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New synthetic chemistry for medicinal chemistry

# Gold-catalyzed formation of heterocycles – an enabling new technology for medicinal chemistry

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**Gold-catalyzed transformations allow efficient access to a wide scope of heterocyclic structures that serve as building blocks and pharmacophores in medicinal chemistry. Compared with other transition metal and Lewis acid catalysis, gold catalysis presents mechanistic divergence, excellent functional group tolerance and/or operational advantages. Emergent applications of gold catalysis have played a key role in the synthesis of biologically active molecules including a drug candidate.**

## Introduction

Heterocycles have been extensively utilized in medicinal chemistry resulting in their incorporation into numerous small molecule drugs. While the most straightforward strategy to introduce heterocycles into drugs is to use commercially available heterocyclic building blocks, it is common for discovery and process chemists to construct heterocycles by either traditional condensation approaches, or more recently, transition metal catalysis [1].

Despite the use of gold and gold salts in heterogeneous catalysis since the 1960s, [2] the era of homogeneous gold catalysis did not start until the end of the 20th century [3]. Since then, numerous methods involving gold catalysis have emerged to construct heterocycles in a novel, convenient and selective fashion.

## Section editor:

Floris P.J.T. Rutjes – Institute for Molecules and Materials, Radboud University Nijmegen, Nijmegen, The Netherlands.

## Advantages of gold catalysis

The advantages of gold catalysis can be viewed by comparison to the traditional modes of activation including Lewis and Brønsted acids as well as other transition metals (Table 1). In contrast to the traditional modes of activation, the vast majority of gold-catalyzed reactions rely on the selective coordination to alkynes, alkenes or allenes as a consequence of the exceptional  $\pi$ -acidity of gold catalysts [3b]. The affinity for  $\pi$ -bonded systems makes gold similar to its periodic neighbors, mercury and platinum; however, gold lacks the toxicity of mercury and is less expensive than platinum [4]. Gold catalysts can also be viewed as a traceless halide by mediating reactions that are traditionally mediated by the  $\pi$ -acidity of electrophilic halides such as diatomic iodine [5]. Oxygen- and nitrogen-containing groups are less prone to coordination with gold and, as a result, water and alcohols are often well tolerated in gold catalysis [6,7]. Gold catalysts also tolerate aerobic conditions because of the high oxidation potential of converting Au(I) to Au(III). Other transition metals and Lewis acids can be less selective toward  $\pi$ -nucleophiles and often require aprotic and anaerobic conditions. Brønsted acids are tolerant of moisture, but functional group compatibility can be a drawback. The compatibility with air and moisture as well as diverse functional groups allows gold-catalyzed transformations to efficiently access structures of

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**Table 1. A general comparison of gold catalysis with traditional modes of activation<sup>a</sup>**

	Gold	Other transition metals	Lewis acid	Brønsted acid
Compatible with moisture/protic solvents	✓	×	×	✓
Compatible with oxygen	✓	×	✓/×	✓
Functional group compatibility	✓	✓	×	✓/×
Potential for tandem and multi-component catalysis	✓	✓	✓/×	✓

<sup>a</sup> Exceptions can be found in all categories.

immense diversity and complexity from much simpler starting materials. Furthermore, distinct from classical carbocations generated with Lewis and Brønsted acids, non-classical carbocation/carbenoid intermediates often lead to well-controlled chemo-, regio-, diastereo- and enantioselective transformations. The unique non-classical carbocation/carbenoid intermediates also allow for tandem catalysis and multi-component reactions in a similar manner to other transition metals such as platinum and palladium. However, gold does not normally cycle between the Au(I) and Au(III) oxidation states like other late transition metals for which oxidative addition and reductive eliminations are common modes of reactivity [8]. The lack of redox-cycling makes gold more like traditional Lewis acids but with a distinct affinity for  $\pi$ -bonded systems.

### General modes of reactivity

The most common examples of heterocycle formation with gold catalysis involve intramolecular cyclizations. The exceptionally selective  $\pi$ -acidity of gold catalysts defines the predominant reactivity of gold catalysts and, as a result,  $\pi$ -donating groups such as alkynes, alkenes and allenes are typical reactants. The complexation of the gold catalyst with the reactant  $\pi$ -system activates the  $\pi$ -system toward attack by a pendant nucleophile. The proposed mechanism involves addition of the heteronucleophile in a *trans* configuration from the complexed gold followed by a subsequent protodeauration that releases the gold catalyst (Scheme 1). Depending on the nature of the substrates, both *exo*- and *endo*-cyclizations and various ring sizes are possible. Nucleophiles are typically carbon, nitrogen, oxygen or sulfur.

In the cases where  $R_2X$  is the nucleophile and X is a divalent oxygen or sulfur, the formation of the trivalent X cation often leads to a subsequent rearrangement (Scheme 2). For example, allyl sulfide **1** cyclizes onto the *ortho*-alkyne and then rearranges to afford the 3-allyl benzothiophene **3** [9]. The reaction presumably proceeds via the zwitterionic gold species **2**.

