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Divergent gold-catalysed reactions of cyclopropenylmethyl sulfonamides with tethered heteroaromatics

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Divergent gold-catalysed reactions of cyclopropenylmethyl sulfonamides with tethered heteroaromatics

Abstract
Cyclopropenylmethyl sulfonamides with tethered heteroaromatics have been demonstrated to undergo divergent gold-catalysed cyclisation reactions. A formal dearomative (4+3) cycloaddition takes place with furan-tethered substrates, yielding densely functionalised 5,7-fused heterocycles related to the bioactive curcusone natural products. Indole-tethered substrates display divergent reactivity giving biologically important tetrahydro-β-carbolines via a Friedel-Crafts mechanism.

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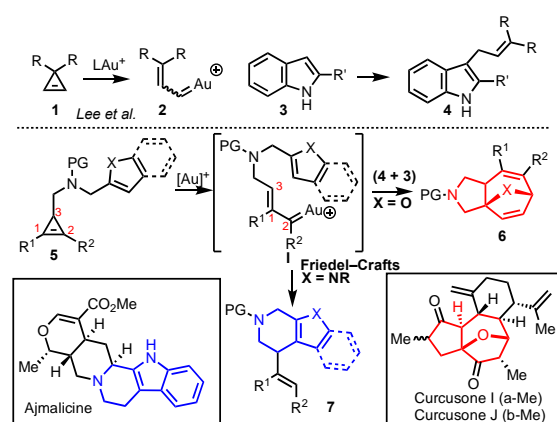## Divergent Gold-catalysed Reactions of Cyclopropenylmethyl Sulfonamides with Tethered Heteroaromatics.

Melanie A. Drew,[a] Sebastian Arndt,[b] Christopher Richardson,[a] Matthias Rudolph,[b] A. Stephen K. Hashmi,*,[b] and Christopher J. T. Hyland*,[a]

Cyclopropenylmethyl sulfonamides with tethered heteroaromatics have been demonstrated to undergo divergent gold-catalysed cyclisation reactions. A formal dearomative (4 + 3) cycloaddition takes place with furan-tethered substrates, yielding densely functionalised 5,7-fused heterocycles related to the bioactive curcusone natural products. Indole-tethered substrates display divergent reactivity giving biologically important tetrahydro-β-carbolines via a Friedel–Crafts mechanism.

Gold-catalysed reactions of cyclopropenes are emerging as powerful tools in organic synthesis.[1] For example, their facile ring opening enables them to act as useful stable precursors to highly versatile and reactive vinyl gold carbene intermediates.[1-5] Cyclopropenes have also been used to study the nature of gold(I) carbene bonding.[6] The accessibility of cyclopropenes with pendant heteroatoms has enabled new emergent methods for intramolecular trapping of these vinyl gold carbenes. Notably, Cossy, Meyer and co-workers demonstrated intramolecular cyclopropanation of mono-substituted vinyl gold carbenes generated from *O*- and *N*-tethered cyclopropenes to form stereodefined bicycles.[3] In contrast, we have shown that C1-C2-disubstituted cyclopropenylmethyl acetates undergo alternative gold-catalysed regioselective ring-opening to form a disubstituted vinyl gold-carbene, which participates in a formal 1,2-acetoxy transfer to form *Z*-acetoxydienes.[4,7] As such, cyclopropenes provide an important, complementary, route to vinyl gold-carbenes along with other important methods from propargyl esters,[8] vinyldiazoesters[9a-h] and via the retro-Buchner reaction of alkenyl- or aryl-cycloheptatrienes. [9i-k] Despite straightforward synthesis via cyclopropenation of alkynes, gold-catalysed intramolecular reactions of cyclopropenes bearing heteroatom tethers at the sp³ C3 position have been far less investigated than the sp² C2-tethered systems.[10] Furthermore, to the best of our knowledge there have been no studies on trapping cyclopropene-derived vinyl gold-carbenes with pendant heteroaromatic systems.[11,12] Lee and co-workers reported
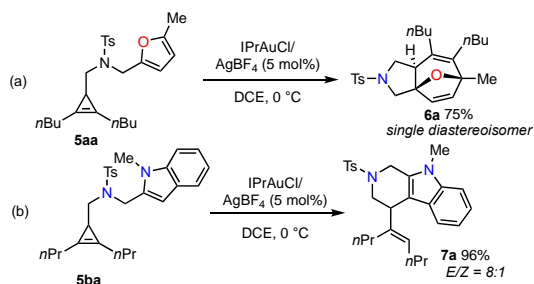

Scheme 1. Au-catalysed reactions of cyclopropenes with a pendant heteroatom.

