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Lipophilic Oligopeptides for Chemo- and Enantioselective Acyl Transfer Reactions onto Alcohols

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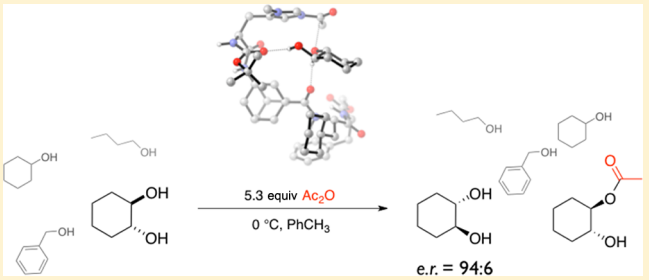
Supporting Information

ABSTRACT: Inspired by the extraordinary selectivities of acylases, we envisioned the use of lipophilic oligopeptidic organocatalysts for the acylative kinetic resolution/desymmetrization of *rac*- and *meso*-cycloalkane-1,2-diols. Here we describe in a full account the discovery and development process from the theoretical concept to the final catalyst, including scope and limitations. Competition experiments with various alcohols and electrophiles show the full potential of the employed oligopeptides. Additionally, we utilized NMR and IR-spectroscopic methods as well as computations to shed light on the factors responsible for the selectivity. The catalyst system can be readily modified to a multicatalyst by adding other catalytically active amino acids to the peptide backbone, enabling the stereoselective one-pot synthesis of complex molecules from simple starting materials.



INTRODUCTION

Stereoselective acylations of chiral or prochiral alcohols are common reactions both in nature and in chemistry. Enzymes can be used for the acylative resolution and desymmetrization of a broad range of secondary alcohols (e.g., cyclic *meso*-1,2- and 1,3-diols, 2,5-hexanediols, 1,4-cyclooctanediols, and acylation of natural products like vitamin C, alkaloids, and hydrocortisone).[1−5] Though enzymatic acylations are highly chemo- and enantioselective, these approaches are often expensive and require stringent reaction conditions and long reaction times, and typically just one enantiomer of the product can be obtained. Also, there is a variety of substrates that cannot be resolved effectively by enzymes (e.g., *trans*-cyclohexane-1,2-diol and primary alcohols).[6] Hence, in the past 20 years, various organic and organometallic catalysts (e.g., amidines,[7] vicinal diamines,[8,9] *N*-alkylimidazoles,[10−14] phosphines,[15,16] phosphinites,[17,18] Cu-complexes[19−21] and 4-aminopyridine derivatives[22,23])[24,25] were successfully applied in kinetic resolutions (KRs),[26,27] desymmetrizations,[28] and dynamic kinetic resolutions (DKR)[29,30] of alcohols, amines, and thiols (Figure 1).

The application of oligopeptides as catalysts for enantioselective transformations has been neglected for a surprisingly long time, though many approaches were inspired by nature.[31,32] Only at the end of the last century did chemists realize the capacity of oligopeptides as active catalysts due to their high diversity and their well-established syntheses based on the coupling of readily available enantiopure amino acids.[31−33] Early prominent examples are the cyclic dipeptides (diketopiperazines) introduced by Inoue in 1981 for the enantioselective hydrocyanation of benzaldehydes[34−38] and the homooligomers of Juliá and Colonna that proved to be highly efficient in epoxidation reactions.[39−42] Wennemers et al. discovered that short proline containing oligopeptides display significantly higher reactivity at comparable enantioselectivities in aldol reactions compared to proline itself, which emphasizes the importance of the peptide backbone (Figure 2).[43−45]

Acyl transfer as part of nature's reaction portfolio is one of the most prominent examples for the use of short non-natural peptide catalysts for enantioselective transformations.[24,25,31] In 1998, Miller and co-workers introduced *N*-alkylimidazole containing peptides (π-methyl histidine derivatives performed best) as acylation catalysts, which proved to be highly selective in various KRs and desymmetrizations.[31,46−49] Especially the KR of racemic *trans*-2-*N*-acetamidocyclohexanol using such peptides was intensively studied and led to the conclusion that a stable yet slightly flexible secondary structure based on intramolecular H-bonding is responsible for the high enantioselectivities (Figure 2).[31,46,49−51] Several attempts were made to improve the selectivities of these peptides by modifying the motifs that are responsible for the formation of a secondary structure (see the peptides of Toniolo[52] and Qu[53] in Figure 2). Though nonpeptidic catalysts were successfully utilized in natural product synthesis of, e.g., epothilone, (−)-baclofen (with Fu's planar chiral ferrocenyl-DMAP derivative),[54] lobeline (with Birman's amidine-based catalysts),[55] and biotin (with Deng's modified cinchona alkaloid catalyst),[56] peptidic approaches may offer chemoselective acylations of complex polyols bearing compounds (e.g.,

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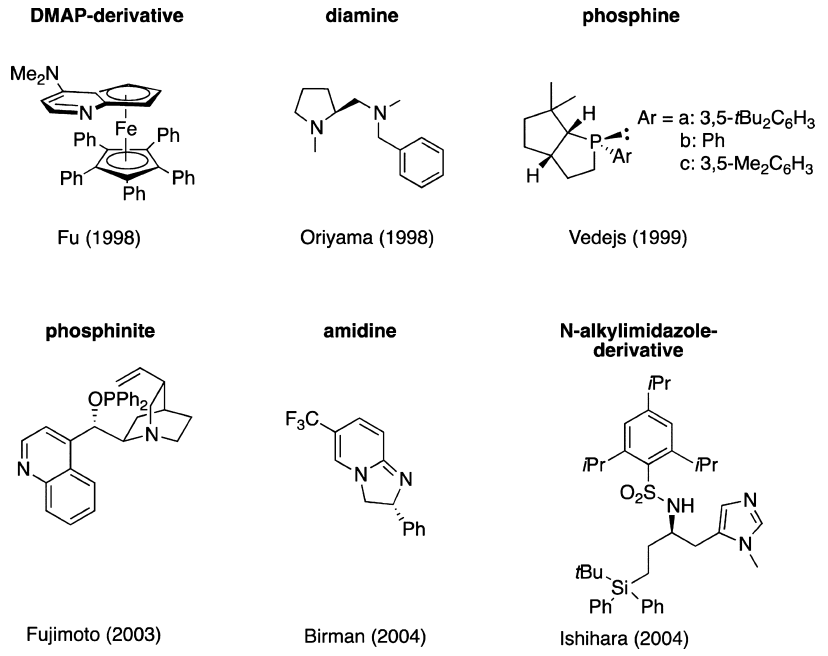

Figure 1. Nonpeptidic organocatalysts capable of selective acyl transfer.

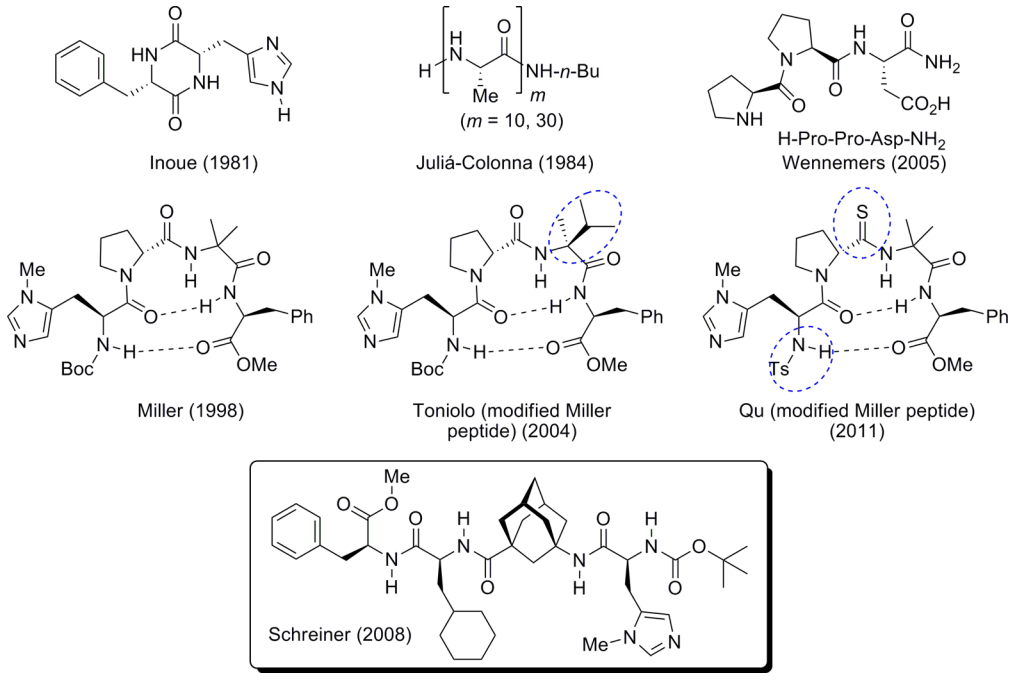

Figure 2. Peptide-based catalysts for enantioselective reactions.

vancomycin[57] and erythromycin A[58]) and even carbohydrates.[59]

In 2008 our group introduced a highly efficient tetrapeptide catalyst for the KR of *trans*-cycloalkane-1,2-diols via acyl transfer (Figure 2).[25,60] In contrast to the established peptide design concepts focusing on secondary structure formation, our approach utilizes a highly lipophilic, structurally less flexible, non-natural adamantane γ-amino acid (^{A}Gly in our shorthand notation) in the center of the peptide. We envisioned that the more flexible amino acids at the *N*- and the *C*-terminus of the peptide would form a "dynamic pocket" like an active site in an enzyme and enable selective acyl transfer. The incorporation of additional lipophilic amino acids would allow the use of nonpolar organic solvents.

The KR of cyclic chiral *trans*-cycloalkane-1,2-diols via acyl transfer was chosen as the test reaction, because no synthetically useful approach for this class of substrates was reported. Additionally, natural products bearing vicinal diols are frequently found (e.g., in steroids, flavonoids, carbohydrates, and pharmaceuticals), and therefore a highly chemoselective peptide would be quite useful.[61] Monoacetylation of *trans*-cycloalkane-1,2-diols utilizing enzymes (*Pseudomonas* lipases) displayed low activities as well as selectivities.[6] In the case of metal catalytic approaches for the KR of *trans*-cycloalkane-1,2-diols, only selective benzoyl transfers utilizing 0.5 equiv of

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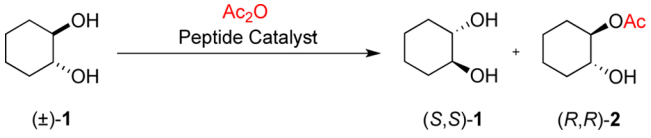
benzoyl chloride with lower selectivities (S = 14 to 22) compared to our approach (S > 50) were reported by Onomura (2003),[19] Reiser (2005),[20] and Pfaltz (2006).[21,62] This is one of the rare cases where a chemical method is significantly more efficient than an enzymatic approach. Later the same peptide or similar peptidic catalysts were successfully applied to selective single- and multicatalytic transformations.[25,63−68]

The identification of such highly enantioselective catalysts is still a formidable challenge and mostly relies on trial and error or extensive screening experiments, because the chemical recognition processes of catalyst and substrate are usually hardly predictable.[32] Here we report a full investigation of our oligopeptide catalyst platform, including catalyst screenings, substrate scope, and chemoselectivity, and present a structural mechanistic model for enantioselective acylations. Additionally, the peptide-catalyzed transfer of various other electrophiles will be described.

RESULTS AND DISCUSSION

Catalyst Screening Using the Acylative KR of *trans*-Cyclohexane-1,2-diol as Test Reaction. A large variety of peptide catalysts was synthesized via automated solid phase peptide synthesis (SPPS) using a Fmoc-strategy; additionally, the chosen peptides were prepared in solution in larger quantities utilizing Boc-strategy. The crude peptides were initially characterized using ESI-MS; purified peptides were characterized by NMR, IR, ESI-MS, and ESI-HRMS (for detailed experimental procedures and analytical data, see Experimental Section and Supporting Information). All peptide catalysts were tested in the KR of racemic *trans*-cyclohexane-1,2-diol **1** (Scheme 1) with acetic anhydride. Addition of a base

Scheme 1. KR of *trans*-Cyclohexane-1,2-diol 1 as Test Reaction



is not required, because the generated acetic acid (pK_a = 4.74) is comparably weak and in equilibrium with the methylimidazolium ion (pK_a = 7.3);[69] always a small amount of unprotonated catalyst is available.

We started our search for a new highly lipophilic peptide by using Boc-π-methyl histidine methylester **3** (Figure 3) as a catalyst to determine whether the acyl transfer onto **1** under our chosen reaction conditions (in toluene; no auxiliary base) is generally possible.[70] The ability to perform the KR in a nonpolar solvent in the absence of base simplifies the purification of the product. The *ee* values and yields for our test reaction (Table 1) with **3** were low. Additionally, we tested **4** introduced by Snapper and Hoveyda in 2006 (**4** showed excellent selectivities in the silylation of racemic and *meso*-1,2-diols) in the acylative KR of *rac*-**1**, but only low selectivity was observed.[71] Our design concept focused on the ^{A}Gly moiety as a sterically demanding and structure-determining spacer that should lead to lipophilic peptides soluble in organic solvents. At first we synthesized various tri-, tetra-, and pentapeptides and placed the rigid ^{A}Gly in the center of the molecule (Figure 3). We hoped separating the more flexible amino acids on the *C*- and *N*-terminus of the peptide would enable the formation of a chiral environment (e.g., "a pocket", vide infra). Several different catalytically active histidine moieties were tested: Boc-L-histidine for peptide **5**; Boc-L-(τ-Bzl)-histidine for **7**, **8**, and **9**; and Boc-L-(π-Me)-histidine for **6**, **10**, **11**, and **12a**.

The results for **3**−**12a** as applied to the KR of *rac*-**1** are summarized in Table 1. A comparison of the tripeptides **5**−**7** having the same peptidic backbone bearing a histidine (**5**), π-methyl histidine (**6**) and a τ-benzyl-histidine moiety (**7**) shows that Boc-L-(π-Me)-histidine is the catalytically most active histidine derivative. Tripeptidic and tetrapeptidic structures produced high yields but moderate selectivities; pentapeptides showed only low selectivities and activities and were not investigated further. Tetrapeptide **12a** was the most selective catalyst and was used as the reference structure for further modifications.

In contrast to enzymes, whose catalytically active sites often only exist in one stereoisomeric form, we readily synthesized *ent*-**12b** (all amino acids D-configured), and as expected, were able to acetylate *S*,*S*-**1** with the opposite selectivity. Switching the positions of L-Val and π-Me-His (**13**) or L-Val and ^{A}Gly (**17**) lowered the selectivities for the KR of *rac*-**1** compared to **12a**. Hence, it is important that ^{A}Gly is in direct neighborhood to the catalytically active His-moiety.

Next we focused on changing the configuration of Val, Boc-(π-Me)-His (**14** and **15**) and of both amino acids (**16**). The best *er* values were obtained for peptides containing homoconfigured Val and His (matched situation for **12a**,**b**, *ent*-**12b**, and **16**). The mismatched configuration of either Val or π-Me-His (**14** and **15**) decreases the selectivity for the KR of *rac*-**1** dramatically (Figure 4).

The catalytic efficiency of **12a** and the results presented in Table 2 encouraged further variations. The use of Boc-L-(π-Me)-His-^{A}Gly-L-Cha-L-Phe-OMe (**12b**) as catalyst gave the highest *ee* in the KR of *rac*-**1**. Indeed, **12b** is the most efficient catalyst for the KR of *trans*-cycloalkane-1,2-diols to date.[25,60] Though having identified a capable catalyst for the selective acylation of *rac*-**1** the role of the *C*-terminal amino acid was investigated by using the Boc-L-(π-Me)-His-^{A}Gly-L-Leu-L-R motif (Table 3) in order to obtain mechanistic insights into the substrate recognition process by the catalyst.