When X is  $sp^2$  hybridized, particularly in the cases of ketones, aldehydes and imines, the addition of X to the gold-activated  $\pi$ -bond forms a putative zwitterionic species, that is, susceptible to intramolecular rearrangements or additional bond-forming steps. (Scheme 3). For example,

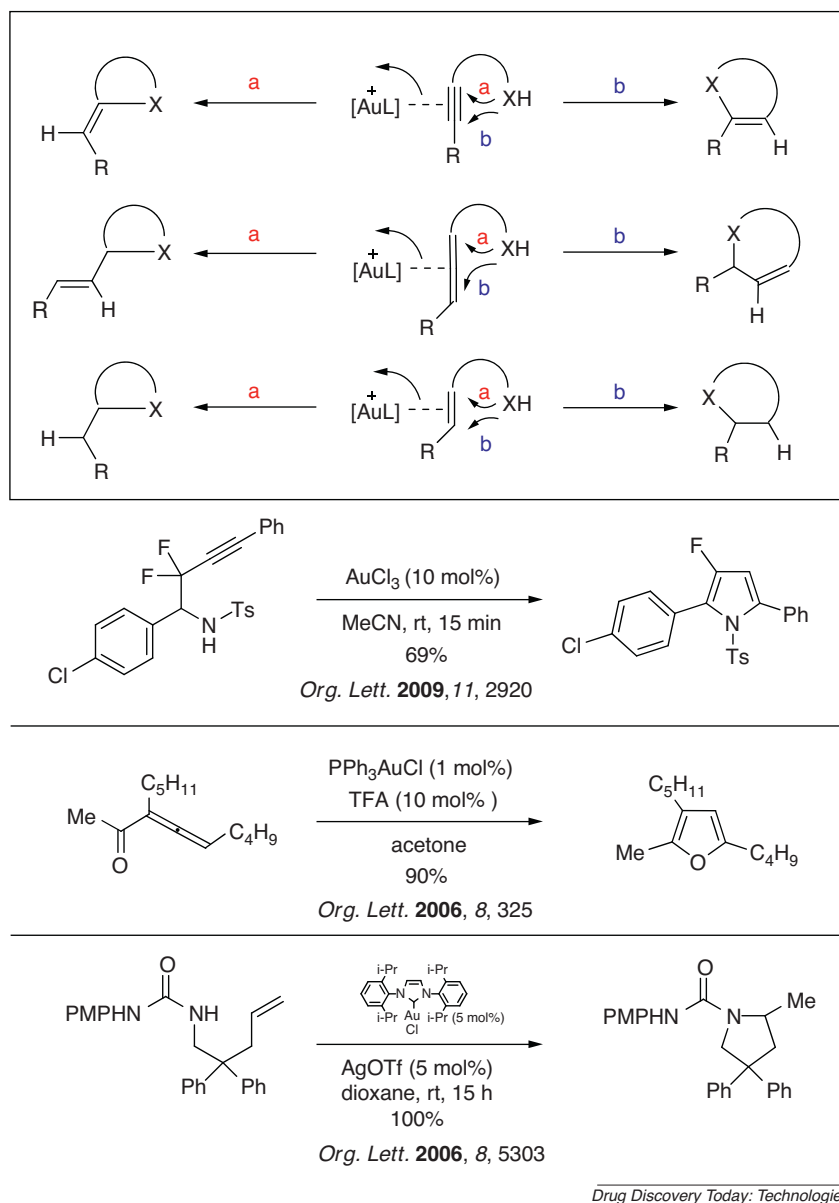
*endo*-cyclization of cyclohexanol **4** affords the putative zwitterionic intermediate **5**, which undergoes a 1,2-alkyl shift to afford the spirocyclic furanone **6** in 95% yield. Alternatively, cyclization of the structurally similar cyclohexenone **7** affords the oxonium **8**, which traps exogenous methanol to afford furan **9**. The examples shown in Scheme 3 demonstrate the power of gold catalysis to afford diverse molecular architectures from structurally similar reactants [10].

The third reaction mode involves a nucleophile that also bears a leaving group thus setting the stage to generate a putative gold carbenoid (Scheme 4). For example, cyclization of the aryl azide **10** with release of dinitrogen affords the gold carbenoid intermediate **11**. Protodeauration and tautomerization then affords pyrrole **12**. In a similar manner, exogenous nucleophiles such as quinoline *N*-oxides and pyridine-*N*-aminides can also be used to access gold carbenoids from alkynes (Scheme 4). Zhang and coworkers demonstrated the gold-catalyzed addition of quinoline *N*-oxide (**13**) to alkyne **14** to afford oxocarbenoid **15** [11]. Condensation with a nitrile and subsequent cyclization afforded 2,5-disubstituted oxazole **16**. While many of the examples use the nitrile as solvent, the authors note that only a 3-fold excess of the nitrile is required for reasonable yields to be attained. Davies and coworkers recently described a similar strategy to prepare 4-aminooxazoles (**19**) from ynamides (**17**) and pyridine-*N*-aminides (**18**) [12]. The transformation is formally a gold-catalyzed [3 + 2]-cycloaddition route to trisubstituted oxazoles.

While often denoted and referred to as carbenoids, intermediates can be represented as cationic organogold species (**20**) or as gold carbenoids (**21**) (Scheme 5). However, the true nature, either non-classical cationic or carbenoid, of organogold intermediates has been the subject of numerous primary research reports and reviews [3h,13]. In general, organogold intermediates can be viewed as existing somewhere on the continuum between non-classical cations and carbenoids [14].

