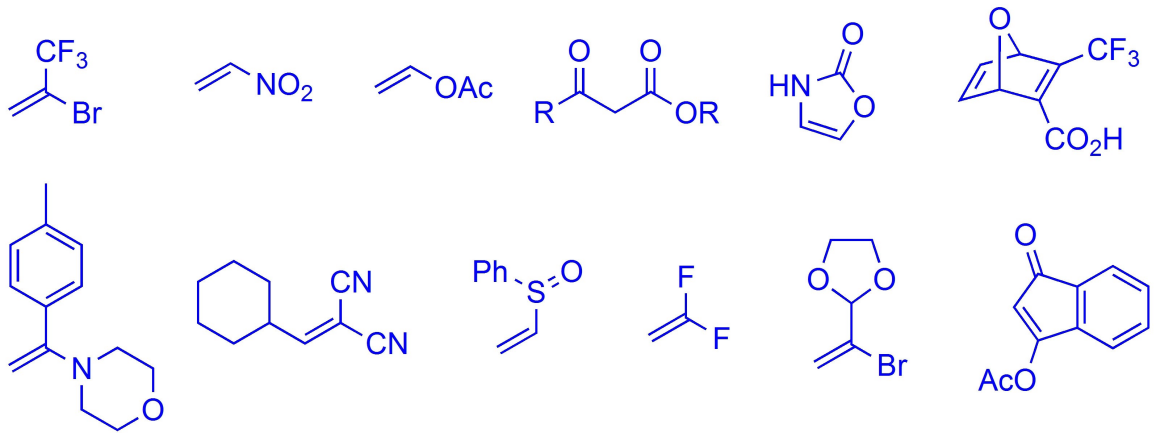
Alkyne Surrogates in Cycloaddition Reactions for the Preparation of Molecules of Interest

Muriel Amatore, Jean-luc Parrain, Laurent Commeiras

selected examples



Abstract: Although alkynes are very good partners for cycloaddition reactions, their use is often associated to several drawbacks, such as multi-steps synthesis, selectivity and stability issues or difficulty to handle for alkynes with low boiling point. In this context, alkyne surrogates have emerged as alternative substitution partners unlocking new opportunities. This review intends to highlight the outstanding power and utility of such compounds for the preparation of high value molecules.

1. Introduction

Among all the transformations to access functionalized cyclic compounds, purely atom-economy couplings are rare and only cycloaddition reactions appear as the most suited approaches. Because several new bonds are formed in a single operation, this strategy brings far-reaching benefits when saving cost, atoms, energy and time is to be considered. Specifically, cycloaddition reactions with acetylene and alkyne derivatives have enabled the preparation of molecules of interest. However, hazards and precautions in handling acetylene, alkynes with low boiling points, cycloalkynes with sizes less than eight-membered ring or unstable alkynes hamper their usefulness. Acetylene itself is known to be practically unreactive in cycloaddition reactions either thermally or photochemically. As a gaseous compound, it is also safety hazardous and difficult to handle at high reaction pressures and temperatures. The use of low-molecular alkynes is also troublesome and strained cycloalkynes are generally *in situ* generated due to their poor stability. To circumvent these shortcomings associated with tedious multi-step synthesis of functionalised alkynes, the use of alkyne equivalents has been devised unlocking new opportunities. This elegant strategy employs an appropriate functionalized alkene bearing an appropriate "leaving group" (LG), and is based on a one-pot, two steps procedure, including firstly cycloaddition reaction followed by the re-formation of the C=C double bond *via* an elimination reaction or in specific cases through a retro-Diels-Alder fragmentation (Figure 1).

The purpose of this review is to highlight recent advances (since 2000 and until 2021) in cycloaddition reactions involving the use of masked acetylene derivatives, also known as alkyne surrogates. To the best of our knowledge, this subject was covered only once in 1984 by De Lucchi and Modena.[1] The following discussion is structured according to the different types of cycloaddition reactions, i.e. (3+2), [4+2], and [2+2+2] cycloaddition reactions and is restricted to only one-pot, two-step cycloaddition/C=C bond formation processes. Related procedures which are not cycloaddition reactions[2] are out of scope of this review.[3]

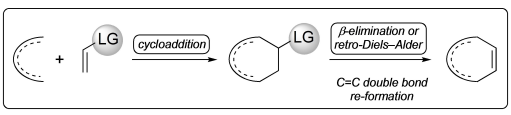
2. 1,3-dipolar cycloaddition reaction

2.1. Synthesis of pyrazoles

Pyrazoles, which are aromatic 5-membered heterocycles containing two adjacent nitrogen atoms, are core structures found in a number of molecules (natural or not) that possess a wide range of pharmaceutical and agricultural activities, as well as chemical properties.[4,5] While the 1,3-dipolar cycloaddition reaction of diazo compounds with alkynes is one of the most frequently used protocols for the synthesis of pyrazole derivatives,[6] the use of alkyne surrogates offers new opportunities in particular as regards regioselectivity issues and structure diversity. In this context, the addition of functionalized vinylsulfoxides with diazoalkanes or nitrile imine 1,3-dipoles resulted in the efficient synthesis of the desired pyrazole derivatives through elimination reaction of a sulfoxide moiety from the sulfinylpyrazoline intermediates.[7]

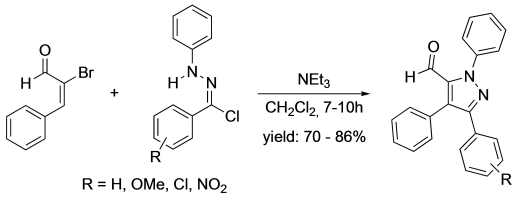
Vinyl halides have been also extensively employed as alkyne surrogates in 1,3-dipolar cycloaddition reactions. In 1989, Burri's group reported the highly regioselective synthesis of oxicam derivatives based on (3+2) cycloaddition reaction of ethyl diazoacetate or diphenylnitrile imine with 4-bromoisothiazolone, acting as a strained cycloalkyne equivalent after final dehydrobromination.[8] More recently, Hammee II and coworkers described the preparation in good yields of 1,3,4,5-tetrasubstituted pyrazoles by a regioselective cycloaddition reaction of nitrile imine, generated *in situ* from *N*-phenylbenzenehydrazonoyl chloride, with α-bromocinnamaldehyde (Scheme 1).[9] In this process, the nature of substituents on the hydrazonoyl chloride partner does not affect either the reactivity or the regioselectivity.

In 2020, Ratovelomanana-Vidal, Phansavath and coworkers demonstrated that non-activated alkenes like α-bromovinyl acetals are both excellent dipolarophiles and alkyne surrogates in the synthesis of pyrazoles.[10] The authors disclosed a straightforward and regioselective synthesis of diverse 3,5-disubstituted pyrazoles from α-bromovinyl acetals and *in situ* generated diazo intermediates in good yields (Scheme 2). In this process, a dehydrobromination/1,3-hydrogen atom transfer (1,3-HAT) sequence is consecutive to the regioselective cycloaddition reaction. This reaction was found to be versatile since

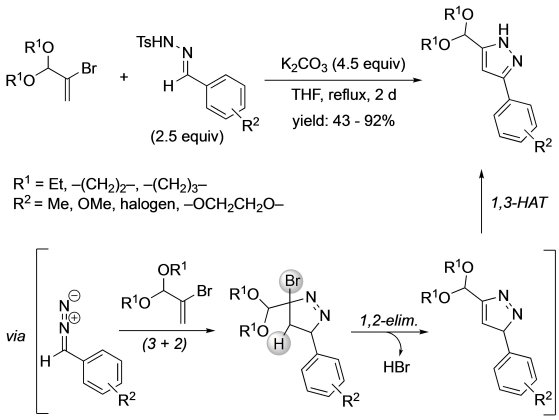


various substituted benzylidene and/or acetal moieties are tolerated on both partners allowing the preparation of a small library of 32 pyrazole derivatives.

