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Organocatalyzed Enantioselective Desymmetrization of Diols in the Preparation of Chiral Building Blocks

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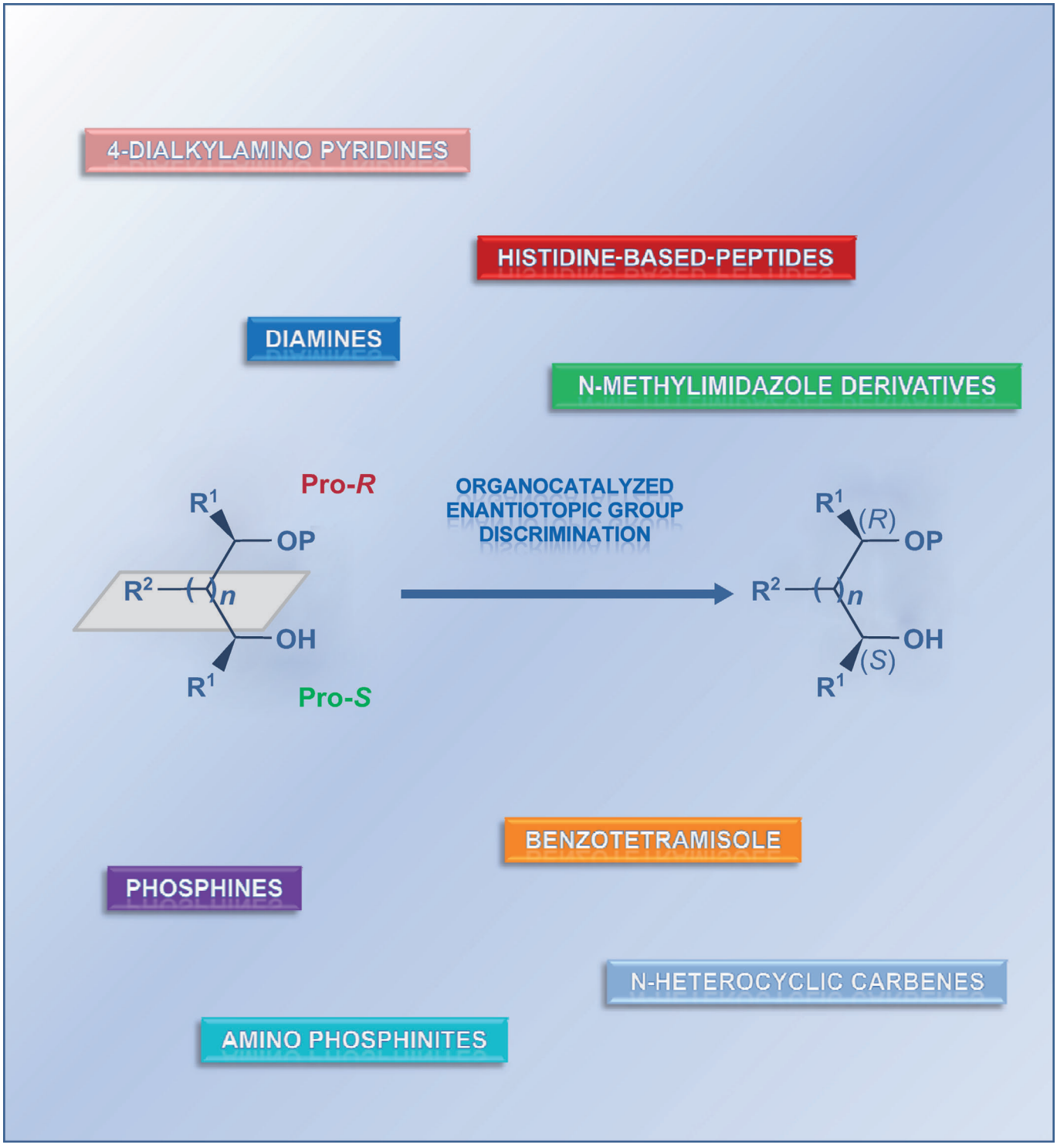


Abstract: Desymmetrization of diols is a powerful tool to the synthesis of chiral building blocks. Among the different approaches to perform discrimination between both enantiotopic hydroxyl groups, the organocatalytic approach has gained importance in the last years. A diverse range of organocatalysts has been used to efficiently promote this enantioselective transformation and this Minireview examines the different contributions in this field.

Keywords: asymmetric catalysis · desymmetrization · diols · enantioselectivity · organocatalysis

Introduction

Enantioselective desymmetrization[1] of prochiral and *meso*-compounds in general and diols (Figure 1) in particular is a powerful methodology for the preparation of chiral building blocks.[2] To perform such desymmetrization reactions, enzymatic procedures have been traditionally employed as a tool;[1d] however, their practical use is often hampered by several limitations as irreproducibility, substrate specificity, availability in only one enantiomeric form, acetyl migration which leads to racemization, and high cost among others.

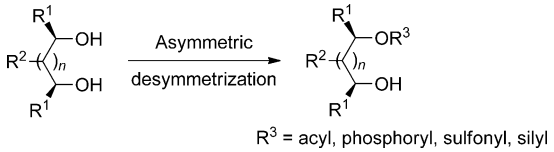


Figure 1. Asymmetric desymmetrization of diols.

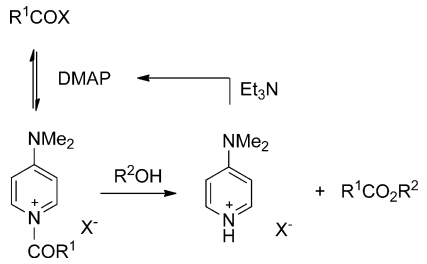
First non-enzymatic approximations to desymmetrization of diols were based on the use of chiral acyl chlorides[3] or other chiral acylating agents[4] to perform enantiodifferentiation. More recently metal-based[5] and metal-free[6] enantioselective catalysis have emerged as useful synthetic alternatives to this end and among them organocatalytic processes are the most attractive strategies from an ecological point of view.

The first desymmetrization of a *meso*-1,4-diol mediated by a chiral organic compound was described in 1985 by Duhamel et al.,[7] but it required a large excess of the chiral compound. Enantioselective benzoylation of *cis*-2-cyclopenten-1,4-diol was performed in the presence of different chiral tertiary amines and the highest *ee* (47%) was observed with the use of 200 mol% of *O*-phenylquinidine. Almost ten years later[8] Vedejs et al. reported on the use of chiral phosphines in the monoacylation of *meso*-1,2-diols. These first results using chiral phosphines as organocatalysts were quite disappointing, owing to low conversion and problems with diacylation and racemization under the reaction conditions.

Since then increasing research has being devoted to the development of efficient organocatalytic methods to perform this transformation. The purpose of this Minireview is to describe the most relevant achievements on organocatalyzed desymmetrization of prochiral and *meso*-diols by their enantioselective acylation, phosphorylation, sulfonylation, or silylation using organocatalysts with different structural features. The different contributions to the subject have been organized into sections according to the class of chiral compound used as organocatalyst.

Chiral 4-Aminopyridine Derivatives

4-Dimethylaminopyridine (DMAP) and its analogues have been used as catalysts in a large range of applications.[9] Their high nucleophilicity have converted them in highly effective catalysts for alcohol acylation. The currently accepted mechanism for this reaction (Scheme 1) involves the formation of an acylpyridinium cation/carboxylate ion pair by the attack of the catalyst to the acyl donor.[10] Transfer of the acyl group into the alcohol forms the ester and protonated DMAP, which is inactive. Catalyst regeneration requires the presence of a tertiary base in the reaction medium.



Scheme 1. Mechanism of DMAP-catalyzed alcohol acylation.

Chiral versions of DMAP[11] (Figure 2) have been designed to perform this reaction in an enantioselective manner and have been used as organocatalysts in the desymmetrization of diols.

In 1998 Fu et al. described[12] the first efficient organocatalyzed desymmetrization of chiral *meso*-1,5-diol **1** by using a planar-chiral derivative of 4-dimethylaminopyridine.[13] Just

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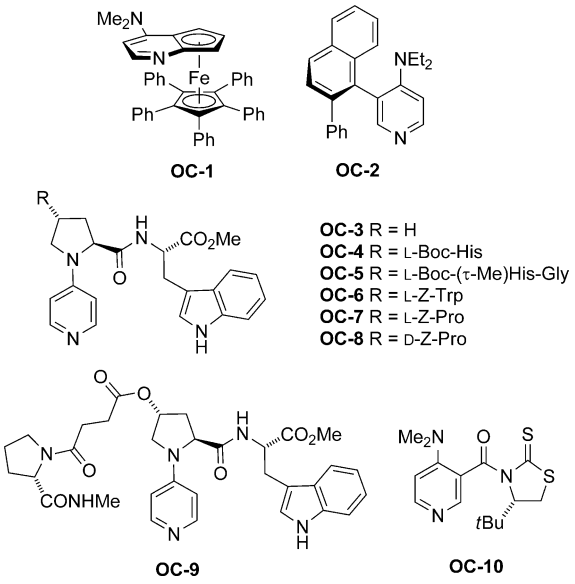
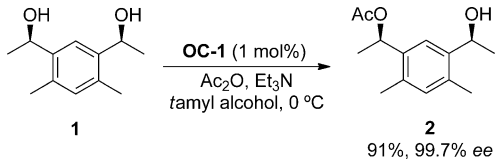


Figure 2. Chiral 4-dialkylaminopyridine derivatives used as organocatalysts in desymmetrization of diols.

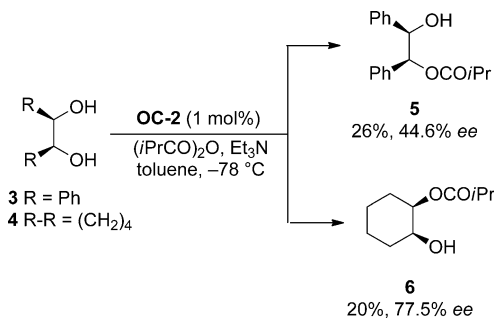
1 mol% of organocatalyst **OC-1** was enough to obtain the desymmetrized monoacetate (**2**) with high yield (91%) and an excellent enantioselectivity (99.7 *ee*) (Scheme 2).



