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DNA-Based Asymmetric Inverse Electron-Demand Hetero-Diels-Alder**

Justine Mansot, Jimmy Lauberteaux, Aurélien Lebrun, Marc Mauduit, Jean-Jacques Vasseur, Renata Marcia de Figueiredo, Stellios Arseniyadis,* Jean-Marc Campagne* and Michael Smietana*

Abstract: While artificial cyclases hold great promise in chemical synthesis, we present here the first example of a DNA-catalyzed inverse electron-demand hetero-Diels-Alder (IEDHDA) between dihydrofuran and various α,β-unsaturated acyl imidazoles. The resulting fused bicyclic O,O-acetals containing three contiguous stereogenic centers are obtained in high yields (up to 99%) and excellent diastereo- (up to >99:1 dr) and enantioselectivities (up to 95% ee) using a low catalyst loading. Most importantly, these results show that the concept of DNA-based asymmetric catalysis can be expanded to new synthetic transformations offering an efficient, sustainable, and highly selective tool for the construction of chiral building blocks.

The field of bio-hybrid catalysis has evolved over the years to become a particularly powerful tool for the construction of carbon–carbon and carbon–heteroatom bonds, with metalloenzymes playing a key role.1 The double stranded helix of DNA has however recently integrated the bio-hybrid catalyst arsenal emerging as a valuable alternative. This new concept, which was first introduced by Roelfes and Feringa in 2005,2 is based on a transfer of chirality of the DNA double helix to a prochiral substrate and relies on a subtle association between an achiral transition metal catalyst and the DNA through either a covalent or a supramolecular interaction. Since the first example, which involved a Diels-Alder cycloaddition between an α,β-unsaturated 2-acyl pyridine and cyclopentadiene using a 9-aminoacridine-derived copper-binding diamine and salmon testes DNA (st-DNA), the concept of DNA-based asymmetric catalysis has been extended to various other synthetic transformations3 by a number of groups around the world. In particular, many efforts have been devoted to unveil new biomimetic DNA-based cycloaddition processes inspired by the seminal [4+2] Diels-Alder cycloaddition4,5 (Figure 1, A). This has resulted in the development of various key cycloaddition reactions including a [2+2] photocatalysed cycloaddition6 using a benzophenone-modified DNA as a photosensitizer (Figure 1, B) and two cyclopropanation reactions using either a Cu-dmbipy-DNA complex7 or a heme-DNA artificial enzyme8 (Figure 1, C). Surprisingly, despite all these efforts, there has been no example of an asymmetric DNA-catalyzed hetero-Diels-Alder cycloaddition reported in the literature so far. As a matter of fact, the number of natural or artificial biocatalysts capable of promoting a hetero-Diels-Alder cycloaddition are rather scarce.9,8 We report here the results of our endeavor which have led to the development of a highly stereoselective DNA-catalyzed inverse electron-demand hetero-Diels-Alder cycloaddition between α,β-unsaturated acyl imidazoles and dihydrofuran leading to the corresponding bicyclic O,O-acetals in high yields and excellent enantio- and diasteroselectivities (Figure 1, D).

The reaction between α,β-unsaturated 2-acyl imidazole9,10 1a and dihydrofuran 2 in the presence of [Cu(dmbipy)(NO3)2] and st-DNA was chosen as the benchmark reaction (Table 1). A thorough optimization study (see SI for the complete study) revealed that a 1:250 ratio between 1a and the heterodienophile 2, 3 mol% of the Cu(II) complex and a 1 mM bp concentration of st-DNA in a MOPS buffer (pH 6.5) at 4 °C for 3 days afforded the best results with the desired bicyclic cycloadduct 3a obtained in 83% ee and a 94:6 endo/exo ratio. Control experiments confirmed that the combination of the metallic cofactor [Cu(dmbipy)(NO3)2] and DNA was necessary to achieve both high conversions and high enantioselectivities. A higher concentration of the biohybrid catalyst did not improve the result...
while reducing the DNA concentration to 0.5 mM affected mainly the conversion. Interestingly, the addition of a co-solvent (2% v/v) such as DMSO, DMF, THF, ACN, DCM, and dioxane increased the substrate solubility as well as the conversion without affecting the stereoselectivity, with THF standing out as the optimum co-solvent (94:6 endo/exo ratio, 83% ee) (Scheme 1). A systematic circular dichroism (CD) study confirmed that the double helical structure of DNA was maintained in the presence of all the aforementioned co-solvents, which is consistent with previous studies reported in the literature. Moreover, varying the nature of the copper(II) complex by replacing 4,4’-dimethyl-2,2’-bipyridine (dmbpy), which binds to st-DNA through groove binding, by phenantroline (phen), which is a good DNA intercalator, or either 2,2’-6,2’-terpyridine (terpy) or dipyrind[3,2-a:2’,3’-c]phenazine (dpdz), which are known to bind to DNA through a mix of minor groove binding and intercalation, had a detrimental effect on both the conversion and the selectivity. These results are in agreement with the ones obtained for the Diels–Alder reaction; groove binding interactions allow more flexibility of the complex while maintaining the substrate in the second coordination sphere of the DNA helix.

