10}H_{14}O_3Na^+$ (M + Na$^+$) 205.0835, found 205.0844.

*1-(Anthracen-9-yl)ethan-1-ol (**26**). Alcohol:* Commercially available. HPLC (OD-H, 10% *i*-PrOH/hexane): 10.4 min (*S*), 21.5 min (*R*). *Propionate ester:* ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.63 (d, *J* = 8.7 Hz, 2H), 8.43 (s, 1H), 8.01 (d, *J* = 7.8 Hz, 2H), 7.57–7.44 (m, 5H), 2.49–2.29 (m, 2H), 1.95 (d, *J* = 6.6 Hz, 3H), 1.11 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 174.1, 132.6, 131.9, 129.6, 129.6, 128.7, 126.1, 125.0, 69.0, 28.0, 21.8, 9.2. IR: 3052, 2981, 1939, 1736, 1670, 1183, 732, 698. MS HR-ESI:: calcd for $C_{19}H_{18}NaO_2^+$ (M + Na$^+$) 301.1199, found 301.1195.

*1-(Anthracen-9-yl)-2,2,2-trifluoroethan-1-ol (**27**). Alcohol:* Commercially available. HPLC (OD-H, 10% *i*-PrOH/hexane): 12.1 min (*S*), 29.2 min (*R*). *Propionate ester:* ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.79 (d, *J* = 9.07 Hz, 1H), 8.57 (s, 1H), 8.39 (d, *J* = 9.3 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.89 (q, *J* = 8.1 Hz, 1H), 7.68–7.51 (m, 4H), 2.63–2.43 (m, 2H), 1.16 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 172.6, 132.0, 131.7, 131.5, 131.3, 131.1, 129.8, 129.5, 127.9, 126.6, 125.2, 122.8, 121.6, 69.0(q, *J* = 137.7 Hz), 27.5, 9.0; IR: 3055, 2986, 1758, 1271, 1178, 1086, 730. MS HR-ESI: calcd for $C_{19}H_{15}F_3NaO_2^+$ (M + Na$^+$) 355.0916, found 355.0917.

*3-Chloro-1-phenylpropan-1-ol (**28**). Alcohol:* Synthesized by borohydride reduction of the corresponding ketone. ^{1}H NMR data (see the Supporting Information) are in agreement with those previously reported.[42] HPLC (AS-H, 1% *i*-PrOH/hexane): 22.5 min (*R*), 26.0 min (*S*). *Propionate ester:* ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.36–7.26 (m, 5H), 5.95 (dd, J_1 = 8.4 Hz, J_2 = 5.4 Hz, 1H), 3.61–3.41 (m, 2H), 2.45–2.16 (m, 4H), 1.14 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 173.6, 139.9, 128.9, 128.4, 126.6, 73.2, 40.9, 39.4, 27.9, 9.3. IR (KBr, cm^{-1}): 3033, 2979, 1740, 1183, 699. MS HR-ESI: calcd for $C_{12}H_{15}ClNaO_2^+$ (M + Na$^+$) 249.0653, found 249.0652.

*1-Phenyl-2-(pyridin-2-yl)ethan-1-ol (**32**). Alcohol:* Synthesized from 2-picoline and benzaldehyde as previously described.[6g,43] ^{1}H NMR data (see the Supporting Information) are in agreement with those previously reported.[43] HPLC (OD-H, 10% *i*-PrOH/hexane): 9.0 min (*R*), 15.4 min (*S*). *Propionate ester:* ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.54 (m, 1H), 7.56 (td, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 7.38–7.26 (m, 5H), 7.14–7.09 (m, 2H), 6.20 (dd, J_1 = 9.0 Hz, J_2 = 5.4 Hz, 1H), 3.41–3.20 (m, 2H), 2.25 (q, *J* = 7.8 Hz, 2H), 1.02 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 173.5, 157.7, 149.6, 140.6, 136.4, 128.7, 128.2, 126.7, 124.1, 121.9, 75.5, 45.6, 27.9, 9.2. IR (KBr, cm^{-1}) 3033, 2980, 2941, 1737, 1182, 763, 700. MS HR-ESI: calcd for $C_{16}H_{17}NNaO_2^+$ (M + Na$^+$) 278.1151, found 278.1152. *Isobutyrate ester:* ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.45 (m, 1H), 7.56 (td, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 7.38–7.24 (m, 5H), 7.14–7.10 (m, 2H), 6.19 (dd, J_1 = 9.0 Hz, J_2 = 5.4 Hz, 1H), 3.40–3.21 (m, 2H), 2.51–2.42 (m, 1H), 1.03 (t, *J* = 7.2 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 176.1, 157.7, 149.6, 140.7, 136.4, 128.7, 128.1, 126.6, 124.1, 121.9, 75.4, 45.7, 34.2, 19.1, 18.9. IR (KBr, cm^{-1}): 3033, 2973, 1734, 1190, 1153, 762, 699. MS HR-ESI: calcd for $C_{17}H_{19}NNaO_2^+$ (M + Na$^+$) 292.1308, found 292.1308.

