DOI: 10.1002/anie.201006128

Acyl Transfer

Organocatalytic Enantioselective Acyl Transfer onto Racemic as well as *meso* Alcohols, Amines, and Thiols**

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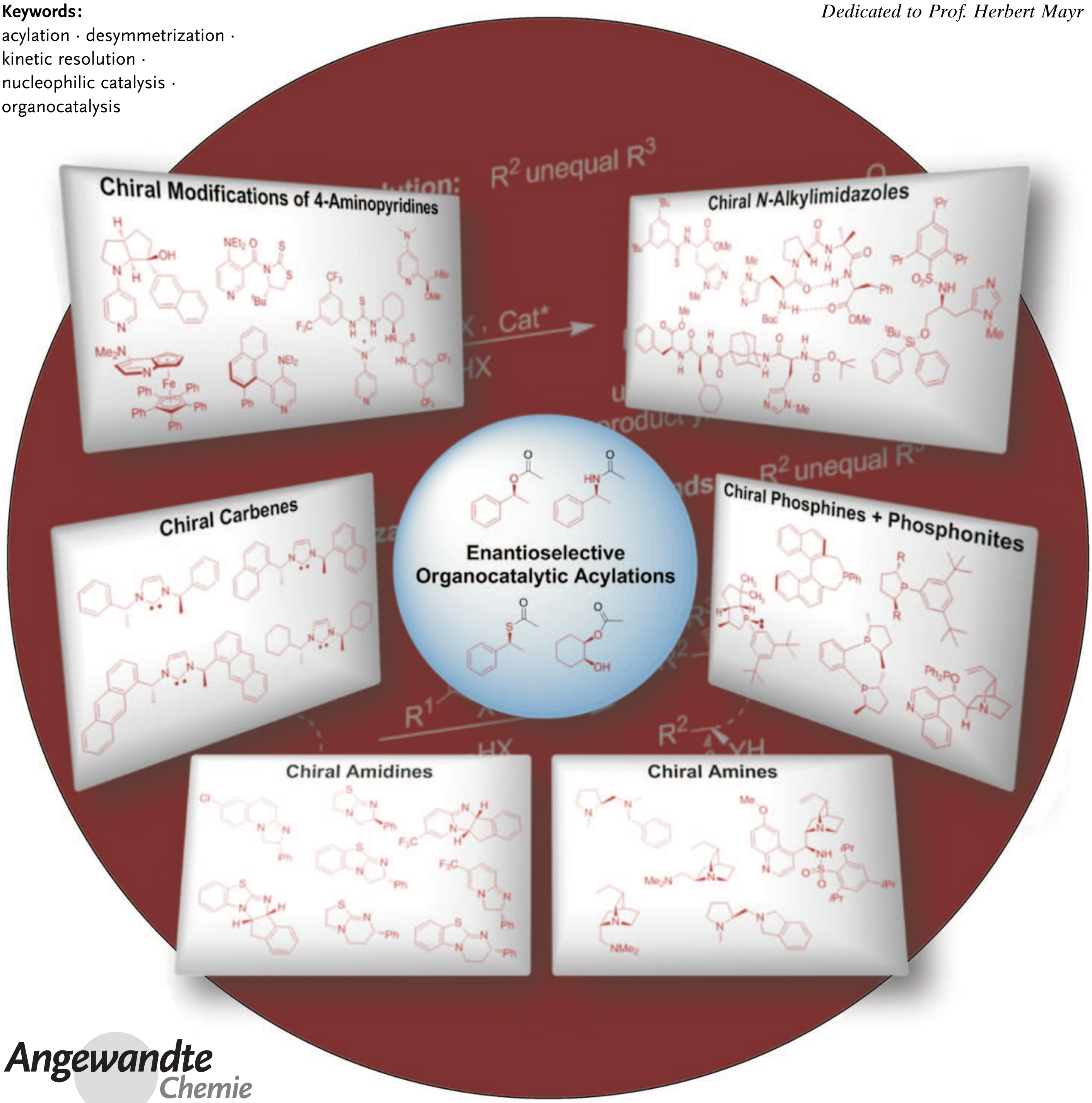
Keywords:
acylation · desymmetrization · kinetic resolution · nucleophilic catalysis · organocatalysis

Dedicated to Prof. Herbert Mayr



Acyl transfer is at the heart of functional-group transfers utilized both in nature and in the chemical laboratory. Acylations are part of the natural assembly machinery for the generation of complex molecules and for energy transport in biological systems. The recognition of covalent acyl–enzyme intermediates led to both mechanistic studies as well as the development of biomimetic approaches. Consequently, chemists first used the tools of nature in the form of enzymes and naturally occurring alkaloids as catalysts, before eventually developing a large variety of synthetic small molecules for selective acyl transfer. In contrast to nature, chemists utilize acylation reactions as a practical way for stereoselection and functional-group protection. Indeed, the number of studies concerning acyl transfer has significantly increased over the last 15 years. This Review examines and highlights these recent developments with the focus as given in the title.

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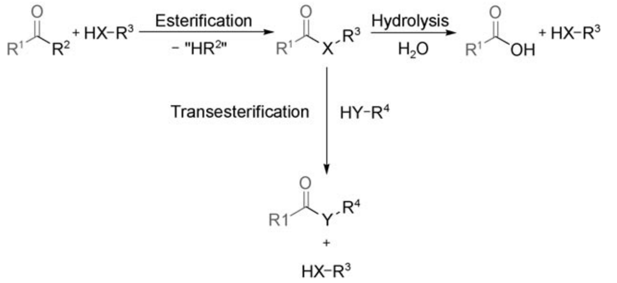
1. Introduction

Among highly successful and preparatively relevant enantioselective organocatalytic transformations,[1,2] acyl group transfer is one of the most common.[3] The reasons are manifold: Typical acylation reagents such as anhydrides, acyl halogenides, and carboxylic acids are commercially available and can be handled easily; reactions can be performed under mild conditions and a large variety of catalysts have been developed. The design of new acyl-transfer organocatalysts is a vibrant area of research, and many mechanistic details are being elucidated in the course of applying these catalysts to an ever-growing number of substrates. The present Review aims to present the status quo of organocatalytic acyl-transfer reactions to put this important transformation into a broader perspective and to help in the development of even better catalysts. Wherever possible, we give mechanistic details of the selected organocatalytic conversions to shed light on the selective acyl-transfer step. Additionally, we compare the individual catalyst within a catalyst family when they were used for similar transformations. In this Review we focus on acyl-transfer reactions onto racemic as well as *meso* alcohols, amines, and thiols: The opening of *meso* anhydrides[1–4] as well as rearrangements[1–3] (e.g., Steglich rearrangements) are beyond the scope of this Review. Metal-[5] and enzymatically[6] catalyzed acylations have been covered elsewhere.

1.1. Archetype Nature

Enantioselective syntheses have been fascinating chemists since the discovery of the existence of enantiomers. Many enantioselective approaches were born by mimicking nature, and one of the naturally important selective reactions is the transfer of an acyl group. Nature uses enzymes (acylases, deacylases, and hydrolases) for the selective transfer (transesterification), addition (esterification), or removal (hydrolysis) of acyl groups (Scheme 1).



Scheme 1. Types of acyl transfers. X, Y = Het. = NH, NR, O, S.

The discovery and isolation of such enzymes led to their investigation as catalysts for enantioselective acylations.[6] Many highly selective protocols have been developed and applied to enantioselective syntheses, typically using various acyl donors (enol esters such as isopropenyl acetate or vinyl acetate are the most common) for the kinetic resolution of racemic alcohols.[6] These enzymatic methods (often of high cost), however, sometimes suffer from requiring very long reaction times (that is, low activity), stringent operating parameters, batch to batch irreproducibility, substrate specificity, and limited possibilities to vary (often only one enantiomeric form is available) and improve a given catalyst.

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[**] This Review is dedicated to Prof. Herbert Mayr for his seminal contributions to understanding organic reactivity.

The known chiral catalysts for the title transformations can be divided into six groups:

- 4-Aminopyridine derivatives
- Combination of thiourea derivatives with 4-aminopyridines
- *N*-Alkylimidazoles
- Amidines
- Vicinal diamines
- Phosphines and phosphinites
- N-Heterocyclic carbenes

All the catalyst families are capable of enantioselective acyl-group transfer. Before we discuss catalysts and reaction conditions in this Review, we provide a short introduction to DMAP and related catalysts, acylation mechanism, and key aspects of enantioselective acylations.

2. DMAP and its Derivatives

2.1. DMAP, its Derivatives, and the Acylation Mechanism

Although achiral chemical esterifications have been known for a very long time, the discovery of the highly effective nucleophilic catalyst **1** (DMAP) by Steglich and Höfle[7] as well as Litvinenko and Kirichenko[8] provided new possibilities for acyl-group transfers by using anhydrides or acyl halides as electrophiles. Hassner et al. improved the highly catalytic active DMAP motif and introduced PPY (**2**),[9] while Steglich and co-workers reported that the constrained DMAP analogue **3**[10] was six times faster than **1** in the acylation of tertiary alcohols. The practical utility of these catalysts led to an intensive investigation of the reaction mechanism.[11–13] The current state of the art regarding DMAP and other nucleophilically catalyzed acylations is summarized in Scheme 2.[12,14] The catalyst attacks the electrophile to form an acylium cation salt with the corresponding counteranion (isolated ion pairs are shown as an example in Scheme 2).[13] This complex transfers the acyl group onto the alcohol and the catalyst is regenerated. While the role of the base is still under investigation,[15] the reaction is regarded as pseudo first order, and the base neutralizes the acid produced during the reaction to avoid catalyst deactivation by protonation.[12] In cases where only weak acids are generated (e.g., acetic acid) and when the basicity of the catalytically active nucleophilic moiety is low, one can perform the reaction without base.[16] However, even in these cases, the use of a base often leads to a rate acceleration, probably by assisting the proton abstraction from the alcohol.[15]

The very detailed studies on DMAP-catalyzed acylations have resulted in this often being taken as the prototype for a nucleophilic acylation reaction mechanism. While this is sensible and probably true for similarly nucleophilic catalysts such as 4-aminopyridine or *N*-methylimidazole derivatives, this is not necessarily the case for other types of catalysts, especially if detailed mechanistic studies are missing or if they are considerably more basic.

2.2. Enantioselective Acyl Transfers onto Alcohols, Amines, and Thiols

Enantioselective acyl transfer reactions onto alcohols, amines, or thiols, as considered in this Review, can be divided into two groups, namely kinetic resolutions[17] and desymmetrizations. Kinetic resolutions are employed to resolve racemic mixtures by selectively acylating one of the enantiomers. The major drawback of this approach is that, even under ideal conditions, the yield of the enantiopure product can be a maximum of only 50%; however, the enantiopure starting material can in most cases be recovered.[17]

Catalytic efficacy in kinetic resolutions is typically expressed using Kagan's equation.[18] This formulation is valid for first-order kinetics for the substrate in the absence of nonlinear effects. The selectivity *S* (rate constant of the fast-reacting enantiomer divided by the rate constant of the slow-reacting enantiomer) is a practical way to compare kinetic resolutions; otherwise, one would have to consider at least two values (*ee* value of the product or starting material as well as the conversion), and comparisons would be much more difficult. From the *ee* values of the recovered starting material and product, one can determine the conversion and the corresponding *S* value [Eq. (1)].[18] This is helpful because the determination of the *ee* values is generally more accurate than

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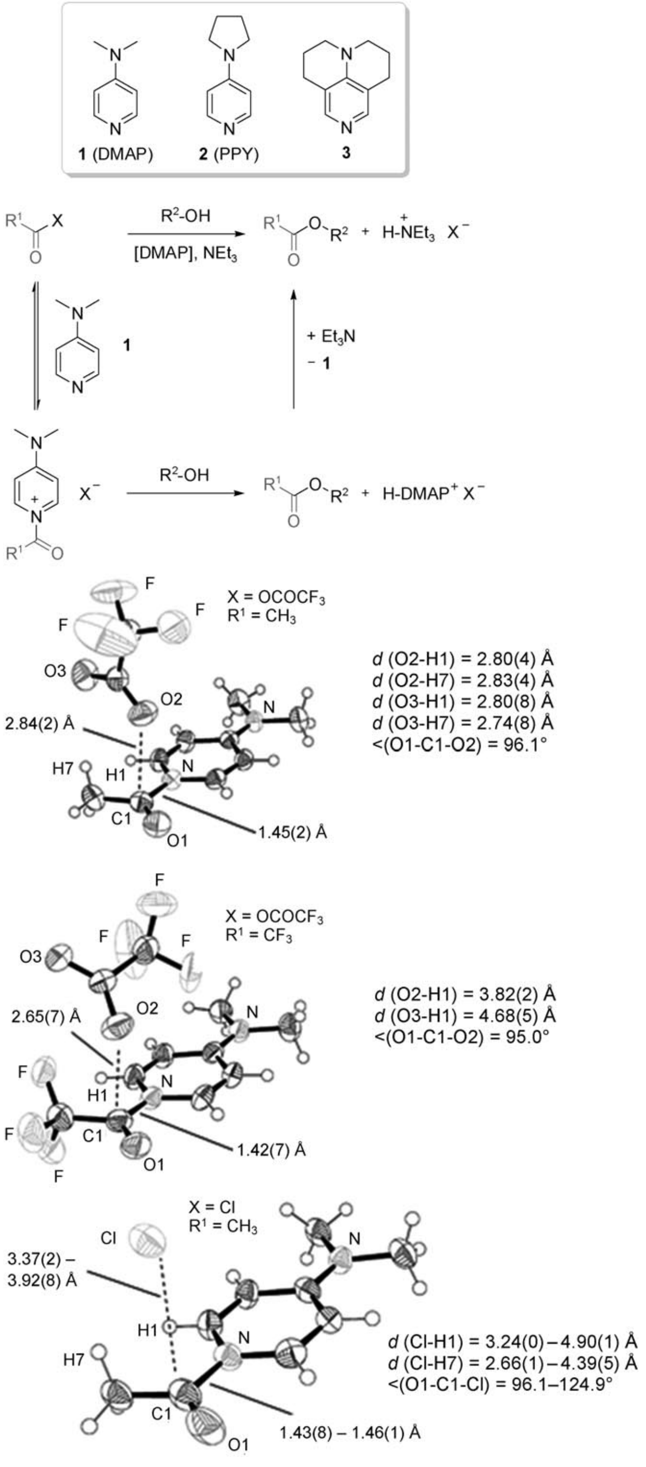
Peter R. Schreiner (born 1965) studied chemistry at the University of Erlangen-Nürnberg, Germany, where he received his PhD in organic chemistry in 1994 with P. von R. Schleyer. In 1995 he completed a PhD with H. F. Schaefer in computational chemistry from the University of Georgia, USA. He completed his Habilitation at the University of Göttingen (1999) in the group of A. de Meijere. He was then associate professor of chemistry at the University of Georgia (1999–2002) before becoming head of the Organic Institute in Giessen in 2002. His prizes include the the Dirac Medal (2003) and the ADUC (1999). He currently serves as an editor for the Journal of Computational Chemistry and as an international advisory board member for the European Journal of Organic Chemistry.



Scheme 2. Catalysts **1**–**3**, reaction mechanism of DMAP-catalyzed acylations, and crystal structures of the acylium ions; X⁻ denotes a common counterion. The mechanism suggests that the catalyst is always protonated.

the determination of the conversions and can be easily performed by chiral GC or HPLC. Kinetic resolutions with *S* values higher than 10 can be regarded as synthetically useful: By driving the reaction past 50% conversion the recovered highly enantiomerically enriched starting material can be isolated (the *ee* value of the product is low and synthetically not useful). Kinetic resolutions with *S* values greater than 50 guarantee high *ee* values for the starting materials and products at close to 50% conversion. *S* values greater than 50 are often not reliable, because of the sensitivity of the logarithmic equation and the uncertainty of the measurements of conversions and *ee* value.[19] However, we decided to present the published *S* values for the highlighted reactions even when they are greater than 50. In this Review we report the *S* values, the conversions, as well as the *ee* values of recovered starting materials and products wherever possible to give the reader all important values describing the corresponding kinetic resolution.

$$C = \frac{ee}{ee+ee'}100 \quad S = \frac{\ln[1-C(1+ee')]}{\ln[1-C(1-ee')]} = \frac{\ln[(1-C)(1-ee)]}{\ln[(1-C)(1+ee)]}$$

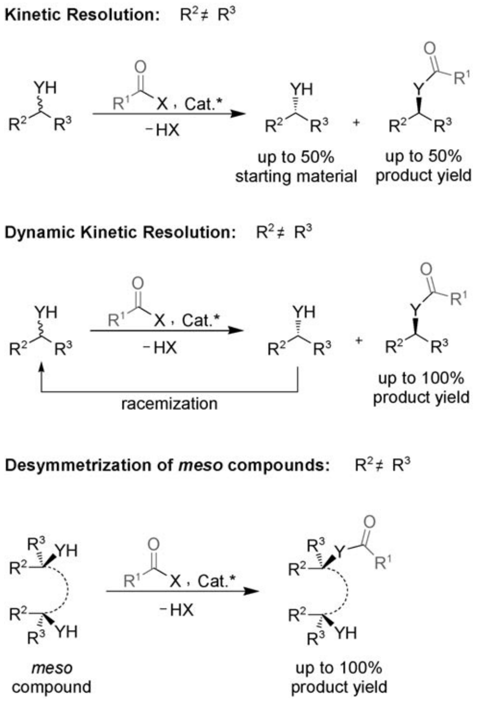
$$S = k_{\mathrm{fast}}/k_{\mathrm{slow}} \tag{1}$$

ee = enantiomeric excess measured for the starting material

ee' = enantiomeric excess measured for the product

C = conversion

Dynamic kinetic resolution is superior to kinetic resolution because the enantiopure product can in theory be isolated in quantitative yield. This method relies on the continuous in situ racemization of the starting compound during the enantioselective acyl transfer;[20] the racemization step is often made possible by an additional catalyst. The desymmetrization of *meso* compounds by acyl transfer is another powerful method where the enantiopure product can be obtained in quantitative yield (Scheme 3).[21]



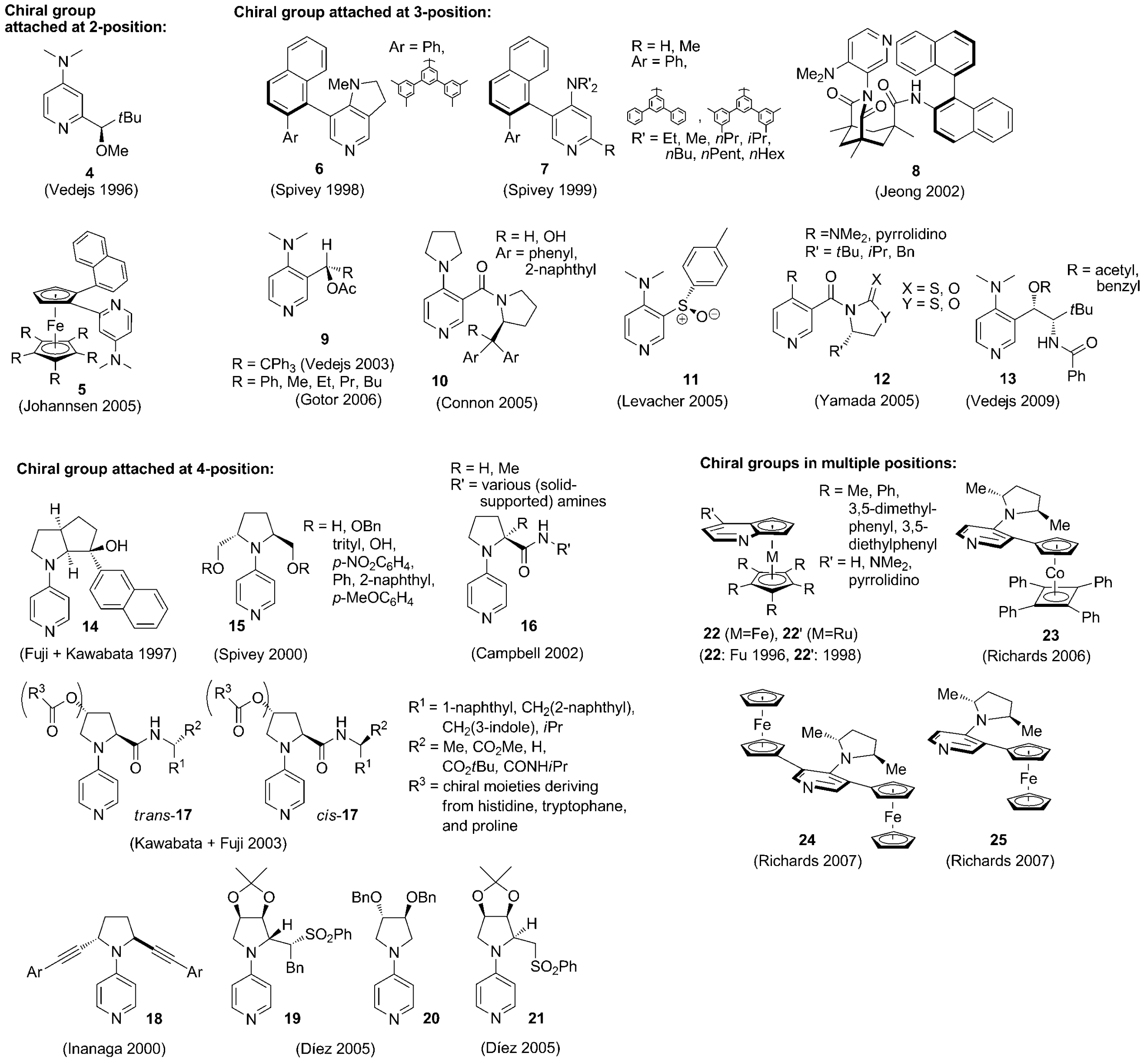
Scheme 3. Principles of acylative kinetic resolutions, dynamic kinetic resolutions, and desymmetrizations. Cat.*: chiral catalyst; Y = NH, NR, O, S; X = OCOR¹, OCOR⁴, OCOOR¹, OH, halide; esters and O-acylated azlactones are additionally used as acyl donors.