intermolecular reactions of furans and indoles (**3**) undergoing direct attack to vinyl gold carbenes **2** derived from the ring-opening of simple cyclopropenes **1** (Scheme 1).[5] We reasoned that employing tethered systems of type **5** should encourage the vinylogous attack of the pendant heteroaromatic based on formation of the most favoured ring-size – ultimately leading to complex heterocycles. Herein, we report the divergent reactivity of disubstituted alkenylgold carbenes **I** derived from cyclopropene derivatives with heteroaromatic groups tethered to a C3 aminomethyl linker (Scheme 1). Our studies reveal the first examples of vinyl gold carbenes undergoing a formal (4 + 3) cycloaddition with a furan tether to yield 5,7-fused heterocycles **6**. This reaction adds to the existing suite of coinage metal-catalysed (4 + 3) cycloaddition processes, including those using allenes[13] and propargyl esters.[14] Crucially, when indole/pyrrole tethers are used, divergent reactivity emerges via a Friedel–Crafts process to give tetrahydro-β-carbolines **7**. Heterocycles **6** are important as they are related structurally to the daphnane/ tigliane/rhamnofolane diterpenes (e.g. curcusones I and J) that have numerous biological activities including anti-HIV, antimicrobial, antitumour, antimalarial and neurotropic activity (Scheme 1b).[15,16] The tetrahydro-β-carboline skeleton obtained from the indole-tethered system is also found in an array of bioactive molecules, including the antihypertensive ajmalicine.[17]

Scheme 2: Initial gold-catalysed reaction of tethered cyclopropenes

To investigate the reactivity of C3-heteroaromatic tethered cyclopropenes, a 5-methylfuran-tethered (**5aa**), an *N*-methylindole-tethered (**5ba**) and a 5-methylthiophene-tethered system (**5c** – not shown) were synthesised.[18] Treatment of the furan-tethered cyclopropene (**5aa**) with the NHC gold catalyst system IPrAuCl/AgBF$_4$ provided the oxa-bridged 5,7-fused cycloadduct **6a** as a single diastereoisomer in good yield (Scheme 2a - for optimisation see Table S1). This product arises from a formal (4 + 3) cycloaddition between an *in-situ* generated vinyl gold carbene and the furan tether. Importantly, gold-phosphine catalysts and the Brønsted acid HNTf$_2$ were incapable of effecting this transformation (see SI). The *N*-Me indole tethered cyclopropene **5ba** diverged in reactivity under the same conditions to give tetrahydro-β-carboline **7a** in excellent yield (Scheme 2b). This latter reaction is consistent with a Friedel–Crafts process involving alkylation

Table 1. Substrate scope for the (4 + 3) dearomative cycloaddition of cyclopropenyl furyl sulfonamides **5**
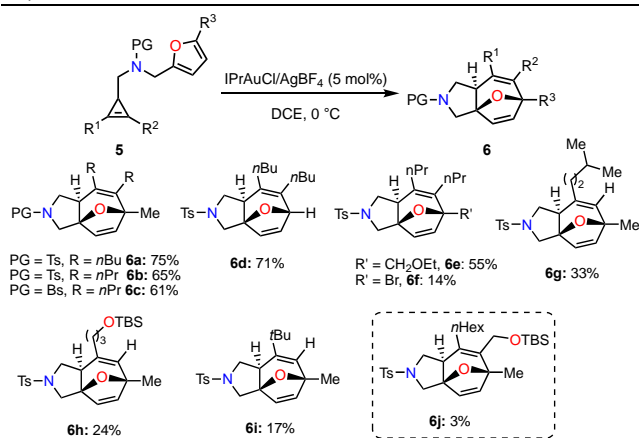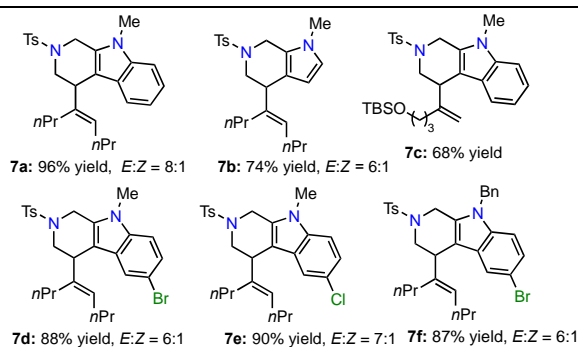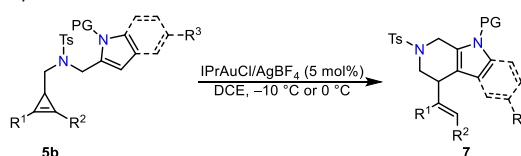

An X-ray crystal structure was obtained for heterocycle **6d** (CCDC 1909426, contains the supplementary crystallographic data).

