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Comas-Barceló, J. and Harrity, J.P.A. (2017) Metal Acetylides in Cycloaddition Reactions. Synthesis, 49 (06). pp. 1168-1181. ISSN 0039-7881

https://doi.org/10.1055/s-0036-1588922

Metal Acetylides in Cycloaddition Reactions

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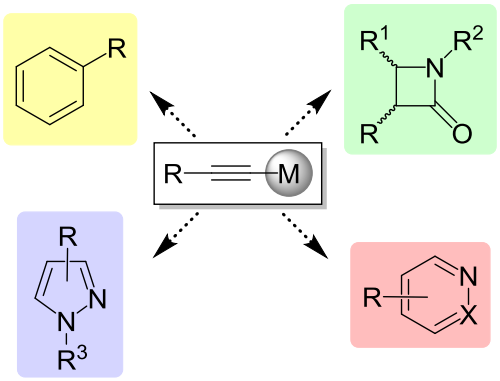


Received:
Accepted:
Published online:
DOI:

Abstract This review highlights recent advances in the synthesis of (hetero)aromatic systems *via* cycloaddition reactions of alkynylmetals with dienes and dipoles. This methodology is advantageous when accessing complex molecules because it offers a short, atom-economic and regioselective route to quickly access scaffolds of broad interest to the chemical sciences.

Key words catalyst, alkyne, cycloaddition, aromatic, heterocycle

1. Introduction

Heterocyclic compounds are ubiquitous in the chemical sciences, and are found in several sectors including the agrochemical and pharmaceutical industries, and in materials science and bioengineering. Accordingly, the development of efficient and selective methods for the synthesis of this class of compounds has attracted much attention throughout the years. While functionalization of a pre-formed heterocycle represents a viable and widely used strategy, ring-forming processes allow complex analogues to be assembled rapidly from simple fragments. In this context, cycloaddition reactions and related processes offer a rich and versatile method by which complex ring systems may be obtained from readily available starting materials.[1,2,3] Moreover, and as this review will demonstrate, by using metal acetylides as substrates, many of these processes can be dramatically improved, both with respect to reaction efficiency and control.

Cycloaddition reactions are a powerful tool to generate complex cyclic molecules while achieving high levels of atom economy, since the majority of the atoms from the starting materials are maintained in the newly generated products. Among them, Diels-Alder and 1,3-dipolar cycloaddition reactions of alkenes or alkynes are especially important in order to generate six- or five-membered rings respectively, many of which are known to be characteristic cores of biologically active compounds.[4,5,6,7]

The simplest alkyne available for synthetic purposes, acetylene, is a gas and is therefore inconvenient to use. For this reason, alkynes with higher molecular weights are more suitable for synthetic applications. In addition, alkynes tend to be quite unreactive, so activation is often needed for these reactions to proceed. A useful way to activate a triple bond is by coordination of a metal cation, thereby allowing control over the reactivity and regiochemistry. In addition, the presence of a carbon-metal bond is highly desirable because it offers a platform for further functionalization at the position bearing the metal fragment.

The following report describes some of the most relevant transformations that lead to heterocycles through cycloaddition reactions using metal acetylides as intermediates.

2. Synthesis and Applications of Metal Acetylides

Although many coordination modes are available to metal-alkyne complexes, those in which the metal is attached through a covalent carbon-metal bond are arguably the simplest and most commonly studied.[8,9] The main advantage that metal acetylides offer over the parent alkyne hydrocarbon is an enhancement of the innate nucleophilicity. In general, metal acetylides can be obtained from terminal alkynes and metal salts in a wide range of solvents and conditions. Base is needed to deprotonate the alkyne thus generating an acetylide anion,

which can attack the metal cation and form the M-C covalent bond. Mild bases (e.g. NEt_3) are usually suitable for this deprotonation, *i.e* it has been observed that the coordination of a metal to a terminal alkyne can lower the pK_a of the terminal proton up to 10 units.[10]

As for their applications, metal acetylides are employed mainly in nucleophilic addition reactions to electrophiles,[9,11,12] or as intermediates in alkyne-coupling reactions, such as the Sonogashira coupling.[13] However, it is also possible to exploit such intermediates as electrophiles. For example, Evano reported the utilization of copper(I) acetylides to synthesise ynamides, ynimines and alkynylphosphonates *via* oxidation of the acetylide and further reaction with nitrogen- and phosphorus-containing nucleophiles.[14]

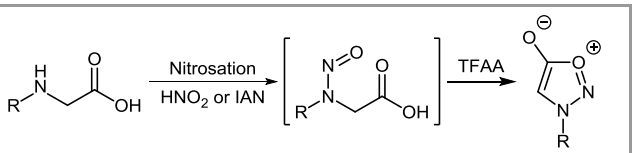
3. Use of Metal Acetylides in Cycloaddition Reactions

As stated before, one of the most relevant uses of metal acetylides is in cycloaddition reactions due to their ability to act as activated alkynes. The most popular example is the synthesis of triazoles from 1,3-dipolar cycloaddition reactions of azides with alkynes using click chemistry, a process known as the copper-catalysed azide-alkyne cycloaddition (CuAAC). This procedure has been extensively reviewed elsewhere and will not be covered here.[15,16,17,18,19] However, it set an important precedent for the preparation of different heterocyclic structures using metal catalysis and cycloaddition reactions, and some relevant examples derived from it will be described.

3.1. The CuSAC Reaction

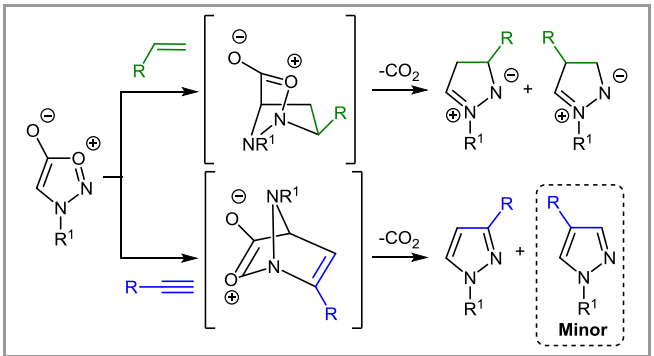
The CuAAC rection represented a change of paradigm in organic synthesis providing a mild, metal-catalysed and robust alternative to pericyclic processes, thereby allowing access to heterocycles with high efficiency and selectivity. Following this trend, in recent years, developments have been made towards an analogous synthesis of pyrazoles *via* copper-promoted cycloaddition reactions between alkynes and sydnones, the latter acting as the 1,3-dipole reagents.

Sydnones are the most studied family of mesoionic compounds, which are a class of heterocycles for which non-charged representations cannot be drawn. They were first discovered by Earl and Mackney in 1935,[20] and in the past few decades they have attracted much attention due to the discovery of their biological activity[21,22,23] and the possibility of undergoing 1,3-dipolar cycloadditions.[24] They can be conveniently prepared from amino acids *via* a 2-step nitrosation and cyclodehydration sequence (Scheme 1).



Scheme 1 General procedure for the synthesis of sydnones. IAN = Isoamyl nitrite, TFAA = Trifluoroacetic anhydride.

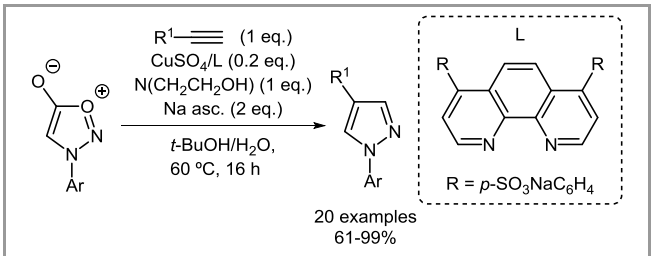
Cycloaddition reactions with sydnones were first described by Huisgen in the 1960s[25,26] and since then, many examples have been reported in the literature employing both alkenes[27] and alkynes. The latter turned out to be more interesting because the cycloaddition chemistry of alkenes is quite complex and is not yet general for the synthesis of heterocyclic products.[24]



Scheme 2 Cycloaddition reactions with sydnones.

