Dearomative (3+2) Cycloaddition of Indoles for the Stereoselective Assembly of Fully Functionalized Cyclopentanoids

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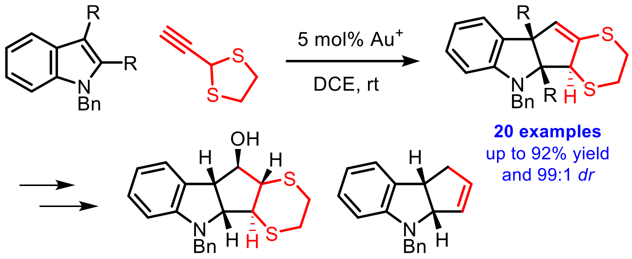
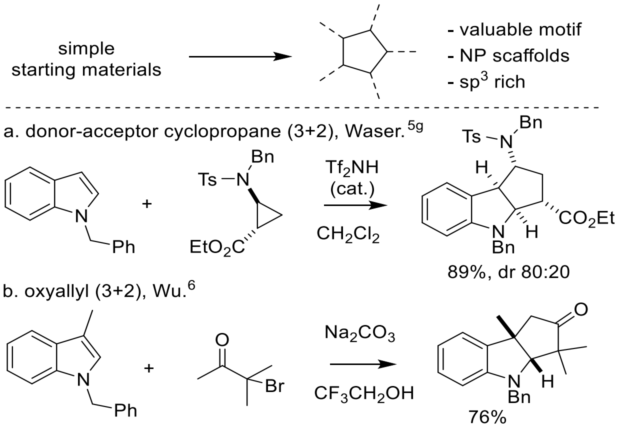
Supporting Information



ABSTRACT: The gold(I)-catalyzed dearomative cyclopentannulation of various indoles with 2-ethynyl-1,3-dithiolane is reported. The method generates three new stereocenters with excellent control of relative stereochemistry and is tolerant to diverse functionalization and substitution patterns on the indoles. The obtained cyclopentane-fused indolines allow for interesting subsequent synthetic manipulations, giving rise to fully substituted cyclopentanes with control of the relative stereochemistry of all five stereocenters. The reported reaction illustrates and elucidates a mechanistic dichotomy underlying gold(I)-catalyzed reactions of 2-ethynyl-1,3-dithiolane.

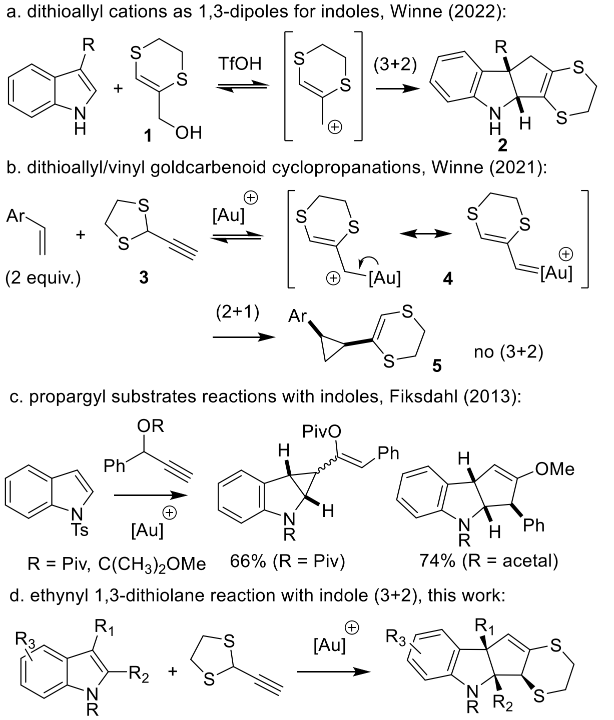
Polycyclic sp^3-rich scaffolds have a wide application potential in fine chemicals and pharmaceutical industries.[1] An interesting scaffold subclass herein is that of functionalized and substituted cyclopentanes.[2] While five-membered carbocycles are prevalent motifs in natural products, synthetic methodologies that enable their construction from readily available building blocks are scarce.[3] Among such methods, the dearomative (3+2) annulation of unactivated indoles has emerged as an attractive strategy (Scheme 1), especially given the fact that the indole motif is extensively represented in both pharmaceuticals and natural products.[4] The use of donor-acceptor cyclopropanes has taken a central place in this synthetic transformation type.[5a] This dearomative transformation is currently heavily investigated, also in asymmetric versions.[5b] The indole cyclopentannulation developed by Waser using aminocyclopropane esters as strained precursors for a 1,3-dipolar reagent is an excellent example of the current state-of-the-art (Scheme 1a).[5g] Conversely, allyl and oxyallyl cations serve as more generic 1,3-dipole reagents to access cyclopentanoids from indoles, as has been introduced by Wu and coworkers (Scheme 1b).[6] The generation of an oxyallyl intermediate from α-haloketones facilitates a (3+2) cycloaddition with N-benzylated indoles. The 1,3-dipoles also require a specific substitution pattern, as does the indole C3-position, but the method clearly shows versatility and has been applied in the synthesis of the core structure of alkaloid natural products.[6b,c]