With these results in hand, we next evaluated the substrate scope by subjecting a variety of α,β-unsaturated 2-acyl imidazoles (1b-o) to our optimized conditions; the results are depicted in Scheme 1. As a general trend, the corresponding bicyclic adducts 3b-o were obtained in moderate to high conversions ranging from 35% to >99%, excellent diastereoselectivities (endo/exo up to >99:1) and high enantioselectivities (ees up to 95%). Hence, the introduction of electron-donating substituents at the para position of the aromatic ring such as a methyl (3b, 89% ee, endo/exo=17:1), a methoxy (3c, 90% ee, endo/exo=9:1) or a thiomethyl (3e, 90% ee, endo/exo=12:1) had a detrimental effect on both the conversion and the selectivity. These results are in agreement with the ones obtained for the Diels–Alder reaction; groove binding interactions allow more flexibility of the complex while maintaining the substrate in the second coordination sphere of the DNA helix.
Table 2. Scale-up of the hetero Diels-Alder reaction and structural determination by NMR.

| Compound | Isolated Yield (scale) | ee (%), dr | | Coupling constants (Hz) | NOE effect |
|----------|------------------------|------------|-----------------------------|-------------|
|          |                        |            |                             | (c, solvent) |
| 3a       | 79% (255 mg, 1.2 mmol)| 88%, 12:1  | +6.0° (0.3, CH₂Cl₂)         | 4.0, 4.5    | strong |
| 3j       | 99% (105 mg, 0.7 mmol)| 73%, >99:1 | +9.7° (0.4, CH₂Cl₂)¹⁷       | 3.8, 6.4    | strong |
| 3l       | 88% (96 mg, 0.5 mmol) | 95%, 32:1  | +12.5° (0.6, CH₂Cl₂)        | 4.1, 4.4    | strong |

The nature of the heterodienophile was also evaluated using a selection of electron-rich alkenes, including 3,4-dihydro-2H-pyran, ethyl vinyl ether, 2-vinylxirane or para-methoxy styrene, but none of them afforded the desired IEDDA product. Considering that these reactions are assumed to proceed through a concerted, but asynchronous transition state, we associate this lack of reactivity with the lower nucleophilicity of these heterodienophiles.¹⁷

The endo-selectivity was confirmed by ¹H NMR analysis of compounds 3a, 3j and 3l, all obtained in high yields at reaction scales ranging from 0.5 to 1.2 mmol, which also demonstrates the robustness of the method (Table 2). Hence, all three compounds adopt a bicyclic cis junction characterized by a low coupling constant between H₃a and H₅a (J(H₅-H₃a) ~ 4.0 Hz) and a W coupling between H₅ and H₃a (J(H₅-H₃a) ~ 1.2 Hz). In addition, the relatively low coupling constant between H₄ and H₃a indicates that these two protons are facing each other. Finally, a NOESY experiment established a correlation between H₄ and H₅a consistent with an endo-selective cycloaddition. As for the absolute configuration, the latter was ascertained by comparing the specific optical rotation value of the endo product 3j (3aR, 4R, 7aS), which was obtained in quasi-quantitative yield on a 105 mg scale, with the one reported in the literature,¹⁸ while all other products were assigned by analogy. Compound 3j was also engaged in a hydrogenation reaction to further support our assignment (Table 2). The reduction of the enol double bond proceeded smoothly and preserved the integrity of the O,O-acetal affording compound 4 as a single diastereoisomer in quantitative yield and with no erosion of the selectivity.¹⁸

In conclusion, we present here the first example of an asymmetric DNA-catalyzed inverse electron-demand hetero-Diels-Alder reaction. The reaction allows the formation of fused
bicyclic O,O-acetals in high yields (up to 99%) and excellent diastereo- and enantioselectivities (up to >99:1 dr, up to 95% ee). The method was applied to a variety of α,β-unsaturated 2-acyl-imidazoles and could be easily scaled up. Most importantly, this reaction, which has no equivalent in the metalloenzyme arsenal obtained through directed evolution, emphasizes furthermore the versatility of DNA-based asymmetric catalysis and its efficacy in mimicking nature’s hetero-Diels-Alderases in water. Ultimately, we hope this will trigger new developments in the field and inspire the development of other cycloaddition reactions.

Conflicts of interest
The authors declare no competing financial interest.

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Keywords: Inverse electron-demand hetero-Diels-Alder • DNA • biohybrid catalysis • Copper • [4+2] cycloaddition

[5] For the presence of 2 v% of co-solvent, all the CD spectra exhibited very similar features with only a slight decrease of the positive band at about 260-280 nm.
Not just a [4+2] cycloaddition! DNA can also catalyse inverse electron-demand hetero-Diels-Alder (IEDHDA) cycloadditions between dihydrofuran and α,β-unsaturated acyl imidazoles. The resulting fused bicyclic O,O-acetals containing three contiguous stereogenic centers can be obtained in high yields (up to 99%) and excellent stereoselectivities (up to >99:1 dr and up to 95% ee) using a low catalyst loading.

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