When performing classical Huisgen cycloadditions with sydnones and terminal alkynes, 1,3-disubstituted pyrazoles are, in general, the major products obtained, generating the corresponding 1,4-disubstituted regioisomers only in trace amounts when these reactions are carried out in the absence of additives (Scheme 2).

Nonetheless, in 2013, Taran reported what could be considered the first example of the analogous *click* sydnone-alkyne cycloaddition reaction using copper catalysis and obtaining the 1,4-disubstituted pyrazole isomer regioselectively (CuSAC = Copper-catalysed sydnone-alkyne cycloaddition reaction).[28] The conditions for the transformation require the copper(II) sulphate – sodium ascorbate system to generate copper(I) *in situ*.

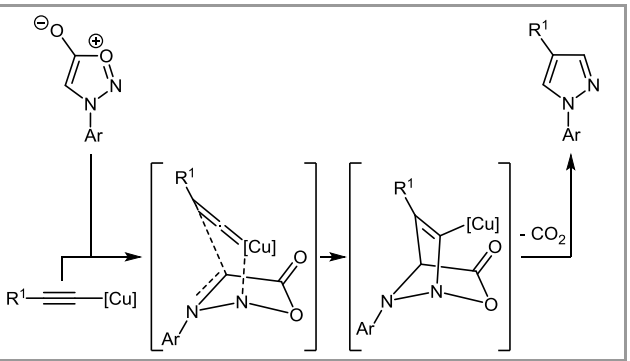


Scheme 3 Taran's CuSAC cycloaddition reaction.

The main difference in this method *versus* the classical *click* reaction is that, in this case, the presence of a ligand is fundamental for the reaction to take place. Indeed, phenanthroline derivatives proved to be very effective in this process. The main advantages of this methodology are the fact that only mild conditions are required (60 ^{0}C – rt), the cycloaddition can be performed in aqueous media and uses sub-stoichiometric amounts of the metal (Scheme 3). However, the reaction times are long: typically ~ 16 hours. Finally, the authors demonstrated the potential applicability of this methodology by preparing an albumin-sydnone bioconjugate, which was successfully reacted with an alkyne bearing a fluorescent Dansyl tag.[28]

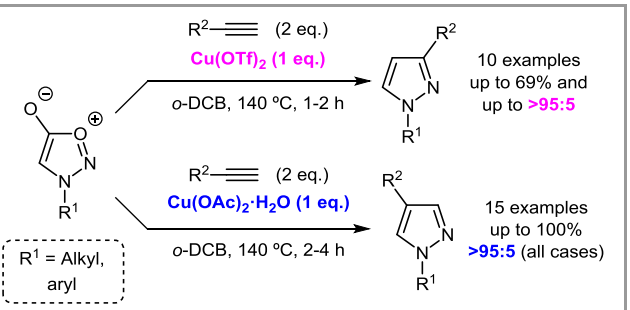
Taran put forward a mechanistic proposal for the Cu-catalysed cycloaddition whereby a copper(I) acetylide was implicated to play a key role, by analogy to the azide-alkyne system. Hence, coordination between the metal and the *N*2 position of the sydnone both increases the nucleophilicity of the alkyne and

the electrophilicity of the sydnone C4 position, thereby promoting cycloaddition (Scheme 4).[28]



Scheme 4 Taran's mechanistic proposal for the CuSAC reaction.

Shortly after, the Harrity group also reported a copper-promoted regioselective sydnone-alkyne cycloaddition process. In this case, by using two different sources of copper(II), both 1,3- and 1,4-disubstituted pyrazoles could be accessed in a regio-complementary fashion (Scheme 5). Although the reaction requires high temperatures, no additional ligands are required and the reaction times are relatively short (< 5 h in all cases).[29]



Scheme 5 Harrity's copper-promoted CuSAC.

Additionally, a new mechanistic proposal based on experimental findings as well as DFT calculations was put forward to explain the formation of both regioisomers in the presence of different Cu(II) Lewis acids. In the case of $Cu(OTf)_2$, where the 1,3-disubstituted isomers were obtained, coordination of the Lewis acidic copper(II) triflate to the exocyclic sydnone oxygen is believed to be responsible for the observed acceleration in the reaction rate. Further evidence for this complex formation was observed when performing infrared measurements, since a shift in the C-O stretching frequency was observed experimentally in the presence of $Cu(OTf)_2$. DFT calculations further supported this proposal, as the complex formed by coordination at the sydnone *O*6 position turned out to be the one possessing the lowest energy (Figure 1).

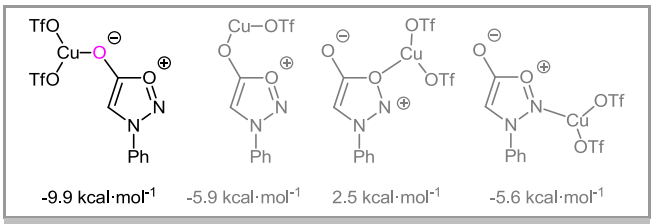
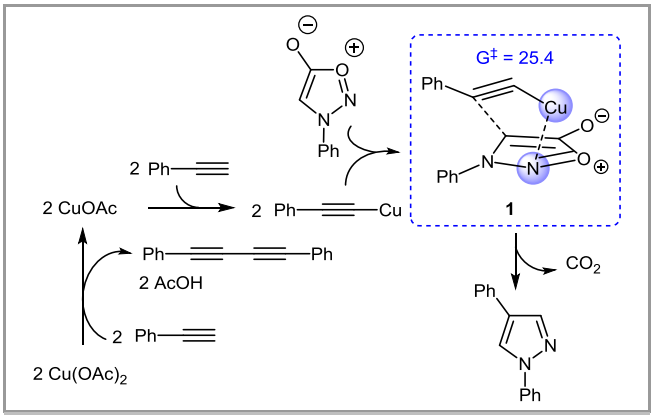


Figure 1 DFT calculated structures for the complexation of $Cu(OTf)_2$ to sydnone.

In contrast, the presence of $Cu(OAc)_2{\cdot}H_2O$ did not cause changes in the infrared spectrum of *N*-phenylsydnone. In this case, the formation of bright coloured precipitates was observed when running the cycloaddition reactions. These insoluble solids were attributed to be copper(I) acetylides, generated from the terminal alkynes and the copper salt *in situ*. Comparison of a sample of copper(I) phenylacetylide isolated from the reaction mixture with a sample prepared according to a literature method[30] confirmed the nature of this reaction intermediate, since both samples delivered the observed 1,4-disubstituted pyrazole product.

Our mechanistic proposal for the $Cu(OAc)_2$ promoted reaction is detailed below, where *in situ* reduction of copper(II) to copper(I) by an excess of the terminal alkyne delivers the copper(I) species required for the generation of the acetylide intermediate. As DFT calculations suggest, coordination between the copper centre of the acetylide and the *N*2 position of the sydnone generates a 6-membered ring transition state (**1**) from which the cycloaddition reaction takes place to deliver the 1,4-disubstituted product in a concerted but asynchronous manner (Scheme 6).[29]

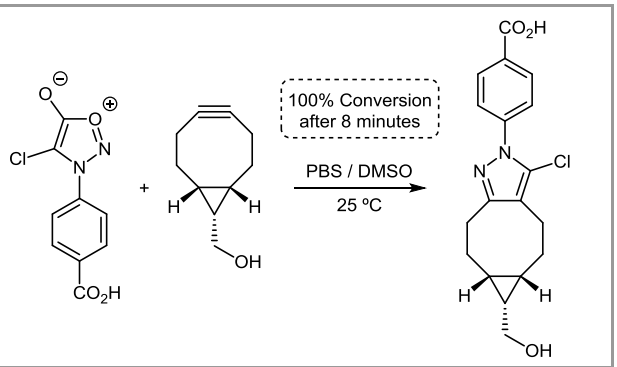


Scheme 6 Harrity group's mechanistic proposal for the $Cu(OAc)_2{\cdot}H_2O$ promoted cycloaddition.

