Asymmetric Copper Catalyzed Azide-Alkyne Cycloadditions

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ABSTRACT: Since it's discovery independently by Sharpless and Meldal in 2002 the copper catalysed azide-alkyne cycloaddition (CuAAC) has become a ubiquitous molecular linking platform. Easy access to substituted 1,4-triazoles can be exploited to engender asymmetry to a myriad of potentially useful targets in high yields. Utilising the CuAAC to form chiral triazolic products in a single step is an attractive and powerful approach for the synthetic chemist. The area of asymmetric CuAAC is still in its infancy compared to more established asymmetric metal mediated transformations, however this leads to exciting challenges that need to be overcome to usher in the next era in the story of the triazole and click chemistry in general. This review details the steps taken into asymmetric CuAAC and the exciting results achieved thus far.

KEYWORDS: copper catalyzed, azide, alkyne, cycloaddition, desymmetrization, kinetic resolution, asymmetric catalysis

1. Introduction

In 2002 the laboratories of Meldal and Sharpless independently reported the highly regioselective Huisgen reaction to selectively form 1,4-triazoles.[1] This copper mediated reaction would soon become a pioneering transformation and lead to the defining of a new area of chemistry. A seminal report in 2001 by Sharpless and co-workers would define the term "*click chemistry*" and the copper catalysed azide alkyne cycloaddition (CuAAC) would be its centre piece.[2]

The CuAAC reaction has been used for a variety of applications and has garnered a reputation as a robust and reliable method for linking two components via an alkyne and a azide, reviews such as those by Meldal *et al*.,[3] Thirumurugan *et al*.[4] and others illustrate the breadth of possible triazole applications [5] The robust nature of the reaction and the triazole moiety itself has meant that research fields such as fragment based drug discovery (FBDD) have been quick to embrace CuAAC and many drug like molecules have been successfully synthesised.[4] In addition areas such as sensing and catalysis have taken to using the triazole as an integral part of their design strategies.[6] The relative ease in which CuAACs can be carried out has led to significant research in the area and applications of this methodology have steadily increased over the past 15 years.[7]

However, despite the ubiquity of the CuAAC reaction there are relatively few examples of asymmetric variants. Installing 1,4-triazoles with stereochemical control and the recovery of enantioenriched compounds could be important for many applications. That the asymmetric CuAAC can also allow for the synthesis of chiral alkynes and azides, as versitle building blocks.[8] is another reason these protocols could be useful for synthesis. Several approaches to influence the stereochemical outcome of the CuAAC reaction to garner chiral 1,4-triazoles have been reported. This review highlights these efforts towards highly enantioselective asymmetric CuAAC reactions and benchmarks this currently under-studied area of asymmetric catalysis. Through drawing together these early examples others may be encouraged to explore and exploit asymmetric CuAAC's (chiral "click"). Thus heralding a new era in the asymmetric triazole story.

1.1. Chiral Starting Materials

One strategy towards chiral triazoles is to form chiral click building blocks. Installing the desired chirality in either the alkyne or azide and then click them together.[9] For example, Temperini and co-workers developed asymmetric azidoselenenylation to enantioselectivly form chiral azides in 2003.[10] This was then used in a CuAAC reaction to afford triazolic compounds in up to 94% *ee*. There has been a wide range of asymmetric methodologies developed for the formation of chiral azides and alkynes, which have been successfully used to synthesise a range of important compounds.[11]

The ability to click together chiral building blocks to form triazolic products can form 3D structural motifs with potent biological activity. This has led to the formation of compounds containing chirality around a triazole, finding wide ranging applications. For example, triazoles have been used as peptide analogues, Zhang and Fan were able to synthesise, through solid phase methodology, peptidotriazoles **1** (Figure 1).[12] Triazole based peptide mimetics are important due to the physiological stability of the triazole moiety in combination with highly modular synthesis, allowing access to unnatural highly functionalised protein sequences. Chiral triazoles also have application in

enzyme inhibition. For example, Patterson *et al.* designed a range of chiral triazoles **2** to inhibit Cathepsin S, a cysteine protease believed to be involved with autoimmune diseases such as rheumatoid arthritis and multiple sclerosis as well as tumour development and growth (Figure 1).[13]

