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Advanced Synthesis & Catalysis

Very Important Publication

Gold-Catalyzed Reactions of 2-Alkynyl-1-indolyl-1,2-diols with Thiols: Stereoselective Synthesis of (*Z*)-α-Indol-3-yl α-(2-Thioalkenyl) Ketones

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Abstract: Propargylic glycols, 2-alkynyl-1-(indol-3-yl)-1,2-diols, react with thiols undergoing a complex but selective gold-catalyzed transformation that gives rise to α-indol-3-yl α-((*Z*)-2-thioalkenyl) ketones. The sequence is triggered by the regioselective thiolation of indolyl diols followed by an attack of the sulfur instead of the indole over the activated alkyne. The final compounds are obtained in remarkably high yields and arise from simple starting materials such as indolyl acyloins, ethynyl magnesium bromide and thiols.

Keywords: gold; homogeneous catalysis; nitrogen heterocycles; rearrangement; sulfur

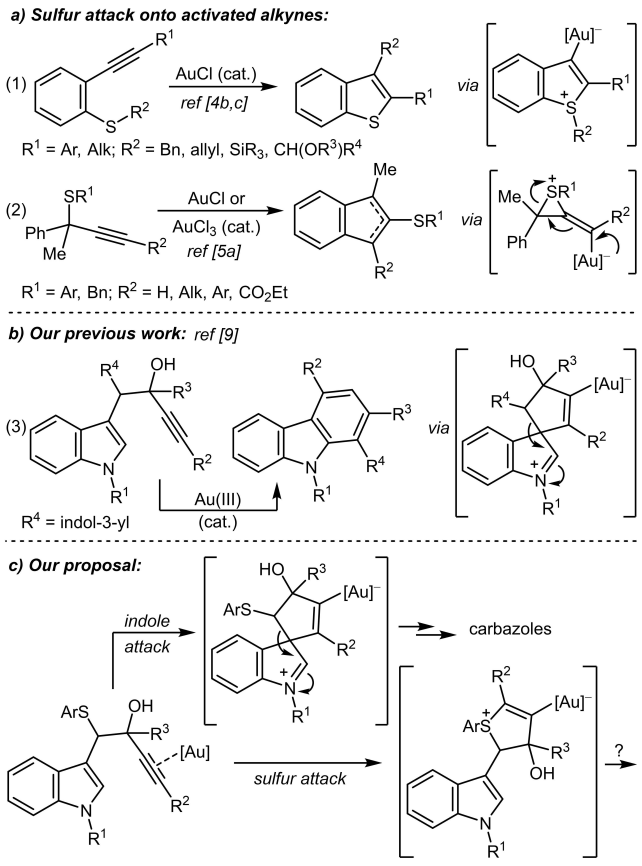
Introduction

Gold-catalyzed reactions are a powerful tool for creating molecular complexity from simple starting materials and a plethora of examples have appeared in the last years.[1] In this field, propargylic alcohols are versatile substrates for their Au-catalyzed transformations that include Meyer-Schuster rearrangement, direct nucleophilic substitution, oxidative rearrangement via α-oxo gold-carbenes, and formal cycloaddition reactions.[1,2] When propargylic alcohols are further functionalized at the α-position with suitable nucleophiles, new possibilities open for evolution after alkyne activation by the gold complex, such as dehydrative cyclizations.[3]

On the other hand, Krause and Nakamura pioneered the Au-catalyzed cycloisomerization reactions involving C–S bond formation (Scheme 1a, eq. 1).[4] When propargylic sulfides and dithioacetals are employed, gold vinylcarbenoids are probably involved as intermediates after 1,2-sulfur migration, similar to propargylic carboxylates, leading to sulfenylated indene derivatives (Scheme 1a, eq. 2).[5] Other 1,2- and 1,3-sulfur shifts have been reported,[6] and more recently the intermolecular cyclopropanation reaction of these sulfur-substituted gold vinylcarbenoids has also been described.[7]

Following our interest in the development of gold-catalyzed reactions involving the functionalization of indoles,[8] we have reported the synthesis of 1-(indol-3-yl)carbazoles from readily available α-bis(indol-3-yl) methyl alkynols through an unexpected and selective 1,2-migration of the indolylmethyl vs. the alkenyl group, which has also been supported by DFT calculations (Scheme 1b, eq. 3).[9]

At this point, we envisaged that related starting substrates, but bearing a thioaryl instead of the second indol-3-yl group, may lead to a different reactivity if the process is triggered by an initial sulfur attack (Scheme 1c).