After the establishment of these methodologies, both the Harrity and the Taran groups have reported modifications of the original procedures to enhance their potential. In 2014 Taran reported a one-pot methodology to prepare 1,4-disubstituted pyrazoles starting from *N*-arylglycines, which are the precursors for the sydnone synthesis. By concatenating these two steps in one single operation, the isolation of the nitrosamine intermediates is avoided, which is advantageous since these compounds are suspected to be carcinogenic. Next, these *in situ* generated sydnone intermediates were subjected to Cu-catalysed cycloaddition conditions, always in the presence of a phenanthroline-type ligand, affording the desired pyrazoles with full regiocontrol.[31]

This methodology has also been expanded to the cycloaddition of 4-bromosydnone derivatives (conveniently prepared by bromination of the sydnone prior to the cycloaddition reaction) to deliver 5-bromopyrazoles that were subsequently used in cross-coupling chemistry.[32]

Another interesting approach is the strain-promoted cycloaddition between sydnone scaffolds and highly strained alkynes such as bicyclo-[6.1.0]-nonyne. In this case, as a kinetic study performed by Taran showed, the strain release resulting from the cycloaddition is such that no metal promoters or catalysts are required. Hence, these reactions take place at room temperature, over a few minutes and in the absence of any additives (Scheme 7).[33]

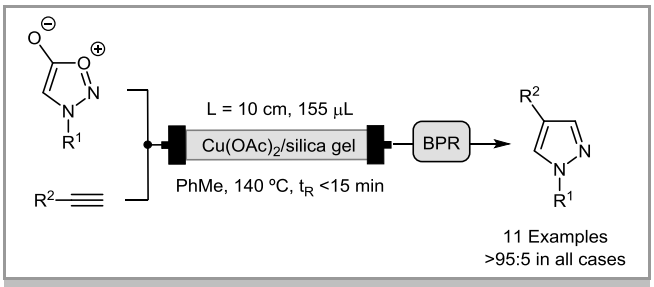


Scheme 7 Strain-promoted cycloaddition between a sydnone and a bicycle-[6.1.0]-nonyne derivative. PBS = phosphate buffer solution.

This strain-promoted strategy has also been expanded to the cycloaddition of 4-fluorosydnone derivatives, which can be conveniently prepared through a Pd-mediated reaction with Selectfluor, as shown by Gouverneur and Taran.[34] These fluorinated pyrazole products are interesting because using a labelled fluorinating agent, successful ^{18}F incorporation was achieved, accessing a range of substrates which can be employed as radiotracers.[34]

Harrity and Rutjes reported a catalytic variant of the copper-promoted cycloaddition by the use of supported catalysis. Attaching $Cu(OAc)_2$ onto a modified silica support by chelating it to amino groups allowed the copper loading to be reduced from stoichiometric amounts to 30 mol%, as well as avoiding the precipitation of the bright insoluble copper(I) acetylide intermediates.

Additionally, the catalyst could be recovered after simple filtration and be reused up to 4 cycles without losing efficiency.[35] As a proof of concept, this report also showed the first example of a pyrazole synthesis employing supported catalysis under continuous flow conditions, where by packing the catalyst in cartridges of variable size, different amounts of pyrazole products could be accessed in good yield, excellent regioselectivity and residence times under 15 minutes (Scheme 8).

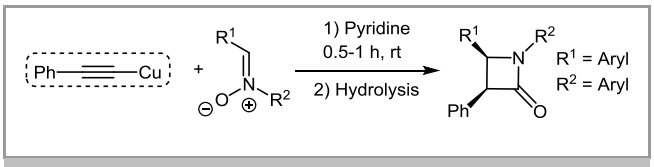


Scheme 8 Copper-supported synthesis of pyrazole under continuous flow.

In conclusion, as shown above, sydnones are interesting partners for metal acetylide-mediated cycloaddition reactions, generating functionalized pyrazoles with interesting properties and different functionalization patterns, with applications in several fields.

3.2. The Kinugasa Reaction with Copper Acetylides

The Kinugasa coupling was first reported in 1972 as "the acetylide reaction" resulting in an interesting tool to generate *cis*-substituted β-lactams stereoselectively from nitrones and copper(I) acetylides (Scheme 9).[36] The same transformation was reported shortly after by Irwin and Ding, highlighting the preferential generation of the *cis* β-lactam over the *trans* analogue,[37] and has been revisited in several occasions during the past decades.[38,39,40]



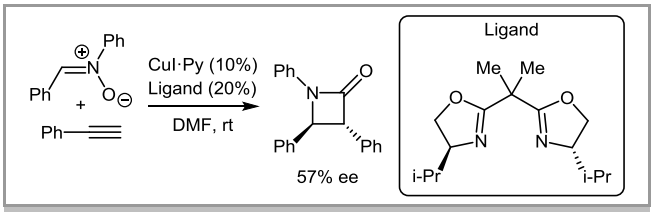
Scheme 9 Orginal acetylide reaction described by Kinugasa in the 1970s.

β-Lactams have generated significant interest in the chemistry community, primarily because of their use as antibiotics. This family of compounds contains penicillins, cephalosporins, monobactams and carbapenems.[41] In addition, they are also interesting as building blocks for the synthesis of more complex molecular structures.[42] More recently, they have been reported to possess anticancer activity[43] and to act as cholesterol absorption inhibitors.[44]

Despite their importance, the current methods to obtain these heterocycles have important limitations either in scope or selectivity, and sometimes require the use of expensive rhodium catalysts or unstable ketenes. For this purpose, the Kinugasa coupling seems a suitable alternative for the stereoselective synthesis of the *cis* isomers using inexpensive copper catalysts.

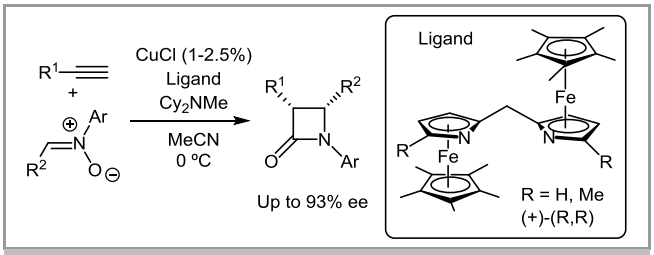
Since Kinugasa's work in the early 1970s, many authors reported new conditions to increase the efficiency of the process and, especially, reduce the metal loading. It should be noted that the original reaction required stoichiometric copper to generate the corresponding acetylide, resulting in considerable amounts of transition metal waste.

In 1995, Miura reported the first catalytic variant using sub-stoichiometric amounts of CuI and a ligand, obtaining the *trans* β-lactam for the first time. Later on, this group also developed an asymmetric variant using chiral ligands (Scheme 10).[45]



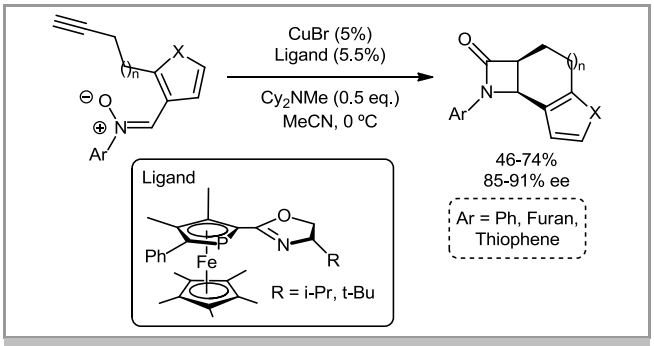
Scheme 10 First catalytic Kinugasa reaction reported by Miura in 1995.

