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Gold-Catalyzed Tandem Oxidation-Migration of 3-Propargyl Indoles: Synthesis of α-Indol-3-yl α,β-Unsaturated Carbonyls

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Dedicated to Professor Joan Bosch on the occasion of his 75th birthday

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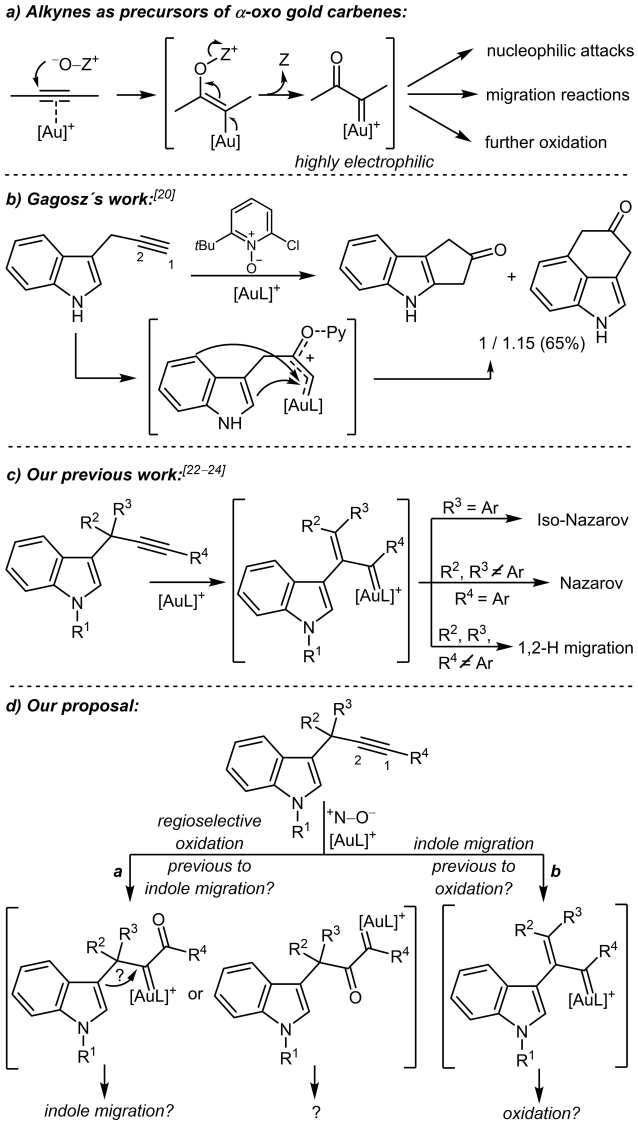
Abstract: α-Indol-3-yl α,β-unsaturated carbonyl compounds are synthesized from 3-propargyl indoles, obtained by direct propargylation of indoles, via a gold-catalyzed tandem oxidation-1,2-indole migration reaction in the presence of pyridine *N*-oxides. Fine-tuning of the catalyst and oxidant enables the reaction of 3-propargyl indoles bearing different substituents. The order of oxidation and indole migration is determined by the terminal or internal nature of the alkyne moiety. In addition, the process can be coupled with additional reactions, allowing an increase in molecular complexity or the design of more elaborated tandem reactions. In this sense, indole derivatives bearing an alkenyl substituent at the alkyne position evolve through a gold-catalyzed tandem oxidation-1,2-indole migration-Nazarov cyclization producing α-indolyl cyclopentenones.

Keywords: carbonyls; gold; homogeneous catalysis; indoles; oxidation

Introduction

Since Zhang and co-workers reported the first generation of highly electrophilic α-carbonyl carbenes via gold-catalyzed intermolecular oxidation of alkynes by *N*-oxides in 2010,[1] a wide range of useful synthetic transformations based on this strategy have been reported in the literature.[2] Significant advances in this field have been achieved using alternative oxidants such as sulfoxides,[3] nitrones,[4] nitro-containing compounds,[5] isoxazoles and anthranils,[6] epoxides,[7]-… The oxidation of a gold-activated alkyne with heteroarene *N*-oxides to produce an α-oxo gold carbene proceeds by the initial formation of an *N*-alkenoxypyridinium intermediate that undergoes heterolytic fragmentation of the weak N–O bond collapsing to the carbene with the release of the deoxygenated heteroarenes. These α-oxo carbenes, which are generated avoiding the use of hazardous α-diazo ketones, can participate in subsequent transformations, such as reactions with internal or external nucleophiles as well as hydride and alkyl migrations or further oxidations to 1,2-diketones (Scheme 1a).