Scheme 1. Previous work and proposed indole *vs* sulfur attack onto gold-activated alkynols.

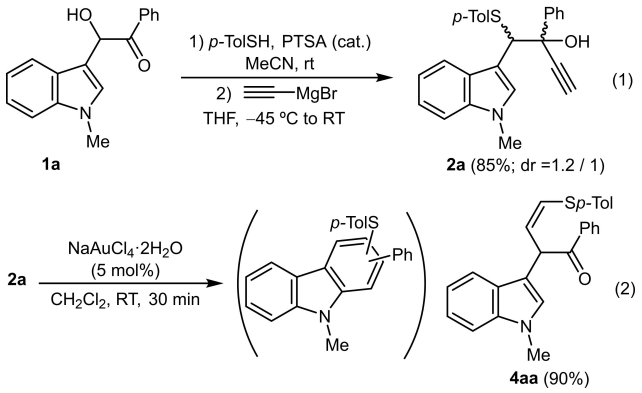
Results and Discussion

To begin with the study, we envisioned that suitable starting material **2 a** could be easily synthesized from readily available indol-3-yl α-acyloins,[10] such as **1 a**, by PTSA-catalyzed thiolation reaction,[11] followed by ethynylation of the carbonyl group (Scheme 2, eq. 1).[12] Surprisingly, the reaction of **2 a** with catalytic amounts of $NaAuCl_4 \cdot 2H_2O$ did not deliver any carbazole as a result of an initial attack of the indole onto the activated alkyne as expected from our previous studies.[9] Instead, the (*Z*)-α-indol-3-yl α-(2-thioalkenyl) ketone **4 aa** was afforded as a single diastereoisomer and in a high yield (Scheme 2, eq. 2).[13] Interestingly, the reaction implies a complex transformation of **2 a** through a formally thioarene 1,4-migration, which involves forming valuable alkenyl thioether functionality,[14] followed by its subsequent selective 1,2-migration in a semipinacol rearrangement.[15]

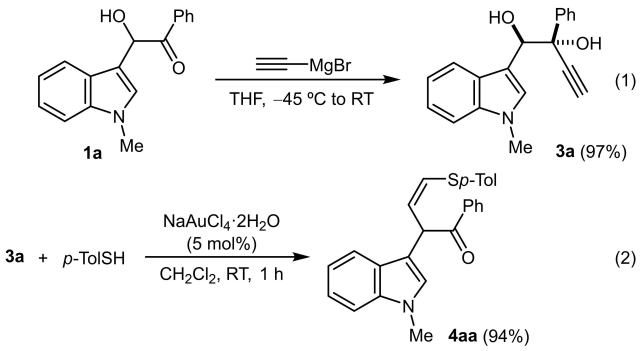
Based on our previous experience in functionalizing indol-3-ylmethanols,[11a] and taking advantage of the ability of $NaAuCl_4 \cdot 2H_2O$ to promote thiolation of alcohols,[16] we hypothesized that a cascade reaction could be designed to obtain **4 aa** directly from indolyl diol **3 a**. This compound, which was synthesized by diastereoselective acetylide addition to ketone **1 a** (Scheme 3, eq. 1),[17] possesses two differently activated hydroxyl groups. The dual role as a σ- and π-Lewis acid (hard/soft) exhibited by the Au(III) catalyst[18] enables the almost quantitative formation of **4 aa** from equimolecular amounts of **3 a** and 4-methylbenzenethiol with a complete stereoselectivity (Scheme 3, eq. 2). Interestingly, neither α-sulfenylated carbonyls, previously reported from gold-catalyzed thiolation of propargylic alcohols,[19] nor α-indolyl ketones, which would come from the pinacol rearrangement of the indolyl diol,[20] were observed.