3. Enantioselective Acyl Transfer Using 4-Aminopyridines as Catalysts

3.1. 4-Aminopyridine Derivatives

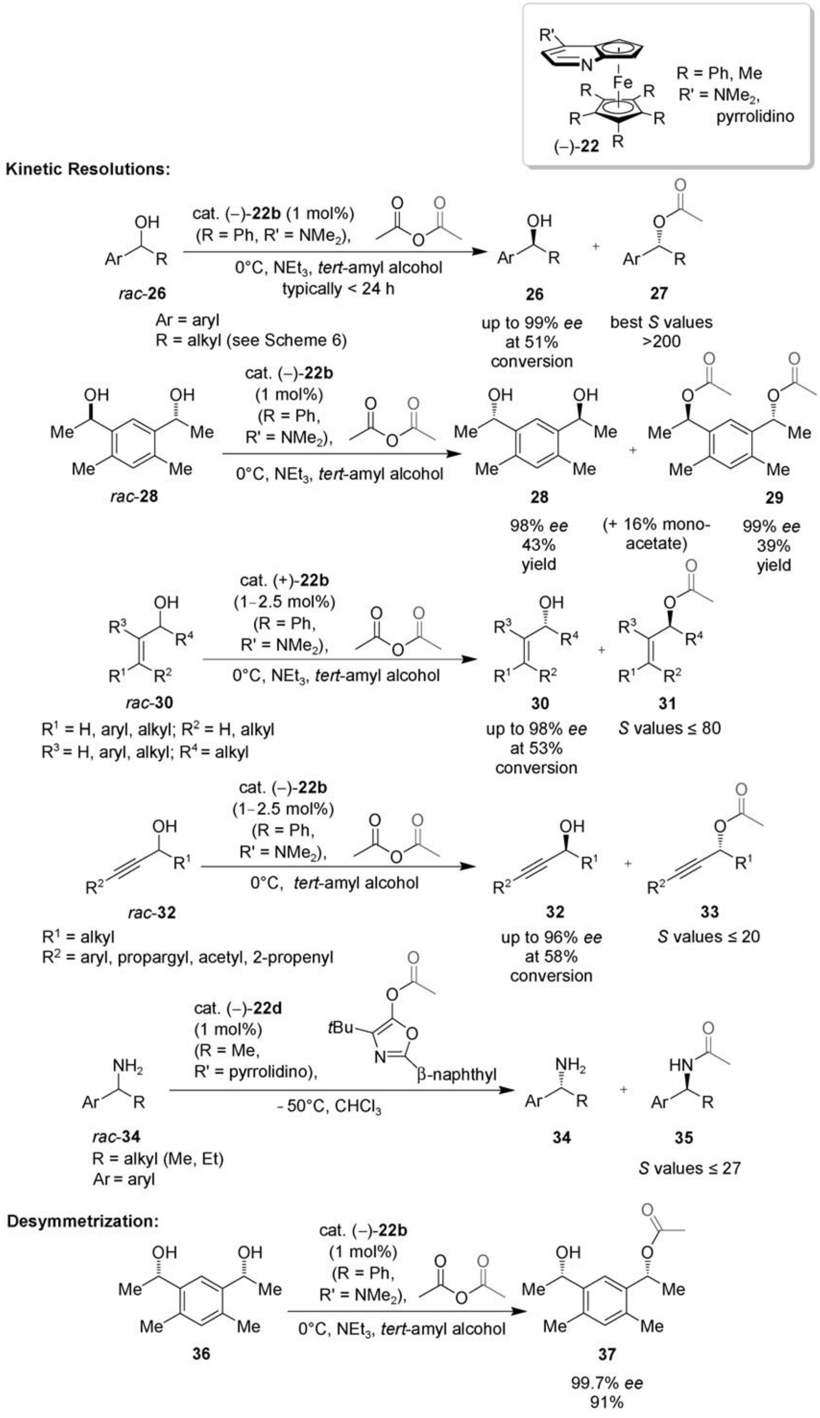
In 1996 Vedejs and Chen introduced **4** as the first member of the "chiral DMAP"[22] family (Scheme 4).[23] Kinetic resolutions of 1-aryl ethanol derivatives with stoichiometric amounts of **4** worked only in the presence two equivalents of a Lewis acid ($ZnCl_2$ or $MgBr_2$) and three equivalents of base, and gave enantiomerically enriched products in 20–44 % yield with an *ee* value of about 90 % (*S* values of up to 45) by using 2,2,2-trichloro-1,1-dimethylethyl chloroformate as the electrophile.[23] Although this protocol utilizes a stoichiometric amount of **4**, it was the starting point for the investigation of chiral DMAP analogues in stereoselective acyl-transfer reactions.

In the same year Fu and co-workers indepently realized the synthesis of planar-chiral ferrocenyl pyrrole (not shown) as well as DMAP analogues **22** (R = Me, R′ = NMe_2, and R = Ph, R′ = NMe_2).[24] In 1998 this family of compounds was expanded by the PPY analogues of **22**.[25] One may question whether these catalysts are consistent with the definition of an organocatalyst, but they are included here because the iron atom of the catalysts apparently shows no direct catalytic activity and can mainly be regarded as a structure-giving moiety; however, the incorporation of the iron arguably leads to a significantly more nucleophilic nitrogen atom in the pyridine ring and a better stabilization of the acylium cation[26,27] than in metal-free analogues. This assumption is widespread,[2,28] but, to our suprise and to the best of our



Scheme 4. Chiral DMAP- and PPY-based catalysts.

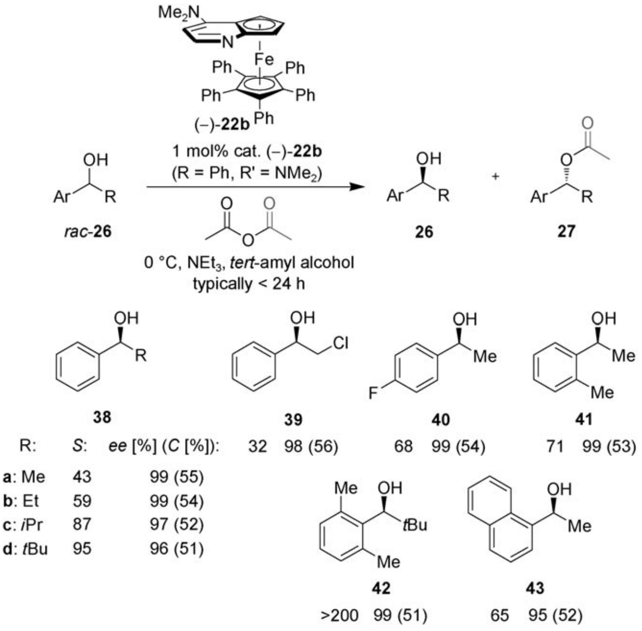
knowledge, neither the nucleophilicities nor the acylium cation stabilization energies of such catalysts have been directly compared to **1** (DMAP) itself. Therefore, we determined the methyl cation affinity (MCA) of **22a** (R = Me, R′ = NMe_2) as proposed by Zipse and co-workers,[29] and compared this value with the MCA of **1**. In analogy to Zipse and co-workers,[29] we used the MP2(FC)/6-31 + G(2d,p)//B98/6-31G(d) level of theory and determined the MCA for the pyridyl nitrogen atom of **1** as 581.5 $kJ\,mol^{-1}$ (Zipse and co-workers published[29] an MCA of 581.2 $kJ\,mol^{-1}$). The MCA of **22a** (R = Me, R′ = NMe_2) at 624.1 $kJ\,mol^{-1}$ is significantly higher than that of **1**, which indeed implies a higher nucleophilicity and better stabilization of the *N*-acylium cation with **22**.



Scheme 5. Performance and applications of Fu's catalyst **22**.

The catalysts of Fu and co-workers were first examined by studying the kinetic resolution of aryl and allyl alkyl alcohols (Scheme 5). Catalyst **22a** (R = Me, R′ = NMe_2) was found to catalyze the kinetic resolution of racemic 1-phenylethanol (**38a**) with an *S* value of 1.7, whereas the replacement of R′ = Me to R′ = Phe improved the enantioselectivity significantly (*S* = 14 under comparable conditions).[30] Under optimized conditions (1 mol % catalyst, *tert*-amyl alcohol, 0 °C) Fu's catalyst **22b** (R = Ph, R′ = NMe_2) shows the best performance of DMAP-based catalysts for the kinetic resolution of racemic secondary aryl alkyl alcohols to date (for a comparison with the catalysts **6–8**, **10**, **12**, **16**, **23**, and **24** see Table 1; for the substrate range see Scheme 6).[31,32] The same catalyst was used for the efficient kinetic resolution of a racemic *trans*-diol **28** and the desymmetrization of a *meso* diol **36**.[31] By using ruthenium instead of iron in the kinetic resolution of *rac*-**38a** with catalyst **22′** (R = Ph, R′ = NMe_2) the *S* value drops from 43 to 10.[26]

The first organocatalytic kinetic resolution of propargylic alcohols **32** was also accomplished with the catalyst system **22**; with an *S* value of 6.4, **22b** (R = Ph, R′ = NMe_2) showed a slightly better performance than **22c** (R = Ph, R′ = pyrrolidino) with an *S* value of 4.5 for the initial experiment with 4-phenyl-3-butyn-2-ol as substrate. Under optimized conditions (without base in this case; Et_3N was found to catalyze an unselective background reaction) *S* values up to 20 could be achieved.[33,34] DMAP analogue **22b** (R = Ph, R′ = NMe_2) was the first organocatalyst also successfully applied to the kinetic resolution of racemic allylic alcohols **30** with good selectivities of up to *S* = 80 (Scheme 5).[35a] Fu and co-workers demonstrated the power of this concept by the synthesis of key intermediates in natural product synthesis. Key intermediate (−)-**44** in Brenna's total synthesis of (−)-baclofen was available through the kinetic resolution of racemic **44** (Scheme 7, top).[35a,b] Additionally, the Fu research group realized the highly effective kinetic resolution of racemic **46**, which led to highly enantiomeric enriched (+)-**46** with 98 % *ee*, *S* = 107 (the enzymatic synthesis of (+)-**46** by kinetic resolution of **46** using an aldolase antibody led only to 96 % *ee* and an *S* value of 17); (+)-**46** is a

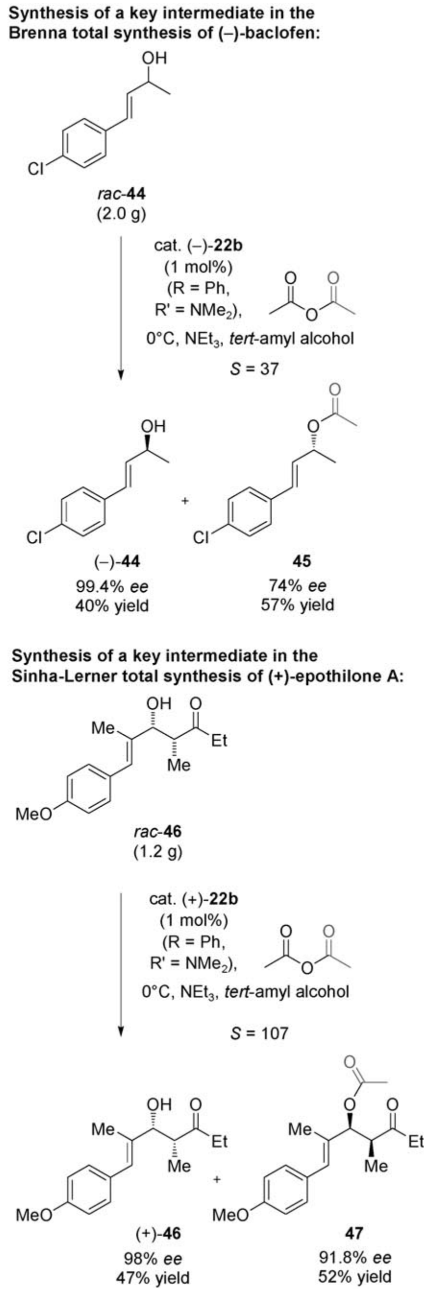


Scheme 6. Kinetic resolution of aryl alkyl alcohols catalyzed by (−)-**22**; the configuration of the slow-reacting alcohol enantiomers are shown.

key intermediate in the Sinha–Lerner total synthesis of epothilone A (Scheme 7, bottom).[35a,c] These two examples were some of the earliest organocatalytic approaches in total synthesis.

Acylative kinetic resolution of racemic amines is one of the the ultimate challenges in the field of kinetic resolution, and is much more difficult than for alcohols. This may be due to the higher nucleophilicity of amines causing a significant background reaction. In 2000 Ie and Fu presented a stoichiometric protocol for the acylation of aryl alkyl amines *rac*-**34** with *ee* values for the amides up to 91% by using chiral *N*-acetylium chlorides based on **22c** (R = Ph, R′ = pyrrolidino).[36] The catalytic protocol of this enantioselective transformation with *S* values up to 27 was realized by using an *O*-acylated enol form of an azalactone as the acylation reagent (Scheme 5). These good results were possible because of the much faster reaction of the acylating reagent with catalyst **22d** (R = Me, R′ = pyrrolidino) than with the primary amine.[37] This protocol was expanded to the kinetic resolution of indolines with *S* values up to 26 by using **22e** (R = 3,5-dimethylphenyl, R′ = pyrrolidino) and the additional additives LiBr and [18]crown-6.[38]

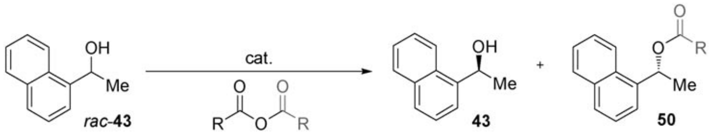
Further planar-chiral metallocene DMAP derivatives introduced by the research groups of Johannsen and Richard were less effective than catalyst **22** developed by Fu and co-workers. Catalyst **5** (2005) developed by Johannsen and co-workers was tested in the asymmetric Steglich rearrangement and resulted in moderate selectivities; no selectivity was observed for the kinetic resolution of 2-phenylethanol (**38a**).[39] Catalyst **23** (2006) developed by Richard and co-workers was tested in the kinetic resolution of racemic **43** (*S* value up to 3; Table 1, entry 8) and in the asymmetric Steglich rearrangement (up to 76% *ee* at full conversion).[40] In 2007 the same research group presented the C_2-symmetric catalyst **24** and the unsymmetrical catalyst **25**; moderate selectivities (up to *S* = 6) were obtained with **24** in the kinetic resolution of racemic **38a** by acyl transfer, whereas **25** led to almost no selectivity (*S* = 1.3).[41] Catalyst **24** catalyzed the kinetic resolution of *rac*-**43** with an *S* value of 3 (Table 1, entry 14).[41]



Scheme 7. The application of (−)-**22** in the synthesis of key intermediates (−)-**44** and (+)-**46** in natural total syntheses by Brenna as well as Sinha and Lerner.

Besides the introduction of chirality to PPY by planar-chiral metal complexes, a set of chiral PPY based catalysts were generated by chiral modification of the PPY pyrrolidine core. The first example was reported by Fuji, Kawabata, and co-workers in 1997; initially **14** was examined in the kinetic

Table 1: Kinetic resolution of racemic 1-(1-naphthyl)ethanol with different catalysts.



Entry	Cat.	R	*T* [°C]	C [%]	*ee*(**43**) [%]	*ee*(**50**) [%]	*S* value
1	(+)-**6** (Ar = Ph)	*i*Pr	−78	65	−88	−48	8
2	(+)-**7a** (Ar = Ph, R = H, R′ = Et)	*i*Pr	−78	22	−26	−91	29
3	(−)-**7a** (Ar = Ph, R = H, R′ = Et)	*i*Pr	−78	45	69	84	24
4	(−)-**7b** (Ar = Ph, R = H, R′ = *n*Bu)	*i*Pr	−78	59	99.9	69	31
5	(−)-**7b** (Ar = Ph, R = H, R′ = *n*Bu)	Me	−78	34	41	79	13
6	(−)-**7c** (Ar = [a], R = H, R′ = Et)	Me	−78	15	17	94	39
7	(−)-**22a** (R = Ph, R′ = NEt_2)	Me	RT	52	89	95	65
8	**23**	*i*Pr	−78	50	32	not given	3
9	**10a** (R = OH, Ar = 2-naphthyl)	*i*Pr	−78	43	−51	−63	9
10	**12a** (R = NMe_2, R′ = *t*Bu, X,Y = S, in TBME[d])	*i*Pr	0	57	95	not given	24
11	**12a** (R = NMe_2, R′ = *t*Bu, X,Y = S, in TBME[d])	*i*Pr	−30	56	97	not given	30
12	**8**	Me	0	72	98	38	8
13	**16a** (R = Me, R′ = [b])	*i*Pr	RT	74	22	not given	1.4
14	**24**	Me	−40	79	−71	not given	3

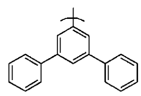
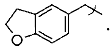
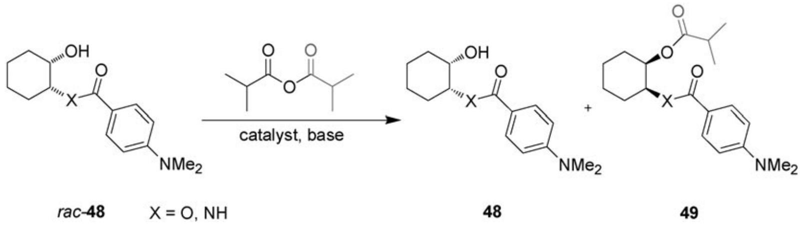
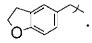
[a]  . [b]  . [c] A negative *ee* value indicates the formation of the opposite enantiomer. [d] TBME = *tert*-butyl methyl ether.

Table 2: Kinetic resolution of *rac*-**48** using the catalysts of Fuji, Kawabata, Spivey, Connon, and Cambell.