The *N*-oxide typically exhibits regioselectively attack at the alkynyl carbon that better accommodates the developing positive charge upon gold coordination.[8] For terminal alkynes, the oxidation always occurs on the internal carbon.[9] However, in the case of internal non-symmetric alkynes, achieving regioselectivity is a challenging issue that has been solved by intramolecular processes[10] or by using substrates bearing polarized alkynes, such as ynones,[11]



Scheme 1. Previous work and proposed gold-catalyzed oxidation of 3-propargyl indoles.

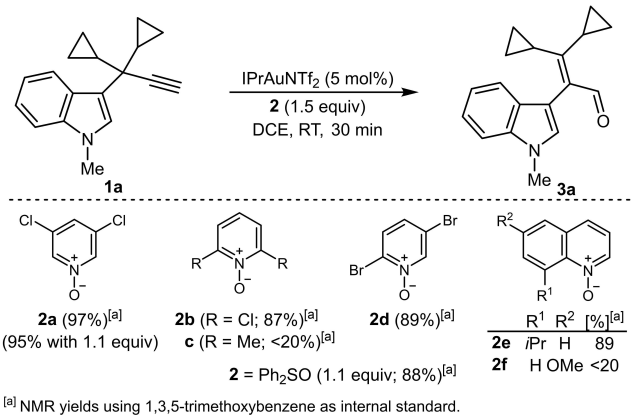
haloalkynes,[12] alkynyl sulfones, sulfoxides, boronates and phosphates,[13] ynamides,[14] ynol (thio)ethers,[15] arylalkynes and enynes,[16] or even propargylic alcohols and ethers.[17] Nevertheless, the oxidation of non-electronically-biased internal alkynes typically results in a mixture of two regioisomers, whose ratio can be controlled by varying steric hindrance at the two ends of the triple bond and, in some cases, by a careful optimization of the catalyst and oxidant. In most cases, the preferred oxygen delivery takes place at the less hindered position of the alkyne.[18]

Few examples of using indoles as nucleophiles to trap α-oxo gold carbene intermediates have been reported.[19] Gagosz et al described the oxidative cyclization of terminal propynyl arenes to indan-2-ones in which the intermediate carbene was trapped intramolecularly by a (hetero)arene ring. These authors described a single example using a simple 3-propargyl indole that yielded a mixture of two tricyclic ketones (Scheme 1b).[20]

In the field of gold-catalyzed reactions, we have studied the reactivity of 3-propargyl indoles,[21] describing the first example of a 1,2-migration of the indole nucleus onto a gold-activated alkyne.[22] This shift provides an α,β-unsaturated gold-carbene intermediate, which evolves via different pathways, mainly depending on the nature of the substituents at the propargylic and terminal positions of the alkyne (Scheme 1c).[23] When one of the propargylic groups is (hetero)aromatic, the indole migration is followed by an aura-iso-Nazarov cyclization, whereas an alternative Nazarov cyclization is observed when the aromatic group is located at the terminal position but not at the propargylic ones.[24] Moreover, when no aromatic substituents (R^2–R^4) are present at these positions, an alternative 1,2-hydride migration occurs leading to 2-indol-3-yl-1,3-butadiene derivatives. At this point, we envisaged that the gold-catalyzed reaction of these 3-propargyl indoles in the presence of an external oxidant, such as an *N*-oxide, could follow two different pathways (Scheme 1d). The outcome depends on whether the oxidation occurs before any other transformation (path a) or if the 1,2-indole shift, as previously described by our group in the absence of additives, takes place first (path b). In the former case, the regioselectivity of the *N*-oxide attack on the gold-activated alkyne is not obvious and two different α-oxo gold carbenes could be generated. If the 1,2-indole migration preferentially occurs (path b), an α,β-unsaturated gold carbene would be obtained. The evolution of these likely intermediates is not evident at this stage.

