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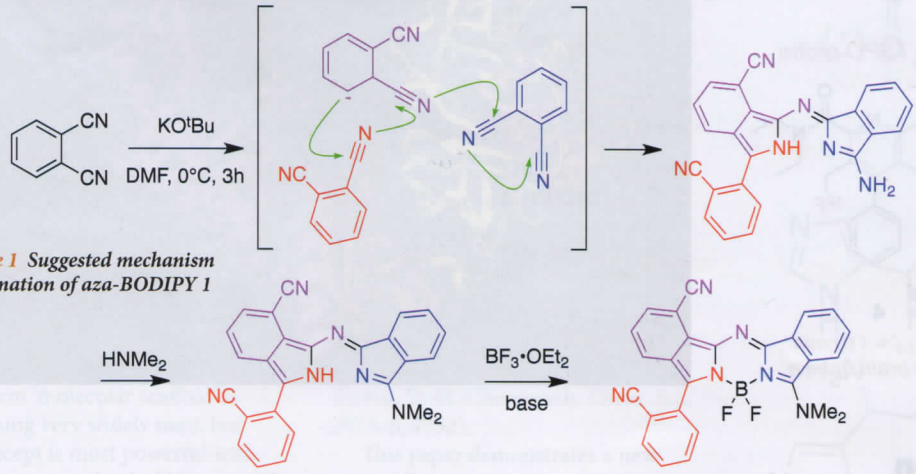
Biomedical



Scheme 1 ***Suggested mechanism for formation of aza-BODIPY 1***

1
100 g scale, 45 %
$\lambda_{max\ abs}$ 591 nm
$\lambda_{max\ emiss}$ 654 nm
Φ = 0.34

Scalable synthesis of an aza-BODIPY dye

Aza-BODIPY dyes are useful fluors that absorb and emit at longer wavelengths than typical BODIPY dyes or fluoresceins. However, applications of aza-BODIPYs are constrained by their syntheses, which involve several steps, and by the fact that most approaches are only suitable for systems containing four aryl groups.

Work by You and co-workers from Nanjing University is therefore a welcome development because they are able to prepare the fluor (**1**, **Scheme 1**) on a 100g scale in 45% yield (*Angew. Chem. Int. Ed.*, 2015, 54, 9070).

The paper focuses on the fluor pH sensitivity, but more exciting is the implication that nucleophiles other than dimethylamine could be added to obtain different fluors, via a very direct approach.

Photoclick reactions of 2H-azirines

It is known that *2H*-azirines can be opened under photochemical conditions to generate nitrile ylids which may undergo 1,3-dipolar addition reactions *in situ*. Absorption of the light in these reactions must occur via some chromophore, and that typically can be a 2-aryl substituent.

The Barner-Kowolliks group at Karlsruhe Institute of Technology, Germany, made that aryl group a pyrene; that was clever because the absorption maximum is around 400nm, just short enough to give the compound sufficient light-stability to be prepared in the lab, but long enough for activation via LEDs.

Reactions of this pyrene *2H*-aziridine (**2**) can therefore be triggered at the flick of a switch to give a variety of cycloadducts, just two of which are shown in Scheme 2.

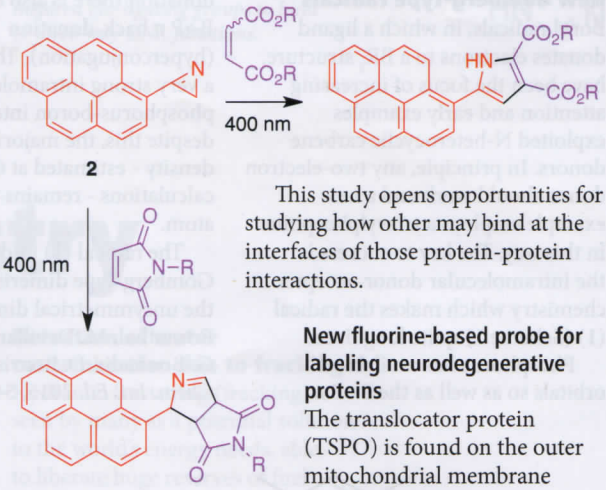
These types of processes may have application in polymer ligation reactions, including biopolymers, and for fashioning other types of new materials.