*tert-Butyl (2R)-2-[(2R)-2-Hydroxy-2-phenylethyl]piperidine-1-carboxylate (**33**).* Alcohol: Synthesized from 1-phenyl-2-(pyridin-2-yl)ethan-1-ol **32** (see above) as previously described.[6g] ^{1}H NMR data (see the Supporting Information) are in agreement with those previously reported.[44] HPLC (OD-H, 2% *i*-PrOH/hexane): 12.6 min (*R*); 26.2 min (*S*). *Propionate ester:* ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.35–7.24 (m, 5H), 5.72 (dd, J_1 = 8.4 Hz, J_2 = 5.7 Hz, 1H), 4.26 (br, 1H), 3.99 (d, *J* = 12.6 Hz, 1H), 2.85 (t, *J* = 12.6 Hz, 1H), 2.41–2.24 (m, 3H), 1.97–1.88 (m, 1H), 1.60–1.49 (m, 5H), 1.43–1.33 (m, 10H), 1.11 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 173.9, 155.0, 140.9, 128.7, 128.2, 126.9, 79.5, 74.1, 36.4, 28.7, 28.1, 27.9, 25.7, 19.2, 9.2. IR (KBr, cm^{-1}) 2975, 2935, 1739, 1689, 1164, 699; MS HR-ESI: calcd for $C_{21}H_{31}NNaO_4^+$ (M + Na$^+$) 384.2145, found 384.2143. *Isobutyrate ester:* ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.34–7.24 (m, 5H), 5.69 (dd, J_1 = 8.4 Hz, J_2 = 6.0 Hz, 1H), 4.27 (br, 1H), 3.99 (d, *J* = 12.6 Hz, 1H), 2.85 (t, *J* = 12.6 Hz, 1H), 2.61–2.51 (m, 1H), 2.32–2.22 (m, 1H), 1.98–1.90 (m, 1H), 1.60–1.49 (m, 5H), 1.43–1.33 (m, 10H), 1.16 (d, *J* = 7.2 Hz, 3H), 1.13 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 176.4, 155.0, 141.0, 128.7, 128.1, 126.7, 79.5, 74.0, 36.4, 34.3, 28.7, 27.9, 25.7, 19.2, 19.1, 19.0. IR (KBr, cm^{-1}) 2973, 2933, 1734, 1689, 1162, 761, 699. MS HR-ESI: calcd for $C_{22}H_{33}NNaO_4^+$ (M + Na$^+$) 398.2302, found 398.2297.

*tert-Butyl (2S)-2-[(2R)-2-Hydroxy-2-phenylethyl]piperidine-1-carboxylate (**34**). Alcohol:* Synthesized from 1-phenyl-2-(pyridin-2-yl)ethan-1-ol **32** (see above) as previously described.[6g] ^{1}H NMR data (see the Supporting Information) are in agreement with those previously reported.[44] HPLC (AD-H, 8% *i*-PrOH/hexane): 9.4 min (*R*); 19.9 min (*S*). *Propionate ester:* ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.33–7.24 (m, 5H), 5.58(t, *J* = 6.9 Hz, 1H), 5.60–3.98 (br, 2H), 2.73 (t, *J* = 12.6 Hz, 1H), 2.42–2.04 (m, 4H), 1.58–1.41 (m, 16H), 1.01 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 173.7, 155.0, 141.3, 128.7, 128.1, 126.6, 79.5, 73.2, 39.1, 36.8, 28.9, 28.6, 27.9, 25.8, 19.3, 9.1. IR (KBr, cm^{-1}) 2977, 2936, 1743, 1689, 1166, 699. MS HR-ESI: calcd for $C_{21}H_{31}NNaO_4^+$ (M + Na$^+$) 384.2145, found 384.2146.