Scheme 1: Rapid Assembly of Functionalized Cyclopentanoids via 1,3-Dipolar (3+2) Cycloaddition of Unactivated Indoles.



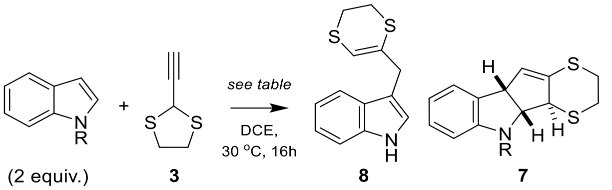
Inspired by the work of Wu and coworkers,[6] our group recently explored the dearomative cyclopentannulation of indoles with the dithioallyl cation precursor **1** (Scheme 2a).[7] The reaction showed potential as a late-stage functionalization tool of unprotected indoles, giving adducts like **2** which can be easily transformed into interesting cyclopentene-fused indole derivatives via hydrodesulfurization. However, in line with the findings of Wu, the stepwise nature of the cationic cyclization reaction necessitates substitution at C3 of indoles to prevent rearomatization and a Friedel-Crafts type of reactivity. In related studies, we found that we could generate the same dithioallyl cation intermediate using a gold(I)-promoted 1,2-sulfur migration in 2-ethynyl-1,3-dithiolane **3** (Scheme 2b).[8a,b] Surprisingly, the gold-coordinated version of the dithioallyl cation did not show 1,3-dipolar reactivity, but rather reacted as a gold-carbenoid in cyclopropanations with various unsaturated substrates. In light of our continued interest in cyclopentanoid synthesis, we were intrigued by reports from Fiksdahl and coworkers describing a mechanistic dichotomy between (2+1) and (3+2) cycloadditions for the reaction of N-tosylated indoles with gold(I)-carbenoids obtained for propargyl esters and acetals (Scheme 2c).[8c] The dichotomy between carbenoid and cation pathways in gold(I) catalysis is a subject of ongoing debate and extensive research.[8d,9] In our research on gold(I)-promoted rearrangement of 1,3-dithiolane **3**, we indeed found that some electron rich substrates also gave a competitive (3+2) cycloaddition.[8a] We then theorized that the gold-promoted dithioallyl approach might also allow a general (3+2) reactivity with indoles, which could give a viable alternative for the established methods in the field (see Scheme 1, 2a and 2c).[8b,d] We thus decided to investigate the synthetic potential of reactions of **3** with indoles, and we can now report the progress made in this area (Scheme 2d).

