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

Justine Mansot, Jimmy Lauberteaux, Aurelien Lebrun, Marc Mauduit, J.J. Vasseur, Renata Marcia de Figueiredo, Stellios Arseniyadis, Jean-marc Campagne, Michaël Smietana

To cite this version:


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

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
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 diastereoselection (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 catalyst arsenal emerging as a valuable alternative. This new concept, which was first introduced by Roelfes and Feringa in 2005, is based on a transfer of chirality of the DNA double helix to a chiral 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 transformations 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 cycloaddition$^{[2,3a-d]}$ (Figure 1, A). This has resulted in the development of various key cycloaddition reactions including a [2+2] photocatalysed cycloaddition$^{[5]}$ 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 enanti- 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)(NO$_2$)$_2$] 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)(NO$_2$)$_2$] and DNA was necessary to achieve both high conversions and high enantioselectivities. A higher concentration of the biohybrid catalyst did not improve the result

---

Figure 1. DNA-based asymmetric cycloadditions

---

[1] J. Mansot, A. Lebrun, Dr. J.-J. Vassur, Prof. Dr. M. Smietana Institut des Biomolécules Max Mousseron, CNRS, UMR 5247 Université de Montpellier, ENSCM Place Eugène Bataillon 34095 Montpellier (France) E-mail: michael.smietana@umontpellier.fr

J. Lauberteaux, Dr. R. Marcia de Figueiredo, Prof. Dr. J.-M. Campagne Institut Charles Gerhardt, Université de Montpellier, CNRS, ENSCM, Avenue Emile Jeanbrau, 34296 Montpellier, France E-mail: jean-marc.campagne@enscm.fr

M. Mauduit Univ Rennes, Ecole Nationale Supérieure de Chimie de Rennes, CNRS, ISCR UMR 6226, F-35000 Rennes (France)

Dr. S. Arseniyadis Queen Mary University of London School of Biological and Chemical Sciences Mile End Road, London, E1 4NS (UK) E-mail: s.arseniyadis@qmul.ac.uk

[**] Supporting information and the ORCID identification numbers for the authors of this article can be found under: https://doi.org/10.1002/chem.202000516
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, 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 \( \alpha,\beta \)-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, 81% ee)
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.\cite{16} The introduction of a slightly electron-withdrawing substituent such as a fluorine atom (3f, 88% ee, endo/exo>12:1) was not detrimental however more electron-deficient aromatic rings such as the p-bromo- and the p-nitrobenzene derivatives led to very low conversions (data not shown). β-Heteroaromatic acyl imidazoles (1g-i) were also found to be excellent substrates as showcased by the high yields and remarkable diastereo- (endo/exo up to >99:1) and enantioselectivities (ees ranging between 76% and 85%) obtained for the resulting bicyclic O,O-acetals 3g-i. Finally, in contrast to the β-aryl- and the β-heteroaryl-substituted substrates (1a-i), complete conversions were observed with practically all the β-alkyl-substituted derivatives (1j-n) tested. Moreover, the endo/exo ratios appeared to decrease and the ees increase as the size of the alkyl chain became more bulky. The prevalence of the 2-acyl-methylimidazole motif in bio-hybrid catalysis was further confirmed by the results obtained with the analogous 2-acyl-isopropylimidazole precursor, which afforded the corresponding cycloadduct 3o in 90% conversion albeit only 61% ee, or with the related α,β-unsaturated 2-acylpyridine, the 1,3-diphenyl-2-propenone and the 2-methyl-1-(thiazol-2-yl)prop-2-en-1-one, which failed to produce any product (data not shown).

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-methoxystyrene, 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.\cite{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 H\textsubscript{7a} and H\textsubscript{3a} (\(\delta\text{J}_{H_7a-H_{3a}} \approx 4.0\) Hz) and a W coupling between H\textsubscript{3} and H\textsubscript{3a} (\(\delta\text{J}_{H_3-H_{3a}} \approx 1.2\) Hz). In addition, the relatively low coupling constant between H\textsubscript{4} and H\textsubscript{3a} indicates that these two protons are facing each other. Finally, a NOESY experiment established a correlation between H\textsubscript{4} and H\textsubscript{7a} by the strong NOE effect (\(\delta\text{J}_{H_4-H_{7a}} \approx 1.2\) Hz).

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 diastereoselectivities (up to >99:1 dr, up to 95% ee). The method was applied to a variety of α,β-unsaturated 2-acyl-imidazo[4,5-c]pyridines 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


[12] In the presence of 2 v/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.

[19] NOESEY experiments confirmed the syn-addition of H2 on the Si face of 31. Strong NOE effects were observed between H2 and both H3 and H4 in compound 4.
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.

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