Results and Discussion

Initially, in search of more predictable regioselectivity in the oxidation, we chose as a model substrate the terminal propargyl indole **1a**. This substrate was easily synthesized from *N*-methylindole and the corresponding tertiary alkynol under Brønsted acid-catalysis according to our previously reported methodology.[21] The reaction of **1a** with different gold catalysts in the presence of 3,5-dichloropyridine *N*-oxide (**2a**) as an external oxidant selectively gave the α-indolylenal **3a** in all the cases,[25] being the highest yield obtained with $IPrAuNTf_2$ [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] (Scheme 2). Various *N*-oxides **2b–f** were tested with this catalyst, but no improvements were observed for any of them compared to **2a**.[26] In addition, we also checked that the amount of the oxidant could be reduced up to 1.1 equiv. without significant loss of efficiency. The structure of **3a** suggested that indole migration had



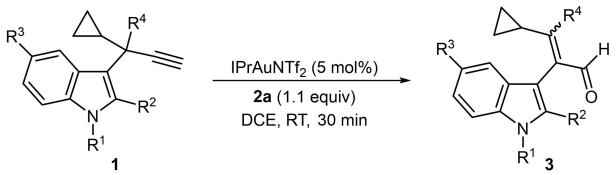
Scheme 2. Au(I)-catalyzed oxidation of terminal 3-propargyl indole **1 a**.

occurred prior to oxidation and so, it appeared that the *N*-oxide had attacked the gold carbene intermediate rather than the alkyne (see Scheme 1d). If the activated alkyne had been attacked first by the *N*-oxide, the regioselectivity would have been the opposite as the one observed. Since it is known that Ph_2SO is able to formally oxidize gold carbenes,[27] we have verified that the same result is obtained as with the other oxidants, supporting our proposal that the migration of the indole takes place first, followed by the oxidation of the carbene intermediate (Scheme 2).

In addition, it is worth noting that while β-indolyl-α,β-unsaturated carbonyls are readily available via C3-alkenylation of indoles with 1,3-dicarbonyls,[28] α-indolyl-α,β-unsaturated carbonyls, such as **3 a**, are more challenging indole derivatives, with few specific examples reported for their preparation.[29]

To assess the scope of the process, a representative set of 3-propargyl indoles **1**, bearing a tertiary center at the propargylic position and a terminal alkyne, were evaluated under the optimized reaction conditions (Table 1). Using substrates with two cyclopropyl groups at the propargylic position and different substituents at the nitrogen atom and at C2 and C5 positions of the indole ring, gave high yields of the corresponding α-indolyl functionalized α,β-unsaturated aldehydes **3** (entries 1–8). Replacing one of the cyclopropyl groups with another alkyl substituent, such as methyl (entries 9–12) or butyl (entry 13), has no significant effect on the efficiency of the reaction, although in these cases the corresponding α,β-unsaturated aldehydes **3** were obtained as ca. 1/1 mixtures of *E*/*Z* diastereoisomers. In addition, the reaction could be scaled up to 3 mmoles of **1 a**, giving 84% yield of **3 a** (670 mg), also reducing the amount of catalyst (entry 1).

Table 1. Synthesis of α-(indol-3-yl)-α,β-unsaturated aldehydes **3**.[a]

