# α,β-Unsaturated 2-Acyl-Imidazoles in Asymmetric Biohybrid Catalysis

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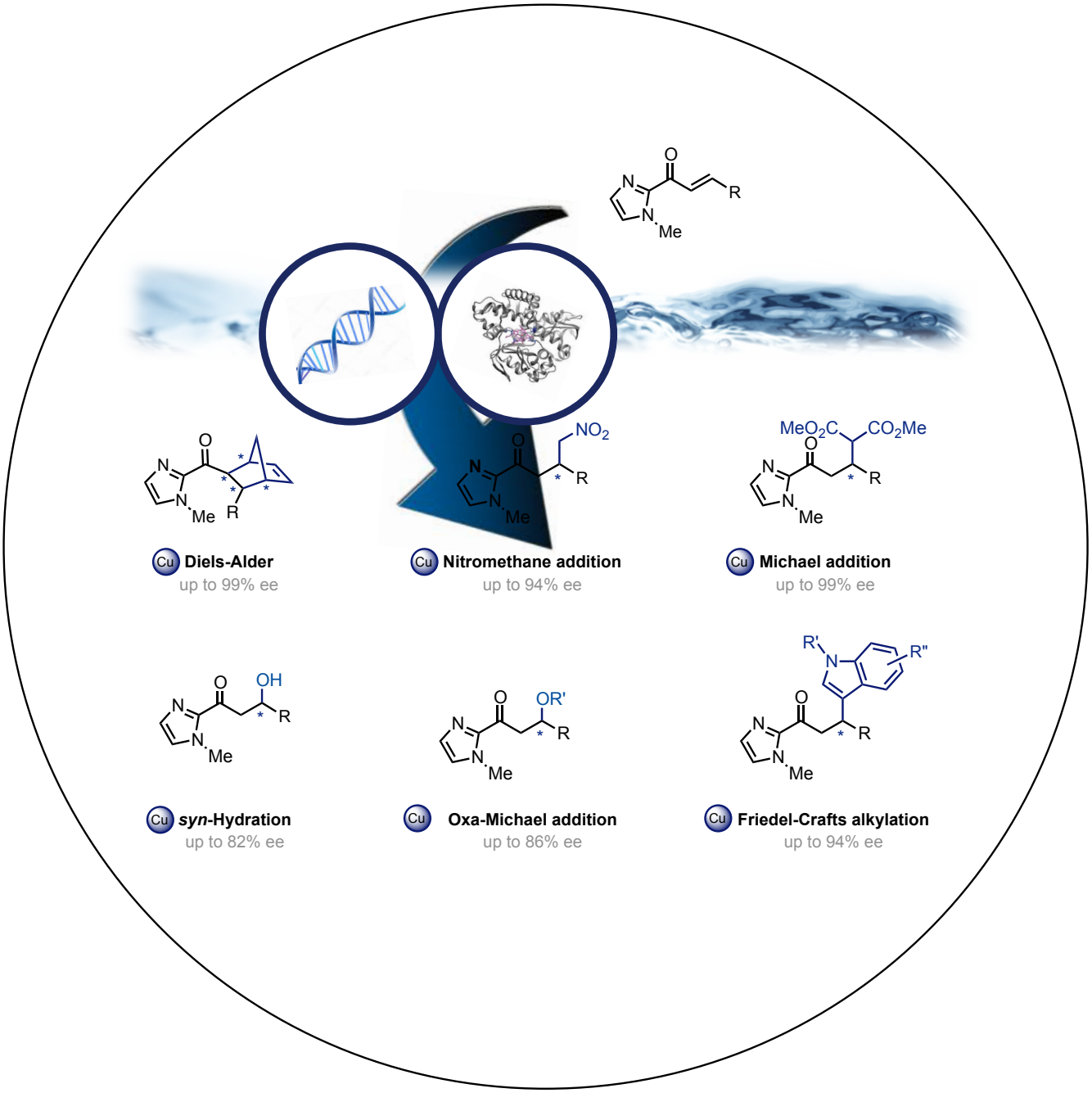

*α,β-Unsaturated acylimidazoles have been used in a plethora of enantioselective transformations over the years and have unsurprisingly become privileged building blocks for asymmetric catalysis. Interestingly however, their use in asymmetric biohybrid catalysis as bidentate substrates able to interact with artificial metalloenzymes has only recently emerged, expanding considerably in the last few years. Easy to prepare and to post-transform, α,β-unsaturated acylimidazoles appear as leading synthons for the asymmetric construction of C–C and C–O bonds. This Minireview highlights the current and increasing interest of these key building blocks in the context of asymmetric biohybrid catalysis with the aim to stimulate further research into their still unexploited potential.*

## 1. Introduction

The conjugate addition of nucleophiles to electron-deficient alkenes is a common strategy for the formation of C–C and C–heteroatom bonds which dates back to the pioneering work of Komnenos in 1883[1] and Michael in 1887.[2] After more than a century of improvements devoted to the optimization of all the reaction parameters, catalytic asymmetric conjugate additions have become highly selective and, most importantly, highly reliable transformations leading to a broad range of optically active compounds with use in fields such as natural product synthesis and medicinal chemistry.[3] Over the years, it has been demonstrated that both organometallic and non-organometallic nucleophiles could be involved.[4] This later class emerged in the early 80's with the description of a diamine/Co(II) complex[5] and later by using chiral bisoxazoline type ligands[6] able to coordinate a variety of metals.[7] It soon emerged that bidentate substrates were ideally fitted to provide the necessary synergistic effect to reach high catalytic performance through an efficient coordination with the chiral metallic complex. Over the years, a number of α,β-unsaturated acyl derivatives (compounds **1**-**7**, Figure 1) were evaluated in a variety of synthetic transformations including Michael and Mukaiyama-Michael type additions, Diels-Alder and hetero-Diels-Alder cycloadditions as well as Friedel-Crafts alkylations.[8–16] However, all the reactions involving the aforementioned substrates required cryogenic conditions to reach high levels of enantioselectivity ultimately limiting the scope. To overcome this drawback, Evans and co-workers introduced the use of α,β-unsaturated 2-acyl-imidazole **8** as a new bidentate substrate.[17] The latter showed an increased reactivity attributed to a lower steric demand and a higher electophilicity of the enone when compared to the α,β-unsaturated-acyl-pyrazoles **1**, oxazolidinones **3**, thiazolidine-2-thiones **4**, phosphonates **5**, benzimidazoles **9,** thiazoles **10** and pyridines **11**.[18] In addition, the chiral Lewis

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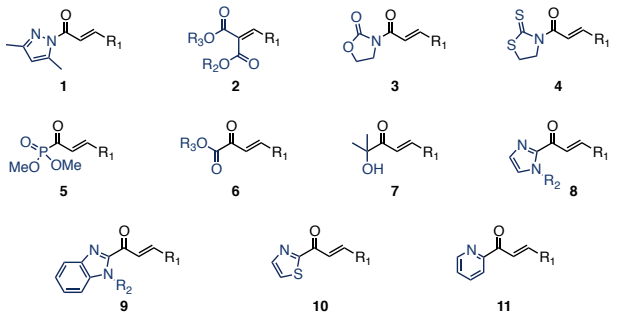


**Figure 1.** Enone commonly used in asymmetric catalysis ($R_1$ = Alkyl, Aryl, $R_2$ = Alkyl, $R_3$ = Alkyl).

acid-catalysed conjugate addition of various indoles in the presence of (PyBox)-Sc(III) led to the corresponding Friedel-Crafts alkylation products with excellent levels of enantioselectivity.