Further optimization using other catalysts provided **2 a** or **4 aa** in lower yields.[21] Thus, we proceed to evaluate the scope of the reaction employing $NaAuCl_4 \cdot 2H_2O$ (5 mol%) as the dual catalyst and equimolecular amounts of diol **3 a** and the thiol coupling partner. Initially, we focused on the diversity of the thiol (Table 1).

To our delight, the process shows a broad variability regarding the thiol coupling partner. Indolyl diol **3 a** efficiently reacted with a diverse range of arenethiols bearing neutral, electron-withdrawing and electron-donating groups in the different positions of the arene (entries 1–15).[22] Remarkably, in almost all

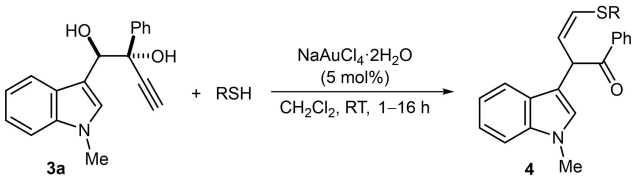


Scheme 2. Preliminary results.



Scheme 3. Synthesis of **4 aa** from indolyl diol **3 a**.

Table 1. Scope of the thiol partner.[a]



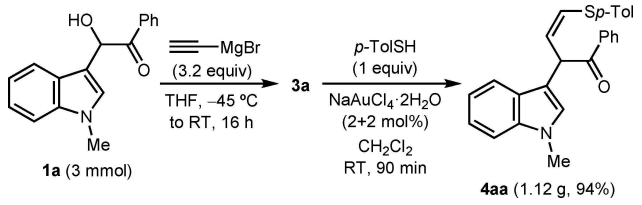
entry	R	product	yield [%][b]
1	*p*-Tol	**4aa**	94[c]
2	Ph	**4ab**	95[c]
3	1-Naphthyl	**4ac**	80
4	2-Naphthyl	**4ad**	96[c]
5	2,4,6-$Me_3C_6H_2$	**4ae**	89
6	4-$MeOC_6H_4$	**4af**	76
7	3,5-$(MeO)_2C_6H_3$	**4ag**	72
8	4-ClC_6H_4	**4ah**	97[c]
9	4-BrC_6H_4	**4ai**	92[c]
10	2-ClC_6H_4	**4aj**	96[c]
11	2-BrC_6H_4	**4ak**	94[c]
12	2-FC_6H_4	**4al**	91
13	4-$(MeCONH)C_6H_4$	**4am**	70
14	4-$NO_2C_6H_4$	**4an**	94[c]
15	2-$NO_2C_6H_4$	**4ao**	93[c]
16	$Me(CH_2)_{11}$	**4ap**	64

[a] *Reaction conditions*: **3a** (1 mmol), RSH (1 mmol), $NaAuCl_4 \cdot 2H_2O$ (5 mol%), CH_2Cl_2 (2 mL), RT, 1–16 h.
[b] Yield of isolated product referred to starting material **3a**.
[c] The final compound did not require purification by column chromatography.

cases, the reaction proceeds with very high yields, and the final product does not require subsequent purification. Only thioarenes bearing electron-donating groups provided **4** in slightly lower yields after column chromatography. Similarly, an alkylthiol, such as dodecanethiol, could be engaged in the reaction affording the 3-alkenyl-2-(indol-3-yl) ketone **4ap** in moderate yield (entry 16). Interestingly, less nucleophilic thiols produced higher yields than their more nucleophilic counterparts, probably due to the interaction of these last ones with the gold catalyst.