How tumour cells fight to breathe

In the tightly packed, low oxygen environment of a solid tumour, rapidly propagating cells tend to suffocate. In response, they use physiological tactics to increase blood supply (angiogenesis), and production of red blood cells in that area (secretion of erythropoietin, *ie* erythropoiesis).

In the molecular mechanisms that facilitate these responses, at the centre of midfield, making all the right moves, are the protein-protein complexes HIF1α•ARNT and HIF2α•ARNT. When there is plenty of oxygen around, the HIF components are oxidised at Pro-residues to hydroxyprolines; this triggers conformational changes leading to ubiquitinylation, and their fate is sealed. However, when oxygen is tight (hypoxia) HIF proteins accumulate, they associate with ARNT. These complexes enter the nucleus and bind specific DNA sequences (hypoxia response elements, HREs), beginning protein expression cascades that lead to angiogenesis, erythropoiesis and other adjustments to the cell's physiology.

Up until a paper by Rastinejad at The Sanford Burnham, Florida, US, there was only limited structural data on HIF•ARNT complexes, and not the ones most relevant to cancer (*Nature*, doi: nature14883). In this landmark contribution, the group reports full structural characterisation of HIF1α•ARNT and HIF2α•ARNT; how these complexes can capture a couple of small molecules known to perturb the process; and how they bind to HREs.



Scheme 2 ***Photoclick reactions triggered by an LED***

This study opens opportunities for studying how other may bind at the interfaces of those protein-protein interactions.

New fluorine-based probe for labeling neurodegenerative proteins

The translocator protein (TSPO) is found on the outer mitochondrial membrane in several key organs like the brain. TSPO is overexpressed in response to brain injury and neurodegeneration hence it can serve as an early indicator for brain tumours, stroke-induced brain injury, and neurodegenerative diseases, such as Alzheimer's.

The most widely used ligand for *in vivo* imaging of TSPO is ^{11}C-labelled (**3**), but this has a poor brain uptake, displays low signal-to-noise ratio, and is inconvenient to make and manipulate due to the short half-life

of ^{11}C ($t_{1/2}$ = 20.4min). Consequently, Sutherland and co-workers made the quinoline-2-carboxamide (4) that imaged TSPO better in positron emission tomography (PET) *in vivo* (*Chem. Sci.* 2015, 7, 4772).

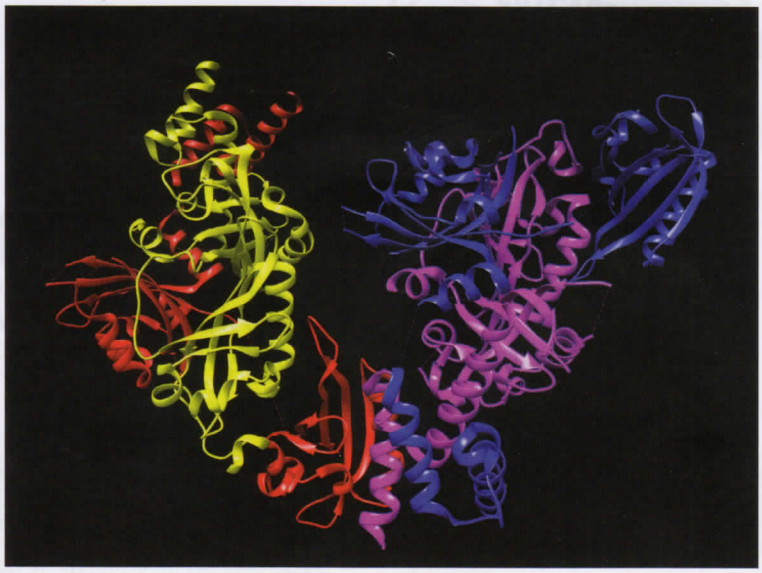
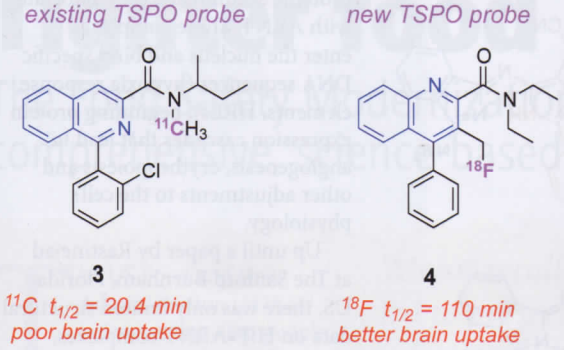