Peptide catalyst **21** with *C*-terminal L-Cha proved to be the most selective, but generally all tested peptides showed high selectivities. This finding implies that the *C*-terminal amino acid in the tetrapeptide does not strongly affect the selectivity of the peptide, and other catalytically active amino acids may be attached and therefore offer their application in multicatalytic approaches.[65,67,68]

Substrate Scope for Peptide 12b-Catalyzed Acylations. In contrast to the selective esterification of 1,2-diols such as **1** (the second OH-group is important as an internal H-bond donor), other biomimetic approaches mostly require monoacetylated 1,2-diols or monoacetylated 1,2-aminoalcohols to achieve high selectivities.[10−12,14,46] In these cases the additional H-bond acceptor of the acyl group serves as a docking position. Therefore acylation catalyst **12b** was tested in the KR of racemic **2**, **22**, and **23** (Figure 5). The latter substrate was successfully used by Miller et al.;[31,46,48,50] in our hands, Miller's catalyst also led to excellent selectivities in the KR of *rac*-**23** (90% *ee* for **23**, 86% *ee* for the diacetylated aminoalcohol, S = 41 at C = 51%, 24 h at 0 °C).[60] As expected, **12b** proved to be unselective in these three cases showing the complementarity to Miller's catalyst (Figure 2); this emphasizes the importance

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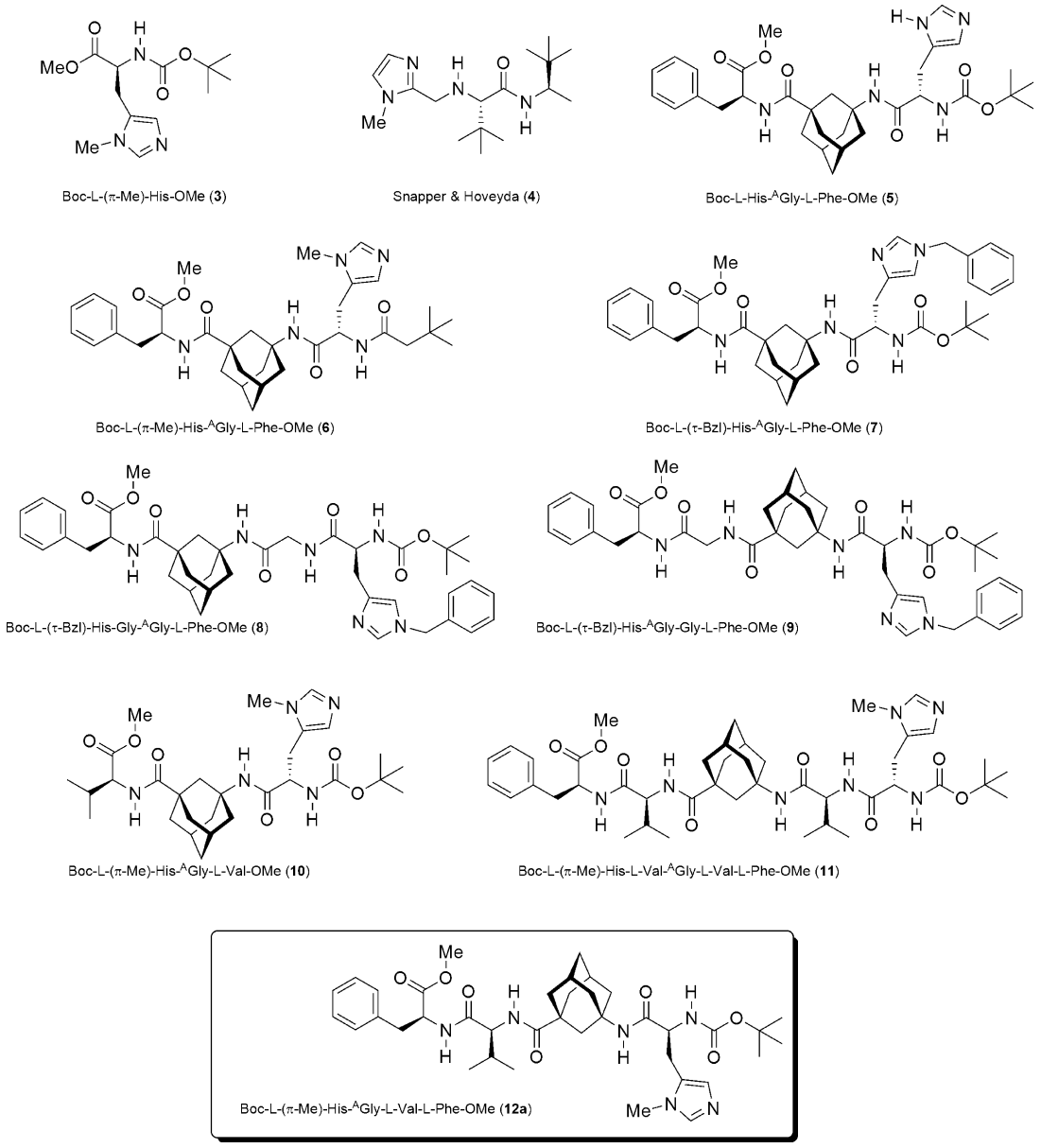

Figure 3. Starting sequences for the search of a selective acyl transfer catalyst.

of the second hydrogen bond donor in the enantiodifferentiating step with **12b**.

The enantioseparation of racemic secondary monoalcohols is another challenging field for acylative KRs. The KR of racemic 1-phenylethanol (**24**) via organocatalytic acyl transfer is one of the most common test reactions in this area (efficient methods often take advantage of selective $\pi-\pi$ interactions between substrate and catalyst)[24,25,73] and was therefore chosen as a test reaction for **12b** as well. Catalyst **12b** promoted this reaction but showed no enantioselectivity (Figure 6).[74] The KR of other racemic secondary alcohols like *exo*-norborneol (**25**) and *rac*-**26** via acylative KR with catalyst **12b** also led to low selectivities (Figure 6). Nonenzymatic examples of KR or desymmetrizations of primary alcohols are rare, because no second functional group, which is usually required to achieve chemical recognition by the catalyst, is close to the hydroxyl group.[75,76] As expected the selectivity of **12b** in the KR of racemic **27** was low (Figure 6), despite significant activity. This finding again implies that the second vicinal OH-group is key for the acylation selectivity.

As the mechanism of action (vide infra) for **12b** in acylative KRs requires a second hydrogen bond donor, a broader range of *meso*- and *rac*-1,2-diols **28**−**37** (Table 4/Scheme 2) was investigated.

The desymmetrization of *meso*-cyclohexane-1,2-diol (**28**) (Table 4) utilizing **12b** was tested under standard conditions (5.3 equiv of Ac_2O, toluene), and an *ee* of 74% was observed. However, the reaction was slightly more selective with base (5.3 equiv of DIPEA; *ee* = 88). Noncyclic analogues like **29** can also be resolved with an *S*-value of 16; apparently **12b** is not only efficient for cyclic vicinal diols. 1,3-, 1,4- and 1,5-diols are also synthetically useful substrates and were therefore tested in the acylative KR with **12b**. Racemic 1,3-diol *rac*-**30** was only poorly resolved, and after 24 h, only 6% of the monoacetylated product was observed. To our delight, moderate selectivities were achieved in the **12b**-catalyzed KR of non-vicinal 1,1′-binaphthyl-2,2′-diol *rac*-**31** (S = 3). Enzymatic[78] and chemical approaches[79] were reported for the resolution of *rac*-**31**; the nonenzymatic methods are based on inclusion complexes[80] or

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Table 1. KR of *trans*-Diol (±)-1 with Peptide Catalysts 3–12a

entry[a]	catal	*t* (h)	yield (%)[c] of (*R*,*R*)-**2**	*er*[c] of (*R*,*R*)-**2**
1[b]	**3**	15	2	46:54
2[d]	**4**	4	11	44:56
3	**5**	42	4	76:24
4	**6**	18	48	69:31
5	**7**	210	10	54:46
6	**8**	210	10	58:42
7[b]	**9**	210	5	53:47
8[b]	**10**	15	1	75:25
9	**11**	15	7	50:50
10	**12a**	18	43	73:27

[a]All reactions were performed at 0 °C in a mixture of 2.25 mL of toluene and 0.85 mL of $CHCl_3$ with 1 equiv (43.6 mg, 0.375 mmol) of racemic substrate **1**, 0.5 equiv of acetic anhydride, and 1 mol % of catalyst. [b]Reaction was performed at −20 °C with 0.1 equiv of acetic anhydride. Without catalyst, no conversions could be observed. [c]Yields and enantiomeric ratios were determined by chiral GC analysis using an internal calibration. [d]Reaction was performed at 0 °C in 4.5 mL of toluene with 1 equiv of racemic substrate **1** (0.025 mmol, 2.9 mg), 5.3 equiv of acetic anhydride, and 2 mol % of catalyst in toluene.

Table 2. Screening of the KR of (±)-1 with Peptide Catalysts 12–17

entry[a]	catal	R	yield (%)[c] of (*R*,*R*)-**2**	*er*[c] of (*R*,*R*)-**2**
1	**12a**[d]	Val	9.9	85:15
2[b]	**12a**-resin[72]	Val	10.2	63:37
3[d]	*ent*-**12b**	Cha	57	12:88
4	**12b**[d]	Cha	8.3	88:12
5[d]	**13**	–	35	57:43
6	**14**	–	9.8	60:40
7	**15**	–	8.1	46:54
8	**16**	–	10.5	21:79
9	**17**	–	5.4	67:33

[a]All reactions were performed at −20 °C for 15 h in a mixture of toluene and $CHCl_3$ with 1 equiv of racemic substrate **1**, 0.1 equiv of acetic anhydride, and 1 mol % of catalyst (raw product, after resin cleavage and evaporating of the solvents; without further purification). Without catalyst, no conversions were observed. [b]Reaction was performed for 24 h. [c]Yields and *er* values were determined by chiral GC analysis using an internal calibration. [d]All reactions were performed at 0 °C in 4.5 mL of toluene with 1 equiv of racemic substrate **1** (0.025 mmol, 2.9 mg), 5.3 equiv of acetic anhydride, and 2 mol % of catalyst.

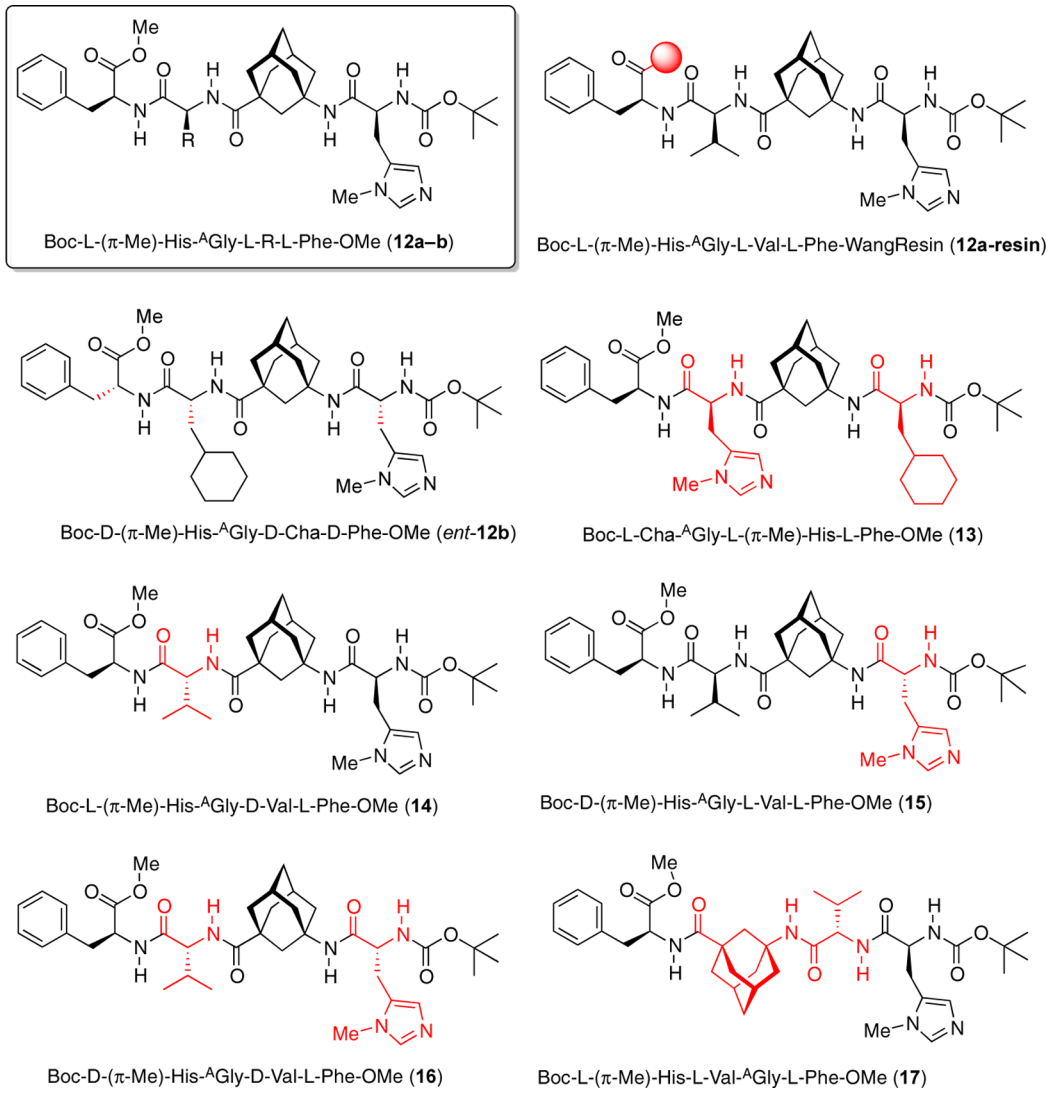

Figure 4. Variation of peptide catalysts. Structural changes of the peptides compared to **12a** and **12b** are drawn in red.

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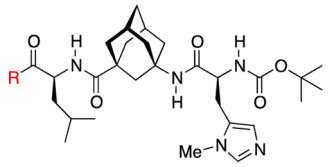
Table 3. Screening of the KR of (±)-1 with Peptide Catalysts 18−21 and 12c: Investigation of the Role of the *C*-Terminal Amino Acid



Boc-L-(π-Me)-His-^{A}Gly-L-Leu-R

entry[a]	catal	R	yield (%)[b] of (*R*,*R*)-**2**	*er*[b] of (*R*,*R*)-**2**
1	**18**	L-Ala-OMe	2.0	86:14
2	**19**	L-Val-OMe	1.6	84:16
3	**20**	L-Leu-OMe	4.9	87:13
4	**21**	L-Cha-OMe	5.1	89:11
5	**12c**	L-Phe-OMe	12.7	86:14

[a]All reactions were performed at −20 °C for 15 h in a mixture of toluene and $CHCl_3$ with 1 equiv of racemic substrate **1**, 0.1 equiv of acetic anhydride, and 1 mol % of catalyst (raw product, after resin cleavage and evaporating of the solvents; without further purification) **18−21** and **12c**. Without catalyst, no conversions were observed. [b]Yields and enantiomer ratios were determined by chiral GC analysis using an internal calibration.

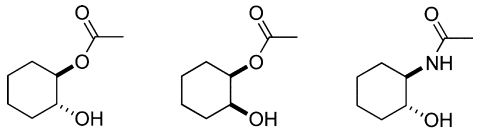


Figure 5. KR of the racemic monoacetylated substrates **2**, **22**, and **23**.

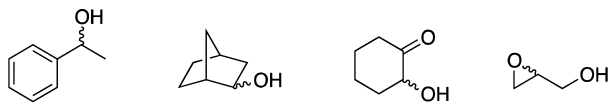


Figure 6. Testing the KR of the racemic monoalcohols **24−27** with catalyst **12b**.

salt formation.[81] Both enantiomers can be obtained in high yields and excellent *ee* values (>99%).[80,82] To the best of our knowledge, no catalytic, nonenzymatic approaches for the acylative KR of *rac*-**31** are known to date. This is the first example for catalyst **12b** displaying moderate selectivity for a substrate class different from 1,2-diols (Table 4). It is also worth mentioning that the KR of **31** with catalyst **12b** and acetic anhydride proceeded rapidly (4 h) under optimal conditions (5.3 equiv of Ac_2O, 0 °C), and the diol was completely converted to the corresponding monoacetylated (64%) and diacetylated (36%) products. Therefore the amount of acetic anhydride was reduced to 0.6 equiv of Ac_2O, which led to a conversion of 43% after 4 h (stirring overnight yielded 60% of monoacetylated product with 33% *ee*), and no diacetylated product was observed. This indicates that the KR of *rac*-**31** is even faster than for our reference diol **1**. In contrast, **12b** proved to be inactive and unselective for **32** and **34** and only moderately active but rather unselective in the desymmetrization experiments with the *meso*-diol **33** (Table 4). An explanation might be the rather rigid structure of **32**, **33**, and **34** and the steric demand of the substrates, as well as the absence of intramolecular hydrogen bonds. Peptide **12b** showed higher activity for the desymmetrization of *meso*-1,3-diol **35** but provided no selectivity. Surprisingly, high activity and moderate selectivity was observed for the desymmetrization of 1,5-diol **36**.[83]

Landais et al. reported an efficient 10-step synthesis of aminocycloheptitols via desymmetrization/functionalization of 7-silylcycloheptatrienes.[84] Further functionalization of the 7-silylcycloheptatrienes gave racemic products. Hence, we investigated the selective acetylation of *rac*-**37** by **12b** because it appeared as an excellent stereochemical test case.