### Selected examples of heterocycles generated with gold catalysis

Despite the recent emergence, the scope of heterocycle formation via gold catalysis has been rapidly expanded. Summarized in Table 2 are selected examples highlighting the



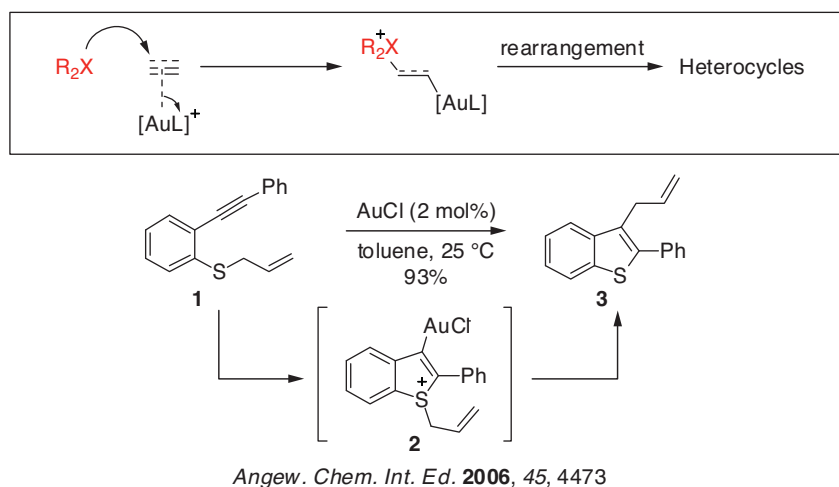
Scheme 1.

diversity of structures that are readily available via gold catalysis. Almost all common saturated and unsaturated heterocycles are included, and some of the examples show that densely decorated heterocycles can be efficiently assembled. It is conceivable that certain novel heterocyclic core structures may serve as a key pharmacophore/scaffold for drug-like molecules.

### Examples of gold catalysis for preparing targets with attractive biological activities

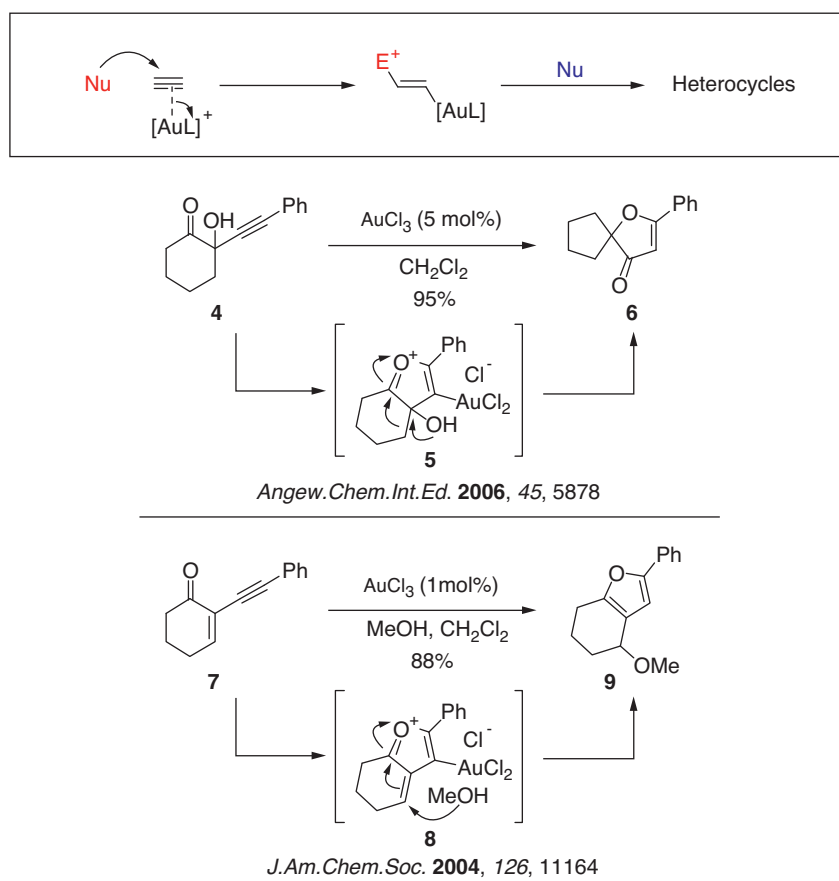
As a well-known class of antibiotics and covalent enzyme modulators,  $\beta$ -lactams are attractive targets in medicinal chemistry. They are in general prone to decomposition in the presence of strong nucleophiles and bases. As such,

organic reactions involving  $\beta$ -lactams should be carefully controlled. Gold catalysis is compatible with the  $\beta$ -lactam functionality due to the mild reaction conditions under neutral pH. Both allene and alkyne cyclizations can provide a variety of  $\beta$ -lactam scaffolds [15]. For example, starting with the allenyl substrate **23**, a convenient 5-*endo*-trig cyclization afforded fused-bicyclic **24** in 65–85% yields (Scheme 6) [16]. The transformation was highly regioselective toward 5-*endo*-trig cyclization. Interestingly, structurally similar substrates underwent other modes of cyclization onto the allene to furnish spiro-, or fused-bicyclic, or bis-heterocyclic scaffolds [17]. As such, gold catalysis became a powerful method to generate numerous structural variations containing the  $\beta$ -lactam motif, which is precisely what medicinal chemists are