*1-(Pyridin-2-yl)ethan-1-ol (**35**). Alcohol:* Synthesized by borohydride reduction of the corresponding ketone. ^{1}H NMR data (see the Supporting Information) are in agreement with those previously reported.[40] (+)-(*R*)-Enantiomer[45] recovered after KR using (*S*)-**2** and

-**3**. HPLC (OD-H, 1% *i*-PrOH/hexane): 25.8 min (*R*), 30.2 min (*S*). *Propionate ester:* ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.54 (d, J = 4.5 Hz, 1H), 7.67−7.61 (m, 1H), 7.27 (d, J = 7.8 Hz, 1H), 7.18−7.13 (m, 1H), 5.88 (q, J = 6.6 Hz, 1H), 2.37 (q, J = 6.6 Hz, 2H), 1.55 (d, J = 6.9 Hz, 3H), 1.12 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 173.9, 160.7, 149.5, 136.9, 122.8, 120.5, 73.0, 28.0, 20.9, 9.3. IR (KBr, cm^{-1}) 3056, 2982, 1739, 1186, 1070, 749. MS HR-ESI: calcd for $C_{10}H_{14}NO_2$ (M + H$^+$) 180.1019, found 180.1018.

*1-(Thiophene-2-yl)ethan-1-ol (**36**).* Alcohol: Synthesized by borohydride reduction of the corresponding ketone. ^{1}H NMR data (see the Supporting Information) are in agreement with those previously reported.[37] (+)-(*R*) Enantiomer[37] recovered after KR using (*S*)-**2** and -**3**. GC (20 m of cyclodextrin-β analytical column, temperature increased from 105 to 125 °C, 0.5 °C/min): 11.8 min (*S*), 12.3 min (*R*). *Propionate ester:* ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.25 (m; 1H), 7.05 (m; 1H), 6.96 (m; 1H), 6.19 (q; J = 6.6 Hz; 1H), 2.33 (q; J = 7.7 Hz; 2H), 1.64 (d; J = 6.6 Hz; 3H), 1.14 (t; J = 7.7 Hz; 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 173.4, 144.6, 126.4, 125.0, 67.3, 27.7, 21.9, 8.9. IR (KBr, cm^{-1}): 2983, 2941, 1738, 1183. MS HR-ESI: calcd for $C_9H_{12}O_2SNa$ (M + Na$^+$) *m*/*z* 207.0456, measured *m*/*z* 207.0453.

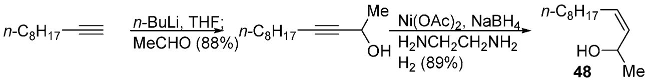
*(3E,5E)-Hepta-3,5-dien-2-ol (**43**).* Alcohol: Synthesized by addition of methylmagnesium chloride to the corresponding aldehyde.[46] ^{1}H NMR data (see the Supporting Information) are in agreement with those previously reported.[46] The enantiomer recovered after KR using (*S*)-**2** and -**3** was assigned the (*R*)-configuration using Mosher ester analysis.[47] HPLC (OD-H, 2% *i*-PrOH/hexane): 8.9 min (*R*), 10.6 min (*S*). *Propionate ester:* ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.20 (dd; J_1 = 15.1 Hz, J_2 = 10.5 Hz; 1H), 6.01 (m; 1H), 5.67 (m; 1H), 5.52 (dd; J_1 = 15.1 Hz; J_2 = 7.7 Hz; 1H), 5.37 (quintet; J = 7.7 Hz; 1H), 2.30 (q; J = 7.4 Hz; 2H), 1.75 (d; J = 7.7 Hz; 1H), 1.43 (d; J = 6.3 Hz; 3H), 1.13 (t; J = 7.4 Hz; 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.7, 131.9, 130.8, 130.6, 129.7, 70.6, 27.9, 20.3, 18.1, 9.1. IR (KBr, cm^{-1}) 2928, 2853, 1735, 1187. MS HR-ESI calcd for $C_{10}H_{16}O_2Na$ (M + Na$^+$) *m*/*z* 191.1043, measured *m*/*z* 191.1057.