The KR of diol *rac*-**37** is rather challenging because of the complex structure (five stereogenic centers) and the potential formation of two product regioisomers **38** and **39**. In principle catalyst **12b** is capable of differentiating between both enantiomeric forms by preferring the acylation of the *R*,*R*-enantiomer (configuration of the hydroxyl-groups). The highest *ee*, but rather low yield (yield = 15%), was observed for the monoacetylated regioisomer **39**. The selectivity for **38** was lower, but the yield was good (yield = 41%) (Scheme 2). We suggest that the high selectivity but lower reactivity of **39** is due to the high steric demand of the dimethylphenylsilyl group in the proximity to the acetylated hydroxyl group. In contrast to all other KR experiments, we found a large amount of diacetylated product **40**.

Chemoselectivity of 12b. The outstanding performance of catalyst **12b** for vicinal diols implies high chemoselectivity, which underlines the close relationship to natural catalysts, e.g., enzymes. Of course, high chemoselectivity is often undesirable in synthetic chemistry, which normally strives for broad substrate scope. However, highly chemoselective catalytic processes are a stringent requirement for one-pot reactions, wherein various chemicals are present in the reaction mixture. This is typically the case for domino,[85] tandem,[85−87] or cascade[86,87] reactions and becomes even more important for multicatalytic reactions.[63,64,67,68,88] Additionally, this approach could be a useful tool for the site-selective acylation of, e.g., polyols.

We performed competition experiments for the acetylation of chemically different alcohols with **12b** to investigate the chemoselectivity of our best catalyst. For comparison we performed the same experiments with 4-dimethylaminopyridine (DMAP) in parallel. Initial studies showed that **12b** is capable of transferring acyl groups selectively to the (*R*,*R*)-enantiomer of *trans*-cycloalkane-1,2-diol **1** out of a mixture of alcohols **41−43** (Table 5). We used the optimized standard reaction conditions for the KR. The reaction was quenched after 1 h and was analyzed by GC. In the presence of **12b** only esters **2** and **44** were observed. Ester **2** proved to be the main product; the *er* of the remaining diol (94% (*S*,*S*)-**1** and 6% (*R*,*R*)-**1**) indicates that indeed (*R*,*R*)-**1** is by far the most reactive compound in the mixture. In contrast, DMAP led to the formation of the esters **2**, **44**, and **45** with **44** being the main product. After 2 h all of the (*R*,*R*)-**1** enantiomer had been acetylated by **12b**, and the catalyst showed higher activity toward **41** than to (*S*,*S*)-**1**. The reactivities for the acetylation of (*S*,*S*)-**1** and **43** by **12b** were comparable.

Catalyst **12b** can also differentiate between *cis*- and *trans*-cyclohexane-1,2-diol; the acetylation of a 1:1 mixture of **1** and **28** resulted in a ratio of 84:16 (**2**/**28**) after 3 h. In contrast, DMAP proved to be less active and showed only a marginal

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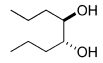
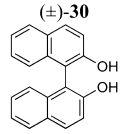
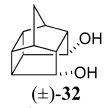
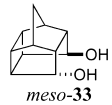
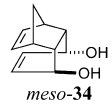
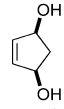
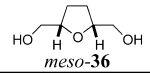
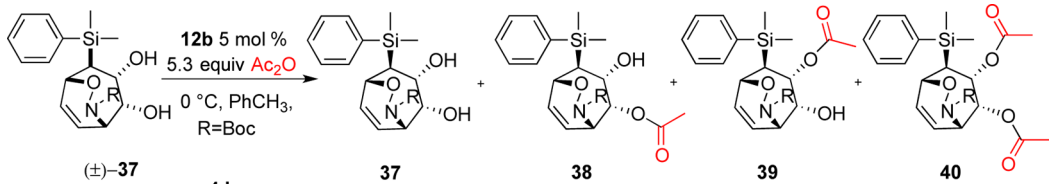
Table 4. Testing the KR and Desymmetrization of Diols 28−36 with 12b

entry[a]	diol	*t* (h)	*T* (°C)	*C* (%)[b]	*ee* (%)[c] remaining diol	*ee* (%)[c] monoacetylated diol	*S*[b]
1	 *meso*-**28**	24	0	88	–	74	–
2	 *meso*-**28**	48	–40	99	–	88	–
3	 (±)-**29**	8	0	61	95	65	16
4	 (±)-**30**	24	0	6	–	11	1
5[e]	 (±)-**31**	24	0	60	50	33	3
6	 (±)-**32**	24	0	5	–	1	1
7[d]	 *meso*-**33**	6	0	90		5	–
8[d]	 *meso*-**34**	5	0	2	–	11	–
9	 *meso*-**35**	24	–20	63	–	4	–
10[d]	 *meso*-**36**	5	0	99	–	39	–

[a]Reaction conditions: 1 equiv of diol in toluene, 5.3 equiv of Ac_2O, and 2 mol % of catalyst **12b** (purified via HPLC). Without catalyst, no conversions were observed. [b]*S*-values and conversions determined using the procedure of Kagan and Fiaud.[77] [c]*ee* values were determined by chiral GC analysis or chiral HPLC. [d]Reaction conditions: 1 equiv of diol in toluene, 5.3 equiv of Ac_2O, 2 mol % of catalyst **12b** and 5.3 equiv of DIPEA. [e]Reaction conditions: 1 equiv of diol in toluene, 0.6 equiv of Ac_2O, and 2 mol % of catalyst (purified via HPLC) **12b**.

Scheme 2. KR of *rac*-37 Utilizing 12b



preference for the *trans*-diol. The results for **12b** (Table 6) are remarkable because both diols should have comparable nucleophilicities and differ only in the configuration of one OH group. We conclude that stronger hydrogen-bond interactions between (*R*,*R*)-**1** and **12b** compared to (*S*,*S*)-, (*R*,*S*)-, and (*S*,*R*)-**1** and **12b** are responsible for (*R*,*R*)-**1** preferential acetylation. The structure of (*R*,*R*)-**1** seems to fit perfectly into the "pocket" formed by **12b**. This extraordinary high chemo- and enantioselectivity is an astonishing feature for a small molecule.

Mechanistic Model for the Enantioselective Acylation with 12b. For a better understanding of the chemical

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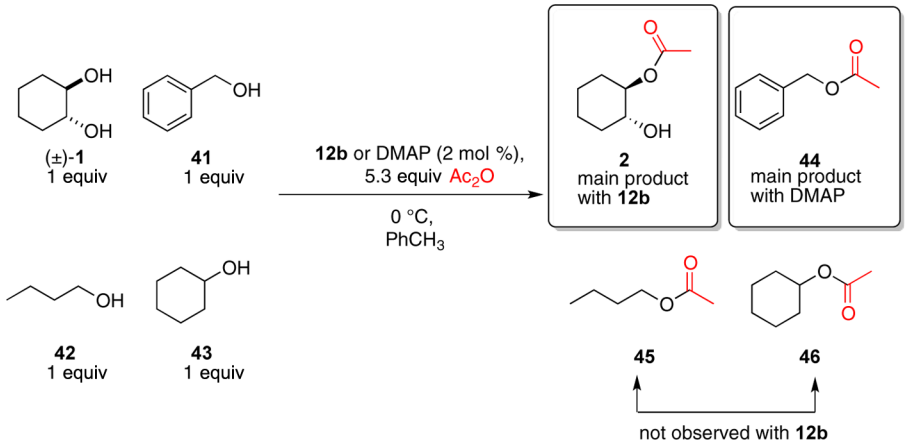
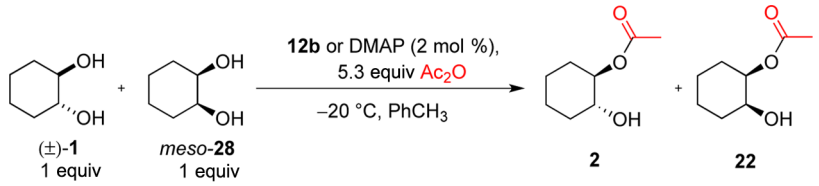
Table 5. Yields (via GC−MS) of 2, 44, 45, and 46 Obtained in the Competitive Acetylation Reaction



entry	catal	t (h)	yield (%) of **2**	yield (%) of **44**	yield (%) of **45**	yield (%) of **46**
1	**12b**	1	59	traces	–	–
2	**DMAP**	1	traces	22	traces	–
3	**12b**	2	65	15	traces	–
4	**DMAP**	2	31	36	13	–
5	**12b**	5	72	32	traces	–
6	**DMAP**	5	59	68	20	–

Table 6. Concurrent and Competitive Acetylation of *trans*-Diol (±)-1 and *meso*-Diol 28 with Catalyst 12b and DMAP



entry[a]	catal	t (h)	yield (%) **2**[b]	*er*[b] **2**	yield (%) **28**[b]	ratio **2**:**28**[b]
1	**12b**	1.5	23	94:6	3	87:13
2	DMAP	1.5	5	50:50	4	56:44
3	**12b**	3	31	91:9	6	84:16
4	DMAP	3	9	50:50	7	56:44
5[b]	**12b**	4.5	36	85:15	11	77:23
6	DMAP	4.5	15	50:50	12	55:44
6	**12b**	7.5	38	80:20	15	72:28
7[b]	DMAP	22	20	50:50	16	55:44

[a]Reactions performed at −20 °C in 4.5 mL of toluene with 1 equiv of racemic substrate **1** (0.025 mmol, 2.9 mg) and *meso* substrate **28** (0.025 mmol, 2.9 mg), 5.3 equiv of acetic anhydride, and 2 mol % **12b** or DMAP. Without catalyst, no conversions were observed. [b]Yield, *er* values, and the **2**:**28** ratios were determined by chiral GC analysis.

recognition process of the substrate by the catalyst responsible for the selectivity, we attempted NMR polarization transfer[89] and IR studies[90] at variable temperatures with **12b**, but we found no evidence for a secondary structure at rt (see Supporting Information for spectroscopic data). We also investigated the possibility of a structure-forming element at the stage of the acylium ion, and therefore NMR spectra of the acylium ion were measured at rt in $CDCl_3$, but again no unusual NOEs indicating a secondary structure were observed.

In 2009 Sunoj et al. performed ONIOM computations at the B3LYP/6-31G(*d*):PM3 level that yielded transition structures for the **12b**-catalyzed acyl transfer onto (*R*,*R*)- and (*S*,*S*)-**1**.[91] These computations nicely explain the observed high enantioselectivities by an energy difference of 4.5 kcal mol^{-1} between the two transition states. Nevertheless, Sunoj's computations could not properly estimate the influence of hydrophobic R-groups in the $i + 2$ position on the selectivity, because the B3LYP/6-31G(*d*):PM3 level of theory does not include dispersion interactions.

Hence, we applied a molecular dynamics search for low-lying conformations of the catalyst/acylium ion adduct and (*R*,*R*)-**1** using the Merck molecular force field (MMFF)[92] and reoptimized the lowest-lying conformation at M06−2X/6-31+G(*d*,*p*), which was parametrized to take into account dispersion interactions.[93,94] The acetylated catalyst **12b** generates a chiral environment around the substrate (Figure 7, right and left). Irrespective of the starting geometry, the most favorable conformer always placed the cyclohexyl group in **12b** in close proximity to **1** (Figure 7). This arrangement helps rationalize why more hydrophobic R-groups provide higher *ee* values, as they enhance the London dispersion interactions with the substrate (Figure 7, right).[95,96]

dx.doi.org/10.1021/jo401195c | J. Org. Chem. XXXX, XXX, XXX−XXX

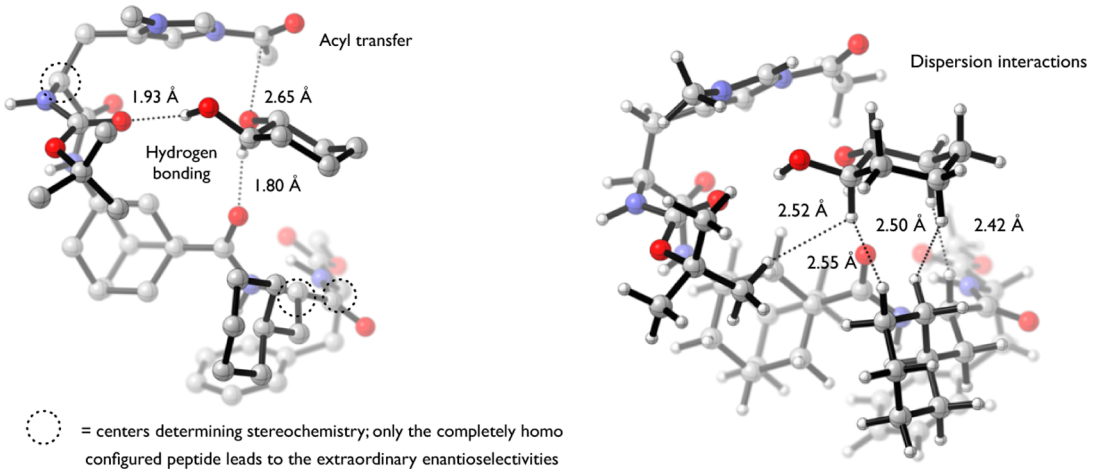
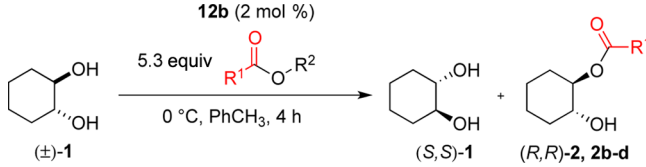


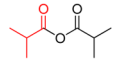
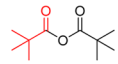
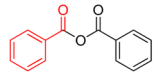
Figure 7. Left: M06−2X/6-31+G(*d,p*)[93,94] optimized structure for the enantioselective acetylation of *trans*-cyclohexane-1,2-diol **1** in the "pocket" of the acetylated catalyst. Hydrogen atoms on the catalyst are omitted for clarity. C = gray, N = blue, O = red.[97] Right: dispersion interactions of substrate and catalyst as judged by the typical van der Waals contacts.

The two geometrically nearest C═O groups apparently provide hydrogen bonding acceptors (Figure 7) needed for chiral recognition of the diols. The model also emphasizes that the ^{A}Gly building block provides a scaffold that separates both ends of the peptide and also holds the centers governing recognition and stereochemistry in place. It seems that *rac*-**1**, as well as the acylium ion adduct have to be present to structure the "active site" of the peptide by dispersion (Figure 7, right) and hydrogen-bonding interactions in a rather dynamic binding event.

Alternative Electrophiles in Group Transfer Reactions Catalyzed via Peptide 12b. In addition to acetic anhydride, we tested a range of electrophiles in KRs and desymmetrization experiments. First of all, we investigated the role of the electrophile by determining the activity and selectivity of **12b** in the KR of *rac*-**1** using various acyl donors (Table 7). All anhydrides reacted with **1** to give the corresponding monoesters in good yields. In contrast, vinyl acetate as electrophile, which is often used in combination with enzymes, provided no conversion. Acetyl chloride gave only 5% of the monoacetylated product after 4 h and resulted in no enantioselectivity, neither for the starting material nor for the product (the background reaction led to similar conversions in the same time). Even addition of base to avoid the protonation of the catalysts only slightly increased the selectivity and reactivity. The finding that acyl chlorides, though they generally have higher carbonyl reactivities than anhydrides, are less reactive in acetyl transfer reactions catalyzed by the nucleophilic catalysts (DMAP) is common.[98−103] The importance of the counterion for the deprotonation of the alcohol was computationally confirmed by Zipse et al.[102−104] The counterion effects were experimentally analyzed by Lutz et al. in their X-ray, NMR- and IR-spectroscopic investigation of *N*-acetyl-DMAP salts.[104] Surprisingly no evidence for the formation of a "tight" ion pair for the *N*-acetyl-pyridinium chloride was found, but in the case of *N*-acetyl-pyridinium acetate the analysis of the X-ray data, as well as the computations, confirmed the existence of a "tight" ion pair. Under our reaction conditions with no additional base the proton transfer has to be accomplished by the counterion, and therefore acetic anhydride reacts faster. The reaction with acetic or isobutyric anhydride proved to be fast compared to the sterically more hindered benzoic and pivalic anhydrides (Table 7). The use of acetic anhydride and isobutyric anhydride led to high selectivities (S >50 for acetic anhydride, *S* = 41 for isobutyric anhydride), whereas for

Table 7. KR of *trans*-Diol (±)-1 with Peptide Catalyst 12b Using Various Acyl Donors



entry[a]	electrophile	ester	*C* (%)[b]	*ee* (%)[c] (*R*, *R*)-**2**	*ee* (%)[c] (*S*, *S*)-**1**	*S*[b]
1		**2**	57	75	>99	>50
2		**2b**	59	71	>99	41
3		**2c**	2	64	2	5
4		**2d**	5	76	4	8
5		**2**	5	–	–	1
6[d]		**2**	27	12	32	2.2
7		**2**	–	–	–	–

[a]All reactions were performed at 0 °C in 4.5 mL of toluene, 1 equiv of racemic substrate **1** (0.025 mmol, 2.9 mg), 5.3 equiv of the electrophile, and 2 mol % of catalyst **12b** (purified via HPLC). Without catalyst, no conversions were observed. [b]*S*-values and conversions determined using the procedure of Kagan and Fiaud.[77] [c]*ee* values were determined by chiral GC analysis. [d]The reactions were performed at 0 °C in 4.5 mL of toluene, 1 equiv of racemic substrate **1** (0.025 mmol, 2.9 mg), 5.3 equiv of the electrophile, 2 mol % of catalyst **12b** and 5.3 equiv of DIPEA.