Additionally, the method is practical to obtain gram-amounts of the desired α-indol-3-yl α-(2-thioalkenyl) ketones **4**. In this sense, compound **4aa** could be accessed in two steps from acyloin **1a** without requiring column chromatography purification (Scheme 4).[21]

Next, we evaluated the reaction of different indolyl diols **3** with a selection of arenethiols (Table 2). Modifications of the substituents at the propargylic position (R^3) are well tolerated (entries 1–9), and even when a methyl group was placed at this position, high yields of the desired α-indol-3-yl α-(2-thioalkenyl) ketones (**4da**, **db**, **dh**) were achieved (entries 7–9). The reaction is not limited to *N*-protected indoles, as *N*H-indoles have also been demonstrated to be productive,

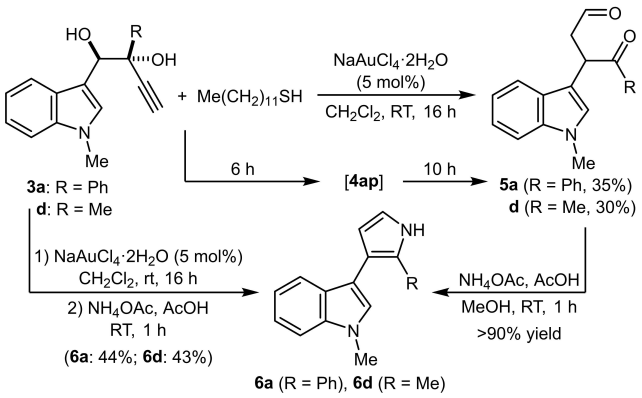


Scheme 4. Gram-scale preparation of **4aa**.

although the reaction proved to be more challenging (entries 10–20, 24–26). Despite lower yields were obtained with *N*H-indoles no side products were identified.

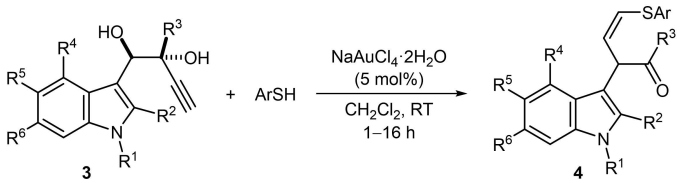
Next, we studied the influence of different substitution patterns in the indole scaffold (entries 13–28). Electronically diverse substituents, such as methoxy or halogens, at positions C-4, C-5 or C-6 of the indole are well tolerated (entries 13–20). Remarkably, C2-methyl-substituted indoles are also useful substrates for this transformation (entries 21–26), although substrates with more sterically demanding substituents like *t*-butyl or phenyl gave rise to a mixture of unidentified compounds or even decomposition (entries 27 and 28). We have also found that starting indolyl diols bearing internal alkynes, with alkyl (*n*-Bu) or aryl (Ph) substituents, instead of terminal ones, afforded a mixture of unidentified compounds or decomposition, respectively.

The high yields obtained, the possibility to scale up, and the simplicity of this method make α-indol-3-yl α-(2-thioalkenyl) ketones **4** valuable building blocks. In this sense, we hypothesized that these substrates could behave as masked versatile 1,4-dicarbonyl compounds. Interestingly, while synthesizing **4ap**, we observed the formation of trace amounts of a by-product derived from the hydrolysis of the thioalkene moiety. In view of this result, we decided to subject diols **3a** and **3d** to the reaction with dodecanethiol and the gold salt catalyst under prolonged reaction times (Scheme 5).



Scheme 5. Synthesis of 3-(pyrrol-3-yl)indoles **6**.

Table 2. Scope of indolyl diols.[a]