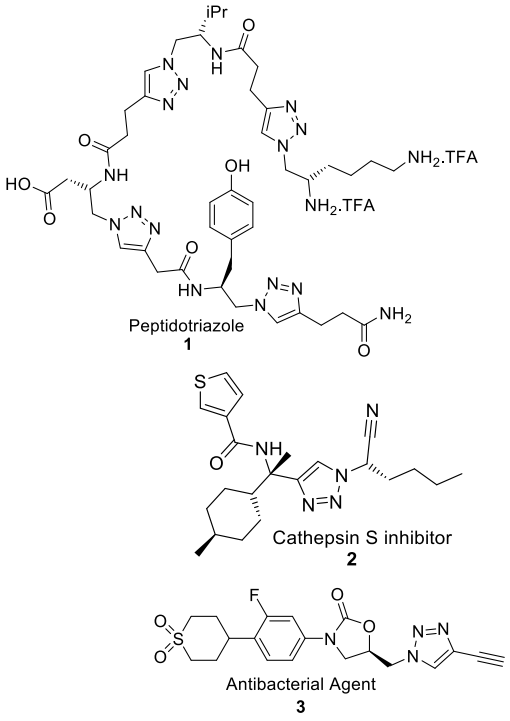


Figure 1. Triazoles formed from chiral starting materials

Antibacterial agents are another area where chiral triazoles were found to create potent biological activity. Reck *et al.* were able to increase the specificity of an existing antibacterial agent by the inclusion of a chiral triazole **3** (Figure 1).[14]

Formation of chiral alkyne and azide building blocks for CuAAC gives access to enantioenriched triazolic species however this is only one approach to engender asymmetry.

Asymmetric CuAAC creates enantioenriched triazoles from racemic or non-chiral starting materials requiring no prior instillation of asymmetry, as the chirality is engendered by the cycloaddition. Therefore, in one step a non-racemic triazole is formed allowing for chiral architectures to be accessed in a highly efficient manner.

2. Creating and Resolving Chirality Through Triazole Formation

2.1. Kinetic Resolution

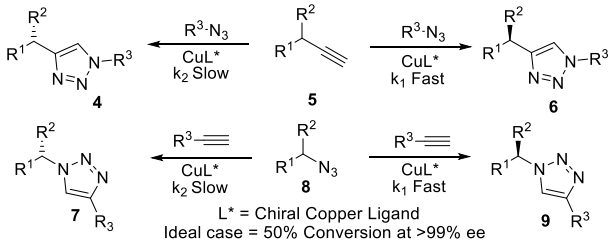
Kinetic resolution (KR) is a key approach to the formation and recovery of enantioenriched materials. By taking advantage of a difference in the rate of reaction of enantiomers it is possible to recover enantioenriched starting materials and products (in this case alkynes/azides and triazoles). Racemic starting materials contain a 50:50 mixture of *R* and *S* enantiomers, if a reaction consumes *R* faster than *S* the remaining starting material will no longer be 50:50 and thus the racemic starting material has become enantioenriched. The mathematical underpinning of this area was developed by Kagan and allows the *ee* and conversion of a reaction to be related to a term known as a selectivity factor (s) (Figure 2, Equation 2).

$$\text{Selectivity Factor } (S) = \frac{k_2}{k_1} \text{ or } \frac{\text{Rate of Fast Reacting Enantiomer}}{\text{Rate of Slow Reacting Enantiomer}} \quad \text{Equation 1}$$

$$s = \ln[(1-c)(1-ee)] \,/\, \ln[(1-c)(1+ee)] \quad \text{Equation 2}$$

Figure 2. Equations relating rate, conversion and enantiomeric excess developed by H. B. Kagan

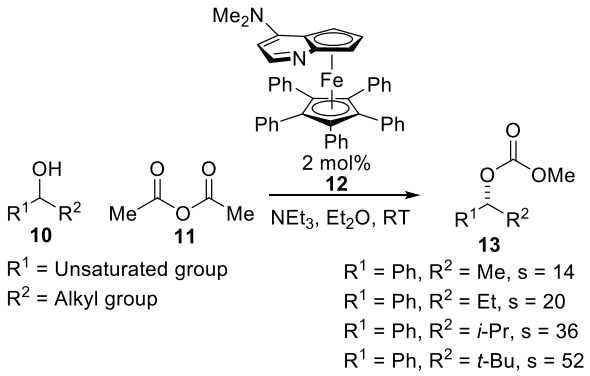
The selectivity factor is based upon the ratio of the rates of reaction of the two enantiomers. For example, if one enantiomer of alkyne **5** undergoes the CuAAC ten times faster than the other the selectivity factor would be 10 (Scheme 1).[15] The selectivity factor therefore is used as a metric to measure the efficiency at which the resolution is occurring.