Scheme 2. Enantioselective acetylation of *meso*-diol 1 using **OC-1** as an organocatalyst.

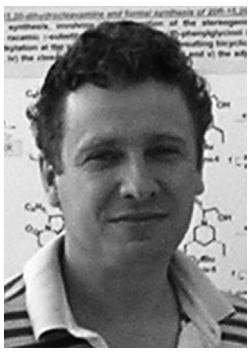
Axially chiral atropoisomeric biaryl 4-diethylaminopyridine **OC-2** showed a moderate efficiency in desymmetrization of *meso*-hydrobenzoin (**3**) and *cis*-cyclohexane-1,2-diol (**4**; Scheme 3).[14]

Chiral 4-pyrrolidinopyridine analogs **OC-3**–**OC-9** with different side chains were tested for desymmetrization of *cis*-

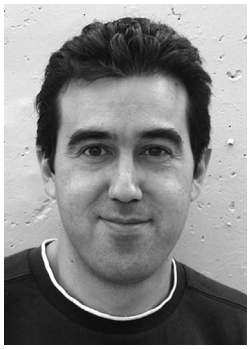


Scheme 3. Enantioselective acylation of *meso*-diols using **OC-2** as an organocatalyst.

María Dolores Díaz-de-Villegas graduated in Chemistry from the University of Zaragoza (Spain) in 1981. In 1985 she received her Ph.D. from the University of Zaragoza. After a period (1986–1988) as Assistant Professor at the University of Zaragoza, in 1989 she joined the Spanish Council for Scientific Research (CSIC) as Tenured Scientist. In 2001, she was promoted to a position of CSIC Research Scientist. Her research interests focus on the development of new methodologies in stereoselective synthesis and enantioselective organocatalysis.



José Antonio Gálvez was born in La Paul, Huesca (Spain) in 1963. He studied chemistry at the University of Zaragoza (Spain), where he obtained his Ph.D. in 1990. After a two-year period at the University of La Rioja (Spain) as Assistant Professor, he returned to the University of Zaragoza in 1993, where he was appointed Senior Lecturer in 1997. His current research interests focus on the asymmetric synthesis of biologically active compounds (alkaloids with a piperidine or pyrrolidine skeleton, azasugars, amino alcohols and amino acids) and the design of new organocatalysts and axially chiral ligands and their applications in asymmetric catalysis.

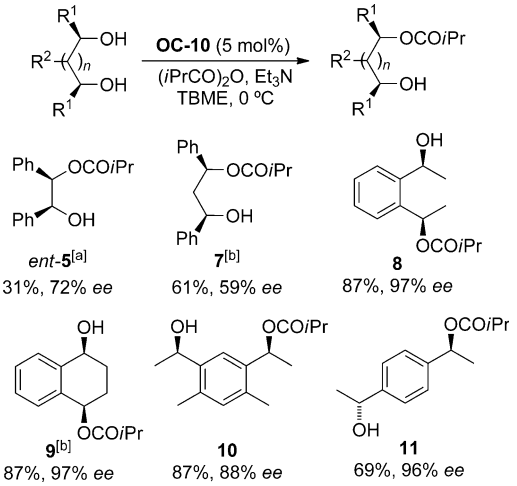


Ramón Badorrey received his Ph.D. in 2000 from the University of Zaragoza (Spain). In 1998 he took a predoctoral position at the Centro de Investigación y Desarrollo de Barcelona (Spain) under the supervision of Prof. G. Valencia. In 2003 he undertook a postdoctoral stay in the Stratingh Institute at the University of Groningen (The Netherlands) under the supervision of Prof. B. L. Feringa and in 2004 he joined the Dipartimento di Chimica G. Ciamician at the Bologna University (Italy) under the supervision of Prof. A. Umani-Ronchi. He is a Senior Lecturer at the University of Zaragoza and investigates the development of enantiopure nitrogen compounds that are easily tuneable for their evaluation as chiral organocatalysts in different enantioselective processes.

Pilar López-Ram-de-Viu, B.Sc. in chemistry at the University of Zaragoza (Spain) in 1987 and received her Ph.D. from the same university in 1991. Between 1992–1993 she took a postdoctoral position at the Conservatoire National des Arts et Métiers (CNAM) of Paris (France) under the supervision of Dr. L. Oliveros. After this period she joined the Department of Organic Chemistry at the University of Zaragoza, where she carried out teaching and research activities, first as Assistant Professor and later as Senior Lecturer. Her research interests focus on the synthesis of optically active compounds with potential biological activity in enantiomerically pure form, combining the use of different stereoselective synthetic strategies and resolution techniques.

cyclohexane-1,2- and *cis*-cyclohexane-1,3-diol by acylation with isobutyric anhydride.[15] In presence the of 5 mol% of catalyst, the reaction occurred with low to moderate enantioselectivity (20–65% *ee*) depending on the organocatalyst and the reaction conditions. Best enantioselectivities were usually obtained with *cis*-cyclohexane-1,2-diol as substrate, but its practical use was hampered by the low chemoselectivity of the reaction that led to the formation of a considerable amount of the corresponding diacylated compound.

More recently, asymmetric desymmetrization of *meso*-1,*n*-diols ($n=2$–6) has been achieved by acylation with isobutyric anhydride in the presence of 5 mol% of chiral DMAP derivative **OC-10**.[16] Enantioselectivities were very different (59–97% *ee*) depending on the distance and spatial disposition of both hydroxyl groups in the substrate (Scheme 4) and, in some cases, the formation of a considerable amount of the corresponding diacylated compound, seriously deteriorated monoester isolated yields.

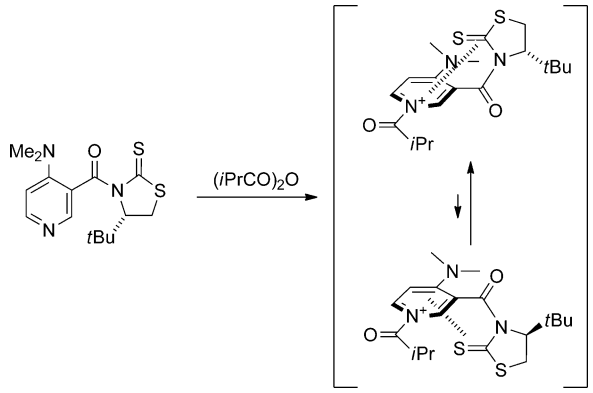


Scheme 4. Enantioselective acylation of *meso*-diols using **OC-10** as an organocatalyst. [a] THF as solvent. [b] Absolute configuration was determined.

N-Acylation of the organocatalyst induces self-complexation through an interaction between the pyridinium ring and the thiocarbonyl group. Conformer distribution calculated by the AM1 method supports the high preference for one conformer over the other as depicted in Scheme 5. The conformation switch process induced by N-acylation would play an important role in enantiotopic group differentiation.

Chiral Diamines

Chiral amines have played a central role in the area of asymmetric catalysis by chiral nucleophiles[17] giving rise to excellent results in catalyzing a broad range of asymmetric transformations. In this context chiral tertiary diamines (Figure 3) have proven to be appropriate organocatalysts to perform diol desymmetrization reactions.



Scheme 5. Self-complexation of **OC-10** induced by N-acylation.

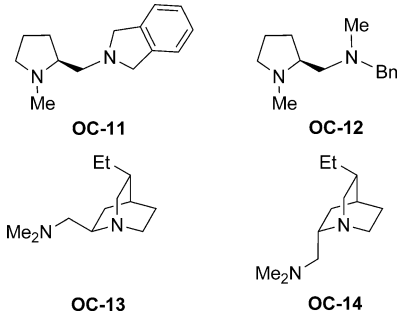


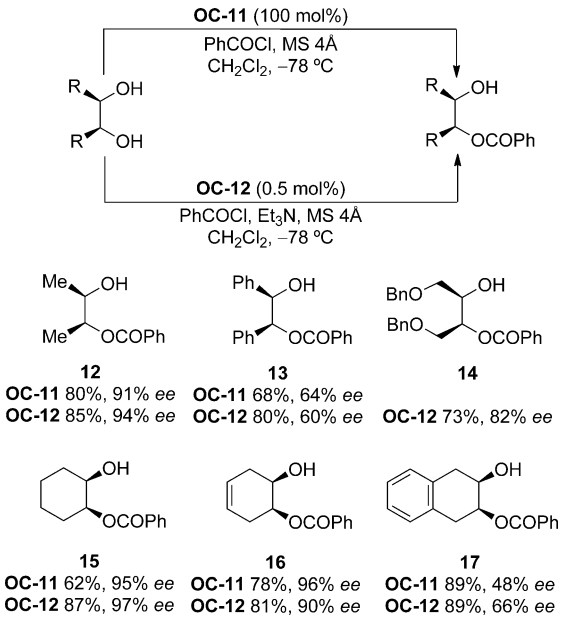
Figure 3. Chiral diamines used as organocatalysts in desymmetrization of diols.

Oriyama et al. described the efficient organocatalyzed desymmetrization of a variety of *meso*-diols by enantioselective benzoylation in the presence of chiral diamines **OC-11** and **OC-12** derived from (*S*)-proline.[18]

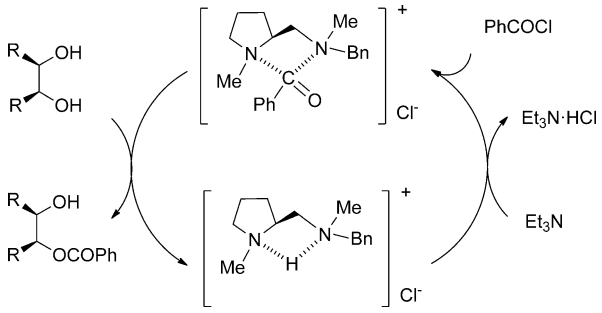
Initial studies were performed with 100 mol% of the chiral diamine **OC-11**, which catalyzed desymmetrization of several *meso*-1,2-diols with moderate to high enantioselectivities. It was observed that reactions were accelerated by the addition of MS 4 Å and monobenzoates were obtained in quite useful yields. High enantioselective benzoylation of *meso*-1,2-diols also occurred in the presence of just 0.5 mol% of chiral diamine **OC-12** and an equimolecular amount triethylamine (Scheme 6).