The synthesis of α,β-unsaturated 2-acyl-imidazoles is relatively trivial and usually relies on either the introduction of the imidazole ring on an α,β-unsaturated acyl precursor or on the formation of the double bond *via* some sort of olefination reaction (Figure 2). Okamoto *et al.* were, to the best of our knowledge, the first to describe the synthesis of α,β-unsaturated acyl imidazoles such as **8** through the addition of the deprotonated *N*-methylimidazole **13** onto α,β-unsaturated-*N*-acyl-pyrrolidine **12** (Figure 2).[19] Other syntheses involve the direct addition of the deprotonated form of **13** on an α,β-unsaturated ester **14**, a carboxylic acid **15**, an acyl chloride **16** or on a Weinreb amide **18**. Similarly, the addition of **13** on an enal **17** followed by an oxidation of the resulting alcohol intermediate can also be envisioned.[20] Ultimately, a tandem aldol/crotonization between aldehyde **19** and *N*-methyl-2-acylimidazole **20**[21,22] or a Wittig reaction with the appropriate phosphorous ylide **21**[17] also leads to the title compound. Finally, the phosphorous ylide can be replaced by a phosphonate derivative such as **22**, which can readily undergo a Horner-Wadsworth-Emmons type olefination.[23,24]

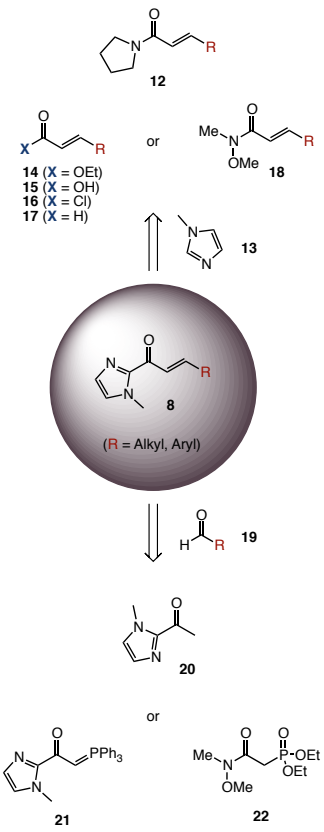


**Figure 2.** Synthesis of **8**

In addition to improving catalytic performances, the imidazole moiety presents the advantage of being very versatile.

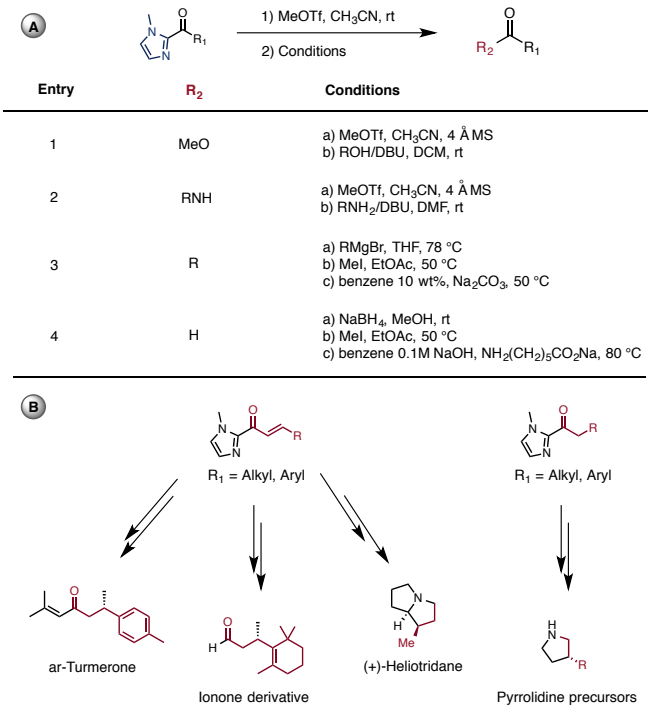


**Figure 3.** Post-transformation of the imidazole moiety.

Indeed, compared to other bidentate enones such as the ones showcased in Figure 1, acyl imidazoles have the advantage of being readily convertible to the corresponding ketones, aldehydes,[25] amides, esters[26-28] or carboxylic acids through simple synthetic transformations (Figure 3a).[29] This particularity has notably been exploited in the synthesis of various natural products and natural product analogues such as (*S*)-ar-turmerone and an ionone derivative,[30] as well as in the synthesis of pyrrolidines,[31] β-hydroxy-β-aminoacids,[27] 12-(*S*)-hydroxyeicosatetraenoic acid [12-(*S*)-HETE][32] and the alkaloid (+)-heliotridane (Figure 3b).[29]

While the development of artificial metalloenzymes for asymmetric catalysis debuted in the 70s,[33-38] it is only recently that α,β-unsaturated-2-acyl-imidazoles have emerged as privileged scaffolds in biohybrid catalysis. It is indeed Scheidt and co-workers that first reported the use of α,β-unsaturated-2-acyl-imidazole **8**.[22] In this seminal article, a conjugate addition of a carbonyl anion was performed in the presence of an *N*-heterocyclic carbene organo-catalyst (NHC) under physiological conditions, thus unveiling the possibility of using α,β-unsaturated-2-acyl-imidazoles in asymmetric biohybrid catalysis in general and DNA-based asymmetric catalysis in particular.

## 2. DNA-based asymmetric catalysis

### 2.1. Natural DNA-helix

The concept of DNA-based asymmetric catalysis, first introduced by Roelfes and Feringa in 2005,[39] relies on a transfer of chirality from the DNA double helix to a pro-chiral substrate using an achiral transition metal catalyst[40] imbedded within the DNA scaffold (Figure 4). The resulting supramolecular architecture provides the necessary chiral microenvironment to induce sufficient enantiodiscrimination.

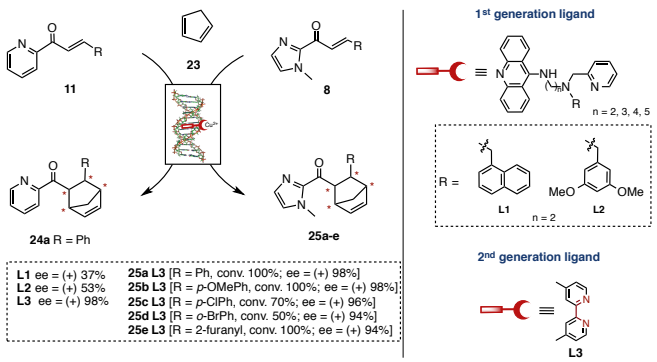


**Figure 4.** DNA-based asymmetric Diels-Alder


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Dr. Jean-Jacques Vasseur earned his PhD degree in 1988 from the University of Montpellier under the guidance of Dr. Bernard Rayner and Prof. Jean-Louis Imbach. From 1990 to 1992 he was a visiting scientist at Isis Pharmaceuticals in Carlsbad (USA). He was appointed Research Director at the CNRS in 1998 and is currently co-director of the Max Mousseron Institute of Biomolecules (IBMM). His research interests lies in various aspects of nucleic acid chemistry focusing on the design of chemically modified DNAs and RNAs and their conjugates for therapeutic and diagnostic applications.

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Prof. Dr. Michael Smietana was educated at the Ecole Normale Supérieure in Paris and received his PhD from the University of Strasbourg (with Dr. Charles Mioskowski). After post-doctoral studies at Stanford (with Prof. Eric T. Kool) he joined Montpellier University in 2004 and was promoted to full Professor in 2012. In 2018 he received the Jean-Marie Lehn award from the Organic Chemistry Division of the French Chemical Society. His current research interests focus on molecular recognition and DNA-based asymmetric catalysis.

