



## GENE DELIVERY WITH POLYCATIONIC FULLERENE HEXAKIS-ADDUCTS

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Polyplexes prepared from plasmid DNA and globular compact polycationic derivatives constructed around a fullerene hexakis-adduct (generation 3 shown in figure 1) core have shown remarkable gene delivery capabilities.

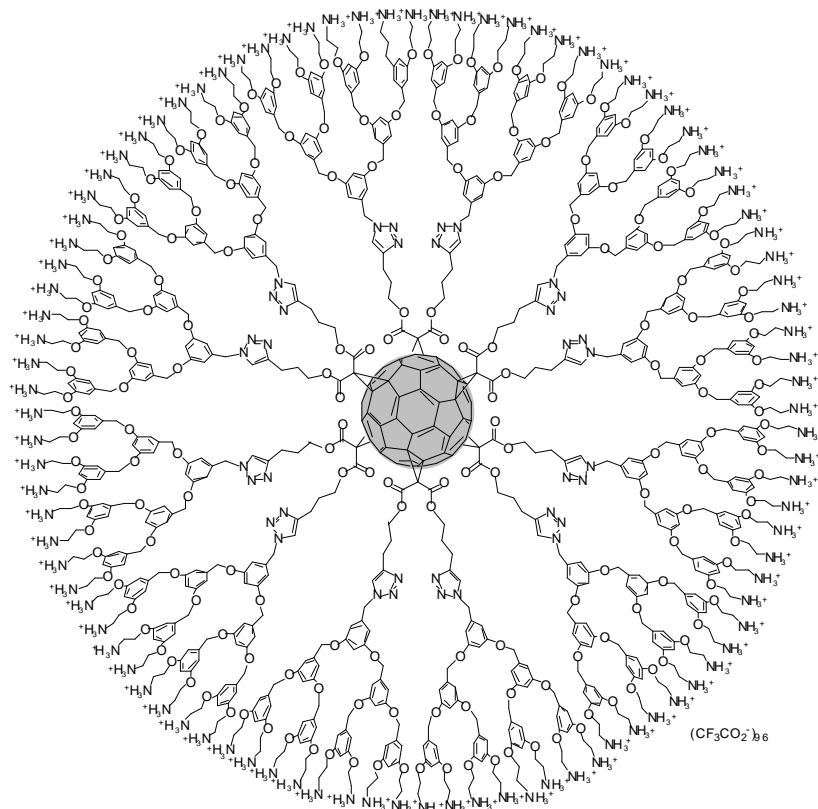


Figure 1. Generation 3 of polycationic fullerene

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*Chem. Commun.*, 2011, **47**, 4640–4642.



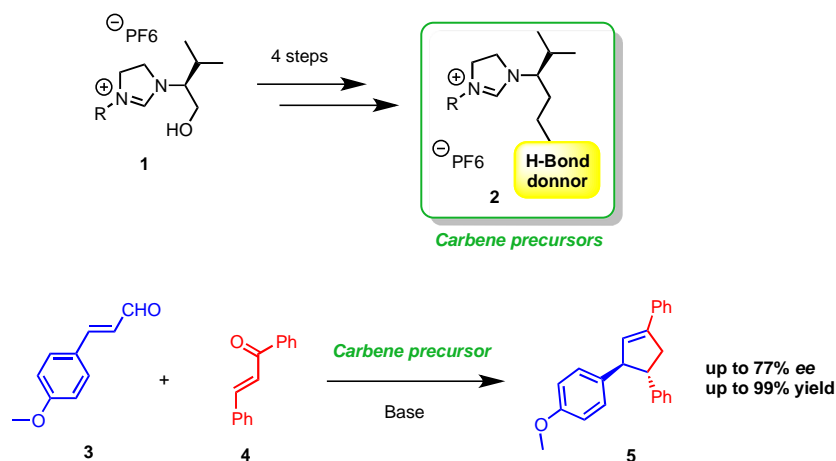
# ENANTIOSELECTIVE ANNULATION REACTION OF HOMOENOLATE CATALYSED BY BIFUNCTIONAL N-HETEROCYCLIC CARBENES

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Since the first isolation and characterisation of stable N-heterocyclic carbenes (NHC) by Arduengo 20 years ago,<sup>1</sup> NHC's have become extremely popular ligands in organometallic reactions, and more recently as powerful organocatalysts.<sup>2</sup> Recently, Nair described the synthesis of racemic *trans*-1,3,4,-triarylcyclopentenes by a remarkable annulation of enals and chalcones catalysed by achiral imidazolium-derived carbenes, reportedly *via* homoenolate equivalent.<sup>3</sup>

In this work a series of new chiral bifunctional NHCs has been synthesised from **1**.<sup>4</sup> These catalysts have proved to be efficient in the enantioselective version of this reaction. For example, the reaction of 4-methoxycinnamaldehyde (**3**) with chalcone (**4**) in the presence of catalytic amount of the NHC precursor **2** and base afforded the cyclopentene **5** in 78% ee. Current work concentrates on the optimization of the molecular structure of the NHC catalyst to reach high yields and enantiomeric excesses in this reaction.