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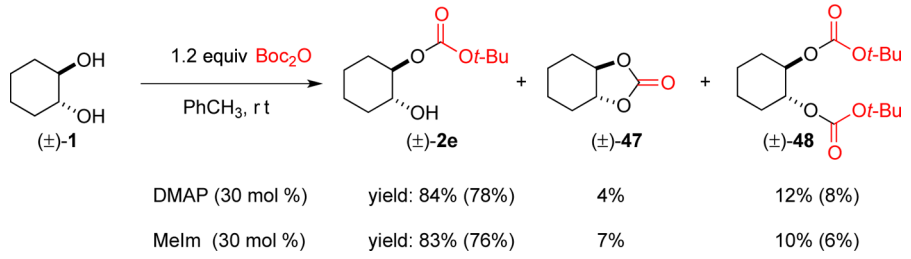
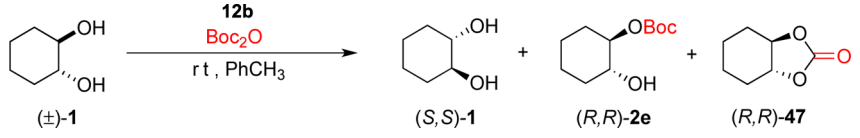
Scheme 3. Reaction of DMAP and MeIm with Boc_2O and Diol *rac*-1 Leading to *O*-Boc-2e, *O,O*-di-Boc-product 48 and the Cyclic Carbonate 47[a]



[a]Yields were determined via GC−MS; yields of isolated products are given in parentheses.

Table 8. KR of *trans*-Cyclohexane-1,2-diol 1 with Boc_2O using Various Reaction Conditions



entry[a]	catal **12b** (mol %)	*t* (h)	C (%)	Boc_2O (equiv)	*er* (*S,S*)-**1**[c]	*er* (*R,R*)-**2e**[c]	*er* (*R,R*)-**47**[c]	*S*[d]
1	2	58	30	1	80:20	15:85	17:83	10.3
2	2	58	30	2	64:36	18:82	17:83	6.3
3	2	36	60	5.3	95:5	18:82	22:78	11.7
4	2	16	58	10	83:17	24:76	28:72	6.2
5	5	16	50	5	80:20	20:80	20:80	7.2
6	10	21	54	2	87:13	18:82	–	9.6
7	5	102	50	2	86:14	14:86	–	12.8
8[b]	10	192	50	2	76:24	24:76	traces	5.2

[a]All reactions were performed in 4.5 mL of dry toluene at rt. [b]This reaction was carried out at 0 °C in 4.5 mL of dry toluene. [c]Yields and enantiomer ratios were determined by chiral GC analysis. [d]*S*-values (selectivity factors) determined by the method of Kagan and Fiaud.[77]

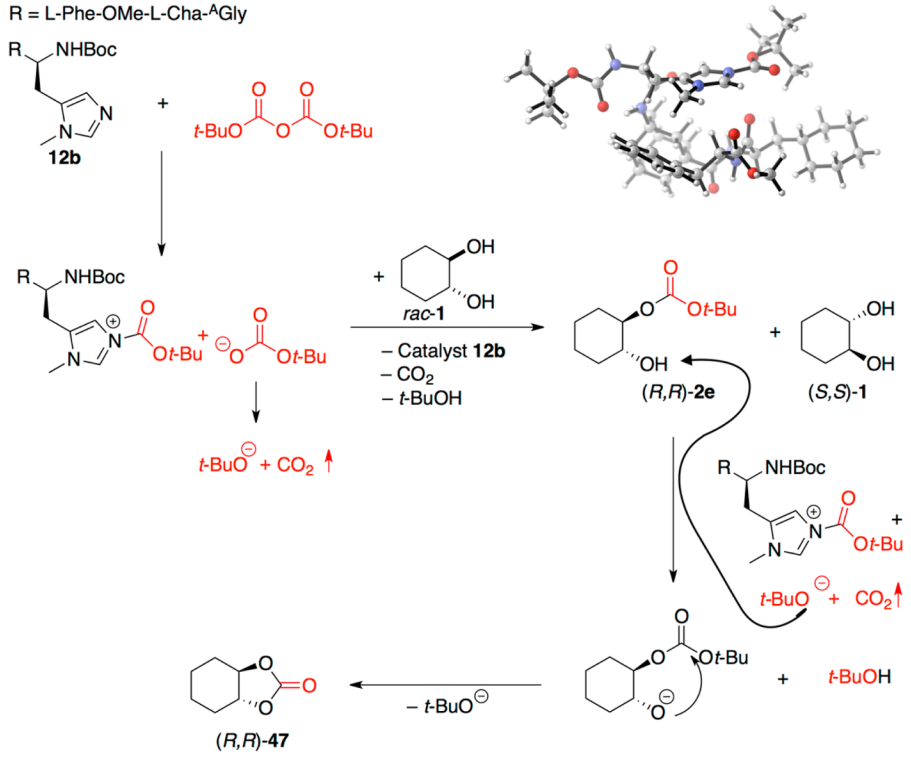
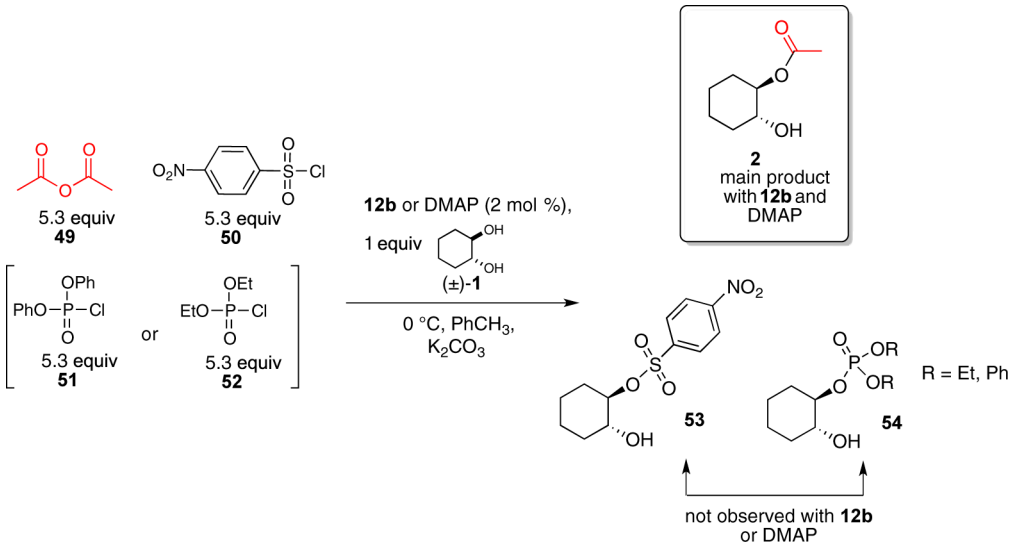


Figure 8. Proposed mechanism of the KR of *trans*-cyclohexane-1,2-diol with Boc_2O and the reoptimized (M06−2X/6-31+G(*d,p*)) structure of the catalyst/*tert*-butoxycarbonylium adduct.

dx.doi.org/10.1021/jo401195c | J. Org. Chem. XXXX, XXX, XXX−XXX

Table 9. Competitive Functionalization of *rac*-1 with 12b and DMAP



entry	catal	*t* (h)	*C* (%)	*er* (%) of **1**[c]	*er* (%) of **2**[c]	*S*
1[a]	**12b**	1	48	85:15	13:87	14
2[b]	**DMAP**	1	16	50:50	50:50	–
3[a]	**12b**	2	50	86:14	14:86	13
4[b]	**DMAP**	2	18	50:50	50:50	–
5[a]	**12b**	3	53	90:10	15:85	14
6[b]	**DMAP**	3	20	50:50	50:50	–
7[d]	**12b**	1	51	93:7	8:92	32

[a]*S*-values and conversions *C* determined using the procedure of Kagan and Fiaud.[77] [b]Conversions were determined by GC–MS analysis. [c]*er* values were determined by chiral GC analysis. [d]Reaction was performed with 5.3 equiv of Ac_2O in absence of other electrophiles.

benzoic anhydride (S = 8) and pivalic anhydride (S = 5), only moderate selectivities were observed.

The direct use of acids as electrophiles in acylation reactions was realized by using peptide **12b** and carbodiimides (DI) for the activation and in situ formation of the anhydrides from carboxylic acid precursor; this constitutes the first enantioselective Steglich esterification.[66]

Other electrophiles such as di-*tert*-butyl dicarbonate (Boc_2O), diphenylchlorophosphate, and various benzenesulfonyl chlorides were also used as electrophiles in the KR of (±)-**1** with **12b**. Miller et al. reported the selective sulfonylation (benzenesulfonyl chlorides)[105] and phosphorylation (diphenylchlorophosphate)[31,106,107] mediated by π-(Me)-histidine containing peptides and achieved an *ee* of 98% in 65% yield for the phosphorylation of a *meso*-inositol derivative. The selective sulfonylation of various functionalized *meso*-1,3-diols was accomplished in high yields and good selectivities (yield up to 76%; *er* up to 97:3).[105] The reactivity of Boc_2O toward alcohols and diols in the presence of 4-(dimethylamino)-pyridine (DMAP) and *N*-methylimidazole (MeIm) has been reported by Hassner et al.[108] The transfer of the Boc-group onto *rac*-**1** was tested utilizing 30 mol % DMAP (30 mol % *N*-methylimidazole) and 1.2 equiv of Boc_2O (Scheme 3).

While the monoacetylated diol (*R*,*R*)-**2** is the only product of the acetylation reaction, the reaction with Boc_2O is more complex, and three products were obtained by the DMAP- and MeIm-catalyzed reaction (Scheme 3). Therefore the KR of *rac*-**1** with Boc_2O required optimization (Table 8).

In principle, the enantioselective transfer of the Boc-group with **12b** is possible, but the reaction requires conditions different from those of the acylation reaction. While the acetylation reactions are most efficient using a large excess of Ac_2O (5.3 equiv) at low temperature (0 °C), the transfer of the Boc-group works best at rt, with 2 equiv of Boc_2O and 5 mol % of **12b**.

The generation of the *O*-Boc protected diol **2e** is catalyzed by **12b**, whereas the formation of the cyclic carbonate **47** only occurs in the presence of a strong base. The reaction mechanism implies that the formation of the *tert*-butoxide during the catalytic cycle probably removes the proton from the second alcohol functionality and therefore promotes cyclization to the cyclic carbonate **47** (Figure 8).[108] Evidence for this proposal comes from the finding that **2e** does not cyclize to **47** in solution even in the presence of catalyst **12b**. In contrast, addition of Boc_2O to the solution gives only the cyclic carbonate **47**.

Using less Boc_2O minimized the formation of *tert*-butoxide, and the rate of cyclization of **2e** decreased. A catalyst loading of 5 mol % and higher temperature accelerates the reaction and avoids the generation of **47**.

Although sulfonylation reactions are widely used in organic synthesis, catalytic asymmetric sulfonyl transfer reactions are rare.[105,109] The KR of *trans*-cyclohexane-1,2-diol with various benzenesulfonyl chlorides were therefore examined. Much to our dismay, *p*-Cl- and *p*-CH_3-benzenesulfonyl chlorides gave no reaction, while *p*-nitrobenzenesulfonyl chloride unselectively provided 14% of the monosulfonylated-*trans*-1,2-cylohexanediol and 8% of the disulfonylated-*trans*-1,2-cylohexanediol after 24 h at rt.

Phosphoryl group transfer plays an important role in natural processes like cell signaling pathways. Histidine containing kinases transfer the phosphoryl group to other nucleophiles.

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Miller et al. successfully applied a histidine-containing peptide catalyst in the asymmetric phosphorylation of myoinositol.[31,106,107] The phosphorylation of *trans*-cyclohexane-1,2-diol mediated by **12b** utilizing $POCl(OPh)_2$ under optimized reaction conditions (10 mol % **12b**, 1 equiv of $POCl(OPh)_2$, 1 equiv of Et_3N, rt, $PhCH_3$), unfortunately, yielded only 40% of the monophosphorylated product.

To test again the chemoselectivity (this time for the electrophile), we performed a competition experiment using different electrophiles (Ac_2O, $POCl(OPh)_2$ or $POCl(OEt)_2$ and *p*-NO_2−SO_2Cl) for the functionalization of *rac*-**1**. The progress of the reaction was monitored via GC−MS and TLC. For reasons of comparability, **12b** and DMAP were used as catalysts in parallel runs (Table 9).

After 1 h, **12b** converted nearly consumed all of (*R*,*R*)-**1** (*C* = 48%). The DMAP-catalyzed reaction is slower and only provided 16% yield after 1 h. Under optimized reaction conditions, only **2** was observed with both catalysts. K_2CO_3 was used as base to avoid protonation of the catalyst. The selectivity of the competitive functionalization experiment (*S* = 14) is lower compared to the acylation experiment (*S* = 32) but still good. These results show the capability of **12b** to chemoselectively acylate *rac*-**1** even in the presence of other good electrophiles.

CONCLUSION AND OUTLOOK

We identified the highly chemo- and enantioselective peptide catalyst **12b** for acyl transfer onto racemic alkane-1,2-diols. In contrast to common peptide design approaches, **12b** does not display a preferred secondary structure but instead recognizes the diols in a dynamic binding event of the acylium cation complex involving hydrogen bonding and dispersion interactions.

Anhydrides proved to be the most efficient acyl source. Competitive experiments for substrates and electrophiles show extraordinary chemoselectivity for cyclic *trans*-alkane-1,2-diols as the substrate and acetic anhydride as the electrophile. Such a narrow substrate scope is usually only observed for enzymes or generally much larger molecules utilized as catalysts. It is therefore a rather surprising finding that a short oligopeptide such as **12b** mimics the behavior of structures that are typically by orders of magnitude more complex, but with the advantage that both substrate enantiomers can selectively be acetylated.

Such exquisite chemoselectivity is the basis for multicatalytic approaches that are now being realized. These provide high potential for rapidly reaching molecular complexity from simple starting materials in one pot, not requiring protective group chemistry.

EXPERIMENTAL SECTION

General Methods. Unless otherwise noted, all chemicals were purchased commercially at the highest purity grade available. Acetic anhydride, acetyl chloride, diphenylchlorophosphate and diethylchlorophosphate were distilled prior use and stored under argon. Potassium *tert*-butylate and K_2CO_3 were dried at 200 °C under a vacuum and stored under argon. DBU, Et_3N, and DIPEA were distilled and dried prior use. All catalytic reactions were carried out under argon atmosphere employing oven- and flame-dried glassware. All solvents were distilled prior use and dried by standard laboratory protocols. ^1H and ^{13}C NMR spectra were recorded on 600, 400, and 200 MHz spectrometers using TMS as an internal standard with chemical shifts given in ppm relative to TMS (δ = 0.00 ppm) or the respective solvent peaks. Two-dimensional NMR experiments were recorded on 600 or 400 MHz spectrometers using apparatus standard pulse sequences and parameters. ESI mass spectra were recorded using methanol solutions of the respective compounds. High resolution ESI mass spectrometry (ESI-TOF) was performed using methanol/water solution of the respective compounds, and MS/HRMS were recorded on a sector field spectrometer (EI-sector field). Analytical thin-layer chromatography (TLC) was performed using precoated polyester sheets Polygram SIL G/UV_{254} Machery-Nagel, 0.2 mm silica gel with fluorescent indicator. Visualization was accomplished by irradiation with UV lamp and/or molybdophosphoric acid solution (5% $H_3[P(Mo_3O_{10})_4]$ in ethanol). Flash column chromatography and filtration was performed using Merck silica gel 60 Å (0.040−0.063 mm).

Availability and Characterization of the Catalysts. *General Procedure I: HBTU/HOBt-Mediated Peptide Coupling on Solid Support.* All peptides were prepared employing standard solid phase peptide synthesis techniques (SPPS), utilizing Fmoc-protected amino acids. 2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) was used as the coupling agent and 1-hydroxybenzotriazole (HOBt) as a racemization suppressant. Couplings: 1 equiv of the amino acid on solid support was shaken twice with 2 equiv of amino acid, 2 equiv of HOBt, 2 equiv of HBTU, and 4 equiv of DIPEA in DMF for 30 min. Fmoc-L-Phe-Wang resin was used as solid support and swollen in DMF for 30 min prior to first Fmoc-cleavage.