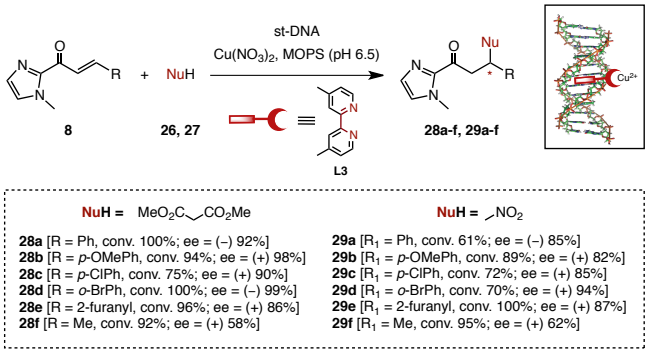



**Figure 5.** DNA-based asymmetric Michael.

This concept was initially tested on the Diels-Alder reaction between azachalcone **11** and cyclopentadiene **23** in the presence of commercially available DNA extracted from salmon testes (st-DNA). The first generation of ligands that were used were derived from the 9-aminoacridine intercalant, which was covalently bound to a Cu(II) binding diamine. High *endo/exo* selectivities were obtained (up to 98/2 in favour of the *endo* product) albeit moderate enantioselectivities (up to 53% ee). Nonetheless, these results demonstrated that the DNA double helix could be used as a powerful source of chirality in the context of asymmetric catalysis.[41]

A follow-up investigation evaluating the influence of the achiral ligand allowed Roelfes and co-workers to identify commercially available 4,4'-dimethyl-2,2'-bipyridine **L3** as an efficient and simpler alternative to **L1** and **L2** leading to an almost complete *endo* selectivity (*endo*/*exo* = 99:1) and excellent enantioselectivities (99% and 98% *ee* at 30 and 5 mol% catalyst loading respectively.[42] Interestingly, similar results were also obtained on β-aryl-substituted α,β-unsaturated acyl imidazoles (Figure 4).[43]

These results prompted Roelfes and co-workers to evaluate other C–C bond forming reactions in presence of DNA.[44] Hence, the addition of nitromethane or dimethyl malonate to **8** allowed the formation of the corresponding Michael addition products with *ees* up to 94% and 99%, respectively (Figure 5).

Mechanistically, the formation of the major enantiomer was proposed to result from the *Si* face attack of the complexed acylimidazole substrate as shown in Figure 6.

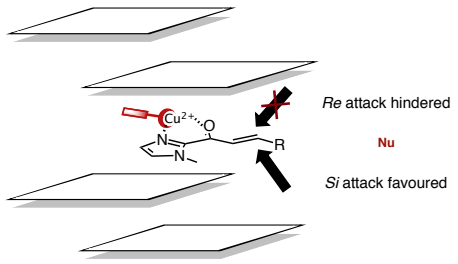



**Figure 6.** Schematic representation of the complexed acylimidazole substrate in DNA.

The nature of the Michael donor was later extended to malonitrile by Li *et al*.[45] Hence, after a thorough screening of the reaction conditions, the use of **L3**/Cu(II) in conjunction with st-DNA was shown to afford excellent conversions and high levels of selectivity (up to 72% ee, Figure 7). Interestingly, the addition of dissymmetric cyanoacetate derivatives generated the two diastereoisomers in roughly the same ratio in up to 84% *ee*.

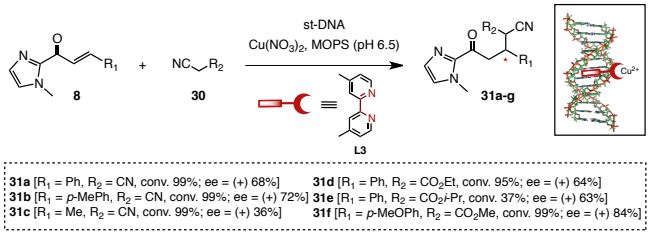
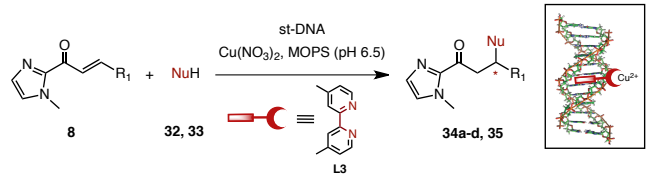



**Figure 7.** DNA-based conjugate addition of malonitrile derivatives.

Another benchmark in the field concerned the optimization of the enantioselective Friedel-Crafts alkylation with indoles.[46] Hence, through binding affinity studies, Roelfes and co-workers were able to show that only 16% of the catalyst was bound to DNA, while at the same time a 30-fold rate enhancement could be observed when the reaction was run in the presence of DNA, thus suggesting that the background reaction was negligible. As a general trend, the reactions all led to full conversions and *ees* reaching up to 83% (Figure 8).



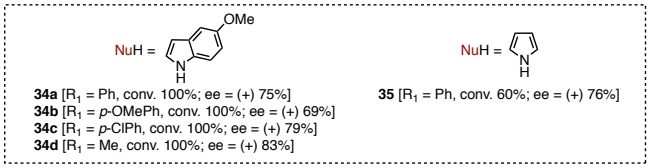




**Figure 8.** DNA-based asymmetric Friedel-Crafts alkylation.

As a general trend, the best selectivities were obtained with substrates bearing an alkyl substituent at the β position of the enone. Most importantly, the authors were able to show that reaction was scalable and that the catalysts could be recycled without any noticeable loss of reactivity or selectivity. Finally, pyrroles were also shown to be compatible with *ees* reaching up to 76%.

A few years later, Sugiyama *et al*. reported an intramolecular version of the Friedel-Crafts alkylation using the bifunctional acylimidazoles **36** (Figure 9).[47] The reactions catalysed by a st-DNA/5,6-dimethyl-1,10-phenanthroline **L4**/Cu(II) complex proved highly selective as up to 78% *ee* were obtained with a 5-methoxy group on the indole ring. In sharp contrast, substrates substituted on the nitrogen afforded much lower selectivities.

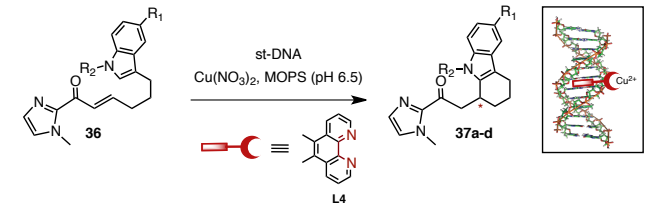
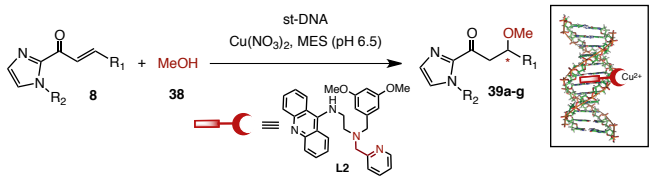



**Figure 9.** DNA-based intramolecular Friedel-Crafts alkylation.

The influence of the co-solvent in the Friedel-Crafts alkylation and the Michael addition was also evaluated.[48] It was notably shown that up to 10% *v/v* of acetonitrile in water

did not affect the binding constant of the catalyst to DNA while allowing an efficient scale-up of the reactions. Furthermore, an acceleration rate of the reaction was noted and attributed to a fast dissociation constant of the product.

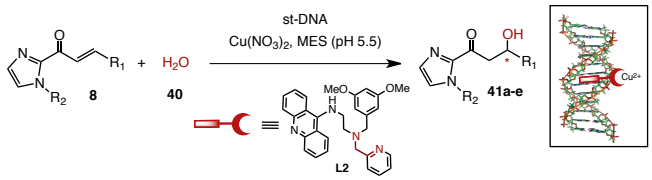
The catalytic enantioselective oxa-Michael addition was also reported by Roelfes and co-workers with up to 86% *ee* (Figure 10).[49] In these experiments, methanol but also ethanol and isopropanol were used in 40% *v/v*, however the conversions dropped when increasing the size of the alkyl group at the β-position of the enone, while no reactivity was observed with β-aromatic substituents. Also worth noting is the formation of the hydration side product in all cases, however this could be minimized by lowering the temperature to −18 °C.




