

In the Lab

Combining Catalyst and Reagent Design for Electrophilic Alkynylation

Johnson Matthey Technology Review features new laboratory research

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About the Research

Alkynes are essential building blocks in synthetic and medicinal chemistry, materials science and chemical biology. Due to their linear geometry and electronic properties, they are important structural elements in supramolecular assemblies and organic materials. The unique reactivity of the triple bond also makes them ideal precursors of other functional groups, not only in a classical chemistry setting, but also for biological applications. The development of new methods to make alkynes is consequently an important field of research in fundamental organic chemistry.

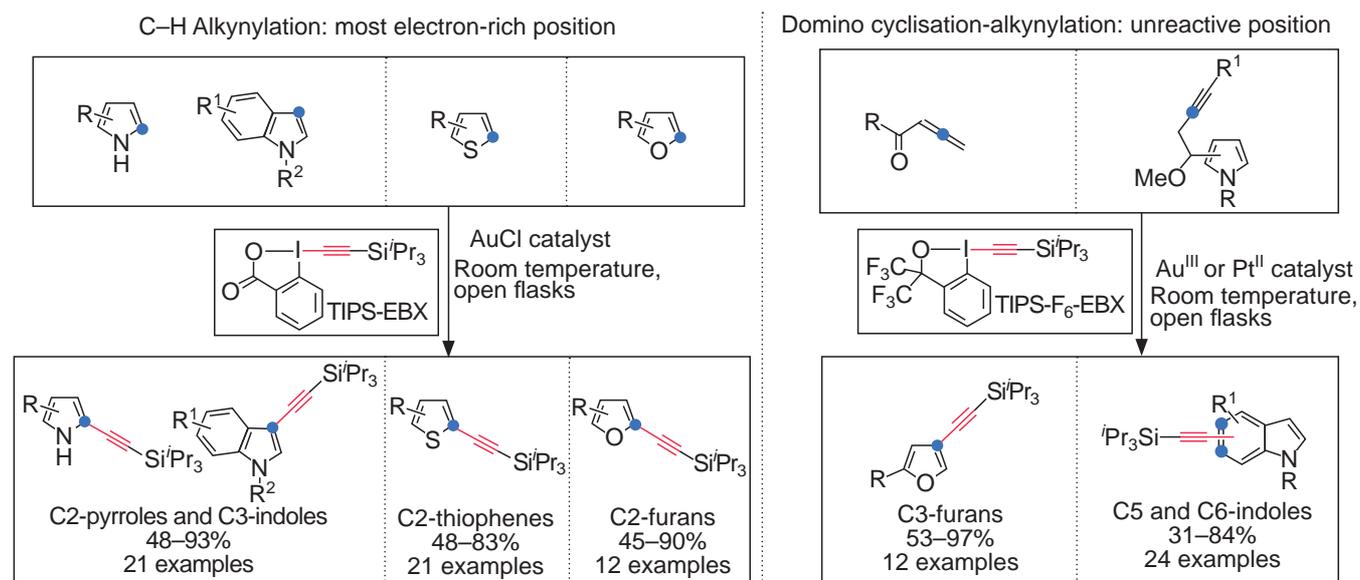
The transfer of terminal alkynes is one of the most successful approaches for introducing triple bonds into organic molecules. This field has been largely dominated by the use of acetylide anions or their equivalents as nucleophiles, due to their ease of formation. Processes such as the Sonogashira coupling and the addition of alkynes to carbonyls are highly reliable and are widely used in synthetic chemistry. Nevertheless, the drawback of this approach is that alkynes can be introduced only to the electrophilic positions of molecules. If good electrophilic alkyne synthons were available, alkyne chemistry would become even more versatile for applications in chemistry and in biology.

About the Researcher



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Waser's group have designed new methods for the introduction of alkynes into organic molecules using transition-metal catalysis and electrophilic alkynylation reagents. The direct alkynylation of electron-rich heterocycles was developed first (**Scheme 1**). The group harnessed the unique properties of ethynylbenziodoxolone (EBX) reagents for the gold-catalysed alkynylation of indoles, pyrroles, thiophenes and furans. The cyclic hypervalent iodine



Scheme I. Gold and platinum-catalysed C–H alkynylation vs. domino cyclisation functionalisation for accessing alkynylated heterocycles

reagent 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX) (**Figure 1**) was initially discovered by Zhdankin and although it displays an enhanced stability in the presence of transition metals, it still acts as a strong electrophilic alkyne source. The alkynylation of heterocycles with TIPS-EBX is a user-friendly method, which proceeds in open flasks at room temperature and can tolerate a broad range of functional groups.

The developed C–H alkynylation is highly selective for the most electron-rich position of heterocycles.