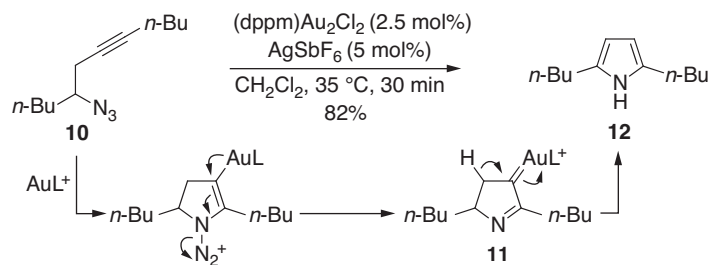
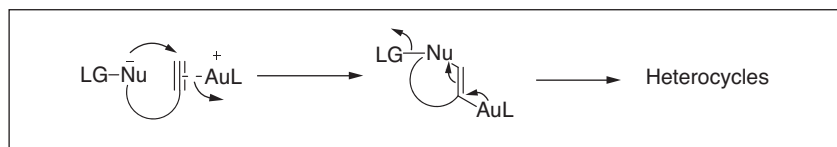
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Scheme 2.

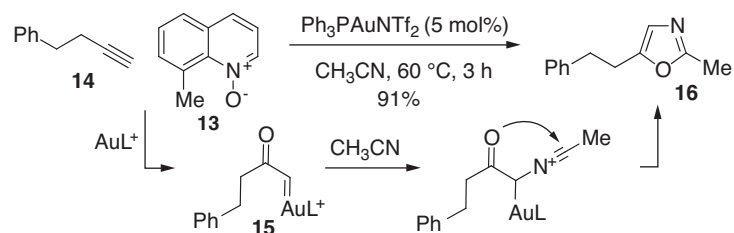


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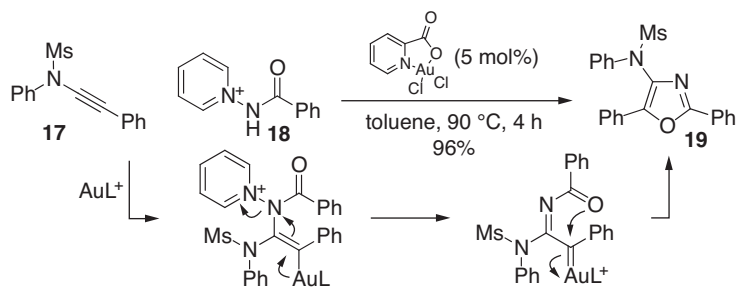
Scheme 3.



*J. Am. Chem. Soc.* **2005**, *127*, 11260



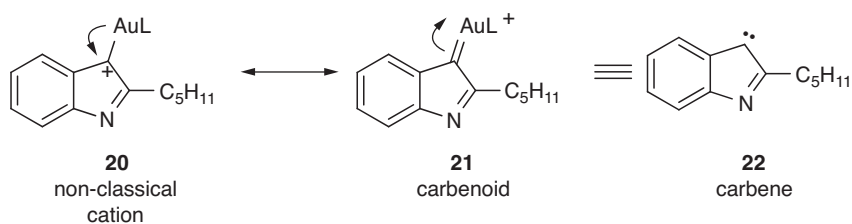
*J. Am. Chem. Soc.* **2011**, *133*, 8482



*Angew. Chem. Int. Ed.* **2011**, *50*, 8931

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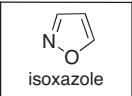
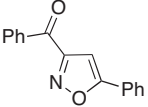
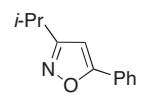
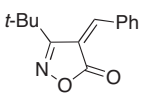
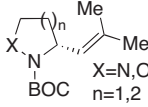
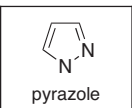
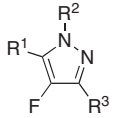
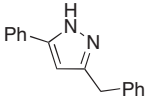
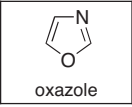
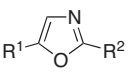
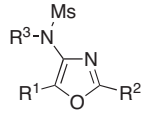
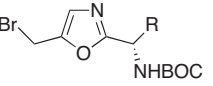
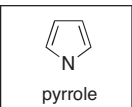
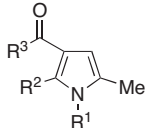
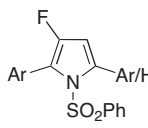
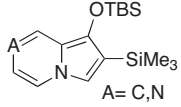
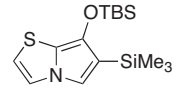
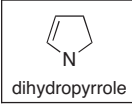
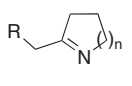
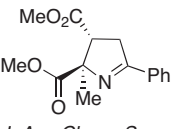
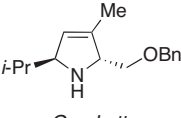
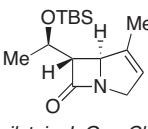
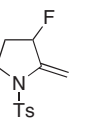
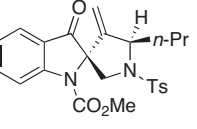
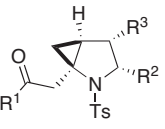
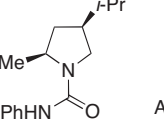
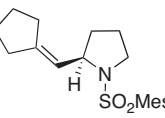
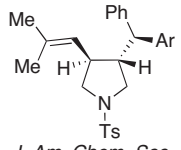
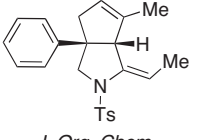
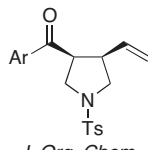
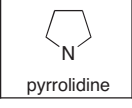
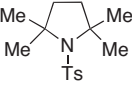