The exact mechanism for acyl transfer with this type of compounds is not clear, but the formation of a rigid chiral *N*-acyl ammonium salt by coordination of the two nitrogen atoms of the chiral diamine to the carbonylic carbon of benzoyl chloride in a bidentate fashion has been proposed (Scheme 7).[18b] The rigidity of this intermediate would play an important role in enantiotopic group discrimination. The presence of a tertiary amine in the reaction medium is required to trap hydrogen chloride.

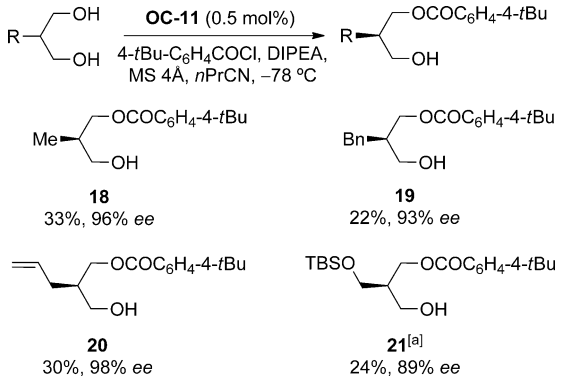
Catalyst **OC-11** probed to be useful in desymmetrization of 2-substituted-1,3-propanediols[19] (Scheme 8) and this synthetic strategy has been used in the desymmetrization of *cis*-



Scheme 6. Enantioselective acylation of *meso*-1,2-diols using **OC-11** or **OC-12** as organocatalysts.

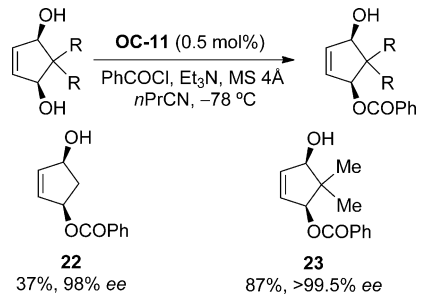


Scheme 7. Proposed mechanism for acyl transfer using tertiary diamines as organocatalysts.



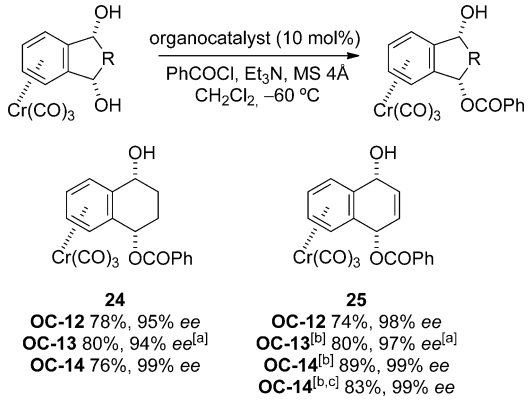
Scheme 8. Enantioselective acylation of 1,3-diols using **OC-11** as an organocatalyst. [a] CH_2Cl_2 as solvent.

2-cyclopentene-1,4-diol (Scheme 9) directed to the synthesis of (*R*)-4-benzoyloxy-2-cyclopenten-1-one.[20]



Scheme 9. Enantioselective acylation of *meso*-2-cyclopentene-1,4-diols using **OC-11** as an organocatalyst.

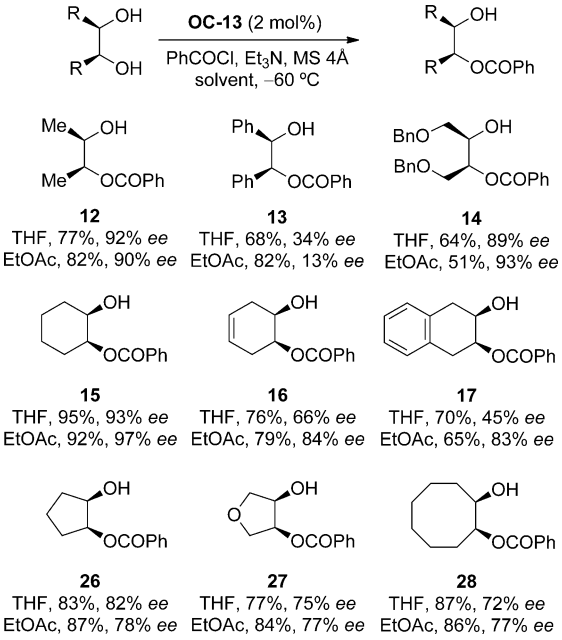
Kündig et al.[21] tested desymmetrization of *meso*-1,4-diol complexes derived from $[Cr(CO)_3(\eta^6$-5,8-naphthoquinone)] and $[Cr(CO)_3(\eta^6$-1,2,3,4-tetrahydronaphthalene-5,8-dione)] by benzoylation in the presence of 10 mol% of chiral diamine **OC-12**. The reaction proceeded smoothly and provided the chiral monobenzoate with good isolated yields and an excellent enantiomeric excess. These results were improved (Scheme 10) with the use of diamines **OC-13** and



Scheme 10. Enantioselective acylation of *meso*-1,4-diol chromium complexes using **OC-12**, **OC-13**, or **OC-14** as organocatalysts. [a] Opposite enantiomer. [b] −40 °C. [c] 2 mol%.

OC-14 (Figure 3) derived from pseudo-enantiomeric cinchonine and cinchonidine even in the presence of a reduced amount of the organocatalyst (2 mol%).

Cinchonine- and cinchonidine-derived diamines **OC-13** and **OC-14** were extremely efficient in the desymmetrization of *cis*-cyclohexane-1,2-diol (**4**).[22] Once optimized, the procedure has been applied to desymmetrization of various *meso*-1,2-diols (Scheme 11). When desymmetrization was conducted in the presence of 2 mol% of chiral amine **OC-13** at −60 °C in THF or ethyl acetate, diacylation was minimized. Depending on the substrate and reaction conditions the corresponding chiral benzoates were obtained with good isolated yields (51–95%) and low to excellent enantioselectivities (up to 97%).



Scheme 11. Enantioselective acylation of *meso*-1,2-diols using **OC-13** as an organocatalyst.

Histidine-Based Peptides

Short peptides, capable to adopt a well-defined secondary structure and suitable for fine-tuning of reactivity and selectivity by replacing single amino acid residues, have found wide application as catalysts in asymmetric synthesis.[23] In this context small π-methylhistidine-containing oligopeptides (Figure 4) have proven to be effective organocatalysts to

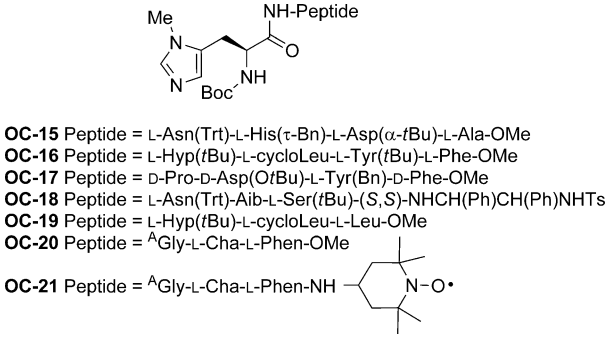
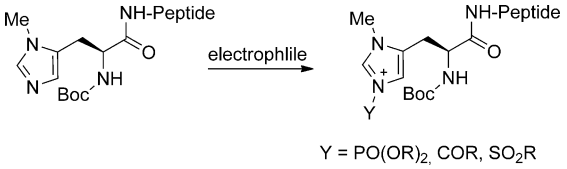


Figure 4. Histidine based peptides used as organocatalysts in desymmetrization of diols.

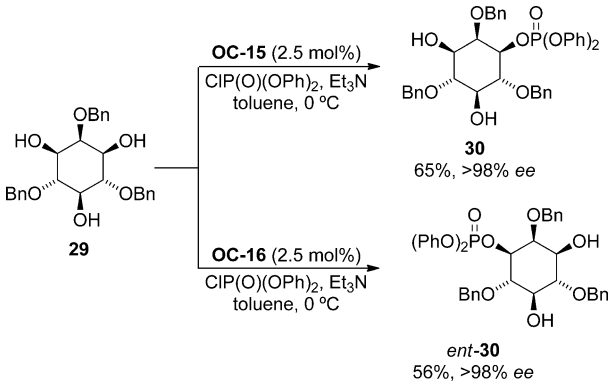
perform desymmetrization of diols by enantioselective phosphorylation, acylation or sulfonylation.

In analogy to histidine-dependent kinases, reaction of the phosphoryl, acyl, or sulfonyl group to alcohols using these histidine oligopeptide organocatalysts is thought to proceed through an *N*-methylimidazolium intermediate generated by nucleophilic attack of the imidazole moiety on the electrophile (Scheme 12).[24]



Scheme 12. Formation of *N*-methylimidazolium intermediates from histidine-based peptides.