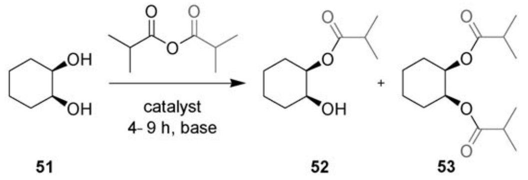
Entry	Cat.	X	*T* [°C]	Conv. [%]	*ee*(**48**) [%]	*ee*(**49**) [%]	*S* value
1	**14** (0.17 M)	NH	20	68	> −99	−48	> 14
2	**14** (0.01 M)	NH	−40	30	−40	−95	54
3	*trans*-**17a** (0.1 M) (without CO_2R^3, $R^1 = CH_2$(2-naphthyl), $R^2 = CO_2Me$	NH	20	70	99	42	11
4	**14**	O	20	72	> 99	not given	> 10
5	(−)-**7a** (Ar = Ph, R = H, R′ = Et)	O	−40	18	−18	−86	16
6	**10b** (R = OH, Ar = Ph)	O	25	78	−93	not given	5
7	**10b** (R = OH, Ar = Ph)	O	−78	69	−97	not given	9
8	**16a** (R = Me, R′ = [a])	O	RT	62	95	not given	13
9	**16a** (R = Me, R′ = [a])	NH	RT	59	96	not given	19

[a]  . [b] A negative *ee* value indicates the formation of the opposite enantiomer.

resolution of monobenzoylated *meso*-(cyclo)alkane-1,2-diols with *S* values of greater than 10 (Table 2, entry 4).[42] Catalyst **14** and the PPY catalyst **17** (introduced by Kawabata et al. in 2003)[43,44] were used as catalysts in the kinetic resolution of *N*-acylated amino alcohols; at room temperature **14** and **17** proved to be moderately efficient, with *S* values between 10 and 20 for **14**[45] and up to 11 for **17** (Table 2, entries 1 and 3, respectively).[43] The best results were reported for catalyst **14** in the kinetic resolution of *rac*-**48** at −40 °C, which resulted in an *S* value of 54 (Table 2, entry 2).[43,45] Catalyst **17** was additionally investigated in the desymmetrization of *meso*-cycloalkane-1,2-diols and *meso*-cycloalkane-1,3-diols.[44] Only moderate selectivities could be achieved by using 5 mol % of catalyst **17**, isobutyric anhydride as the electrophile, and collidine as an additional base (up to 65 % *ee* at 61 % yield; Table 3, entry 3).[44]

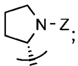
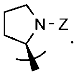
To elucidate the reaction mechanism Kawabata and co-workers investigated the neutral and the acylated catalyst **14** by NMR spectroscopy and proposed an open conformation for non-acylated **14** and a closed conformation dominated by

Table 3: Desymmetrization of *meso*-**51** with catalysts **7** and **17**.

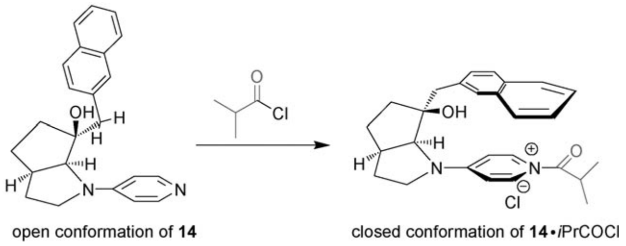


Entry	Cat.	Yield **52** [%]	*ee*(**52**) [%]	Yield **53** [%]
1	*trans*-**17b**[a] (without CO_2R^3, $R^1=CH_2$(3-indole), $R^2=CO_2Me$)	59	60	26
2	*trans*-**17c**[a] (with CO_2R^3, $R^3=$[b], $R^1=CH_2$(3-indole), $R^2=CO_2Me$)	64	63	28
3	*trans*-**17d**[a] (with CO_2R^3, $R^3=$[c], $R^1=CH_2$(3-indole), $R^2=CO_2Me$)	61	65	27
4	(−)-**7** (Ar = Ph, R = H, R′ = Et)[d]	20	78	not given

[a] 5 mol% catalyst, 1.3 equiv (iPrCO)$_2$O, 20°C, collidine as base.

[b] ; Z = benzyloxycarbonyl. [c] .

[d] 1 mol% catalyst, 2.0 equiv (iPrCO)$_2$O, −78°C, NEt_3 as base.



Scheme 8. Conformation change of catalyst **14** during the formation of the *N*-acylium cation.

π–π and cation–π bonding for acylated **14** (Scheme 8). The best results for this catalyst were obtained with arylated substrates, which suggests that π–π interactions between the substrate and catalyst play an important role.[42] This is an impressive example where an active conformation of a conformationally flexible catalyst forms *during* the stereo-differentiating step.

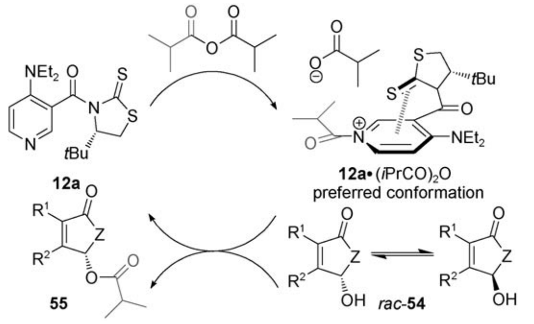
The chiral PPY derivative **16** (2002/2003) developed by Campbell and co-workers is based on proline and can be easily varied by changing the amine component. Many catalysts (some on a solid support) were thus synthesized and tested in the kinetic resolution of racemic monobenzoylated *cis*-cyclohexane-1,2-diol derivatives **48** with isobutyric anhydride, and *S* values up to 13 could be obtained (Table 2, entry 8). Whereas the kinetic resolution of secondary monoalcohols catalyzed by **16** is not selective (*S* values of up to 1.4, Table 1, entry 13), **16** is an effective catalyst in the kinetic resolution of monoprotected amino alcohols (*S* values of up to 19; Table 2, entry 9). The catalysts bound to the solid support could be recycled quantitatively and remained active as well as selective.[46]

Connon and co-workers (2005) followed the fit-inducing concept of Fuji et al. (Scheme 8) in their synthesis of the catalyst class **10**. The catalysts **10** were tested in the kinetic resolution of racemic 1-(1-naphthyl)ethanol **43** (*S* values up to 9; Table 1, entry 9) and monobenzoylated *cis*-cyclohexane-1,2-diol derivatives **48** (*S* values up to 9; Table 2, entries 6 and 7).[47]

The first C_2-symmetric PPY analogue **18** (with the chiral modification on the pyrrolidine ring) was synthesized by Inanaga and co-workers in 2000; the application of **18** in the kinetic resolution of secondary alcohols led to *S* values up to 14.[48] In the same year Spivey et al. published the synthesis of the C_2-symmetric 4-(pyrrolidino)pyridine derivatives **15**, which did not lead to high selectivities in the kinetic resolution of racemic 1-phenylethanol (**38a**; best result for R = OBn with $S=2$).[49] Diez et al. (2005) followed this strategy and synthesized the C_2-symmetric catalyst **20** and the catalysts **19** and **21** (all three catalysts based on the PPY core), which led to low enantioselectivities in the kinetic resolution of 1-phenylethanol (**38a**; *S* values up to 2).[50]

Whereas all PPY-based catalysts have the chiral modification at the pyrrolidine core, the chiral non-metal-based DMAP analogues are mostly modified at the pyridine ring. The investigation of chiral DMAP-based nucleophiles by Spivey et al. resulted in the development of axial-chiral catalysts **6**[51] and **7**.[52] In 2000 these catalysts were tested in the enantioselective kinetic resolution of secondary alcohols and gave moderate to good results (Table 1, entries 1–6).[53] Variations of **7** (Ar = Ph, R′ = Et) by using R = Me instead of R = H resulted in a lower enantioselectivity for the same reaction.[54] An improvement of catalyst **7** was achieved by varying the R′ group (R′ = *n*-butyl showed the best performance; Table 1, entry 4);[55] the variation of the aryl moiety also led to better selectivities[56] (Table 1, entry 6). Catalyst (−)-**7** was also tested in the kinetic resolution of monobenzoylated *meso*-(cyclo)alkane-1,2-diols such as **48** (Table 2, entry 5) and in the desymmetrization of *meso*-(cyclo)alkane-1,2-diols such as **51** (Table 3, entry 4).[57] Structural investigations (rotational barriers and racemization energies) of the axial-chiral catalysts **6** and **7** were additionally performed.[51,52,58] It could be shown that rotation around the chiral axis of biaryls **6** and **7** is sufficiently slow at ambient temperature to allow their chiral separation and to prove their stability against racemization.

The DMAP-based catalyst **12** introduced in 2005 by Yamada et al. also underwent a conformational switch during the formation of the acylium cation (Scheme 9). Catalyst **12a** ($R=NMe_2$, R′ = *t*Bu, X,Y = S) is effective in the kinetic resolution of 1-aryl ethanols, with up to 97% *ee* for the recovered starting material at 56% conversion and *S* values up to 30 (Table 1, entries 10 and 11).[59,60] The same catalyst was less effective in the kinetic resolution of allyl alkyl, propargyl alkyl, and alkyl alkyl alcohols (*S* values from 2.3 to 10).[59,60] Application of catalyst **12** ($R=NMe_2$, R′ = *t*Bu, X = S, Y = O or S) to the kinetic resolution of racemic diols and the desymmetrization of *meso* diols bearing a phenyl moiety also led to moderate to excellent selectivities.[60] The dynamic



Scheme 9. Catalytic cycle for the dynamic kinetic resolution of hemiaminals **54** (R^1,R^2 = −CH=CH−CH=CH− or R^1 = H; R^2 = Et, Ph) with **12a** (R = NMe_2, R′ = *t*Bu, X,Y = S). Z = $NCOR^3$, O; R^3 = Me, Et, *i*Pr; *t*Bu, Ph.

kinetic resolution of various racemic hemiaminals **54** with **12a** (R = NMe_2, R′ = *t*Bu, X,Y = S) led to *ee* values up to 88, with yields typically greater than 90% (Scheme 9).[61]

Catalyst **8** synthesized by Jeong et al. consists of three basic elements: DMAP as the catalytically active component, binaphthyl as the chiral segment, and Kemp's triacid as the linker; the chiral modification is again located on the pyridine ring. The catalyst was tested in the kinetic resolution of secondary alcohols, with *S* values of up to 21 obtained (for the performance of **8** in the kinetic resolution of racemic **43**, see Table 1, entry 12).[62] DMAP analogue **11** bearing a sulfoxide moiety as the chiral unit on the pyridine ring, as introduced by Levacher and co-workers (2005), gave only moderate enantioselectivities in the kinetic resolution of secondary alcohols (*S* values up to 4.5).[63]

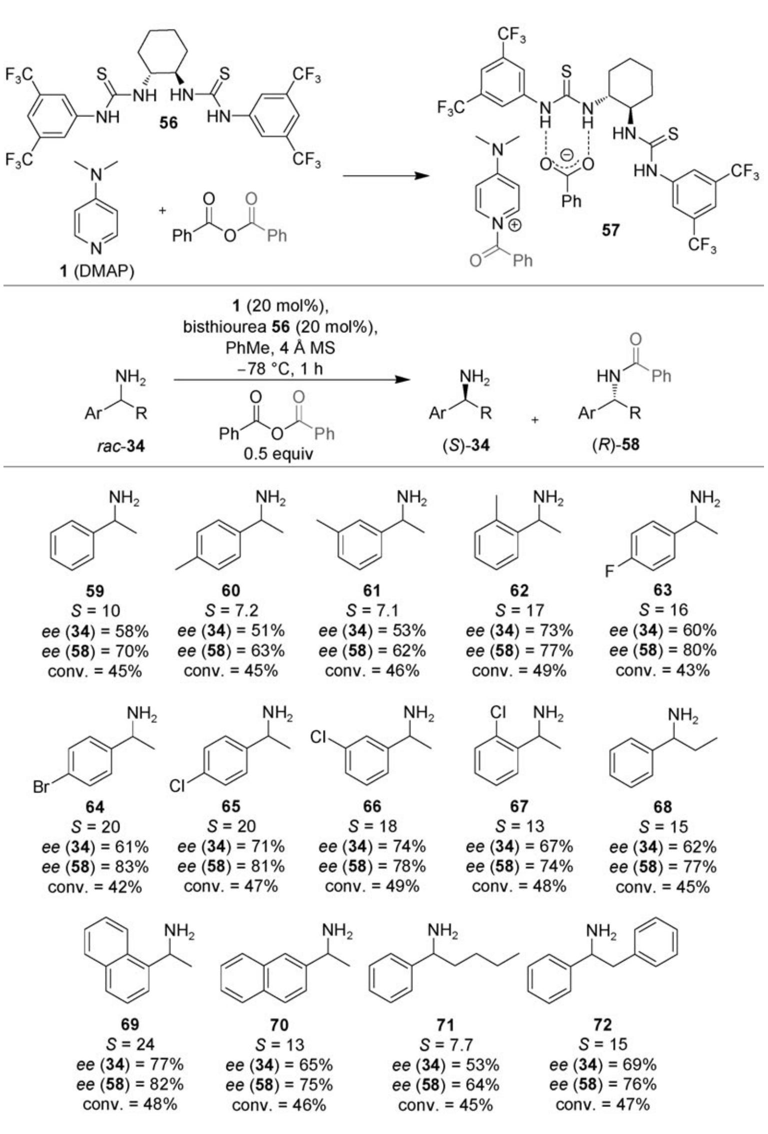
In 2006 Gotor and co-workers published the biocatalytic synthesis of the catalyst family **9** (R = Ph, Me, Et, Pr, Bu).[64,65] The catalysts were applied to the kinetic resolution of racemic 1-phenylethanol (**38a**) by using 2,2,2-trichloro-1,1-dimethylethyl chloroformate as the alkoxy carbonylating reagent, Et_3N as the base, and $ZnCl_2$ as the Lewis acid additive. The best result was obtained with **9a** (R = Bu), which led to an *S* value of 10 (38% *ee* for the recovered starting material and 75% *ee* for the product at 34% conversion). In addition, **9g** (R = Ph, Me, Bu) was tested in the Steglich rearrangement of prochiral enol carbonates.[65]

Catalyst **9** (R = CPh_3) introduced in 2003 by Vedejs and co-workers proved to be ineffective in kinetic resolution experiments[66] (the best result was obtained for the isobutyroylation of 1-(1-naphthyl)ethanol (**43**) with *S* = 4.4), but to be highly efficient in the enantioselective transfer of a carboxy group in the Steglich rearrangement of achiral enol carbonates to chiral azlactones.[67] This protocol was also applied successfully to oxazole enol carbonates, furan enol carbonates, benzofuran-derived enol carbonates, and indole-derived carbonates.[66,67] In 2009 Vedejs and co-workers introduced the catalyst **13** for the enantioselective rearrangement of indolyl acetates and carbonates.[68]

Besides the catalysts presented above, there are additional chiral 4-aminopyridine based catalysts, which, to the best of our knowledge, were not tested in an enantioselective acyl-transfer reaction and are therefore shown in a footnote.[69]

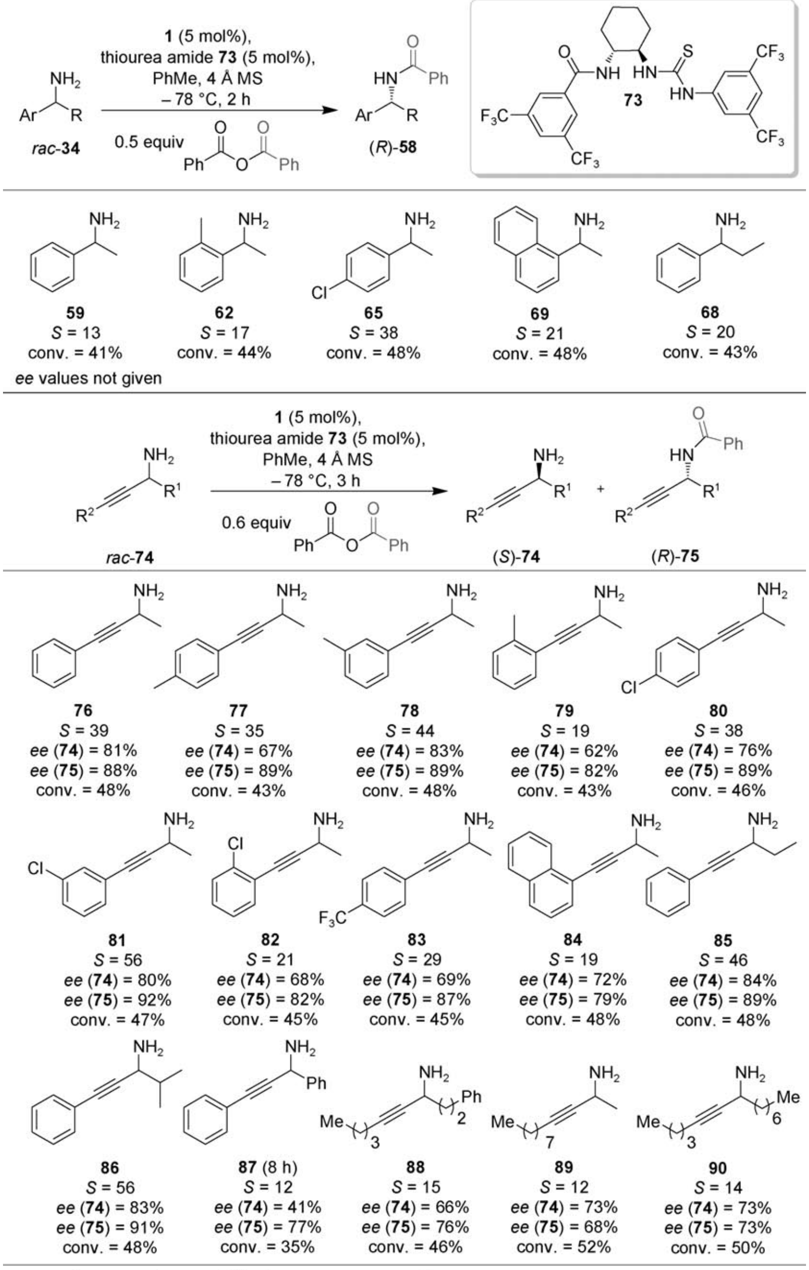
3.2. Combination of Thiourea Derivatives with DMAP

In 2009 Seidel and co-workers presented a chiral, hydrogen-bonding thiourea (**56**) with **1** as a catalyst combination for the kinetic resolution of racemic secondary amines **34**.[70] The combination of 20 mol% bisthiourea **56** (chiral monothioureas proved less effective) and 20 mol% DMAP led to good selectivities (*S* values up to 24, which means 77% *ee* for the recovered amine and 82% *ee* for the product). The mecha-



Scheme 10. The ternary complex and performance of the catalyst combination DMAP + **56** in the kinetic resolution of aryl alkyl amines.

nism of the reaction is not completely understood, but it seems that the complexation of the acylium counterion by **56** led to a ternary complex **57** capable of transferring the stereochemical information (Scheme 10).[70] This concept of anion binding[71] was successfully transferred to the kinetic resolution of racemic propargylic amines **74** by the same research group.[72] It was found that thiourea amide **73** is more efficient than bisthiourea **56** in the case of propargylic amines **74** and for most aryl alkyl amines **34** (*S* values up to 56 for propargylic amines and up to 38 for aryl alkyl amines; Scheme 11).[72]



conversions, *ee* values, and *S* values are averages of two runs

Scheme 11. Performance of the catalyst combination DMAP + **73** in the kinetic resolution of aryl alkyl amines **34** and propargylic amines **74**.

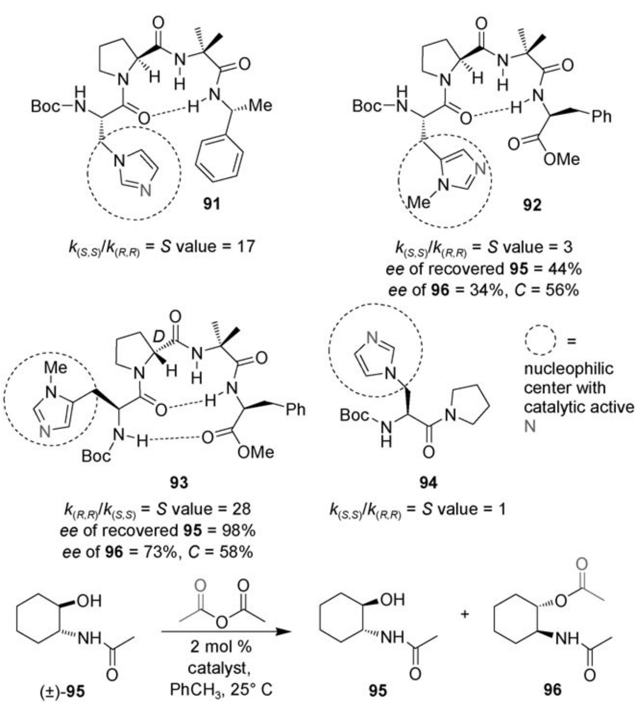
4. N-Alkylimidazoles

As outlined in the Introduction, nature provides enzymatic acyl transfer in a highly efficient and specific way. Can these enzymes (typically with a molecular weight of several thousand Daltons) be reduced to small organocatalysts without losing efficiency and specificity? Indeed, proof-of-principle acyl-transfer studies were realized by Miller and co-workers in 1998 by introducing small peptide-based catalysts with a nucleophilic moiety.[73,74] Inspired by an ester hydrolysis (imidazole, carboxylate, and β-CD units as moieties responsible for catalytic activation and selective transformation),[75] the Miller research group developed the histidine-based enzyme-like catalysts **91**–**93** (Scheme 12).