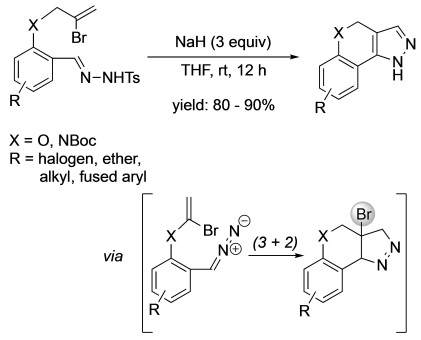
The synthesis of valuable pyrazole-fused dihydrobenzopyrane or dihydroquinoline derivatives was investigated *via* an intramolecular 1,3-dipolar cycloaddition reaction by the group of Chandrasekahar in 2001 (Scheme 3).[11] When the tosylhydrazones featuring a vinylbromide group as alkyne equivalent are subjected to an excess of base, a cycloaddition/dehydrobromination/1,3-HAT cascade occurs to cleanly furnish the corresponding heterocycles in good yields whatever the nature of both the link and the substituents.



Scheme 1. 1,3-dipolar cycloaddition reaction of *N*-phenylbenzenehydrazonoyl chloride derivatives with α-bromocinnamaldehyde.



Scheme 2. 1,3-dipolar cycloaddition reaction of *in situ* generated diazo intermediates with α-bromovinylacetals.



Scheme 3. Synthesis of dihydrobenzopyrano- and dihydroquinolinopyrazoles *via* an intramolecular 1,3-dipolar cycloaddition reaction.

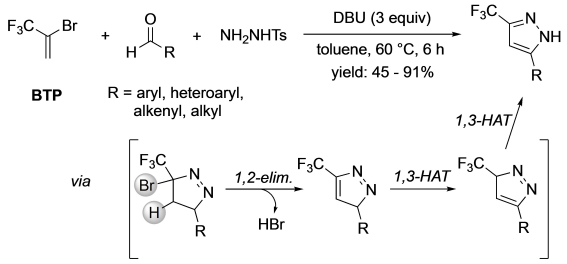
Muriel Amatore was born in Paris in 1979 and obtained her Ph.D. in 2006 with Dr. C. Gosmini (UPEC, France). She carried out three post-doctoral research stays in enantioselective organocatalysis (Princeton University, Prof. D. W. C. MacMillan) and organometallic catalysis (Ecole Polytechnique, Dr. C. Gosmini/ Université Pierre et Marie Curie, Dr. Corinne Aubert) before achieving a permanent position as assistant professor at UPMC (2010). In 2018, she moved to Aix-Marseille Université to join the group of Prof. Thierry Constantieux (iSm2, STeRéO). Her current research interests center on the development of transition metal-catalysed and organocatalysed processes for their application in stereoselective synthesis.

Laurent Commeiras received his PhD degree in organic chemistry in 2002 from Aix-Marseille University under the guidance of Dr. Jean-Luc Parrain. He then joined the group of Prof. Sir Jack E. Baldwin at the University of Oxford as post-doctoral researcher. In 2003, he went back to Aix-Marseille University to start his independent career first as an associate professor then as a full professor. His research interests concern the total synthesis of natural and biologically active compounds and the development of new methodologies including the formation of hetero-, poly- and spirocyclic complex structures.

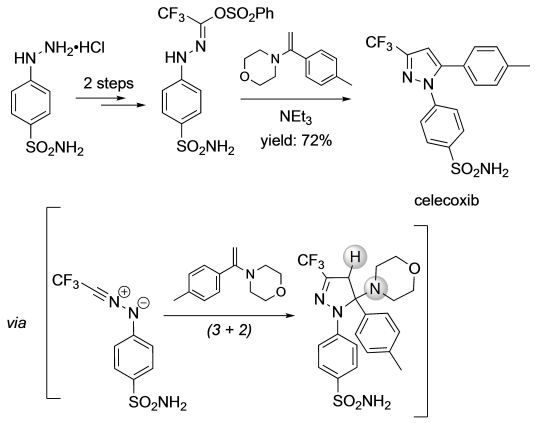
Jean-Luc Parrain obtained his PhD in Chemistry at the University of Nantes (France) under the supervision of Professor Jean-Paul Quintard. After post-doctoral studies in the laboratory of Prof. Steve Davies at the University of Oxford (UK), he joined the CNRS in 1990 and he moved to Aix-Marseille University in 1995. His research interests include new catalytic reactions toward new synthetic methods, development of organo element (Sn, Si and B) reagents, total synthesis of natural compounds and, more recently, spatially resolved functionalization of surfaces.

Ma and coworkers disclosed an elegant 1,3-dipolar cycloaddition reaction of trifluorodiazoethane with alkynes to regioselectively access to 3-trifluoromethylpyrazoles.[12] However, the reaction requires the *in situ* preparation of gaseous trifluorodiazoethane. To overcome this practical drawback, Zhu, Jiang and coworkers reported very recently a convenient multicomponent procedure between the easy to handle 2-bromo-3,3,3-trifluoropropene (BTP), playing the role of both dipolarophile and alkyne surrogate, aldehydes and tosylhydrazine in presence of base, which allows to prepare a library (52 examples) of 3-trifluoromethylpyrazoles in mainly good yields and as single regioisomers (Scheme 4).[11] A mechanism involving a (3+2) cycloaddition reaction, HBr elimination and two 1,3-HAT is proposed to explain the observed regioselectivity. This reaction is general and a variety of aromatic, heteroaromatic, unsaturated and aliphatic aldehydes with different functional groups are tolerated. It is noteworthy, that this process is scalable to 100 mmol scale, without observing a decrease of yields, and allows the preparation of four advanced building blocks for the synthesis of biologically active compounds named celecoxib, mavacoxib, SC-560 and AS-136A.

Few years before, Oh and coworkers described a straightforward stepwise synthesis of celecoxib featuring a 3-trifluomethylropyrazole moiety.[14] The last key-step is a 1,3-dipolar cycloaddition reaction between an *in situ* generated trifluoromethyl nitrile imine and an electron rich enamine acting as both dipolarophile and alkyne equivalent. The desired 3-trifluoromethylpyrazole derivative was obtained in very good yield and as unique regioisomer (Scheme 5).



Scheme 4. Synthesis of 3-trifluoromethylpyrazoles by a multicomponent process.

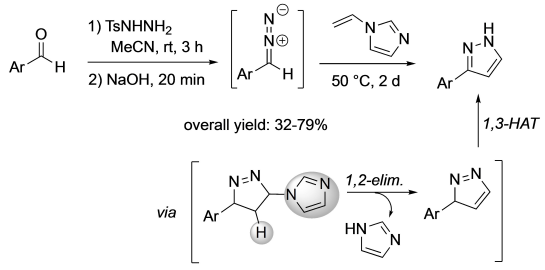


Scheme 5. Total synthesis of celecoxib.