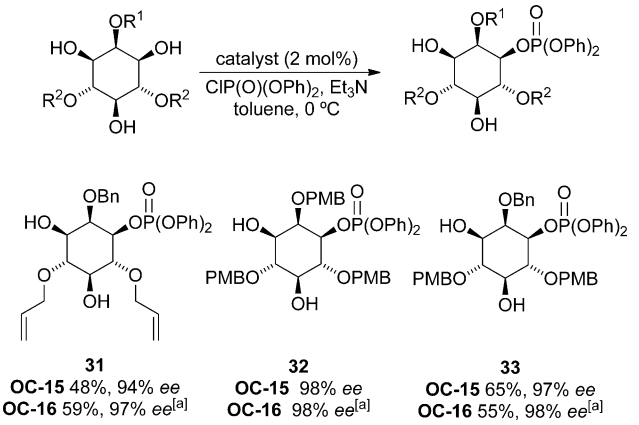
Several peptide libraries based on modified histidine residues were tested by Miller et al. as organocatalysts in the regio- and enantioselective monophosphorylation of *myo*-inositol derivative **29**.[25] This research led to the development of complementary peptide organocatalysts **OC-15** and **OC-16** for the enantiodivergent synthesis of D-*myo*-inositol-1-phosphate **30** and D-*myo*-inositol-3-phosphate **31** (Scheme 13). When the reaction was performed in toluene



Scheme 13. Enantioselective monophosphorylation of *myo*-inositol derivative **29** using **OC-15** or **OC-16** as organocatalysts.

at 0 °C using diphenylchlorophosphate as the phosphorylating reagent and in the presence of 2.5 mol % of peptide **OC-15** and triethylamine, enantiomerically pure compound **30** (>98 % *ee*) was obtained in 65 % isolated yield. Using 2.5 mol % of peptide **OC-16** as organocatalyst enantiomerically pure compound *ent*-**30** (>98 % *ee*) was obtained in 56 % isolated yield. Both catalysts were highly active and selective when toluene was used as a solvent. With **OC-15** enantioselectivity was not substantially altered when the reaction was conducted in solvents with different dielectric constants, Et_2O, CH_2Cl_2, THF, or CH_3CN. In contrast, with **OC-16** enantioselectivity was highly dependent on the reaction medium. This phenomenon has been attributed to the different robustness of the secondary structure of both peptides in solvents of varying polarities. Compounds **30** and *ent*-**30** have been used as intermediates in the synthesis of deoxy-*myo*-inositol phosphates for the study of ligand–receptor interactions.[26]

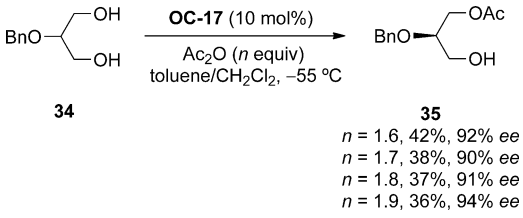
To obtain other suitable intermediates for the synthesis of inositol polyphosphates and complex molecules with unsaturated side chains, *myo*-inositol derivatives with various protecting groups have been screened as substrates in desym-



Scheme 14. Enantioselective monophosphorylation of *myo*-inositol derivatives using **OC-15** or **OC-16** as organocatalysts. [a] Opposite enantiomer.

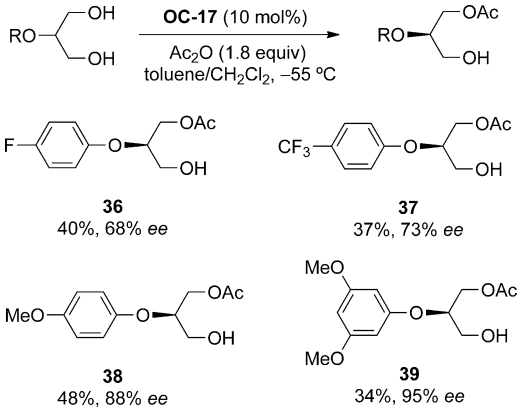
metrization by enantioselective phosphorylation in the presence of **OC-15** and **OC-16**.[27] The corresponding monophosphates were obtained with high enantioselectivity (94–98% *ee*) and quite useful yields (Scheme 14). Compound *ent*-**33** was the starting material in the total synthesis of several inositol polyphosphates[27] and from **33** and *ent*-**33** phosphatidylinositol derivatives with arachidonate side chains have been obtained.[28]

Extensive screening of libraries of peptides has allowed the identification of other catalytically active histidine-derived peptides, which has resulted in the optimization of organocatalysts to perform desymmetrization of diols by enantioselective acylation. Acetylation of 2-*O*-benzylglycerol (**34**) with acetic anhydride, using 10 mol% of **OC-17** as organocatalyst, provided the corresponding monoacetate **35** with an enantioselectivity and yield that depended on the amount of acylating agent (Scheme 15).[29]



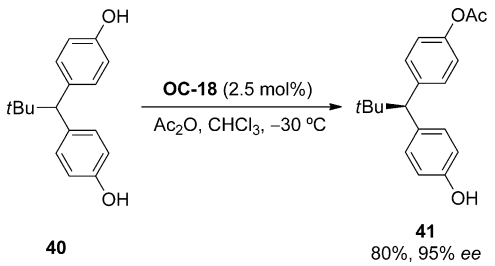
Scheme 15. Enantioselective monophosphorylation 2-*O*-benzylglycerol **34** using **OC-17** as an organocatalyst.

The ratio mono/diacetate also depended on the amount of acylating agent and an increase in the amount of acetic anhydride led to an increase in the enantiopurity of the monoacetylated compound with a concomitant increase in the amount of diacetylated compound. When the amount of acetic anhydride was in the range 1.6–1.9 equivalents compound **35** with >90% *ee* was isolated in 36–42% yield. Substitution on the 2-*O*-benzyl group did not improve these results (Scheme 16).



Scheme 16. Enantioselective monophosphorylation glycerol derivatives using **OC-17** as an organocatalyst.

Peptide **OC-18** has shown an impressive performance in desymmetrization of bis(phenol) **40** under optimized reaction conditions,[30] which involved the use 2.5 mol% of catalyst in chloroform at −30 °C (Scheme 17).

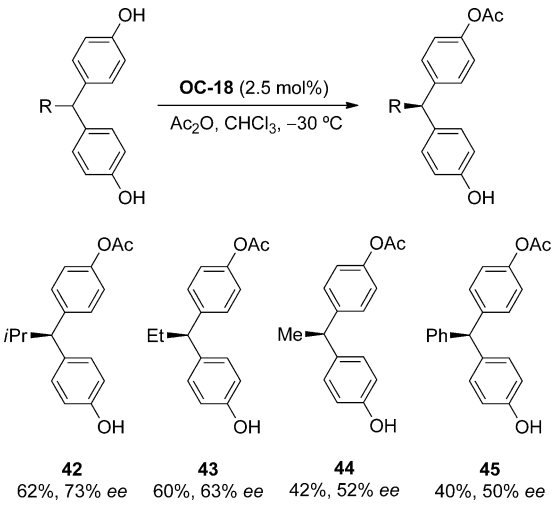


Scheme 17. Enantioselective acetylation of bis(phenol) **40** using **OC-18** as an organocatalyst.

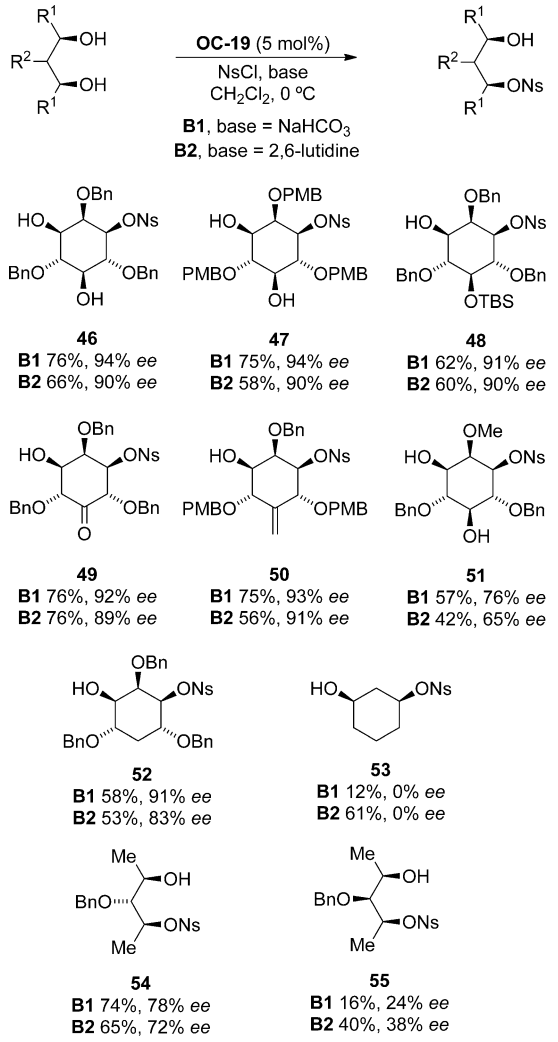
Reduction of the steric bulk of the alkyl substituent produced a decrease in the enantioselectivity of the reaction (Scheme 18) and also led to the formation of the corresponding diacetate in some extent.

Histidine-derived peptides have proven to be also useful in desymmetrization of *meso*-1,3-diols through enantioselective monosulfonylation.[24] In this case peptide **OC-19** showed the best performance. Under optimized reaction conditions, which consisted in performing the reaction at 0 °C in the presence of 5 mol% of peptide, using *p*-nitrobenzenesulfonyl chloride as the sulfonylating agent, and using a biphasic system of saturated aqueous $NaHCO_3/CH_2Cl_2$ (1:2 v/v) or 2,6-lutidine in CH_2Cl_2 as base/solvent combination, *myo*-inositol derivatives and other related compounds were monosulfonylated with good yields and enantioselectivities. In general with the biphasic system yields and enantioselectivities were better. Monosulfonylation of simpler cyclic substrates and acyclic 1,3-diols led to worse results (Scheme 19).

Schreiner et al. have described[31] a new approach to desymmetrization of *meso*-diols by enantioselective acylation using histidine-derived peptide **OC-20** containing an ada-

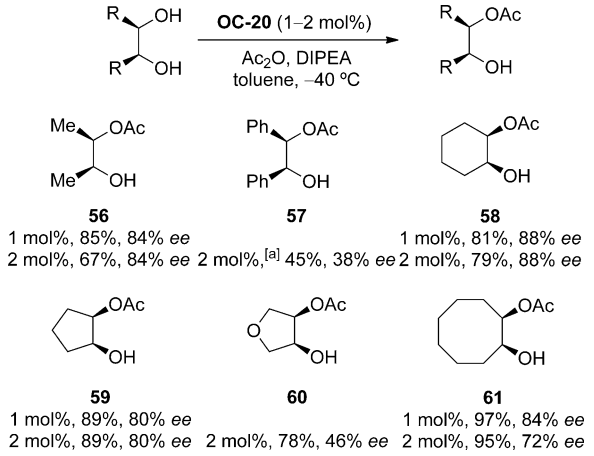


Scheme 18. Enantioselective acetylation of bis(phenols) using **OC-18** as an organocatalyst.