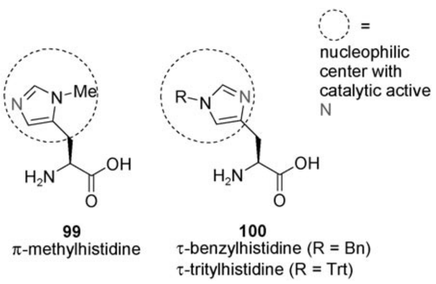
Miller and co-workers used the alanine derivative **98** for the first peptide catalysts (e.g., **91**)[73] and then switched to π-methylhistidine (**99**) as the catalytically active moiety (Scheme 13).[74] *N*-alkyl imidazole derivatives **98** and **99** proved to be efficient as catalytically active acyl transfer moieties when incorporated into peptides because **98** and **99** are more nucleophilic and less basic; it is the opposite for **97** and **100**, which lead to lower activity or catalytic inefficiency.[76,77]

The selectivity and reactivity of compounds **91**–**94** were tested in the kinetic resolution of a racemic monoacylated amino alcohol such as **95** at 25 °C. Whereas the catalyst **94** showed no enantiomeric preference, peptide **91** catalyzed the acylation reaction with an *S* value of 17.[75,78] This can be regarded as proof of the importance of the peptide backbone and the corresponding secondary structure for selective acetyl transfer. For alcohols without additional hydrogen-bond acceptors in their direct neighborhood (acetyl group), such as 1-(1-naphthyl)ethanol (**43**), no selectivity was observed with catalyst **91**. Even the acetylation of *trans*-1-acetoxycyclohexane-2-ol **149** ($n=2$) with peptide **91** led to an *S* value of only 1.4, which emphasizes the high substrate specificity of these peptide catalysts.[73] The peptides **92** and **93** (the only difference is the configuration of the proline moiety) significantly differs in the resolution of *rac*-**95**, with an *S* value of 3 for **92** (L-proline) and 28 for **93** (D-proline), and the preference for the opposite stereochemistry (Scheme 12). In contrast to **92**, catalyst **93** adopts a *β*-hairpin conformation, which led to two internal hydrogen bonds and an inverted and higher enantioselectivity (Schemes 12 and 14).[74,75,78]

This proposal was supported by an investigation of the catalytic efficiencies of the peptides **101**–**106**.[75,78–80] The differences between the peptides should be emphasized

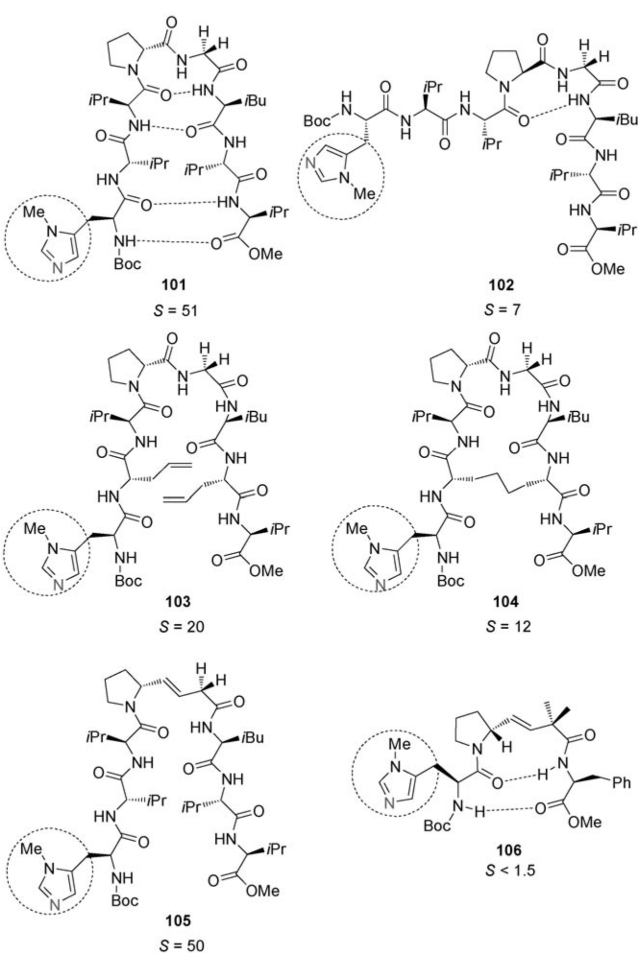


Scheme 12. Miller's catalysts **91**–**94** in the kinetic resolution of *rac*-**95**.

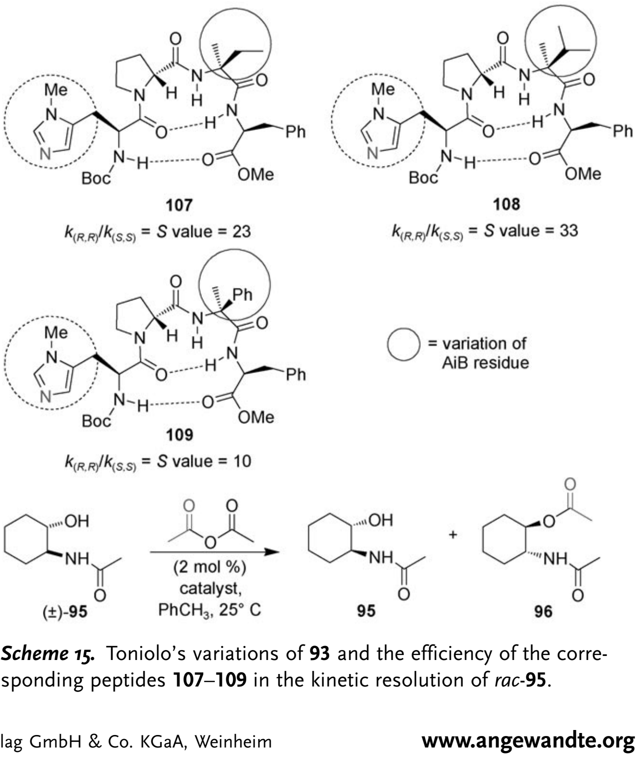


Scheme 13. Histidine derivatives **97**, **99**, and **100** as well as substituted alanine **98**.

before discussing their catalytic efficiency: **101** and **102** only differ in the configuration of proline. Peptides **103** and **104** are very similar to peptide **101**; **103** is the precursor for **104**, which was synthesized by metathesis to produce a rigid analogue of **101**. Peptide **105** is closely related to **101** and peptide **106** is closely related to **93**; in both cases the proline-aminoisobutyric acid (Pro-AiB) amide functionality is replaced by a double bond that does not act as a hydrogen-bonding donor or acceptor. The related peptides **101**–**105** and peptide **106** were all tested as catalysts in the kinetic resolution of racemic **95** and gave quite different results. Peptides **101** and **105**



Scheme 14. Miller's catalysts **101**–**106** and their efficiency in the kinetic resolution of *rac*-**95**.



Scheme 15. Toniolo's variations of **93** and the efficiency of the corresponding peptides **107**–**109** in the kinetic resolution of *rac*-**95**.

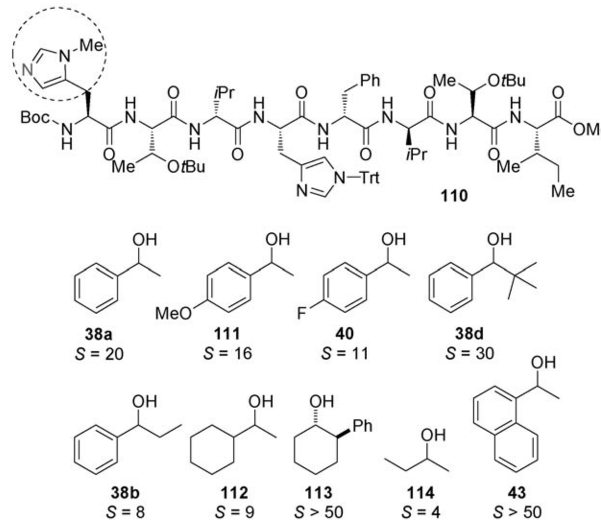
showed the best performance ($S = 51$ and 50, respectrively) followed by peptide **103** ($S = 20$) and peptide **104** ($S = 12$). The worst performance was observed for the catalysts **102** ($S = 7$) and **106** ($S < 1.5$), which led to the following requirements for a successful peptide catalyst in the kinetic resolution of *N*-acylated 2-aminocycloalkane-1-alcohols:[75,78,79]

1. The peptide should be capable of forming a stable β-hairpin-like secondary structure (**101** (D-Pro) is more selective than **102** (L-Pro)).
2. The peptide should have some degree of flexibility (**101**, **103**, and **105** are more selective than **104**).
3. For tetrapetides, the amide functionality between the proline and aminoisobutyric acid is important for selective acetyl transfer, because of the hydrogen-bonding interaction of the substrate with this moiety (**106** shows no selectivity in contrast to **93**).
4. For octapeptides, the amide functionality between the proline and amino isobutyric acid is not important because this Pro-AiB linkage is far away from the reaction center and therefore not responsible for selectivity (**101** and **105** show the same selectivity).

In 2004 Toniolo and co-workers tried to improve the efficiency of tetrapeptide **93** by stabilizing the turn structure and the interactions shown in Scheme 12. They varied **93** by replacing the AiB amino acid by several other non-natural amino acids (peptides **107**–**109**; Scheme 15). The use of (α-Me)-valine (**108**) led to an improved performance in the kinetic resolution of *rac*-**95** (S value of 33; compared to $S = 28$ for **93**).[81]

Peptides **93** and **101**, which are highly efficient in the kinetic resolution of racemic *trans*-2-(*N*-acetylamino)cyclohexane-1-ol (**95**), were also effective in the kinetic resolution of the corresponding racemic five- and seven-membered-ring substrates. In contrast, **93** and **101** were less efficient when *cis*-configured *N*-acylated 3-amino-1-alcohols (e.g., *cis*-4-acetamidocyclopent-2-en-1-ol) were used as the racemic substrates (S(**93**) = 4, S(**101**) = 1).[78] This is again reflected in the high substrate specificity of the peptide catalysts; therefore, it is typically necessary to synthesize and test a large number of peptide libraries for a certain transformation. Miller and co-workers developed fluorescence-based assays for high-throughput identification of active catalysts in selected transformations.[82–84]

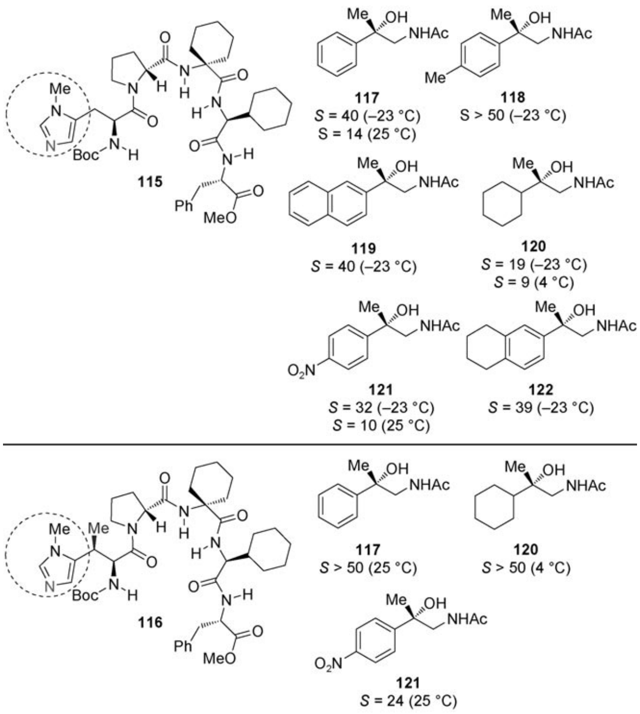
Miller and co-workers used these assays for screening catalysts for the kinetic resolution of racemic secondary and tertiary alcohols. For the secondary alcohols, 1-phenylethanol (**38a**) was used as the screening substrate, with acetic anhydride as the electrophile. Octapeptide **110** was identified out of a large variety of peptides (approximately 10^5) to be the most effective (Scheme 16). For alcohols bearing an aromatic moiety, **110** selectively catalyzed the reactions (S values from 11 to >50) except for *sec*-phenylpropanol **38b** (R = Et; $S = 8$). Non-aromatic alcohols gave only moderate S values of 9 for **112** and 4 for **114**.[83]



Scheme 16. Efficiency of peptide **110** in the kinetic resolution of racemic secondary alcohols.

Mechanistic studies towards structure–selectivity relationships of these octapeptides were also conducted with an alanine scan[85] that is typically used in peptide chemistry to elucidate the role of key residues. The individual residues (amino acids) of the investigated peptide are systematically replaced by alanine to probe the role of the substituted amino acids. The scan showed the importance of the π-methylhistidine and τ-tritylhistidine moieties; the former may be regarded as a nucleophilic and the latter as a basic moiety.[76]

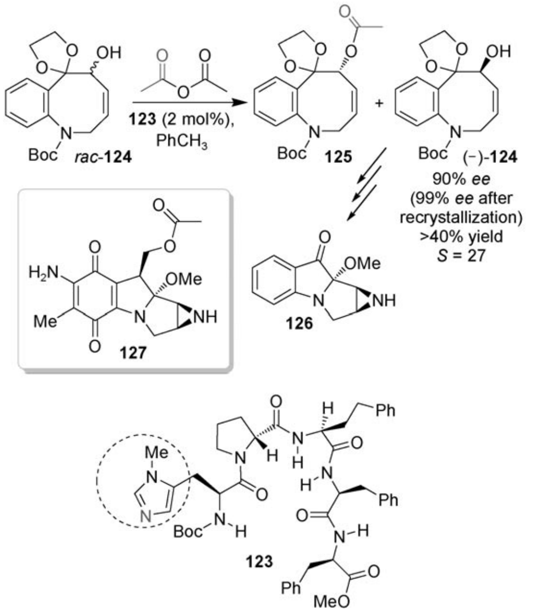
By using a similar screening strategy, **115** was identified as a catalyst for the kinetic resolution of racemic tertiary alcohols **117**–**122**, with S values up to >50 (Scheme 17) at



Scheme 17. Efficiency of the catalysts **115** and **116** in the kinetic resolution of racemic tertiary alcohols.

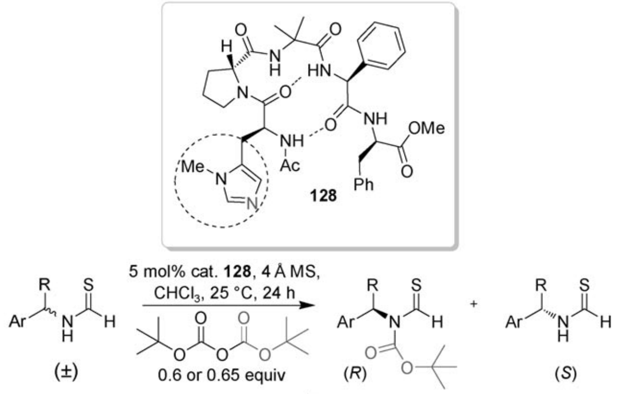
10 mol % catalyst loading.[84] Replacing the π-methylhistidine moiety of peptide **115** with the methylated β-methyl-π-methylhistidine residue (peptide **116**) improved the catalytic efficiency significantly (Scheme 17).[86]

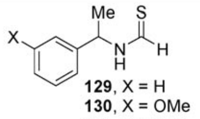
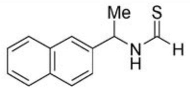
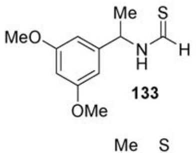
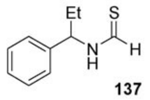
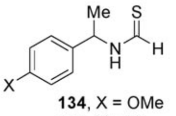
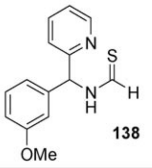
By utilizing diversity-based catalyst screening Miller and co-workers found **123** to be the most efficient catalyst out of 152 peptides for the acylative enantioseparation of **124** to prepare key intermediate (−)-**124** in the total synthesis of mitosane **126**, the core structure of mitomycin C (**127**). The kinetic resolution of **124** with acetic anhydride and 2 mol % of **123** gave 90 % *ee* for recovered (−)-**124** in greater than 40 % yield ($S = 27$). A single recrystallization afforded (−)-**124** with greater than 99 % *ee* (Scheme 18).[87]



Scheme 18. Efficiency of **123** in the kinetic resolution of *rac*-**124** as the key step in the synthesis of the core structure of mitomycin C **127**.

In 2010 Miller and co-workers investigated peptide **128** for the kinetic resolution of formamides and thioformamides in the presence of di-*tert*-butyldicarbonate (Boc_2O).[88] As the formamides showed only moderate reactivity, the authors focused on thioformamides, which provided S values of up to 44 at 52 % conversion (for **133**, Scheme 19). The enantioenriched *N*-Boc-protected products can be easily converted into the corresponding formamides or *N*-Boc-protected amines (unfortunately, no *ee* values are given for the corresponding products).



Substrate	S value (conversion)	e.r. recovered starting material	Substrate	S value (conversion)	e.r. recovered starting material
 **129**, X = H	12.8 (51%)	86.5:13.5	 **136**	13.8 (54%)	90.8:9.2
130, X = OMe	32.5 (52%)	95.5:4.5			
131, X = OPh	25.2 (58%)	97.5:2.5			
132, X = Br	12.5 (52%)	88:12			
 **133**	43.7 (52%)	96.5:3.5	 **137**	9.4 (52%)	85:15
 **134**, X = OMe	12.2 (52%)	88.2:11.8	 **138**	5.6 (53%)	79:21
135, X = Ph	10.2 (53%)	86.5:13.5			

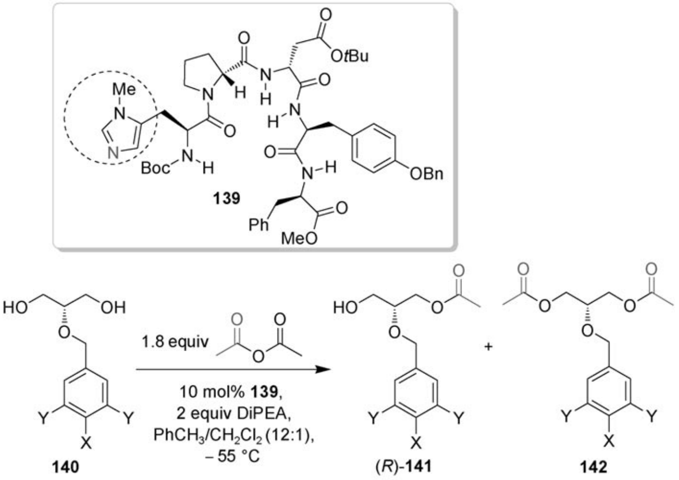
For racemic substrate **129**, (*R*)-**129** was found to be the fast-reacting enantiomer and (*S*)-**129** to be the recovered starting material. The other cases were not established.

Scheme 19. Miller's catalyst **128** in the kinetic resolution of thioformamides.