General Procedure II: Fmoc-Cleavage on Solid Support. Cleavage of *N*-terminal Fmoc-protective groups was accomplished by shaking the solid phase supported peptide twice in 25% piperidine in DMF (25 min). Prior to the next coupling step, the resin was washed 5 times with DMF, DCM and DMF. For storing, the resin should be washed 5 times with DMF, DCM and diethyl ether and kept in a refrigerator until use.

General Procedure III: Peptide Cleavage from the Resin. Peptides were cleaved from their resins as methyl esters by shaking the functionalized resin twice for 2 days with methanol/Et_3N/THF (9:1:1). The resin was filtered off and washed several times with chloroform. The collected solutions were concentrated under reduced pressure and purified via flash silica gel chromatography eluting with chloroform/methanol (95:5).

General Procedure IV: EDC/HOBt-Mediated Peptide Coupling in Solution. The same equivalents of *N*-protected amino acids or peptide fragments, 1.1 equiv of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), 1.1 equiv of HOBt and 1.1 equiv of Et_3N were dissolved in DCM and stirred for 12 h at rt. The reaction mixture was diluted with EtOAc and extracted with 0.5 M citric acid (4×) and saturated $NaHCO_3$ solution. The solvent was removed under reduced pressure, and the crude product was dried in a desiccator over paraffin wax and P_2O_5.

General Procedure V: Cleavage of the −O^{t}Bu-Protecting Group (Boc). The Boc-protected peptide was dissolved in a solution of HCl in 1,4-dioxane (4.0 M) and stirred for 1 h. The excess of HCl was removed by bubbling argon through the solution. After evaporation of the solvent under reduced pressure, the deprotected peptide was coupled without further purification.

The peptides were characterized via electrospray mass spectrometry and used in the screening experiments without further purification. Peptides of interest were purified via HPLC or silica flash gel chromatography. Standard procedures for the solid phase Fmoc-based peptide synthesis as well as the Boc-based solution phase peptide chemistry can also be found in previous publications.[61,68,69,71] The general procedure for the catalytic reactions can be found in the literature.[61,68,69] *S*-values and conversions were calculated according to Kagan's equations.[77] The enantiomeric excess values for the esters and recovered unreacted alcohols were determined by chiral stationary phase HPLC or chiral GC.

*Boc-L-(π-Me)-His-OMe (**3**).* Amino acid **3** is a byproduct occurring during the Wang resin cleavage of the *N*-terminal Boc-L-(π-Me)-histidine peptides. The methyl esters can be purified and isolated via HPLC. The crude product was purified by preparative HPLC (eluent: TBME/CH_3OH 93:7) UV-detector λ = 254 nm, E_{max} = 2.56; refractometer; Column 1 = 250 nm, *d* = 8 mm, LiChrosorb Diol (7

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μm, Merck); retention time (**3**) = 6.50 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.32 [s, 1 H, H_{Ar}, C*H* (His)]; 6.71 [s, 1 H, H_{Ar}, C*H* (His)]; 5.19 [d, 1 H, *J* = 7.3 Hz, N*H*], 4.52−4.40 [m, 1 H, H_α]; 3.67 (s, 3 H, OCH_3); 3.51 (s, 3 H, NCH_3); 3.11−2.91 [m, 2 H, H_β]; 1.35 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 171.6 (C═O); 155.0 (C═O); 138.3; 128.2; 126.4; 80.2; 53.0; 52.5; 31.3; 28.2; 26.8. IR (KBr): $\tilde{\nu}$/cm^{-1} = 2978; 1746; 1709; 1507; 1438; 1367; 1290; 1253; 1217; 1200; 1167. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{13}H_{22}N_3O_4^+$ 284.1605, found 284.1610.

*Hoveyda's Catalyst: (−)-(S)-N-((R)-3,3-Dimethylbutan-2-yl)-3,3-dimethyl-2-((1-methyl-1H-imidazol-2-yl)methylamino)butanamide (**4**).* Catalyst **4** was purchased and used without further purification.

*Boc-L-His-^{A}Gly-L-Phe-OMe (**5**).* For preparation and analytics, see Ph.D. thesis of Lukas Wanka.[110]

*Boc-L-(π-Me)-His-^{A}Gly-L-Phe-OMe (**6**) and Boc-L-(τ-Bzl)-His-^{A}Gly-L-Phe-OMe (**7**).* Analytical data of peptide **6** and **7** were identical to those reported in literature.[111]

*Boc-L-(τ-Bzl)-His-Gly-^{A}Gly-L-Phe-OMe (**8**).* Peptide **8** was synthesized using standard Fmoc-coupling procedures. ESI-MS: *m*/*z* = 741.4 [M + H]$^+$ (calcd *m*/*z* = 741.4); *m*/*z* = 763.4 [M + Na]$^+$ (calcd *m*/*z* = 763.4); *m*/*z* = 1481.2 [2M + H]$^+$ (calcd *m*/*z* = 1481.8); *m*/*z* = 1503.2 [2M + Na]$^+$ (calcd *m*/*z* = 1503.8).

*Boc-L-(τ-Bzl)-His-^{A}Gly-Gly-L-Phe-OMe (**9**).* Peptide **9** was synthesized using standard Fmoc-coupling procedures. ESI-MS: *m*/*z* = 741.5 [M + H]$^+$ (calcd *m*/*z* = 741.4); *m*/*z* = 763.4 [M + Na]$^+$ (calcd *m*/*z* = 763.4); *m*/*z* = 1481.3 [2M + H]$^+$ (calcd *m*/*z* = 1481.8); *m*/*z* = 1503.3 [2M + Na]$^+$ (calcd *m*/*z* = 1503.8).

*Boc-L-(π-Me)-His-^{A}Gly-L-Val-OMe (**10**).* Peptide **10** was synthesized using standard Fmoc-coupling procedures. ESI-MS: *m*/*z* = 560.3 [M + H]$^+$ (calcd *m*/*z* = 560.3); *m*/*z* = 582.3 [M + Na]$^+$ (calcd *m*/*z* = 582.3); *m*/*z* = 1141.1 [2M + Na]$^+$ (calcd *m*/*z* = 1141.7).

*Boc-L-(π-Me)-His-L-Val-^{A}Gly-L-Val-L-Phe-OMe (**11**).* Peptide **11** was synthesized using standard Fmoc-coupling procedures. ESI-MS: *m*/*z* = 806.5 [M + H]$^+$ (calcd *m*/*z* = 806.5); *m*/*z* = 828.4 [M + Na]$^+$ (calcd *m*/*z* = 828.5); *m*/*z* = 1633.3 [2M + Na]$^+$ (calcd *m*/*z* = 1633.9).

*Boc-L-(π-Me)-His-^{A}Gly-L-Val-L-Phe-OMe (**12a**) and Boc-L-(π-Me)-His-^{A}Gly-L-Cha-L-Phe-OMe (**12b**).* Synthesis and analytical data can be found in the literature.[60]

*Boc-L-(π-Me)-His-^{A}Gly-L-Val-L-Phe-WangResin (**12a**-resin).* No characterization possible; **12a-resin** was characterized by cleaving the peptides from the peptide loaded resin. A small amount of loaded resin **12a** was used for the catalytic experiments.

*Boc-D-(π-Me)-His-^{A}Gly-D-Cha-D-Phe-OMe (ent-**12b**).* The crude product was purified by preparative HPLC (eluent: TBME/CH_3OH 90:10) UV-detector λ = 254 nm, E_{max} = 2.56; refractometer; column l = 250 mm, *d* = 8 mm, LiChrosorb Diol (7 μm, Merck); retention time (***ent*-12b**) = 6.60 min. 176 mg (0.23 mmol; 77%) of ***ent*-12b** were isolated as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.34 [s, 1 H, H_{Ar}, C*H* (His)]; 7.25−7.14 [m, 3 H, H_{Ar} (Phe)]; 7.09−7.01 [m, 2 H, H_{Ar} (Phe)]; 6.78 [s, 1 H, H_{Ar}, C*H* (His)]; 6.45 [d, *J* = 7.8 Hz, 1 H, N*H*]; 5.92 [d, *J* = 7.9 Hz, 1 H, N*H*]; 5.69 [s, 1 H, N*H*]; 5.09 [d, *J* = 8.2 Hz, 1 H, N*H*]; 4.78 −4.69 [m, 1 H, H_α]; 4.43−4.31 [m, 1 H, H_α]; 4.16−3.99 [m, 1 H, H_α]; 3.64 (s, 3 H, OCH_3); 3.53 (s, 3 H, NCH_3); 3.09−2.96 [m, 2 H, H_β]; 2.96−2.89 [m, 2 H, H_β]; 2.13 [s, 2 H, adamantane]; 1.95−1.77 [m, 6 H, adamantane + Cha]; 1.71−1.49 [m, 12 H, adamantane + Cha]; 1.44−1.38 [m, 1 H, Cha]; 1.37 [s, 9 H, $C(CH_3)_3$]; 1.23−0.98 [m, 4 H, Cha]; 0.92−0.71 [m, 2 H, Cha]. ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 176.3 (C═O); 171.8 (C═O); 171.6 (C═O); 169.7 (C═O), 155.4 (C═O); 138.3; 135.7; 129.2; 128.6; 128.3; 127.2; 80.5; 54.4; 53.2; 52.3; 50.7; 42.5; 42.1; 40.3; 40.3; 39.5; 38.2; 38.0; 37.8; 35.1; 34.2; 33.5; 32.7; 31.5; 29.1; 29.1; 28.3; 26.8; 26.3; 26.1; 26.1. ESI-MS: *m*/*z* = 761.6 [M + H]$^+$ (calcd *m*/*z* = 761.5); *m*/*z* = 783.5 [M + Na]$^+$ (calcd *m*/*z* = 783.4); *m*/*z* = 1543.3 [2M + Na]$^+$ (calcd *m*/*z* = 1543.9). HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{42}H_{61}N_6O_7^+$ 761.4596, found 761.4610. IR (KBr): $\tilde{\nu}$/cm^{-1} = 3313; 2922; 2853; 1747; 1665; 1509; 1450; 1366; 1248; 1169.

*Boc-L-Cha-^{A}Gly-L-(π-Me)-His-L-Phe-OMe (**13**).* Peptide **13** was synthesized using standard Fmoc-coupling strategy. 184 mg (0.24 mmol; 80%) of **13** were isolated as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.58 [s, 1 H, H_{Ar}, CH (His)], 7.25−7.13 [m, 3 H, H_{Ar} (Phe)], 7.00 [d, 2 H, J= 8 Hz, H_{Ar} (Phe)], 6.82 [s, 1 H, H_{Ar}, CH (His)], 6.39 [d, 1 H, J= 8 Hz, NH (Phe)], 5.89 [s, 1 H, NH (Cha)], 4.88 [s, 1 H, NH (^{A}Gly)], 4.65 [q, 1 H, J= 7.2 Hz, H_α (Phe)], 4.51 [q, 1 H, J= 7.2 Hz, H_α (Cha)], 3.98−3.89 [m, 2 H, H_α (His) + NH (His)], 3.64 [s, 3 H, OCH_3], 3.60 [s, 3 H, NCH_3], 3.10−3.01 [m, 1 H, H*β* (Phe)], 3.00−2.91 [m, 3 H, H*β* (His) + H_β (Phe)], 2.17−2.09 [m, 2 H, adamantane], 2.03−1.78 [m, 7 H, adamantane + Cha], 1.75−1.50 [m, 12 H, adamantane + Cha], 1.38 [s, 9 H, $C(CH_3)$], 1.27−1.01 [m, 4 H, Cha], 0.97−0.74 [m, 2 H, Cha]. ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 176.7 (C═O); 171.9 (C═O); 171.5 (C═O); 170.2 (C═O); 155.8 (C═O); 137.9, 135.8, 129.1, 128.6, 127.6, 127.1, 77.2, 53.8, 52.5, 52.0, 51.7, 42.6, 42.4, 40.5, 40.3, 39.9, 38.1, 37.9, 37.5, 35.2, 34.1, 33.7, 32.7, 32.0, 39.1, 28.3, 26.6, 26.4, 26.3, 26.1. ESI-MS: *m*/*z* = 761.3 [M + H]$^+$ (calcd *m*/*z* = 761.5). HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{42}H_{61}N_6O_7^+$ 761.4596, found 761.4575.

*Boc-L-(π-Me)-His-^{A}Gly-D-Val-L-Phe-OMe (**14**).* Peptide **14** was synthesized using standard Fmoc-coupling strategy. The crude product was purified by preparative HPLC (eluent: TBME/CH_3OH 90:10) UV-detector λ = 254 nm, E_{max} = 2.56; refractometer; column l = 250 mm, *d* = 8 mm, LiChrosorb Diol (7 μm, Merck); retention time (**14**) = 4.20 min. 193 mg (0.27 mmol; 91%) of **14** were isolated as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.38 [s, 1 H, H_{Ar}, C*H* (His)]; 7.31−7.20 [m, 3 H, H_{Ar} (Phe)]; 7.17−7.11 [m, 2 H, H_{Ar} (Phe)]; 7.00 [bs, 1 H, N*H*]; 6.83 [s, 1 H, H_{Ar}, C*H* (His)]; 6.35 [bs, 1 H, N*H*]; 6.27 [d, 1 H, *J* = 8.4 Hz, N*H*]; 5.31 [d, 1 H, *J* = 6.4 Hz, N*H*]; 4.91−4.84 [m, 1 H, H_α]; 4.35 [dd, J_1 = 8.0 Hz, J_2 = 5.7 Hz, 1 H, H_α]; 4.32−4.24 [m, 1 H, H_α]; 3.70 (s, 3 H, OCH_3); 3.56 (s, 3 H, NCH_3); 3.22−3.14 [m, 1 H, H_β]; 3.05−2.95 [m, 3 H, H_β]; 2.23−1.55 (m, 14 H, adamantane); 2.16−2.08 [m, 1 H, H_β]; 1.42 (s, 9 H, $C(CH_3)_3$); 0.77 [d, 3 H, *J* = 6.8 Hz, H_γ (Val)]; 0.69 [d, 3 H, *J* = 6.8 Hz, H_γ (Val)]. ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 176.4 (C═O); 171.7 (C═O); 171.0 (C═O); 169.7 (C═O), 155.4 (C═O); 138.2; 136.0; 129.1; 128.6; 128.4; 127.1; 80.2; 57.3; 54.2; 53.2; 52.4; 52.3; 42.7; 42.7; 40.0; 38.5; 38.1; 38.1; 35.0; 31.5; 31.4; 29.1; 29.1; 28.3; 27.2; 19.3; 17.5. ESI-MS: *m*/*z* = 707.4 [M + H]$^+$ (calcd *m*/*z* = 707.4); *m*/*z* = 729.3 [M + Na]$^+$ (calcd *m*/*z* = 729.4); *m*/*z* = 1413.1 [2M + H]$^+$ (calcd *m*/*z* = 1413.8). HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{38}H_{55}N_6O_7^+$ 707.4127, found 707.4140. IR (KBr): $\tilde{\nu}$/cm^{-1} = 3312; 2912; 1745; 1661; 1509; 1455; 1367; 1248; 1169.

*Boc-D-(π-Me)-His-^{A}Gly-L-Val-L-Phe-OMe (**15**).* Peptide **15** was synthesized using standard Fmoc-based SPPS strategy. ESI-MS: *m*/*z* = 707.4 [M + H]$^+$ (calcd *m*/*z* = 707.4); *m*/*z* = 729.4 [M + Na]$^+$ (calcd *m*/*z* = 729.4); *m*/*z* = 1435.0 [2M + Na]$^+$ (calcd *m*/*z* = 1435.8).

*Boc-D-(π-Me)-His-^{A}Gly-D-Val-L-Phe-OMe (**16**).* Peptide **16** was synthesized using standard Fmoc-based SPPS strategy. ESI-MS: *m*/*z* = 707.5 [M + H]$^+$ (calcd*m*/*z* = 707.4); *m*/*z* = 729.4 [M + Na]$^+$ (calcd *m*/*z* = 729.4); *m*/*z* = 745.3 [M + K]$^+$ (calcd *m*/*z* = 745.4); *m*/*z* = 1435.1 [2M + Na]$^+$ (calcd *m*/*z* = 1435.8).

*Boc-L-(π-Me)-His-L-Val-^{A}Gly-L-Phe-OMe (**17**).* Peptide **17** was synthesized using standard Fmoc-based SPPS strategy. ESI-MS: *m*/*z* = 707.4 [M + H]$^+$ (calcd *m*/*z* = 707.4); *m*/*z* = 729.3 [M + Na]$^+$ (calcd *m*/*z* = 729.4); *m*/*z* = 1435.1 [2M + Na]$^+$ (calcd *m*/*z* = 1435.8).