Scheme 19. Enantioselective monosulfonylation of *meso*-1,3-diols using **OC-19** as an organocatalyst.

mantane amino acid. To avoid racemization of the desymmetrized compound due to acyl migration during workup, the authors combined the acyl transfer step with an in situ oxidation of the obtained monoacyl derivatives. The protocol that lead to an optimized result in enantioselective acyl transfer involved the performance of the reaction with acetic anhydride in the presence of *N*,*N*-diisopropylethylamine (DIPEA) as base and 1–2 mol% of **OC-20** in toluene at −40 °C (Scheme 20). Subsequent addition of 60 mol% of



Scheme 20. Enantioselective acetylation of *meso*-diols using **OC-20** as an organocatalyst. [a] −20 °C.

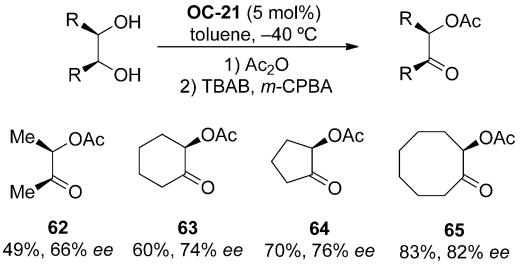
(2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), eight equivalents of *meta*-chloroperoxybenzoic acid (*m*-CPBA), and 30 mol% tetrabutylammonium bromide to the reaction mixture led to the corresponding α-acetoxy ketones in good isolated yields and without erosion in enantioselectivity. It is worth mentioning that absolute configuration of compound obtained in monoacetylation of *cis*-cyclohexane-1,2-diol using **OC-20** was correctly predicted by Shinisha and Sunoj on the basis of the relative energies of substrate and chiral peptide complexes calculated using DFT.[32]

The multicatalyst system **OC-21** has been designed to perform one pot desymmetrization/oxidation of *meso*-diols.[33] With this catalyst oxidation step occurred under milder conditions than in the separate protocols. Under optimized reaction conditions yields and selectivities in desymmetrization of several *meso*-diols are generally good (Scheme 21).

N-Methylimidazole Derivatives

Several compounds containing an *N*-methyimidazole moiety (Figure 5) have been designed to be used as chiral organocatalytic agents in the desymmetrization of diols.

To perform direct conversion of prochiral diols into chiral silyl ethers by an enantioselective silylation reaction chiral organocatalysts have been designed taking into account that appropriate compounds should contain a Lewis basic moiety, capable to increase the electrophilicity of silyl halide



Scheme 21. Enantioselective acetylation of *meso*-diols using **OC-20** as an organocatalyst.

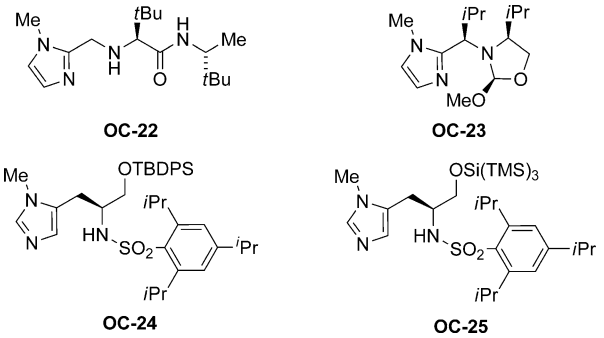


Figure 5. *N*-Methylimidazole derivatives used as organocatalysts in desymmetrization of diols.

reagent, and a group that could be involved in hydrogen bonding, to establish substrate–catalyst binding. Compound **OC-22**, which contains an *N*-methylimidazole moiety (Figure 5), fulfills these requirements and has found application as organocatalysts in desymmetrization of diols by enantioselective silylation.[34]

Highly enantioselective silylation of *meso*-1,2-diols has been achieved in THF at low temperature with the use of *tert*-butyldimethylsilylchloride and in the presence of DIPEA and 20–30 mol% of **OC-22** (Scheme 22).

This transformation has been extended to enantioselective monosilylation of 1,3-diols. With this class of substrates enantioselectivities are usually lower (Scheme 23).

In this case the formation of a transition state has been proposed[34] (Figure 6) in which the imidazole moiety of **OC-22** serves as a donor ligand to the silicon atom, promoting re-distribution of electron density and enhancement of silicon electrophilicity. Binding of the substrate to two Lewis basic binding sites in the catalyst—a secondary amine and

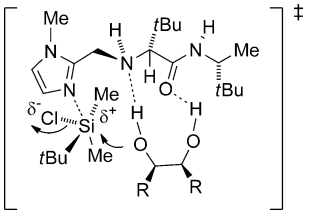
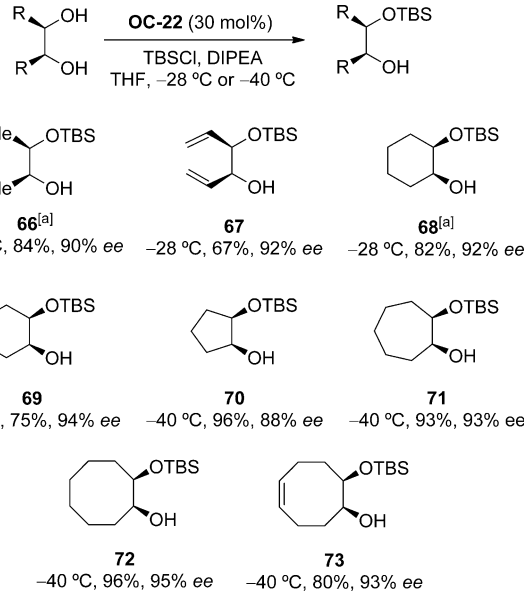
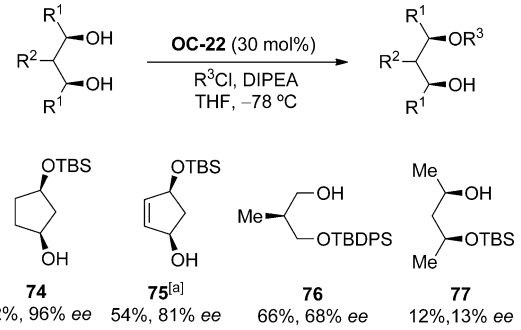


Figure 6. Proposed transition state model for enantioselective silylation of diols.



Scheme 22. Enantioselective silylation of *meso*-1,2-diols using **OC-22** as an organocatalyst. [a] 20 mol%.



Scheme 23. Enantioselective silylation of 1,3-diols using **OC-22** as an organocatalyst. [a] 20 mol%.

an amide oxygen atom—through hydrogen-bond interactions leads to the preferential silylation of one enantiotopic alcohol.

Variations in catalyst structure that difficult substrate–catalyst association by hydrogen-bonding led to inefficient catalyst.[34a] Variations on the [(1-methyl-1*H*-imidazol-2-yl)methyl]amino moiety (**OC-26** to **OC-29**, Figure 7) caused the complete loss of activity of the catalyst used to obtain compound **75** (for structure see Scheme 23). Variations on the 3,4,4,-trimethylpentanoyl moiety (**OC-30** to **OC-33**, Figure 7) caused a considerable decrease in the activity and enantioselectivity of the catalyst used to obtain compound **75**.

Compound **OC-22** also behaved as a very effective organocatalyst in enantioselective monosilylation of 1,2,3-triols.[35] When the steric demand of the central carbon substituent decreased, the enantioselectivity also decreased (Scheme 24). A reversal of selectivity was observed when the central carbon substituent was a methyl substituent,

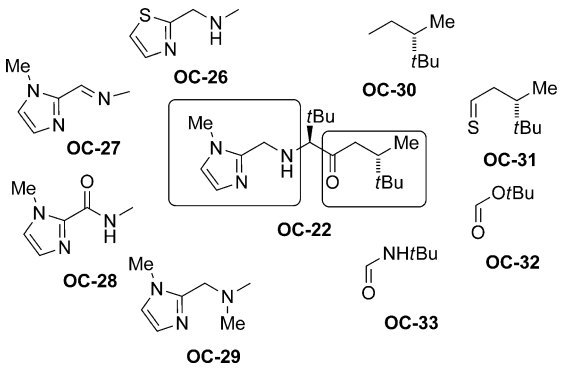
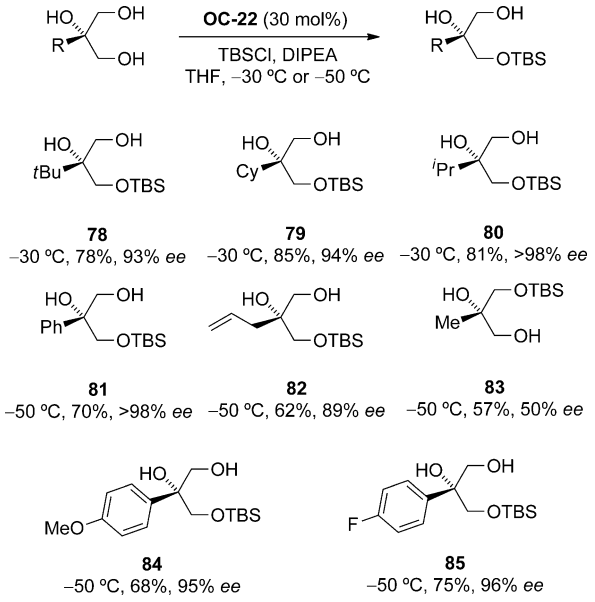


Figure 7. Structurally modified organocatalyst tested in synthesis of compound **75**.