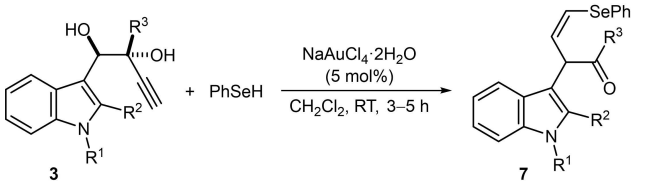
entry	3	R^1	R^2	R^3	R^4	R^5	R^6	Ar	4	yield [%][b]
1	**3b**	Me	H	4-FC_6H_4	H	H	H	*p*-Tol	**4ba**	95
2	**3b**	Me	H	4-FC_6H_4	H	H	H	Ph	**4bb**	92
3	**3b**	Me	H	4-FC_6H_4	H	H	H	4-ClC_6H_4	**4bh**	87
4	**3c**	Me	H	4-$MeOC_6H_4$	H	H	H	*p*-Tol	**4ca**	94
5	**3c**	Me	H	4-$MeOC_6H_4$	H	H	H	Ph	**4cb**	93
6	**3c**	Me	H	4-$MeOC_6H_4$	H	H	H	4-ClC_6H_4	**4ch**	92
7	**3d**	Me	H	Me	H	H	H	*p*-Tol	**4da**	89
8	**3d**	Me	H	Me	H	H	H	Ph	**4db**	90
9	**3d**	Me	H	Me	H	H	H	4-ClC_6H_4	**4dh**	93
10	**3e**	H	H	Ph	H	H	H	*p*-Tol	**4ea**	70
11	**3e**	H	H	Ph	H	H	H	Ph	**4eb**	75
12	**3e**	H	H	Ph	H	H	H	4-ClC_6H_4	**4eh**	74
13	**3f**	H	H	Ph	Cl	H	H	*p*-Tol	**4fa**	72
14	**3g**	H	H	Ph	H	Br	H	*p*-Tol	**4ga**	81
15	**3g**	H	H	Ph	H	Br	H	Ph	**4gb**	78
16	**3g**	H	H	Ph	H	Br	H	4-ClC_6H_4	**4gh**	76
17	**3h**	H	H	Ph	H	MeO	H	*p*-Tol	**4ha**	67
18	**3h**	H	H	Ph	H	MeO	H	Ph	**4hb**	73
19	**3h**	H	H	Ph	H	MeO	H	4-ClC_6H_4	**4hh**	60
20	**3i**	H	H	Ph	H	H	Cl	*p*-Tol	**4ia**	78
21	**3j**	Me	Me	Ph	H	H	H	*p*-Tol	**4ja**	91
22	**3j**	Me	Me	Ph	H	H	H	Ph	**4jb**	92
23	**3j**	Me	Me	Ph	H	H	H	4-ClC_6H_4	**4jh**	94
24	**3k**	H	Me	Ph	H	H	H	*p*-Tol	**4ka**	68
25	**3k**	H	Me	Ph	H	H	H	Ph	**4kb**	66
26	**3k**	H	Me	Ph	H	H	H	4-ClC_6H_4	**4kh**	71
27	**3l**	H	Ph	Ph	H	H	H	*p*-Tol	–[c]	–
28	**3m**	H	*t*-Bu	Ph	H	H	H	*p*-Tol	–[d]	–

[a] *Reaction conditions*: **3** (1 mmol), ArSH (1 mmol) $NaAuCl_4 \cdot 2H_2O$ (5 mol%), CH_2Cl_2 (2 mL), RT, 1–16 h.
[b] Yield of isolated product referred to starting material **3**.
[c] Only decomposition products were observed.
[d] A mixture of unidentified compounds was obtained.

After 16 h, we isolated the 1,4-dicarbonyl compounds **5a** and **5d** in 35% and 30% yield, respectively. With these 1,4-dicarbonyl compounds in hand, we performed the Paal-Knorr pyrrole synthesis,[23] affording 3-(1*H*-pyrrol-3-yl)-indoles **6a** and **6d**. Further studies allowed us to implement a one-pot procedure to synthesize these pyrrolyl indoles **6a**,**d** directly from indolyl diols **3** in two sequential reaction steps achieving higher overall yields of these interesting 3-heteroarylindole derivatives **6** (Scheme 5).