*Boc-L-(π-Me)-His-^{A}Gly-L-Leu-L-Ala-OMe (**18**).* Peptide **18** was synthesized using standard Fmoc-based SPPS strategy. ESI-MS: *m*/*z* = 645.4 [M + H]$^+$ (calcd *m*/*z* = 645.4); *m*/*z* = 667.4 [M + Na]$^+$ (calcd *m*/*z* = 667.4).

*Boc-L-(π-Me)-His-^{A}Gly-L-Leu-L-Val-OMe (**19**).* Peptide **19** was synthesized using standard Fmoc-based SPPS strategy. ESI-MS: *m*/*z* = 673.4 [M + H]$^+$ (calcd *m*/*z* = 673.4); *m*/*z* = 695.4 [M + Na]$^+$ (calcd *m*/*z* = 695.4).

*Boc-L-(π-Me)-His-^{A}Gly-L-Leu-L-Leu-OMe (**20**).* Peptide **20** was synthesized using standard Fmoc-based SPPS strategy. ESI-MS: *m*/*z* = 687.4 [M + H]$^+$ (calcd *m*/*z* = 687.4); *m*/*z* = 709.3 [M + Na]$^+$ (calcd *m*/*z* = 709.4); *m*/*z* = 1395.1 [2M + Na]$^+$ (calcd *m*/*z* = 1395.9).

*Boc-L-(π-Me)-His-^{A}Gly-L-Leu-L-Cha-OMe (**21**).* Peptide **21** was synthesized using standard Fmoc-based SPPS strategy. ESI-MS: *m*/*z* = 727.5 [M + H]$^+$ (calcd *m*/*z* = 727.5); *m*/*z* = 749.4 [M + Na]$^+$ (calcd *m*/*z* = 749.5); *m*/*z* = 1475.3 [2M + Na]$^+$ (calcd *m*/*z* = 1475.9).

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Chiral-GC Properties and Characterization Data of the Alcohols. *trans-Cyclohexane-1,2-diol (**1**).* Alcohol **1** is commercially available. The GC retention times and characterization of **1** can be found in the literature.[60]

*trans-1-Acetoxycyclohexan-2-ol (**2**).* The GC retention times, the availability, as well as the characterization of **2a** can be found in the literature.[60]

trans-1,2-Diacetoxycyclohexane. Enantiomers of *trans*-1,2-diacetoxycyclohexane were separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: 140 °C isothermal. Retention times: $t_{R,1}$ = 8.2 min; $t_{R,2}$ = 8.5 min. The analytical data were in accordance with the literature.[112]

*2-Hydroxycyclohexyl isobutyrate (**2b**), 2-Hydroxycyclohexyl pivalate (**2c**), and 2-Hydroxycyclohexyl benzoate (**2d**).* The GC retention times, the proof of the GC retention time, as well as the characterization of **2b**, **2c**, and **2d** can be found in the literature.[66]

*tert-Butyl-2-hydroxycyclohexyl carbonate (**2e**).* Enantiomers of the mono-*tert*-butoxycarbonylated product **2e** were separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: 100−250 °C, 2 °C/min. Retention times: $t_{R,1}$ = 27.6 min; $t_{R,2}$ = 27.4 min. NMR data are in accordance with the literature.[119]

*cis-1-Acetoxycyclohexane-2-ol (**22**).* The GC retention times, the availability, as well as the characterization of **22** can be found in the literature.[65,67]

cis-1,2-Diacetoxycyclohexane. The GC retention time, the availability, as well as the characterization of diacetylated **22** can be found in the literature.[65,67]

*trans-2-Acetamidocyclohexane-1-ol (**23**).* Enantiomers of alcohol **23** were separated by chiral GC employing a 30 m Chiraldex G-TA column (Astech). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: 130−180 °C, 2 °C/min. Retention times: $t_{R,1}$ = 25.0 min; $t_{R,2}$ = 25.8 min.

Racemic *trans*-2-amino-cyclohexan-1-ol hydrochloride (purchased and used without further purification) (0.904 g, 6.0 mmol) was treated with 0.3 M NaOH in ethanol (0.24 g in 20 mL) and stirred for 1 h at rt. Then the precipitate (NaCl) was filtered off. The ethanol was removed in vacuo, and the remaining solid was treated with 30 mL of $CHCl_3$ for 10 min. The precipitate was again filtered off, and the removal of the solvent in vacuo gave 0.586 g (5.1 mmol) of *trans*-2-amino-cyclohexan-1-ol as colorless powder. Analytical data of the *trans*-2-amino-cyclohexan-1-ol were essentially identical to those reported in the literature.[113]

Racemic *trans*-2-amino-cyclohexan-1-ol (0.691 g, 6.0 mmol) was treated with acetic anhydride (742 μL, 8 mmol) in the presence of DMAP (0.147 g, 1.2 mmol) in 25 mL of $CHCl_3$, and the resulting solution was stirred for 8 h at rt (25 °C). $CHCl_3$ was then removed in vacuo, and the monoacetylated product ((±)-**23**) was purified by silica flash gel chromatography (EtOAc/MeOH 75:25, R_f (**23**) = 0.44). Isolated racemic (±)-**23** (0.359 g, 2.3 mmol) was characterized and then subjected to the GC assay described above to prove the origin of the GC signals. Analytical data of the monoacetylated amino alcohol **23** were essentially identical to those reported in the literature.[47,114]

trans-1-Acetoxy-2-acetamidocyclohexane. Retention times: $t_{R,1}$ = 19.5 min; $t_{R,2}$ = 19.8 min. Analytical data of the diacetylated amino alcohol were essentially identical to those reported in literature.[47,114]

*1-Phenylethanol (**24**).* Racemic 1-phenylethanol **24** was purchased and used without further purification. Enantiomers of alcohol **24** were separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: 100−135 °C, 1 °C/min. Retention times: $t_{R,1}$ = 18.6 min; $t_{R,2}$ = 19.5 min.

1-Phenyl-1-acetoxy-ethane. Retention times: $t_{R,1}$ = 13.1 min; $t_{R,2}$ = 14.7 min. The racemic acylated compound was purchased and used to prove the GC retention times.

*exo-Bicyclo[2.2.1]heptan-2-ol (exo-norborneol) (**25**).* Racemic bicyclo[2.2.1]heptan-2-ol **25** was purchased and used without further purification. Enantiomers of alcohol **25** were separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: 80−160 °C, 2 °C/min. Retention times: $t_{R,1}$ = 20.9 min; $t_{R,2}$ = 21.3 min.

exo-2-Acetoxy-bicyclo[2.2.1]heptane. Enantiomers of the acetate of **25** were not separated by chiral GC under these conditions. Retention time: t_R = 16.8. The product was not isolated; a mixture of monoacylated and diacylated product were synthesized via DMAP catalysis. The products were not separated because the GC signals could clearly be allocated.

*2-Hydroxycyclohexanone (**26**).* 2-Hydroxycyclohexanone **26** was purchased as dimer (in solution the racemic monomer is formed) and used without further purification. Enantiomers of alcohol **26** were separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: 80−160 °C, 2 °C/min. Retention times: $t_{R,1}$ = 8.1 min; $t_{R,2}$ = 8.4 min.

2-Acetoxycyclohexanone. The GC retention times as well as the characterization can be found in the literature.[65]

*2-Oxiranylmethanol (**27**).* Racemic 2-oxiranylmethanol **27** was purchased and used without further purification. Enantiomers of alcohol **27** were separated by chiral GC employing a 30 m FS-Hydrodex γ-TBDAc column (Macherey Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: 60 °C isothermal for 3 min; then 60−100 °C, 2 °C/min. Retention times: $t_{R,1}$ = 10.8 min; $t_{R,2}$ = 10.9 min.

2-Oxiranylmethyl acetate. Retention times: $t_{R,1}$ = 17.1 min; $t_{R,2}$ = 17.5 min. Analytical data and synthesis of the acetate were identical to those reported in the literature.[115]

*cis-Cyclohexane-1,2-diol (**28**).* Alcohol **28** is commercially available. The GC retention time and characterization of **28** can be found in the literature.[65,67]

*trans-Octane-4,5-diol (**29**).* Enantiomers of **29** were separated by chiral GC employing a 30 m FS-Hydrodex β-TBDAc column (Macherey Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: 100 °C−160 °C, 2 °C/min. Retention times: $t_{R,1}$ = 21.1 min; $t_{R,2}$ = 21.4 min. Synthesis of the alcohol: To a mixture of 4-octene oxide (1 mmol, 126 mg) in toluene (100 μL), trifluoroacetic acid (1 mmol, 77 μL) was added. After stirring for 24 h at rt, water (2 mmol, 36 μL, 2.0 equiv) and DIPEA (5.3 mmol, 0.9 mL, 5.3 equiv) were added, and the reaction mixture was stirred for additional 24 h. Chromatography on silica gel in EtOAc as mobile phase afforded diol (±)-**29**. Analytical data of the diol ((±)-**29**) were identical to those reported in the literature.[116]

trans-4-Acetoxyoctane-5-ol. Retention times: $t_{R,1}$ = 15.6 min; $t_{R,2}$ = 16.2 min. Racemic *trans*-octane-3,4-diol ((±)-**29**) (0.3 mmol) was treated with acetic anhydride (37 μL, 0.4 mmol) in the presence of DMAP (7.3 mg, 0.06 mmol) in 2 mL of dichloromethane, and the resulting solution was stirred for 3 h at rt (25 °C). Dichloromethane was then removed in vacuo, and the monoacylated product was purified by silica flash gel chromatography (EtOAc). Isolated racemic acetylated **29** was analytically characterized and then subjected to the GC assay described above to prove the origin of the GC signals. Analytical data of the monoacylated product were identical to those reported in the literature.[117]

*trans-Cyclohexane-1,3-diol (**30**).* Racemic *trans*-cyclohexane-1,3-diol **30** was purchased and used without further purification. Enantiomers of diol **30** were separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: 60 °C isothermal for 2 min; then 60−140 °C, 1 °C/min. Retention times: $t_{R,1}$ = 53.5 min; $t_{R,2}$ = 54.3 min.

trans-3-Cyclohexane-1-ol. Retention times: $t_{R,1}$ = 51.1 min; $t_{R,2}$ = 51.9 min. *trans*-Diol **30** (0.118 g, 1.0 mmol) was treated with acetic anhydride (95 μL, 1.0 mmol) in the presence of DMAP (0.019 g, 0.15 mmol) in 10 mL of DCM, and the resulting solution was stirred

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overnight at rt (25 °C). DCM was then removed in vacuo, and the monoacetylated product was purified by silica flash gel chromatography (EtOAc, R_f = 0.46). Isolated racemic monoacetylated **30** (0.082 g, 0.7 mmol; 70%) was characterized and then subjected to the GC assay described above to prove the origin of the GC signals.[118] Additionally 0.035 g of the diacylated diol (EtOAc, R_f = 0.63; 18 mmol; 18%) were obtained. The NMR data are in accordance with the literature.[118]

*[1,1′-Binaphthalene]-2,2′-diol (Binaphtol) (**31**).* Racemic [1,1′-binaphthalene]-2,2′-diol (Binaphtol) (**31**) was purchased and used without further purification. Enantiomers of diol **31** were separated by using HPLC employing a 25 cm, d = 0.46 cm Chiralpak IB column (Daicel). Eluent: Hexane/Isopropanol 95:5; flow = 1 mL/min; UV-detector λ = 254 nm. Retention times: $t_{R,1}$ = 32.7 min; $t_{R,2}$ = 35.0 min.

2′-Hydroxy-[1,1′-binaphthalen]-2-yl acetate. Retention times: $t_{R,1}$ = 14.1 min; $t_{R,2}$ = 16.0 min. Monoacetylated **31** was not isolated; a mixture of monoacylated and diacylated product was synthesized via DMAP catalysis. The products were not separated because the HPLC-signals could clearly be allocated.

*Octahydro-1,5,4-(epipropane[1,1,3]triyl)pentalene-2,8-diol (**32**).* Racemic **32** was purchased from the University Lodz and used without further purification. Enantiomers of diol **32** were separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: 180 °C isothermal. Retention times: $t_{R,1}$ = 35.8 min; $t_{R,2}$ = 37.9 min.

8-Hydroxyoctahydro-1,5,4-(epipropane[1,1,3]triyl)pentalen-2-yl acetate. Retention times: $t_{R,1}$ = 20.7 min; $t_{R,2}$ = 21.4 min. Racemic diol **32** (0.089 g, 0.5 mmol) was treated with acetic anhydride (66 μL, 0.7 mmol) in the presence of DMAP (0.012 g, 0.1 mmol) in 20 mL of Et_2O, and the resulting solution was stirred overnight at rt (25 °C). Et_2O was then removed in vacuo, and the monoacetylated product was purified by silica flash gel chromatography (EtOAc, R_f = 0.49). Isolated racemic monoacetylated product (0.051 g, 0.23 mmol; 46%) was characterized and then subjected to the GC assay described above to prove the origin of the GC signals. ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm = 4.71−4.68 [m, 1 H]; 4.68−4.65 [m, 1 H]; 2.81−2.76 [m, 1 H]; 2.76−2.71 [m, 2 H]; 2.60−2.46 [m, 3 H]; 2.38−2.33 [m, 2 H]; 2.04 [s, 3 H, CH_3]; 1.73 [d, 1 H, J = 10.6 Hz]; 1.37 [bs, 1 H, OH]; 1.34 [d, 1 H, J = 11.0 Hz]. ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm = 170.3 (C═O); 74.5; 73.1; 48.9; 44.5; 44.1; 43.0; 42.1; 40.6; 38.8; 36.2; 34.9; 21.4. HRMS (EI-sector field) m/z: $[M]^+$ calcd for $C_{13}H_{16}O_3^{\bullet+}$ 220.109, found 220.109. IR (KBr): $\tilde{\nu}$/cm^{-1} = 3320; 2974; 2954; 2864; 1740; 1730; 1370; 1276; 1249; 1238; 1095; 1043.

Octahydro-1H-2,4,1-(epiethane[1,1,2]triyl)cyclobuta[cd]-pentalene-5,7-diyl diacetate. Retention times: $t_{R,1}$ = 17.0 min; $t_{R,2}$ = 17.3 min. Racemic diol **32** (0.089 g, 0.5 mmol) was treated with acetic anhydride (66 μL, 0.7 mmol) in the presence of DMAP (0.012 g, 0.1 mmol) in 20 mL of Et_2O, and the resulting solution was stirred overnight at rt (25 °C). Et_2O was then removed in vacuo, and the diacetylated product was purified by silica flash gel chromatography (EtOAc, R_f = 0.58). Isolated racemic diacetylated **32** (0.020 g, 0.08 mmol; 16%) was characterized and then subjected to the GC assay described above to prove the origin of the GC signals. ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm = 5.52 [s, 1 H]; 4.64 [t, 1 H, J = 3.9 Hz]; 2.79−2.74 [m, 1 H]; 2.68−2.64 [m, 1 H]; 2.62−2.57 [m, 2 H]; 2.50−2.43 [m, 2 H]; 2.41−2.36 [m, 1 H]; 2.33−2.88 [m, 1 H]; 2.01 [s, 3 H, CH_3]; 1.92 [s, 3 H, CH_3]; 1.65 [d, 1 H, J = 10.8 Hz]; 1.26 [d, 1 H, J = 10.7 Hz]. ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm = 170.8 (C═O); 170.8 (C═O); 77.3; 74.1; 46.3; 45.1; 44.3; 43.0; 40.9; 39.5; 38.9; 36.4; 35.0; 21.5; 21.5. HRMS (EI-sector field) m/z: $[M]^+$ calcd for $C_{15}H_{18}O_4^{\bullet+}$ 262.121, found 262.122. IR (KBr): $\tilde{\nu}$/cm^{-1} = 2973; 2867; 1740; 1377; 1363; 1275; 1238; 1100; 1047; 1016.

*Octahydro-1H-2,4,1-(epiethane[1,1,2]triyl)cyclobuta[cd]-pentalene-5,7-diol (**33**).* *meso*-**33** was purchased from the University Lodz and used without further purification. Achiral diol **33** was separated from the other compounds of the reaction mixture using chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: 100−250 °C, 5 °C/min. Retention time: t_R = 28.4 min.