A few years later, in 2002, Fu reported another catalytic variant using CuCl and bis(azaferrocene)ligands. Using these ligands, the diastereoselective synthesis of the *cis* β-lactam ring was finally achieved for the first time with ee >70% (11 examples, R^1, R^2 = both aromatic and aliphatic, 42-65% yield) and using catalytic copper (Scheme 11).[42]



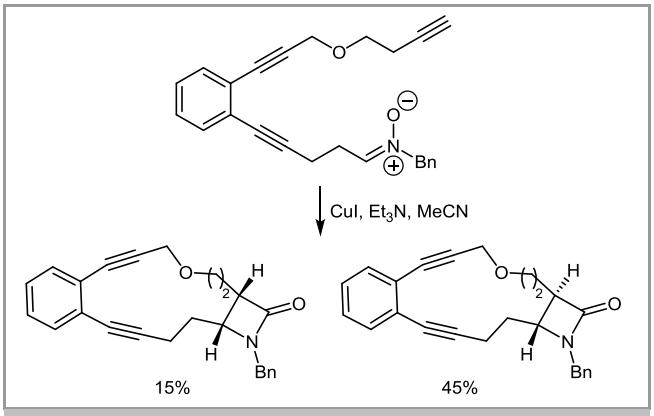
Scheme 11 First catalytic Kinugasa reaction to access *cis* β-lactams reported by Fu in 2002.

Shortly after, the same group also reported an intramolecular approach to the Kinugasa coupling. In this case, they were able to generate *cis β*-lactam rings embedded in polyaromatic systems with excellent levels of enantiomeric excess. In addition, both aromatic and heteroaromatic substituents (i. e. furan, thiophene) were tolerated maintaining the catalytic copper loading (Scheme 12).[46]



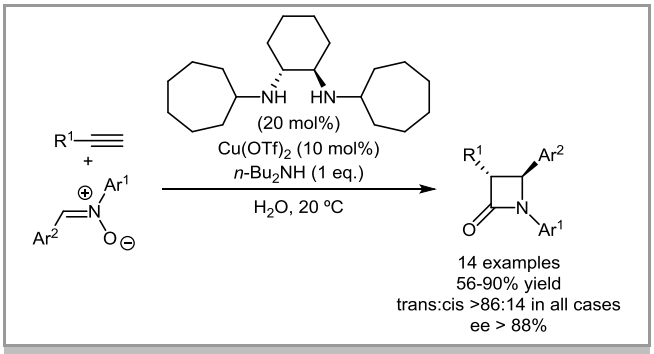
Scheme 12 Intramolecular Kinugasa reaction towards cis β-lactams.

A few years later, in 2006, Basak reported an interesting intramolecular alternative using the Kinugasa reaction to access macrocyclic scaffolds incorporating the β-lactam moiety with different configurations. An example is shown in Scheme 13.[47] Tang reported an air and moisture stable catalyst for the asymmetric Kinugasa coupling that circumvented the need for inert atmosphere reactions.[48] Moreover, this process highlighted the potential utility of Cu(II) salts as active catalysts rather than the traditionally used Cu(I) complexes. The use of 10 mol% of $Cu(ClO_4)_2{\cdot}6H_2O$ afforded the *cis* β-lactam products with high enantiocontrol (>70% ee; 12 examples, R^1, R^2 = aromatic, 33-98% yield).



Scheme 13 Intramolecular Kinugasa reaction proposed by Basak.

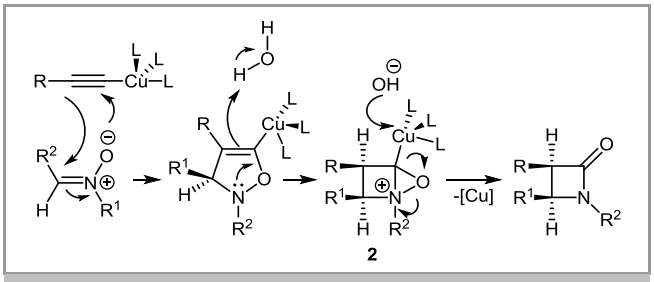
In a similar manner, in 2013, Feng reported the first asymmetric approach to *trans* β-lactams by means of catalytic $Cu(OTf)_2$ and the use of chiral *vic*-diamine ligands, as shown in Scheme 14.[49] Recently, Furman also showed how *N*-PINAP atropoisomeric ligands enhance the entantioselectivity of this reaction.[44]



Scheme 14 Feng's asymmetric conditions to access *trans* β-lactams.

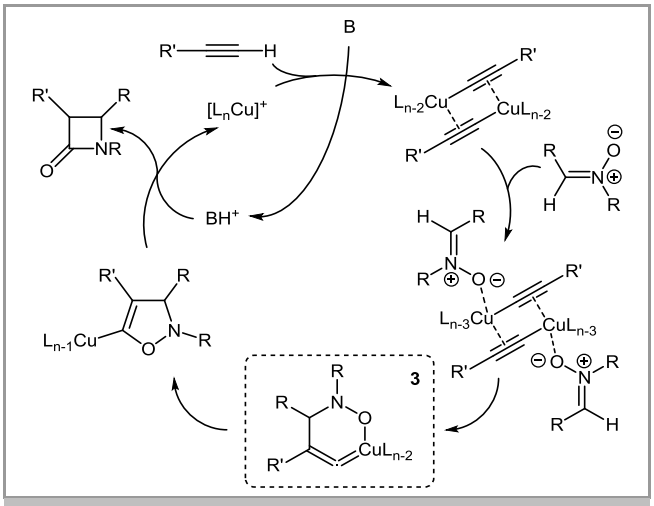
Finally, efforts have been made to develop conditions that allow the Kinugasa reaction to be performed in water, with a view to applying this chemistry in biological media.[50] Pezacki has worked extensively in this direction, developing micelle promoted methods in aqueous conditions,[51] and more interestingly, the first reported Kinugasa reaction inside cells. The latter transformation took place between endocyclic nitrones and Alexa488-labelled alkynes, and was catalysed by Cu(I)-histidine complexes in the presence of sodium ascorbate. This methodology allows cellular labelling in a selective fashion, as it's compatible with *in vivo* CuAAC click couplings, thus expanding the possibilities of cellular surface targeting using this strategy.[52]

The mechanism of the Kinugasa coupling remains the subject of much debate. The first mechanistic proposal was reported by Ding and Irwin in the 1970s, and it is based on the formal [3 + 2] cycloaddition of a copper acetylide and the nitrone. The isoxazoline intermediate undergoes rearrangement to form the bicyclic intermediate **2,** which ring opens to the β-lactam product. This proposal has been supported by mass spectrometry studies and ^1H NMR deuterium incorporation experiments (Scheme 15).[37]



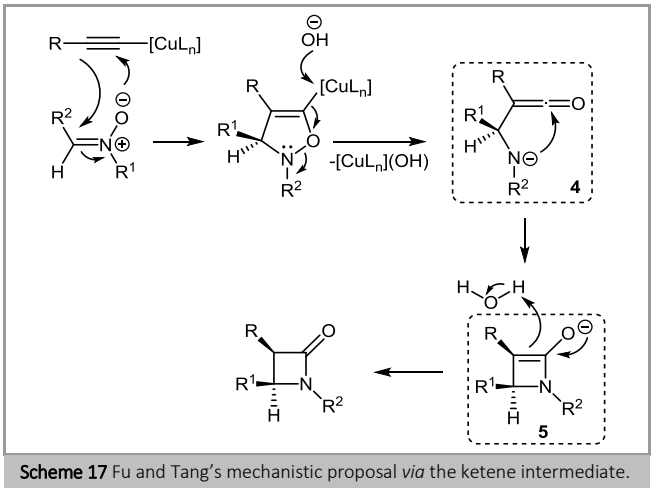
Scheme 15 Ding and Irwin's mechanistic proposal for the Kinugasa reaction.