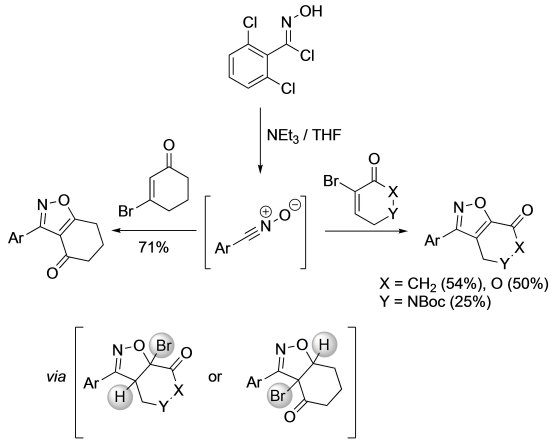
In 2003, Aggarwal and coworkers developed a one-pot, three- steps procedure for the regioselective preparation of 3-substituted pyrazoles from diazo intermediates and electron-rich enamine *N*-vinylimidazole as acetylene equivalent (Scheme 6).[15] In this reaction, diazo intermediates are first prepared from the condensation of tosylhydrazine with aromatic or heteroaromatic aldehydes followed by a basic treatment. *N*-Vinylimidazole is then added to furnish the desired pyrazoles in fair to good yields after elimination reaction of imidazole moiety from the corresponding cycloadducts and isomerization of the double bond. The reactivity of vinyl acetate as alkyne surrogate was also evaluated. However, acetic acid released in the course of the reaction was at the origin of side products formation.

2.2. Synthesis of isoxazoles

Isoxazole derivatives which are valuable heterocycles with significant biological applications, are mainly prepared by a 1,3-dipolar cycloaddition reaction of nitrile oxides with alkynes. Unfortunately, regioselectivity issues (synthesis of 4- and 5-regioisomers) often arise. However, the use of activated alkenes as alkyne equivalents results in higher regiocontrol due to steric and/or electronic effect of the leaving group on the alkene. Indeed, 4-substituted isoxazoles were isolated as major isomers when the cycloaddition reaction was performed with 2-methylthiovinyl phenylketone,[16] 2-methoxyvinyl phenyl ketone[17] or the pyrrolidine enamine derived from β-ketoesters[18] as alkyne equivalents. On the other hand, the regioselectivity of the cycloaddition reaction could be reversed when reacting the captodative olefine (1-benzoatevinyl phenyl ketone) with benzonitrile oxide.[19] This regiocontrol has been also anticipated by Easton and coworkers with 2- or 3-bromocyclohex-2-enone derivatives used as cyclic alkyne surrogates (Scheme 7).[20] When the 2,6-dichlorobenzohydroximoyl chloride is subjected to triethylamine, a cycloaddition reaction between the *in situ* generated nitrile oxide and the alkyne equivalent occurs, followed by an HBr elimination, to regioselectively



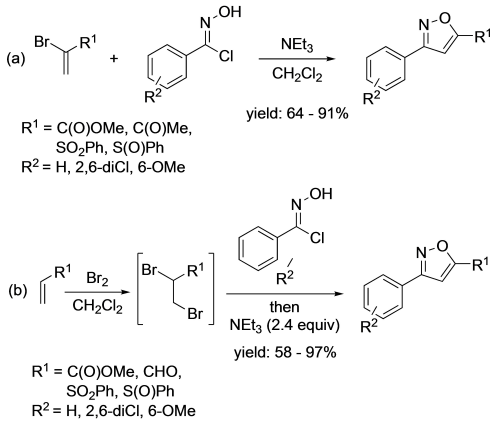
Scheme 6. One-pot, three-steps procedure for the regioselective preparation of 3-substituted pyrazoles.



Scheme 7. Regioselective synthesis of isoxazoles-fused cyclohexenones.

furnish the desired isoxazoles-fused cyclohexenones in fair to good yields.

Similarly, 1,1-disubstituted bromoalkenes have been employed as alkyne surrogates by the group of Hamme II for the regioselective preparation of 3,5-disubstituted isoxazoles through 1,3-dipolar cycloaddition.[21] The authors showed that when the 2-bromoacrylic acid methyl ester or 3-bromobut-3-en-2-one are submitted to arylnitrile oxide intermediates, the corresponding cycloadduct is obtained in good yields, whatever the nature of the substituents on the aryl moiety of the dipole, and with a total regiocontrol (Scheme 8a). Similar results were observed starting from phenyl vinyl sulfones or sulfoxides. Since 5-regioisomers are exclusively obtained, this methodology offers a complementary approach to the use of alkynyl sulfones leading to the opposite regioselectivity.[22] Because of the relative instability of bromoalkenes, the same group developed a one-pot process in which the two cycloaddition partners are *in situ* generated (Scheme 8b).[23] One more time, the cycloadducts were efficiently and regioselectively obtained. Several activated groups are tolerated both on the starting vinyl bromides and on the α-chlorobenzaldoximes, demonstrating the versatility of the process.

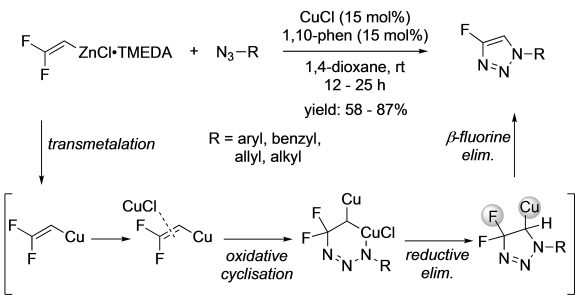


Scheme 8. Regioselective synthesis of isoxazoles from 1,1-disubstituted bromoalkenes or 1-substituted alkenes.

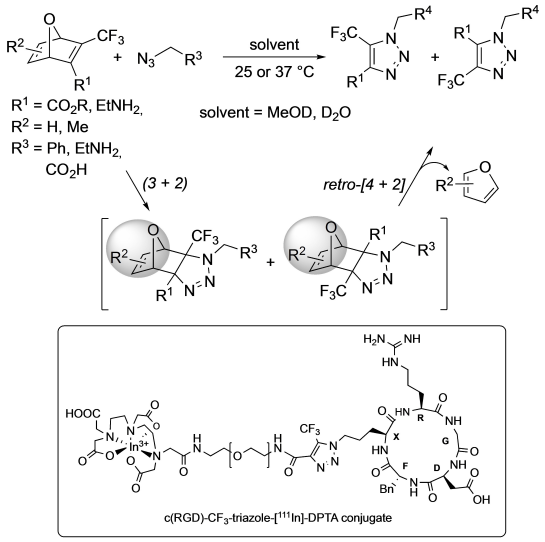
2.3. Synthesis of triazoles

Substituted 1,2,3-triazoles which are among the most important heterocyclic compounds, have found wide uses in pharmaceuticals, agrochemicals and industrial applications since they can be regioselectivity prepared by copper[24] or ruthenium-catalysed[25] Huisgen 1,3-dipolar cycloaddition reaction between an azide and an alkyne. However, because of the pronounced reactivity and the difficult in handling fluoroacetylene, the synthesis of 4- or 5-fluorotriazoles remains tedious. In this context, during their studies for the preparation of fluorovinyl compounds, Ichikawa and coworkers reported in 2020 the use of 2,2-(difluorovinyl)zinc chloride·TMEDA as an equivalent of fluoroacetylene (Scheme 9).[26] When this latter is subjected to a copper-catalysed 1,3-dipolar cycloaddition with benzylic-, allylic-, aryl- or alkyl azides, 1-substituted 4-fluorotriazoles derivatives are obtained in good yields (58–87%) and with a complete regiocontrol. Additional experiments support a mechanism involving transmetalation, oxidative cyclisation, reductive elimination and β-fluorine elimination steps.

