**INTRODUCTION**

Heterocycles are vital to our everyday lives as pharmaceuticals, agrochemicals and in biological processes. To put their importance into perspective, 6/10 of the top selling drugs currently on the market contain a heterocycle (Figure 1) (1). Owing to their importance extensive research has been conducted on the synthesis of heterocycles (2). Due to collective societal and political pressure, the development of more environmentally friendly processes that limit the amount of overall waste and decrease energy burdens are increasingly important (3). One approach to overcome these challenges that is used extensively in all areas of contemporary synthesis is catalysis (4). A catalyst is a compound that lowers the energy required to effect a chemical reaction, but is not consumed in the reaction and therefore has the potential to be recycled. Herein, we outline recent advances in an important form of catalysis, gold multifaceted catalysis (gold-MFC), in which a gold species activates more than one mechanistically distinct step in a reaction process (Figure 2) (5). A gold-MFC approach allows for the conversion of simple starting materials to added-value compounds. This more effective use of the catalysts minimises workup, isolation and purification steps, leading to increased yields and decreased overall waste production. Whilst this concept has previously been referred to in the literature as auto-tandem catalysis (6), single-pot catalysis (7, 8), domino-catalysis and dual catalysis (9), we will use the term multifaceted catalysis throughout this review to emphasise the gold catalysts’ ability to interact with both n-electrons and lone-pairs on heteroatoms (10).

**GOLD-MFC: AROMATIC HETEROCYCLES**

An important area of research in which a gold multifaceted catalysis approach has made a significant impact is in the synthesis of aromatic heterocycles, such as pyrroles, furans and indoles. For example, a known procedure for the convergent synthesis of pyrroles is the reaction of oximes with alkynes under thermal superbasic conditions (DMSO/LiOH), the Trofimov reaction (11). Importantly, this reaction allows for the direct formation of both a C–C and C–N bond from unactivated alkynes. This powerful transformation is underutilised due to the harsh reaction conditions that result in poor yields and low levels of product chemo-/regioselectivity (12). However, due to the potential of the Trofimov reaction in synthesis, catalytic variants seeking to improve the yield and selectivity whilst removing the need for strongly basic conditions have been developed (13, 14).

Recently, Camp et al. used a gold-MFC approach to mitigate many of the problems associated with the formation of pyrroles from oximes and alkynes. The authors demonstrated that the key steps of the process, conversion of oximes $\text{1}$ and alkynes $\text{2a,b}$ to $\text{O-vinylxoximes 3a,b}$ via 1,4-addition and transformation of the in situ formed $\text{O-vinylxoximes to pyrroles 6a,b}$, are catalysed by the same gold catalyst (Scheme 1 | Camp) (15). Thus, a number of highly substituted pyrroles were synthesised in a regiocontrolled manner via a gold-MFC process. An alternative gold-MFC method for the synthesis of substituted pyrroles and furans was recently disclosed by Blanc et al.,

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**ABSTRACT**

Systems in which one catalyst can activate more than one mechanistically distinct step in a reaction process, multifaceted catalysis (MFC), are an increasingly important method in organic synthesis. A MFC approach allows for the conversion of simple starting materials to added-value compounds, whilst potentially limiting the overall costs in terms of time, expense and waste. This review highlights the utility of a MFC approach by focusing on recent gold multifaceted catalysis (gold-MFC) methods for the synthesis of heterocycles.
which involved multiple intramolecular cyclisations that were promoted by the same gold catalyst. Treatment of acetoxylated alkynyl oxaranes and aziridines 7 with various nucleophiles in the presence of a gold catalyst afforded the desired aromatic heterocycles 11 (Scheme 1 | Blanc) (16). The gold serves to activate both the alkyne 8 towards nucleophilic addition of the acetate to form alkenes and the alkenes for intramolecular addition of the alkoxide or amide. A variety of nucleophiles including alcohols and thioles were found to be compatible with the reaction conditions and either pyroles (x = NTs) or furans (x = O) can be synthesised using this methodology.