with the vinylgold carbene. Use of the more aromatic and less nucleophilic thiophene tether of derivative **5c** resulted in diene **8** (not shown, see SI) forming – likely via a 1,2-H shift and subsequent dearuation. With the reactivity pattern of the tethered cyclopropenylmethyl sulfonamides established, the substrate scope for the (4 + 3) cycloaddition was explored (Table 1). Shortening the alkyl chains R^1 and R^2 by one carbon produced heterocycle **6b** in good yield and the reaction conditions also tolerated a change in protecting group to a brosyl and provided **6c** also in good yield. The importance of a substituent in the furan 5-position was probed by preparing cyclopropenyl furyl sulfonamide **5ad** (R^3 = H), which provided the oxa-bridged 5,7-fused heterocycle **6d** in good yield. Cycloadduct **6d** also provided X-ray quality crystals that gave

definitive structural assignment and relative configuration. Changing R^3 to a –CH$_2$OEt substituent gave heterocycle **6e**, however, heterocycle **6f** was isolated in low yield, which was likely due to the

Table 2. Substrate scope for the Friedel–Crafts cyclisation of cyclopropenyl pyrrolyl- and indolyl-sulfonamides **5**


The synthesis of **7c** was conducted at –10 °C. An X-ray crystal structure was obtained for heterocycle **7a** (CCDC 1909427 contains the supplementary crystallographic data.)

presence of an electron-withdrawing bromo-substituent in the R^3 position. Unsymmetrical, mono-substituted cyclopropenyl furyl sulfonamides **5ag-5ai** were investigated, although yields for the corresponding heterocycles **6g-6i** dropped substantially which, in our previous experience, is due to the less-substituted cyclopropenes being unstable towards decomposition. The unsymmetrical, disubstituted substrates **5aj** (R^1 = –C$_6$H$_{13}$, R^2 = –CH$_2$OTBS) and **5ak** (R^1 = Ph, R^2 = Me – not shown, see SI) failed to produce significant amounts of the corresponding heterocycles **6j** and **6k**. In the case of **5aj** the diene was the major product, likely a result of the OTBS facilitating a 1,2-H shift. The presence of two aryl substituents on the cyclopropene (**5al** – not shown, see SI) also prevented the cycloaddition from occurring, presumably because of the additional stabilisation of the gold carbene by the aromatic substituent resulting in a poor reactivity. The substrate scope with respect to indole and pyrrole-tethered cyclopropenes was next explored (Table 2).

The indole could also be exchanged with a pyrrole ring to produce heterocycle **7b** in good yield. To our delight, when the monosubstituted cyclopropene example **5bc** was reacted, heterocycle **7c** was obtained in good yield, which contrasts with the low yield obtained for the (4 + 3) cycloaddition reaction with the analogous furan-tethered substrate (**6h**). Pleasingly, we found that inductively electron-withdrawing halogens (Br and Cl) in the 5-position of the indole ring were well-tolerated, giving heterocycles **7d** and **7e** in excellent yields. Such products are (*vide infra*) amenable to further functionalisation through cross-coupling reactions. A benzyl protecting group for the indole was well-tolerated giving

heterocycle **7f** in excellent yield, however, as expected, the electron-withdrawing tosyl group shut down the reaction pathway, which we attribute to the reduced nucleophilicity of the pyrrole, resulting in diene formation. A proposed mechanism for the formation of 5,7-fused heterocycles **6** from cyclopropenyl furyl sulfonamides **5a** involves gold-activation of the electron-rich cyclopropene double bond that leads to rapid ring-opening furnishing the alkenylgold-carbene intermediate **I** (Scheme 3).
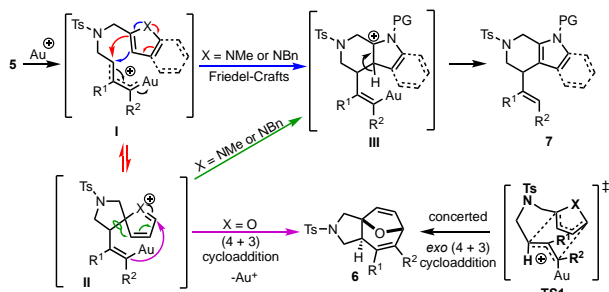
Scheme 3. Proposed mechanism for the formation of **6** and **7**