In addition, in order to avoid the use of metals which can be toxic to biological systems, alternative metal-free 1,3-dipolar cycloaddition have been developed. One of them includes enamine- or enolate-mediated organocatalytic (3 + 2) cycloaddition reactions. In these processes, the enamine or enolate moieties play, *inter alia*, the role of alkyne surrogates. These elegant protocols have been recently reviewed and therefore they are not discussed in the following section.[27] Another procedure developed by Bertozzi and coworkers to avoid the use of metal consists of the utilisation of cyclooctyne in a strain-promoted azide-alkyne (3 + 2) cycloaddition reaction (SPAAC).[28] Based on these results, Rutjes and coworkers devised trifluoromethyl substituted oxonorbornadiene derivatives as suitable partners for metal-free SPAAC with various azides for the straightforward synthesis of 1,4,5-substituted triazoles, obtained as a mixture of two regioisomers (Scheme 10).[29] From a mechanistic point of view, the reaction first involves a (3 + 2)



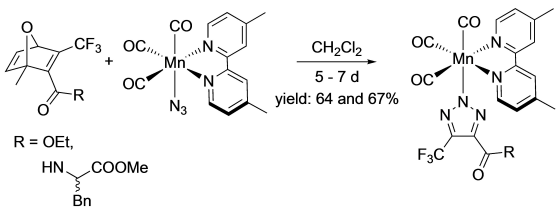
Scheme 9. Synthesis of 1-substituted 4-fluorotriazoles.



Scheme 10. Metal-free triazole synthesis as a tool for bioconjugation.

cycloaddition reaction between azide and the most electron-deficient double bond of norbornadiene derivative, delivering the corresponding tricyclic triazoline intermediates, which rapidly undergo a retro-Diels-Alder reaction to furnish the desired 1,4,5-triazoles *via* expulsion of a furan moiety. If R^2=H, the monosubstituted 1,4,5-triazole, arising from the cycloaddition reaction on the other norbornadiene double bond, can be isolated up to 16%. The formation of this side product could be suppressed by introducing a methyl substituent on the most electron-rich double bond (R^2=Me). It is worth noting that these electron-deficient oxonorbornadienes react faster than the corresponding trifluoromethyl substituted alkynes and provide identical 1,4,5-substituted triazoles. This efficient metal-free methodology was nicely applied to ligate several bio (macromolecules) under physiological conditions.

A related procedure was developed by Schatzschneider and coworkers for the synthesis of *N*-triazolate-linked Mn(bpy)$(CO)_3$-ethyl ester and *N*-triazolate-linked Mn(bpy)$(CO)_3$-phenylalanine bioconjugate in which the manganese centre is bond to the central N-2 nitrogen atom (Scheme 11).[30]



Scheme 11. Biorthogonal coupling reactions.

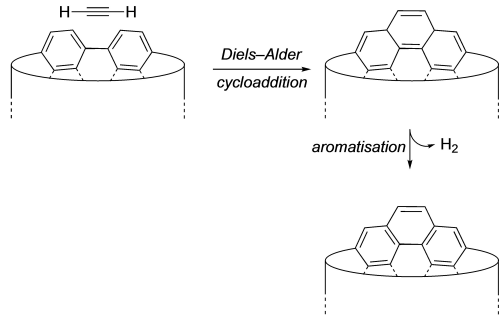
3. [4 + 2] cycloaddition reactions

3.1. Synthesis of carbon nanotubes (CNTs)

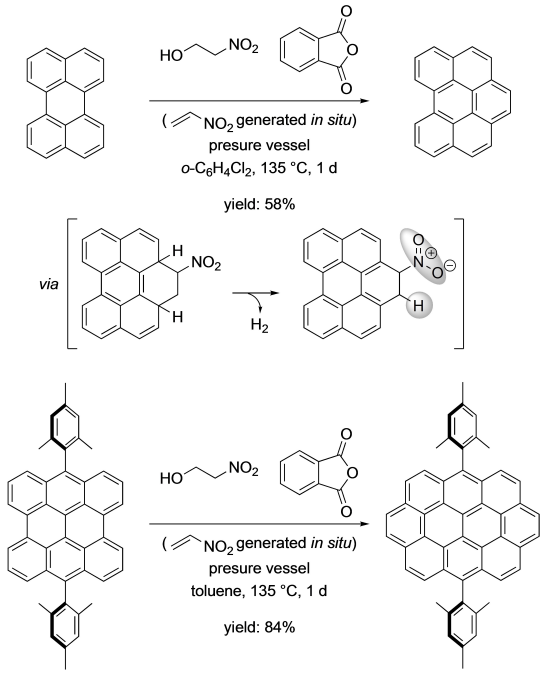
Although carbon nanotubes (CNTs) with uniform properties in terms of chirality and structure (diameter and [*m*, *n*] index) are interesting materials for molecular scale electronics, their selective synthesis from graphite as single-diameter and single-chirality nanotubes is still challenging. Most of the existing methods for their preparation usually require tedious purification of the desired material from a complex mixture of the chiral, zig-zag and armchair CNTs. In this context, one of the strategies for the highly selective synthesis of CNTs calls for the development of metal-free chemical methods allowing a controlled elongation of a small cylindrical hydrocarbon template by repetitive annulation/aromatisation sequence. In 2009, Scott and coworkers confirmed the reactivity of known poorly reactive polycyclic aromatic hydrocarbon (PAHs) bay regions of perylene and bisanthene derivatives as model substrates in Diels-Alder reactions with acetylenedicarboxylate.[31] However, the preparation of CNTs based on this strategy (new ring featuring only hydrogen atoms) implies the use of acetylene as dienophile and of course, in a late stage, a suitable hydrocarbon template (Scheme 12).

Unfortunately, besides being difficult to handle, acetylene acts as a poor dienophile in Diels-Alder reactions. To overcome this issue, the authors envisioned to perform similar cycloaddition reactions with *in situ* generated or freshly distilled nitroethylene (Scheme 13).[32] Guided by computational calculations, nitroethylene was a suitable dienophile and bay regions of planar perylene and 7,14-dimesitylbisanthene were mono- and doubly-converted to the corresponding benzene rings with 58 and 84% respectively. In this process, a dehydrogenative and nitrous acid elimination sequence is consecutive to the regioselective cycloaddition reaction. Phenyl vinyl sulfoxide, firstly reported by Paquette, Magnus and coworkers,[33] was less efficient and reacted only with 7,14-dimesitylbisanthene in a low yield.

Another approach within carbon nanotube growth was reported shortly after by Jasti and coworkers based on a different template.[34] They synthesized a cycloparaphenylene featuring a perylene core as a CNT sidewall curved template



Scheme 12. Diels-Alder cycloaddition/aromatisation sequence for the controlled synthesis of CNTs.

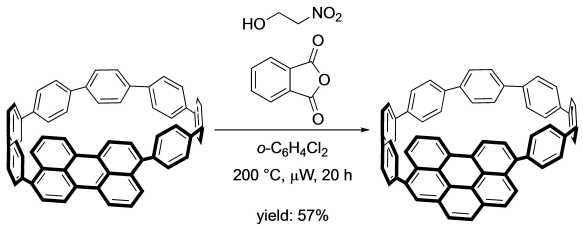


Scheme 13. Diels-Alder cycloaddition/aromatisation sequence for the controlled synthesis of CNTs from planar templates.

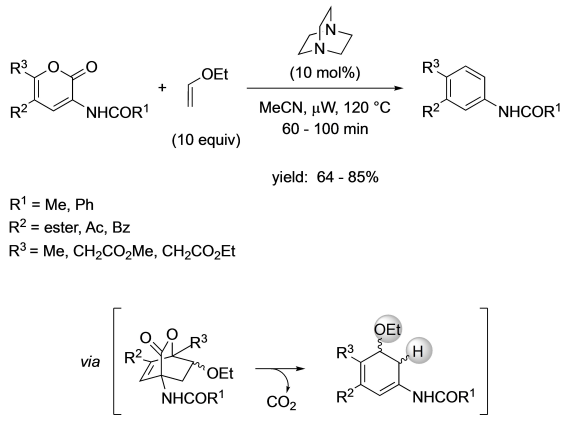
and investigated its reactivity in Diels-Alder cycloaddition reaction with nitroethylene as masked acetylene. As a proof of concept, around 57% yield of a non-separable mixture was isolated containing the desired mono-cycloadduct in a (1.2:1) ratio with the starting material (Scheme 14).