Scheme 2: Dithioallyl cation chemistry and rationale for the work



Our previous work involving gold(I)-promoted cycloadditions of **3** and more generic alkene substrates established a set of standard conditions to promote rearrangement of **3** to a reactive allyl cation/vinyl carbenoid species **4** (*cf.* Scheme 2b).[8a] In an initial experiment, we found that these conditions, when applied to indole as a substrate did not lead to the formation of either a (2+1) or (3+2) dearomatized cycloadduct (Table 1, entry 1). Instead, we observed the predominant formation of the C3-allylated Friedel-Crafts-type adduct **8** as the major product. Both tosyl- and Boc-protected indoles lacked all reactivity towards **3** under our standard conditions (entries 2 and 3). However, *N*-methylated indole gave a surprising outcome (entry 4). Here, a single reaction product was formed in moderate yield, assigned as a single diastereomer of the (3+2) cycloadduct **7** (R =Me), without a trace of any other adduct formed. An improved yield of this interesting dearomatized product could be achieved by switching to the more reliable chloride scavenger sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBArF, entry 5).[9g] *N*-Benzylated indole proved to be even more reactive under these conditions, giving an excellent isolated yield of the dearomatized (3+2) adduct, although here the formation of a minor diastereomer could also be observed (entry 6). Again, no trace of a Friedel-Crafts allylated product **8** or a vinylcyclopropanes adduct (*cf.* **5**) could be detected. In our previous study of gold(I)-catalyzed reactions of **3**,[8a] an excess of the olefin substrate was required to achieve good yields. However, with *N*-benzyl indole, we were pleased to find that a synthetically useful isolated yield could still be achieved under equimolar conditions of substrate and reagent (entry 10). The clear mechanistic differences and the potential synthetic utility of this novel transformation prompted us to further investigate the reactivity of **3** with various *N*-benzylated indoles.

Table 1: Influence of indole N-substitution and catalyst



Entry	catalysts (5 mol%)	R	**8**	**7**^{a}	*dr*
1	IPrAuCl/AgSbF$_6$	H	30%	2%	-
2	IPrAuCl/AgSbF$_6$	Ts	0%	0%	-
3	IPrAuCl/AgSbF$_6$	Boc	0%	0%	-
4	IPrAuCl/AgSbF$_6$	Me	0%	45% (40%)	*>99:1*
5	IPrAuCl/NaBArF	Me	0%	71% (65%)	*>99:1*
6	**IPrAuCl/NaBArF**	**Bn**	**0%**	**99% (90%)**	***(20:1)***
7	IPrAuCl/NaBArF	Bn	0%	89% (83%)^b	*(19:1)*
8	[(IPr)Au(MeCN)][BF$_4$]	Bn	0%	85% (nd%)	*(22:1)*
9	JohnPhosAuCl/AgSbF$_6$	Bn	0%	72% (nd%)	*(18:1)*
10	IPrAuCl/NaBArF	Bn^c	0%	75% (nd%)	*(20:1)*
11	IPrAuCl/NaBArF	Bn	0%	77% (nd%)	*(21:1)*

^{a}NMR yields were determined using 1,3,5-trimethoxybenzene as an internal standard (Isolated yields). ^{b}Performed at room tempreature. ^{c}Experiment with 1 equiv. of indole. All test reactions were performed at 0.5 mmol scale of **3**.

We started our investigation of the substrate scope by dearomatizing *N*-benzyl indole on a 0.5 mmol scale. The reaction gave product **7a** in a reproducible yield of 92% (Figure 1). This scale-up experiment also provided single crystals **7a**, of which the stereochemical identity could be unambiguously confirmed via single crystal X-ray diffraction analysis.