*(3E)-4-(2,6,6-Trimethylcyclohex-1-en-1-yl)but-3-en-2-ol (**44**). Alcohol:* Synthesized by borohydride reduction of the corresponding ketone. ^{1}H NMR data (see the Supporting Information) are in agreement with those previously reported[48] (+)-(*R*) enantiomer[48] recovered after KR using (*S*)-**2** and -**3**. HPLC (OD-H, 100% hexane): 33.3 min (*S*), 38.1 min (*R*). *Propionate ester:* ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.06 (m; 1H), 5.42−5.36 (m; 2H), 2.30 (q; J = 7.6 Hz; 2H), 1.95 (m; 2H), 1.63 (s; 3H), 1.62−1.56 (m; 2H), 1.44−1.40 (m; 2H), 1.33 (d; J = 6.1 Hz, 3H), 1.12 (t; J = 7.6 Hz; 3H), 0.96 (s; 3H), 0.95 (s; 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.7, 136.5, 132.9, 129.9, 71.3, 39.3, 33.8, 32.6, 28.6, 28.0, 21.2, 20.5, 19.2, 9.2. MS HR-ESI: calcd for $C_{16}H_{26}O_2Na$ (M + Na$^+$) *m*/*z* 273.1825, measured *m*/*z* 273.1833. IR (KBr, cm^{-1}): 2964, 2929, 2866, 1738, 1187.

*(3E)-6-Phenylhex-3-en-2-ol (**45**). Alcohol:* Synthesized from 3-phenylpropanal as previously described.[49] ^{1}H NMR data (see the Supporting Information) are in agreement with those previously reported.[49] (+)-(*R*)-Enantiomer[49] recovered after KR using (*S*)-**2** and -**3**. Absolute configuration confirmed using Mosher ester analysis.[47] HPLC separation achieved using the corresponding phenylcarbamate (see below). *Propionate:* ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.34−7.29 (m; 2H), 7.24−7.19 (m; 3H), 5.76 (dt; J_1 = 15.2 Hz, J_2 = 6.6 Hz; 1H), 5.51 (dd; J_1 = 15.2, J_2 = 6.5 Hz; 1H), 5.36 (quintet; J = 6.5 Hz; 1H), 2.73 (t; J = 7.6 Hz; 2H), 2.42−2.36 (m; 2H), 2.34 (q; J = 7.6 Hz; 2H), 1.31 (d; J = 6.5 Hz; 3H), 1.17 (t; J = 7.6 Hz; 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.7, 141.6, 132.0, 130.3, 128.4, 128.2, 125.8, 70.7, 35.4, 33.9, 27.9, 20.3, 9.1. MS HR-ESI calcd for $C_{15}H_{21}O_2Na$ (M + Na$^+$) *m*/*z* 255.1356, measured *m*/*z* 255.1358. IR (KBr, cm^{-1}): 2980, 2932, 1736, 1189. *N-Phenylcarbamate:* ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.46 (m; 2H), 7.36 (m; 4H), 7.25 (m; 3H), 7.13 (m; 1H), 6.76 (s; 1H), 5.88 (dt; J_1 = 15.4 Hz, J_2 = 6.6 Hz; 1H), 5.59 (dd; J_1 = 15.4 Hz, J_2 = 6.6 Hz; 1H), 5.41 (quintet; J = 6.6 Hz; 1H), 2.77 (t; J = 6.6 Hz; 2H), 2.43 (q; J = 6.6 Hz; 2H), 1.41 (d; J = 6.6 Hz; 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 152.9, 141.5, 138.0, 132.3, 130.2, 128.9, 128.4, 128.2, 125.8, 123.2, 118.6, 71.9, 35.3, 33.9, 20.5. IR (KBr, cm^{-1}) 3321, 3027, 2979, 2931, 1704, 1600, 1539, 1444, 1313, 1223, 1049.0. MS HR-ESI: calcd for $C_{19}H_{21}NO_2Na$ (M + Na$^+$) *m*/*z* 318.1464, measured *m*/*z* 318.1465. HPLC (OD-H, 20% *i*-PrOH/hexane): 27.4 min (*R*), 33.9 min (*S*).

*(3Z)-4-Phenylbut-3-en-2-ol (**47**). Alcohol:* Synthesized by partial hydrogenation of 4-phenyl-3-butyn-2-ol as previously described.[50] ^{1}H NMR data (see the Supporting Information) are in agreement with those previously reported.[51] (−)-(*S*) enantiomer[52] recovered after KR using (*R*)-**2**. HPLC (OD-H, 5% *i*-PrOH/hexane): 6.1 min (*S*), 12.1 min (*R*). Absolute configuration was additionally confirmed by hydrogenation to 4-phenylbutan-2-ol and HPLC comparison with a sample obtained by hydrogenation of resolved *trans*-isomer **37** (see below). *Propionate ester:* ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.42−7.30 (m; 5H), 6.58 (d; J = 11.6 Hz; 1H), 5.88 (dq; J_1 = 9.0 Hz, J_2 = 6.3 Hz; 1H), 5.71 (dd; J_1 = 11.6 Hz, J_2 = 9.0 Hz; 1H), 2.34 (q; J = 7.6 Hz; 2H), 1.42 (d; J = 6.3 Hz; 3H), 1.17 (t; J = 7.6 Hz; 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.5, 136.3, 131.4, 130.8, 128.5, 128.3, 127.3, 67.6, 27.8, 20.8, 9.0. IR (KBr, cm^{-1}) 2980, 2940, 1733, 1190. MS HR-ESI calcd for $C_{13}H_{16}O_2Na$ (M + Na$^+$) *m*/*z* 227.1043, measured *m*/*z* 227.1048. *4-Phenylbutan-2-ol:* HPLC (OD-H, 10% *i*-PrOH/hexane, 0.5 mL/min): 12.8 min (*R*), 18.0 min (*S*).