3.2. Synthesis of benzene derivatives

A synthesis of substituted anilines from electron-poor 2*H*-pyran-2-ones and ethyl vinyl ether as acetylene equivalent was developed by Kranjc and coworkers.[35] The reaction proceeds with good yields through a microwave-assisted Diels-Alder cycloaddition/aromatisation sequence using DABCO (1,4-diazabicyclo[2.2.2]octane) as basic catalyst to lower reaction temperature (120 °C instead 160 °C) without compounds decomposition (Scheme 15). Under heating, a spontaneous retro-Diels-



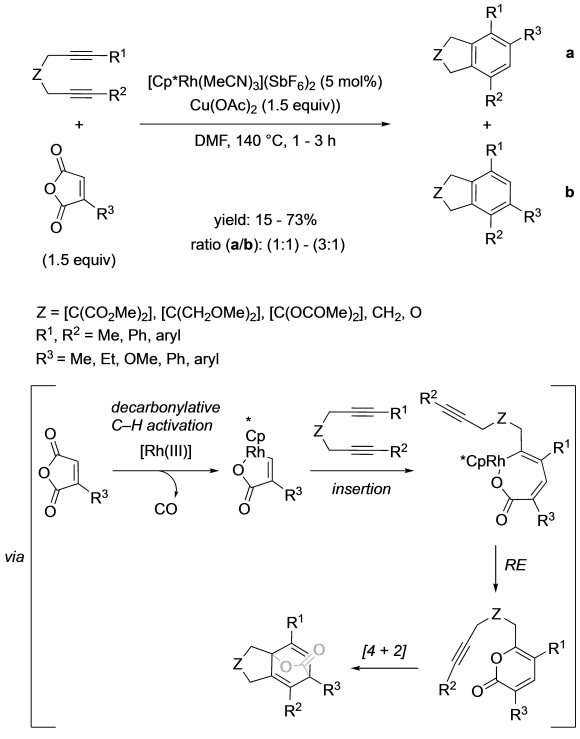
Scheme 14. Diels-Alder cycloaddition/aromatisation sequence for the controlled synthesis of CNTs from macrocyclic curved template.



Scheme 15. Diels-Alder cycloaddition/aromatisation sequence for the synthesis of substituted anilines.

Alder reaction followed by CO_2 elimination from oxabicyclo [2.2.2]octene intermediates furnishes the corresponding cyclohexadienes which are prone to elimination of ethanol, favored under basic catalysis.

Matsuda and his group have reported a formal [2+2+2] cyclotrimerization of 1,6-diynes with maleic anhydrides as low boiling point alkyne surrogates (Scheme 16).[36] According to their strategy based on C–H bond functionalisation, α-pyrones



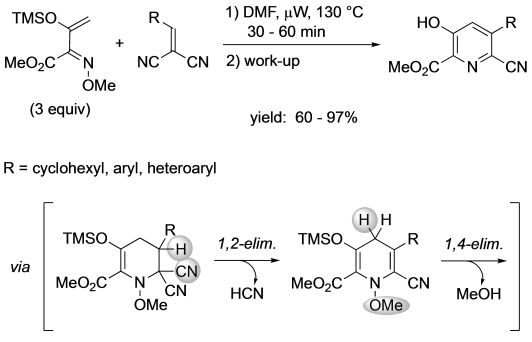
Scheme 16. Formal [2+2+2] cycloaddition using maleic anhydrides as alkyne equivalents for the synthesis of benzene derivatives.

are easily obtained as intermediates *via* a rhodium(III)-catalysed decarbonylative coupling between maleic anhydride and one alkyne moiety. The later undergo [4 + 2] cycloaddition reaction to afford unstable oxabicyclo[2.2.2]octadiene adducts which are rapidly converted to the corresponding aromatic compounds following a decarboxylative retro-Diels-Alder reaction. The substrate scope of the reaction includes symmetric 1,6-diynes featuring various tethers and alkyl or aromatic groups at alkyne termini, non-symmetric diynes albeit with low regioselectivity and different maleic anhydrides. Although moderate yields are generally obtained, this approach demonstrated the synthetic potential of maleic anhydrides as alkyne equivalents through unprecedented formal expulsion of CO–O–CO function.

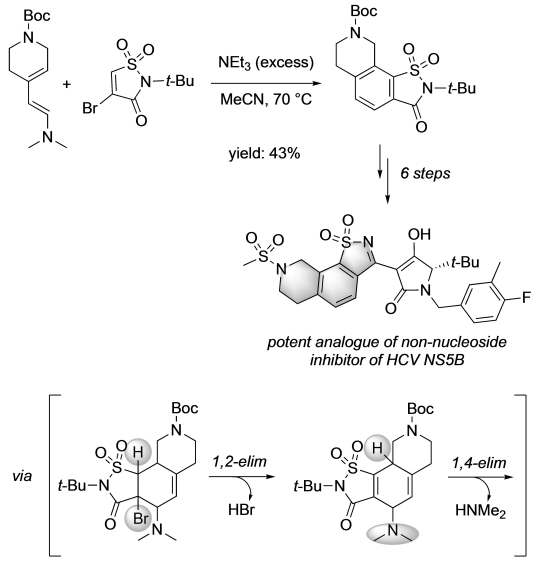
3.3. Synthesis of heteroaromatic derivatives

Hetero-Diels-Alder (HDA) cycloadditions of azadienes with designed alkenes bearing a leaving group as masked alkynes allows the straightforward preparation of valuable highly substituted 3-hydroxypyridines scaffolds. In this context, Jacob, Arndt and coworkers reported the aza-Diels-Alder reaction of a *O*-alkylated oxime azadiene derivative with various α,α-dicyanoalkenes under microwave activation with excellent results in terms of yields, chemo- and regioselectivities (Scheme 17).[37] Under these conditions, the [4 + 2] cycloadducts rapidly evolve to the corresponding 3-hydroxypyridines *via* spontaneous 1,2- and 1,4-eliminations of HCN and methanol.

In the course of their studies on the development of new non-nucleoside inhibitors of HCV NS5B polymerase, de Vicente and coworkers demonstrated promising results for analogues featuring a benzo[d]isothiazole-1,1-dioxide core.[38] The elegant synthesis of the most potent analogue incorporating additional cyclic sulfonamide and 3-methyl-4-fluorobenzyl groups is based on an efficient Diels-Alder reaction with the 4-bromoderivative of an isothiazol-3(2*H*)-one-1,1-dioxide as a masked 5-membered cycloalkyne dienophile (Scheme 18). The presence of an excess of base allows a double elimination sequence to occur furnishing the desired benzo[d]isothiazole-1,1-dioxide scaffold. Further transformations from this intermediate provide the targeted analogue.



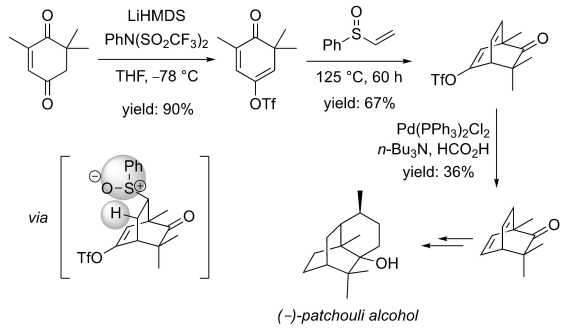
Scheme 17. Diels-Alder cycloaddition/aromatisation sequence for the synthesis of substituted 3-hydroxypyridines.