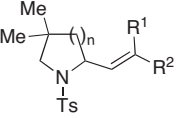
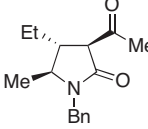
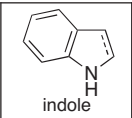
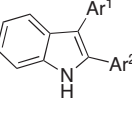
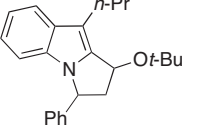
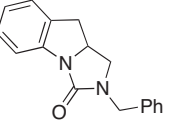
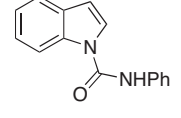
**Scheme 4.**

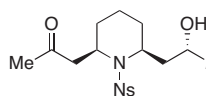
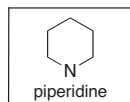


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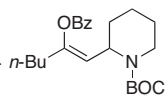
**Scheme 5.**

**Table 2. Selected examples of heterocycles derived from gold-catalyzed transformations**

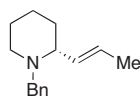
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 pyrazole	 <i>Org. Lett.</i> <b>2011</b> , 13, 4220	 <i>Angew. Chem. Int. Ed.</i> <b>2011</b> , 50, 5560		
 oxazole	 <i>J. Am. Chem. Soc.</i> <b>2011</b> , 133, 8482 <i>Chem. Eur. J.</i> <b>2010</b> , 16, 956 <i>Org. Lett.</i> <b>2004</b> , 6, 4391	 <i>Angew. Chem. Int. Ed.</i> <b>2011</b> , 50, 8931	 <i>Org. Biomol. Chem.</i> <b>2011</b> , 9, 4017	
 pyrrole	 <i>Tetrahedron: Asymmetry</i> <b>2001</b> , 12, 2715	 <i>Org. Lett.</i> <b>2009</b> , 11, 2920	 <i>J. Am. Chem. Soc.</i> <b>2006</b> , 128, 12050 <i>Org. Lett.</i> <b>2010</b> , 12, 5538	 <i>J. Am. Chem. Soc.</i> <b>2005</b> , 127, 11260
 dihydropyrrole	 <i>Heterocycles</i> <b>1987</b> , 25, 297	 <i>J. Am. Chem. Soc.</i> <b>2011</b> , 133, 3517	 <i>Org. Lett.</i> <b>2004</b> , 6, 4121	 <i>Beilstein J. Org. Chem.</i> <b>2011</b> , 7, 622
	 <i>Beilstein J. Org. Chem.</i> <b>2011</b> , 7, 1379	 <i>Org. Lett.</i> <b>2011</b> , 13, 3458	 <i>Tetrahedron</i> <b>2009</b> , 65, 1809	 <i>Org. Lett.</i> <b>2006</b> , 8, 5303
	 <i>Science</i> <b>2007</b> , 317, 496	 <i>J. Am. Chem. Soc.</i> <b>2011</b> , 133, 5500	 <i>J. Org. Chem.</i> <b>2010</b> , 75, 4542	 <i>J. Org. Chem.</i> <b>2010</b> , 75, 6031
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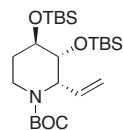
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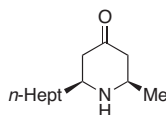
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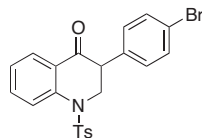
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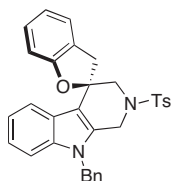
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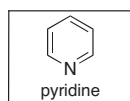
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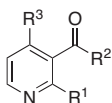
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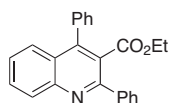
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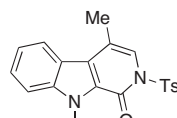
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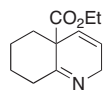
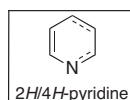
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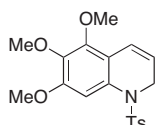
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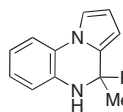
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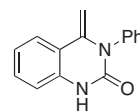
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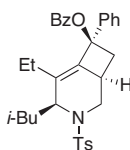
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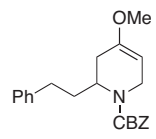
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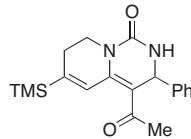
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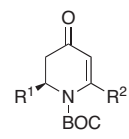
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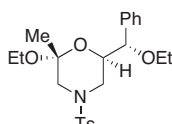
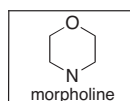
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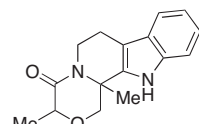
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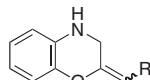
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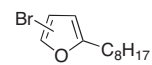
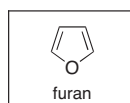
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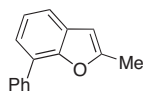
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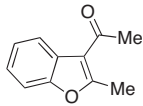
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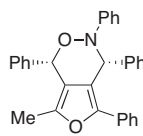
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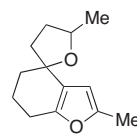
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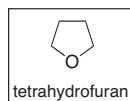
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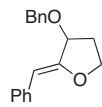
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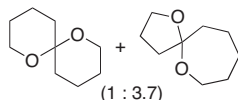
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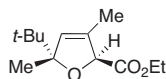
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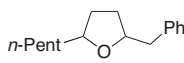
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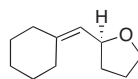
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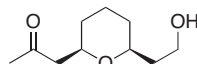
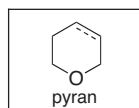
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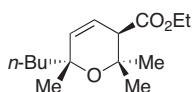
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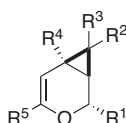
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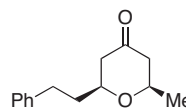
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2007, 72, 7359



