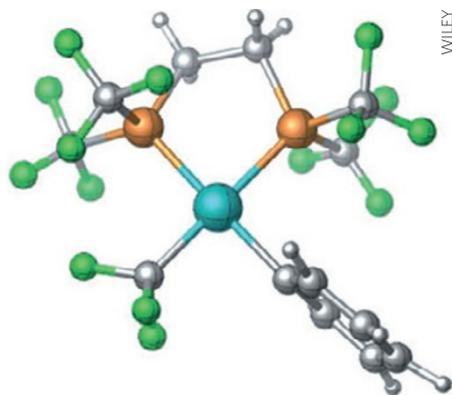


COMPUTATIONAL LIGAND DESIGN

Reduction to practice

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Computationally predicting the structure of molecules with desired reactive properties is not only intellectually satisfying, but can also be a big saver of time and resources: in particular, avoiding the need for numerous ‘trial-and-error’ screenings is a significant attraction. Such predictions, however, still pose a big challenge to chemists — successful examples of molecules with pre-designed

reactivity, followed by their synthesis and subsequent experimental validation, are rare.

It is in this context that Franziska Schoenebeck and co-workers from RWTH Aachen University and ETH Zürich began studying reductive elimination of trifluoromethyl groups. Reductive elimination of ArCF_3 from palladium(II) centres is the final step in the Pd-catalysed synthesis of trifluoromethylarenes, but it is known to be a challenging process. It depends largely on the properties of the coordinated ligand — only a handful of ligands are capable of prompting such chemistry and all have large bite angles. Smaller bite-angle compounds had proved ineffective, including the simple ligand 1,2-bis(diphenylphosphino)ethane (DPPE). Previous analysis by Schoenebeck and co-workers had explained this as a destabilization of the reductive elimination transition state by the bulky phenyl substituents on DPPE, rather than being directly related to the bite angle. Modification at this position could therefore be a fruitful route to avoid transition-state destabilization and, ideally, to also destabilize the starting complex.

Computational results showed that any replacement for phenyl on DPPE should be small. Coupled with a desire to destabilize the starting complex, this led to the idea of using CF_3 , not just as a leaving group but also to replace the phenyl groups of DPPE — this was proposed to cause destabilization by electrostatically repelling the leaving groups. Calculations on this hypothetical structure predicted a barrier to activation similar to those of successful wide bite-angle ligands. The next step was to make the complex and see if it worked. After some optimization the Pd(II) complex with the designed ligand plus phenyl and CF_3 leaving groups was synthesized and clean reductive elimination to PhCF_3 was observed. EB

ASYMMETRIC PHOTOCHEMISTRY

Making light work

Science **344**, 392–396 (2014)

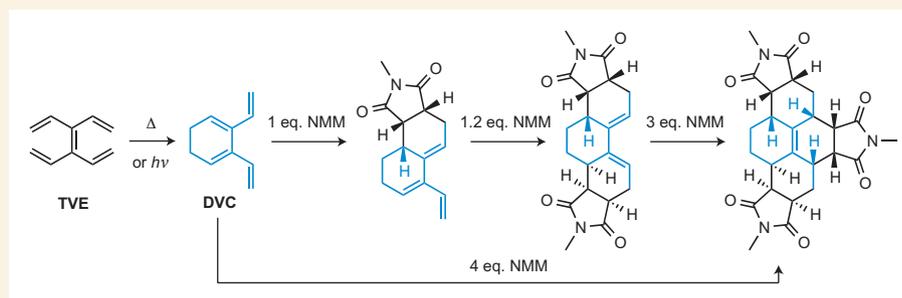
Cycloadditions are a powerful class of reaction due to their ability to form multiple new bonds and highly substituted centres in a single step. Chemists have achieved impressive stereochemical control over many thermally promoted cycloaddition

CONJUGATED HYDROCARBONS

Vinyl destination

Highly unsaturated hydrocarbons are often very reactive, and tetravinylethylene (TVE) looks, on paper, to be no exception. It is the smallest possible vinylic molecule that is both cross-conjugated and through-conjugated, and its synthesis has only been reported once before, using a four-step sequence to give an overall yield of 0.1%. As with similar molecules that contain multiple alkenes, it is potentially useful in the formation of complex hydrocarbon skeletons using Diels–Alder cascades, and so a simpler synthetic procedure to give TVE with higher yields is desirable.

Now, the combined efforts of a team led by Anthony Willis and Michael Sherburn from the Australian National University and Michael Padden-Row from the University of New South Wales have resulted in the discovery of a deceptively simple synthesis of TVE. Starting from tetrachloroethylene, four Stille cross-coupling reactions with vinyltributyltin in one solvent-free step gives a TVE yield of 64%, in batches of up to 7 grams at a time. In contrast to what might be assumed based on the instability



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of similar dendralenes and other related structures, they found that neat TVE was stable in air and at ambient temperatures. The same synthetic strategy could also be used to make a family of five substituted symmetrical TVE-based molecules.

Tetravinylethylene can also be used as a precursor to divinyl cyclohexadiene (DVC) by thermally promoted electrocyclozation. Both TVE and DVC were found to participate as dienes in sequences of Diels–Alder reactions with *N*-methylmaleimide (NMM) to create several fused cyclic hydrocarbon ring systems (pictured).

Not only were much higher regio- and stereoselectivities observed than with [4]dendralene — similar to both TVE and DVC in terms of size and number of $\text{C}=\text{C}$ bonds — but unexpected Diels–Alder reaction sequences were also observed and rationalized using density functional theory calculations. Simple methods to create complex fused ring structures with multiple stereocentres and substituents are a boon to synthetic chemists, and TVE looks like it could be a welcome addition to the toolbox of small-molecule precursors for such systems. CH