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## SCREENING FOR BIOORTHOGONAL CHEMICAL LIGATION REACTIONS

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The post-genomic era has seen a huge increase in the importance of imaging techniques, which culminated in the noble prize 2008<sup>[1]</sup>. In order to be able to address a wider variety of biological targets and to reduce the alterations in the investigated organism a two step process was proposed<sup>[2]</sup>. In this strategy as a first step a small reporter tag is introduced into the organism via its own biosynthetic machinery or any other means and then in a second step this tag is label via a reactive reporter containing e.g. a dye for imaging or a biotin for isolation purposes.

We have developed a three step screening process for new bioorthogonal ligation reactions. In a facile and easy to access HPLC screening assay the reactions are tested for their reactivity and are compared versus SpAAC (Strain promoted Alkyne Azide Cycloaddition). In a second step the reactions are compared to CuAAC (Copper catalyzed AAC) via a fluorescence based assay with the help of the dye/quencher pair Dansyl/Dabsyl. In order to establish bioorthogonality both assays offer the opportunity to work in different complex biological media e.g. serum and cell lysate. In the last step the reactions are tested in living HuH7 cells to proof the suitability of the reactions in living organism. In order to do so, we established a test system utilizing modified paclitaxel to which TAMRA is ligated via the bioorthogonal reaction. The intensity of localised fluorescence inside the cells after several subsequent washing steps then proofs the grade of suitability of the new reactions.

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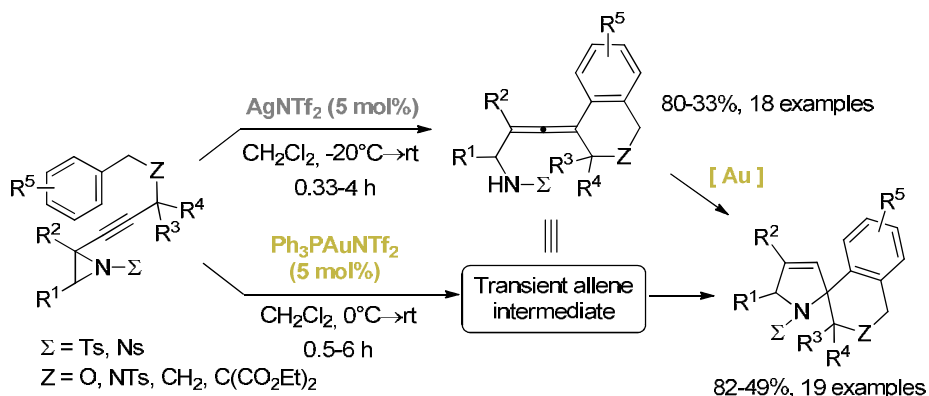
# COINAGE METALS-CATALYZED REACTIONS OF ARYL ALKYNYL AZIRIDINES: SILVER(I)-SINGLE VS GOLD(I)-DOUBLE CYCLIZATIONS

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Since the early 2000s, the utility of gold (I) or (III) salts has attracted the synthetic organic chemists' attention. This interest is mostly due to their strong  $\pi$  acidity, conferring them the properties of carbophilic Lewis acids. For this reason, gold salts were extensively used in the past few years for the activation of unsaturated carbon-carbon bonds, allowing the access to molecular complexity. Along carbophilicity, it has been demonstrated that gold salts also exhibit strong  $\sigma$  acidity<sup>1</sup>, although this aspect seems to be underrated when focusing on recent synthetic developments. The same considerations can be made about the reactivity of silver(I) salts, which possess identical properties but to a lower extent.

In our laboratory, recent work on coinage metals-mediated cascade reactions highlighted this dual Lewis acid character. Indeed, treatment of alkynyl-oxirane or -aziridine scaffolds by Au(I) or Ag(I) salts in the presence of internal or external nucleophiles led to various cores of potent synthetic utility such as divinylketones, furans or pyrroles<sup>2</sup>. In the present work, we demonstrate that a wide range of alkynylaziridines carrying a conveniently positioned aryl group could be converted into allenylidene isochromans, isoquinolines or tetrahydronaphthalene derivatives with silver(I) salts, and into 1-azaspiro[4.5]decane derivatives with gold(I) complexes<sup>3</sup>.