Miller and co-workers also successfully applied peptide catalysts to the acylative desymmetrization of alcohols. In 2005 the desymmetrization of *meso* glycerol derivatives **140** could be achieved with up to 97 % *ee* by using 10 mol % of the pentapeptide catalyst **139** (Scheme 20).[89]

A very impressive example of the power of nucleophilic peptide catalysis was shown by Miller and co-workers in 2006. The desymmetrization of *meso* substrate **146** is a formidable challenge because of the large distance between the two OH groups (9.79 Å, O–O) as well as between the OH groups and the prochiral stereogenic center (5.75 Å, O–C(sp^3)). Enzymatic approaches by hydrolysis of *meso* compound **144** proved to be moderately selective, with *ee* values up to 55 % at low conversions. Peptide **143**, identified by the screening of peptide libraries, catalyzed the monoacetylation of **146** with an impressive enantioselectivity for **145** of 95 % *ee* and 80 % yield of the isolated product (Scheme 21).[90] Further mechanistic investigations led to the proposal of two possible mechanisms (Scheme 22). Besides the nucleophilic pathway, a general base catalyzed pathway has to be considered because of the low pK_a value of the phenolic OH groups (Scheme 22).[91]

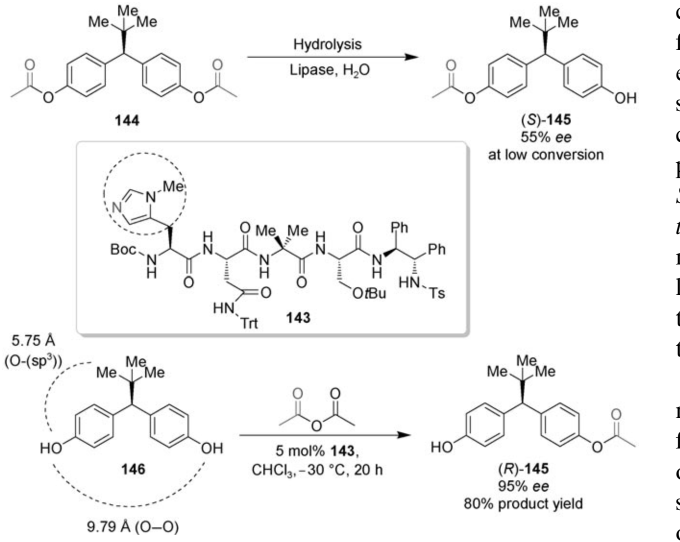
Moderate to good chemoselectivities could be achieved by using peptide catalysts in the acylation of carbohydrates.[92,93] Miller et al. used this approach to show the



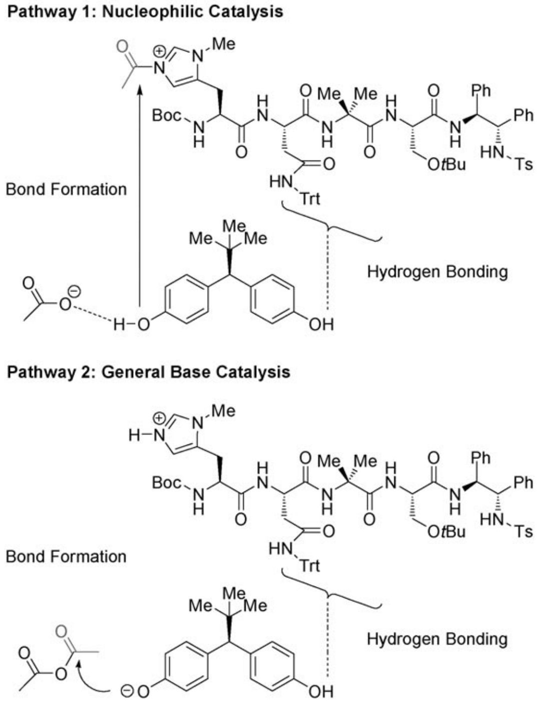
Entry	X	Y	ee 141 [%]	Yield (R)-141 [%]	141/142 ratio
1	H	H	91	37	39:61
2	F	H	68	40	50:50
3	CF_3	H	73	37	43:57
4	OMe	H	88	48	51:49
5	H	OMe	95	34	37:63

Scheme 20. Efficiency of **139** in the desymmetrization of **140**.

site-selective derivatization of erythromycin A by using a tetrapeptide with a proline-AiB turn.[93] The catalytic thionoformate transfer (thionoformate groups can be easily deoxygenated under Barton–McCombie conditions) proved to be more difficult and required the use of additives, for example, $FeCl_3$.[94]



Scheme 21. Efficiency of **143** in the desymmetrization of **146**.

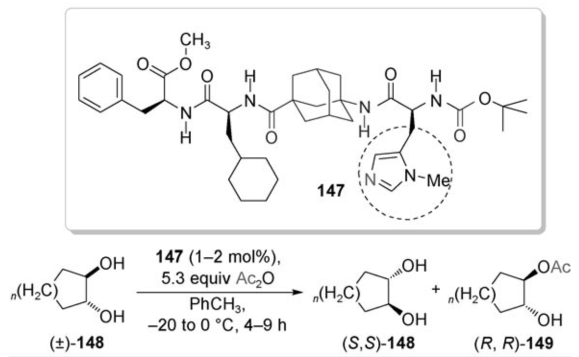


Scheme 22. Mechanistic model for the desymmetrization of **146**.

In 2008, Schreiner and co-workers introduced peptide catalyst **147** for the kinetic resolution of racemic *trans*-cycloalkane-1,2-diols **148**. This approach did not follow the oligopeptide catalyst design principles of Miller and co-workers, which emphasize the formation of catalytically important secondary structures, as indicated by internal hydrogen bonds (Schemes 12, 14, and 15). The incorporation of a rigid non-natural γ-aminoadamantane carboxylic acid (^{A}Gly in the shorthand notation to show the functional-group relationship to α-amino acids)[95] leads to a more lipophilic and somewhat structurally less flexible oligopeptide that readily dissolves in nonpolar organic solvents. Enantiomeric excess values typically of $>99\%$ (for the remaining diols) and S values >50 could be realized in the kinetic resolution of racemic *trans*-cycloalkane-1,2-diols **148** (Scheme 23).[16]

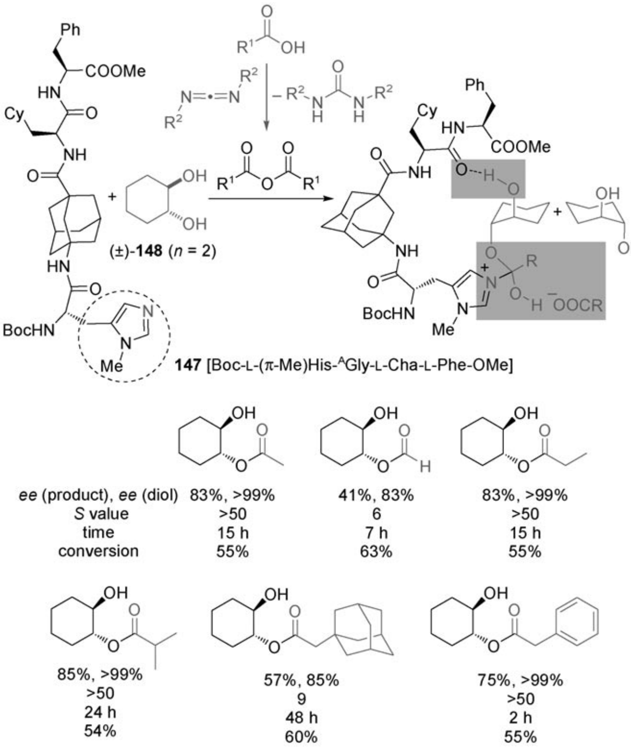
The first enantioselective Steglich esterification protocol using catalyst **147** and carboxylic acids as electrophiles was developed for the resolution of *trans*-cycloalkane-1,2-diols.[96] The reaction proceeds through in situ formation of an anhydride from the uncatalyzed reaction of an *O*-acylisourea and an acid. The use of acids instead of the anhydrides is a clear advantage when a particular anhydride is not stable (as, for example, for formic acid) or not readily available (as, for example, for phenylacetic acid). Comparable yields and selectivities could be achieved with acetic acid for the *trans*-cycloalkane-1,2-diols **148** as for the direct use of the preformed acetic anhydride as the electrophile. Additionally, S values >50 could be reached for the kinetic resolution of *trans*-cyclohexane-1,2-diol (**148**, $n=2$) with propionic, phenylacetic, or isobutyric acid and catalyst **147** (Scheme 24). If lower S values are acceptable, the reaction is also applicable to aromatic and sterically hindered carboxylic acids as well as to formic acid.

Peptide **147** was also applied successfully to the desymmetrization of *meso*-(cyclo)alkane-1,2-diols **150**. This transformation proved to be difficult because of the racemization of the monoacylated product **151**. Schreiner and co-workers showed that this racemization can be avoided by using a direct one-pot TEMPO oxidation protocol that leads to α-acetoxy ketones **152** (Scheme 25).[97]

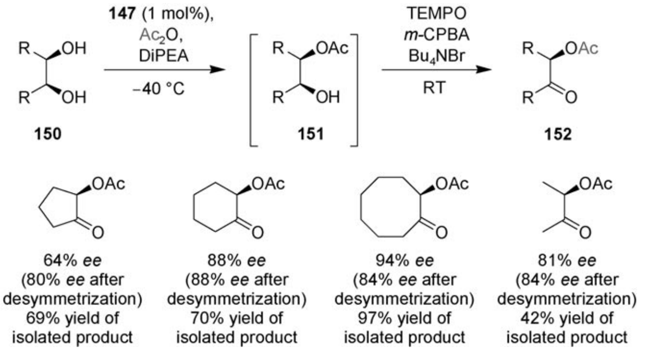


Entry	n	ee (148) [%]	ee (149) [%]	Yield 148 [%]	S value
1	2	>99	78	37	>50
2	1	>85	49	37	> 8
3	3	>99	79	41	>50
4	4	>99	85	44	>50

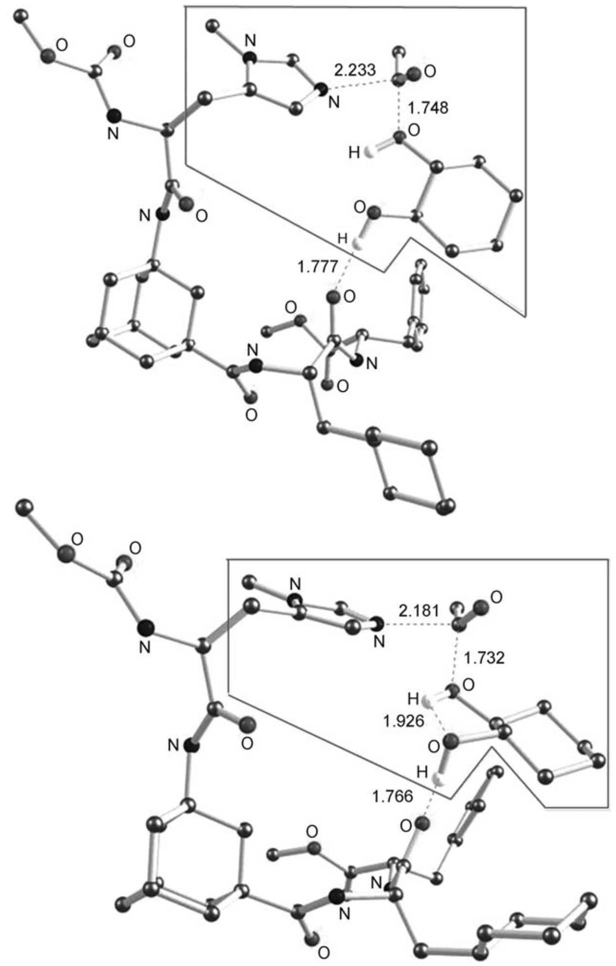
Scheme 23. Enantioselective kinetic resolution of *trans*-cycloalkane-1,2-diols **148** with peptide catalyst **147**.



Scheme 24. The Steglich esterification catalyzed by **147** exemplarily shown for racemic *trans*-cyclohexane-1,2-diol **148** ($n=2$) as the substrate (upper part); substrate scope (lower part).

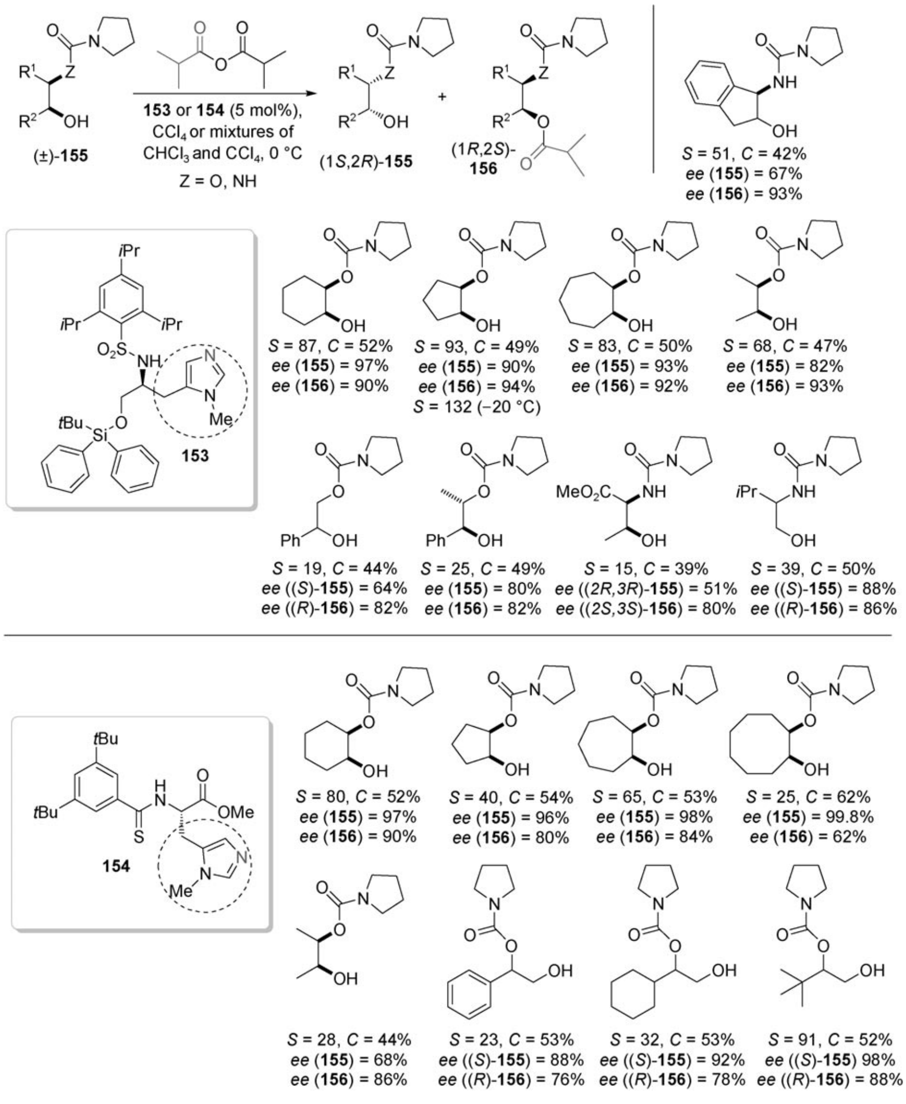


Scheme 25. Desymmetrization of **150** with peptide catalyst **147** and subsequent oxidation.



Scheme 26. Optimized low-lying transition structures for the acyl transfer catalyzed by **147** (Moc instead Boc) to (*1R,2R*)-**148** ($n=2$; top) or to (*1S,2S*)-**148** ($n=2$; bottom) at the ONIOM2(B3LYP/6-31G(d):PM3) level. Only selected hydrogen atoms are shown for clarity. The framed parts represent the higher B3LYP level and the nonframed part the lower PM3 level in the ONIOM2 partitioning. Distances are given in Å. The upper structure is 4.5 kcal mol^{-1} more stable.

Shinisha and Sunoj were able to shed light on the mechanism of these selective acylations by using ONIOM computations.[98] The authors confirmed the hypothesis of Schreiner and co-workers that peptide **147** does not form a stable secondary structure. Neither the modeled peptide alcohol complexes nor the low-lying transition states for acyl transfer are dominated by intramolecular hydrogen bonds of the peptide (Scheme 26). Additionally, the stereochemical outcome of the kinetic resolution of racemic *trans*-cyclohexane-1,2-diols (**148**, $n=2$) was rationalized computationally. The energetically lowest-lying transition state for the acylation of (R,R)-**148** ($n=2$) with catalyst **147** has a 4.6 kcal mol^{-1}



Scheme 27. Efficiency of **153** and **154** in the kinetic resolution of (±)-**155**.

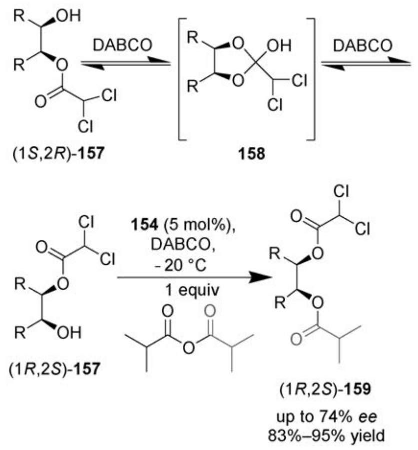
(4.5 kcal mol^{-1} for **147** with a Moc instead of a Boc protecting group) lower relative activation barrier compared to the lowest-lying transition structure for the acylation of (*S*,*S*)-**148** (*n* = 2; Scheme 26).[98]

A nonpeptidic biomimetic acylation approach was introduced by Ishihara et al. in 2004. Catalyst **153** proved to be highly effective in the kinetic resolution of racemic monoacylated 1,2-diols and amino alcohols **155** (*S* values of up to 93; Scheme 27). The authors proposed a transition structure where the sulfonylamino proton is preferentially bound through hydrogen bonding to the carbamoyl group of the 1*R*,2*S* enantiomer. Immobilization of the catalyst led to a decrease in the selectivity, but it could be reused six times without loss of activity and selectivity. Variation of catalyst **153** led to identification of the moieties responsible for the enantioselective acyl transfer, and to the conclusion that the R-SO_2-NH-R group is necessary for high selectivities.[99] Catalyst **153** was also applied efficiently to the kinetic resolution of racemic carboxylic acids (not the main aspect of this Review).[100] A similar π-methylhistidine-based approach was chosen by Qu and co-workers in 2008 with the introduction of **154**, which proved to be highly selective in the kinetic resolution of (±)-**155** as well (*S* values up to 91, Scheme 27).[101]

Catalyst **154** could also be used in the dynamic kinetic resolution of racemic monoacylated dichloroacetates (based on *meso* 1,2-diols) **157** (Scheme 28).[102] The use of DABCO as an additional base leads to racemization through the cyclic *meso* intermediate **158** (Scheme 28). The use of isobutyric anhydride as an electrophile resulted in *ee* values of up to 74 % at 90 % yield for the diacylated products **159**.[102]

5. Amidines

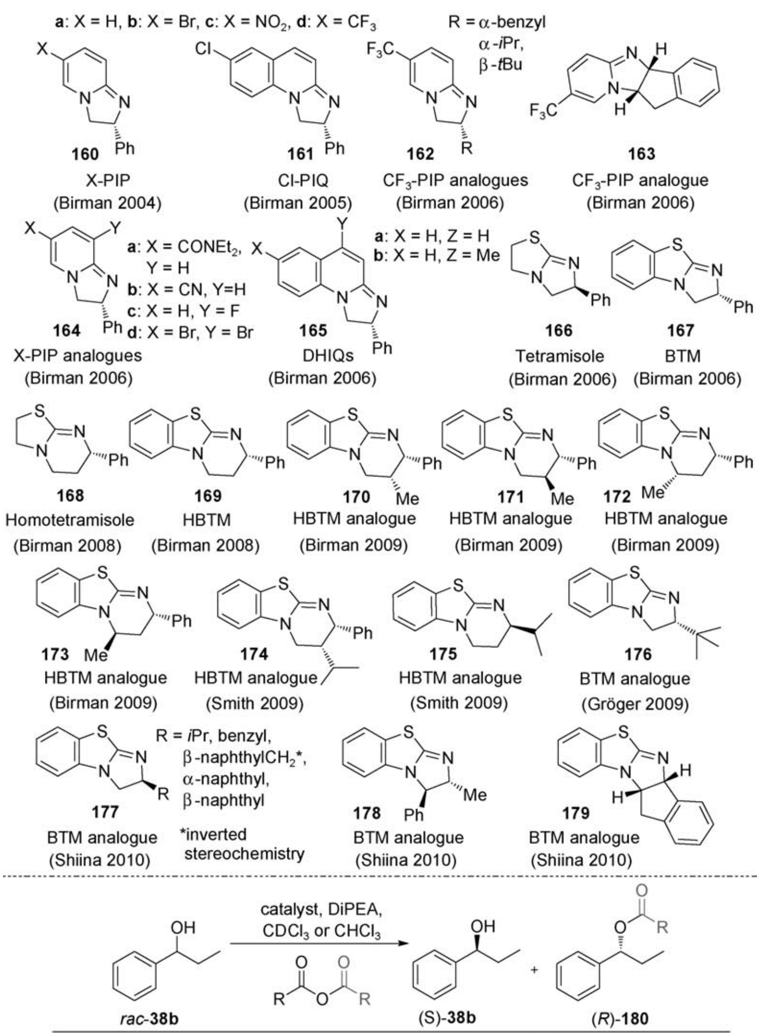
The first representatives of this class of chiral acylation catalysts based on an amidine (dihydroimidazole) moiety were introduced by Birman et al. in 2004. The catalysts **160** (**a**: X = H, **b**: Br, **c**: NO_2, **d**: CF_3) were tested in the kinetic resolution of secondary alcohols (Scheme 29); **160 d** proved to be the most effective.[103] Replacing the pyridine moiety of **160** with a quinoline moiety (**161**) led to significant improvement of the catalytic efficiency for the kinetic resolution of