In recent years, two other mechanistic proposals that are variants of the scheme proposed by Ding and Irwin have emerged. The proposal put forward by Chmielewski and Furman[53] is inspired by the mechanistic studies by Sharpless and Fokin for the CuAAC triazole synthesis, in which a metallated 6-membered ring intermediate (**3**) is believed to be a key species in this transformation (Scheme 16).[10]



Scheme 16 Furman and Chmielewski's proposal, based on CuAAC.

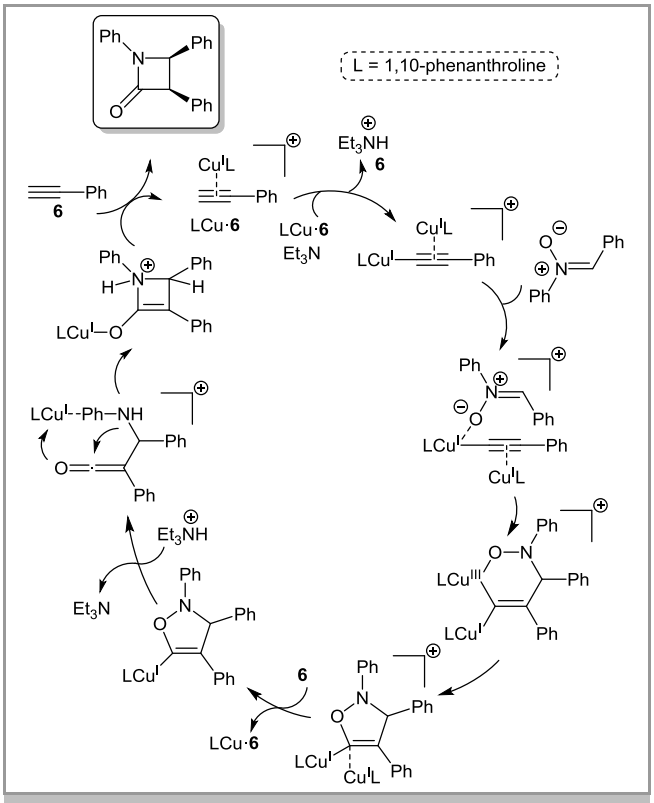
An alternative sequence that relies on the formation of a ketene intermediate was subsequently put forward by DeShong.[54] Further experimental evidence for this hypothesis was provided by the groups of Fu[46] and Tang[55] amongst others, who have been able to trap the enolate intermediate **5** with electrophiles such as allyl halides.



Scheme 17 Fu and Tang's mechanistic proposal *via* the ketene intermediate.

In order to shed further light on the mechanism of the Kinugasa reaction, Himo recently reported the first full theoretical mechanistic study. In Himo's work, both the non-catalysed and the copper-promoted reaction were analysed in depth using DFT methods. A key finding in this report was the discovery of the participation of a two copper centre-based acetylide,[56] a species that had also been identified in the past in the CuAAC reaction.[10,57,58,59,60] Interestingly, the proposed mechanism that arose from this investigation merged aspects of the two previous schemes (the 6-membered ring **3** and the ketene intermediate **4**), in order to produce a viable overall reaction profile (Scheme 18).

In summary, the Kinugasa reaction exploits copper acetylides for the efficient and atom economic generation of β-lactam derivatives allowing, at the same time, control of the stereochemistry of the desired products depending on the ligand choice and the reaction conditions.



Scheme 18 Himo's mechanistic proposal for the Kinugasa reaction based on DFT calculations.

3.3. Reactions of Pyrones and Aluminum Acetylides

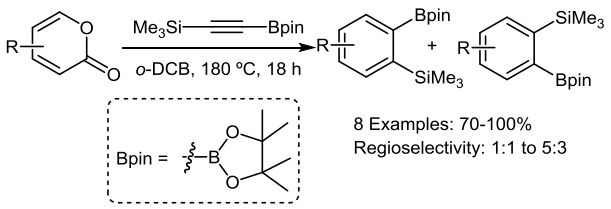
1. Synthesis of benzene derivatives:

Substituted aromatic compounds are basic building blocks with many applications, and there are a plethora of methods available to access these scaffolds. However, many of these approaches have limitations with respect to controlling the regiochemistry of functionalization. For example, the regiochemistry of electrophilic aromatic substitution reactions of benzene is subject to substrate control where directing group effects determine product substitution patterns.

Cycloaddition reactions offer an alternative means of assembling benzene derivatives, and have the advantage of exploiting already functionalized starting materials that can be

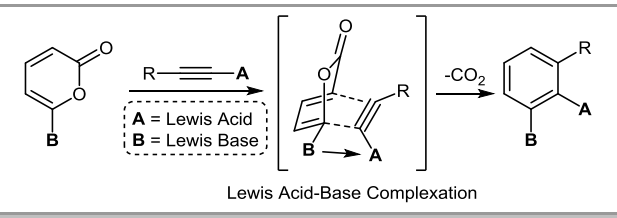
carried through to the aromatic products. In this context, 2-pyrones have been used in thermally promoted [4 + 2] cycloaddition reactions with both alkenes and alkynes generating carbocyclic scaffolds for organic synthesis.[61]

The cycloaddition reaction of 2-pyrones and alkynes bearing a functionalizable carbon-metal bond offers an opportunity to directly access useful benzene-derived scaffolds. In this regard, Harrity and co-workers have explored the thermally promoted reaction of 2-pyrones and alkynylboronates. While this process successfully delivers a variety of aromatic boronates, there are some drawbacks associated with this method such as harsh reaction conditions and the formation of regioisomeric mixtures. A representative example is provided in Scheme 19.[62,63,64,65]



Scheme 19 Thermal cycloaddition between pyrones and alkynylboronates.

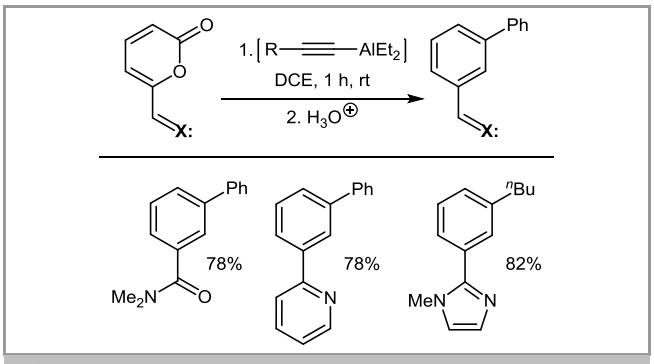
In an effort to address the limitations associated with alkynylboronate cycloadditions, Harrity and co-workers have been exploring the potential of acetylide derivatives bearing Lewis acidic metal groups to promote cycloaddition with dienes bearing suitably disposed Lewis bases. As shown in Scheme 20, pre-association of the substrates should promote cycloaddition thereby reducing reaction temperatures and times, while simultaneously controlling product regiochemistry.[66]



Scheme 20 Directed cycloaddition approach applied to the pyrone system.