GOLD-MFC: NON-AROMATIC HETEROCYCLES

Gold multifaceted catalysis has also made an impact in the synthesis of non-aromatic heterocycles. For example, α-pyrones are vital intermediates for the synthesis of compounds that exhibit a variety of biological activities including anti-cancer, HIV-1-inhibitors, anti-allergic and anti-microbial. As a result of their important bioactivities, α-pyrones have attracted a significant amount of research into their synthesis. A recent report by Abatrbi et al. described a general multistep route for the synthesis of α-pyrones, which required the use of 2-iodobenzoic acids and allenyl-tributyltin reagents under palladium mediated coupling conditions (17). Whilst, a number of important compounds were synthesised, the process is not atom economical and requires the use of toxic tin compounds. An alternative approach to α-pyrones synthesis that avoids many of the drawbacks of traditional α-pyrones synthesis was recently reported by Schreiber et al. and highlights the utility of a gold-MFC process. A number of α-pyrones were synthesised directly from terminal alkynes and propiolic acids under gold-catalysed conditions. Thus, activation of the terminal alkyne toward nucleophilic addition of the carboxylic acid yielded enols 13 (Scheme 2 | Schreiber) (18). Subsequent activation of the propiolic esters 14 allows for facile addition of the enol to afford oxoniums 15, which after tautomerisation and protodeauration gave the desired α-pyrones 16 in good overall yield. Importantly, it was shown that the gold catalyses both of the key steps of the one-pot process by independently synthesising an intermediate similar to 13 and subjecting it to the optimised conditions. Although gold is commonly used as a π-Lewis acid to activate alkene and alkyne moieties, it has also been shown to exhibit catalytic behaviour through interactions with oxygen and nitrogen lone-pairs (19). For example, He et al. recently demonstrated that a gold (I) catalyst promoted the ring opening of a diaziridine as part of a gold-MFC approach to 3-pyrazolines (Scheme 2 | He) (20). Thus, gold-catalysed ring opening of diaziridine 17, followed by insertion of the alkyne into the cationic carbon centre afforded alkyne-hydrazine intermediate 20. Activation of alkyne 20 by the gold allowed for facile intramolecular hydroamination to give the desired five-membered N,O-heterocycles 28 in good overall yield.

Wu and Shi combined the ability of gold to activate both alkenes and alkynes to afford unsaturated isoxazoles 28 from sulfonamide-substituted 1,1-vinylidencyclopropanediesters 22 (Scheme 3) (21). Gold-catalysed intramolecular hydroamination followed by ring-opening of the product vinylcyclopropane and protodeauration afforded alkyne 25. Hydration of the gold activated alkyne 26 followed by protodeauration gave the desired five-membered N,O-heterocycles 28 in good overall yield. 1-Arylnaphthalenes, another class of medicinally important non-aromatic heterocycles, can also be synthesised using
FUTURE PERSPECTIVES / CONCLUSIONS

Through the continued development of gold-MFC processes important biologically active compounds may be synthesized in an increasingly economical manner in terms of time, waste and the environment. By catalysing multiple steps in a reaction sequence, costly and time-consuming workup, isolation and purification steps can be minimised. Importantly, the mild and selective nature of a gold-MFC process will allow for the synthesis of novel heterocyclic motifs, opening up unexplored chemical space for development. The advantages of a gold-MFC approach to synthesis include step-economy, mild reaction conditions and access to novel structures. Continued research in this emerging area will focus on exploiting the benefits of multifaceted catalysis to both increase the sustainability of existing reactions and for the development of novel chemical processes.

REFERENCES AND NOTES


In this brief review, we have focused on a small number of illustrative examples, as there has not been sufficient space to discuss all of the excellent studies on gold multifaceted catalysis. We refer the reader to several recent reviews for a more comprehensive coverage of the subject [5-7, 9, 10]. We thank GlaxoSmithKline for funding a summer fellowship for (J.B.).
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