*(3Z)-3-Dodecen-2-ol (**48**) Alcohol.* Synthesized from 1-decyne as described below.

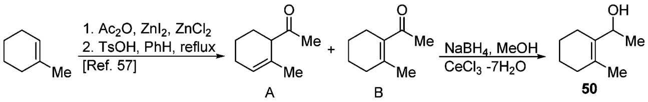


(a) Preparation of 3-Dodecyn-2-ol.[52] A solution of 1-decyne (996 mg, 7.23 mmol) in 9 mL of THF was cooled to −78 °C, treated with *n*-BuLi (2.9 mL, 2.5 M), and allowed to warm to 0 °C. After 15 min, the reaction mixture was cooled to −78 °C, and a solution of acetaldehyde (0.45 mL, 8.0 mmol) in 3 mL of THF was added dropwise. The mixture was again allowed to warm to 0 °C, stirred at that temperature for 2 h, quenched with saturated aqueous NH$_4$Cl, and extracted with Et$_2$O. The extract was dried over Na$_2$SO$_4$, concentrated, and subjected to flash chromatography (10→15% EtOAc/hexane) to afford 1.16 g of the expected alcohol (88% yield). *(a) Preparation of 3-Dodecen-2-ol **48**.*[52] Performed analogously to the literature procedure referenced above.[50] A solution of NaBH$_4$ (53 mg, 1.4 mmol) in 2 mL of EtOH was added to a solution of Ni(OAc)$_2$·4H$_2$O (342 mg, 1.37 mmol) in 60 mL of EtOH. To the resulting black suspension were added ethylenediamine (172 mg, 2.86 mmol) and 3-dodecyn-2-ol (1.935 g, 10.6 mmol). The flask with purged with hydrogen, and the reaction mixture was stirred at rt for 2 h until completion (^{1}H NMR). The hydrogen atmosphere was removed, activated charcoal was added, and the reaction mixture was filtered through a plug of Celite and extracted with Et$_2$O. The extract was washed with water and brine, dried over Na$_2$SO$_4$, and concentrated. Flash chromatography (5→10% EtOAc/hexane) afforded 1.740 g of the pure *Z*-allylic alcohol ^{1}H NMR data (see the Supporting Information) are in agreement with those previously reported.[52] (−)-(*S*)-Enantiomer[52] was recovered after KR using (*R*)-**2**. HPLC separation achieved using the corresponding phenylcarbamate (see below). *Propionate ester:* ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.64 (m; 1H), 5.52−5.44 (m; 1H), 5.35 (m; 1H), 2.28 (q; J = 7.5 Hz; 2H), 2.14 (m; 2H), 1.4−1.2 (m; 15 H), 1.14 (t; J = 7.5 Hz; 3H), 0.87 (m; 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 173.7, 133.1, 129.3, 66.9, 31.8, 29.5, 29.4, 29.3, 27.9, 27.3, 22.6, 20.9, 14.1, 9.1. IR (KBr, cm^{-1}): 2925.9, 2855.1, 1737.7, 1188.3. MS HR-ESI: calcd for $C_{15}H_{28}O_2Na$ (M + Na$^+$) *m*/*z* 263.1987, measured *m*/*z* 263.1984. *N-Phenylcarbamate:* ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.38 (m; 2H), 7.29 (m; 2H), 7.04 (m; 2H), 6.55 (s; 1H), 5.66 (m; 1H), 5.51 (m; 1H), 5.41 (m; 1H), 2.17 (m; 2H), 1.34 (d; J = 6.3 Hz; 3H), 1.26 (m; 12H), 0.87 (t; J = 6.7 Hz; 3H). ^{13}C NMR