Scheme 1. General scheme showing strategies towards kinetic resolution utilising CuAAC

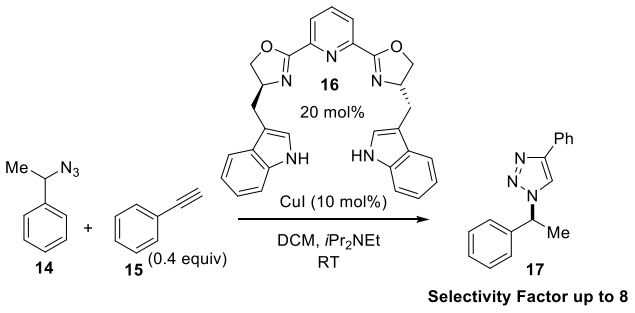
The two general strategies which can be targeted in kinetic resolution CuAAC are to start with either a racemic alkyne **5** or chiral azide **8** and exploit a difference in the rate of reaction of their enantiomers. The best possible outcome from a kinetic resolution is to recover 50% enantiopure starting material **5/8** and to form 50% enantiopure product **6/9** in order to do this a selectivity factor of around a thousand is required. A selectivity factor this high is very difficult to obtain and in excess of what most enzymes can even achieve. However, if a selectivity of twenty can be achieve this can still be useful in synthetic chemistry. At s = 20 in order to recover enantiopure starting materials the reaction would need to be run until 61% conversion. This would mean that 39% enantiopure starting material could be recovered. This is therefore the reason why the selectivity factor has become a benchmark for how efficient a kinetic resolution process is.

Kinetic resolution is an established field within asymmetric catalysis and has been used to access a wide variety of enantioenriched species. For example, Fu and co-workers have pioneered the area of secondary alcohol **10** kinetic resolution, utilising planar chiral dimethylaminopyridine (DMAP) catalysts **12** Fu has achieved extremely high selectivity factors (s>50) (Scheme 2).[16] With the right substrate selectivity factors in excess of 100 have been observed using this system and related ones.[17] This methodology therefore allows the recovery of single enantiomer secondary alcohols, crucial building blocks in many organic syntheses, and demonstrates the value of kinetic resolution.



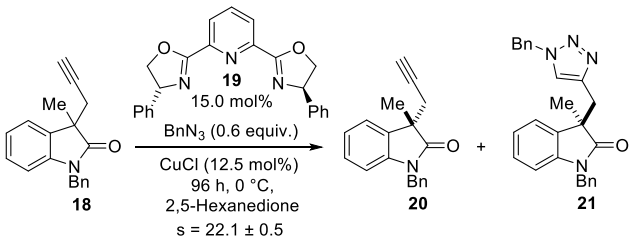
Scheme 2. Fu and co-workers kinetic resolution of secondary alcohols utilising planar chiral DMAP catalysis.

Thus far there has only been one published example of kinetic resolution of azides using CuAACs. Fokin and Finn in 2005 reported the KR of α-benzylic azides **14** utilising a Cu-PyBOX complex derived from indole appended PyBox **16** (20 mol%) and copper iodide (10 mol%).[18] They were able to obtain selectivity factors of up to 8 ± 0.5, in the reaction of benzylic azide **14** and phenyl acetylene **15** to give the kinetically resolved triazole **17**(Scheme 3).



Scheme 3. Kinetic resolution of α-benzylic azides Meng *et al.*

In addition to resolution of racemic azides a series of racemic α-benzylic alkynes were also exposed to resolution reaction conditions. In the case of terminal alkynes no resolution was observed (s = 1).[18] It was proposed that the copper acetylide forms and due to the linear nature of alkynes, the resolvable stereogenic centre is placed spatially distant from the ligands chiral influence. This was presented as the reasoning behind terminal alkynes being resistant to resolution compared with azides, which were proposed to approach the ligand facially, thus chiral relay could occur. In the intervening years greater understanding of PyBOX copper complexes has shown that (at least in the solid state) complexation does not occur in a mono-nuclear fashion, a dimeric species is formed in the presence of copper (I) ions.[19] Fokin and Finn's pioneering work demonstrated that CuAAC is a reaction which can be applied to kinetic resolution and laid the groundwork for others to explore this methodology.