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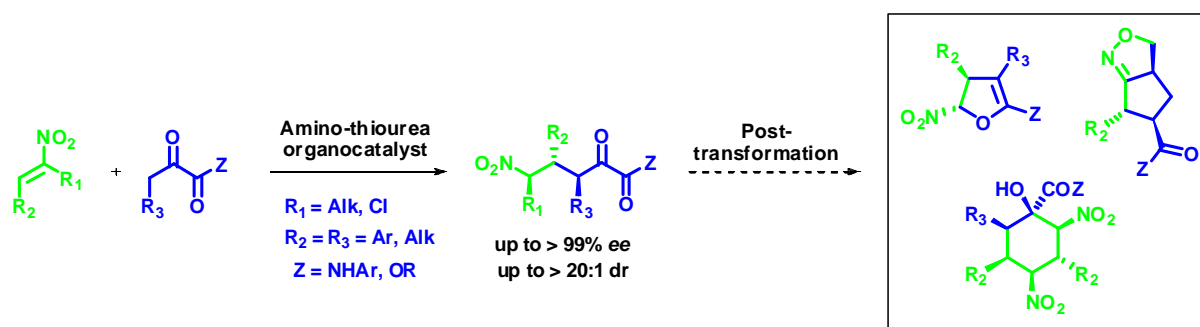
# NOVEL REACTIVITY OF 1,2-DICARBONYL COMPOUNDS IN ASYMMETRIC SYNTHESIS

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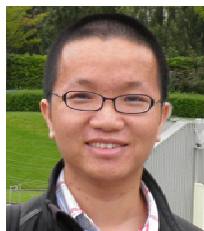
Nowadays, the development of eco-compatible processes is becoming more and more important given our planet's environmental situation. To fulfill these ecological and economical needs, the research towards organocatalytic enantioselective methods to access enantiopure molecules has received much attention in the last ten years.<sup>1</sup> Such methodologies have many advantages in terms of efficiency, selectivity and environmental benefits. More particularly, the asymmetric organocatalysed Michael addition of various nucleophiles to nitroolefins represents a very useful reaction as the reaction products can easily be converted into highly functionalised cyclic or acyclic building blocks.

In this context, we became interested in the challenging reactivity of 1,2-dicarbonyl compounds as pronucleophiles in organocatalyzed transformations as only few examples have been reported so far.<sup>2</sup> We successfully developed the first enantioselective organocatalysed Michael additions of  $\alpha$ -ketoamides and  $\alpha$ -ketoesters onto nitroolefins with excellent stereoselectivities and very good yields.<sup>3,4</sup> The Michael adducts can be used as versatile synthetic platforms to make five-membered carbo- and heterocycles, as well as six-membered carbocycles with the creation and control of additional stereocenters.



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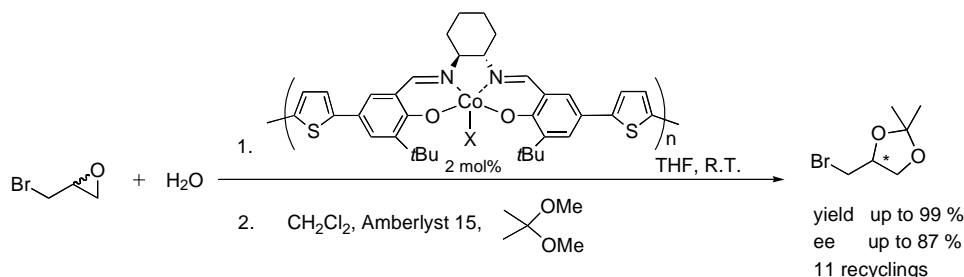
# ELECTROCHEMICALLY AND CHEMICALLY POLYMERIZED SALEN COBALT COMPLEXES FOR THE HYDROLYTIC KINETIC RESOLUTION OF TERMINAL EPOXIDES.

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Hydrolytic Kinetic Resolution (HKR) of epoxides catalyzed by Jacobsen's salen cobalt complex represents one of the most powerful procedures to get enantioenriched epoxides. Holding considerable promise with regard to meeting all criteria ever expected for a kinetic resolution, it has been applied for the commercial production of several useful chiral building blocks<sup>1</sup>. Enormous efforts have been devoted to recover the catalyst of this reaction, but no existing catalytic system is stable enough to be recycled more than 10 cycles because of the continuing deactivation of the catalyst in presence of the starting materials.<sup>2</sup>

Electrochemical polymerization has been verified as efficient strategy for the heterogeneization of salen chromium complexes in various asymmetric transformations in our lab<sup>3</sup>. To apply this strategy to the HKR of epoxides, 10 electrochemically polymerizable salen cobalt complexes have thus been synthesized and tested in the dynamic HKR of various terminal epoxides. Enantioselectivity of these complexes in homogeneous conditions depends strongly on the nature of the axial ligand ( ee varied from 0 to 97 %).