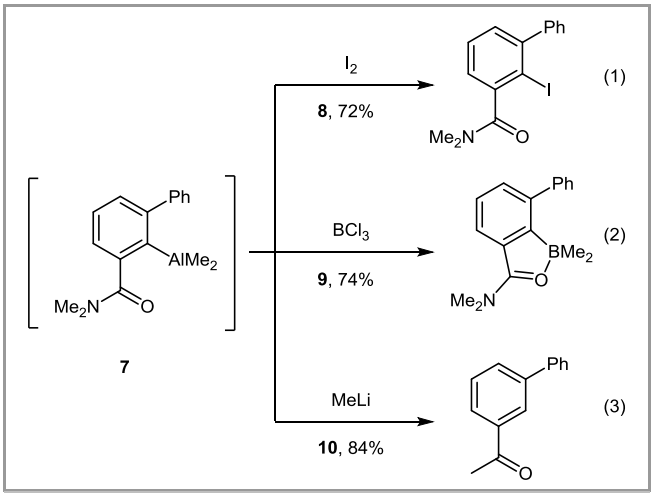
The Harrity group reported in 2013 the successful realisation of the participation of alkynylaluminum species in cycloaddition reactions with 2-pyrones. A selection of 2-pyrones bearing Lewis basic groups at *C*2 were designed to promote coordination with the aluminum acetylides and, in turn, improve the cycloaddition reaction. As a result, diversely functionalized benzene rings were obtained under mild conditions in moderate to good yields (41-78%).[67]

Directing groups such as amides (including a Weinreb amide) or heterocycles including pyridines, thiazoles, imidazoles or pyrazoles successfully promoted the cycloaddition. However, less Lewis basic functionalities such as esters or thioamides did not react and the starting diene was recovered in these cases (Scheme 21).



Scheme 21 Examples of directed cycloadditions between Lewis basic pyrones and aluminum acetylides.

In addition, the incorporation of the aluminum group in the final product offers a further advantage due to the relative reactivity of the Al-C bond, allowing subsequent functionalization processes to take place and increasing the level of complexity of the products. Indeed, besides typical reaction with electrophiles such as iodine (Scheme 22.1), transmetallation upon treatment with boron trichloride was also observed (Scheme 22.2). Alternatively, the corresponding methyl ketone **10** could also be generated by treating intermediate **7** with methyl lithium (Scheme 22.3).[67]



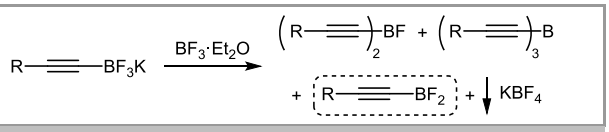
Scheme 22 Further functionalization examples of the arylalanes after cycloaddition.

3.4. Directed Cycloadditions of Boron Acetylides

The aluminum acetylide – Lewis base substituted pyrone system demonstrated how the presence of directing groups affects both the reaction rate and regioselectivity of the cycloadditions. However, the use of organoaluminum species is not always practical due to its pyrophoric character and sensitivity. Similar methodologies using more easily handled substrates would therefore be highly desirable to access different families of substituted heterocycles using this strategy.

Alkynylboron reagents such as alkynyldifluoroboranes offer an interesting alternative to Al-acetylides due to their easy preparation *in situ* by treatment of alkynyltrifluoroborates, which are bench stable solids, with Lewis acids such as $BF_3{\cdot}Et_2O$ or Me_3SiCl (Scheme 23).[68,69] In addition, the incorporation of boron-containing groups in the final molecule would be useful due to the broad array of transformations that

they can participate in such as cross coupling reactions, oxidation or halogenation processes.

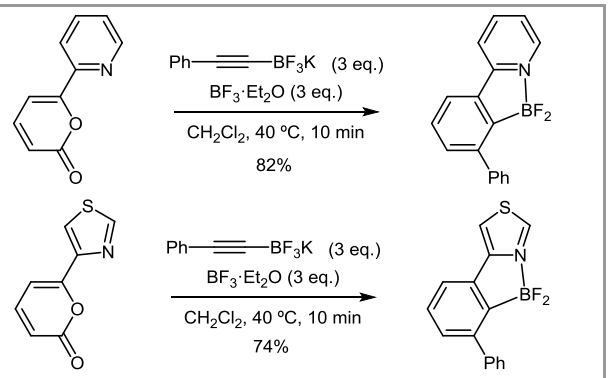


Scheme 23 *In situ* generation of difluoroboranes from trifluoroborate salts and $BF_3{\cdot}Et_2O$.

For these reasons, the participation of alkynyldifluoroboranes in substrate directed cycloaddition reactions towards small heterocyclic molecules has been studied by Harrity and co-workers. The most relevant examples of cycloaddition reactions using this methodology reported to date will be discussed in the following section.

1. Pyrones:

The *in situ* generation of alkynyldifluoroboranes resulted in smooth cycloaddition reactions with a similar selection of 2-pyrones to those employed in the alkynylaluminum chemistry. The reaction conditions were again found to be much milder (40 °C, 10 minutes) than generally required in traditional thermal reactions (180 °C, 18 h; Scheme 19). More interestingly, total control of the regioselectivity of the products was achieved such that the C-B bond was incoroporated adjacent to the Lewis basic group in all cases (Scheme 24).[70]



Scheme 24 Directed cycloadditions between Lewis basic pyrones and difluoroboranes generated *in situ* using Lewis acid.

Despite the high efficiency of these reactions, the formation of alkynylated by-products could be observed in most cases; as exemplified with the amide derivatives shown in Figure 2, indicating that disproportionation of organoborane intermediates could be occurring.

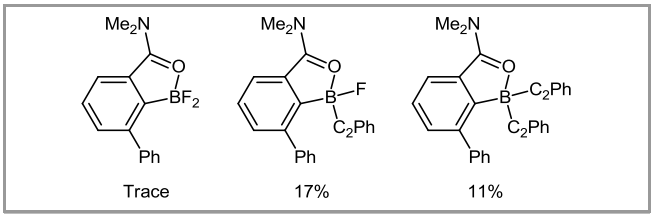
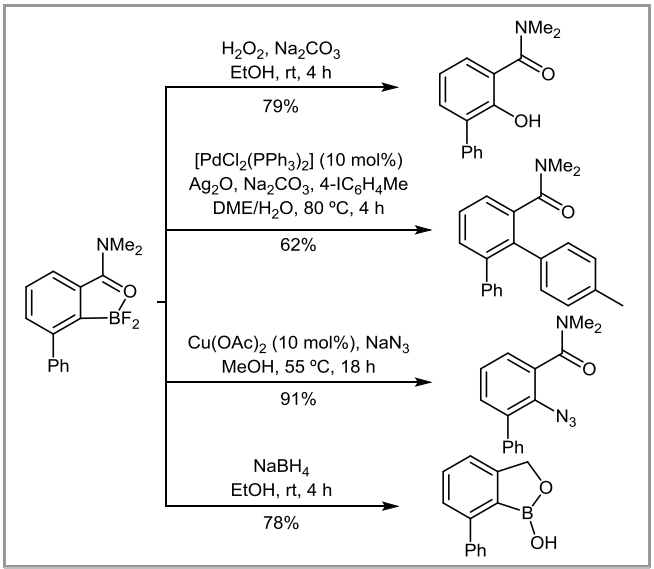