Scheme 4. Kinetic resolution of terminal alkynes, Brittain *et al.*

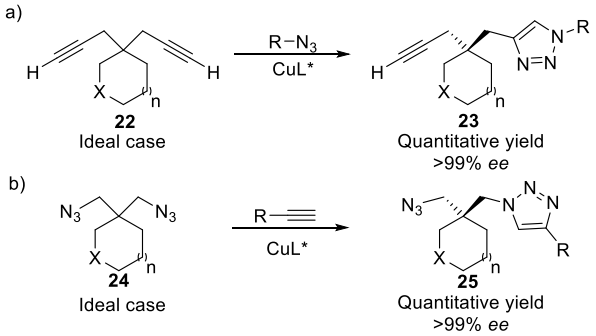
In 2015 work by Brittain *et al.* (the authors of this review) showed that the resolution of terminal alkynes is possible through a CuAAC reaction. Using a mono alkyne appended oxindole **18** they were able to demonstrate that kinetic resolution is a methodology that is applicable to alkynes (Scheme 4). Using a phenyl substituted PyBOX **19** (15 mol%) in the presence of copper(I) chloride (12.5 mol%) and a dione solvent (2,5-hexanedione), selectivity factors in excess of twenty (s = 22) were observed. The dione solvent appeared to be critical in obtaining good selectivity, this was also observed in a desymmetrization reaction carried out by Zhou and co-workers (see section 2.2). This observed selectivity adds weight to the idea that these reactions are proceeding through a non-mononuclear pathway. In this case the alkyne must be placed within the ligands sphere of chiral influence. However, due to the linear nature of alkynes no selectivity (as observed by Fokin and Finn) should occur, however this is not the case. As mentioned throughout this review a possible non-mononuclear species could help explain how the alkyne is able to be influenced by the ligand. This work proves that alkynes in addition to azides are suitable candidates for kinetic resolution methodologies.

Kinetic resolution utilising the CuAAC reaction is very much an emerging field, taking inspiration from these first reports hopefully others can apply resolution methodology to a whole range of terminal alkynes and azides. These first reports demonstrate that kinetic resolution is a technique that can be applied successfully to azides in addition to alkynes. As with desymmetrization understanding the method of selectivity will be of vital importance to the future development of this area.

2.2. Desymmetrization

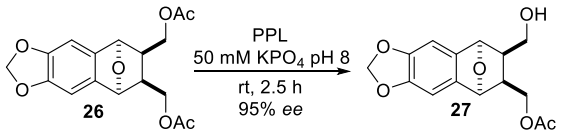
Desymmetrization is defined by IUPAC as "the modification of an object which results in the loss of one or more symmetry elements, such as those which preclude chirality (mirror plane, centre of inversion, rotation-reflection axis), as in the conversion of a prochiral molecular entity into a chiral one". This strategy is particularly attractive to the synthetic chemist, as a desymmetrization reaction can take a non-chiral starting material and produce a single enantiomer of product with a quantitative theoretical maximum yield.[21] In the case of the CuAAC reaction a starting material which contains two terminal alkynes **22** or two azides **24** to form a triazole **23/25** through reaction of one of the two possible, would lead to a single enantiomer of 1,4-triazole (Scheme 5). The disadvantage of desymmetrization is in potential overreaction. It is abso-

lutely critical to be able to perturb double reaction leading to racemic product (in this case bis-triazoles) and in turn reducing the yield of desymmetrized product.



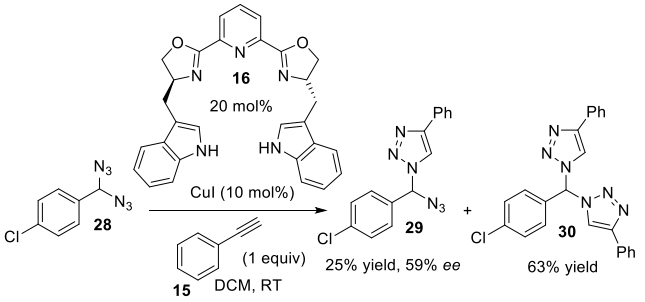
Scheme 5. General CuAAC desymmetrization strategies

Desymmetrization is a methodology which has been employed to make numerous biologically active compounds.[22] For example, Berkowitz and co-workers employed enzymatic desymmetrization in their synthesis of (-)-Podophyllotoxin and (-)-Picropodophyllin.[23] Using porcine pancreatic lipase (PPL) and a late stage meso diol **26** they were able to recover desymmetrized product **27** in 95% *ee* (Scheme 6). From this late stage intermediate they were able to carry out the formation of two natural products with potent antimitotic activity.[24] The ability to use desymmetrization as a means to access these types of compounds demonstrates its value as a methodology.