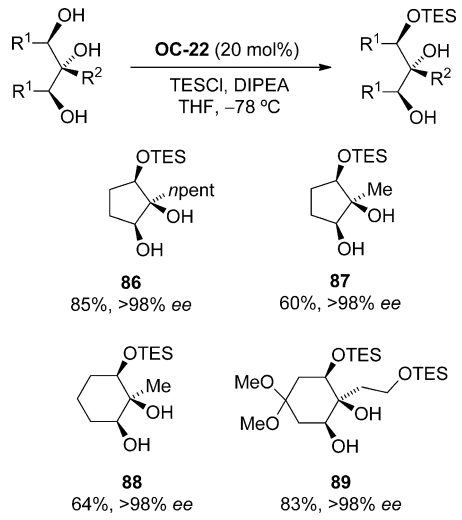


Scheme 24. Enantioselective silylation of acyclic 1,2,3-diols using **OC-22** as an organocatalyst.

which has been attributed to the smaller size of the methyl substituent compared to the hydroxymethylene moiety.

Cyclic *meso*-1,2,3-triols are also adequate substrates for this transformation. In this case a less sterically demanding silylating agent was used to achieve maximum efficiency in enantioselective monosilylation (Scheme 25). Enantiomerically pure **90**, obtained in 83% yield, has been used as intermediate in total syntheses of cleroindicins D, F, and C.[35]

To explain the observed enantioselectivities a different transition-state model (Figure 8) has been proposed for acyclic or cyclic triols.[35] For acyclic triols substrate–catalyst binding with the large substituent away from the amino acid based structure, which minimizes unfavorable steric repulsion, is consistent with the higher enantioselectivities observed in desymmetrization of substrates with a large substituent at C_2. In contrast, for cyclic triols the steric course of the reaction might be directed by substrate-catalyst association in an *exo* mode.



Scheme 25. Enantioselective silylation of cyclic *meso*-1,2,3-triols using **OC-22** as an organocatalyst.

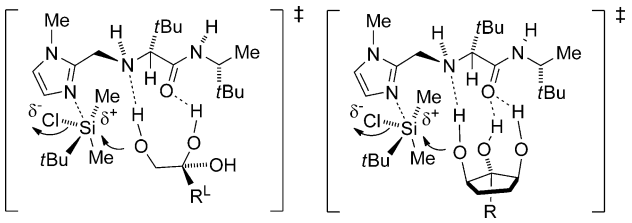


Figure 8. Proposed transition state models for enantioselective silylation of 1,2,3-triols.

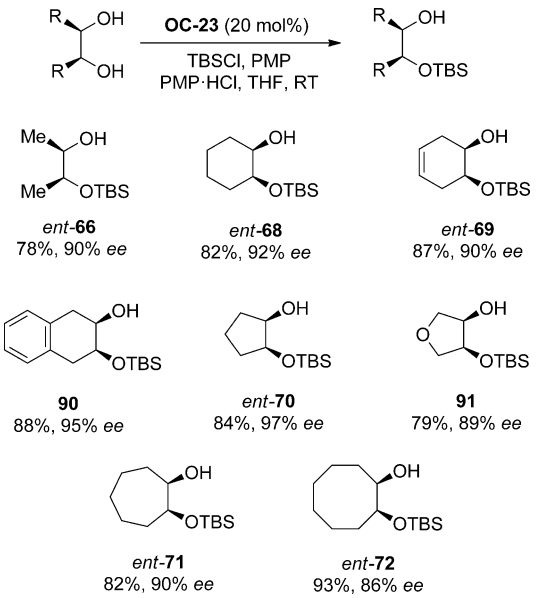
Tan et al.[36] have designed bifunctional catalysts containing a 2-methoxy oxazolidine moiety, as substrate binding site by reversible covalent bonding, and a *N*-methylimidazole group, as a catalytically active residue to promote enantioselective silyl transfer to *meso*-diols. Optimization of the catalyst structure led to **OC-23**, which has proven to be very efficient in desymmetrization by enantioselective silylation with *tert*-butyldimethylsilylchloride for a range of *meso*-1,2-diols.

The reaction in THF at room temperature and in the presence of pentamethylpiperidine (PMP), PMP·HCl, and 20 mol% of **OC-23** led to the corresponding monosilyl derivatives, with good yields and enantioselectivities (Scheme 26).

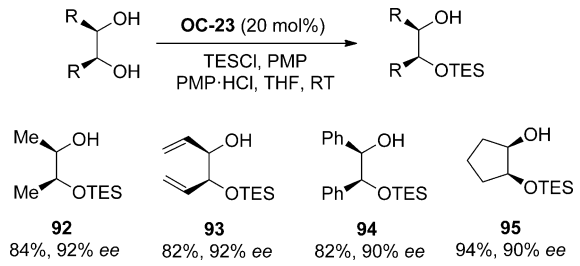
With the use of triethylsilylchloride, the results for enantioselective silyl transfer were improved as the reaction time was shorter and less silylating agent was required. These new conditions were used to perform the efficient monosilylation of acyclic *meso*-1,2-diols (Scheme 27).

In the proposed catalytic cycle for silylation[36] the reversible binding of the diol directs functionalization to the free alcohol (Scheme 28).

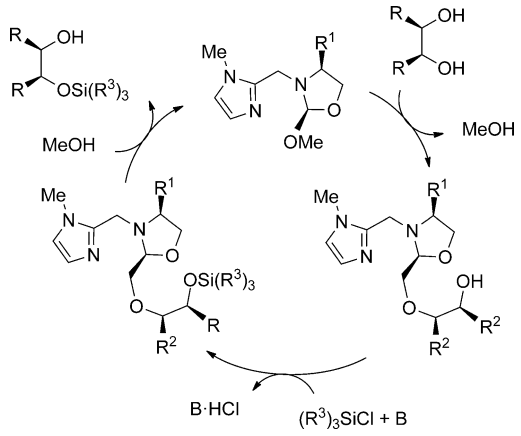
Bifunctional catalysts **OC-24** and **OC-25** containing an *N*-alkylimidazole, as nucleophilic base, and a sulfonamide moiety, capable of interacting with a Brønsted basic site of



Scheme 26. Enantioselective silylation of *meso*-1,2-diols using **OC-23** as an organocatalyst.

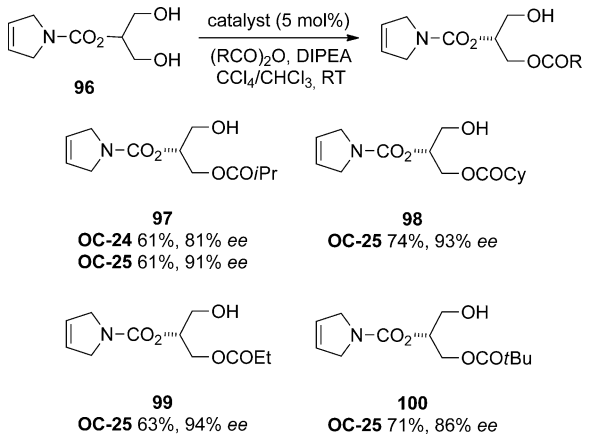


Scheme 27. Enantioselective silylation with TESCl of *meso*-1,2-diols using **OC-23** as an organocatalyst.



Scheme 28. Proposed catalytic cycle for silylation of diols using **OC-23** as an organocatalyst.

the diol through hydrogen bonding, have been designed to promote enantioselective acylation of glycerol derivatives. 2-*O*-Pyroc-glycerol (**96**; Pyroc = 3-pyrroline-1-carbonyl) was selected as a substrate for this transformation due to the strong Brønsted basicity of the Pyroc group, which would lead to a strong hydrogen-bonding interaction with the sulfonamidyl proton of the organocatalyst.[37] It was observed that, when acylation of **96** with isobutyric anhydride in CCl_4/$CHCl_3$ was conducted in the presence of 5 mol% of **OC-24** and DIPEA, the yield of monoacylated compounds was maximized and the formation of diacylated compound was minimized working at room temperature. In these conditions enantioselectivity was better with the use of **OC-25** as organocatalyst. A dependence of the reactivity and enantioselectivity on the carboxylic anhydride was also observed (Scheme 29). When *N*-Pyroc-2-amino-1,3-propanediols were used as substrates in the same reaction conditions enantioselectivities were considerably lower (11–59% *ee*).



Scheme 29. Enantioselective acylation of glycerol derivative **96** using **OC-24** and **OC-25** as organocatalysts.

A transition-state assembly in which the pro-(*R*) hydroxy group of 2-*O*-Pyroc-glycerol **96** is placed close to the acylammonium moiety (Figure 9) has been proposed to rationalize the high level of induction observed in the acylation reaction.

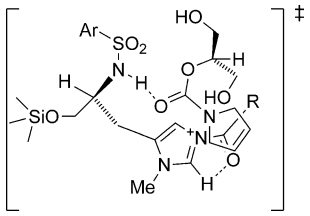


Figure 9. Postulated transition state assembly for acylation of **96** using **OC-24** or **OC-25** as organocatalysts.

Phosphines

It has been known for a long time that phosphines form *P*-acylphosphonium salts by reaction with acyl donors and behave as efficient catalyst in the acylation of alcohols. This is probably why chiral phosphines (Figure 10) were one of the first organocatalysts used in desymmetrization of diols by enantioselective acylation.

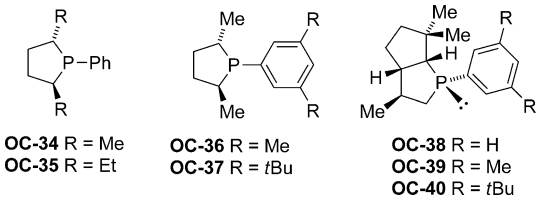
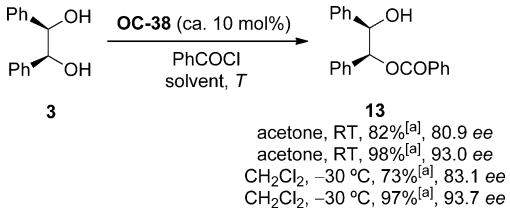


Figure 10. Chiral phosphines used as organocatalysts in desymmetrization of diols.