Scheme 18. Diels-Alder cycloaddition/double elimination sequence for the synthesis of benzo[d]isothiazole-1,1-dioxide core.

3.4. Synthesis of bicyclo[2.2.2]octadienones

1,3,3-Trimethylbicyclo[2.2.2]octa-5,7-dien-2-one is a key intermediate in the total synthesis of patchouli alcohol developed by Stork's group using a vinyl radical cyclisation strategy.[39] On the paper, a straightforward method to access this bicyclo[2.2.2]octa-5,7-dien-2-one frameworks is the Diels-Alder reaction of a 2,6,6-trimethyl-2,4-cyclohexadienone with acetylene. However, such reaction would suffer from several drawbacks like tedious preparation and relative instability towards dimerisation reaction of 2,4-cyclohexadienone core or difficulty to handle gaseous acetylene. To overcome such issues, Liao and coworkers described an alternative strategy based on the use of relatively stable 4-triflyoxy-2,6,6-trimethyl-2,4-cyclohexanedienone, readily obtained from the enolisable 4-ketoisophorone according to Cacchi's procedure,[40] and phenyl vinyl sulfoxide as acetylene equivalent (Scheme 19). Thermal extrusion of phenyl sulfenic acid from the obtained cycloadduct and final reduction reaction afforded the desired intermediate in a 22% overall yield. On the contrary, perfluoroalkyl vinyl sulfoxides do not react as alkyne surrogates as they appear more reactive dienophiles and most of the time, not prone to subsequent elimination of the sulfinyl group due to a reduced basicity of the oxygen atom in the formed cycloadduct.[41] In this context, Wakselman and co-workers reported only one example of such elimination furnishing a dibenzobarralene derivative albeit with low conversion by reaction of anthracene with perfluorohexyl vinyl sulfoxide.



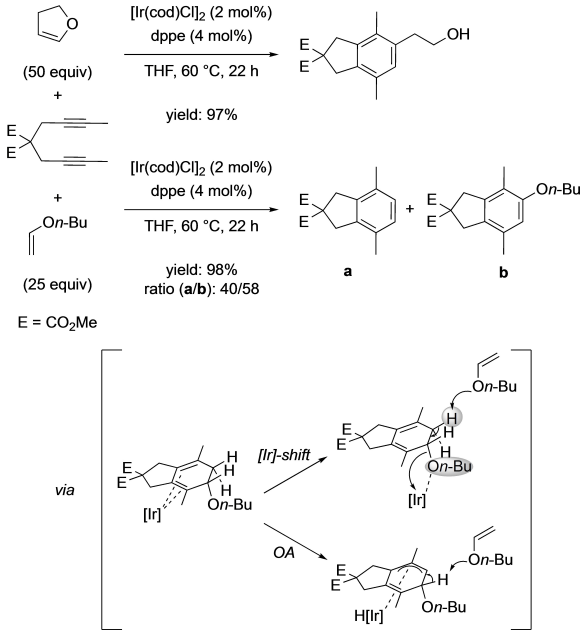
Scheme 19. Diels-Alder cycloaddition/elimination sequence for the synthesis of benzo[d]isothiazole-1,1-dioxide core.

4. [2+2+2] cycloaddition reactions

Transition metal-catalysed cross-alkyne cyclotrimerisation reaction is one of the most valuable method for the straightforward access to substituted benzene derivatives. Nonetheless, these reactions often suffer from poor regioselectivity and difficulty to handle gaseous alkynes. To overcome this selectivity issue, some partially intramolecular [2+2+2] cycloaddition reaction of diynes with alkynes have been developed with success. Another original alternative is to carry out a formal cross-alkyne cyclotrimerization reaction by using alkyne surrogates. The regioselectivity of the reaction is often directly controlled by supplementary coordination of the metal centre with a temporary Lewis base moiety included in the selected leaving group of the alkyne equivalent.

4.1. Synthesis of substituted benzene rings

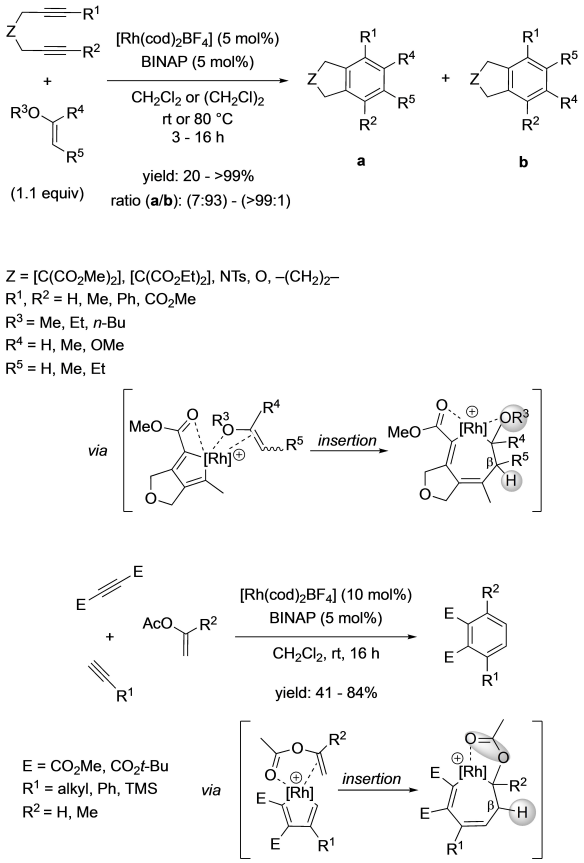
To the best of our knowledge, such formal cross-alkyne cyclotrimerisation was firstly reported by Stephan and coworkers under palladium catalysis in 1993.[42] The reaction of a preformed palladium complex with dimethyl acetylenedicarboxylate and an excess of vinyl propionate or vinyl ether afforded selectively the corresponding aromatic compounds isolated alongside with propionic acid or alcohol, thus confirming a β-H elimination step from the cyclohexadiene intermediate. Since this original report, this strategy has been extended to other more efficient catalytic systems. The commercially available $[Ir(cod)Cl]_2$ complex was found to be an active catalyst for the [2+2+2] cycloaddition reaction of 1,6-diynes with 2,3-dihydrofuran and *n*-butyl vinyl ether, furnishing the unexpected aromatic compounds in nearly quantitative yields (Scheme 20, top).[43] In the special case of acyclic vinyl ether, a side aromatic product still featuring an ether moiety was isolated. A plausible mechanism has been proposed by the authors for these aromatisation reactions including the cleavage of a C–O bond (Scheme 20, bottom). Reactions are proceeding through a classical [2+2+2] mechanism to afford the corresponding cyclohexadiene intermediates coordinated to iridium. A shift of the iridium centre to the oxygen atom initiates a subsequent E2