**39a** [$R_1$ = Me, $R_2$ = Me, conv. 100%; ee = (+) 24%]
**39b** [$R_1$ = *t*-Bu, $R_2$ = Me, conv. 43%; ee = (+) 81%]
**39c** [$R_1$ = *i*-Pr, $R_2$ = Me, conv. 82%; ee = (+) 64%]
**39d** [$R_1$ = *i*-Pr, $R_2$ = Et, conv. 74%; ee = (+) 52%]
**39e** [$R_1$ = *i*-Pr, $R_2$ = *i*-Pr, conv. 60%; ee = (+) 57%]
**39f** [$R_1$ = *i*-Pr, $R_2$ = *n*-Pr, conv. 65%; ee = (+) 86%]
**39g** [$R_1$ = *n*-pentyl, $R_2$ = Me, conv. 76%; ee = (+) 35%]

**Figure 10.** DNA-based asymmetric oxa-Michael addition.

The first example of a non-enzymatic *syn*-hydration was reported by Roelfes and co-workers in 2010 using st-DNA in association with the same **L2**/Cu(II) metallic co-factor used for the oxa-Michael addition (Figure 11).[50] Under these conditions, α,β-unsaturated 2-acyl imidazoles could be readily converted to the corresponding β-hydroxy ketones in up to 72% *ee*. In all these experiments, only the β-methyl substituted acyl imidazole led to full conversions albeit with low *ees*, while substrates bearing a β-*t*-butyl moiety led to higher *ees* but lower conversions. Surprisingly, replacing the methyl by an *i*-propyl group on the imidazole ring led to a racemic mixture of products, thus highlighting the impact of the steric hindrance induced by the substrate as well as the coordination sphere environment on the stereoselectivity of the reaction.




**41a** [$R_1$ = Me, $R_2$ = Me, conv. 100%; ee = (+) 28%]
**41b** [$R_1$ = *i*-Pr, $R_2$ = Me, conv. 71%; ee = (+) 60%]
**41c** [$R_1$ = *t*-Bu, $R_2$ = Me, conv. 55%; ee = (+) 72%]
**41d** [$R_1$ = Me, $R_2$ = *i*-Pr, conv. 100%; ee = (+) 3%]
**41e** [$R_1$ = *n*-pentyl, $R_2$ = Me, conv. 75%; ee = (+) 47%]

**Figure 11.** DNA-based asymmetric *syn*-hydration.

## 2.2 Synthetic DNA-helix

### 2.2.1 Supramolecular approach

The results obtained with natural DNA clearly highlight the importance of the binding between the metallic co-factor and the double helix. This prompted the community to next evaluate the influence of specific sequences on the reaction rate and ultimately on the enantioselectivity. A first set of experiments was run on the Diels-Alder cycloaddition between acylpyridine **11** (Figure 1) and cyclopentadiene using various **L3**/Cu(II)/DNA complexes.[51] While no apparent sequence-selectivity could be established, the GC rich 12 mer sequence d(TCAGGGCCCTGA)$_2$, **ODN1**, led to slightly higher *ees* (99.4% *ee*) compared to st-DNA (98.5% *ee*).

A similar study was performed on the Friedel-Crafts alkylation using this time α,β-unsaturated 2-acyl imidazole **8** as a model substrate.[46] Similarly to the Diels-Alder cycloaddition, **ODN1** led to usually higher *ees* and conversions than st-DNA, while AT-rich oligonucleotides were found to induce a decrease of *ees*.

Interestingly, in the case of the intramolecular Friedel-Crafts alkylation with 2-acyl imidazole **36** (Figure 9), Sugiyama and co-workers showed that AT-rich duplexes gave rise to higher enantioselectivities.[47] To understand these results a theoretical investigation was undertaken by modelling 28 conformations of **ODN2** d(CAAAAATTTTTG)$_2$ with **L4**/Cu(II). The simulations revealed a higher binding energy of **ODN2** toward the pro-(*S*) conformation of 2-acylimidazole **36**. Moreover, a shorter distance between the two carbons involved in the newly formed C–C bond was observed in the case of the pro-*S* complex more in line with the expected transitional state.[52]

This sequence-selectivity was also evaluated in the case of the *syn*-hydration, where higher selectivities were obtained with sequences bearing an AT-rich central segment, however the structure of the ligand was also shown to be crucial.[53]

Finally, in the case of the oxa-Michael addition, AT-rich **ODN2** gave rise to higher *ees* [82% conv.; 43% *ee*] than the GC-rich sequence **ODN1** [68% conv.; 19% *ee*] (Figure 11), albeit still lower than st-DNA.[49]

These results prompted our group to devote our first efforts in the field of biohybrid catalysis toward the control of the enantioselective outcome. While many studies evaluated various parameters including the influence of the metallic co-factor to selectively access one specific enantiomer, the inversion of selectivity were generally partial, often very ligand-specific and thus unpredictable.[39,54] Taking into account the best selectivities obtained so far in the Friedel-Crafts alkylation of α,β-unsaturated 2-acyl imidazole **8**, we synthesized the mirror image of **ODN1**, **ODN4**, using L-nucleotide phosphoramidites. As expected, the use of the left-handed L-d(TCAGGGCCCTGA)$_2$ **ODN4** sequence in the presence of the **L3**/Cu(II) complex afforded the opposite enantiomer with the exact the same enantioselectivity than the one obtained with **ODN1** (Figure 12).[21] The method was also validated on the conjugate addition of dimethyl malonate and nitromethane, thus showcasing the generality of the method.

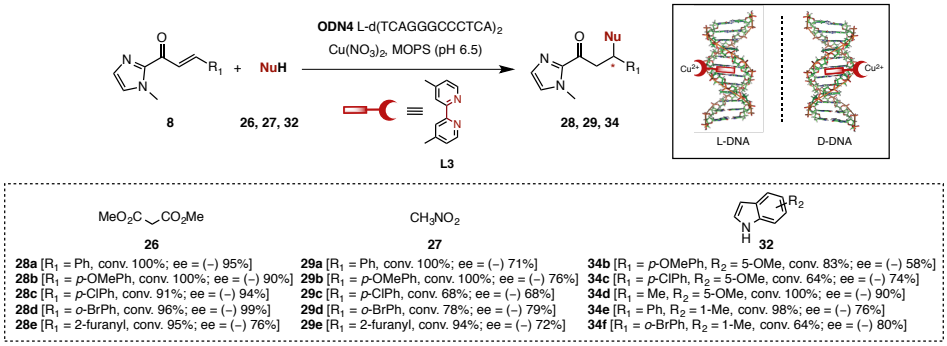



**Figure 12.** Mirror image DNA-based asymmetric catalysis.

We later applied this concept to short double-stranded RNA sequences,[55] which are known to adopt a different helical shape (A-form helix) with a large and shallow minor groove and a deeper and tighter major groove. Although the enantioselectivities achieved were lower than the ones obtained with DNA, we found that the GC rich 16-mer **ORN1**, L-(CAGUCAGUACUGACUG)$_2$, provided the best selectivities with up to 54% *ee* and an expected inversion of selectivity depending on the D or L nature of the sequence (Figure 13).

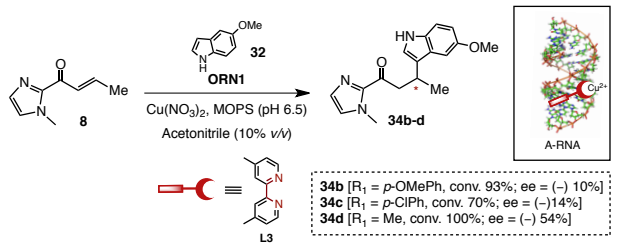



**Figure 13.** RNA-based asymmetric Friedel-Crafts alkylation. [**ORN1** L-(CAGUCAGUACUGACUG)$_2$].

Achieving sequence-specificity was another challenge we decided to tackle. Hence, instead of evaluating the sequence dependency of a given reaction, we envisioned to design sequence-specific catalysts. The well-known minor groove binder Hoechst-33258, recognized for its strong affinity for AT-rich regions of DNA, was selected and modified to incorporate a Cu(II) binding site (Figure 14).[56]

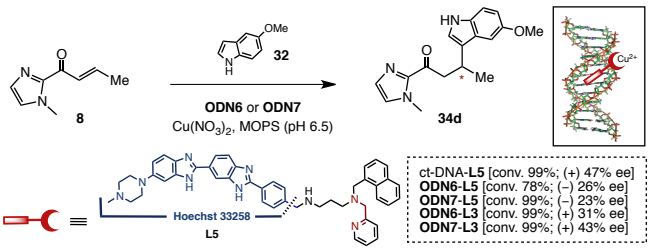



**Figure 14.** DNA-based asymmetric Friedel-Crafts alkylation with minor groove-binding ligands. [**ODN6:** 5'-d(CG**AATT**CGTT TTCG**AATT**CG)-3', **ODN7:** 5'-d(CG**TATA**CGTTTTCG**TATA**CG)-3'].