7-Hydroxyoctahydro-1H-2,4,1-(epiethane[1,1,2]triyl)cyclobuta-[cd]pentalen-5-yl acetate. Enantiomers of the monoacetate of **33** were separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: 140 °C isothermal for 55 min; then 140−250 °C, 20 °C/min and then 250 °C for 5 min. Retention times: $t_{R,1}$ = 58.9 min; $t_{R,2}$ = 59.1 min. *Preparation*: *meso*-Diol **33** (0.089 g, 0.5 mmol) was treated with acetic anhydride (66 μL, 0.7 mmol) in the presence of DMAP (0.012 g, 0.1 mmol) in 20 mL of Et_2O, and the resulting solution was stirred overnight at rt (25 °C). Et_2O was then removed in vacuo, and the monoacetylated product was purified by silica flash gel chromatography (EtOAc/hexane 1:1, R_f = 0.30). Isolated racemic monoacetylated **33** (0.099 g, 0.45 mmol; 90%) was characterized and then subjected to the GC assay described above to prove the origin of the GC signals. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 4.89 [t, 1 H, J = 3.8 Hz]; 4.18 [d, 1 H, J = 12.4 Hz]; 3.76 [td, 1 H, J_1 = 12.4 Hz, J_2 = 3.4 Hz]; 2.84−2.76 [m, 1 H]; 2.72−2.58 [m, 3 H]; 2.53−2.47 [m, 1 H]; 2.45−2.33 [m, 3 H]; 2.11 [s, 3 H, CH_3]; 1.69 [d, 1 H, J = 10.7 Hz]; 1.11 [d, 1 H, J = 10.8 Hz]. ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 169.3 (C═O); 73.0; 72.0; 45.4; 43.0; 43.0; 42.5; 39.7; 39.2; 38.1; 35.6; 34.3; 21.4. HRMS (EI-sector field) m/z: $[M]^+$ calcd for $C_{13}H_{16}O_3^{\bullet+}$ 220.110, found 220.110. IR (KBr): $\tilde{\nu}$/cm^{-1} = 3545; 2964; 2864; 1744; 1436; 1368; 1311; 1268; 1224; 1150; 1098; 1077; 1038.

7-Hydroxyoctahydro-1H-2,4,1-(epiethane[1,1,2]triyl)cyclobuta-[cd]pentalen-5-yl diacetate. The achiral diacetate of **33** was separated from the other compounds of the reaction mixture using chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: 100−250 °C, 5 °C/min. Retention time: t_R = 25.7 min. *Preparation*: *meso*-Diol **33** (0.089 g, 0.5 mmol) was treated with acetic anhydride (66 μL, 0.7 mmol) in the presence of DMAP (0.012 g, 0.1 mmol) in 20 mL of Et_2O, and the resulting solution was stirred overnight at rt (25 °C). Et_2O was then removed in vacuo, and the diacetylated product was purified by silica flash gel chromatography (EtOAc/hexane 1:1, R_f = 0.41). Isolated diacetylated **33** (0.010 g, (0.04 mmol; 8%) was characterized and then subjected to the GC assay described above to prove the origin of the GC signals. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 4.58−4.53 [m, 2 H]; 2.82−2.71 [m, 2 H]; 2.62−2.51 [m, 2 H]; 2.45 [s, 2 H]; 2.39−2.30 [m, 2 H]; 2.00 [s, 6 H, CH_3]; 1.62 [d, 1 H, J = 10.8 Hz]; 1.06 [d, 1 H, J = 10.8 Hz]. ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 171.1 (C═O); 72.2; 43.0; 42.2; 39.2; 35.3; 34.1; 21.6. HRMS (EI-sector field) m/z: $[M]^+$ calcd for $C_{15}H_{18}O_4^{\bullet+}$ 262.121, found 262.124. IR (KBr): $\tilde{\nu}$/cm^{-1} = 2969; 2942; 2927; 2858; 1728; 1449; 1438; 1374; 1366; 1305; 1269; 1245; 1165; 1095; 1076; 1067; 1053; 1017.

*1,4,4a,5,8,8a-Hexahydro-1,4-methanonaphthalene-5,8-diol (**34**).* *meso*-**34** was purchased from the University Lodz and used without further purification. Achiral diol **34** was separated from the other compounds of the reaction mixture using chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: 100−250 °C, 5 °C/min. Retention time: t_R = 23.1 min.

8-Hydroxy-1,4,4a,5,8,8a-hexahydro-1,4-methanonaphthalen-5-yl acetate. Retention times: $t_{R,1}$ = 22.5 min; $t_{R,2}$ = 22.7 min. *Preparation*: *meso*-Diol **34** (0.089 g, 0.5 mmol) was treated with acetic anhydride (66 μL, 0.7 mmol) in the presence of DMAP (0.012 g, 0.1 mmol) in 20 mL of Et_2O, and the resulting solution was stirred overnight at rt (25 °C). Et_2O was then removed in vacuo, and the monoacetylated product was purified by silica flash gel chromatography (EtOAc/hexane 1:1, R_f = 0.29). Isolated racemic monoacetylated **34** (0.037 g, 0.18 mmol; 36%) was characterized and then subjected to the GC assay described above to prove the origin of the GC signals. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 5.88 [dd, 1 H, J_1 = 5.5 Hz, J_2 = 2.8 Hz]; 5.81 [dd, 1 H, J_1 = 5.5 Hz, J_2 = 2.8 Hz]; 5.49−5.43 [m, 1 H]; 5.40−5.34 [m, 1 H]; 5.32−5.26 [m, 1 H]; 4.52−4.43 [m, 1 H]; 3.09−2.98 [m, 2 H]; 2.89−2.80 [m, 2 H]; 2.12 [s, 3 H,

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CH_3]; 1.90 [s, 1 H]; 1.39−1.27 [m, 2 H]. ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 170.8 (C═O); 135.6; 135.5; 132.1; 126.9; 69.8; 66.5; 48.9; 45.7; 45.0; 41.8; 38.5; 21.1. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{13}H_{16}O_3Na^+$ 243.0992, found 243.0992. IR (KBr): $\tilde{\nu}$/cm^{-1} = 3451; 2972; 1739; 1669; 1373; 1243; 1033.

1,4,4a,5,8,8a-Hexahydro-1,4-methanonaphthalene-5,8-diyl diacetate. Retention time: t_R = 22.4 min. *Preparation*: *meso*-Diol **34** (0.089 g, 0.5 mmol) was treated with acetic anhydride (66 μL, 0.7 mmol) in the presence of DMAP (0.012 g, 0.1 mmol) in 20 mL of Et_2O, and the resulting solution was stirred overnight at rt (25 °C). Et_2O was then removed in vacuo, and the diacetylated product was purified by silica flash gel chromatography (EtOAc/hexane 1:1, R_f = 0.49). Isolated diacetylated **34** (0.055 g, 0.21 mmol; 42%) was characterized and then subjected to the GC assay described above to prove the origin of the GC signals. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 5.86−5.82 [m, 2 H]; 5.44−5.34 [m, 4 H]; 3.11−3.02 [m, 2 H]; 2.88−2.82 [m, 2 H]; 2.14 [s, 6 H, CH_3]; 1.31 [q, 2 H, J = 8.7 Hz]. ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 170.6 (C═O); 135.5; 128.0; 69.4; 48.4; 45.8; 38.0; 21.1. HRMS (EI-sector field) m/z: [M]$^+$ calcd for $C_{15}H_{18}O_4^{\bullet+}$ 262.121, found 262.122. IR (KBr): $\tilde{\nu}$/cm^{-1} = 2979; 2967; 2934; 2882; 1743; 1371; 1304; 1244; 1227; 1366; 1248; 1169.

Cyclopent-4-ene-1,3-diol (35). *meso*-Cyclopent-4-ene-1,3-diol **35** was purchased and used without further purification. Achiral diol **35** was separated from the other compounds of the reaction mixture using chiral GC employing a 30 m Chiraldex G-TA column (Astech). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: 100−180 °C, 2 °C/min. Retention times: t_R = 13.0.

4-Hydroxycyclopent-2-en-1-yl acetate. Retention times: $t_{R,1}$ = 13.7 min; $t_{R,2}$ = 14.2 min. *Preparation*: *meso*-Cyclopent-4-ene-1,3-diol **35** (0.150 g, 1.5 mmol) was treated with acetic anhydride (186 μL, 2 mmol) in the presence of DMAP (0.018 g, 0.15 mmol) in 20 mL of dichloromethane, and the resulting solution was stirred overnight at rt (25 °C). Dichloromethane was then removed in vacuo, and the monoacetylated product was purified by silica flash gel chromatography (EtOAc, R_f = 0.47). Isolated racemic monoacetylated **35** (0.160 g, 1.1 mmol) was characterized and then subjected to the GC assay described above to prove the origin of the GC signals. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 6.13−6.10 [m, 1 H]; 6.00−5.97 [m, 1 H]; 5.52−5.47 [m, 1 H]; 4.75−4.70 [m, 1 H]; 2.81 [td, 1 H, J_1 = 14.6 Hz, J_2 = 7.3 Hz]; 2.20 [bs, 1 H, OH]; 2.06 [s, 3 H, CH_3]; 1.66 [td, 1 H, J_1 = 14.6 Hz, J_2 = 3.9 Hz]. ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 170.8 (C═O); 138.5; 132.5; 77.1; 74.8; 40.5; 21.2. IR (KBr): $\tilde{\nu}$/cm^{-1} = 3434; 3084; 2941; 1723; 1403; 1375; 1244; 1189; 1103; 1034. Analytical data of monoacetylated **35** differ slightly from those reported in the literature.[119]

Cyclopent-4-ene-1,3-diyl diacetate. Retention time: t_R = 14.8. *Preparation*: *meso*-Cyclopent-4-ene-1,3-diol **35** (0.150 g, 1.5 mmol) was treated with acetic anhydride (186 μL, 2 mmol) in the presence of DMAP (0.018 g, 0.15 mmol) in 20 mL of dichloromethane, and the resulting solution was stirred overnight at rt (25 °C). DCM was then removed in vacuo, and the diacetylated product was purified by silica flash gel chromatography (EtOAc, R_f = 0.58). The isolated diacetate of **35** (0.063 g, 0.3 mmol; 20%) was characterized and then subjected to the GC assay described above to prove the origin of the GC signals. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 6.09 [d, 2 H, J = 0.5 Hz]; 5.55 [ddd, 2 H, J_1 = 7.4 Hz, J_2 = 3.9 Hz, J_3 = 0.7 Hz]; 2.88 [td, 1 H, J_1 = 15.0 Hz, J_2 = 7.5 Hz], 2.06 [s, 6 H, CH_3]; 1.74 [td, 1 H, J_1 = 15.0 Hz, J_2 = 3.8 Hz]. ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 170.6 (C═O); 134.6; 76.6; 37.1; 21.1. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_9H_{12}O_4Na^+$ 207.0628, found 207.0624. IR (KBr): $\tilde{\nu}$/cm^{-1} = 2951; 1737; 1435; 1366; 1329; 1233; 1194; 1076; 1020.

(Tetrahydrofuran-2,5-diyl)dimethanol (36).[83] *meso*-**36** was prepared by the group of Christian Stark (University of Leipzig, now at the University of Hamburg, Germany) and used without further purification. Achiral diol **36** was separated from the other compounds of the reaction mixture using chiral GC employing a 30 m Chiraldex G-TA column (Astech). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: 100−180 °C, 2 °C/min. Retention time: t_R = 23.9 min.

(5-(Hydroxymethyl)tetrahydrofuran-2-yl)methyl acetate. Retention times: $t_{R,1}$ = 22.3 min; $t_{R,2}$ = 23.0 min. *Preparation*: *meso*-Diol **36** (0.066 g, 0.5 mmol) was treated with acetic anhydride (71 μL, 0.75 mmol) in the presence of DMAP (0.005 g, 0.0375 mmol) in 5 mL of DCM, and the resulting solution was stirred overnight at rt (25 °C). DCM was then removed in vacuo, and the monoacetylated product was purified by silica flash gel chromatography (EtOAc, R_f = 0.26). Isolated racemic monoacetylated **36** (0.053 g, 0.31 mmol; 62%) was characterized and then subjected to the GC assay described above to prove the origin of the GC signals. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 4.20−4.00 [m, 4 H]; 3.72−3.63 [m, 1 H]; 3.49−3.39 [m, 1 H]; 2.44 [bs, 1 H]; 2.04 [s, 3 H, CH_3]; 2.01−1.73 [m, 3 H]; 1.71−1.60 [m, 1 H]. ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 171.2 (C═O); 80.5; 77.3; 66.6; 64.5; 28.0; 26.7; 20.9. IR (KBr): $\tilde{\nu}$/cm^{-1} = 3461; 2948; 1774; 1741; 1420; 1372; 1237; 1187; 1050. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_8H_{14}O_4Na^+$ 197.0784, found 197.0784.

(Tetrahydrofuran-2,5-diyl)bis(methylene) diacetate. Retention time: t_R = 28.0 min. *Preparation*: *meso*-Diol **36** (0.066 g, 0.5 mmol) was treated with acetic anhydride (71 μL, 0.75 mmol) in the presence of DMAP (0.005 g, 0.0375 mmol) in 5 mL of DCM, and the resulting solution was stirred overnight at rt (25 °C). DCM was then removed in vacuo, and the diacetylated product was purified by silica flash gel chromatography (EtOAc, R_f = 0.51). Isolated diacetylated **36** (0.012 g, 0.06 mmol; 12%) was characterized and then subjected to the GC assay described above to prove the origin of the GC signals. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 4.18−4.07 [m, 4 H]; 3.98−3.90 [m, 2 H]; 2.03 [s, 6 H, CH_3]; 2.00−1.90 [m, 2 H]; 1.72−1.59 [m, 2 H]. ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 171.0 (C═O); 77.5; 66.5; 27.7; 20.9. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{10}H_{16}O_5Na^+$ 239.0890, found 239.0885. IR (KBr): $\tilde{\nu}$/cm^{-1} = 2953; 2884; 1742; 1452; 1371; 1238; 1098; 1042.

Substrate (37). The diol **37** was synthesized by Y. Landais.[84] Enantiomers of diol **37** were separated by HPLC employing a 25 cm, d = 0.46 cm Chiralpak IC column (Daicel). Eluent: Hexane/Isopropanol 93:7; flow = 1 mL/min; UV-detector λ = 254 nm. Retention times: $t_{R,1}$ = 15.87 min; $t_{R,2}$ = 17.48 min.

Substrate (38). Retention times: $t_{R,1}$ = 12.72 min; $t_{R,2}$ = 21.29 min.

Substrate (39). Retention times: $t_{R,1}$ = 23.44 min; $t_{R,2}$ = 37.84 min.

Substrate (40). Retention times: $t_{R,1}$ = 19.43 min; $t_{R,2}$ = 29.25 min.

The analytical data for **37** and **40** were in accordance with the literature.[84] *Preparation*: Racemic diol **37** (0.043 g, 0.11 mmol) was treated with acetic anhydride (11.5 μL, 0.12 mmol) in the presence of DMAP (2.7 mg, 0.02 mmol) in 7 mL of DCM, and the resulting solution was stirred for 2 h at rt (25 °C). DCM was then removed in vacuo, and the monoacetylated products (±)-**38**, (±)-**39** and the diacylated product **40** were purified by silica flash gel chromatography (EtOAc/hexane (1:1), R_f (**38**) and (**39**) = 0.2; R_f (**40**) = 0.3. Isolated racemic (±)-**38** and (±)-**39** (0.026 mg, 0.06 mmol; 54%; colorless solid) and **40** (0.014 g, 0.03 mmol; 27%; colorless solid) were characterized and then subjected to the HPLC assay described above to prove the origin of the signals. NMR data for **38** and **39** are as follows. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.56−7.50 [m, 2 H]; 7.33−7.26 [m, 3 H]; 6.38−6.25 [m, 2 H]; 5.50 [t, 1 H, J_3 = 4.0 Hz]; 4.88−4.82 [m, 1 H]; 4.64−4.56 [m, 1 H]; 4.23 [bs, 1 H]; 2.04 [s, 3 H]; 1.99 [s, 1 H]; 1.62 [q, 1 H, J_3 =2.5 Hz]; 1.41 [s, 9 H]; 0.42 [s, 3 H]; 0.40 [s, 3 H]. ^{13}C NMR (50 MHz, $CDCl_3$): δ/ppm = 169.6 (C═O); 155.1 (C═O); 137.1; 134.2; 134.0; 129.3: 127.4; 82.1; 75.0; 73.6; 68.6; 54.8; 38.6; 28.2; 21.0; −2.9; −3.7.