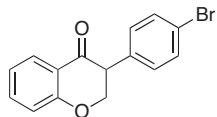
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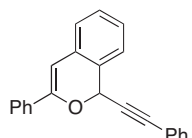
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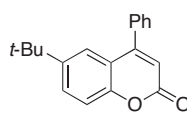
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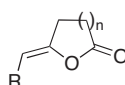
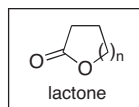
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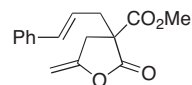
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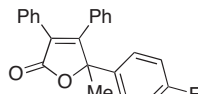
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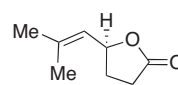
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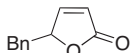
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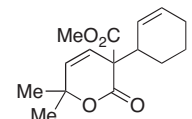
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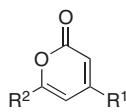
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*Tetrahedron Lett.*  
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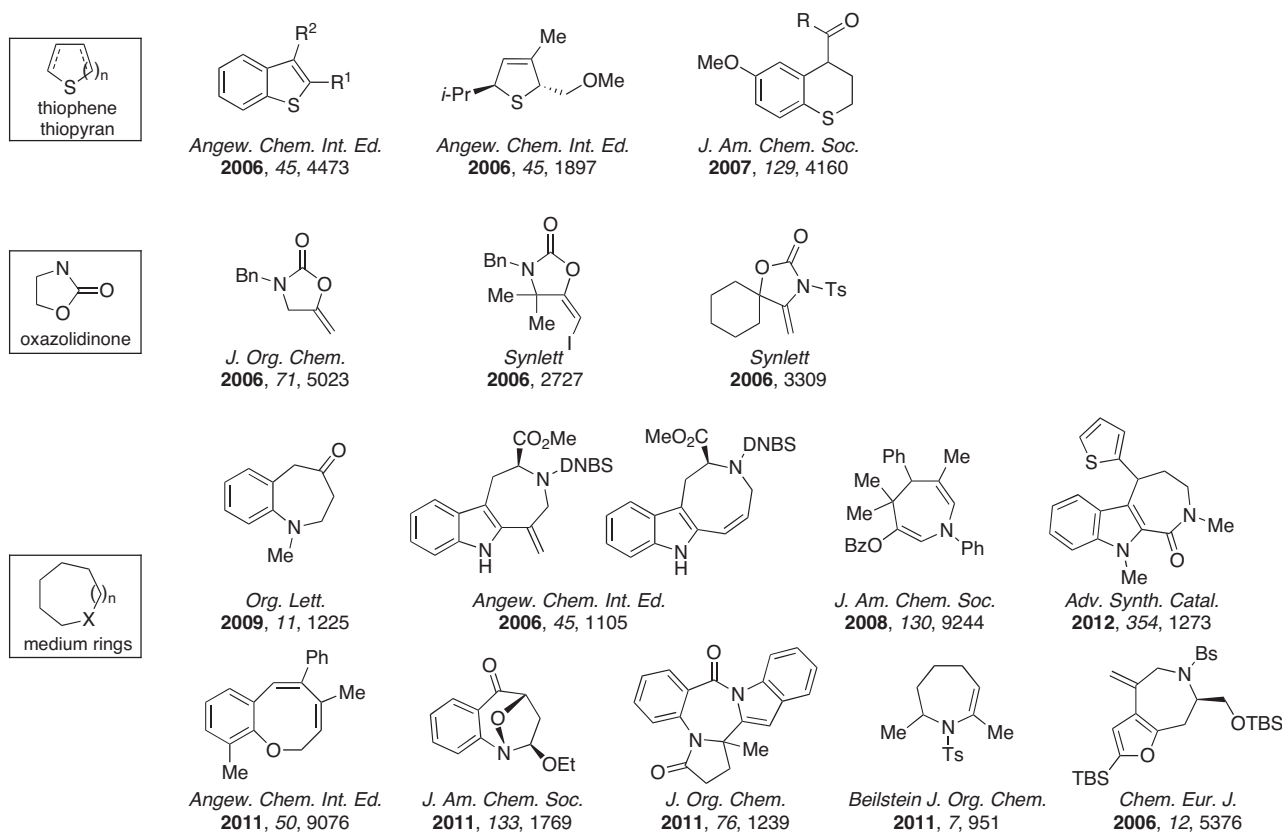