Scheme 28. Dynamic kinetic resolution of racemic **157** with peptide catalyst **154**. R = cyclopentane–cyclooctane, swissane, cyclohexene, cyclooctene, Me, Pr.

secondary aryl alkyl and cinnamyl alcohols (Schemes 29 and 30). This can be explained by the additional π–π interaction (Scheme 30, below the table).[103,104]

The proposed π–π interaction-dominated transition state of **160d** for the acyl transfer was confirmed by Houk and co-workers, who investigated the transition structures for the acetyl transfer of acetylated **160d** to 1-phenylethanol (**38a**).[105] In the case of (*S*)-1-phenylethanol, the unstacked transition geometry is energetically favored over the closed or stacked conformation, whereas the slipped-stacked geometry is preferred in the case of (*R*)-1-phenylethanol.[105] The relative energy difference between the lowest-energy transition-state structures of the two phenylethanol enantiomers (slipped-stacked TS geometry for (*R*)-1-phenylethanol and unstacked TS geometry for (*S*)-1-phenylethanol) of 1.9 kcal mol^{-1} (at the B3LYP/6-31G(d) level of theory) is in good agreement with the experimental value of 1.5 kcal mol^{-1} (Scheme 31).[105] Replacing the phenyl group of the catalyst **160d** by alkyl or benzyl groups (catalysts **162**) led to a significantly lower performance in the kinetic resolutions of aryl alkyl alcohols.[106] This finding strongly suggests that the phenyl group of the catalyst is essential for its catalytic efficiency, maybe because of additional π–π or π–cation interactions with an unsatured moiety of the substrate. Additional variational studies on catalysts **160** and **161** resulted in the catalysts **163**–**165**.[106] All three catalysts or catalyst families proved to be less selective in the chosen kinetic resolution (*rac*-**38b**) than **160** and **161**.[106]



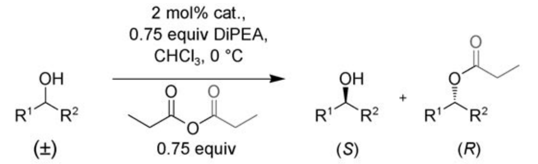
Cat.	Mol%	*t* [h]	*T* [°C]	R	*C* [%][a]	*ee* (38) [%][a]	*ee* (180) [%][a]	*S* value[a]
160a	20	1	RT	Me	21	13	49	3.3
160b	20	1	RT	Me	25	25	74	8.6
160c	20	1	RT	Me	14	13	82	11
160d	20	1	RT	Me	38	49	79	14
160d	2	8	0	Me	43	60	81	17
160d	2	8	0	Et	39	59	91	36
161	2	8	0	Et	53	95	84	41
166	10	6	0	Et	53	92	81	31[b]
167	4	24	0	Et	47	95	86	109
166	10	3	RT	Et	31	41	90	28[b]
167	4	2.2	RT	Et	49	88	92	72
168	1	1.7	RT	Et	47	77	85	30
169	1	1.5	RT	Et	48	77	84	26

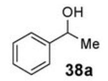
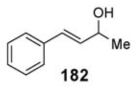
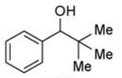
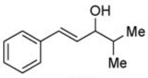
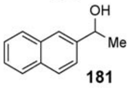
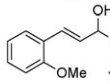
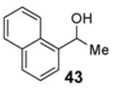
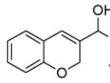
[a] Conversions, *ee* values, and S values are averages of two runs.
[b] Inverted stereochemistry.

Scheme 29. Chiral amidine-based catalysts (upper part) and performance in the kinetic resolution of *rac*-**38b** (lower part).

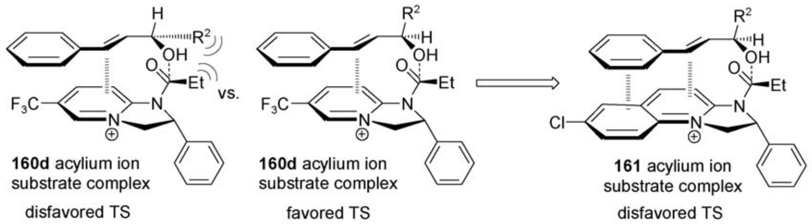
In 2006 Birman et al. tested commercially available tetramisole **166** and the benzannelated analogue BTM (**167**) as catalysts in the kinetic resolution of aryl alkyl alcohols and propargylic alcohols (Scheme 29; Table 4).[107,108] The same observations can be made for **166** and **167** as for **160** and **161** (the transition states of **166** + **167** are similar to those of **160** + **161**, Scheme 30): the additional aromatic moiety leads to stronger π–π or π–cation interactions and higher selectivities. BTM (**167**) is the most efficient amidine-based catalyst for the kinetic resolution of racemic aryl alkyl and propargylic alcohols to date (similar to the protocol of Fu and co-workers,[33] no base was used for propargylic alcohols; Table 4).[107]

Excellent selectivities could be achieved with catalyst **167** for the kinetic resolution of 2-oxazolidinones by *N*-acylation. This transformation was performed at room temperature with various modifications of the oxazolidinone core (**191**, **193**–**204**) and led to *S* values ≥ 50 (Scheme 32).[109] Catalyst (*S*)-**167** also performed well in the acylative desymmetrization of lobelanidine (**205**) when propionic acid anhydride was used as the electrophile. A > 99 % *ee* with 92 % yield of isolated **206** could be achieved by using 20 mol % of catalyst (*S*)-**167**. Jones oxidation of **206** and subsequent hydrolysis of the corresponding propionic ester **207** gave the enantiopure natural compound (−)-lobeline (**208**, Scheme 33). In the same manner, the non-natural enantiomer (+)-lobeline could be synthesized by using (*R*)-**167**.[110] Chen and co-workers successfully applied catalyst (*R*)-**167** ((*R*)-BTM) to the kinetic resolution of 2,2-difluoro-3-hydroxy-3-aryl propionates. The reactions were performed at room temperature in ethyl acetate for 0.5 to 5.5 h; *S* values between 1 and 47 could be achieved by using this protocol.[111]



Substrate	**160d** *S* value *ee* (alcohol)/ *ee* (product) (conv./time)	**161** *S* value *ee* (alcohol) / *ee* (product) (conv./time)	Substrate	**160d** *S* value *ee* (alcohol)/ *ee* (product) (conv./time)	**161** *S* value *ee* (alcohol) / *ee* (product) (conv./time)
 **38a**	26 42% / 89% (32% / 8 h)	33 96% / 78% (55% / 8 h)	 **182**	11 13% / 81% (14% / 8 h)	27 67% / 86% (44% / 8 h)
 **38d**	85 86% / 94% (48% / 52 h)	117 71% / 96% (42% / 8 h)	 **183**	21 38% / 87% (30% / 8 h)	24 88% / 79% (53% / 8 h)
 **181**	42 88% / 87% (50% / 8 h)	74 95% / 91% (51% / 2 h)	 **184**	6 24% / 67% (27% / 8 h)	31 97% / 77% (56% / 8 h)
 **43**	56 92% / 89% (51% / 8 h)	55 99.7% / 80% (56% / 8 h)	 **185**	26 83% / 82% (50% / 8 h)	57 99.7% / 81% (55% / 4 h)

Conversions, *ee* values, and *S* values are averages of two runs.

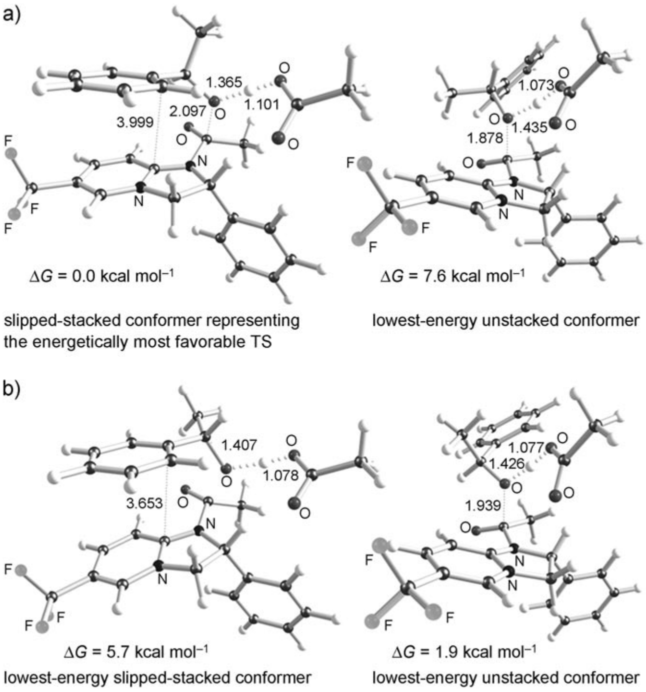


Scheme 30. Efficiency of catalysts **160d** and **161** in the kinetic resolution of aryl alkyl and cinnamyl alcohols and proposed transition-state (TS) models showing the important π–π interactions.

Homotetramisole (**168**) and homobenzotetramisole (**169**), introduced by Birman and Xi in 2008, catalyzed the kinetic resolution of aryl alkyl alcohols with good selectivities (Scheme 29). The use of **169** as the catalyst in the kinetic resolution of racemic aryl cycloalkanols led to *S* values up to 107 (Table 5).[108]

Zhang and Birman tried to improve the efficiency of the original HBTM system by synthesizing the catalysts **170**–**173** with an additional stereogenic center. The catalysts **170**, **172**, and **173** showed similar or improved selectivity in the kinetic resolution of racemic 1-phenylpropanol (**38b**) compared to HBTM (**169**). Amidines **170** and **172** also proved to be more efficient in the kinetic resolution of racemic **113**. Taking into account its synthetically accessibility, the authors chose **170** to compare its performance with the previously synthesized amidine-based catalysts in the acylation reactions described above. A better performance could only be observed in the kinetic resolution of racemic **113**, **209**, and **212**.[112] In 2009 Smith and co-workers published an amidine-catalyzed enantioselective Steglich rearrangement involving the transfer of a carboxy group, and tested catalysts **174** and **175** along with **169** in the rearrangement of oxazolyl carbonates.[113] In the same year Dietz and Gröger introduced the BTM analogue **176**, which resulted in no enantiomeric excess in an acylative Steglich rearrangement used as the test reaction.[114]

In 2007 Shiina et al. presented a protocol for the kinetic resolution of alcohols catalyzed by tetramisole-based catalysts by using free carboxylic acids as acylating reagents.[115] Unreactive anhydrides such as *para*-methoxybenzoic anhydride (PMBA) or pivalic anhydride serve as condensation reagents through the tetramisole-catalyzed in situ formation of the corresponding mixed anhydride. This mixed anhydride is catalytically activated by **167** and reacts with the preferred alcohol enantiomer to give the desired product ester (for the proposed mechanism see Scheme 34). The formation of the undesired ester by-product (resulting from the catalytic acylation of the alcohol with the unreactive anhydride) can be suppressed by the choice of the anhydride species. The best results for the kinetic resolution of secondary aryl alkyl alcohols were achieved by using 5 mol% BTM (**167**) as the catalyst, PMBA as the anhydride, and various acids as electrophiles, which led to *S* values of up to 88 (Table 6).


a)

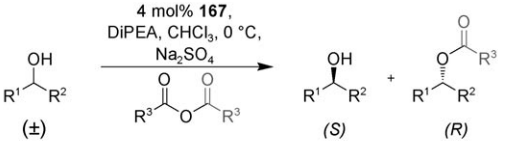
slipped-stacked conformer representing the energetically most favorable TS
lowest-energy unstacked conformer

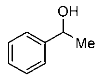
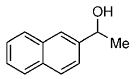
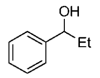
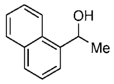
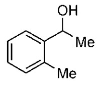
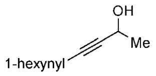
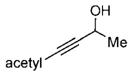
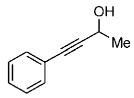
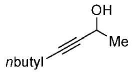
b)

lowest-energy slipped-stacked conformer
lowest-energy unstacked conformer

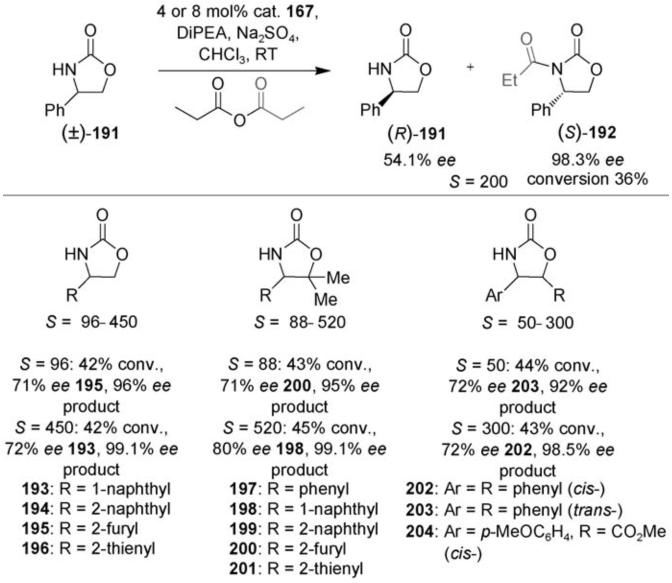
Scheme 31. a) Lowest-energy TS structures for the acetyl transfer of acetylated **160d** to (*R*)-1-phenylethanol. b) Lowest-energy TS structures for the acetyl transfer of acetylated **160d** to (*S*)-1-phenylethanol. Distances are given in Å.

Table 4: Efficiency of catalyst **167** in the kinetic resolution of aryl alkyl and propargylic alcohols.[a]

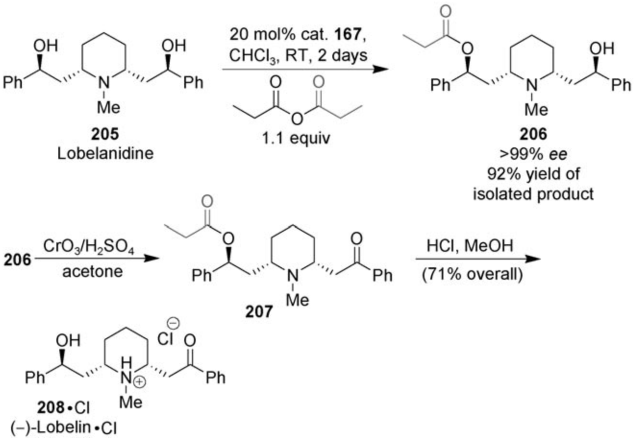


Entry	Substrate	R^3	*S* value *ee*(alcohol)/*ee*(product) (conv./time)	Entry	Substrate	R^3	*S* value *ee*(alcohol)/*ee*(product) (conv./time)
1	 **38a**	Et	80 88%/93% (49%/33 h)	8	 **181**	Et	108 92%/94% (50%/10.5 h)
2		*i*Pr	104[b] 80%/95% (46%/33 h)	9		*i*Pr	226 84%/98% (46%/10.5 h)
3	 **38b**	Et	109 86%/95% (47%/24 h)	10	 **43**	Et	128 93%/95% (49%/8.5 h)
4		*i*Pr	145 80%/97% (45%/36 h)	11		*i*Pr	184 93%/96% (49%/8.75 h)
5	 **186**	Et	209 96%/96% (50%/33 h)	12	 **188**	Et	32[c] 89%/83% (52%/2 h)
6		*i*Pr	355 89%/98% (48%/33 h)	13	 **189**	Et	26[c] 93%/78% (55%/1.5 h)
7	 **187**	Et	31[c] 99.6%/69% (59%/10.5 h)	14	 **190**	Et	13[c,d] 54%/76% (42%/25 h)

[a] Conversions, *ee* values, and *S* values are averages of two runs. [b] Average of three runs. [c] No D*i*PEA and Na$_2$SO$_4$ used. [d] 10 mol% catalyst.



Scheme 32. Efficiency of catalyst **167** in the kinetic resolution of racemic 2-oxazolidinones.

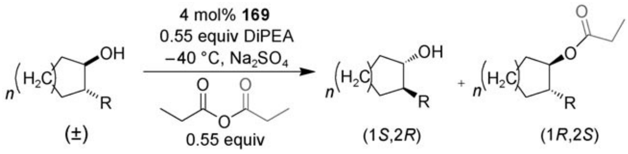


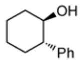
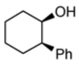
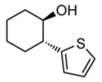
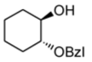
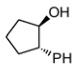
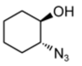
Scheme 33. Efficiency of catalyst **167** in the desymmetrization of **205** as part of the total synthesis of (−)-lobeline.

In 2009 this protocol was successfully applied to the BTM-catalyzed kinetic resolution of various 2-hydroxy alkanoates **215** with pivalic anhydride and diphenylacetic acid, which resulted in good enantioselectivities for the recovered alcohols (up to 94% *ee*) and the product esters (up to 97% *ee*) at reasonable conversions and *S* values between 47 and 202 (Scheme 34).[116] Additionally, in 2008[117] and 2010[118] Shiina et al. presented protocols for the kinetic resolution of racemic carboxylic acids (not the main aspect of this Review) by using various BTM analogues as catalysts; the known catalysts ((*R*)- and (*S*)-**167** and (*S*)-**176**) were tested, and a series of new BTM analogues **177**, **178**, and **179** were introduced and investigated in these transformations.[117,118]

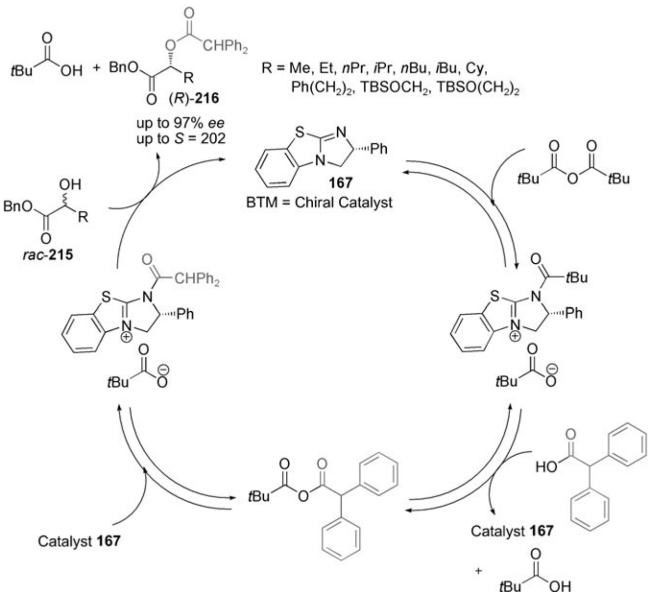
Very recently (2010) and during the review process of this manuscript Fossey and Deng published the synthesis of planar chiral ferrocene-based PIP analogues as acylation catalysts.[119] Excellent *S* values up to 1892 (99.8% *ee* of the

Table 5: Efficiency of catalyst **169** in the kinetic resolution of aryl cycloalkanols.[a]



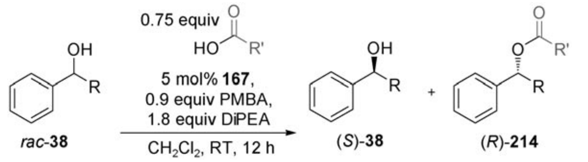
Entry	Substrate		*S* value *ee*(alcohol)/*ee*(product) (conv./time)	Entry	Substrate		*S* value *ee*(alcohol)/*ee*(product) (conv./time)
1		**113**	107 95 %/93 % (51 %/10 h)	4		**211**	28 72 %/86 % (46 %/12 h)
2		**209**	44 71 %/91 % (44 %/10 h)	5		**212**	5.6 25 %/63 % (28 %/10 h)
3		**210**	66 95 %/89 % (51 %/7 h)	6		**213**	10 26 %/77 % (26 %/10 h)

[a] The absolute configuration of the fast-reacting enantiomer is shown. Conversions, *ee* values, and *S* values are averages of two runs.



Scheme 34. Mechanism of the kinetic resolution of *rac*-**215** with diphenylacetic acid as the electrophile and BTM (**167**) as the catalyst.

Table 6: Kinetic resolution of *rac*-**38** with carboxylic acids as the electrophiles and BTM (**167**) as the catalyst.