Figure 1 ***Yellow and magenta chains of HIF2α surrounded by red and blue chains of ARNT***



3

^{11}C $t_{1/2}$ = 20.4 min
poor brain uptake

4

^{18}F $t_{1/2}$ = 110 min
better brain uptake

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Organic chemistry

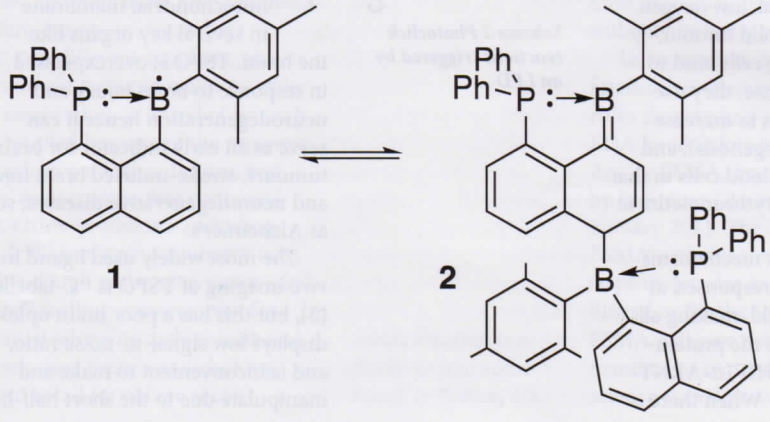
New Gomberg-type radicals

Boryl radicals, in which a ligand donates electrons to a BR_2 structure, have been the focus of increasing attention and early examples exploited N-heterocyclic carbene donors. In principle, any two-electron donor should work and a new example employs a triarylphosphine in this way. The key to success is the intramolecular donor-acceptor chemistry which makes the radical (1) (Scheme 1) quite long lived.

Phosphorus has available d orbitals so as well as the P→B σ donation there is also a form of B→P π back-donation (hyperconjugation). This produces a very strong intramolecular phosphorus-boron interaction but despite this, the majority of the spin-density - estimated at 60-70% by DFT calculations - remains on the boron atom.

The radical (1) undergoes a Gomberg-type dimerisation to form the unsymmetrical dimer (2) (A. J. Rosenthal, M. Devillard, K. Miqueu, G. Bouhadir, D. Bourissou, *Angew. Chem. Int. Ed.* 2015, **54**, 9198).

Scheme 1 ***The Gomberg-type dimerisation of a new type of boron-centred radical.***



1 **2**

Selective synthesis of C_2 symmetric difunctional rac-crown ethers

Intramolecular chemistry of a different type is put to work by Lacour's group in Geneva where they have been studying amidation of α,β-unsaturated esters in reactions that form β,γ-unsaturated amides and consequently create stereogenic centres at the α-carbon. These structures contain crown ethers, which span the alkene in the starting material (Scheme 2) and when two of these features are placed on opposite sides of the crown in (3), a remarkable long-range stereocontrol effect produces (4) in a diastereoisomer ratios as high as >49:1(M. Vishe, R. Hrdina, A. I. Poblador-Bahamonde, C. Besnard, L. Guénée, T. Bürgic,.J. Lacour, *Chem. Sci.*, 2015, **6**, 4923).

Good results are obtained with potassium *tert*-butoxide leading to the suggestion that K^+ sits above (or below) the crown of oxygen atoms and brings the two amides to the same face of the ring. This *cis* form provides a chiral (rac)-product in preference to the *trans* meso alternative.

It is quite unusual to have good control of rac/meso selectivity in the synthesis of difunctional chiral compounds. In this case, the chiral