As previously mentioned, first results using phosphines described by Vedejs et al.[8] were quite disappointing. Monoacetylation of *cis*-cyclohexane-1,2-diol (**4**) in the presence of **OC-34** or **OC-35** led to chiral monoacetate with moderate conversion (66 and 80%, respectively) and enantioselectivity (67 and 45% *ee*, respectively). Moreover under these reaction conditions, the obtained monoacetate readily racemized by acetyl migration. Benzoylation of the same substrate was significantly slower. On the other hand, acetylation of *meso*-hydrobenzoin (**3**) using **OC-34** gave modest enantioselectivity (27% *ee*). Chiral monoacetate with improved enantiomeric purity was obtained forcing the reaction to higher conversion, but the formation of diacetate was also increased. The most promising results (69% *ee* at 84% conversion) were obtained on benzoylation of **3** with benzoic anhydride in the presence of chiral phosphine **OC-34**.

Best results were obtained in benzoylation of **3** catalyzed by chiral phosphines **OC-36** and **OC-37** and phosphabicyclooctane derivatives **OC-38** to **OC-40**.[38] The reaction showed good levels of enantioselectivity, and a good reactivity and reproducibility with the appropriate catalyst loading. Approximately 40 mol% of phosphine was necessary to achieve reasonable rates, whereas reactions promoted by phosphabicyclooctane derivatives provided the corresponding chiral monobenzoate with lower catalyst loadings. Optimal results were obtained in enantioselective benzoylation of **3** with benzoic anhydride in acetone at room temperature or methylene chloride at −30 °C and in the presence of about 10 mol% of **OC-38**. Extending reaction times to achieve high conversion (>97%) led to monobenzoates with high enantioselectivity levels (up to 93.7%), due to kinetic resolution of the initially formed monobenzoates in an additional benzoylation, which produced the corresponding dibenzoates with a concomitant decrease in the amount of isolable chiral compound (Scheme 30).



Scheme 30. Enantioselective acylation of *meso*-hydrobenzoin **3** using **OC-38** as an organocatalyst. [a] Conversion.

Although not detected, it has been postulated that alcohol acylations catalyzed by phosphabicyclooctane derivatives probably involve a *P*-acylphosphonium carboxylate intermediate and a tight ion-pair transition state.[39]

Amino Phosphinites

Chiral catalysts containing a Lewis basic phosphinite group and a Brønsted basic tertiary amino group have been designed to be used as catalysts in desymmetrization of diols (Figure 11).

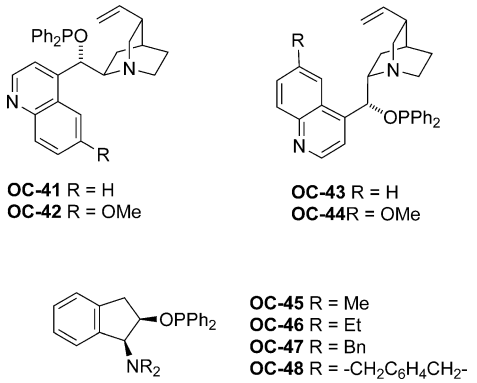
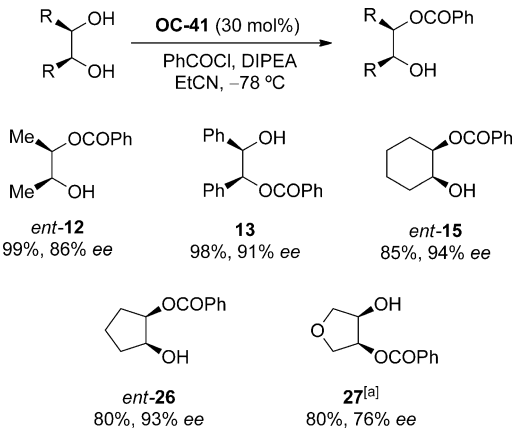


Figure 11. Amino phosphinite derivatives used as organocatalysts in desymmetrization of diols.

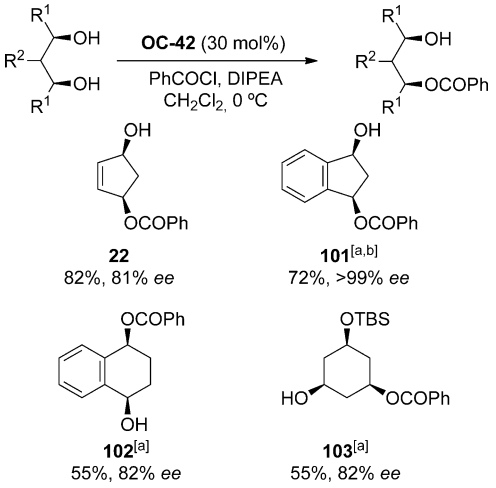
Fujimoto et al. reasoned that these bifunctional catalysts can cooperatively activate the acylating reagent and trap the proton in the monoacylation reaction. The phosphinite moiety and not the amino group is assumed to serve as a Lewis base to activate the acylating reagent.[40]

Among phosphinite derivatives of different cinchona alkaloids (**OC-41** to **OC-44**) initially tested for this reaction, cinchonine derivative **OC-41** led to optimal results in desymmetrization of *meso*-hydrobenzoin (**3**). When benzoylation reaction was conducted in propanonitrile at −78 °C, and in the presence of DIPEA and 30 mol% of phosphinite **OC-41** (as a mixture containing about 15% phosphinate), monobenzoylated diol **13** was obtained in 98% yield and 91% *ee*. Good results were also obtained in enantioselective monobenzoylation of other *meso*-1,2-diols under the same reaction conditions (Scheme 31).[41] Nevertheless no enantioselectivity was observed in the acylation of acyclic 1,3-diols in the presence of phosphinite derivatives of cinchona alkaloids.[42]

On the other hand phosphinite derivatives of cinchona alkaloids were effective organocatalyst for enantioselective benzoylation of cyclic *meso*-1,3- and 1,4-diols. With these substrates the highest enantioselectivity was observed in the presence of the phosphinite derivative of quinidine **OC-42**.[42] With the use of **OC-42** as organocatalyst the best results in enantioselective acylation were obtained when the reaction was performed with benzoyl chloride, in methylene chloride as solvent, at 0 °C, and in the presence of DIPEA



Scheme 31. Enantioselective acylation of *meso*-1,2-diols using **OC-41** as an organocatalyst. [a] Absolute configuration not determined.

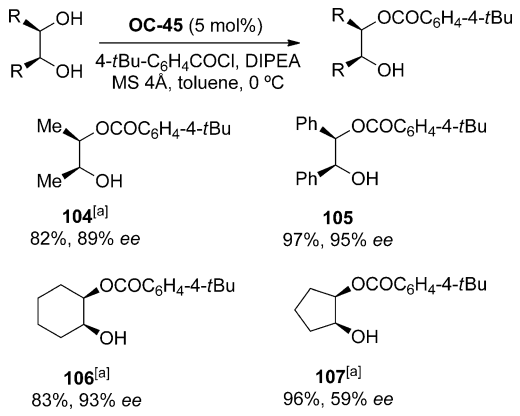


Scheme 32. Enantioselective acylation of *meso*-1,2-diols using **OC-42** as an organocatalyst. [a] Absolute configuration not determined. [b] 20 mol%

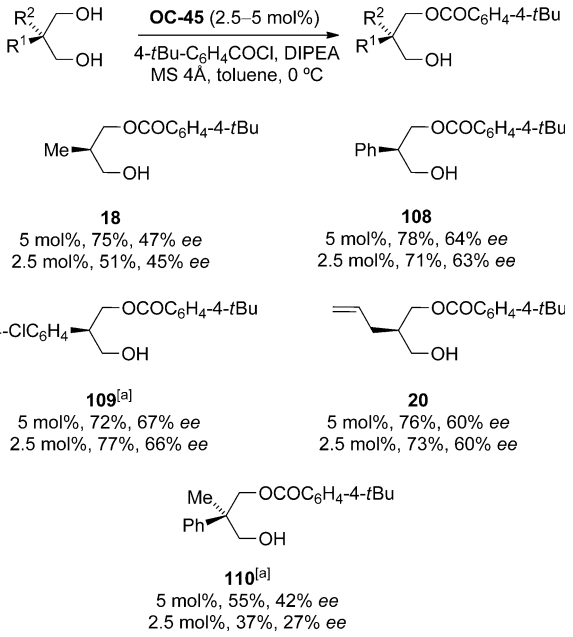
and 30 mol% of phosphinite (as a mixture containing about 2% phosphinate) (Scheme 32).

Very recently Fujimoto et al. have described[40] a series of new amino phosphinites organocatalysts (**OC-44** to **OC-48**) derived from *cis*-aminoindanol. Among them **OC-45** promoted enantioselective acylation of *meso*-hydrobenzoin (**3**) with excellent yield and enantioselectivity when the reaction was performed in toluene at 0 °C, using 4-*tert*-butylbenzoyl chloride as the acylating agent and in the presence of DIPEA, 4 Å molecular sieves, and **OC-45**, even with a 5% mol of catalyst loading. The presence of 4 Å molecular sieves was necessary to achieve good yields and enantioselectivities. The procedure has been extended to enantioselective acylation of different *meso*-1,2-diols (Scheme 33).

Although acylation of 1,3-diols was enantioselective, under the same reaction conditions the yield and level of stereoinduction were considerably lower. It is worth mentioning that in some cases both were maintained even with the use of a 2.5 mol% of catalyst loading (Scheme 34).



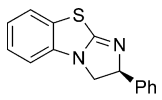
Scheme 33. Enantioselective acylation of *meso*-1,2-diols using **OC-45** as an organocatalyst. [a] Absolute configuration not determined.



Scheme 34. Enantioselective acylation of 1,3-diols using **OC-45** as an organocatalyst. [a] Absolute configuration not determined.