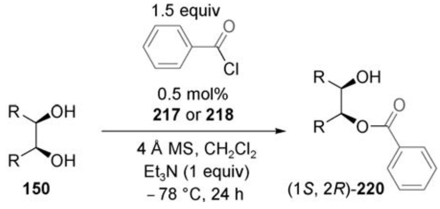
Entry	R	R^1	*ee*(**38**) (yield) [%]	*ee*(**214**) (yield) [%]	*S* value
1	Et	Et	76 (40)	89 (40)	39
2	Et	Ph(CH$_2$)$_2$	75 (46)	90 (41)	43
3	Et	Ph(CH2)$_3$	69 (45)	90 (39)	39
4	Et	Me$_2$CH(CH$_2$)$_2$	71 (38)	83 (43)	23
5	Et	CH$_2$=CH-(CH$_2$)$_2$	91 (38)	86 (47)	42
6	Et	MeOCH$_2$	38 (51)	82 (32)	15
7	Et	Cy	51 (40)	76 (53)	12
8	*i*Pr	Et	81 (43)	90 (39)	47
9	*i*Pr	Ph(CH$_2$)$_2$	64 (53)	92 (38)	46
10	*t*Bu	Et	44 (67)	93 (32)	42
11	*t*Bu	Ph(CH$_2$)$_2$	58 (54)	96 (36)	88

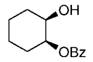
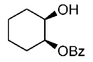
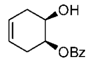
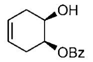
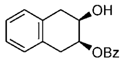
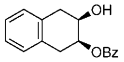
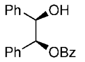
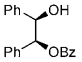
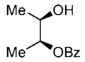
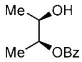
product and 62.0 % *ee* for the recovered starting material at 38.3 % conversion) could be realized in the acylative kinetic resolution of secondary aryl alkyl alcohols.[119]

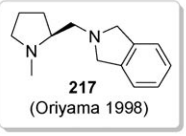
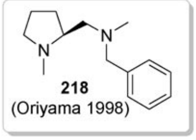
6. Vicinal Diamines

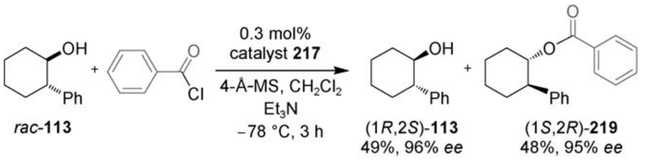
The application of chiral tertiary amine catalysts in acyl-transfer reactions began in 1932.[120] Wegler used naturally occurring tertiary amine based alkaloids (e.g., brucine) for the kinetic resolution of 1-phenylethanol (**38a**); although the selectivities were only moderate, the proof of principle was established.[120] In 1998, the first highly efficient amine-based catalysts for acyl transfer were reported by Oriyama and co-workers with their synthesis of the chiral proline-based di(*tert*-amine) catalysts **217** and **218**. Remarkably, catalyst **217** was the first organocatalyst with an *S* value greater than 100. Actually, diamine **217** was synthesized as a ligand for Sn^{II} complexes.[121] Initially, Oriyama et al. used such an Sn^{II}-**217** complex as a catalyst in the acylative kinetic resolution of racemic secondary alcohols[122] before recognizing that Sn^{II} salts are, in fact, unnecessary. The catalysts **217** and **218** proved to be very selective in the desymmetrization of *meso* alcohols **221**–**225** even without any metal salts (Table 7).[123] Catalyst **217** also showed high efficiency in the kinetic resolution of racemic secondary alcohols (e.g., *rac*-**113**), with *S* values of up to 160 (Scheme 35).[124] Catalyst **218** (0.3 mol % catalyst loading) was also applied to the kinetic resolution of racemic primary alcohols such as glycerol derivatives, and resulted in *S* values of up to 16.[125] A polymer-bound version of **218** was introduced by Janda and

Table 7: Oriyama's amine-based catalysts and their efficiency in the desymmetrization of *meso* alcohols **221**–**225**.



	217[a]				218[b]		
entry	Product		*ee* [%] (yield [%])	entry	Product		*ee* [%] (yield [%])
1		**221**	**95** (62)	6		**221**	**96**[c] (83)
2		**222**	**96** (78)	7		**222**	**90**[c] (81)
3		**223**	**48** (89)	8		**223**	**66**[c] (89)
4		**224**	**64** (68)	9		**224**	**60** (80)
5		**225**	**91** (80)	10		**225**	**94**[c] (85)

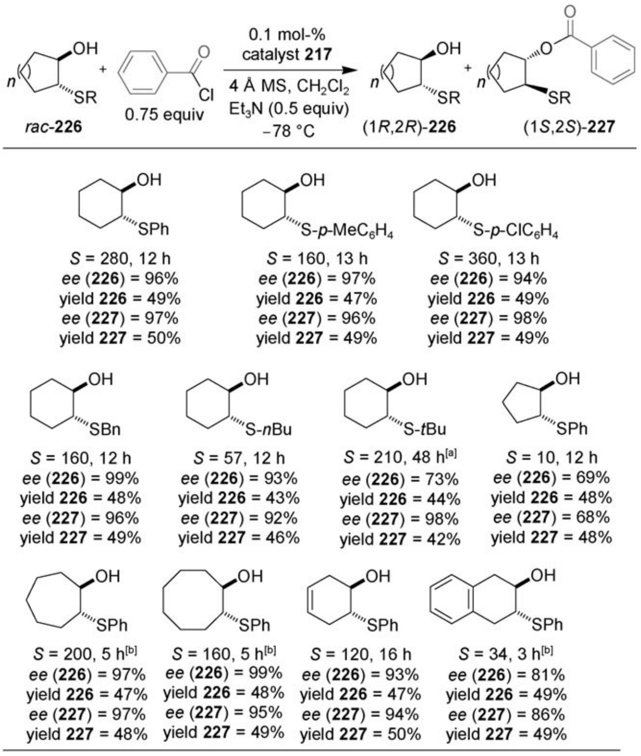
[a] 
217
(Oriyama 1998)
. [b] 
218
(Oriyama 1998)
. [c] 3 h.



Scheme 35. Efficiency of catalyst **217** in the kinetic resolution of *rac*-**113**.

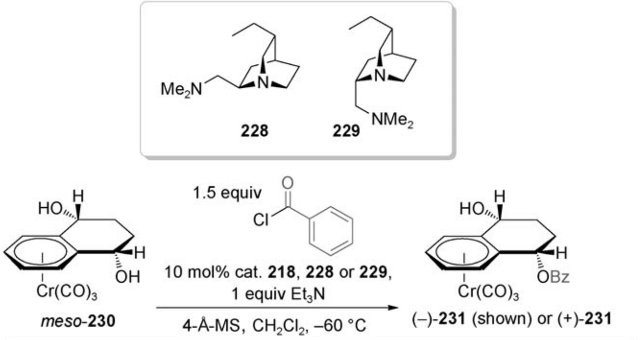
co-workers in 2001 and tested in the kinetic resolution of a wide range of racemic secondary alcohols. The best result was obtained for *rac*-**113**, with 96% *ee* (44% yield) for ester **219** and 85% *ee* (45% yield) for the recovered starting material ($S = 134$).[126]

Catalyst **217** was succesfully applied by Kawamata and Oriyama in 2010 to the kinetic resolution of racemic cyclic *β*-hydroxy sulfides **226**. Good to excellent selectivities were observed, with *S* values >50 for the majority of the substrates; only in the case of the five-membered-ring substrate the selectivities were moderate (Scheme 36).[127] In 2004 Kündig et al. investigated chiral diamine catalysts in the desymmetrization of a *meso* Cr^0 complex (**230**) by utilizing catalyst **218** and the new cinchona alkaloid based diamine catalysts **228** and **229**, which afforded excellent yields and enantioselectivities (Scheme 37).[128] In 2008 **228** and **229** were used in the desymmetrization of *meso* 1,2-diols **150** (Table 8). The best results (up to 97% *ee* at 92% yield; Table 8, entry 1) were achieved by using 2 mol% of catalyst **229**.[129]



[a] 3 mol% of catalyst **217** used. [b] 0.5 mol% of catalyst **217** used.

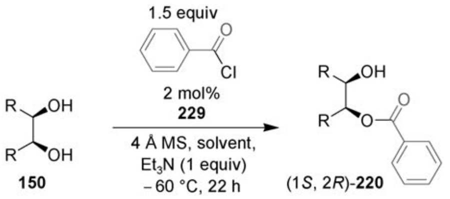
Scheme 36. Efficiency of catalyst **217** in the kinetic resolution of *rac*-**226**.

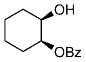
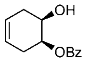
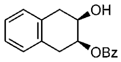
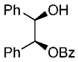
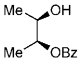
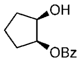
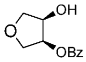
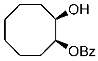
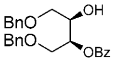


Cat.	*t* [h]	Yield **231** [%]	*ee* (**231**) [%] (configuration)
218	22	78	95 (−)
228	23	80	94 (+)
229	22	76	99 (−)

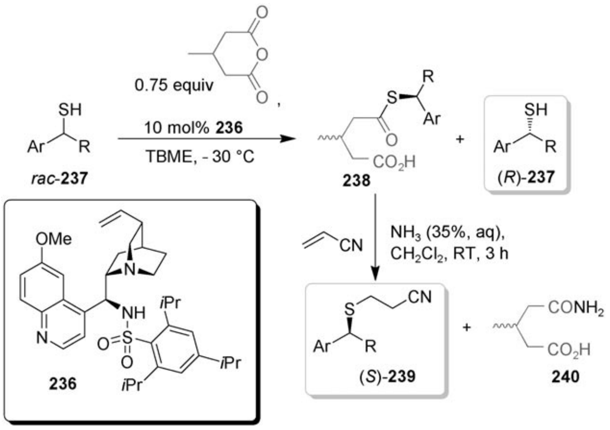
Scheme 37. Desymmetrization of *meso*-**230** with catalysts **218**, **228**, and **229**.

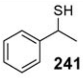
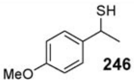
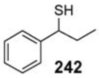
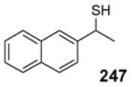
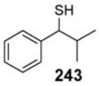
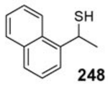
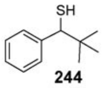
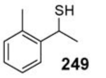
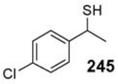
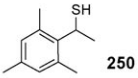
Table 8: Kündig's diamine-based catalyst **229** in the desymmetrization of *meso* 1,2-diols **150**.



Entry	Product		THF: *ee* [%] (yield [%]) EtOAc: *ee* [%] (yield [%])
1		**221**	93 (95) 97 (92)
2		**222**	66 (76) 84 (79)
3		**223**	45 (70) 83 (65)
4		**224**	34 (68) 13 (82)
5		**225**	92 (77) 90 (82)
6		**232**	82 (83) 78 (87)
7		**233**	75 (77) 77 (84)
8		**234**	72 (87) 77 (86)
9		**235**	89 (64) 93 (51)

The first example of an organocatalytic kinetic resolution of racemic thiols was realized very recently (2010) by the Connon research group, who used a novel cinchona-based sulfonamide catalyst **236** and secondary aryl alkyl thiols **237** as substrates.[130] The use of a *meso* anhydride as the electrophile led to the concomitant desymmetrization of the anhydride. The results for the kinetic resolution of *rac*-**237** are summarized in Scheme 38. The performance of **236** in the kinetic resolution was determined by converting the combined thioester diastereomers into the product **239**. The *ee* value of **239** corresponds to the *ee* value of the product from a kinetic resolution with an achiral and non-*meso* electrophile. In particular *ortho*-substituted aryl groups led to high *S* values of up to 265 (Scheme 38). The efficiency of **236** for the desymmetrization of the *meso* anhydride (not the focus of this Review) can be determined by analyzing the *ee* value of the hemiamide **240**; 93 % *ee* for the isolated hemiamide was achieved in the case of racemic thiol **248**.[130]



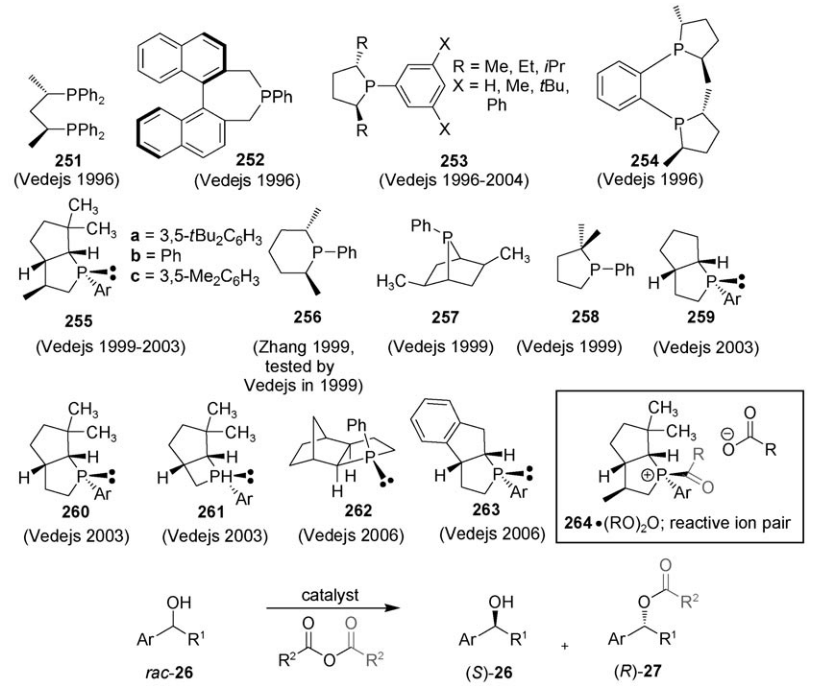
Substrate	*S* value *ee*(**237**) / *ee*(**239**) (conv./time)	Substrate	*S* value *ee*(**237**) / *ee*(**239**) (conv./time)
 **241**	15 97% / 57% (63% / 68 h)	 **246**	15[a] 87% / 69% (56% / 120 h)
 **242**	19 91% / 72% (56% / 74 h)	 **247**	10 82% / 60% (58% / 74 h)
 **243**	26 90% / – (54% / 68 h)	 **248**	37 90% / 85% (51% / 96 h)
 **244**	52 94% / 87% (52% / 96 h)	 **249**	126 95% / 94% (50% / 48 h)
 **245**	11 95% / 51% (65% / 72 h)	 **250**	265 98% / 96% (50% / 48 h)

[a] 0.9 equiv of *meso* anhydride used.

Scheme 38. Kinetic resolution of racemic thiols **237** with concomitant desymmetrization of a *meso* anhydride using catalyst **236**.

7. Phosphines and Phosphinites

In 1993 Vedejs and Diver reported that achiral tributylphosphines have a similar catalytic efficiency as DMAP in the acylation of alcohols with anhydrides.[131] It was shown that trialkyl phosphines were by far the most active, followed by aryl dialkyl phosphines and diaryl alkyl phosphines. As the authors found evidence that *P*-acylphosphonium salts were



Cat.	mol%	*t* [h]	*T* [°C]	R^2	Ar	R^1	*C* [%]	*ee* (**26**) [%]	*ee* (**27**) [%]	*S*
253a (R=Me, X=H)	–	–	RT	Me	Ph	Me	44	–	34	2.7
253a (R=Me, X=H)	–	–	RT	*m*-ClC_6H_4	Ph	Me	51	–	34	2.8
253a (R=Me, X=H)	–	–	RT	Me	Ph	*t*Bu	27	19	–	3.8
253a (R=Me, X=H)	16	421	RT	*m*-ClC_6H_4	Ph	*t*Bu	25	–	81	12–15
255a (3,5-*t*$Bu_2C_6H_3$)	4	1	RT	*i*Pr	Ph	Me	42	62	84	22
255a (3,5-*t*$Bu_2C_6H_3$)	2.5	4	−20	*i*Pr	Ph	Me	29	38	93	42
255a (3,5-*t*$Bu_2C_6H_3$)	2.8	42	−40	*i*Pr	Ph	*i*Pr	47	84	95	100
255b (Ph)	4.9	65	−40	*i*Pr	Ph	*t*Bu	46	79	93	67
255a (3,5-*t*$Bu_2C_6H_3$)	3.9	7	−40	*i*Pr	1-naphthyl	Me	30	41	97	99
255a (3,5-*t*$Bu_2C_6H_3$)	12.1	16	−40	*i*Pr	mesityl	Me	44	79	99	369
255a (3,5-*t*$Bu_2C_6H_3$)	3.5	4	−40	*i*Pr	2-tolyl	Me	50	95	95	145
253b (R=Me, X=Me)	20	96	RT	*m*-ClC_6H_4	Ph	*t*Bu	20	–	–	17[a]
253c (R=Me, X=*t*Bu)	20	144	RT	*m*-ClC_6H_4	Ph	*t*Bu	27	–	–	4.5[a]

[a] Inverted stereochemistry.[139]

Scheme 39. Chiral phosphine catalysts and their efficiency in the kinetic resolution of *rac*-**26**.

formed from phosphines and appropriate acyl donors, the analogy to DMAP-based acylium salts (Scheme 2) became even more apparent.[131] Consequently, in 1996 Vedejs et al. introduced chiral phosphines as nucleophilic acylation catalysts. The catalysts **251**–**254** were tested in the desymmetrization of *meso* diols, but only moderate selectivities were observed. Catalyst **253a** (R = Me, X = H) proved to be the most effective and was additionally used as the catalyst in the kinetic resolution of *rac*-**26** with Ar = Ph, R^1 = *t*Bu (**38d**), which resulted in 81 % *ee* for the product at 25 % conversion (Scheme 39; Ar = Ph, R^1 = *t*Bu, R^2 = ClC_6H_4). These values correspond to *S* = 12 based on the *ee* value of the product and *S* = 15 based on the *ee* value of the starting material.[132]

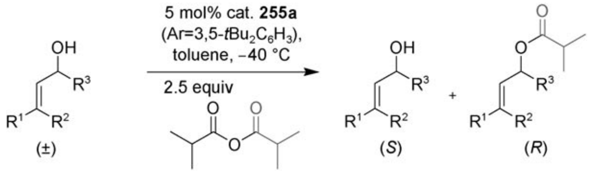
Bicyclic **255a**,**b** (Ar = 3,5-*t*$Bu_2C_6H_3$ and Ph; Vedejs 1999) were the first highly selective phosphine-based catalysts and showed excellent performance in the kinetic resolution of *rac*-**26**, with *S* values up to 369 (Scheme 39).[133,134] In the same year Vedejs et al. tested the catalysts **256** (published by Zhang),[135] **257**, and **258** in the kinetic resolution of *rac*-**26** (Ar = Ph, R^1 = *t*Bu) with chlorobenzoic anhydride as the electrophile; the catalysts proved to be not or only marginally reactive.[136] Catalysts **255c** (Ar = 3,5-$Me_2C_6H_3$), **259**, **260**, and **261** were introduced in 2003 for mechanistic studies, but turned out to be less efficient than **255a**.[134,137] Catalyst **255a** was also successfully applied to the kinetic resolution of allylic alcohols, with *S* values up to 82 (Table 9, entry 8).[133,138]

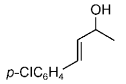
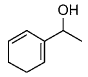
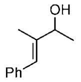
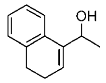
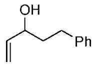
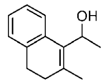
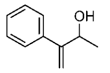
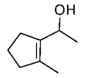
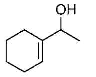
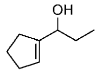
The catalysts **253** and **255** were also used in the desymmetrization of *meso*-hydrobenzoin (*meso*-**275**) with benzoic or isobutyric anhydride as electrophiles. The monocyclic catalysts **253** showed higher selectivities but much lower activities, and required high catalyst loadings of 35–41 mol % (Table 10, entries 1–3). Therefore, the use of the bicyclic catalysts **255** seems to be preparatively more useful.[139]

In 2006 MacKay and Vedejs introduced phosphine catalysts **262**[140] and **263**,[140] whose efficiency in the kinetic resolution of racemic aryl alkyl alcohols **26** proved to be lower than catalyst family **255**;[140] catalysts of type **255** are the most effective phosphine catalysts for enantioselective acyl transfer to date. Vedejs et al. employed the corresponding BH_3 complexes of the phosphines as catalyst precursors; the free phosphines are released by warming the complexes in the presence of pyrrolidine.[133,134,137,140,141] In 2004 MacKay and Vedejs showed that the tetrafluoroboric acid salts of these catalysts can also be employed; in situ deprotonation with Et_3N liberates the catalyst.[142] Mechanistic and conformational studies[137] as well as parallel kinetic resolution experiments[143] were additionally performed.[141]

In 2003 Fujimoto and co-workers reported the synthesis of a chiral phosphinite derivative based on a cinchona alkaloid **278**. The combination of a Lewis-basic trivalent phosphorus center and a Brønsted-basic tertiary amino group led to an efficient bifunctional acylation catalyst that cooperatively activated the acylating reagent (the phosphinite moiety) and trapped the proton from the alcohol (tertiary amine residue); this is why we decided to classify **278** as a phosphinite catalyst. It was first applied to the desymmetrization of *meso* 1,2-diols; good selectivities and yields were obtained, but required very high catalyst loadings of 30 mol % (Scheme 40).[144] This highly selective protocol was then applied to the desymmetrizations of *meso* 1,3- and 1,4-diols, and resulted in moderate to very good enantioselectivities of up to > 99 % (Scheme 40).[145] Catalyst **281** performed well in the kinetic resolution of *trans*-1,2-diols especially for hydrobenzoin (*S* = 525, Scheme 41). The use of **282** under otherwise the same conditions resulted in a poor enantioselectivity, which can be regarded as convincing evidence for the importance of the phosphinite unit (Scheme 41).[146]

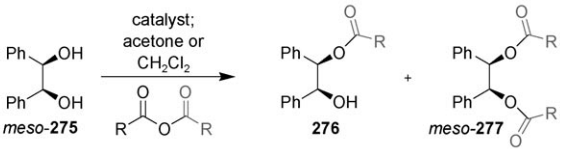
Table 9: Efficiency of catalyst **255 a** (Ar = 3,5-di[*t*Bu]Ph) in the kinetic resolution of allylic alcohols.