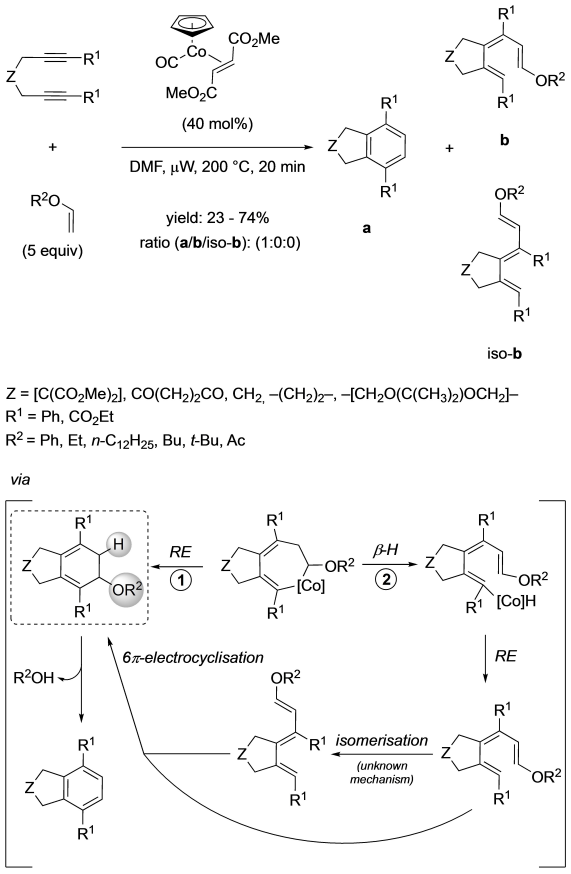
Scheme 20. Formal and partially intramolecular cross-alkyne cyclotrimerisation reaction using enol ethers as alkyne surrogates under iridium catalysis.

elimination reaction assisted by another vinyl ether molecule yielding the non-substituted benzene derivatives. With acyclic vinyl ether, a competitive reaction pathway is involved. Starting from the irida-coordinated cyclohexadiene intermediate, a π-allyl iridium hydride species is formed through oxidative addition of the metal centre to the allylic C–H bond. The substituted aromatic compound is obtained *via* an *anti* β–H elimination assisted by the vinyl ether.

Non gaseous enol ethers and acetates can be employed as easy to handle acetylene equivalents partners in the regioselective rhodium-catalysed formal cross-alkyne cyclotrimerisation reaction described by Tanaka and co-workers.[44] A cationic rhodium(I)/BINAP complex was able to catalyse the partially intramolecular [2+2+2] cycloaddition reaction of diynes with enol ethers with high yields and excellent regioselectivity starting from non-symmetric diynes bearing methyl and ester groups at alkyne termini. In this case, stabilisation of the cationic rhodium centre by coordination of the carbonyl and alkoxy groups is responsible for the regioselective insertion of the enol ether into the rhodacyclopentadiene intermediate (Scheme 21, top). Compared to iridium catalysis, the use of more Lewis acidic cationic rhodium allows to suppress the formation of the aromatic side product still featuring an ether moiety by facilitating final reductive elimination and subsequent dehydroalkoxylation. The intermolecular [2+2+2] cycloaddition reaction of two alkynes with vinylic acetates was also developed with success (Scheme 21, bottom). Two key points are at the origin of the high regioselectivity observed in this intermolecular reaction. On one hand, the steric repulsions existing between the alkyne termini and the ligand framework



Scheme 21. Formal cross-alkyne cyclotrimerisation reaction using enol ethers and vinylic acetates as alkyne surrogates under rhodium catalysis.

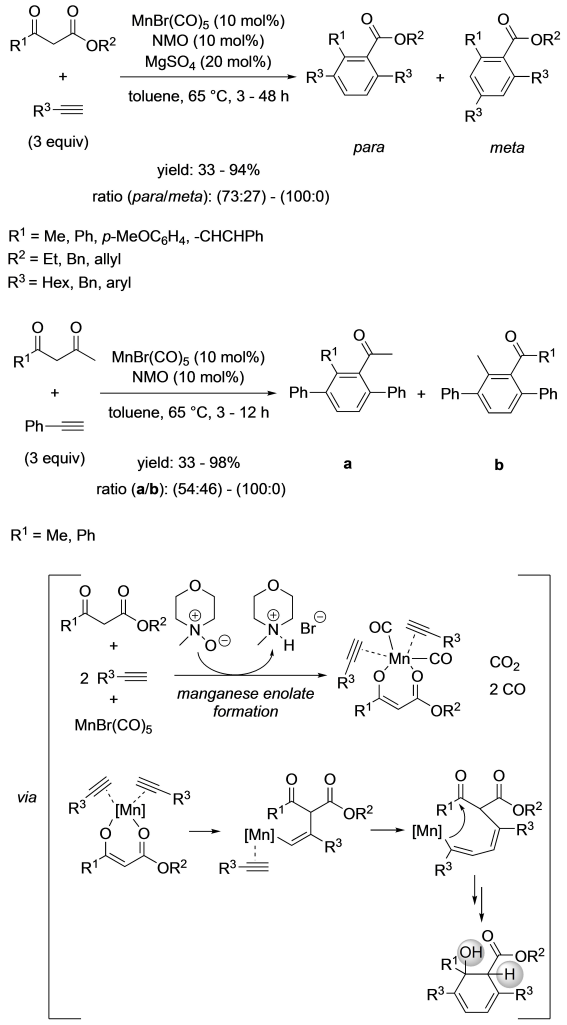


Scheme 22. Formal cross-alkyne cyclotrimerisation reaction using enol ethers as alkyne surrogates under cobalt catalysis.

direct the formation of a unique rhodacyclopentadiene intermediate. On the other hand, additional bidentate coordination of the vinyl acetate partner directs the regioselective insertion of the alkene moiety to afford the desired aromatic product after reductive elimination and dehydroacetoxylation sequence.

A formal cobalt-catalysed partially intramolecular [2+2+2] cycloaddition reaction of 1,6-diynes with acetylene was reported by Gandon, Aubert, and co-workers as an alternative to iridium or rhodium catalysis (Scheme 22).[45] At the low temperatures required for the sensitive $[CpCo(C_2H_4)_2]$ catalyst, the unexpected 1,3,5-hexatrienes were formed sometimes in competition with the aromatic derivatives arising from an oxidative demetalation/dehydroalkoxylation sequence of the corresponding cobalta-1,5-cyclohexadiene complexes, depending on the nature of the reaction partners. The use of the thermally and air-stable [CpCo(dimethylfumarate)][46] catalyst allowed to run the reactions at higher temperatures up to 200 °C, affording exclusively the aromatic compounds. Under these drastic conditions, the transient hexatriene intermediates can be fully converted to the desired aromatic derivatives *via* a 6π-electrocyclisation/dehydroalkoxylation sequence. The latter approach completes the previous transition metal-catalysed methodologies employing enol ethers as acetylene surrogates.

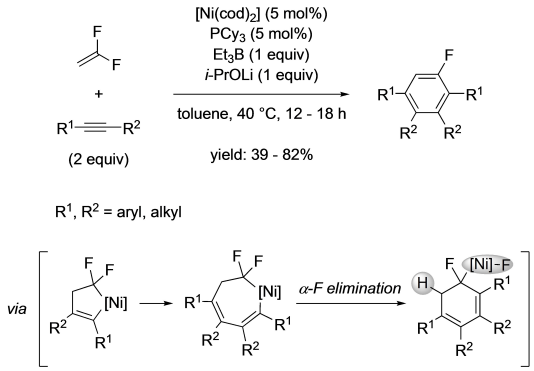
Nakamura and coworkers showed that 1,3-dicarbonyl compounds in equilibrium with their enol form could also react as alkyne surrogates for the synthesis of benzene derivatives (Scheme 23).[47] The complex of non-toxic manganese MnBr $(CO)_5$ is able to catalyse the formal intermolecular [2+2+2] cycloaddition between two terminal alkyne units and β-ketoester or 1,3-diketone partners with only water as by-product. Additives such as *N*-methylmorpholine *N*-oxide (NMO) and $MgSO_4$ are necessary to observe efficient conversions for both catalyst and 1,3-dicarbonyl compound activation and in order to prevent side reactions of ester groups due to the presence of released water in the medium. This methodology provides diversely substituted aromatic compounds with high *para*/*meta* regioselectivity excepted with aliphatic alkynes or non-symmetric 1,3-diketones. Interestingly, compared to traditional methods based on cross-coupling reactions, *para*-terphenyl derivatives that represent valuable structures for material applications are easily obtained under these conditions. Mechanistic studies revealed that among two competitive pathways, the reaction proceeds preferentially *via* the formation