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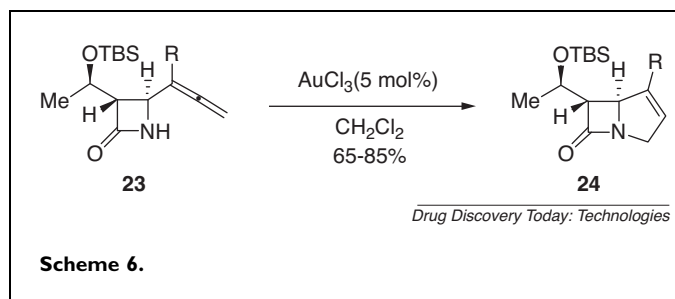
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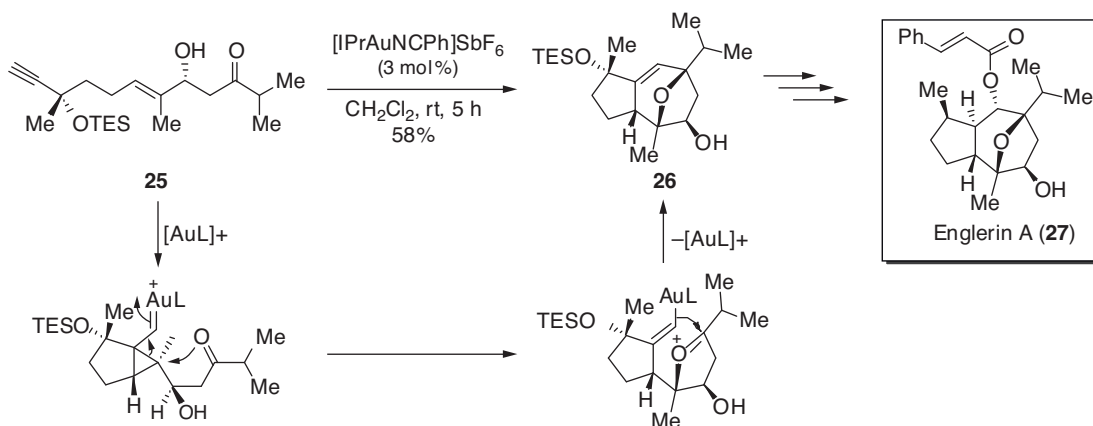
looking for when they build diverse scaffolds to explore structure–activity relationships.

Englerins A (**27**) is a natural product that exhibits 1–2 orders of magnitude higher potency than taxol against certain cancer cell lines. The Echavarren group took advantage of the gold-catalyzed [2 + 2 + 2] alkyne/alkene/carbonyl cycloaddition of 1,6-enyne **25** to form two C–C and one C–O bonds in a domino fashion (Scheme 7) [18]. Remarkably, the propargylic stereogenic center imposes excellent control of stereochemistry leading to virtually a single diastereomer (**26**) in 58% yield. It should be noted that the allylic alcohol in the substrate did not need to be protected, and this process can be routinely performed at 0.5–1 g scale. The facile stereoselective formation of the bicyclic scaffold from a structurally less complex linear substrate highlighted the utility of this powerful gold-catalyzed transformation.



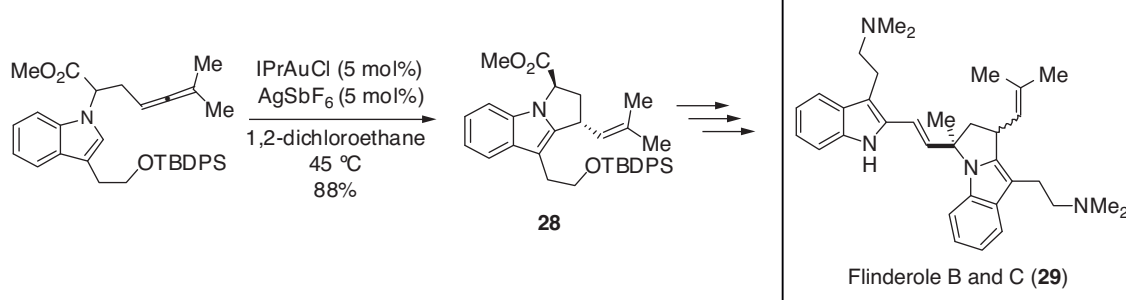
Indole alkaloid flinderoles B and C (**29**) were identified as antimalarial natural products. The Toste group envisioned the use of a gold-catalyzed allene hydroarylation to assemble the tricyclic core of the natural product (**28**) (Scheme 8) [19]. The choice of ligand was crucial to the success of the reaction – while triphenylphosphinegold (I) failed to induce the cyclization, the more electropositive *N*-heterocyclic carbene gold afforded the desired tricyclic intermediate as a single diastereomer in excellent yield.