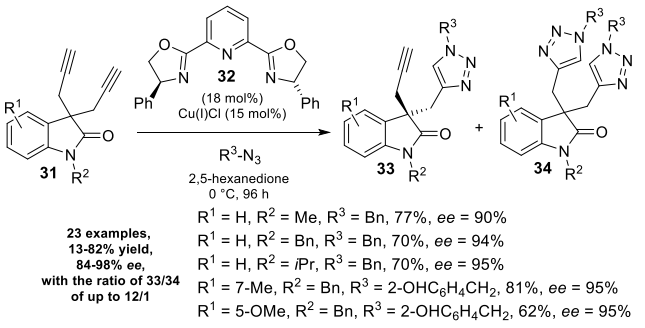
Scheme 6. Enzymatic desymmetrization used in the synthesis of (-)-Podophyllotoxin and (-)-Picropodophyllin, Berkowitz and co-workers

The first reported desymmetrization using CuAACs was reported by Fokin and Finn in 2005.[18] Employing *gem*-diazide **28** with an indole appended pyridine bisoxazoline (PyBox) ligand **16** (20 mol%) and copper iodide catalyst (10 mol%), a 25% yield of 59% *ee* desymmetrized product **29** was achieved (Scheme 7).[25] However, overreaction was a problem in this example and a yield of 63% of the undesired bis-triazole **30** was obtained. Although only moderate selectivity was observed this was the very first example of a successful desymmetrization through CuAAC. The selectivity observed demonstrates that carrying out the CuAAC with stereocontrol is possible and lays the groundwork for future asymmetric click desymmetrizations. In fact, to the best of our knowledge this remains the sole example of CuAAC desymmetrization using a bis-azide system.



Scheme 7. Desymmetrisation of bis-alkyne systems, Fokin and Co-workers

The first report of desymmetrization of bis-alkyne systems *via* copper catalysed *click chemistry* came in 2013 by Zhou and co-workers, in their pioneering work terminal alkyne appended quaternary oxindoles were successfully desymmetrized. Taking bis-alkyne **31** with a PhPyBox ligand **32** (18 mol%) and copper (I) chloride (15 mol%) catalyst up to 98% *ee* desymmetrized product **33** was recovered (Scheme 8)[26] They found that using a dione (2,5-hexanedione) as a solvent for the reaction was critical in obtaining good selectivity. They noted that in general carbonyl containing solvents were superior for their desymmetrization, after observing a leap in selectivity when moving from dichloromethane (67% *ee*, 11% yield) to acetone (75% *ee*, 20% yield). A wide range of carbonyl containing solvents were screened, with 2,5-hexanedione emerging as the solvent of choice. The dione gave the best selectivity (90% *ee*, 32% yield). No rationale was given for this observation, perhaps the coordinating ability of oxygen could play a role in achieving selectivity. Zhou and co-workers were able to successfully control overreaction, to the undesired bis-triazole, by cooling the reaction to 0 °C for 96 h, a ratio of up to 12:1 between the desired mono reacted **33** and undesired double reacted **34**. Scope was probed in the azide, N-protecting group and aromatic ring and high *ee* values were obtained in all cases (Scheme 8)

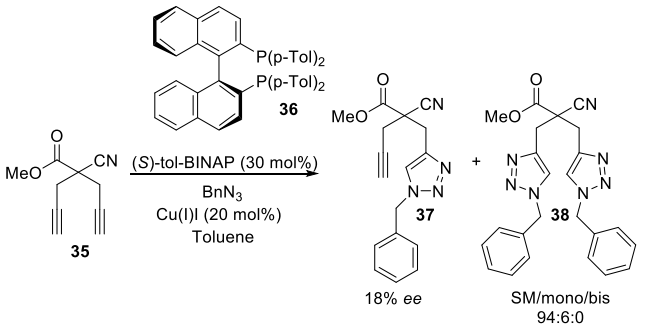


Scheme 8. Desymmetrisation of quaternary oxindoles Zhou et al.

