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To cite this version:


HAL Id: hal-02512892
https://hal.umontpellier.fr/hal-02512892
Submitted on 16 Apr 2020

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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 diastereoselectivity (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. The double stranded helix of DNA has however recently integrated the bio-hybrid catalytic arsenal emerging as a valuable alternative. The 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-aminacridine-derived copper-binding diamine and salmon testes DNA (st-DNA), the concept of DNA-based asymmetric catalysis has been extended to various other synthetic transformations[5] by a number of groups around the world including ours.[14] In particular, many efforts have been devoted to unveil new biomimetic DNA-based cycloaddition processes inspired by the seminal [4+2] Diels-Alder cycloaddition[2a-3a] (Figure 1, A). This has resulted in the development of various key cycloaddition reactions including a [2+2] photocatalysed cycloaddition[6] using a benzophenone-modified DNA as a photosensitizer (Figure 1, B) and two cyclopropanation reactions using either a Cu-dmbipy-DNA complex[6] or a heme-DNA artificial enzyme[7] (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.[8,9] 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 diastereoselectivities (Figure 1, D).

The reaction between α,β-unsaturated 2-acyl imidazole[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 O,O-acetals in high yields and excellent enantio- and diastereoselectivities (Figure 1, D).

Figure 1. DNA-based asymmetric cycloadditions

[**] Supporting information and the ORCID identification numbers for the authors of this article can be found under: https://doi.org/
Table 1. Systematic study.24

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<th>Cu^II-dmbipy (mM%)</th>
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<th>Co-solvent (%)</th>
<th>Conv (%)</th>
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Reactions conditions: 1a (1 mM), 2 (250 equiv), in a 20 mM MOPS buffer solution pH 6.5 for 3 d at 4 °C. Conversions, de, and ee were determined by High Pressure Liquid Chromatography (HPLC) analysis.

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,11 which is consistent with previous studies reported in the literature.2 Moreover, varying the nature of the copper(II) complex by replacing 4,4′-dimethyl-2,2′-bipyridine (dmdbpy), which binds to st-DNA through groove binding, by phenanthroline (phen), which is a good DNA intercalator, or either 2,2′-6′,2′-terpyridine (terpy) or dipyrirdo[3,2-a′:2′,3′-c]phenazine (dpdz), which are known to bind to DNA through a mix of minor groove binding and intercalation,13 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=19:1) gave the best results.

Scheme 1. Reaction scope.24 All reactions were carried out with st-DNA (1 mM bp concentration), 1a-o (1 mM), 2 (250 equiv), and [Cu(dmbipy)NO3]2 (0.03 mM) in a 20 mM MOPS buffer solution pH 6.5 with 2% THF as co-solvent for 3 d at 4 °C. Conversions and ees were determined by High Pressure Liquid Chromatography (HPLC) analysis.
ee, endo/exo >99:1), did not alter the selectivity, however it is worth pointing out the decrease in reactivity observed in the case of the thioanisole derivative most probably due to the ability of the sulfur atom to chelate copper ions. The introduction of a slightly electron-withdrawing substituent such as a fluorine atom in the case of the thioanisole derivative most probably due to the ability of the sulfur atom to chelate copper ions. The introduction of a slightly electron-withdrawing substituent such as a fluorine atom in the case of the thioanisole derivative most probably due to the ability of the sulfur atom to chelate copper ions. 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.

The endo selectivity was confirmed by \(^1\)H 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 H\(_4\) and H\(_{7a}\) (\(\langle J \rangle H_4-H_{7a}\approx 4.0\) Hz) and a W coupling between H\(_3\) and H\(_{3a}\) (\(\langle J \rangle H_3-H_{3a}\approx 1.2\) Hz).

In addition, the relatively low coupling constant between H\(_4\) and H\(_{7a}\) indicates that these two protons are facing each other. Finally, a NOESY experiment established a correlation between H\(_4\) and H\(_5\) in compounds 3a and 3j, 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, 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 with no erosion of the selectivity.

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-acylimidazoles 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.

Acknowledgements

This research was supported by the Agence Nationale de la Recherche (D-CYSIV project; ANR-2015-CE29-0021-01).

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

[8] In 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.
[15] NOESY experiments confirmed the syn-addition of H2 on the Si face of 3i. Strong NOE effects were observed between H2 and both Hα and Hβ in compound 4.

10.1002/chem.202000516
Accepted Manuscript
Not just a [4+2] cycloaddition! DNA can also catalyse inverse electron-demand hetero-Diels-Alder (IEDHDA) cycloadditions between dihydrofuran and \( \alpha,\beta \)-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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