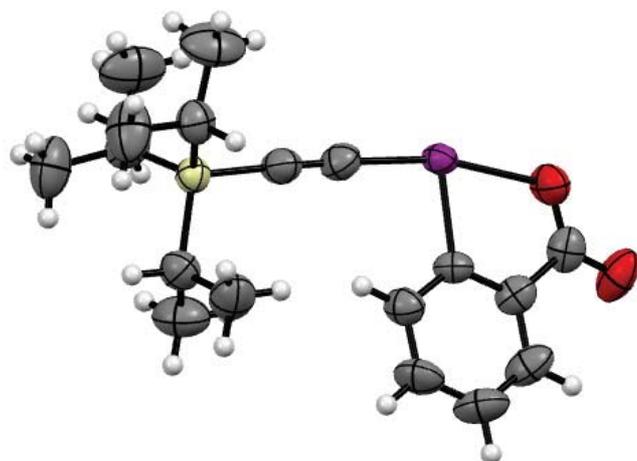
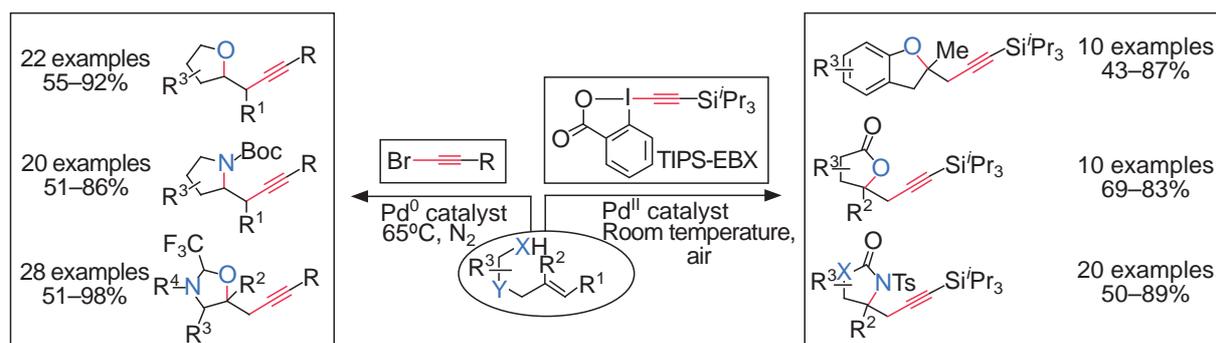


Fig. 1. X-ray structure of TIPS-EBX

To access triple bonds on other positions of aromatic rings, the group decided to use a new strategy based on a domino cyclisation-alkynylation process (**Scheme I**). This approach was first applied to the synthesis of 3-alkynylated furans starting from allene ketones. The key for success was electronic tuning of the hypervalent reagent, with TIPS-F₆-EBX being most successful. The synthesis of indoles alkynylated on the benzene ring is even more challenging, due to the much higher reactivity of the pyrrole ring. In this case, no successful C–H functionalisation method has yet been reported. Using the platinum-catalysed domino cyclisation-alkynylation of homopropargylic alkynyl pyrrole ethers, 5- or 6-alkynylated indoles could be synthesised in good yield and selectivity. Overall, the domino strategy is therefore highly complementary to C–H alkynylation.

To introduce alkynes onto C–sp³ centres, Waser's group focused on the metal-catalysed multi-functionalisation of olefins. The intramolecular oxy- and amino-alkynylation of olefins using TIPS-EBX and a palladium(II) catalyst to give lactones and lactams at room temperature in open flasks was developed first (**Scheme II**). To access tetrahydrofurans and pyrrolidines, the combination of a Pd(0) catalyst and alkynyl bromides was more successful. In this case, the reaction was run at 65°C under inert gas. Currently, the transformation cannot be made intermolecularly.



Scheme II. Palladium-catalysed olefin oxy- and amino-alkynylation

Nevertheless the group recently reported a first step in this direction by the use of an *in situ* tethering strategy for palladium-catalysed synthesis of vicinal aminoalcohols bearing an alkyne group starting directly from allyl amines. The use of trifluoroacetaldehyde in its commercially available hemiacetal form as a tether played an important role in this reaction.

In conclusion, the metal-catalysed electrophilic alkynylation approach has allowed heterocyclic and aliphatic alkynes to be synthesised with high efficiency. The obtained products are expected to be highly useful as building blocks in synthetic and medicinal chemistry, as well as in materials science.

Selected Publications

U. Orcel and J. Waser, *Angew. Chem. Int. Ed.*, 2015, **54**, (17), 5250

Y. Li and J. Waser, *Angew. Chem. Int. Ed.*, 2015, **54**, (18), 5438

Y. Li, J. P. Brand and J. Waser, *Angew. Chem. Int. Ed.*, 2013, **52**, (26), 6743

J. P. Brand and J. Waser, *Chem. Soc. Rev.*, 2012, **41**, (11), 4165

S. Nicolai, C. Piemontesi and J. Waser, *Angew. Chem. Int. Ed.*, 2011, **50**, (20), 4680

S. Nicolai and J. Waser, *Org. Lett.*, 2011, **13**, (23), 6324

J. P. Brand and J. Waser, *Angew. Chem. Int. Ed.*, 2010, **49**, (40), 7304

S. Nicolai, S. Erard, D. Fernández González and J. Waser, *Org. Lett.*, 2010, **12**, (2), 384

J. P. Brand, J. Charpentier and J. Waser, *Angew. Chem. Int. Ed.*, 2009, **48**, (49), 9346