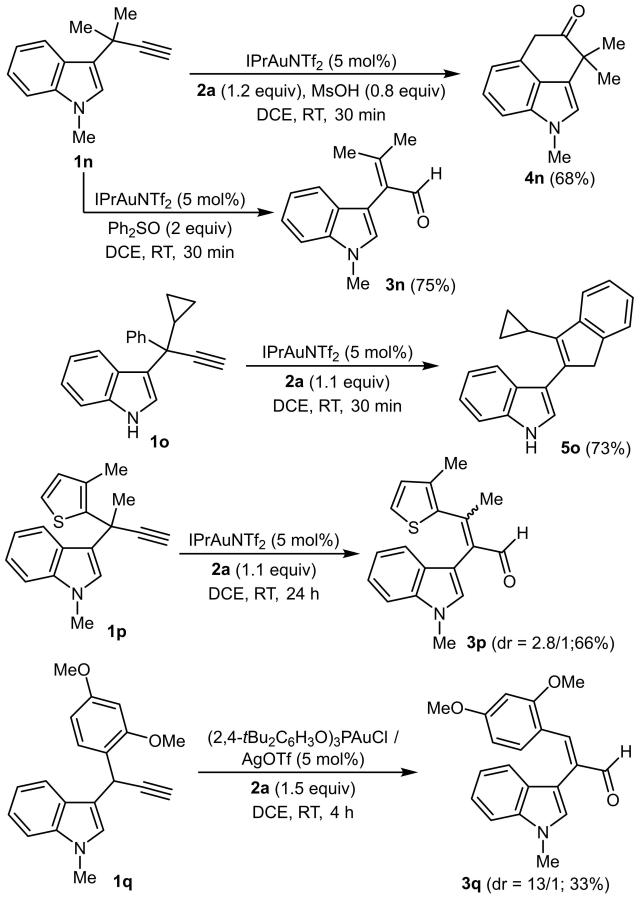


entry	**1**	R^1	R^2	R^3	R^4	**3**	yield [%][b]
1	**1 a**	Me	H	H	cC_3H_5	**3 a**	90 (84)[c]
2	**1 b**	Me	Me	H	cC_3H_5	**3 b**	88
3	**1 c**	Me	Ph	H	cC_3H_5	**3 c**	75
4	**1 d**	H	H	H	cC_3H_5	**3 d**	92
5	**1 e**	H	Me	H	cC_3H_5	**3 e**	89
6	**1 f**	H	Ph	H	cC_3H_5	**3 f**	81
7[d]	**1 g**	H	H	Br	cC_3H_5	**3 g**	93
8	**1 h**	H	H	CO_2Me	cC_3H_5	**3 h**	88
9[e]	**1 i**	Me	Me	H	Me	**3 i**	85
10[e]	**1 j**	Me	Ph	H	Me	**3 j**	94
11[e]	**1 k**	H	H	H	Me	**3 k**	70
12[e]	**1 l**	H	Ph	H	Me	**3 l**	90
13[e]	**1 m**	Me	H	H	*n*Bu	**3 m**	74

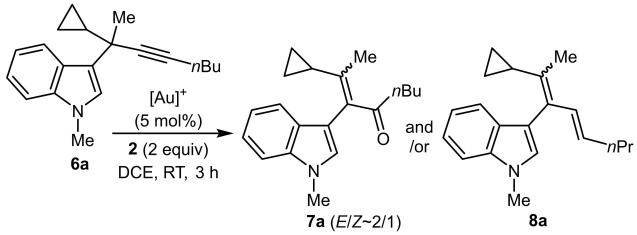
[a] *Reaction conditions*: **1** (0.5 mmol), $IPrAuNTf_2$ (5 mol%), **2 a** (0.55 mmol), DCE (2.5 mL), RT, 30 min, unless otherwise established.
[b] Yield of isolated product referred to the corresponding 3-propargyl indole **1**.
[c] Isolated yield using **1 a** (3 mmol) and $IPrAuNTf_2$ (2 mol%).
[d] Reaction time = 2 h.
[e] Obtained as a ca 1/1 mixtures of *E*/*Z* diastereoisomers, except **3 i** that was obtained as a 1/4 *E*/*Z* mixture.

However, a different result was observed with indole **1n**, which possesses two methyl groups at the propargylic position. Under standard conditions, which required the addition of a Brønsted acid for completion, the tricyclic ketone **4n** was obtained instead of the expected aldehyde **3n** (Scheme 3). This reactivity was the same as that reported by Gagosz et al for the parent 3-propargyl indole (see Scheme 1b).[20] Interestingly, by changing the external oxidant to Ph_2SO, **3n** was selectively formed and isolated in good yield. Not unexpectedly, when an aromatic group is located at the propargylic position, such as in substrate **1o**, the reaction yielded 3-indenyl indole **5o**, indicating that no oxidation has occurred and that the initial 1,2-indole migration was followed by an aura-iso-Nazarov cyclization (Scheme 3, see also Scheme 1c).[22,23] If this pathway is avoided, either due to the absence of aromatic substituents at the propargylic position (Table 1) or because the aromatic group lacks free *ortho*-positions, as with the starting indole **1p**, the tandem migration-oxidation is again the preferred pathway. This leads to the expected α,β-unsaturated aldehyde **3p** in moderate yield (Scheme 3). Finally, when the secondary 3-propargyl indole **1q** was subjected to standard conditions, low conversion and significant decomposition were observed. After some reoptimization, the desired α-indolylenal β-monosubstituted **3q** was obtained, albeit with low yield (Scheme 3). This lower efficiency can be explained by considering that the initial indole migration is more favored for tertiary substrates than for secondary ones due to the Thorpe-Ingold effect.[30]