Scheme 1. Dynamic HKR of epibromohydrin with polymerized salen cobalt complexes

In the other hand, most efficient and available complex was polymerized chemically or electrochemically and engaged into HKR of epibromohydrin. Among these recoverable catalysts, one polymer generated electrochemically, which contains both non-nucleophilic axial ligand and nucleophilic ligand, could afford the desired product with excellent yield (up to 99 %) and ee (up to 87%) even after 11 runs. (schema 1)

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# TETRAAZAARENES BY THE CERAMIDONINE APPROACH

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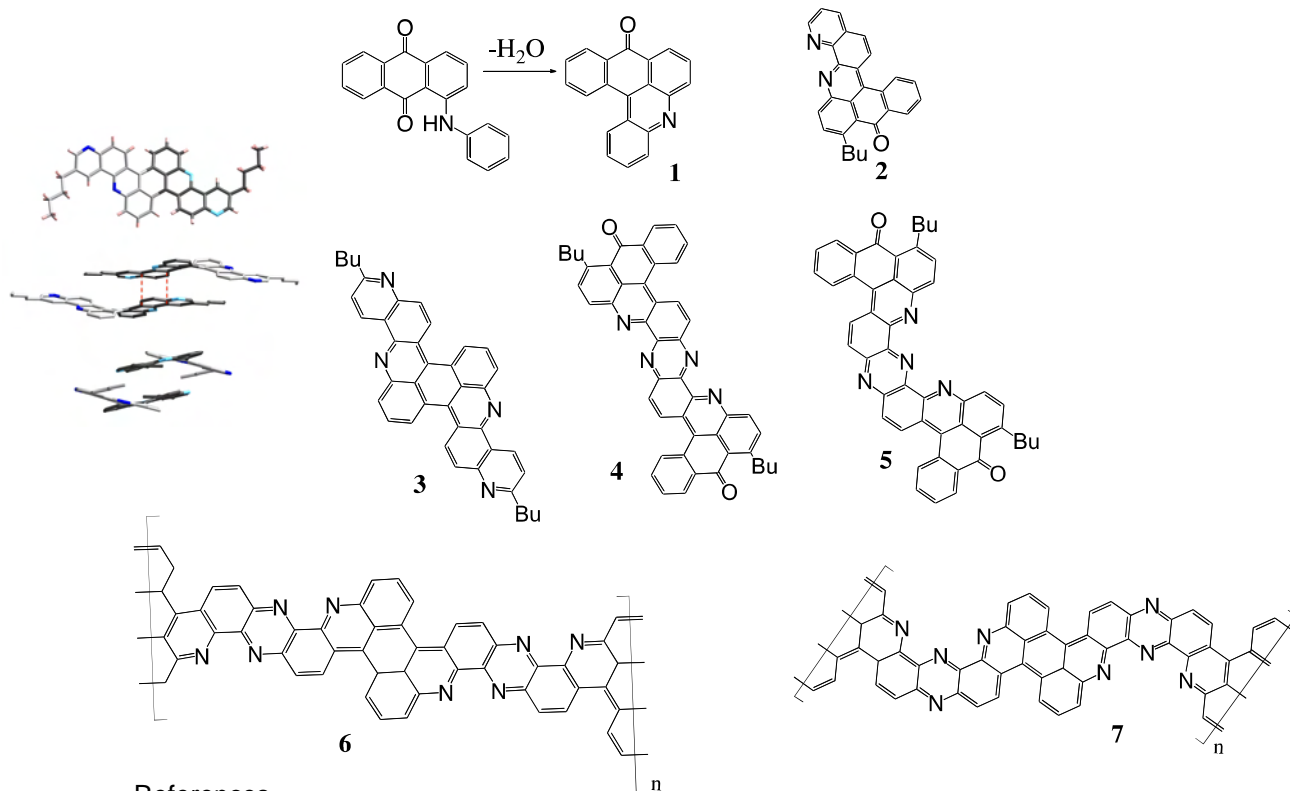
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The synthesis of extended heteroarenes *via* the acid-promoted dehydrocyclisation of arylamino-anthraquinones is examined as an approach to highly conjugated electron acceptor materials and eventually to heterographene nanoribbons. Whilst the latter perspective is found to remain challenging, the former is exemplified by the synthesis of extended tetraazaheterocycles bearing solubilising alkyl substituents. The heart-shaped azaketone Ceramidonine **1** is accessible via condensation of aniline with 1-substituted anthraquinones followed by acid-catalyzed ring closure. We have found that analogous condensations of azaaromatic amines such as 8-aminoquinoline lead to ceramidonines such as **2** with potentially metal-chelating bay regions. Double condensation-cyclization sequences with either azaaromatic diamines or 1,5-disubstituted anthraquinones lead to extended nonplanar cera-bisamidines and bis-ceramidonines such as **3**, **4** and **5**, which are key stepping stones to electron-deficient and multiply chelating ribbon-type polymers such as **6** and **7**.