The fact that a C2,C3-unsubstituted indole serves as a viable substrate type in dearomative (3+2) cycloaddition is an important improvement over other allyl-cation based methods, and even for donor-acceptor cyclopropanes, where C3- or C2-alkylation is often found to be competitive.[5,6] We were pleased to note that *N*-benzyl indoles are quite permissive with respect to their C2,C3-substitution pattern (Figure 1, **7b-f**), as good to excellent yields (60-90%) and generally high to excellent stereoselectivity was observed. Moreover, the same *cis/trans* stereochemistry was consistently produced in these reactions. An interesting observation was that substitution at C2 slightly reduced reactvity and also the yield, compared to unsubstituted C2 indoles, suggesting an influence of steric factors on the reaction mechanism (*vide infra*). Likewise, [*b*]-annulated indoles fused with five, six, or seven membered carbocycles readily gave the propellane-type dearomatized cycloadducts **7g-i** in good yield and stereoselectivity, with a notable erosion of diastereoselectivity for **7g**, which may be related to subtle steric factors. Suitable single crystals were obtained for **7h** and its crystal structure showed the same relative stereochemistry as for **7a** (See SI). As observed with electron withdrawing substituents on the indole nitrogen (see Table 1 entries 2&3), we found that any electron withdrawing substituent (carbonyl, nitro, nitrile) at C2 or C3 also shut down all reactivity of the indole (see SI). Assignment of the minor stereoisomer (when formed) was possible by NMR analysis, indicating a *cis*-*cis* relationship of all hydrogen atoms on the three formed stereocenters (see SI).

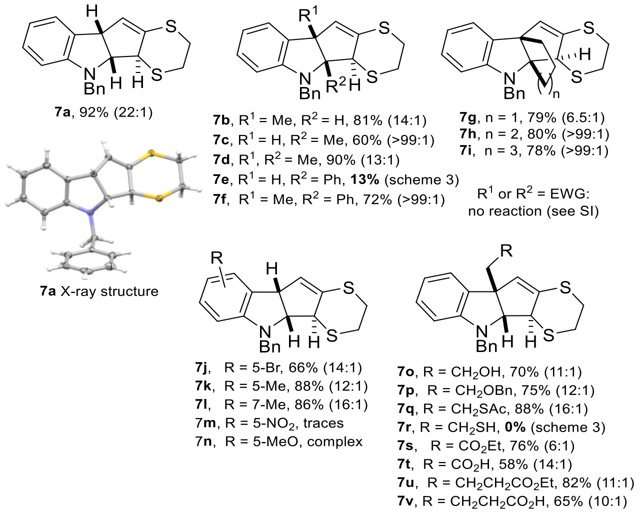


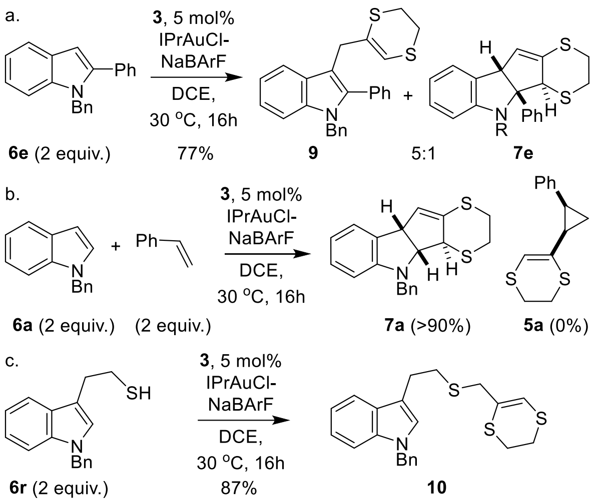
Figure 1. Substrate Scope and Functional Group Tolerance.

To further understand the scope of the reaction, we also investigated the impact of substituents on more remote carbons of the aromatic indole nucleus. We observed that the presence of halide or alkyl groups on the indole ring did not significantly affect the yields or stereoselectivity (**7j-l**). Strong electron-withdrawing groups such as a nitro group inhibited the reactivity, as only traces of adduct could be observed (**7m**, also see SI). Surprisingly, an electron donating group on C5 also affected reactivity, as side products were formed here related to competitive electrophilic aromatic substitution happening at various positions (**7n**, see SI).