At this point, we decided to investigate the behavior of 3-propargyl indoles bearing internal alkynes. Initially, we focused on tertiary substrates, and indole **6a** was chosen as a model, taking into account that the presence of aromatic groups at the propargylic or terminal position should be avoided to prevent the competitive Nazarov and iso-Nazarov processes. Considering the previous results, 3,5-dichloropyridine *N*-oxide (**2a**) was used as an external oxidant and different gold(I) complexes were tested, resulting in different mixtures of α-indolyl α,β-unsaturated ketone **7a** and 2-indolyl-1,3-diene derivative **8a** (Scheme 4). In addition to the oxidation product **7a**, a competitive pathway leading to the diene **8a**, resulting from an indole migration followed by a 1,2-hydride migration,[23] also occurred. The highest yields and selectivities were obtained with the catalytic systems $IPrAuNTf_2$ and $[2,4\text{-}(t\text{Bu})_2C_6H_3O]_3PAuCl/AgNTf_2$, without significant silver effect and with no improvement by varying the *N*-oxide (Scheme 4).[25] In particular, the use of Ph_2SO as the oxidant led exclusively to the diene **8a**, supporting that oxidation of a carbene intermediate is unlikely to be involved in this process. In addition, in this case the use of 2 equiv. of **2a** improved the yield and selectivity, especially for the phosphite gold catalyst, probably due to the fact that an excess of the oxidant would favour the attack of the *N*-oxide on the alkyne and thus disfavour the initial indole migration that would lead to **8a**. Therefore, both catalytic systems, $IPrAuNTf_2$ and $[2,4\text{-}(t\text{Bu})_2C_6H_3O]_3PAuCl/AgNTf_2$, were selected together with 2 equiv. of **2a**.



Scheme 3. Limitations and particular cases for the tandem indole migration-oxidation of terminal 3-propargyl indoles.



[Au]+	2	Ratio 7a/8a	7a yield [%][a]
$IPrAuNTf_2$	**2a**	18/1	79
$(ArO)_3PAuCl/AgNTf_2$[b]	**2a**	20/1	86
$IPrAuNTf_2$	Ph_2SO	<1/20	–

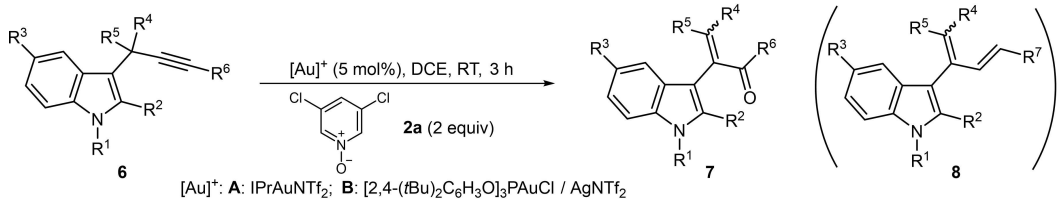
[a] NMR yield using 1,3,5-trimethoxybenzene as internal standard. [b] Ar = 2,4-$(t\text{Bu})_2C_6H_3$.

Scheme 4. Au(I)-catalyzed oxidation of internal 3-propargyl indole **6a**.