(75 MHz, $CDCl_3$): δ 152.9, 138.0, 133.4, 129.2, 129.0, 123.2, 118.6, 68.0, 31.9, 29.53, 29.45, 29.26, 29.25, 27.8, 22.6, 21.2, 14.1. IR (KBr, cm^{-1}): 3323, 2926, 2854, 1704, 1603, 1538, 1443, 1312, 1221, 1051. MS HR-ESI: calcd for $C_{19}H_{30}NO_2Na$ ($M + Na^+$) m/z 326.2091, measured m/z 326.2100. HPLC (OD-H, 6% *i*-PrOH/hexane): 6.8 min (*S*), 20.3 min (*R*).

*4-Methylpent-3-en-2-ol (**49**). Alcohol:* Synthesized by borohydride reduction of the corresponding ketone. ^1H NMR data (see the Supporting Information) are in agreement with those previously reported.[39] (*S*)-Enantiomer recovered after KR using (*R*)-**2**. HPLC separation achieved using the corresponding phenylcarbamate (see below). The absolute configuration was established by hydrogenation to 4-methyl-2-pentanol and HPLC comparison of the corresponding *p*-nitrobenzoate with a sample derived from commercially available (*R*)-4-methyl-2-pentanol (see below). *Propionate ester:* ^1H NMR (300 MHz, $CDCl_3$): δ 5.58 (m; 1H), 5.15 (m; 1H), 2.28 (q; *J* = 7.7 Hz; 2H), 1.71 (s; 6H), 1.24 (d; *J* = 6.3 Hz; 3H), 1.11 (t; *J* = 7.7 Hz; 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 136.1, 125.0, 68.0, 27.9, 25.7, 20.9, 18.2, 9.1. IR (KBr, cm^{-1}): 2923, 2853, 1735, 1191. MS HR-EI: calcd for $C_9H_{16}O_2$ (M^+) m/z 156.1150, measured m/z 156.1146. *N-Phenylcarbamate:* ^1H NMR (300 MHz, $CDCl_3$): δ 7.37 (m; 2H), 7.29 (m; 2H), 7.04 (m; 1H), 6.60 (s; 1H), 5.65 (m; 1H), 5.24 (m; 1H), 1.81 (s; 3H), 1.79 (s; 3H), 1.39 (d; *J* = 6.3 Hz; 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.0, 138.1, 136.6, 129.0, 124.9, 123.2, 118.5, 69.1, 25.7, 21.2, 18.3. IR (KBr, cm^{-1}): 3320, 2975, 2931, 1701, 1600, 1539, 1444, 1230, 1063, 1046, 1026. MS HR-EI: calcd for $C_{13}H_{18}NO_2$ ($M + H^+$) m/z 220.1332, measured m/z 220.1330. HPLC (OD-H, 12% *i*-PrOH/hexane): 5.2 min (*S*), 20.2 min (*R*). *4-Methylpentan-2-yl 4-nitrobenzoate:*[53] HPLC (OD-H, 100% hexane): 18.7 min (*S*), 20.4 min (*R*).

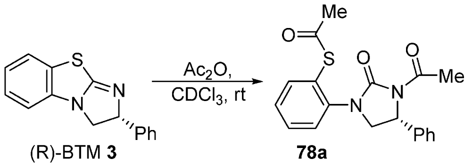
*1-(2-Methylcyclohex-1-en-1-yl)ethan-1-ol (**50**). Alcohol:* Synthesized as described below.