Among all the ligands that were synthesized and evaluated in the Cu(II)-catalysed Friedel-Crafts alkylation of α,β-unsaturated 2-acyl imidazole **8** with 5-methoxyindole **32**, ligand **L5** provided the best selectivities (up of 47% *ee* with ct-DNA). Although moderate, higher selectivities were obtained with the ligand having the highest binding affinity with DNA, thus reinforcing a possible correlation between affinity and selectivity.

Sequence specific targeting of DNA was also at the centre of the recent work published by Qiao and co-workers.[54] A four unit pyrrole-polyamide groove binder known for its high affinity toward DNA was selected and covalently modified with a 4,4′-dimethyl-2,2′-bipyridine (**L6**, Figure 15).

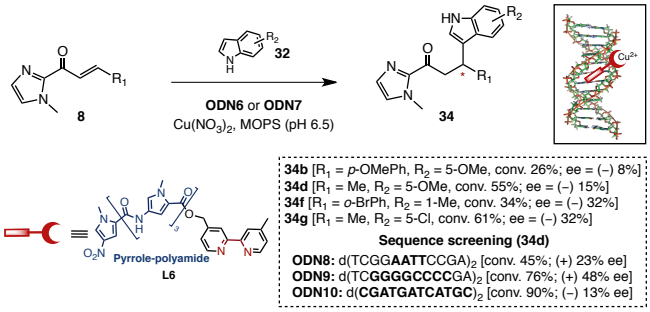



**Figure 15.** DNA-based asymmetric Friedel-Crafts alkylation using pyrrole-polyamide **L6**.

The Cu(II)-catalysed Friedel-Crafts alkylation of α,β-unsaturated 2-acyl imidazole **8** with 5-methoxyindole was again selected as a model reaction. A screening of both self-complementary AT and GC-rich oligonucleotides identified **ODN9**, d(TCGGGGCCCCGA)$_2$, as the lead sequence (up to 48% *ee*). Circular dichroism spectra and singular value decomposition analyses suggested that different binding modes could co-exist depending on the nature of the sequence therefore affecting the enantioselectivity. It is worth pointing that most asymmetric Diels-Alder reactions reported in the literature involving a Cu-ligand complex bound to a synthetic ds-DNA through a supramolecular approach were run on α,β-unsaturated 2-acyl pyridine **11**. A notable exception was recently described by Hennecke and co-workers who used synthetic DNA hairpins to catalyse a Diels-Alder between cyclopentadiene and α,β-unsaturated 2-acyl imidazole **8**.[57]

### 2.2.2 Covalent approach

The anchoring strategy used to link the transition metal complex to DNA is a critical parameter that influences the nature of the second coordination sphere provided by the bio-scaffold. The supramolecular anchoring approach of a metallic-cofactor to DNA allows a modular assembly of the biohybrid catalyst and permits a rapid optimization of the reaction conditions. In contrast, the covalent anchoring approach allows to specifically position the metallic co-factor independently of its binding affinity to DNA but requires multiple synthetic steps to assemble each biohybrid catalyst.

Taking advantage of the reactivity of bifunctional platinum complexes towards DNA, Gjonaj and Roelfes synthesized a bipyridine-platinum complex and covalently attached it to st-DNA. After addition of Cu(NO$_3$)$_2$, the new DNA-based catalyst **L7** was evaluated in the benchmark Friedel-Crafts alkylation of α,β-unsaturated 2-acyl imidazole **8** with 5-methoxyindole **32** (Figure 16).[58] Although the *ees* were

slightly lower than the ones obtained with the typical supramolecular approach, this new biohybrid catalyst proved particularly robust as showcased by a series of 10 recycling experiments that led to no noticeable erosion of either the reactivity or the selectivity.

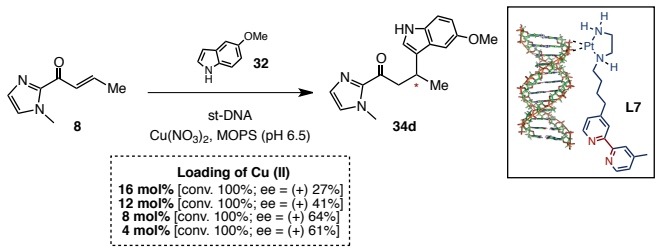
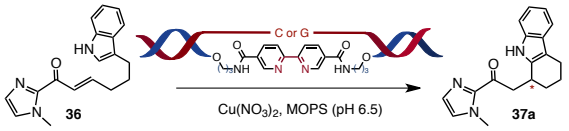



**Figure 16.** DNA-based asymmetric Friedel-Crafts alkylation using a cisplatin ligand.

Park and Sugiyama later developed various synthetic DNA-based hybrid catalysts containing an intrastrand bipyridine ligand. The latter were prepared by incorporating a 2,2′-bipyridine-5,5′-dicarboxylic acid moiety within a specific 13-mer (**ODN11**) or an auto-complementary single-strand 29-mer (**ODN14**) sequence (Figure 17).[59] The modified 13-mer oligonucleotide was then associated with a complementary strand containing either a G or a C nucleobase against the ligand and the resulting biohybrid catalysts were evaluated in the intramolecular Friedel-Crafts alkylation of acyl imidazole **36**. As a general trend, the catalysts containing a cytosine facing the bipyridine led to higher selectivities (84% *ee* with **ODN11**/**ODN13** and 86% *ee* with the hairpin **ODN16** *vs* 17% *ee* with **ODN11**/**ODN12**).




**ODN11** 5'-GCATGGXCACGGT-3'
**ODN12** 3'-CGTACCGGTGCCA-5'
[conv. 20%; ee = (+) 17%]

**ODN11** 5'-GCATGGXCACGGT-3'
**ODN13** 3'-CGTACCCGTGCCA-5'
[conv. 71%; ee = (+) 84%]

**ODN14** 5'-GCATGGXCACGGTTTTACCGTGCCCATGC-3'
[conv. 80%; ee = (+) 86%]

**Figure 17.** DNA-based asymmetric intramolecular Friedel-Crafts alkylation using an intrastrand bipyridine ligand.

These results prompted the authors to investigate further the role of the cytosine within the catalytic pocket. Hence, various counter-strands incorporating a triethylene glycol (**ODN15a**) or an alkyl linker (**ODN15b** and **ODN15c**) opposite to cytosine were prepared and evaluated in the Diels-Alder reaction between both α,β-unsaturated 2-acyl imidazole **8** and α,β-unsaturated 2-acyl pyridine **11** and cyclopentadiene (**23**). The best results were obtained with the triethylene glycol linker which afforded *ees* ranging between 88 and 92% (Figure 18).[60]