Scheme 23. Formal cross-alkyne cyclotrimerisation reaction using 1,3-dicarbonyl derivatives as alkyne surrogates under manganese catalysis.

of a manganese enolate of the 1,3-dicarbonyl compound and a subsequent carbometalation reaction with alkyne unit before a final nucleophilic addition on a carbonyl moiety.[48] In the same time, Takai's group reported also a related manganese-catalysed formal [2+2+2] cycloaddition reaction of terminal alkynes with 1,3-dicarbonyl compounds affording the benzene derivatives in yields up to 88% and excellent regioselectivities.[49]

Conventional methodologies for the preparation of fluoroarene derivatives are generally based on the installation of a fluorine atom on a preformed aromatic ring. An interesting intermolecular approach was developed by Ichikawa and coworkers aimed at their straightforward synthesis from simple alkynes and 1,1-difluoroethylene as alkyne surrogate under nickel catalysis (Scheme 24).[50] The corresponding penta-substituted fluoroarenes were obtained in moderate to good yields



Scheme 24. Formal cross-alkyne cyclotrimerisation reaction using 1,1-difluoroethylene as alkyne surrogates under nickel catalysis.

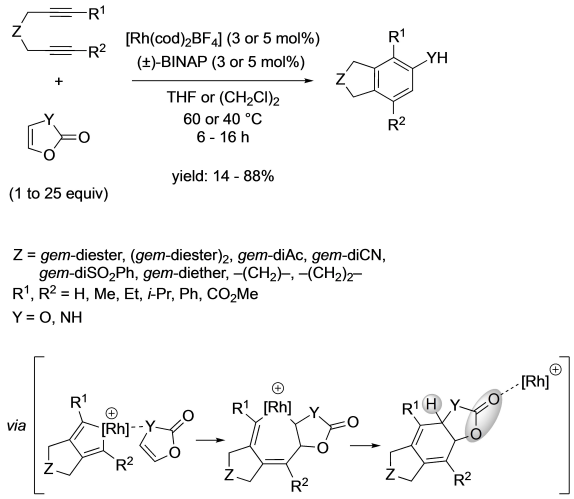
and excellent regioselectivity. According to the authors, the reaction proceeds through a nickel-mediated α-fluorine elimination/β-hydride elimination sequence resulting in a cleavage of the C–F and C–H bonds of 1,1-difluoroethylene. Et_3B and *i*-PrOLi are required in order to regenerate the nickel(0) catalyst from the released nickel(II) hydrofluoride species *via* a transmetalation/reductive elimination sequence mediated by the corresponding borate derivative.

4.2. Synthesis of substituted phenols and anilines

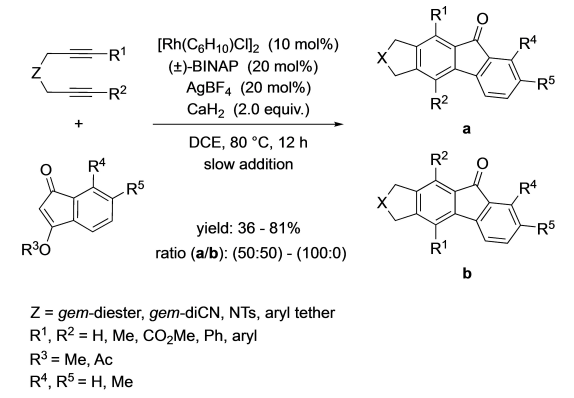
New routes for the rapid preparation of substituted phenols and anilines based on a partially intermolecular [2+2+2] cycloaddition reaction of 1,6- and 1,7-diynes as key-step have been explored respectively by Tanaka's[51] and Louie's[52] groups under rhodium catalysis. According to their strategies, unstable hydroxyacetylene and free ynamine can be easily replaced by equivalent forms consisting in vinylene carbonate and 2-oxazolone. A spontaneous decarboxylation of the corresponding cycloadduct favoured by assistance of the rhodium catalyst allows to release, in moderate to good yields, the desired substituted phenol and aniline derivatives (Scheme 25). In the case of [2+2+2] cycloaddition reactions with 2-oxazolone, complete regioselectivity was observed using an unsymmetrical diyne probably due to pre-coordination of the nitrogen atom on the metal centre and selective insertion of the polarised double bond into the rhodacyclopentadiene intermediate.

4.3. Synthesis of substituted fluorenones

Our group recently described an original procedure for the straightforward formation of fluorenone derivatives as precursors for the synthesis of valuable compounds with a large field of applications including material sciences (Scheme 26).[53] Based on a [2+2+2] cycloaddition reaction, the novelty of this methodology compared to existing ones[54] stems from the possibility to involve 3-acetoxy and 3-alkoxyindenones as



Scheme 25. Formal cross-alkyne cyclotrimerisation reaction using vinylene carbonate and 2-oxazolone as alkyne surrogates under rhodium catalysis.



Scheme 26. Formal cross-alkyne cyclotrimerisation reaction using 3-acetoxy and 3-alkoxyindenones as cycloalkyne surrogates under rhodium catalysis.

benzocyclopentynone surrogates. The reaction offers a direct access to various substituted fluorenone frameworks in satisfactory yields up to 81% starting from symmetrical 1,6-diynes. No regioselectivity could be observed when employing unsymmetrical diynes, except for substrates featuring at least one ester group at the alkyne terminus. As highlighted by the rapid synthesis of a fused polycyclic fluorenone (anthracene-type derivative), this process arises as an interesting route to new π-conjugated systems for photovoltaic applications. From a mechanistic point of view, after a well-established [2+2+2] rhodium-catalysed cycloaddition reaction, subsequent rearomatisation of the cyclohexadiene intermediate occurs with elimination of an alcohol or a carboxylic moiety to furnish the fluorenone compound. An additional coordination of the rhodium centre with the ester group of non-symmetric diynes is at the origin of the excellent regioselectivity observed with such substrates.

5. Conclusion

Although functionalized alkynes are very good partners for cycloaddition reactions, the use of acetylene, alkynes with low boiling points or instable cycloalkynes with sizes less than eight-membered ring suffers from several drawbacks which hamper their usefulness. In this context, several groups have designed efficient and attractive routes, using a functionalized alkene bearing an appropriate "leaving group" and based on a one-pot, two steps procedure, including firstly the cycloaddition reaction followed by the re-formation of the C=C double bond *via* an elimination reaction or in specific cases through a retro-Diels-Alder fragmentation. Alkyne surrogates, in that perspective, are an outstanding opportunity for the controlled synthetic access to molecules of interest.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: alkyne surrogate · alkyne equivalent · carbocycles · cycloaddition · heterocycles

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[2] According to IUPAC, a cycloaddition reaction is a reaction in which two or more unsaturated molecules (or parts of the same molecule) combine with the formation of a cyclic adduct in which there is a net reduction of the bond multiplicity. See: *IUPAC. Compendium of Chemical Terminology*, 2nd ed. (the "Gold Book"), Compiled by A. D. McNaught, A. Wilkinson, Blackwell Scientific Publications, Oxford (**1997**), Online version (**2019**) created by S. J. Chalk, ISBN 0-9678550-9-8, https://doi.org/10.1351/goldbook.
[3] Alkyne surrogates has been also used in annulation reactions. See for example J. Nishii, M. Miura, *ACS Catal.* **2020**, *10*, 9747–9757 and references cited therein.
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