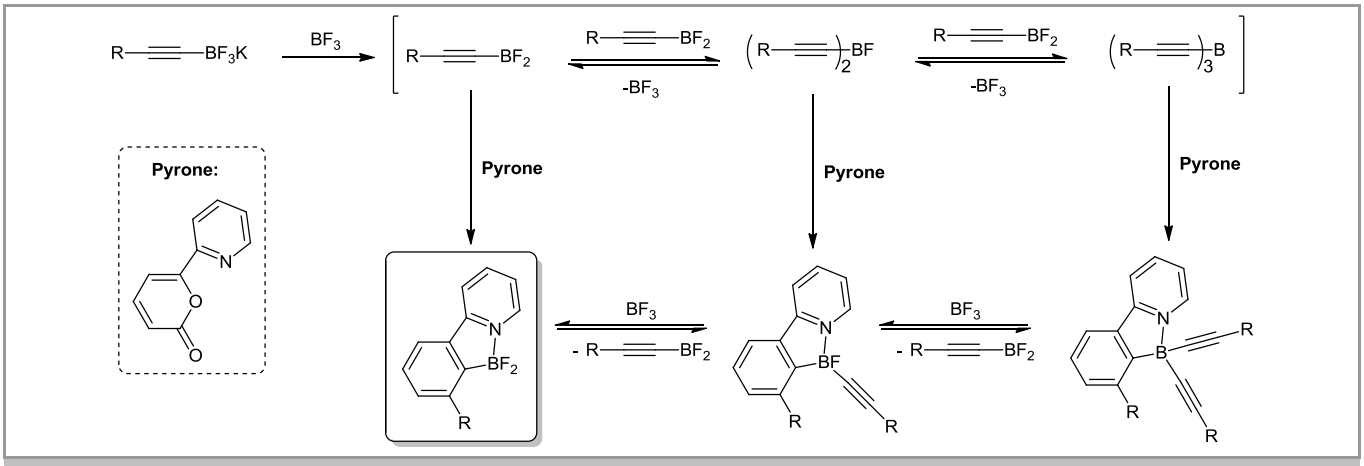
Figure 2 Difluoroborane, monofluoroalkynylborane and dialkynylborane adducts generated by cycloaddition of the 2-pyrone carboxamide derivative and potassium phenylethynyltrifluoroborate.

To try to correlate and explain these findings, in 2014, Harrity and Meijer published the first mechanistic study based on both experimental and theoretical results to propose a mechanism for the directed cycloadditions between 2-pyrones bearing Lewis basic moieties and the Lewis acidic alkynyldifluoroboranes. They demonstrated that the key steps for the transformation are a rapid and reversible formation of a tris(alkynyl)borane (Scheme 26) that undergoes cycloaddition with the Lewis basic 2-pyrone generating the corresponding dialkynylborane adduct in first instance. In addition, the corresponding difluoroborane and monofluoroborane benzene adducts are also generated, albeit in smaller quantities, *via* the reaction of the corresponding alkynyldifluoro- and alkynylmonofluoroboranes. A second disproportionation process then takes place to equilibrate these intermediates and generate the thermodynamically most stable difluoroborane cycloadduct.[71]

Finally, the $-BF_2$ moiety incorporated during the cycloaddition reaction serves as a versatile functionalization handle to further expand the applicability of the directed strategy; allowing the preparation of a wide range of substrates by taking advantage of the rich chemistry of the borane group.



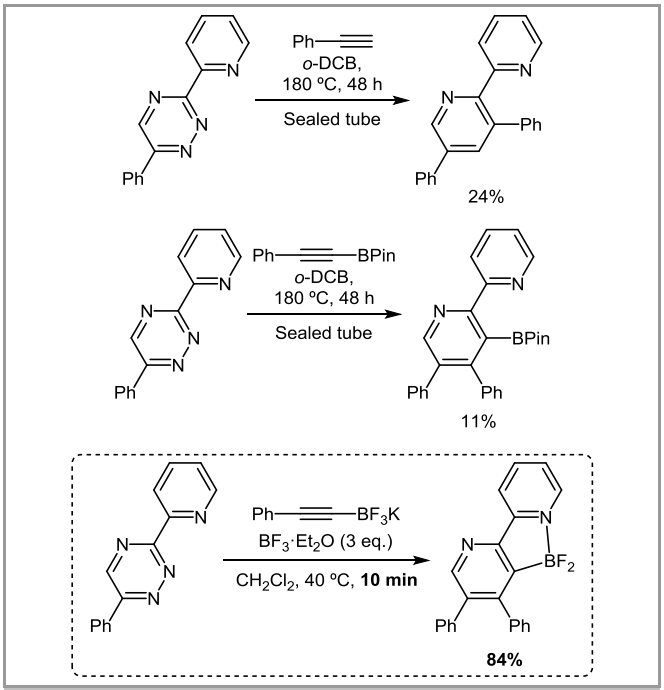
Scheme 25 Functionalization examples of the $-BF_2$ moiety after cycloaddition.



Scheme 26 Overall mechanistic proposal for the directed cycloaddition reactions between pyrones and alkynyltrifluoroborates.

2. Triazines:

In the past, 1,2,3- , 1,3,5- and 1,2,4-triazines have been shown to participate in cycloaddition reactions with alkynes, albeit displaying different reactivity trends. The cycloaddition chemistry of 1,2,3-[72,73] and 1,3,5-triazines[74,75] with alkynes to access substituted pyrimidine derivatives has been extensively studied by Boger. Generally speaking, the reaction conditions required for cycloaddition of 1,2,4-triazines are generally milder than the other triazine isomers, nonetheless, they still require long reaction times and temperatures > 160 °C, as exemplified in Scheme 27. This chemistry is very appealing however as it allows access to highly substituted pyridines within a short reaction sequence.

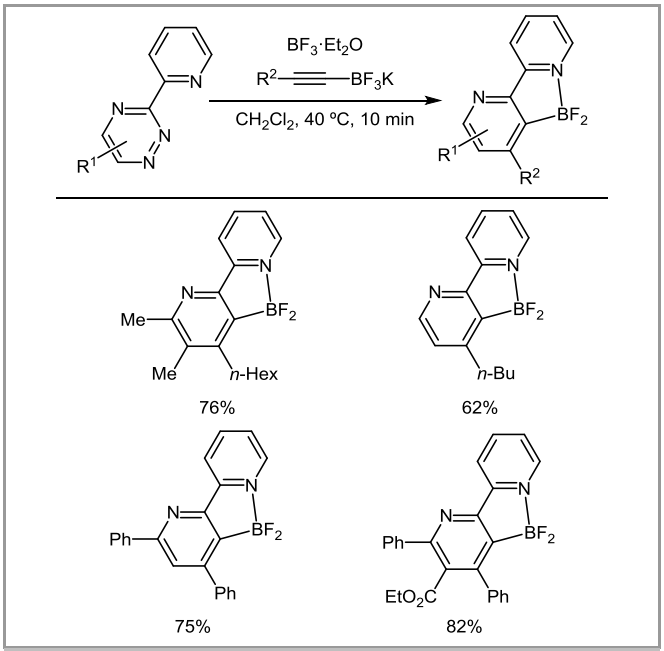


Scheme 27 Direct comparison of reaction conditions between thermal and directed cycloadditions between triazines and alkynes.

Remarkably, employing *in situ* generated alkynyldifluoroboranes in reactions of 1,2,4-triazines bearing Lewis basic donors leads to significant rate enhancements as compared to traditional thermally promoted cycloaddition/retro-cycloaddition processes. These directed reactions proceed at just above room temperature and within 10 min (Scheme 27).[76]

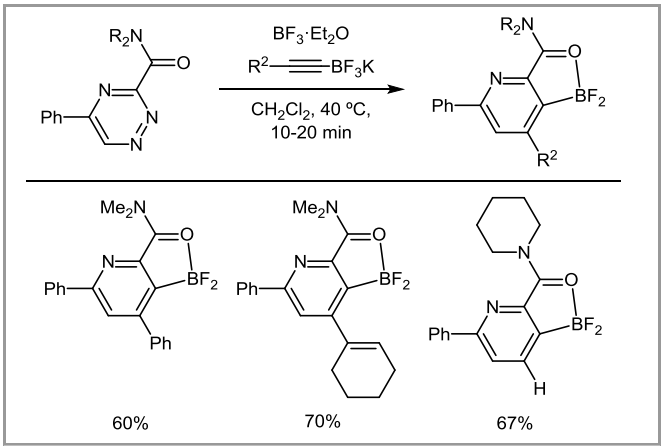
This methodology has been successfully extended to synthesise a range of functionalized bipyridine scaffolds bearing a range of substitution patterns in good to excellent yields and with complete regiocontrol, using 2-pyridyl as the Lewis basic donor (Scheme 28).