Next, we envisioned that other organochalcogenides could be easily obtained by replacing the thiol coupling partner. Organoselenium derivatives are relevant compounds with notable applications in pharmaceuticals and material science.[24] This has attracted a growing interest in the synthesis of a diverse variety of organoselenium compounds. In this sense, replacing the thiol with a selenol will provide access to α-indol-3-yl α-(2-selenoalkenyl) ketones. Thus, the reaction of a variety of indolyl diols **3** with equimolecular amounts of benzeneselenol proceeds smoothly, giving rise to the related alkenylselenides **7** in high yields (Table 3). Remarkably, the transformation is similar to the previous case, being entirely stereoselective, and only the *Z* isomers are observed. Additionally, the nature of the diol **3** has a minimal effect in this case, and (*Z*) α-indol-3-yl α-(2-selenoalkenyl) ketones **7** can be obtained almost quantitatively, even when unprotected *NH*-indoles are used (entry 5).

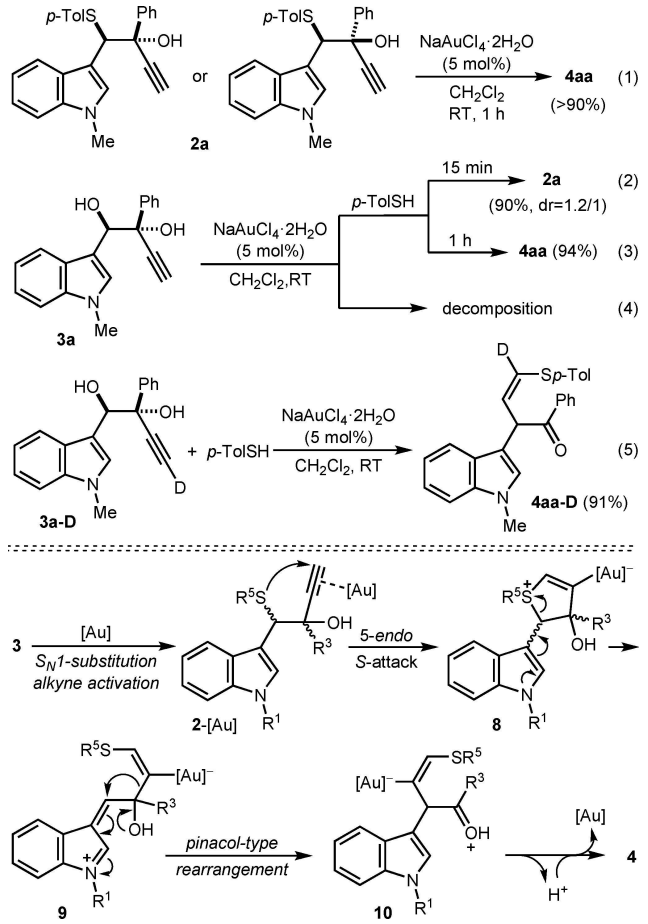
Table 3. Synthesis of α-indol-3-yl α-(2-phenylselenoalkenyl) ketones **7**.[a]



entry	**3**	R^1	R^2	R^3	product	yield [%][b]
1	**3a**	Me	H	Ph	**7a**	87
2	**3b**	Me	H	4-FC_6H_4	**7b**	84
3	**3d**	Me	H	Me	**7d**	88
4	**3j**	Me	Me	Ph	**7j**	83
5	**3k**	H	Me	Ph	**7k**	85

[a] *Reaction conditions*: **3** (1 mmol), PhSeH (1 mmol) $NaAuCl_4 \cdot 2H_2O$ (5 mol%), CH_2Cl_2 (2 mL), RT, 3–5 h.
[b] Yield of isolated product referred to starting material **3**.