In the desymmetrization of quaternary oxindoles Zhou and co-workers suggested a dinuclear copper-ligand complex might be involved in the reaction. A negative non-linear effect (NLE) was observed between the *ee* of the product **33** and the enantiopurity of the ligand employed. This effect could be rationalised by a non-mononuclear catalytic species and that the homochiral dimer is less

reactive than the corresponding heterodimer.[27]

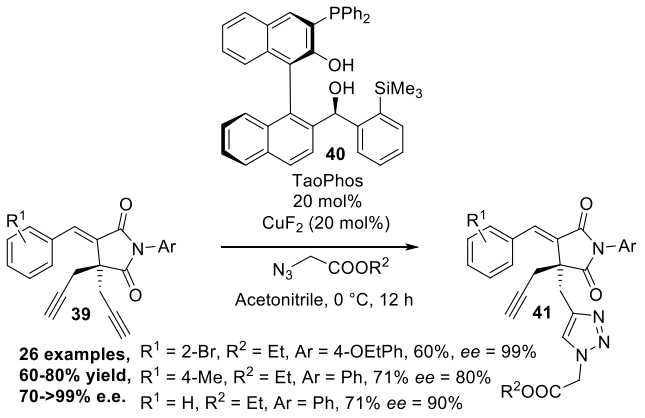
Stephenson and co-workers using prochiral 2,2-diyne **35** were able to desymmetrize challenging acylic substrates.[28] They were able to obtain an *ee* of 18% in the desymmetrized product **37** when (*S*)-tol-BINAP **36** was mixed with Cu(I) and used as a chiral catalyst (Scheme 9).



Scheme 9. Desymmetrization of linear bis-alkyne systems, Stephenson *et al.*

Stephenson *et al.* faced the challenging nature of desymmetrization and the tendency for overreaction to undesired bis-triazole **38**. Therefore the reaction was only run until low conversion was observed, in this case a ratio of 94:6:0 (SM:mono:bis) **35:37:38** was obtained. This work showed that enantioenrichment can be achieved on very challenging linear systems though CuAAC desymmetrization. The rotational freedom of linear systems might make obtaining high yields and enantiopurity more challenging than in conformationally restricted heterocyclic systems. It should be noted that the authors screened a range of ligands which had not been previously employed for asymmetric CuAAC reactions. However, as evidenced by the observed *ee*'s and noted by the authors none managed to match the PyBOX type ligand structure.[25] Further detailed mechanistic work to rationalize the selectivity observed with bisoxazoline ligand structures is required.

The observations made by Zhou and Stephenson have led others to search for ligands which could also influence the stereochemical outcome of the asymmetric CuAAC reaction. Previously Ar-BINMOL-Phos ligands were used in catalytic asymmetric alkynylation of aldehydes,[29] and one inparticular (TaoPhos) **40** was successfully employed in the desymmetrization of maleimide-based bis-alkynes **39** by Xu and co-workers(Scheme 10).[30]



Scheme 10. Desymmetrisation of maleimide based bis-alkynes, Xu and Co-workers

It was observed that a range of maleimides **39** were susceptible to desymmetrization when a catalyst derived from a 1:1 mixture of TaoPhos **40** and CuF_2 was employed. A range of conditions and additives were tested; it was found that acetonitrile gave the best selectivity with tetrahydrofuran (THF) coming a close second. They also attempted the addition of commonly used click additives, a study of equivalents of trimethylamine (TEA) with enantiomeric excess showed that it did help boost the yield of the reaction but with concomitant loss in enantioselectivity. Scope of the desymmetrization to give mono triazoles **41** was probed and the reaction appeared to be tolerant to a diverse array of functional groups in all positions.

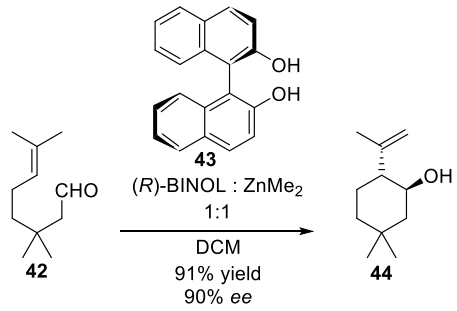
A nonlinear experiment was also carried out by Xu and co-workers in their desymmetrization of maleimides and an NLE was observed. As the *ee* of the TaoPhos was increased the *ee* of the desymmetrized product did not increase linearly, a positive NLE was noted i.e. the increase in *ee* of the product was greater than the increase in the *ee* of the ligand. Again as in previous reports this NLE suggests that the catalytic intermediate is more complicated than a mono-nuclear species and points towards a dimeric one being responsible for selectivity.[31]

So far ligands based upon pyridine bis-oxazoline architectures appear to have the widest scope, however with the area still in its infancy better ligands may emerge. Thus far detailed mechanistic and computational studies have not been carried out in depth. With more data in hand the ability to smartly design reactions based around the critical components will allow desymmetrisation to be applied to a myriad of exciting targets in the future.