In order to assess functional group tolerance, we investigated various N-benzylated indoles with a functionalized C3-alkyl side chain (**7o-v**). We observed that free hydroxyl, free carboxylic acid, ether, ester and thioesters were all well tolerated. A free thiol was not tolerated (**7r**, also see Scheme 3). Even though all dearomatized adducts of the type **7** contain a basic amine function (aniline), we found that in general basic amines (such as primary amines) are not tolerated, as these likely deactivate the catalyst.

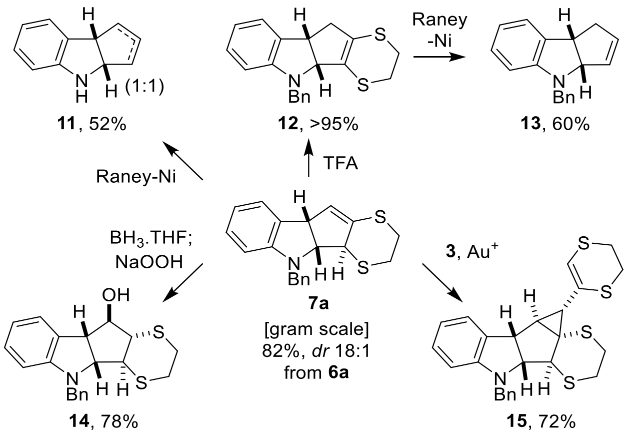
The gold(I)-catalyzed indole dearomatization proceeds with remarkable efficiency given the many possible alternative reaction pathways. We observed a major side reaction in only one of the normally activated indoles, being the C2-arylated indole **6e** (Scheme 3a). Here, the Friedel-Crafts type C3-allylated product **9** was actually formed as the major product (*cf.* **8** in Table 1). This result is indicative of a stepwise cationic mechanism operating in these reactions (*vide infra*), similar to that of allyl cation (3+2) cycloadditions.[6,7] However, in contrast to previously reported allyl cation cycloadditions of indoles,[6a,7] cyclization onto the C2 is the sole pathway in this gold-mediated cycloaddition, even if rearomatization is possible (*viz* **7a**,**c**,**j**,**k**,**l**). In other gold(I)-catalyzed indole dearomatizations, the competing pathway is a (2+1) cyclo-addition (Scheme 2c).[8c] Intrigued by the absence of (2+1) products, we set up a direct competition reaction between styrene and *N*-benzyl indole **6a** (Scheme 3b). This only gave conversion of the indole, with the styrene remaining untouched. As styrene is converted to the vinylcyclopropane **5a** in good yield in about the same reaction time under the same conditions (in the absence of **6a**), it can be concluded that the rate-limiting step is the generation of the reactive cation **4** from the dithiolane **3** and that this intermediate is more readily engaged by indoles than by styrenes, explaining the observed selectivity. Finally, the outcome of the reaction of the free thiol-containing substrate **6r** is also of interest (Scheme 3c). The thiol did not inhibit the gold(I)-catalyst, but fully outcompeted the indole nucleus as a nucleophile, giving almost full conversion to the *S*-allylated product **10**.