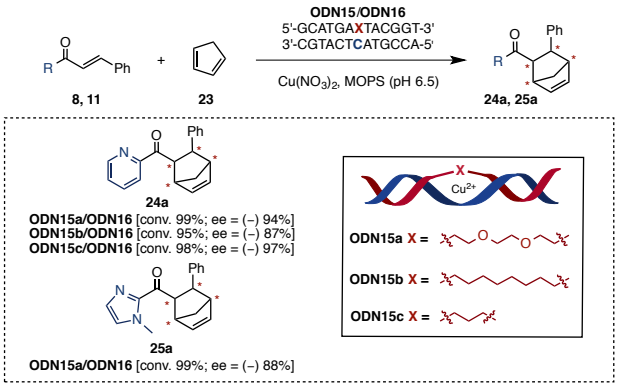



**Figure 18.** DNA metalloenzyme-based asymmetric Diels-Alder.

### 2.2.3 Solid-Supported DNA helix

The use of solid-supported DNA for asymmetric catalysis was first introduced by Park and Sugiyama based on a non-covalent immobilization of DNA on ammonium-functionalized silica beads.[61] The method proved highly effective with selectivities reaching up to 94% *ee* in the Diels-Alder cycloaddition between α,β-unsaturated 2-acyl pyridine **11** and cyclopentadiene. Following these results, the authors also developed DNA-silica minerals made from cationic Mg(II) ions, *N*-trimethoxysilylpropyl-*N*,*N*,*N*-trimethylammonium chloride (TMAPS), tetraethoxysilane (TEOS) and a Cu/ligand complex.[62]

Considering the crucial importance of heterogeneous catalysis for industrial applications, our group has also embarked on the development of an eco-friendly and recyclable biohybrid catalyst. Our approach, which relied on the use of commercially available cellulose-supported (CS) DNA in conjunction with a Cu(II)/**L3** complex, led to high levels of selectivity in both the Friedel-Crafts alkylation and the Michael addition on α,β-unsaturated 2-acyl imidazole **8** (Figure 19).[63] Moreover, we demonstrated that the CS-ct-DNA-Cu(II)/**L3** biohybrid catalyst could be recycled up to 10 times without any loss of reactivity or selectivity and even adapted to a single-pass continuous-flow process.

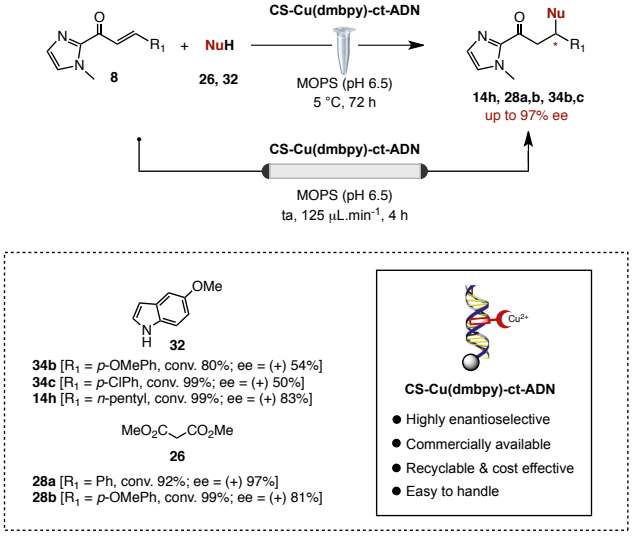



**Figure 19.** CS-ct-DNA-based asymmetric Friedel-Crafts alkylation and Michael addition.

## 2.4 G-quadruplex

### 2.4.1 Supramolecular approach

G-Quadruplex (G4DNA) are secondary structures composed of four-stranded G-rich DNA sequences. The core consists of four guanines bases associated through Hoogsteen hydrogen bonds forming planar square arrangements. These structures are stabilized by monovalent cations (preferably K+) that sit in the centre and interact with eight guanines. Depending on their unimolecular or bimolecular nature, G4DNA are distinguished by their topological variety which include mainly parallel, anti-parallel or '3+1' hybrids (Figure 20).[64–67]

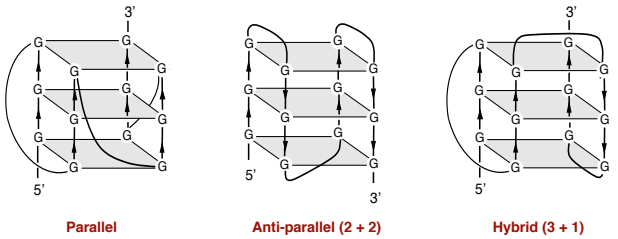



**Figure 20.** G4DNA conformations.

Considering these different arrangements and their respective ability to bind to a large variety of ligands, G4DNA also appeared as privileged bioscaffolds for asymmetric catalysis.[68] In the case of G4DNA-based biohybrid catalytic systems, both the supramolecular and covalent anchoring strategies were evaluated on the benchmark Diels-Alder cycloaddition, the Friedel-Crafts alkylation and the Michael addition.

The first example of a G4-based asymmetric catalysis was reported by Moses and co-workers in 2010 on the standard Diels-Alder cycloaddition between azachalcone **11** and cyclopentadiene.[69] G4DNA forming sequences such as ***h-Tel*** d(AGGGTTAGGGTTAGGGTTAGGG) and ***c-Kit*** d(AGGGAGGGCGCTGGGAGGAGG) were selected and evaluated in the presence of Cu(II) and ligand **L3**. Despite an excellent *endo/exo* diastereoselectivity and high conversions (up to 85%), the *ees* were rather moderate (up to 34%). Nonetheless, these results demonstrated the ability of G4DNA to act as good chiral scaffolds. Interestingly, Li *et al*. later demonstrated that G4DNA/Cu(II) could catalyse the reactions in the absence of ligand in up to 74% *ee*.[70] Moreover, the importance of the conformation was emphasized by the observation of an inversion of selectivity between parallel and anti-parallel G-quadruplexes. This reversal of selectivity was also observed with ***h-tel-***Cu(II) in the presence of different alkali metal ions (Figure 21).[71] Hence, the enantioselectivity could be switched from (–) 58% to (+) 67% by simply changing the nature of the alkali metal ion form $Na^+$ to $K^+$. This inversion was attributed to a structural transformation from an antiparallel to a hybrid-type G-quadruplex structure.[72]

The same group also prepared a terpyridine **L8**/Cu(II) complex having a high affinity to ***h-tel*** (Figure 21). The resulting biohybrid catalyst induced a 73-fold rate acceleration compared to **L8** and *ees* up to 99%.[73]

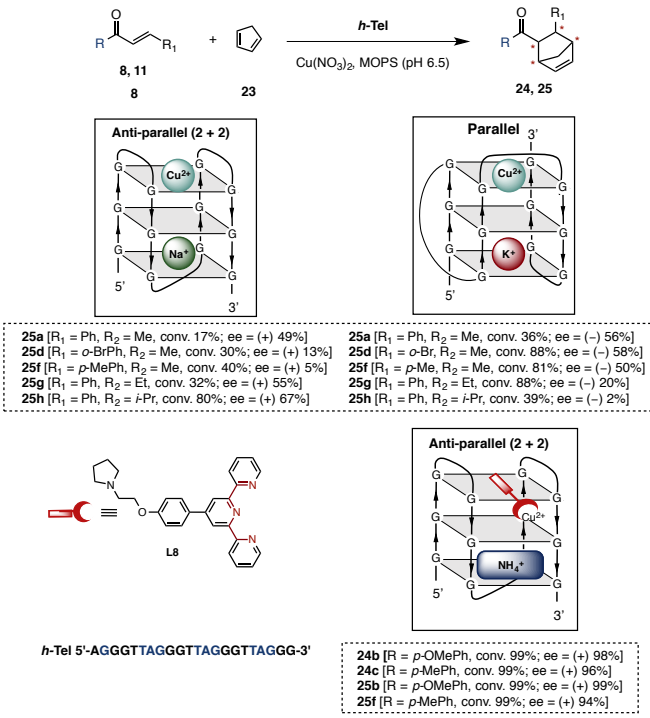



**Figure 21.** *h*-Tel G4DNA-catalysed asymmetric Diels-Alder.

The importance of the conformation of the G4DNA was also confirmed in both the Friedel-Crafts alkylation[74] and the Michael addition.[75] Hence, the selectivity outcome of a given reaction can easily be set by fine-tuning the conditions (choice of the alkali metal ions, the ligands, the co-solvents…). On the down side, the *ees* obtained with G4DNA catalysts never exceeded 75%, far below the selectivities generally obtained in the field.