Entry	Substrate	*ee*(alcohol) [%]	*ee*(product) [%]	*S* value (*C*/*t*)	Entry	Substrate	*ee*(alcohol) [%]	*ee*(product) [%]	*S* value (*C*/*t*)
1	 **265**	78	63	10 (55 %/12 h)	6	 **270**	90	81	34[a] (53 %/7 h)
2	 **266**	67	82	21 (45 %/27 h)	7	 **271**	96	87	55 (53 %/72 h)
3	 **267**	42	45	4 (48 %/41 h)	8	 **272**	64	95	82[a] (40 %/25 h)
4	 **268**	46	74	11 (38 %/19 h)	9	 **273**	> 99	49	25[a] (67 %/46 h)
5	 **269**	90	88	49[a] (50 %/14 h)	10	 **274**	56	94	52 (38 %/46 h)

[a] Reaction in heptane solution.

Table 10: Desymmetrization of *meso* hydrobenzoin **275** catalyzed by **253** and **255**.

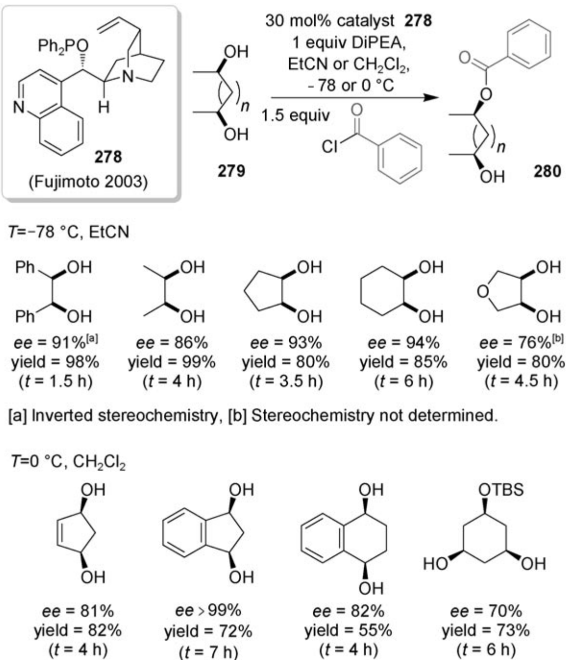


Entry	Cat.	Mol %	*t*	*T* [°C]	R	Solvent	*C* [%]	**276**/**277**	*ee*(**276**) [%]
1	**253 b** (R = Me, X = Me)	38	4 h	RT	C_6H_5	CH_2Cl_2	20	> 20:1	78
2	**253 c** (R = Me, X = *t*Bu)	41	1.5 h	RT	C_6H_5	CH_2Cl_2	20	> 20:1	87
3	**253 d** (R = Me, X = Ph)	35	17 h	RT	C_6H_5	CH_2Cl_2	32	> 20:1	87
4	**255 c** (3,5-$Me_2C_6H_3$)	5.5	10 min	RT	C_6H_5	CH_2Cl_2	61	9:1	65[a]
5	**255 a** (3,5-$t$$Bu_2C_6H_3$)	6	9.5 h	RT	*i*Pr	acetone	43	> 20:1	73[a]
6	**255 a** (3,5-$t$$Bu_2C_6H_3$)	4.1	5 min	RT	C_6H_5	CH_2Cl_2	64	5:1	61[a]
7	**255 b** (Ph)	12.4	2.2 h	RT	*i*Pr	acetone	40	NA[b]	81[a]
8	**255 b** (Ph)	12	17 min	RT	C_6H_5	CH_2Cl_2	58	33:1	69[a]
9	**255 b** (Ph)	12	26 h	−78	*i*Pr	acetone	8	> 20:1	88[a]
10	**255 b** (Ph)	9	72 h	RT	C_6H_5	acetone	98	1.1:1	93[a]
11	**255 b** (Ph)	10	22 h	−30	C_6H_5	CH_2Cl_2	97	2.6:1	94[a]

[a] Inverted stereochemistry. [b] NA = not available.

8. N-Heterocyclic Carbenes

Achiral acyl-transfer reactions promoted by stoichiometric amounts of carbenes have been known since 1994 (Bakhtiar and Smith).[147,148] Almost simultaneously, the research groups of Nolan and Hedrick reported the first carbene-catalyzed transesterification reactions.[147,149] In 2004 Suzuki et al. published the first example of N-heterocyclic carbenes as catalysts for enantioselective acylative kinetic resolutions.[150] Carbene **286** catalyzed the kinetic resolution of racemic secondary aryl alkyl alcohols **26**, in the presence of vinyl acetate as the electrophile, with moderate selectivities (up to 58 % *ee* for the product and 37 % *ee* for the starting material at conversions between 36 % and 85 %; $S \leq 4$); the carbenes were generated from their precursor salts **285** using *t*BuOK.[150] In 2005 Maruoka and co-workers tested acetic anhydride and various vinyl acetates as electrophiles in the kinetic resolution of aryl alkyl alcohols catalyzed by (*R*,*R*)-**286 a** and (*R*,*R*)-**286 c**. The use of vinyl diphenylacetate as the electrophile led to significantly increased selectivities. Maruoka and co-workers employed this approach to resolve aryl alkyl and allyl alkyl alcohols with the catalysts (*R*,*R*)-**286 a** and (*R*,*R*)-**286 c** (*S* values up to 80; Table 11, entry 2).[151] In addition to the nucleophilic mechanism shown in Scheme 42,



Scheme 40. Efficiency of catalyst **278** in the desymmetrization of *meso* diols **279**.

an alternative general base-catalyzed pathway was proposed by Movassaghi and Schmidt.[152]

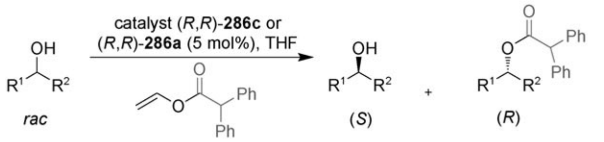
9. Conclusions and Outlook

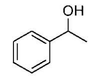
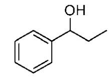
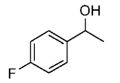
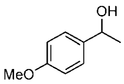
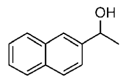
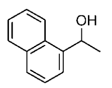
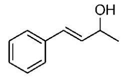
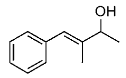
All the six organocatalyst families presented include catalysts or catalyst combinations (e.g., DMAP + chiral thiourea) that are highly efficient in the enantioselective acylation of alcohols, amines, and thiols. Many of the shown transformations can effectively compete with enzymatic and metal-catalyzed approaches.

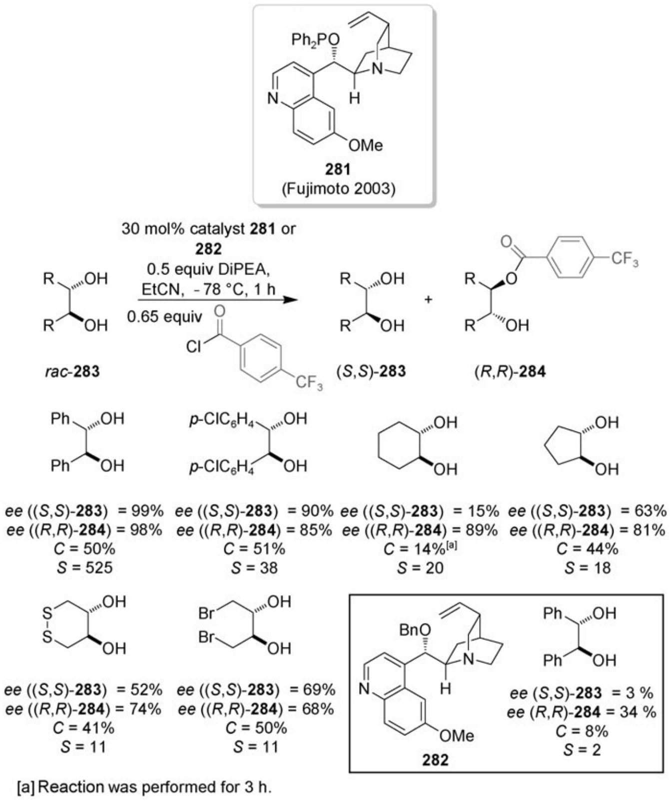
The group of chiral DMAP/PPY-based catalysts is dominated by the planar-chiral catalyst **22** of Fu et al., which provides excellent selectivity for a wide range of acylations. The families **7** (Spivey et al.), **12** (Yamada et al.), and **14** (Fuji and Kawabata et al.) also proved to be highly effective in selected transformations. Remarkably, in all cases high selectivity could only be achieved with substrates bearing aromatic moieties, which led to the conclusion that π–π interactions play an important role. With the combination of DMAP and a chiral thiourea for selective acyl transfer, Seidel et al. opened up new possibilities for using the highly active but achiral DMAP moiety by introducing stereoselectivity through complexation of the acylium counterion with a chiral thiourea derivative.

The biomimetic acyl-transfer systems introduced by Miller et al. differ from the other catalyst groups. Peptide or peptide-like catalysts (molecular weights typically between 500 and 1000 $\mathrm{g\,mol^{-1}}$) are synthetically available through well-established solid-phase or solution-phase protocols and can be easily diversified. Readily assembled short peptide

Table 11: Performance of chiral carbenes **286c** and **286a** as catalysts in the kinetic resolution of aryl alkyl or allyl alkyl alcohols.

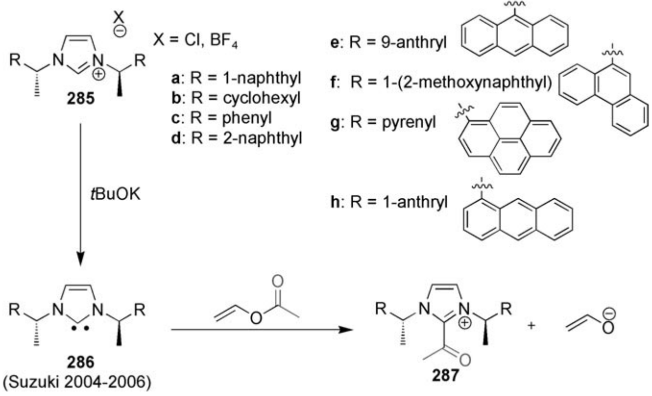


Entry	Substrate		Catalyst	Conditions: T [°C], *t* [h]	Ester: *ee* [%], (yield [%])	*S value*
1		**38a**	(*R*,*R*)-**286c**	−78, 3	93 (33)	46
2			(*R*,*R*)-**286a**	−78, 3	96 (32)	80
3		**38b**	(*R*,*R*)-**286a**	−78, 0.5; −20, 3.5	92 (33)	38
4		**40**	(*R*,*R*)-**286c**	−78, 3	90 (35)	33
5			(*R*,*R*)-**286a**	−78, 4	91 (39)	42
6		**111**	(*R*,*R*)-**286a**	−78, 2; −40, 3	94 (30)	48
7		**181**	(*R*,*R*)-**286c**	−78, 1.5	93 (35)	46
8			(*R*,*R*)-**286a**	−78, 6	95 (27)	56
9		**43**	(*R*,*R*)-**286a**	−78, 4; −40, 0.5	94 (29)	47
10		**182**	(*R*,*R*)-**286c**	−78, 3.5	84 (27)	16
11		**266**	(*R*,*R*)-**286c**	−78, 1; −40, 2	87 (33)	22



[a] Reaction was performed for 3 h.

Scheme 41. Efficiency of catalysts **281** and **282** in the kinetic resolution of *rac*-**283**.



Scheme 42. Proposed in situ formation of chiral carbenes **286** from precursors **285** and the formation of the catalytically active ion pair **287**.

catalyst screenings for selective acyl-transfer reactions make this catalyst type particularly promising and provide a link to biochemical transformations. A clear example of this is the frequently observed high substrate specificities of oligopeptide catalysts. The catalyst–substrate interactions in this group are mainly dominated by hydrogen-bonding interactions, and the catalysts as well as the substrates often require hydrogen-bond acceptor or donor groups. The catalysts of Miller, Ishihara, Qu, and Schreiner fulfill many of these requirements, and are highly efficient in the presented reactions—often without the need for an additional base. The field of selective biomimetic catalysis in general as well as for selective acyl-transfer reactions is growing and shows high potential.

The highly selective desymmetrizations of *meso* 1,2-diols with the di(*tert*-amine) catalysts of Oriyama et al. (**217** and **218**) as well as Kündig et al. (**228** and **229**) are rare cases where a benzoyl group is selectively transferred and acid chlorides are used as electrophiles. For most of the other presented catalysts, anhydrides of alkanoic acids are the preferred electrophiles. Whereas chiral amine-based catalysts are rarely used for acyl transfers, chiral amidines have been intensively studied since their introduction by Birman et al. in 2004. BTM (**167**) and HBTM (**169**), in particular, proved to be highly efficient in several kinetic resolution and desymmetrization reactions with alcohols as substrates. The substrate scope and the proposed transition structures for these transformations (Scheme 30) and computational studies (Scheme 31) emphasize the π–π interactions responsible for the selective acyl transfer. Apart from the chiral Steglich esterification from Schreiner et al. (Scheme 24), the application of catalyst **167** (Shiina et al.) to the acylative kinetic resolution of racemic alcohols are rare examples that allow the direct use of acids as the electrophiles. The kinetic resolution of racemic secondary aryl alkyl thiols with concomitant desymmetrization of a *meso* anhydride presented by Connon et al. was the first organocatalytic approach to resolve racemic thiols.

The group of phosphine-based catalysts is dominated by Vedejs catalyst class **255**, which showed high efficiency in kinetic resolution and desymmetrization reactions. Again, high selectivity could only be achieved with unsatured alcohols as substrates, thus emphasizing the formation of π–π interactions between the catalyst and substrate. Often the free phosphine catalysts are not air stable and are prepared in situ from air-stable precursors so that the reactions have to be performed under *inert* atmospheres. This is possibly the reason for the small numbers of publications in this area over the last five years. The combination of phosphinite-based catalysts **278** and **281** (highly efficient in the desymmetrization and kinetic resolution of diols) of Fujimoto et al. and benzoyl or *para*-trifluoromethylbenzoyl chloride as electrophiles requires very high catalyst loadings of 30 mol %.

The small family of chiral-carbene-catalyzed acylations (to the best of our knowledge there are only three publications to date) was introduced by Suzuki and co-workers in 2004. The best results were realized with carbenes and aromatic substrates (π–π interactions). The carbenes form in situ by deprotonation of their precursor salts.

One of the future goals in the field of organocatalytic acylations is the identification and application of new active and selective catalysts. Enantioselective organocatalytic acyl transfer is a powerful tool for the enantioseparation of racemic alcohols, thiols, and amines or the desymmetrization of *meso* compounds, especially in cases where organocatalysis is superior to metal-based and enzymatic approaches. Although there are many procedures for secondary alcohols, advances are still required for tertiary alcohols, and especially amines as well as thiols. In contrast to the organocatalytic transfer acylations, organocatalytic phosphorylations,[153] silylations,[154] and sulfonylations[155] remain largely unexplored.

The selective and direct addressing of different OH groups in important molecules such as carbohydrates or glycopeptide antibiotics (e.g., vancomycin) is a contemporary challenge, and thus nucleophilic organocatalysis seems to be a promising approach in this area. Only a small number of examples of chemo- and regioselective acylations of monosacharides and carbohydrates are known (and partially noted in this Review).[92–94,156] These examples and the impressive desymmetrization by Miller and co-workers[90,91] (Schemes 21 and 22) give hope that, for example, the various OH groups of vancomycin can be selectively addressed directly.

The identification of new catalysts (for any reaction) is generally challenging. Most new catalysts are identified by trial and error or by time-consuming screening of catalysts. An efficient catalyst for one particular transformation is often highly substrate-specific and not useful for other substrate classes. Of course, this implies high chemoselectivity, which is, however, often not desirable in the chemical laboratory, where the development of robust and broadly applicable methods is sought. A better understanding of the mechanisms of catalyzed acyl transfer is, therefore, highly desirable. New mechanistic insights obtained by using computational or analytical methods are likely to lead to the rational design of new catalysts.

10. Abbreviations

Aib	α-aminoisobutyric acid (α-methylalanine)
B3LYP	Becke 3-parameter (exchange), Lee, Yang, and Parr (correlation); hybrid functional; density functional theory
B98	Becke's 1998 revisions to the B97 hybrid functional density functional theory implementation
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BTM	benzotetramisole
Bu = *n*Bu	*n*-butyl
Bz	benzoyl
*t*Bu	*tert*-butyl
*t*BUOK	potassium-*tert*-butoxide
C	conversion
Cha	cyclohexylalanine
m-CPBA	*meta*-chlorobenzoic acid
β-CD	β-cyclodextrin
DABCO	1,4-diazabicyclo[2.2.2]octane
DHIQ	1,2-dihydroimidazo[1,2-*a*]quinoline
DMAP	4-dimethylaminopyridine
D*i*PEA	*N*,*N*-diisopropylethylamine
GC	gas chromatography
^{A}Gly	adamantyl glycine, 3-aminoadamantane carboxylic acid
HBTM	homobenzotetramisole
Hex = *n*Hex	*n*-hexyl
HPLC	high-pressure liquid chromatography
MCA	methyl cation affinity
Moc	methyloxycarbonyl
MP2(FC)	second-order Møller–Plesset perturbation theory (frozen core)
MS	molecular sieves
ONIOM	our own *n*-layered integrated molecular orbital and molecular mechanics
*n*Pent	*n*-pentyl
PIP	2-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridine
PIQ	2-phenyl-2,3-dihydroimidazo[1,2-*a*]quinoline
PMBA	*para*-methoxybenzoic anhydride
PPY	4-pyrrolidinopyridine
Pr = *n*Pr	*n*-propyl
*i*Pr	isopropyl
Pro	proline
rac	racemic
S	Kagan's *S* value
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-piperidin-1-oxyl
Trityl	triphenylmethyl
Trt	trityl (triphenylmethyl)
Ts	toluene-4-sulfonyl (tosyl)
TS	transition state
Z	benzyloxycarbonyl

This work was supported by the Deutsche Forschungsgemeinschaft (SPP1179).

Received: September 30, 2010
Revised: December 14, 2010

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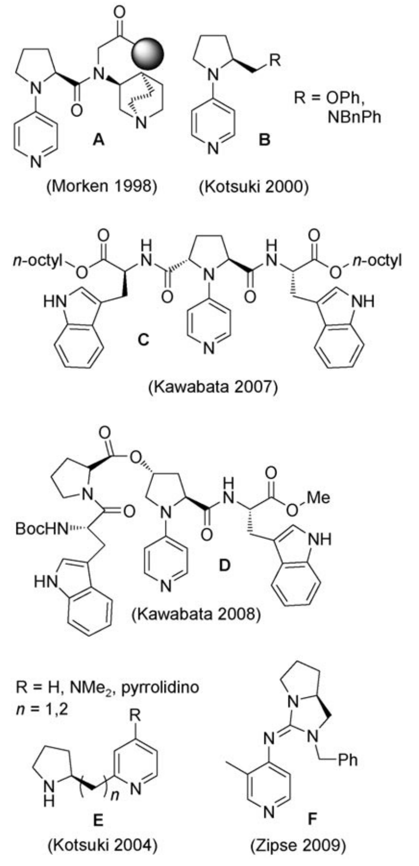

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