Acylation of 1-methylcyclohexene followed by acid-catalyzed isomerization was carried out as described in the literature[54] to afford a mixture of isomeric ketones A and B, which could be separated completely only by flash chromatography on silica gel impregnated with 10% $AgNO_3$ (0→2% EtOAc/hexane). Pure ketone B (92 mg, 0.666 mmol) and $CeCl_3{\cdot}7H_2O$ (248 mg, 0.666 mmol) were dissolved in 2 mL of MeOH. Solid $NaBH_4$ (50 mg, 1.32 mmol) was added at rt. After being stirred for 1 h, the reaction mixture was quenched with aqueous NH_4Cl and extracted three times with Et_2O. Drying the extract over $MgSO_4$ gave 78 mg of **50** (84% yield), which was pure by NMR. ^1H NMR (300 MHz, $CDCl_3$): δ 4.84 (q; *J* = 6.3 Hz; 1H), 1.94 (m; 3H), 1.65 (s; 3H), 1.67−1.5 (m; 5H), 1.21 (d; *J* = 6.3 Hz; 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.8, 128.1, 66.7, 32.3, 22.99, 22.98, 22.2, 20.8, 18.6. IR (KBr, cm^{-1}): 2924, 1727, 1284. MS HR-ESI: calcd for $C_9H_{17}O$ ($M + H^+$) 141.1274, found 141.1274. (−)-(*R*)-Enantiomer recovered after KR using using (*S*)-**2** and -**3**. Absolute configuration assigned using Mosher ester analysis.[47] HPLC separation achieved using the corresponding N-phenylcarbamate (see below). *Propionate ester:* ^1H NMR (300 MHz, $CDCl_3$): δ 5.79 (q; *J* = 6.6 Hz; 1H), 2.28 (q; *J* = 7.5 Hz; 2H), 1.95 (m; 4H), 1.68 (s; 3H), 1.60−1.45 (m; 4H), 1.24 (d; *J* = 6.6 Hz; 3H), 1.11 (t; *J* = 7.5 Hz; 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 129.4, 69.9, 32.1, 27.8, 23.0, 22.84, 22.80, 18.9, 18.5, 9.2. IR (KBr, cm^{-1}): 2924, 2854, 1737, 1462. MS HR-ESI: calcd for $C_{12}H_{20}O_2Na$ ($M + Na^+$) m/z 219.1356, measured m/z 219.1355. *N-Phenylcarbamate:* ^1H NMR (300 MHz, $CDCl_3$): δ 7.38 (m; 2H), 7.29 (m; 2H), 7.04 (m; 1H), 6.52 (s; 1H), 5.83 (q; *J* = 6.6 Hz; 1H), 2.02−1.97 (m; 4H), 1.73 (s; 3H), 1.62−1.52 (m; 4H), 1.32 (d; *J* = 6.6 Hz; 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.1, 138.2, 129.9, 129.3, 129.0, 123.2, 118.5, 71.1, 32.1, 23.1, 22.83, 22.82, 18.9,18.7; IR (KBr, cm^{-1}): 3310, 2929, 1698, 1601, 1538, 1443, 1225, 1050. MS HR-ESI: calcd for $C_{16}H_{22}NO_2$ ($M + H^+$) m/z 260.1645, measured m/z 260.1642. HPLC (OD-H, 10% *i*-PrOH/hexane): (*R*)-enantiomer: 11.6 min; (*S*)-enantiomer: 5.0 min.

*Naphthalen-2-ylmethyl Propanoate (**80**). Alcohol:* Commercially available. *Propionate:* Previously reported without characterization.[55] ^1H NMR (300 MHz, $CDCl_3$): δ 7.87−7.83 (m, 4H), 7.52−7.46 (m, 3H), 5.30 (s, 2H), 2.53−2.39 (m, 2H), 1.20 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.3, 133.5, 133.2, 133.1, 128.4, 128.0, 127.7, 127.3, 126.3, 126.2, 126.2, 125.9, 66.3, 27.6, 9.1. IR: 2923, 1732, 1176. MS HR-ESI: calcd for $C_{14}H_{14}O_2Na^+$ ($M + Na^+$) m/z 237.0886, measured m/z 237.0890.

4. Deactivation of BTM in the Presence of Moisture: A Control Experiment.



To a solution of BTM (30 mg, 0.12 mmol) and Ac_2O (50 μL, 0.53 mmol) in 1 mL of $CDCl_3$ in an NMR tube was added 5 μL of water. The reaction progress was monitored by ^1H NMR. The color of the solution slowly changed to brown. After one week, 31 mg (74% yield) of the product (1-acetyl-2-oxo-3-[2-(acetylthio)phenyl]-4-phenyl-2,3,4,5-tetrahydroimidazole, **78a**) was isolated by flash chromatography (EtOAc/hexanes 1:2). ^1H NMR (300 MHz, $CDCl_3$): δ 7.56−7.26 (m, 9H), 5.46 (dd, J_1 = 9.3 Hz, J_2 = 2.9 Hz, 1H), 4.22 (t, *J* = 9.3 Hz, 1H), 3.56 (dd, J_1 = 8.7 Hz, J_2 = 2.9 Hz, 1H), 2.57 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.3, 170.3, 153.9, 140.8, 139.7, 137.5, 131.3, 129.0, 128.9, 128.1, 127.8, 127.4, 125.6, 54.6, 52.9, 30.2, 24.0. IR (film, cm^{-1}): 1729, 1692, 1376. MS FAB: calcd for $C_{19}H_{18}O_3N_2S$, ($M + Na^+$) m/z 377.0935, found 377.0930.