Scheme 3: Competing Reactivity Patterns



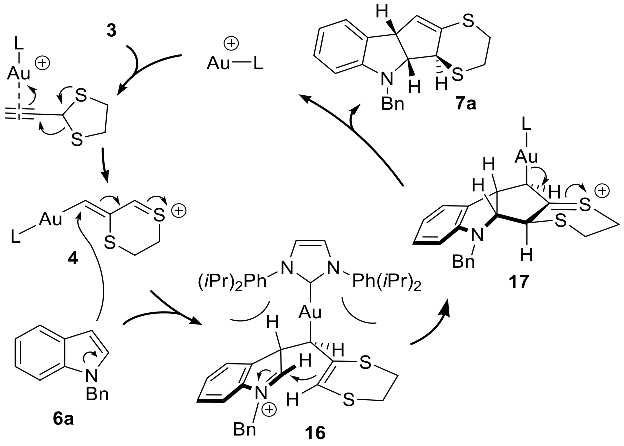
To further demonstrate the synthetic utility of the novel indole dearomatization reaction, we performed a gram-scale synthesis of the dearomatized indole **7a**, giving good yield and selectivity (Scheme 4). The chemoselective hydrodesulfurization of **7a** using Raney-nickel was more troublesome than expected,[8a,10] as it afforded a pair of inseparable cyclopentene-fused indoline isomers (**11**). The issue can be circumvented by treating **7a** with trifluoracetic acid which prompts a swift alkene migration, giving the isomer **12** in quantitative yield. This isomer can then be chemoselectively hydrodesulfurized with Raney-nickel to give the attractive cyclopentene synthetic intermediate **13**. This transformation underscores the advantage of the 1,4-dithiane moiety.[10] Hydroboration of the alkene in **7a** gave a regio- and stereoselective conversion to the fully substituted cyclopentane **14** with control over the relative stereochemistry of all five stereocenters. Finally, when the product **7a** is resubjected to the same conditions of its own synthesis, it undergoes a swift and fully stereoselective vinylcyclopropanation reaction with **3** to give **15** as a single diastereomer. As expected, when equimolar amounts of dithiolane **3** and indole **6a** are used in the synthesis of **7a** (Table 1, entry 10), traces of **15** can be observed as a minor side product.

Scheme 4: Downstream Synthetic Transformations



Based on the observed reactivity trends, a plausible mechanism for the gold(I)-promoted reaction of **3** and *N*-benzyl indoles can be suggested (Scheme 5). The complexation of alkyne **3** to the cationic gold catalyst is followed by a rapid 1,2-sulfur-migration, resulting in the resonance-stabilized cationic intermediate **4**. Subsequently, this cation is engaged by a rapid nucleophilic attack from the indole C3-position, giving the iminium-type intermediate **16**. This intermediate is likely short lived, and immediately cyclizes further to give the thionium intermediate **17**, which will readily undergo deauration to form the alkene in the final product **7a**. In non-gold(I)-coordinated cationic indole cyclization we studied earlier,[7] this iminium intermediate is actually quite long lived, and reluctant to undergo cyclization. The coordination to gold could favor the cyclization step of **16** to **17** by an extreme Thorpe-Ingold type effect brought about by the large steric demand of the covalently bonded catalyst complex. This limitation of rotational freedom around the carbon-carbon bonds and the close catalyst coordination to both bond forming steps can also explain the high stereoselectivity that is observed in these reactions as well as the differences in the series **7g-h-i**.[9h,i] At the same time, the steric bulk of the gold center and its orientation can be expected to prevent the approach of any basic species, so that the C3-proton cannot be easily abstracted from **16**, and a rearomatization pathway is effectively blocked. When the indole nitrogen is not alkylated, as in the reaction with indole itself (Table 1, entry 1), the iminium intermediate of the type **16** may undergo a proto-deauration by this acidic proton, as is observed for the reaction of thiol **6r**, then followed by rearomatization to give **8**. For the sterically encumbered substrate **6e**, the non-coplanar C3-phenyl group impedes the cyclization step (**16→17**), allowing time for deprotonation/protodeauration, which explains the formation of side product **9**.

Scheme 5: Mechanistic Rationale



In conclusion, we have developed an efficient catalytic (3+2) cycloaddition reaction for indoles, characterized by a high level of stereocontrol.[11] It expands the normal scope of the allyl cation-type transformations to reliably include C3-unsubstituted indoles. These aspects can be related to a stepwise, gold(I)-coordinated allyl cation cycloaddition mechanism. The synthetic versatility of the method has been demonstrated by access to a variety of fully functionalized cyclopentanoids with control over all five stereocenters. Further studies of synthetic applications and methodological refinements of this method are ongoing and the results of these will be reported in due course.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Electronic Supplementary Information (ESI) contains experimental procedures, and characterization data for all new compounds (available as PDF)

Accession Codes

CCDC 2340696-2340697 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures
data_request/cif, or by emailing data_request@ccdc.cam.ac. uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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