GlaxoSmithKline developed a selective 5-HT<sub>4</sub> receptor agonist (**34**) as a potential treatment for disorders of the gastrointestinal tract (Scheme 9). The synthesis relied on a key dihydrobenzopyran intermediate (**31**). The initial synthesis involved accessing **31** by way of a thermal Claisen rearrangement; however, significant investments were made to control the purity and safety issues of this route including attempts to develop a continuous flow reaction [20]. Additional studies explored the use of the transition metal-catalyzed aromatic Claisen rearrangement [21]. Platinum, silver and gold salts were explored. Silver afforded a low mass balance due to the formation of by-products that were also observed in the thermal Claisen rearrangement. Platinum afforded improved results, but a major portion of the mass balance was the des-propargyl phenol **32** and a minor by-product was the ketone **33**, probably a consequence of adventitious water. Gold catalysts, however, afforded greatly improved yields of **31** with minimal formation of **32** and



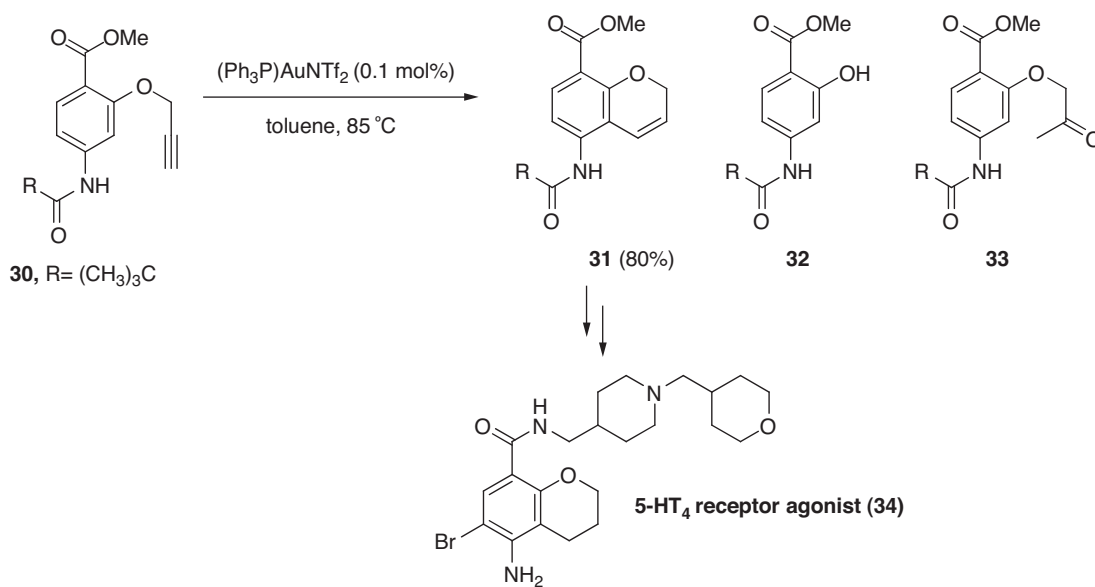
Drug Discovery Today: Technologies

Scheme 7.



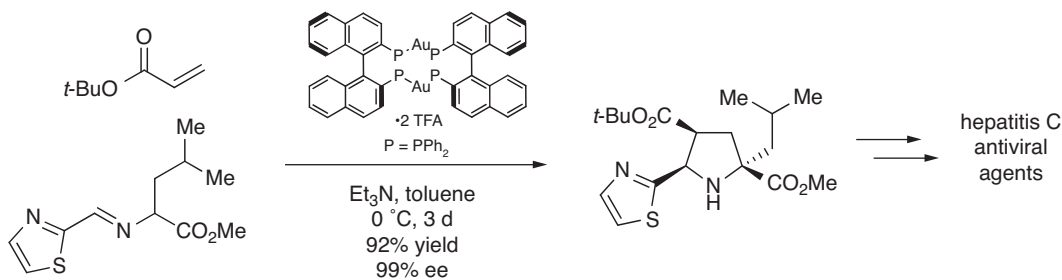
Drug Discovery Today: Technologies

Scheme 8.



Drug Discovery Today: Technologies

Scheme 9.



Scheme 10.

**33.** With only 0.1 mol%  $(\text{Ph}_3\text{P})\text{AuNTf}_2$  at  $85^\circ\text{C}$  the desired product **31** was isolated in 80% yield with the by-product formation held at under 3%. The authors note that the low catalyst loading and the ease of synthesis made the gold-catalyzed route superior to the thermal route when total cost and operational convenience were considered.

The Nájera group demonstrated the synthesis of hepatitis C antiviral agents with a gold-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with electron deficient olefins (Scheme 10) [22]. A chiral BINAP-gold(I) trifluoroacetate complex mediated the 1,3-dipolar cycloaddition between *t*-butyl acrylate and an azomethine ylide at ambient temperature and afforded the cycloaddition product in greater than 92% yield and 99% enantiomeric excess. The authors suggest that the trifluoroacetate counterion acts as a Brønsted base while the gold complex acts as a Lewis acid. The transformation is also feasible on more sterically congested substrates [23].

### Conclusions and prospects

Heterocycle-containing molecules constitute especially important targets in the pharmaceutical industry. Homogeneous gold catalysis represents a new frontier to access a wide range of heterocycles. These reactions are based upon the activation of alkynes, allenes and sometimes alkenes by the gold species, or cycloisomerizations with tethered heteroatoms. The gold-catalyzed transformations are convenient, and often accomplished under remarkably mild conditions. In addition to excellent control of chemo-, regio- and diastereoselectivity in many reactions, highly enantioselective gold catalysis has also emerged. Further developments in the areas of catalytic multi-component or tandem reactions [24], oxidative coupling [25] and cycloaddition [26] reactions will provide additional methods for the rapid construction of complex molecules from simple and commercially available feedstocks. Finally, the broad substrate scope and diverse product scaffolds that are obtained from gold-catalyzed reactions will undoubtedly increase the impact of these transformations on medicinal chemistry. Numerous applications of

gold catalysis in the synthesis of biologically active compounds have validated the emerging utility of these synthetic methods.

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