Isothioureas

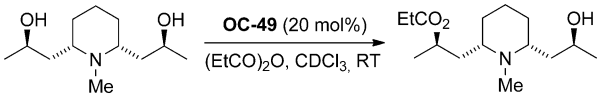
Amidines, guanidines, and related isothioureas are organic bases that can act as nucleophilic catalysts in acyl transfer reactions.[43] The nucleophilic attack of these compounds to an acyl donor generates a charged, activated, N-acyl intermediate, which upon reaction with a nucleophile forms the corresponding acylated product. These compounds have been widely used as organocatalysts in acylation of alcohols. Chiral amidines and related compounds have been postulated as potential enantioselective acylation catalysts in desymmetrization of diols.[44] In this context chiral isothiourea **OC-49** (Figure 12) has been used as organocatalyst in desymmetrization of lobelanidine **111**, directed to the synthesis of lobeline.[45]



OC-49

Figure 12. Structure of chiral isothiourea **OC-49**.

After some experimentation to find optimal reaction conditions, the enantioselective monoacylation of lobelanidine **111** was performed at room temperature with propionic anhydride as acylating agent, in chloroform as solvent, and using 20 mol% of **OC-49** as organocatalyst. After two days, enantiomerically pure monoacylated compound **112** was isolated in 92% yield (Scheme 35). Similar results were obtained in the presence of DIPEA, using *ent*-**OC-49** as organocatalyst, which led to the formation of enantiomerically pure *ent*-**112** in 88% yield as determined by ^{1}H NMR spectroscopy.



111 **112**
92, > 99% *ee*

Scheme 35. Enantioselective acylation of lobelanidine **111** using **OC-49** as an organocatalyst.

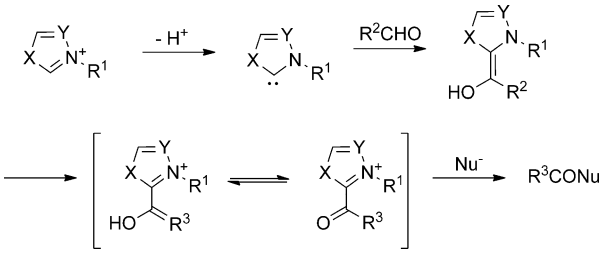
N-Heterocyclic Carbenes

Carbenes are neutral species that possess a bivalent carbon atom with an electron sextet, which confers to them a high reactivity. Earlier, carbenes could not be isolated and were regarded as reactive intermediates. However, carbenes containing heteroatoms on either side of the carbene atom, for example, N-heterocyclic carbenes (NHCs), are a particular class of carbenes, as the presence of atoms capable to donate electron density into the vacant π-orbital provides stable and isolable compounds.

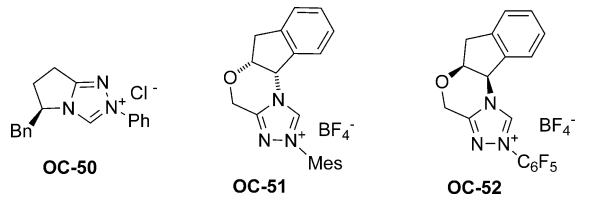
N-Heterocyclic carbenes, which are usually derived from azolium salts, have found application as versatile organocatalysts in a broad range of chemical transformations. One interesting process is the activation of aldehydes as acyl anion equivalents.[46] This activation takes place through the addition of the carbene compound to the aldehyde followed by an internal redox oxidation, an elimination, or an electrophilic trapping—depending on the starting aldehyde—in which the functionalized substituent on the aldehyde has a reactive cooperation.[46a] Subsequent reaction of this intermediate with appropriate nucleophiles yields carboxylic acid derivatives and the original carbene catalyst (Scheme 36).

The use of chiral carbenes generated by the deprotonation of chiral azolium salts (Figure 13) as a catalyst, has allowed desymmetrization of diols using this approach.

In this context Rovis et al. reported[47] on the conversion of α-bromocyclohexanecarboxaldehyde **113** into a suitable acylation agent by the addition of carbene, generated by the deprotonation of azolium salt **OC-50** with triethylamine, and subsequent internal redox reaction. In the presence of



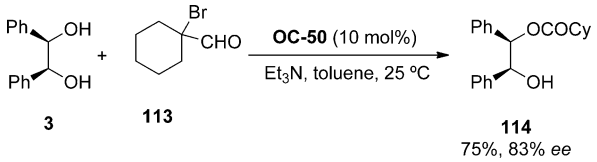
Scheme 36. Activation of aldehydes as acylheteroazolium salts.



OC-50 **OC-51** **OC-52**

Figure 13. Structure of chiral azolium salts used as precatalysts to generate chiral N-heterocyclic carbenes.

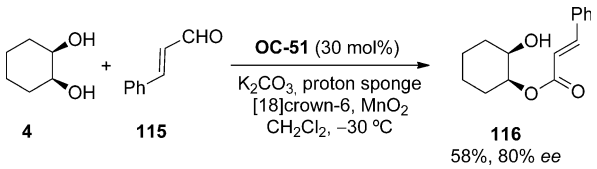
meso-hydrobenzoin (**3**) the reaction in toluene at 25°C cleanly afforded monoacylated diol **114** in 75% yield and 83% *ee* (Scheme 37).



3 **113** **114**
75%, 83% *ee*

Scheme 37. Enantioselective acylation of *meso*-hydrobenzoin (**3**) using a carbene generated from **OC-50** as an organocatalyst.

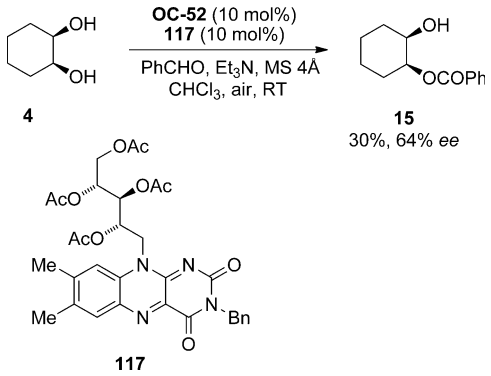
Among the different chiral triazolium salts screened by Scheidt et al.[48] **OC-51** provided the best results in the enantioselective monoacylation of *cis*-cyclohexane-1,2-diol (**4**) with cinnamaldehyde **115**. In this case formation of the acyl anion equivalent required the presence of base and a suitable oxidant, (MnO_2). Selectivity and reactivity of the reaction depended on the reaction conditions and were the highest when acylation was performed in methylene chloride, at −30°C, in the presence of [18]crown-6, and using both potassium carbonate and a proton sponge as bases. In these conditions acyl transfer was suppressed and monoacylated diol **116** was obtained in 58% yield and 80% *ee* (Scheme 38).



4 **115** **116**
58%, 80% *ee*

Scheme 38. Enantioselective acylation of *cis*-cyclohexane-1,2-diol (**4**) using a carbene generated from **OC-51** as an organocatalyst.

The combination of a chiral N-heterocyclic carbenes and a redox-active flavin has turned out to be an effective system to promote desymmetrization of *cis*-cyclohexane-1,2-diol (**4**) by its direct esterification with benzaldehyde under air. In this context **OC-52** served as a precatalyst for the asymmetric benzoylation of *cis*-cyclohexane-1,2-diol (**4**).[49] The carbene was generated using triethylamine as base and oxidative esterification of benzaldehyde was performed in chloroform at room temperature and in the presence of 10 mol% of **OC-52** and 10 mol% of riboflavin derivative **117** as oxidant (Scheme 39). Monobenzoate **15** with 64% *ee* was isolated in only 30% yield due to the concomitant formation of dibenzoate. The chirality of **117** plays no role in the steric course of the reaction and monobenzoate with opposite configuration *ent*-**15** with a similar enantiopurity (62% *ee*) was isolated in 33% yield using the corresponding enantiomeric triazolium salt as precatalyst.



Scheme 39. Enantioselective acylation of *cis*-cyclohexane-1,2-diol (**4**) using a carbene generated from **OC-52** as an organocatalyst.

Conclusion and Outlook

In recent years asymmetric organocatalysis has emerged as a powerful and useful approach for the enantioselective synthesis of chiral compounds. The efficiency of organocatalysts with different structural features in the desymmetrization of prochiral and *meso*-diols has been discussed in this Minireview.

Desymmetrization of cyclic or acyclic *meso*-1,2-diols has been performed with practically all the organocatalysts described in this Minireview. Chiral 4-aminopyridine derivatives promote their acylation with isobutyric anhydride. Enantioselective benzoylation has been performed in the presence of chiral diamines derived from (*S*)-proline or cinchona alkaloids, chiral phosphines, and chiral amino phophinites derived from cinchona alkaloids. Tandem acetylation/oxidation in the presence of histidine-based peptides minimizes acetyl migration and allows a more efficient desymmetrization. *N*-Alkylimidazole derivatives catalyze a highly efficient enantioselective silylation of *meso*-1,2-diols. Finally oxidative esterification of aldehydes catalyzed by N-heterocyclic carbenes has also lead to the desymmetrization of *meso*-1,2-diols.

Desymmetrization of 2-substituted-1,3-diols is believed to be more difficult and challenging than that of *meso*-1,2-diols, and the organocatalytic approach has been less explored. Stereoinduction in enantioselective acylation of 2-substituted-1,3-diols in the presence of chiral aminophophinites is only moderate. On the other hand acylation using chiral diamines derived from (*S*)-proline as organocatalysts provides monoacylated compounds with good levels of enantioselectivity albeit isolated yields of purified compounds are only moderate.

Different approaches have been developed to desymmetrize 1,2,3-triols with different structural features. Histidine-based peptides with the appropriate structure have been used to promote enantioselective acetylation of simple glycerol derivatives, and enantioselective phosphorylation and sulfonylation of *myo*-inositol derivatives. Monoacetylated glycerol derivatives and phosphoryl and sulfonyl *myo*-inositol derivatives are obtained with high enantioselectivity and moderate to good yields. Enantioselective monosilylation of more complex 2-substituted-1,2,3-triols in the presence of *N*-alkylimidazole derivatives is an efficient strategy to obtain chiral monosilylated compounds with good yields and enantioselectivities.

We believe that asymmetric organocatalysis provides a valuable alternative to enzymatic procedures, usually applied to carry out diol desymmetrization, so in the near future, new and more powerful and efficient organocatalysts with broader substrate scope will be developed. This would allow the use of smaller amounts of the organocatalyst acting as chirality inductor resulting in cheaper and cleaner processes.

Acknowledgements

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