In order to improve the performances of the G4DNA, a covalent anchoring strategy was also evaluated, thus circumventing the issues related with the binding affinity of the ligand.

### 2.4.2 Covalent approach

The covalent positioning of a bipyridine ligand into the G4DNA was first reported by Jäschke and co-workers.[76] New G4DNA biohybrid catalysts were obtained by covalently attaching a **L3**/Cu(II) complex *via* different linkers of varying length. The evaluation of these new G4DNA catalysts on the asymmetric Michael addition of dimethyl malonate on α,β-unsaturated 2-acyl imidazole **8** revealed the importance of the positioning of the ligand, the length of the linker and the topology of the G4DNA. Interestingly, a stunning inversion of the selectivity was observed when using **ODN17**, which carries the modification at position 12 compared to **ODN18** which bears the exact same ligand at position 10 (Figure 22). Also worth pointing out is the catalyst recyclability, which was later demonstrated by reusing the catalyst over 10 times without any erosion of the selectivity.[77]

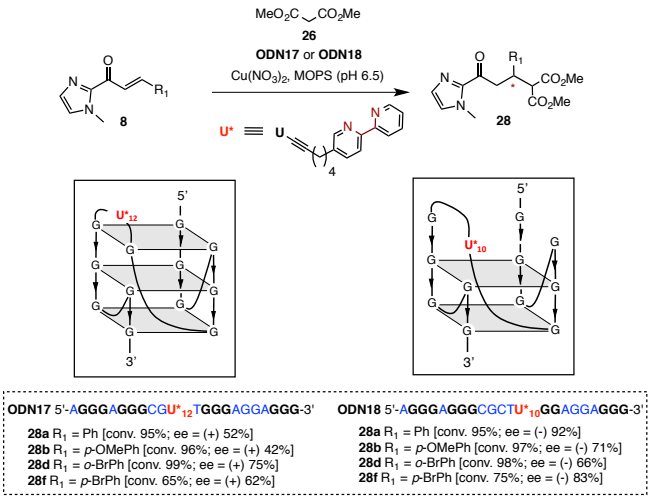



**Figure 22.** G4DNA-based asymmetric Michael addition through a covalent modification.

## 3. Peptide and Protein-based asymmetric catalysis

The design of artificial metalloenzymes incorporating a synthetic transition-metal catalyst into a protein-binding site also represents an emerging approach to engineer biohybrid catalysts. Similar to DNA-based biohybrid catalysts, covalent, dative, or non-covalent anchoring strategies can be applied to polypeptidic scaffolds. Artificial metalloproteins and artificial metalloenzymes have attracted a tremendous amount of attention over the last two decades and their design and catalytic activity have been depicted in several excellent reviews.[37,38,78-86] While our intention is to highlight the pivotal role played by α,β-unsaturated-2-acyl-imidazole **8** in the context of peptide and protein-based asymmetric catalysis, we owe to mention the important role played by acylpyridines in the development of peptide- and protein-catalysed asymmetric Diels-Alder reactions. Based on their earlier studies on the Lewis acid-catalysed Diels-Alder reaction in water between α,β-unsaturated-2-acyl-pyridine **11** and cyclopentadiene,[87,88] Engberts and co-workers reported for the first time the use of a hybrid complex capable of promoting a Diels-Alder reaction with up to 74% *ee* for the major *endo* isomer.[89,90] Following these results, Reetz and co-workers developed a phtalocyanine-copper complex capable of interacting with various albumin proteins to promote the Diels-Alder between acyl pyridine **11** and cyclopentadiene to afford the corresponding Diels-Alder *endo* product in up to 98% *ee*.[91] Interestingly, the experiment run with 1,3-diphenylprop-2-en-1-one in place of **11** led to only 5% yield and 56 % *ee* thus demonstrating the positive influence of the bidentate ligand. This reaction has since been frequently used as a model reaction to evaluate new biohybrid scafflods in the context of asymmetric Diels-Alder reactions in water.[36,92-99]

### 3.1 Artificial metalloenzymes

Roelfes *et al*. selected the bovine Pancreatic Polypeptide **bPP**,[100,101] a 36 residue polypeptide hormone as a new biohybrid scaffold.[102] The natural peptidic hormone was truncated to 31 residues and grafted at the Tyr7 position with an

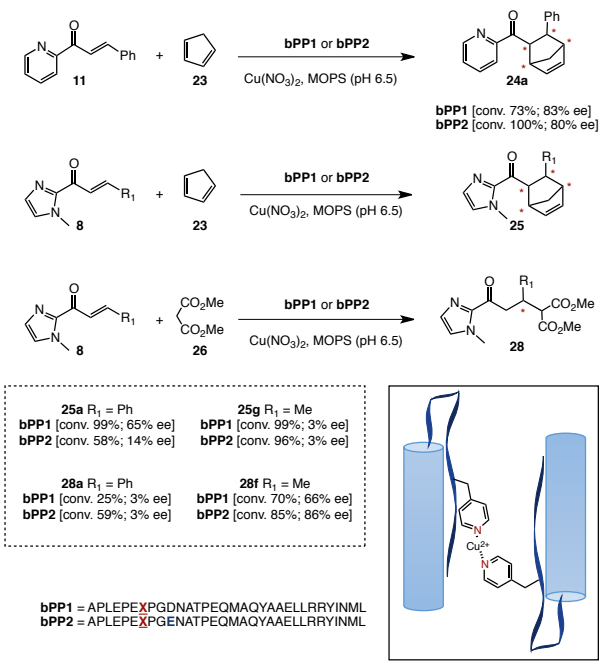



**Figure 23.** Bovine Pancreatic Polypeptide **bPP** as scaffold for asymmetric transformations.

active site by introducing a non-proteinogenic amino acid capable of binding a Cu(II) ion. The **bPP** variants were evaluated in the Cu(II)-catalysed Diels-Alder and Michael addition with α,β-unsaturated substrates **8** and **11** (Figure 23). The results showed that peptides containing L-3-pyridylalanine led to good enantioselectivities on both the Diels-Alder (up to 83% *ee*) and the Michael addition (up to 86% *ee*).

While this latter biohybrid catalyst was obtained by solid phase synthesis, the same group reported a few years later the *in vivo* incorporation of a metal-binding non-proteinogenic amino acid into the transcription factor Lactoccocal multidrug resistance Regulator (**LmrR**).[103] The *in-vivo* incorporation enabled the generation of **LmrR** mutant variants that permit a rapid optimization and a precise positioning of the bipyridine ligand (BpyAla) inside the **LmrR.** Application of these artificial metalloenzymes in the catalytic enantioselective Friedel-Crafts alkylation of α,β-unsaturated acyl imidazole **8** with various
indoles led to *ees* up to 83% and paved the way for directed evolution of artificial metalloenzymes

The concept was later extended to three other proteins (**QacR**, **CgmR** and **RamR**) belonging to the **TetR** family of Multidrug Resistance Regulators.[104] Among them, one **QacR** mutant induced up to 94% *ee* in the Cu(II)-catalysed enantioselective Friedel-Crafts alkylation with a reverse of selectivity compared to other mutants including **LmrR**-based artificial metalloenzymes (Figure 24).