In addition to 2-pyridyl-, other directing groups such as various amide derivatives proved to be successful in this transformation delivering the corresponding difluoroborane products in high yield (Scheme 29).



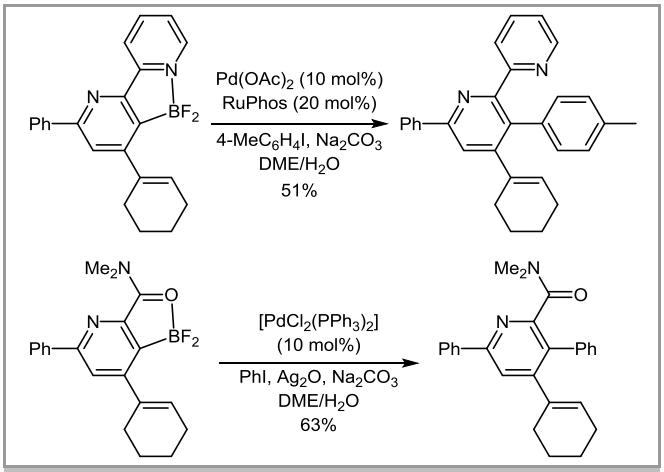
Scheme 28 Directed cycloadditions with triazines bearing a 2-pyridyl directing group.

Satisfactorily, the authors showed that in this case the complexity of the pyridine derivatives could be increased by means of Suzuki-Miyaura cross-coupling reactions on the -BF_2 moiety, generating the corresponding polyaromatic substrates, as shown in Scheme 30.[76]



Scheme 29 Directed cycloadditions using 1,2,4-triazines bearing amides as directing groups.

Interestingly, this methodology has been further exploited by the groups of Harrity and Bräse to develop a new family of fluorophores known as BOBIPYs (Figure 3), which are based on a borylated bipyridyl scaffold. These compounds show promising fluorescence properties and can be incorporated to peptoid fragments by means of 'click' chemistry to deliver novel biological tags for the development of new bioimaging agents.[77]



Scheme 30 Cross-coupling reactions to functionalise the pyridine adducts after cycloaddition.

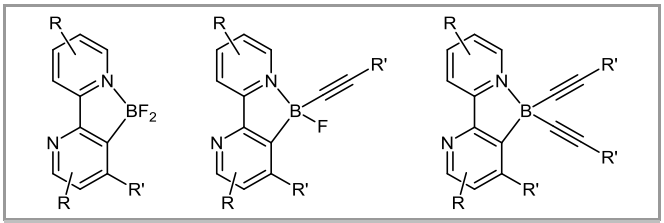
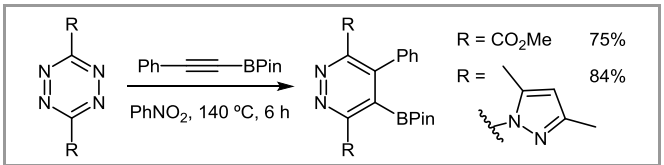


Figure 3 Generic structures for the BOBIPY fluorophores.

3. Tetrazines:

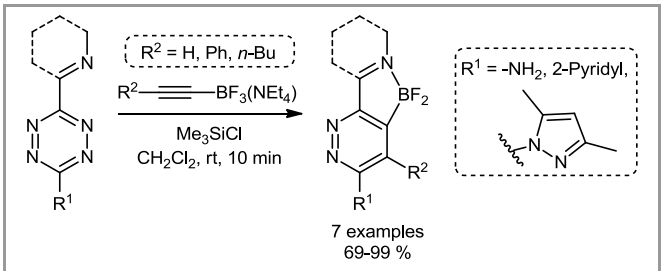
In a similar manner to the triazine system, tetrazine analogues are able to undergo inverse electron-demand Diels-Alder reactions with alkynes to generate substituted pyridazines after nitrogen extrusion, in a process known as the Carboni-Lindsey reaction.[78] Although this methodology has been broadly employed in total synthesis (see for example the synthesis of Ningalin D reported by Boger[79]) and biomedical applications,[80] it generally suffers from harsh reaction conditions (high temperature and/or long times) unless highly activated dienophiles are employed.[81,82]

In an attempt to broaden the scope of this transformation, the Harrity group have reported the possibility to perform these cycloadditions with alkynyl boronic esters to generate the corresponding pyrazidines in good yield, albeit still requiring high reaction temperatures for these transformations to take place (Scheme 31).[83,84]



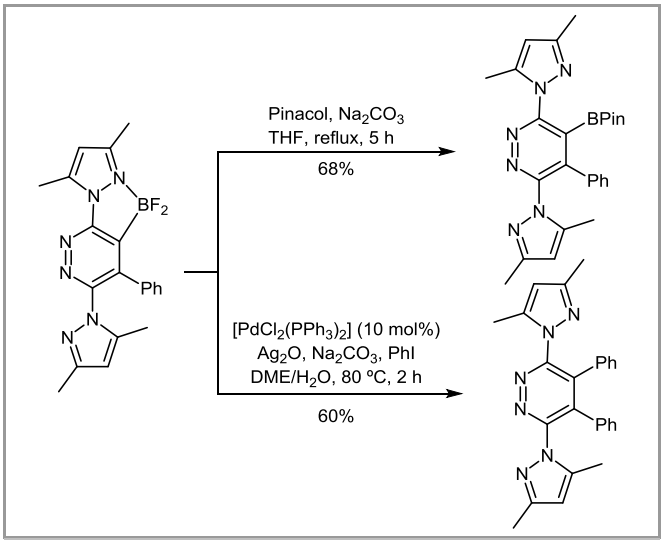
Scheme 31 Cycloaddition reaction between alkynylboronates and 3,6-disubstituted tetrazines.

Once again, the reaction was found to be promoted when alkynyltrifluoroborate salts were employed in conjunction with a Lewis acid. For this purpose, the cycloadditions proceeded at room temperature when a mild promoter such as Me_3SiCl was employed. In this case, the chosen Lewis basic groups were 2-pyridine and 3,5-dimethylpyrazole (Scheme 32).[85]



Scheme 32 Directed cycloadditions between tetrazines and trifluoroborate salts in the presence of a Lewis acid.

By analogy to previous examples, the $-BF_2$ moiety offered a window for further functionalization using standard procedures such as the Suzuki-Miyaura cross-coupling. Moreover, it was demonstrated that the more traditional pinacol boronic ester derivatives could be generated from the Lewis acid-base complexes (Scheme 33).



Scheme 33 Examples of functionalization of the -BF_2 moiety of the cycloaddition products.

4. Conclusions

A variety of examples of cycloaddition reactions that generate interesting carbocycle or heterocycle-containing molecules has been discussed featuring the use of metal acetylides as a source of activated alkynes. The use of metal acetylides presents several advantages, the most significant being their activation towards ring forming reactions, often resulting in mild and selective synthetic methods. Moreover, they have also resulted in the improvement of many procedures, reducing the amount of metal promoters required from stoichiometric or super-stoichiometric amounts to low catalytic loadings, thus contributing to a more sustainable heterocycle synthesis.

The use of these species in cycloaddition reactions offers, compared to the traditional methods to synthesize heterocycles, a straightforward alternative since in one single step, all the fragments are assembled together achieving higher atom economy, giving access to densely functionalized scaffolds bearing a functionalizable carbon-metal bond, and often starting from very simple starting materials. Further advances in this field promise to uncover new strategies and reactions that allow complex high value chemical entities to be efficiently assembled within short and sustainable sequences.

Acknowledgment

This work was supported by to the FP7 Marie Curie Actions of the European Comission *via* the ITN ECHONET NETWORK (MCITN-2012-316379).

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Biosketches

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