2.3. Desymmetrization to form Atropisomers

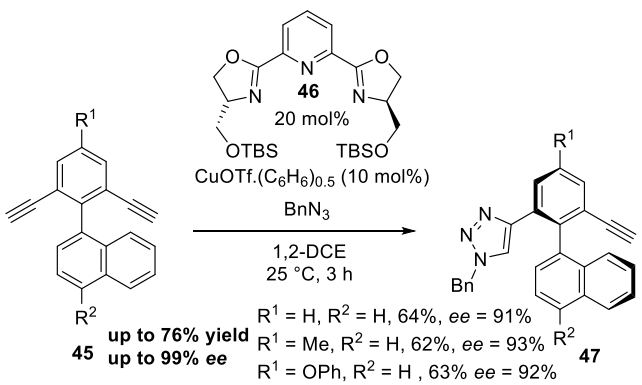
Atropisomerism takes advantage of restricted rotation around a single bond to create chirality. Steric interactions can raise the barrier to rotation around a single bond to the point of locking its conformation. Compounds which exhibit atropisomerisim are sometimes referred to as axially chiral and are potentially very useful for several applications. Asymmetric catalysis is one such arena where atropisomers have been used. Ligands such

as BINAP and BINOL, which utilise atropisomerism, have seen use as highly enantioselective catalysts and their cores have been elaborated to form families of ligands.[32] The utility of BINOL as a ligand was demonstrated by Yamamoto and co-workers.[33] Using a catalyst derived from mixing a 1:1 mixture of (*R*)-BINOL and dimethyl zinc, unsaturated aldehyde **42** was successfully cyclised to product **43** in 91% yield and 90% ee (Scheme 11). Several natural products also exhibit restricted rotation, existing as single enantiomers, compounds such as Kotanin[34] and Michellamine B utilise atropisomerism. These can have potent biological activity, for example, michellamine B has been studied as an anti-human immunodeficiency virus (HIV) drug candidates.[35]



Scheme 11. Asymmetric cyclisation of unsaturated aldehydes using BINOL, Yamamoto and co-workers

The ability for the CuAAC reaction to be used to selectively form single atropisomers through a desymmetrization approach has been studied by Osako and Uozumi (Scheme 12).[36] A bis-alkyne appended biaryl system **45** in combination with a silyl protected PyBox ligand and copper (I) triflate catalyst was employed to achieve enantiomeric excesses of up to 99% in the atropisomeric product **47**. Interestingly Osako and Uozumi did note that they could not achieve good selectivity (<35% *ee*) with any azides other than benzyl azide. Thus more research is required to figure out why the reaction is not tolerant to other azides. However, this methodology does demonstrate that asymmetric CuAAC can be employed to form axially chiral molecules as single enantiomers and this makes them attractive for a myriad of applications, asymmetric catalysts being just one. Osako and Uozumi also showed scope in R^1 and R^2 (Scheme 12) around the aromatic rings showing good to excellent *ee* in all cases.



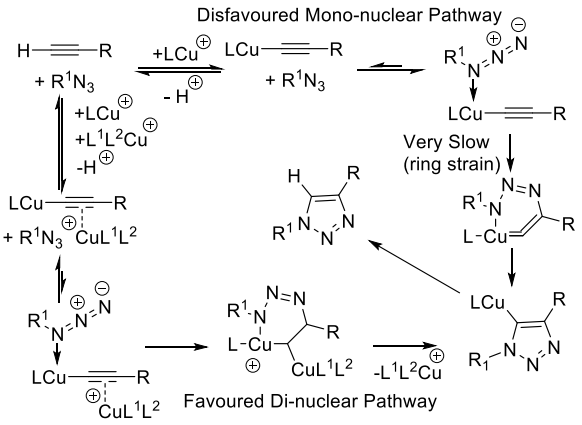
Scheme 12. Formation of atropisomers using CuAAC, Osako and Uozumi