Interestingly, when applied to the conjugate addition of water, the *N*-methyl-2-imidazolyl moiety was found to be not compatible with the active site of the LmrR artificial metalloenzyme whereas the hydration of α,β-unsaturated acyl pyridine **11** was achieved with up to 84% ee.[105]

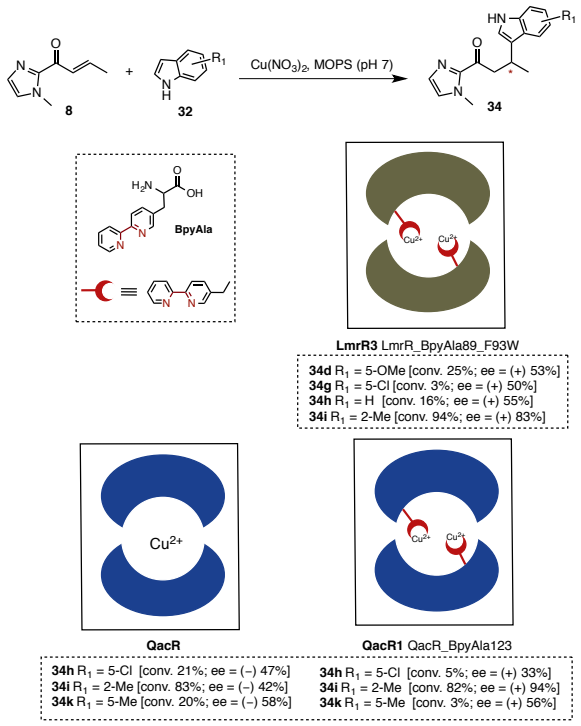



**Figure 24.** **LmrR**- and **QacR**-based asymmetric Friedel-Crafts alkylation.

The supramolecular assembly of an **LmrR**-based artificial metalloenzyme was also envisioned by combining a **LmrR** variant with a Cu(II) complex of phenanthroline ligand **L4** (Figure 25).[106] The rationale behind the study was based on the ability of planar aromatic ligands to bind to the **LmrR** hydrophobic pocket. The supramolecular approach proved to be superior to the covalent approach with *ees* up to 94% in the Cu(II)-catalysed enantioselective Friedel-Crafts alkylation.

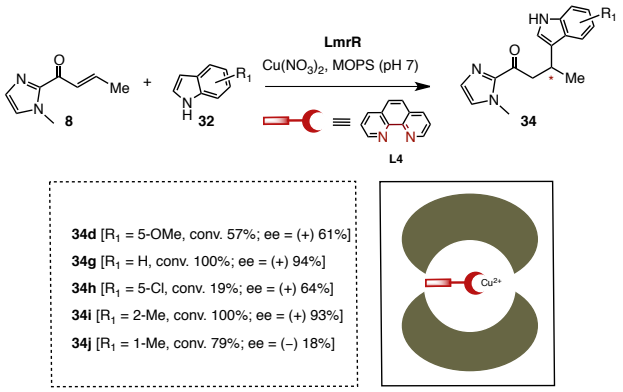



**Figure 25.** Supramolecular approach for the **LmrR**-based asymmetric Friedel-Crafts alkylation.

These results prompted the authors to design a metal regulated **LmrR**-based artificial metalloenzyme combining both supramolecular and covalent anchoring strategies. The catalytic site was composed of the Cu(II)/**L4** ligand described above, while the regulatory site was introduced covalently by standard site directed mutagenesis technique[92] resulting in the formation of a dimeric protein containing two metal binding moieties. (Figure 26).[107]

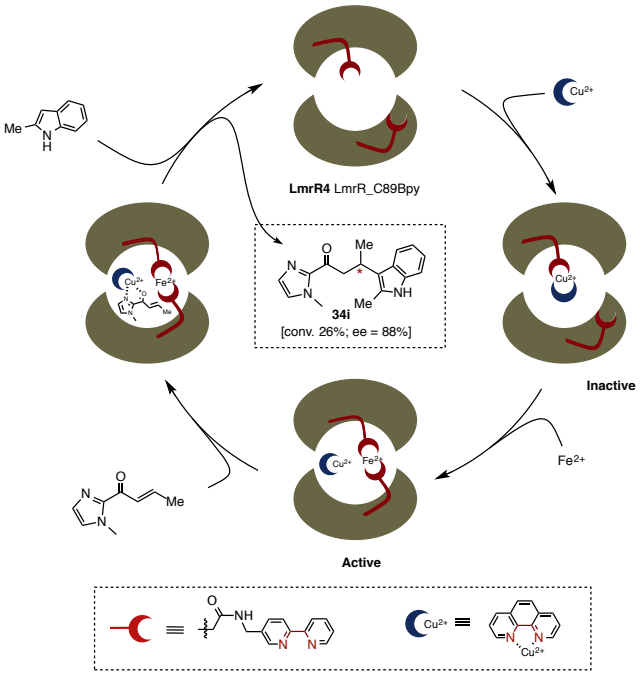



**Figure 26.** Metal ion regulated **LmrR**-based asymmetric Friedel-Crafts alkylation.

In the absence of $Fe^{2+}$ ions, the 2-2'-bipyridine ligand covalently linked to **LmrR** binds to the catalytically active Cu(II)/**L4** complex and deactivates the artificial metalloenzyme. The addition of $Fe^{2+}$ ions traps the 2-2'-bipyridine ligands and frees the active $Cu^{2+}$ complex, which subsequently reactivates the catalyst. Hence, when applied to the Friedel-Crafts alkylation between α,β-unsaturated acyl imidazole **8** and 2-methyl indole, selectivities up to 88% *ee* were obtained thus demonstrating the synthetic potential of programmable artificial biohybrid catalysts.

### 3.2 Peptide

Recently, Hermann and co-workers identified cyclic peptides as a novel metallopeptide design containing only natural amino acids. The peptide scaffold was assembled by solid-phase peptide synthesis and cyclized by an intramolecular disulfide linkage between cysteines at the *N*- and *C*-terminus. To determine the importance of a particular residue, a small library of 15 cyclic nonapeptides was synthesized and optimized using the alanine scanning technique.[108] The ability of the histidine to complex $Cu^{2+}$ ions allowed to avoid the use of additional binding ligands.

These peptides were first evaluated on the Cu(II)-catalysed Diels-Alder cycloaddition, which led to the selection of shorter peptides that were ultimately used in the asymmetric Cu(II)-catalysed Friedel-Crafts alkylation. Interestingly, the truncated hexapeptide CGIARC afforded the highest selectivities with *ees* up to 99% in the Diels-Alder cycloaddition and 86% in the Friedel-Crafts alkylation (Figure 27).

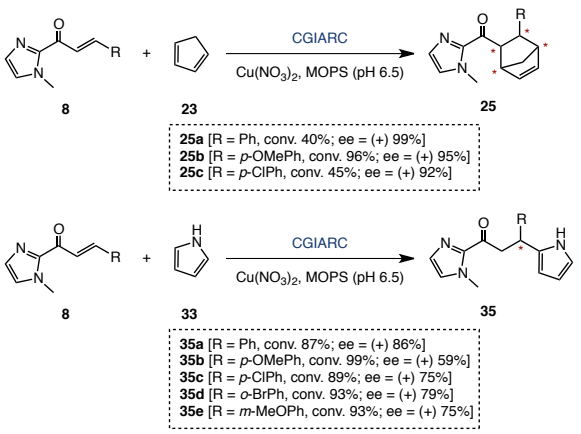



**Figure 27.** Cyclic peptide-based asymmetric Diels-Alder and Friedel-Crafts alkylation.

## 4. Conclusion

Biohybrid catalysis has emerged recently as a particularly powerful tool for the enantioselective synthesis of chiral building blocks and $\alpha,\beta$-unsaturated acyl imidazoles have undoubtedly been a key to this success. Indeed, these substrates have not only been found to be highly versatile, they were also shown to exhibit interesting reactivity patterns, a high compatibility with a large variety of bioscaffolds and are easily post-transformed. While various highly enantioselective C–C and C–O bond forming reactions have been unveiled, the use of $\alpha,\beta$-unsaturated acyl imidazoles in the context of asymmetric biohybrid catalysis is clearly still in its infancy and a plethora of new reactions are expected in the years to come.

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**Keywords:** Biohybrid catalysis • DNA • Acyl imidazole • Artificial metalloenzyme

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