We carried out some control experiments to gain further insight into the plausible mechanism (Scheme 6). As noted in the preliminary studies (Scheme 2), compound **2a** reacts with the Au(III) catalyst affording α-indol-3-yl α-(2-thioalkenyl) ketone **4aa**. First, we checked that the reactivity of each diastereoisomer of **2a** was almost the same as similar yields of **4aa** were obtained in both cases (Scheme 6, eq. 1). Additionally, further studies demonstrated that diol **3a** is fully consumed, affording almost quantitatively **2a**, after reaction with 4-methylbenzenethiol and catalytic amounts of $NaAuCl_4 \cdot 2H_2O$ in only 15 minutes (Scheme 6, eq. 2). Exposure to longer reaction times (1 h) only gives rise to α-indol-3-yl α-(2-thioalkenyl) ketone **4aa** (Scheme 6, eq. 3). These experiments support that compound **2a** is a likely intermediate in the cascade reaction. In the absence of the external nucleophile we only observed decomposition (Scheme 6, eq. 4), even under Brønsted acid-catalysis, though Antilla et al. had reported a chiral Brønsted acid-catalyzed pinacol rearrangement of related indolyl diols.[20] To gain further evidence about the migration and the diastereoselectivity observed in the obtained alkenylthioether, we decided to perform deuterium-labeled experiments. Compound **3a-D**, bearing a deuterated alkyne moiety, was synthesized[21] and subjected to standard reaction conditions. Interestingly, only compound **4aa-D**, in which the deuterium atom label and thioarene moiety are placed at the same carbon atom, was afforded (Scheme 6, eq. 5). This result suggests that, after alkyne activation, a *S*-atom attack occurs at the alkyne terminal position.



Scheme 6. Control experiments and mechanistic proposal.

Considering these findings, a plausible mechanism is depicted in Scheme 6. Initially, gold activation of the hydroxy group in diol **3** enables S_N1-substitution reaction, giving rise to intermediate **2**. Then, due to its carbophilic nature, the gold salt triggers alkyne activation delivering intermediate **2**-[Au]. This species evolves through a nucleophilic 5-*endo* attack of the sulfur atom, affording a sulfonium organogold intermediate **8**. The higher stabilization of positive charges provided by the indole nucleus allows the migration of the thio group after C–S bond cleavage, affording indolyl iminium intermediate **9**.[25] Subsequent pinacol-type rearrangement takes place via a selective [1,2]-alkenyl migration, with retention of the alkene configuration. Finally, the obtained intermediate **10** evolves through protodeauration, releasing α-indol-3-yl α-(2-thioalkenyl) ketone **4** and regenerating the active gold catalyst.

Conclusion

In summary, we have developed a cascade reaction to the completely stereoselective synthesis of (*Z*)-α-indol-3-yl α-(2-thioalkenyl) ketones from 2-alkynyl-1-(indol-3-yl)-1,2-diols and thiols. The gold(III) dual behavior, as a σ- and π-Lewis acid, plays a crucial role in this transformation, activating both the alcohol and the alkyne, enabling the S_N1 thiolation reaction and the subsequent 5-*endo* cyclization forming a sulfonium

intermediate. The presence of the indole scaffold enables an unusual 1,4-migration of the thioorganolyl group and the subsequent pinacol-type rearrangement involving selective 1,2-migration of the alkenyl thioether moiety. Additionally, this strategy was successfully extended to the synthesis of related organoselenium derivatives. The method was proved to be practical, scalable and straightforward, which would allow the use of α-indol-3-yl α-(2-thioalkenyl) ketones as valuable building blocks and masked versatile 1,4-dicarbonyl compounds.

Experimental Section

General Procedure for the Synthesis of α-Indol-3-yl α-(2-Thioalkenyl) Ketones 4 (Tables 1 and 2)

A round-bottom flask was charged with indolyl diol **3** (1 mmol), CH_2Cl_2 (2 mL) and the corresponding thiol (1 mmol) at RT. The mixture was allowed to stir for 5 min and $NaAuCl_4 \cdot 2H_2O$ (20 mg, 0.05 mmol, 5 mol%) was added to the solution. The resulting reaction mixture was allowed to stir at RT until full depletion of **3** was determined by TLC (1–16 h). Then, the reaction was quenched by addition of few drops of NH_4Cl (saturated aqueous solution). The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated at reduced pressure affording pure enough ketones **4**. When further purification is required, ketones were purified on silica gel flash column chromatographic using a mixture of *n*-hexane and ethyl acetate as eluent. Ketones **4** were stored 0 °C to avoid alkene isomerization. Characterization data and NMR spectra are presented in the Supporting Information.

Acknowledgements

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