Conjugate nucleophilic attack from the furan 2-position to the vinylgold carbene then forms the spirocyclic intermediate **II**. Nucleophilic attack of the vinyl gold onto the oxonium ion provides the observed heterocycle **6** (purple arrows) and regenerates the gold(I) catalyst. The major diastereoisomer obtained in the cycloaddition reaction matches that of the curcusone I and J natural products and also that obtained from the previously reported Au-catalysed allene (4 + 3) cycloaddition to furans.[13b] If a stepwise mechanism is operating, it is suggested that initial nucleophilic attack of the furan might be reversible, and that only one diastereoisomer of **II** undergoes favourable cyclisation to the observed diastereoisomer of the product. While there have been no reports of vinyl gold carbenes of type **II** undergoing concerted cycloaddition reactions, such a process cannot be ruled out. If a concerted pathway is occurring from **I** then *exo* **TS1** would explain the relative stereochemistry of the cycloaddition product. Similar transition states have been proposed for (4 + 3) cycloaddition reactions with allene-derived gold allylic cations stabilised by gold at the central carbon.[11] The regioselectivity of the cycloaddition with monosubstituted cyclopropene substrates can be explained based on the preferential ring-opening to place the gold on the less substituted carbon atom. This observation matches that reported previously and our own computational studies. [3,4,7] Two plausible Friedel–Crafts-type mechanisms for cyclopropenyl indolyl (and pyrrole) sulfonamides **5b** are postulated (Scheme 3). [19] Each pathway invokes the alkenylgold(I) carbene intermediate *I as a crucial initial species by the same cyclopropene ring opening chemistry*. The first proposed pathway involves attack from the nucleophilic 3-position of the indole in intermediate **I** (blue arrows) to generate intermediate **III**, which could subsequently form heterocycle **7** following re-aromatisation and protodeauration. The proposed pathway for the pyrrole-tethered system involves attack from the nucleophilic 2-position of the pyrrole ring to generate intermediate **II** (red arrows). A Wagner–Meerwein shift (green arrows) then provides intermediate **III** which, following re-aromatisation and protodeauration, delivers the observed heterocycle **7**.[20] In both reactions, conjugate attack on the alkenylgold carbene may be facilitated by the NHC-ligand reducing carbocation character at C8, combined with the formation of a more favourable 5-membered vs 7-membered ring. Chemical transformations were performed on heterocycles **6** and **7** to demonstrate their versatility. Desilylation of heterocycle **6h** using
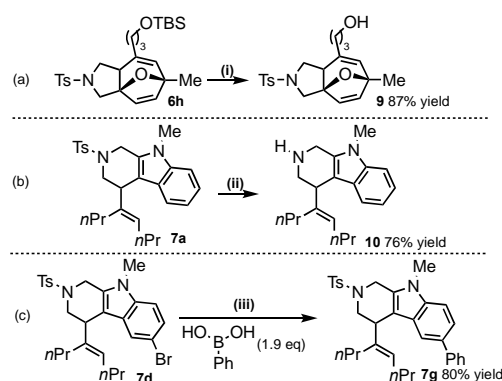
Scheme 4. Conditions: **(i)** TBAF (2 eq), THF, rt; **(ii)** Mg (50 eq), MeOH/THF (3:1), sonication; **(iii)** Pd(dppf)Cl$_2$·CH$_2$Cl$_2$ (12 mol%), K$_2$CO$_3$ (2.3 eq), dioxane:H$_2$O (4:1), 85-95 °C

TBAF in THF at rt gave the corresponding alcohol **9** in 87% yield (Scheme 4a). Tosyl de-protection with Mg in MeOH/THF was successfully performed with heterocycle **7a** to obtain the free amine **10** in 76% yield (Scheme 4b). A Suzuki cross-coupling was carried out on **7d** and heterocycle **7g** was obtained in 80% yield (Scheme 4c). This result proved important as the range of accessible products could be further expanded for heterocycles **7** given the vast range of commercially available boronic acids. In conclusion, the gold(I)-catalysed rearrangements of cyclopropenyl sulfonamides **5** (Scheme 1) can be controlled via the identity of the tethered heterocycle. When an indole tether is present, a Friedel–Crafts reaction provides tetrahydro-β-carbolines **7** in excellent yields and good *E:Z* selectivities. However, when a furan is present, a (4 + 3) dearomative cycloaddition ensues to provide highly complex 5,7-fused heterocycles **6** in moderate to good yields as single diastereoisomers. To the best of our knowledge, this is the first example of a dearomatising cycloaddition to a cyclopropene-derived gold carbene. The facile synthesis of cyclopropenes of this type (three generally high-yielding steps) is an additional benefit and provides complementary substitution at R^1 and R^2 compared to the previously reported allene (4 + 3) cycloaddition reactions. Given that these relatively simple starting materials can be transformed into highly complex heterocyclic structures that are precursors to numerous biologically active natural products, this method could represent a more efficient route for accessing these molecules. Future work is aimed at investigating longer tethers and *O*-linkers in place of the *N*-linkers, to expand the range of heterocycles accessible. Enantioselective variants of the two reactions and further mechanistic studies are also currently under investigation.

Conflicts of interest

There are no conflicts to declare.

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