Procedure for the Competitive Catalytic Run with Alcohols 1, 41, 42, and 43. The conditions for the kinetic resolutions for the competitive catalytic runs are given exemplary by the following experimental protocol. Catalyst **12b** (1.9 mg, 0.0025 mmol) was dissolved in 500 μL of dry toluene. 100 μL of this catalyst solution (0.0005 mmol, 2 mol %) were added to a clear solution of the alcohols **1**, **41**, **42**, and **43** (0.025 mmol of each alcohol) in 4.65 mL of dry toluene. The reaction mixture was cooled to 0 °C, and 25 μL (0.1325 mmol, 5.3 equiv of acetic anhydride) of a solution of 100 μL of acetic anhydride in 100 μL of toluene (cooled to 0 °C) were then added with an Eppendorf pipette and allowed to stir at 0 °C. After the reaction, the reaction mixture was quenched with methanol and directly

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analyzed by GC and/or chiral GC analysis. The same conditions were used for the competitive catalytic run with DMAP (0.0025 mmol) as catalyst (for the chromatograms, see the Supporting Information). All signals were detected by GC-FID employing a 30 m 5890_V UP5 (Machery Nagel). *T* (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: 60 °C−250 °C, 15 °C/min. Retention times: **1** t_R = 6.69 min; **41** R= 6.33 min; **42** t_R = 1.44 min; **43** t_R = 4.09 min; **2** t_R = 8.57 min; **44** t_R = 8.02 min; **45** t_R = 2.21 min; **46** t_R = 2.37 (chromatograms for the **12b**-catalyzed run can be found in the Supporting Information).

*(3a,7a)-Hexahydrobenzo-1,3-dioxo-2-one (**47**).*[108] Enantiomers of the cyclic carbonate **47** were separated by chiral GC employing a 30 m FS-Hydrodex *β*-6TBDM column (Macherey Nagel). *T* (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: 100−250 °C, 2 °C/min. Retention times: $t_{R,1}$ = 29.5 min; $t_{R,2}$ = 29.7 min. *Preparation*: *trans*-Diol **1** (0.50 g, 4.3 mmol) was treated with Boc_2O (2.94 mL, 12.9 mmol) in the presence of DMAP (0.52 g, 4.3 mmol) in 10 mL of dry acetonitrile, and the resulting solution was stirred overnight at rt (25 °C). Acetonitrile was then removed in vacuo, and the *O*,*O*-di-*tert*-butoxylated product ((±)-**48**) and the cyclic carbonate ((±)-**47**) were purified by silica flash gel chromatography (hexane/EtOAc (3:1), R_f (**48**) = 0.52; R_f (**47**) = 0.26). Isolated racemic (±)-**47** (0.421 g, 3.0 mmol) and (±)-**48** (0.145 mg, 0.46 mmol) were characterized and then subjected to the GC assay to prove the origin of the GC signals. ^{1}H NMR (400 MHz, $CDCl_3$): *δ*/ppm = 3.96 [m, 2 H], 2.19 [m, 2 H], 1.92−1.80 [m, 2 H], 1.69−1.55 [m, 2 H], 1.42−1.29 [m, 2 H]. ^{13}C NMR (100 MHz, $CDCl_3$): *δ*/ppm = 155.1 (C═O), 83.5, 28.2, 23.2

*tert-Butylcyclohexane-1,2-diyl dicarbonate (**48**).* Enantiomers of the di-*tert*-butoxycarbonylated product **48** were not separated by chiral GC employing a 30 m FS-Hydrodex *β*-6TBDM column (Macherey Nagel). *T* (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: 100−250 °C, 2 °C/min. Retention time: $t_{R,1}$ = 39.6 min. *Preparation using DMAP as catalyst*: *trans*-Diol **1** (0.58 g, 5.0 mmol) was treated with Boc_2O (1.26 mL, 5.5 mmol) in the presence of DMAP (0.182 g, 1.5 mmol) in 100 mL of dry toluene, and the resulting solution was stirred overnight at rt (25 °C). Toluene was then removed in vacuo, and the *O*-*tert*-butoxylated product ((±)-**2e**), the *O*,*O*-di-*tert*-butoxylated product ((±)-**48**) and the cyclic carbonate ((±)-**47**) were purified by silica flash gel chromatography (DCM/MeOH (19:1), R_f (**48**) = 0.81; R_f (**47**) = 0.71; R_f (**2e**) = 0.62). Isolated racemic (±)-**2e** (0.842 g, 3.9 mmol, 78%) and (±)-**48** (0.126 mg, 0.4 mmol, 8%) were characterized and then subjected to the GC assay described to prove the origin of the GC signals. (±)-**87** could just be isolated in traces and was therefore synthesized using different reaction conditions. The NMR data for (±)-**2e** and (±)-**48** are in accordance with the literature.[108] *Preparation using N-methylimidazole as catalyst*: *trans*-Diol **1** (0.58 g, 5.0 mmol) was treated with Boc_2O (1.26 mL, 5.5 mmol) in the presence of *N*-methylimidazole (123.2 *μ*L, 1.5 mmol) in 100 mL of dry toluene, and the resulting solution was stirred overnight at rt (25 °C). Toluene was then removed in vacuo, and the *O*-*tert*-butoxylated product ((±)-**2e**), the *O*,*O*-di-*tert*-butoxylated product ((±)-**48**) and the cyclic carbonate ((±)-**3**) were purified by silica flash gel chromatography (DCM/MeOH (19:1), R_f (**48**) = 0.81; R_f (**47**) = 0.71; R_f (**2e**) = 0.62). Isolated racemic (±)-**2e** (0.821 g, 3.8 mmol, 76%) and (±)-**48** (0.94 g, 0.3 mmol, 6%) were characterized and then subjected to the GC assay described to prove the origin of the GC signals. (±)-**47** could just be isolated in traces and was therefore synthesized using different reaction conditions. The NMR data for (±)-**2e** and (±)-**48** are in accordance to the literature.[108]

*Description of the Preparative Kinetic Resolution Experiment of (±)-**1** with Boc_2O.* Catalyst **12b** (38 mg, 0.05 mmol, 5 mol %) and diol (±)-**1** (116.2 mg, 1 mmol) were dissolved in 160 mL of dry toluene. 0.46 mL (2.0 mmol, 2.0 equiv) of Boc_2O was added and then allowed to stir for 48 h at rt. The reaction mixture was quenched with 10 mL of methanol and then filtered using 40 g silica gel suspended with DCM to remove the catalyst. The solvent was removed under reduced pressure. The crude product was directly purified via silica gel column chromatography (DCM/methanol (19:1)). 104.2 mg (0.48 mmol, 48.1%) of **2e** (R_f = 0.62) and 52.1 mg (0.45 mmol, 44%) of **1** (R_f = 0.71) were isolated and directly characterized by chiral GC and NMR.

*General Procedure: Enantioselective Boc-Protection of rac-**1**.* 2.9 mg (0,025 mmol) of *rac*-**1** were dissolved in 4.45 mL of dry toluene. 1, 2, 5, or 10 mol % (0.38 mg, 0.76 mg, 1.9 mg or 3.8 mg) of **12b** and 5.74, 11.49, 28.88, or 54.7 *μ*L (0.025 mmol, 0.05 mmol, 0.1325 or 0.25 mmol) of Boc_2O were added, and the mixture was stirred at rt. The conversion and *ee* were determined by chiral GC. A stock solution was prepared: 4 mg **12b** in 800 *μ*L of dry toluene.

*trans-2-Hydroxycyclohexyl-4-nitrobenzenesulfonate (**53**).* Enantiomers of the sulfonylated diol **53** were separated by using HPLC employing a 25 cm, *d* = 0.46 cm Chiralpak IB column (Daicel). Eluent: Hexane/Isopropanol 90:10; flow = 0.7 mL/min; UV-detector *λ* = 254 nm. Retention times: $t_{R,1}$ = 27.8 min; $t_{R,2}$ = 31.9 min.

*Sulfonylation of rac-**1** Using **12b** as Catalyst.* 116.2 mg (1.0 mmol) of *rac*-**1**, 2 mol % (15.2 mg) of **12b**, and 288 mg of 4-nitrobenzenesufonyl chloride were dissolved in 5 mL of dry DCM, and 2 mL of a saturated $NaHCO_3$ solution was added. The two-phase system was stirred for 24 h. The products were purified via flash chromatography eluting with ethyl acetate/pentane (3: 1). 42 mg (0.13 mmol, 14%) of **53** (R_f = 0.52) and 39 mg (0.08 mmol, 8%) of disulfonylated diol (R_f = 0.61) were isolated as yellowish solids. The enantiomeric excess of **1** was determined by chiral GC. ^{1}H NMR (400 MHz, $CDCl_3$): *δ*/ppm = 8.33 [d, *J* = 12 Hz, 2 H], 8.08 [d, *J* = 12 Hz, 2 H], 4.36 [m, 1 H], 3.52 [m, 1 H], 1.99 [t, *J* = 12 Hz, 2 H], 1.85 [s, 2 H], 1.65 [m, 2 H], 1.43 [m, 1 H], 1.31−1.11 [m, 3 H]. ^{13}C NMR (100 MHz, $CDCl_3$): *δ*/ppm = 150.3, 142.9, 129.1, 124.4, 87.9, 72.0, 32.6, 31.2, 24.0, 23.3. IR (KBr): ν/cm^{-1} = 3538, 2939,1609, 1534, 1351, 1185, 1095, 1076, 981, 926. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{12}H_{15}NO_6SNa^+$ 324.0512, found 324.0513.

trans-Cyclohexane-1,2-diyl bis(4-nitrobenzenesulfonate). ^{1}H NMR (400 MHz, $CDCl_3$): *δ*/ppm = 8.29 [d, *J* = 8 Hz, 4 H], 7.98 [d, *J* = 8 Hz, 4 H], 4.48 [m, 2 H], 2.04−1.94 [m, 2 H], 1.62−1.55 [m, 2 H], 1.52−1.38 [m, 2 H], 1.28−1.12 [m, 2 H]· ^{13}C NMR (100 MHz, $CDCl_3$): *δ*/ppm = 150.8, 142.4, 129.1, 124.5, 81.3, 31.0, 22.6. IR (KBr): ν/cm^{-1} = 2950, 1610, 1538, 1351, 1186, 1094, 977, 919. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{18}H_{18}N_2O_{10}S_2Na^+$ 509.0295, found 509.0300.

Sulfonylation Test Reactions. 11.6 mg (0,1 mmol) of *rac*-**1** was dissolved in 4.5 mL of dry toluene. 5 mol % (3.8 mg) of **12b**, 12.8 *μ*L (0.11 mmol) of 2,6-lutidine and 20.96 mg (0.11 mmol) of tosylchloride/21.1 mg (0.11 mmol) of 4-chlorobenzenesulfonyl chloride/18.2 *μ*L (0.11 mmol) of trifluoromethanesulfonic anhydride were added and allowed to stir for 24 h. The conversion was determined by TLC using EtOAc/hexane as eluent.

trans-2-Hydroxycyclohexyl diphenyl phosphate (54-Ph). Enantiomers of **54**-Ph were separated by chiral GC employing a 30 m FS-Hydrodex *β*-6TBDM column (Macherey Nagel). *T* (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: 140 °C isotherm 13 min; 140−250 °C, 2 °C/min; 250 °C isotherm 15 min. Retention times: $t_{R,1}$ = 37.5 min; $t_{R,2}$ = 37.9 min (**54**-Ph); $t_{R,1}$ = 10.4 min; $t_{R,2}$ = 10.9 min (**1**). *Preparation using DMAP as catalyst*: 580 mg (5 mmol) of *rac*-**1**, 0.826 mL (5 mmol) of Et_3N and 183 mg (1.5 mmol) of DMAP were dissolved in dry toluene. 1.035 mL (5 mmol) of diphenylchlorophosphate were added, and the mixture was stirred for 12 h at rt. The solvent was removed under reduced pressure, and the crude mixture was purified via silica gel chromatography utilizing ethylacetate/hexane (3:2) as eluent. 578 mg (1.6 mmol, 33.2%; R_f = 0.35) of a colorless solid were isolated. *Preparation using **12b** as catalyst*: The same reaction was accomplished with 3 mmol of *rac*-**1** using 22 mg (0.03 mmol) of **12b** as catalyst. The reaction was stopped at a conversion of 50%. The crude product was purified by preparative HPLC (eluent: TBME/Hexane 60:40) UV-detector *λ* = 254 nm, E_{max} = 2.56; refractometer; column l = 250 mm, *d* = 8 mm, LiChrosorb Diol (7 *μ*m, Merck); 417 mg (1.2 mmol) of a colorles solid were isolated. The product seems to be sensitive toward acids. ^{1}H NMR (400 MHz, $CDCl_3$): *δ*/ppm = 7.41−7.31 [m, 4 H, H_{Ar} (Phe], 7.29−7.17 [m, 6 H, H_{Ar} (Phe], 4.34 [m, 1 H, H_α ($OP(OPh)_2$)], 3.61 [m, 1 H, H_α (OH)], 2.95 [s, 1 H, OH], 2.17−2.09 [m, 1 H], 2.08−2.00 [m, 1 H], 1.77−1.64 [s, 2 H], 1.49−1.40 [m, 1 H], 1.36−

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1.19 [m, 3 H]. ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 150.6, 129.8, 125.5, 120.1, 85.3, 73.3, 32.4, 31.2, 23.9, 23.5. IR (KBr): ν/cm^{-1} = 3471.6, 2936.6, 1589.0, 1489.5, 1265.4, 1186.9, 1086.4, 1018.2, 955.4, 774.0. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{18}H_{21}O_5PNa^+$ 371.1025, found 371.1019.

trans-2-Hydroxycyclohexyl diethyl phosphate (54-Et). Enantiomers of **54**-Et were separated by chiral GC employing a 30 m FS-Hydrodex β-6TBDM column (Macherey Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: 140 °C isotherm 13 min; 140−250 °C, 2 °C/min → 250 °C isotherm 15 min. Retention times: $t_{R,1}$ = 28.4 min; $t_{R,2}$ = 28.9 min (**54-Ph**); $t_{R,1}$ = 10.4 min; $t_{R,2}$ = 10.9 min (**1**). *Preparation using DMAP as catalyst*: 290 mg (2.5 mmol) of *rac*-**1**, 0.35 mL (2.5 mmol) of DIPEA and 91.6 mg (0.75 mmol) of DMAP were dissolved in dry toluene. 0.36 mL (2.55 mmol) of diethylchlorophosphate were added, and the mixture was stirred for 12 h at rt. The solvent was removed under reduced pressure, and the crude mixture was purified via Al_2O_3 gel chromatography utilizing acetonitrile as eluent. 425 mg (1.6 mmol, 67%; R_f = 0.49) of a colorless liquid were isolated. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 4.13−4.01 [q, 4 H, J = 6.8 Hz, O−CH_2−R], 4.00−3.96 [m, 1 H, H_α (OP(OEt)$_2$)], 3.63 [s, 1 H, OH], 3.53−3.47 [m, 1 H, H_α (OH)], 2.14−1.91 [m, 2 H], 1.70−1.58 [m, 2 H], 1.40−1.12 [m, 4 H], 1.32−1.27 [t, 6 H, J = 7.0 Hz, CH_3]. ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 83.2, 73.5, 64.1, 32.9 31.7, 24.0, 23.6, 16.1. IR (Film): ν/cm^{-1} = 3404.3, 2938.6, 1453.1, 1258.4, 1028.0. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{10}H_{21}O_5PNa^+$ 275.1022, found 275.1019.

Competition Experiment with Different Electrophiles. 2.9 mg (0.025 mmol) of *trans*-cyclohexane-1,2-diol **1**, 13.5 μL (0.1325 mmol) of Ac_2O, 27 mg (0.1325 mmol) of 4-nitrobenzenesulfonyl chloride, 19 μL (0.1325 mmol) of POCl(OEt)$_2$, and 80 mg (0.58 mmol) of K_2CO_3 were dissolved in 4.5 mL of abs. toluene, and the mixture was cooled to 0 °C. 2 mol % of peptide **1** was added, and the reaction was monitored via GC and TLC (the sulfonylated product cannot be detected via GC) and chiral GC. For reasons of comparability, the same reaction was performed with 2 mol % of DMAP as catalyst. All signals were detected by GC-FID employing a 30 m 5890_V UP5 (Machery Nagel). T (Injector + Detector) = 250 °C. Splitflow = 80 mL/min. Precolumn pressure = 0.8 bar. Conditions: 100 °C−250 °C, 15 °C/min. Retention times: **54-Ph** and **54-Et** were not detected; *trans*-cyclohexane-1,2-diol **1** t_R = 6.9 min; Acylated product **2** t_R = 8.8 min; **POCl(OEt)$_2$** t_R = 6.7 min; **POCl(OPh)$_2$** t_R = 15.2 min; **DMAP** t_R = 9.5 min. TLC: EtOAc = eluent (*Rac*-**1** R_f = 0.15 n.f.; **53** R_f = 0.6 f.; **54-Ph** R_f = 0.5 f.; **54-Et** R_f = 0.3 n.f.; **2** R_f = 0.6 n.f.; **POCl(OPh)$_2$** R_f = 0.7 f.; **SO_2ClPh-*p*-NO_2** R_f = 0.65 f.) f. = shows fluorescence; n.f. = shows no fluorescence. The spots were first detected under UV light and then by phosphomolybdic acid. The GC retention times and characterization of **1** can be found in the literature.[60]

■ ASSOCIATED CONTENT

Supporting Information

NMR and IR spectra, as well as computational data and additional references. 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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