We then examined the substrate scope of various tertiary 3-propargyl indoles having internal alkynes **6** (Table 2). For the *n*butyl-substituted alkynes **6a–c**, increasing the steric hindrance at the propargylic position led to an increased ratio of the undesired dienes **8** (entries 1–3), ranging from almost complete selectivity to **7a** (for R^5 = Me) to high selectivity to **8**c (for R^5 = *i*Pr). Replacing the primary alkyl group as a substituent of the alkyne with a secondary one (cC_6H_{11}) led to the complete suppression of the oxidation pathway, resulting in the selective formation of the corresponding diene **8d** (entry 4). These results seem to indicate that the presence of two bulky groups at either end of the triple bond prevents the intermolecular attack of the *N*-oxide. We reasoned that replacing the butyl group as R^6 substituent with a methyl or cyclopropyl one would minimize diene formation, and thus favour the desired formation of ketones **7**. Indeed, propargyl indoles **6e–g** gave excellent selectivity and yields of the corresponding α,β-unsaturated ketones **7e–g** (entries 5–7), even when **6g**, sterically crowded at the propargylic position, was used (entries 6 and 7 vs 2). Similar tendencies were observed for 1,2-dimethyl-3-propargyl indoles **6h–k** (entries 8–11), for *N*H-3-propargyl indoles **6l–m** (entries 12 and 13), for 2-phenyl-3-propargyl indoles **6n–o** (entries 14 and 15), and for 5-functionalized indoles **6p–q** (entries 16 and 17). Thus, an appropriate selection of the propargylic and alkyne substituents, enabled the synthesis of a variety of α-indolylenones **7** in high yields.[31]

We then turned our attention to internal 3-propargyl indoles **9**, which feature a secondary center at the propargylic position. Indole **9a** was selected as the model substrate, and we evaluated its reaction with 3,5-dichloropyridine *N*-oxide (**2a**) using the two optimized gold catalytic systems, which yield superior outcomes for tertiary substrates (Scheme 5). In this case, in addition to the α-indolyl-α,β-unsaturated ketone **10a**, which has an analogous structure to the ketones **7** derived from tertiary propargylic indoles **6**, the β-indolyl-α,β-unsaturated ketone **11a** was also obtained as a byproduct. Its formation could be understood by considering a competitive 1,2-aryl migration, instead of the 1,2-indole migration, after an initial regioselective oxidation at the C-1 position (Scheme 5). After brief experimentation, better selectivity and yield were obtained by using the phosphite gold complex in the presence of $AgSbF_6$.

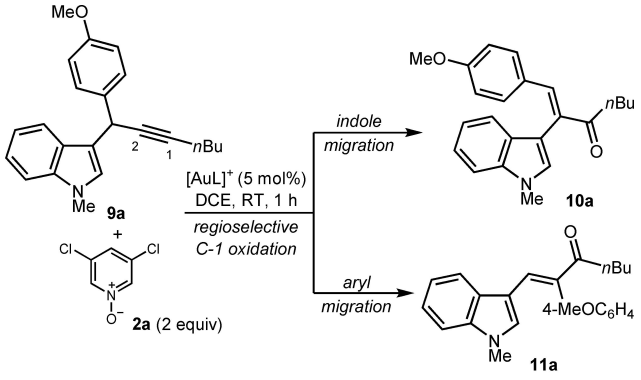
Table 2. Synthesis of α-(indol-3-yl)-α,β-unsaturated β,β-disubstituted ketones **7**: scope and limitations.[a]



[Au]$^+$: **A**: IPrAuNTf$_2$; **B**: [2,4-(*t*Bu)$_2$C$_6$H$_3$O]$_3$PAuCl / AgNTf$_2$

