NICKEL PHOTOREDOX CATALYSIS

## Doubling up

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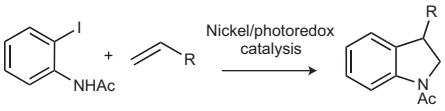
Nickel catalysis has gone from strength to strength in recent years. The success of nickel is often ascribed to its ability to adopt numerous oxidation states, with all four from 0 to +3 being readily accessible. Typically in cross-coupling reactions, a nickel centre will go through either a Ni(II)/Ni(0) or a Ni(III)/Ni(I) cycle, though recent work has shown that it is possible to go through several oxidation states in one reaction, and this allows some interesting reactivity to be observed. Now, Sarah Tasker and Timothy Jamison at MIT have made use of nickel's interesting redox behaviour, combining nickel-catalysis and photoredox-catalysis to synthesize indolines.

Unlike for indoles — their unsaturated counterpart — one-step annulation reactions to yield indolines are rare and often have limited scope. Based on the




groups' previous work in nickel catalysed cross-couplings, they considered combining a Heck coupling with carbon–nitrogen bond formation. It was postulated that a substrate containing an appropriately placed nitrogen atom could intercept one of the intermediates of the Heck reaction, forming a new nitrogen–carbon bond and creating the indoline core. Unfortunately very little product was observed — indeed it appeared that no catalytic turnover was being achieved owing to the difficultly of C$sp^3$–N reductive elimination from a Ni(II) intermediate. Tasker and Jamison then turned to photoredox catalysis in order to convert the stable Ni(II) intermediate into a more labile Ni(III) species via a one-electron oxidation. The use of a $Ru(bpy)_3(PF_6)_2$ photoredox catalyst and visible-light irradiation gave yields above the catalyst loading and further optimization gave yields of up to 90% of the heterocyclic product.

With a functioning catalytic system in hand, the scope of the coupling was explored. The reaction was shown to be relatively insensitive to electronic effects, with both electron-donating and electron-withdrawing groups tolerated on the arene. It was somewhat more limited by sterics, and arenes with substituents in the 3- or 6-positions gave reduced yields. The alkene coupling partner could be varied widely with generally good yields overall. *EB*

SYNTHETIC BIOLOGY

## Caught in a TRAP

*ACS Chem. Biol.* http://doi.org/6j9 (2015)

Many processes inside cells are controlled by protein–protein interactions and therefore developing new methods to regulate the assembly of protein structures

HYDROGELS

# Coordination driven gelation

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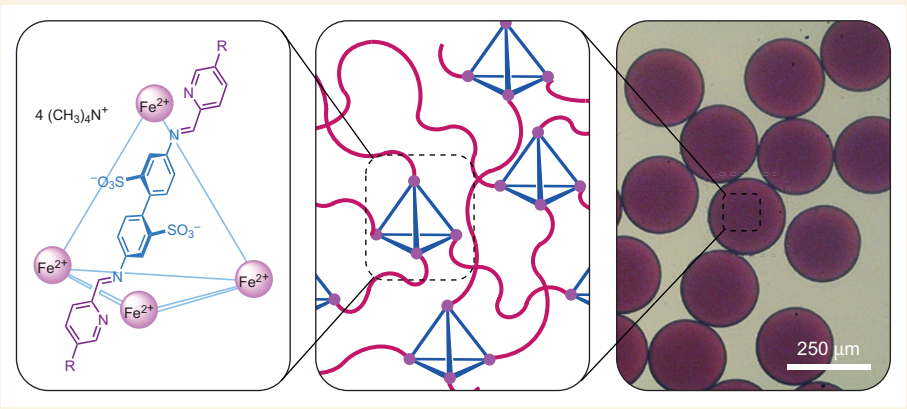
Hydrogels are an intriguing class of material — despite being composed principally of water, they are solid thanks to an internal hydrophilic network. Mucus, a sticky biological hydrogel, typically consists of networks of protein–polysaccharide polymer chains, whilst soft contact lenses, which are both strong and gas permeable, are made from silicone-based hydrogels. These two examples demonstrate the breadth of both hydrogel properties and potential applications.

While much is now known about how to make hydrogels, chemists are still working to add functionality. To this end they have recently exploited the interaction between organic ligands and metal ions to generate the non-covalent crosslinking necessary to turn a solution of polymers into an aggregated gel. Extending this approach, Jonathan Nitschke and his team from the University of Cambridge and Tokyo Institute of Technology, have employed a clever technique to achieve ligand synthesis, cage formation and gelation in a single step. Previously, they succesfully employed the synthesis of supramolecular cages by metal-templated condensation of rigid bisamines and 2-formylpyridines.






However in this instance, since the formylpyridines used are already pre-functionalized by substantial polyethylene glycol chains ($M_n$ = 1000 g mol$^{-1}$), the complexation into a cage upon addition of metal ions simultaneously enforces polymer aggregation, and thus drives gelation. By controlled mixing of precursor solutions within a microfluidic reactor, Nitschke and colleagues are also able to fabricate regularly sized microparticles of their cage-crosslinked hydrogels.

Within the hydrogel, the cages retain their ability to selectively host guest-molecules with complementary steric and electronic properties. Since the imine bond formation is reversible, disassembly of the cage can be triggered by the introduction of competitive amines or aldehydes, which releases the payload and ultimately causes dissolution of the entire hydrogel. These properties may render these materials practically useful, perhaps as drug delivery vehicles. For example, a similar supramolecular cage could selectively host a therapeutic payload within a biocompatible hydrogel. The application of an external stimulus, or indeed a change in local environment (such as pH) could then trigger payload release. *TF*