Osako and Uozumi followed up their report of atropisomer formation with a mechanistic study into the reaction.[37] Using different equivalents of benzyl azide they probed the enantiopurity of the desymmetrized material. They found that increasing the amount of benzyl azide in the reaction improved the enantiopurity of the product (BnN_3 equiv. = 1, product = 80% *ee*, BnN_3 equiv. = 2, product = 97% *ee*). From this observation they concluded that two asymmetric induction processes were occurring in the reaction. Firstly, a desymmetrization was occurring to give the wanted mono-triazole **47**, this would then react through a kinetic resolution process with more benzyl azide to the undesired bis-triazole. Therefore, increasing the equivalents of benzyl azide in the reaction caused the minor enantiomer of the mono-triazole to be consumed quicker to the bis-triazole, in the process increasing the ee of the remaining mono-triazole. Next an NLE study was carried out, a positive NLE was observed and thus suggested that the reaction was being catalysed by a non mono-nuclear species. This mechanistic study fits with data from other examples of asymmetric CuAAC.

2.4. Desymmetrization Mechanistic Studies

As shown above several researchers have carried out NLE experiments to probe the catalytic species responsible for selectivity in their respective asymmetric CuAACs. Osako, Uozumi, Zhou *et al.* and Xu and co-workers have all reported observing NLE's for their transformations.[26,30,36] NLEs point towards a possible non-mononuclear catalytically active species for a reaction, in this case a CuAAC. The phenomena of NLEs can be rationalied by a more reactive dimeric species. This supports mechanistic work on the standard achiral CuAAC reaction, between 2011 and 2015 evidence has pointed towards muti-nuclear copper species being involved during catalysis.[38] In 2013 Fokin and co-workers employed a copper isotope enrichment cross over study using an extra isotopically enriched copper catalyst and taking advantage of the stability of copper N-heterocyclic carbene (NHC) triazolide species, it was observed that the isotopic distributions between the starting copper acetylide and the resulting CuNHC-triazolide complex were not the same, thus more than one copper centre was involved in catalysis.[39] From control experiments they determined that the isotopic enrichment must take place within the cycloaddition step. This was elaborated independently by both Straub and Bertrand, in these reports di-nuclear copper acetylides were successfully crystallised for the first time.[40] The use of these preformed di-copper acetylides in comparison to mono-nuclear copper acetylides showed that the dinuclear species gave a much greater rate of reaction than the mono, thus it was concluded that the CuAAC follows a dinuclear catalytic cycle on kinetic grounds. The kinetic difference in the two pathways was explained through the larger amount of ring strain that the metallocylic intermediate contains during the cycle. Therefore, a di-nuclear pathway where this strain is minimised is followed be-

cause it is much faster (Scheme 13).



Scheme 13. Catalytic cycle of the CuAAC showing that the di-nuclear pathway is followed on kinetic grounds

This new understanding of the catalytic cycle appears to help explain why NLEs are observed in asymmetric Cu-AAC reactions. The observed di-nuclear nature of the asymmetric catalytic examples through NLE studies in combination with the di-nuclear nature of the catalytic cycle appear to be closely linked to selectivity. It appears as if the orientation of the two copper centres within the catalytically active species could be the critical factor in observing good selectivity within an asymmetric CuAAC, however, more work is need to prove this is the case. The dimeric nature of copper PyBox complexes in the solid phase is well known in the literature, and this may well be the reason as to why this ligand architecture has displayed the widest scope thus far, however firm evidence to support this has yet to be presented.[19a,19c]

Summary and Outlook

As seen throughout this short review the examples of successful asymmetric CuAAC's is at present small compared with other common metal mediated transformations. However, this does lead the CuAAC reaction to be an intriguing reaction for future methodology development. The fundamental underpinnings of the mechanism of selectivity in the examples given above will be key to the development of this area. Detailed mechanistic and computational studies are required to model these reactions to discover how the asymmetry is truly being engendered. The catalytic cycle of the CuAAC has seen heavy revision in the last 10 years and therefore it is safe to assume that modelling asymmetric transition states may be a tough challenge. However, the true nature of asymmetry needs to be understood before smart catalytic design can be applied to desired targets. If it could be possible to work on these challenges a universal protocol for asymmetric CuAAC may be within reach, this would revolutionise the area and truly bring the spirit behind click chemistry to its asymmetric brother. Universal asymmetric CuAAC reactions would be an extremely desirable synthetic tool, a reaction which could take two racemic materials and link them together in a stereoselective manner with high yields would lead to the ability to make complex motifs with the upmost ease. Hopefully with further work and understanding, this is an achievable goal.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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