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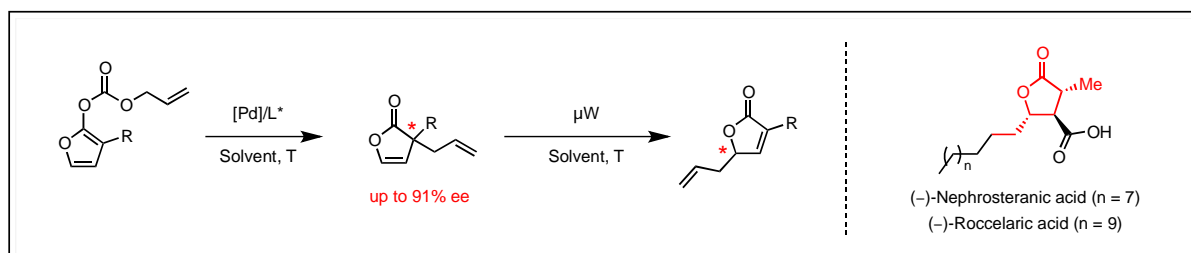


## EXPLORING CHEMICAL REACTIVITIES TO MAXIMIZE STRUCTURAL DIVERSITY: APPLICATION TO NATURAL PRODUCT TOTAL SYNTHESIS

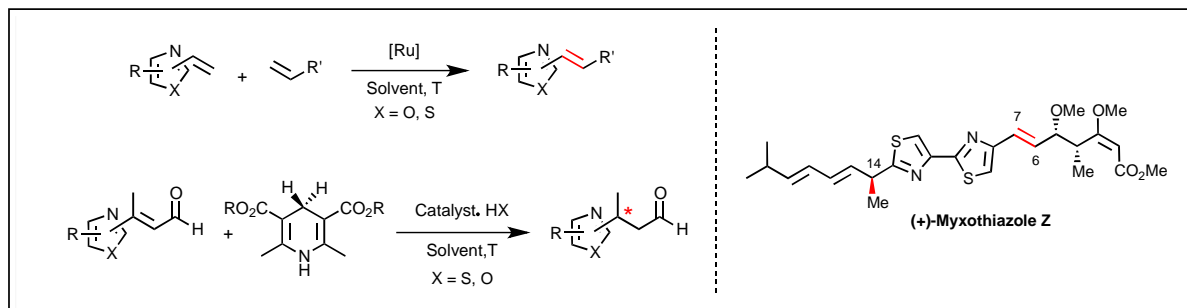
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For the past several years, the group has focused on the development of useful synthetic tools and executing creative and efficient routes towards natural products with promising biological profiles. In this context, we recently applied the enantioselective palladium-catalyzed decarboxylative allylic alkylation reaction to a new class of substrates, namely allyl dienol carbonates. This method allowed a particularly straightforward access to furanones bearing an  $\alpha$ -quaternary stereogenic center in both high yields and high enantioselectivity. Additionally, by subjecting these furanones to a stereospecific [3,3]-sigmatropic Cope rearrangement, we were able to afford the analogous  $\gamma$ -allylated furanones which were eventually used in the total synthesis of two natural products: (-)-nephrosteranic acid and (-)-roccelagic acid.<sup>[1]</sup>



We've also been interested in the development of useful synthetic tools toward the synthesis of thiazol-containing natural products as this motif is present in a number of compounds exhibiting interesting biological properties. Surprisingly, while the olefin cross-metathesis and the enantioselective organocatalytic conjugate reduction of  $\alpha,\beta$ -unsaturated aldehydes have been widely used on a number of substrates, there were no examples involving thiazol-containing substrates. These two key transformations were eventually developed<sup>[2],[3]</sup> and applied to the total synthesis of various natural products including melithiazole C,<sup>[4]</sup> cystothiazole A<sup>[5]</sup> and more recently (+)-myxothiazole Z<sup>[6]</sup>.



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