6. Inhibition of BTM by Alcohol Substrates. *6a. Comparison of the Reaction Rates of (2-Naphthyl)methanol and (±)-1-Phenylethanol.* (2-Naphthyl)methanol **79** (79 mg, 0.50 mmol), racemic 1-phenylethanol (±)-**7** (68 mg, 0.50 mmol), (*S*)-BTM *ent*-**3** (10 mg, 0.040 mmol), and *i*-Pr_2NEt (174 μL, 1.0 mmol) were dissolved in $CDCl_3$ in a 1 mL volumetric tube (final concentration: 0.50 M (2-naphthyl)methanol, 0.50 M 1-phenylethanol, 0.040 M BTM, 1.0 M *i*-Pr_2NEt). The mixture was transferred into an NMR tube, neat propionic anhydride (128 μL, 1 mmol) was added at room temperature, and the reaction progress was monitored by ^1H NMR. In 10 min, the conversion of (2-naphthyl)methanol into the corresponding propionate ester **80** reached ca. 30%, while that of 1-phenylethanol was ca. 3%. Thus, the consumption of propionic anhydride by the latter was not expected to provide much interference when monitoring the acylation of the former. The *C*H-O peaks of the alcohols and the esters did not overlap and could be integrated with fair accuracy.

All subsequent experiments were performed at room temperature using the stock solutions listed below (in deuterated chloroform). The reaction progress was monitored by comparing the integration of the *C*H-O peaks of the reactant alcohols and the corresponding esters in the ^1H NMR spectra of the reaction mixtures: Stock solution A: 1.0 M (2-naphthyl)methanol, 1.0 M *i*-Pr_2NEt. Stock solution B: 0.20 M (*S*)-BTM, 1.0 M *i*-Pr_2NEt. Stock solution C-1−C-5: 1.0 M 1 [(±)-**7**, (±)-**25**, (±)-**37**, (*S*)-**37** (97% ee), (*R*)-**37** (93% ee), respectively], 0.20 M (*S*)-BTM, 1.0 M *i*-Pr_2NEt.

6b. Background Reaction Check. Propionic anhydride (64 μL, 0.50 mmol, 1.0 equiv) was added to 0.50 mL of stock solution A. After

4 h, no acylation of (2-naphthyl)methanol was detected by NMR (Table 9, entry 1).

6c. Catalyzed Acylation of (2-Naphthyl)methanol in the Absence of Other Alcohols. To stock solution A (0.40 mL) was added stock solution B (0.10 mL) followed by propionic anhydride (64 μL, 0.50 mmol), resulting in a reaction mixture with the following initial concentrations of the reactants: 0.80 M (2-naphthyl)methanol **79**, 0.040 M (*S*)-BTM, 1.0 M $(EtCO)_2O$, 1.0 M *i*-Pr_2NEt. Conversion of (2-naphthyl)methanol reached 50% in 28 min (Table 9, entry 2).

*6d. Catalyzed Acylation of (2-Naphthyl)methanol **79** in the Presence of Other Alcohols. Typical Procedure.* One milliliter aliquots of Stock Solutions A and C-1 were each treated with propionic anhydride (128 μL, 1.0 mmol, 1 equiv). Within 1.5−2 min of mixing, a 0.1 mL aliquot of reaction mixture C-1 was added to a 0.4 mL aliquot of reaction mixture A resulting in the following initial concentrations of the reactants: 0.80 M (2-naphthyl)methanol **79**, 0.20 M (±)-1-phenylethanol **7**, 0.04 M (*S*)-BTM, 1.0 M *i*-Pr_2NEt, 1.0 M $(EtCO)_2O$. At that time, the conversion of **7** into its ester was estimated to be 49%. Monitoring by NMR continued. The conversion of **7** did not change substantially over time, while that of **79** reached 50% after 45 min (Table 9, entry 3, column 4).

After aging reaction mixture C-1 for 2 h at room temperature, a new 0.1 mL aliquot was withdrawn from it and added to 0.4 mL of freshly prepared reaction mixture A (stock solution A + $(EtCO)_2O$). The conversion of **7** at that point was 82%. The half-life of **79** in the resulting mixture was 51 min (Table 9, entry 3, column 5). The procedure described above was repeated with stock solutions C-2−C-5. The results are summarized in Table 9, entries 4−7.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

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Notes

The authors declare no competing financial interest.

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