entry	**6**	R^1	R^2	R^3	R^4	R^5	R^6	[Au]$^+$	ratio **7**/**8**[b]	product(s)	ratio *E*/*Z*[b]	yield [%][c]
1	**6a**	Me	H	H	cC_3H_5	Me	*n*Bu	**B**	>20/1	**7a**	1/1.3	81
2[d]	**6b**	Me	H	H	cC_3H_5	cC_3H_5	*n*Bu	**B**	1.6/1	**7b**+**8b**	–	56+30
3[d]	**6c**	Me	H	H	cC_3H_5	*i*Pr	*n*Bu	**A**	1/6	**8c**	1.8/1	44
4	**6d**	Me	H	H	cC_3H_5	Me	cC_6H_{11}	**A**	<1/20	**8d**	1/1	73
5	**6e**	Me	H	H	cC_3H_5	Me	cC_3H_5	**A**	>20/1	**7e**	1/1	75
6	**6f**	Me	H	H	cC_3H_5	cC_3H_5	Me	**A**	>20/1	**7f**	–	82
7	**6g**	Me	H	H	cC_3H_5	cC_3H_5	cC_3H_5	**A**	>20/1	**7g**	–	92
8	**6h**	Me	Me	H	cC_3H_5	Me	*n*Bu	**B**	5/1	**7h**+**8h**	1/1 (6/1)	66+11
9	**6i**	Me	Me	H	cC_3H_5	Me	cC_3H_5	**A**	>20/1	**7i**	1/2	76
10	**6j**	Me	Me	H	cC_3H_5	cC_3H_5	cC_3H_5	**A**	>20/1	**7j**	–	92
11	**6k**	Me	Me	H	Me	Me	cC_3H_5	**A**	>20/1	**7k**	–	78
12[e]	**6l**	H	H	H	cC_3H_5	Me	*n*Bu	**A**	>20/1	**7l**	1.6/1	75
13	**6m**	H	H	H	cC_3H_5	Me	$(CH_2)_2Ph$	**A**	16/1	**7m**	1/1.7	89
14	**6n**	H	Ph	H	cC_3H_5	Me	cC_3H_5	**A**	>20/1	**7n**	2.3/1	90
15	**6o**	H	Ph	H	cC_3H_5	cC_3H_5	cC_3H_5	**A**	>20/1	**7o**	–	86
16	**6p**	H	H	Br	cC_3H_5	cC_3H_5	cC_3H_5	**A**	>20/1	**7p**	–	86
17	**6q**	H	H	CO_2Me	cC_3H_5	cC_3H_5	cC_3H_5	**A**	>20/1	**7q**	–	82

[a] *Reaction conditions*: **6** (0.5 mmol), gold catalyst (5 mol%), **2a** (1 mmol) DCE (2.5 mL), RT, 3 h unless otherwise stated.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] Isolated yield referred to the corresponding starting 3-propargyl indole **6**.
[d] Reaction time: 24 h.
[e] Reaction time: 6 h.



[AuL]$^+$	**10a** / **11a** ratio[a]	yield **10a** [%][b]
IPrAuNTf$_2$	2.4 / 1	50
[2,4-(*t*Bu)$_2$C$_6$H$_3$O]$_3$PAuCl / AgNTf$_2$	2.7 / 1	52
[2,4-(*t*Bu)$_2$C$_6$H$_3$O]$_3$PAuCl / AgSbF$_6$	3.5 / 1	65

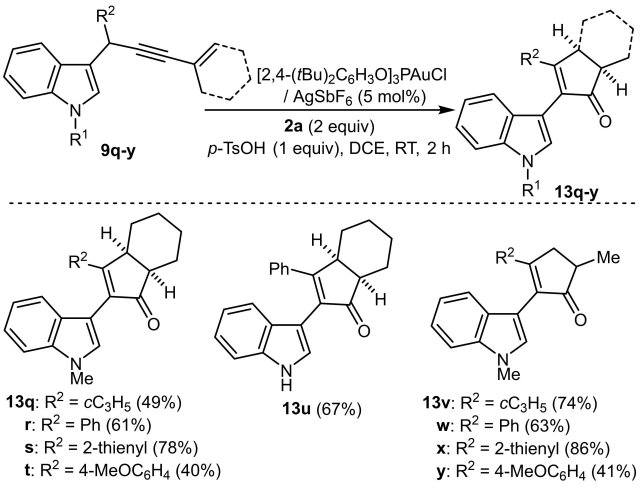
[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. **10a** and **11a** were obtained as almost exclusively *E* isomers. [b] Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.

Scheme 5. Tandem oxidation-migration of secondary 3-propargyl indole **9a**.

The scope of this synthesis of α-indolyl-β-monosubstituted-α,β-unsaturated ketones **10** was explored (Table 3). Moderate to excellent selectivities (**10**/**11** ratios) were obtained for substrates **9a–j** bearing (hetero)aromatic groups at the propargylic position (R^3), allowing the isolation of the corresponding ketones **10** in moderate to good yields (entries 1–10). A higher competitive effect was observed for highly electron-rich aromatic substituents (entries 1 and 2). In addition, for butyl-substituted alkynes, trace amounts of α,β-unsaturated ketones **12** were observed in the crude reaction mixtures, arising from the initial *N*-oxide attack to the more hindered position of the alkyne (C-2) and subsequent 1,2-hydride migration. Not surprisingly, almost complete selectivity was achieved by increasing the nucleophilicity of the indole nucleus, such as with substrates **9f,g**, which favored indole migration over the competitive aryl migration (entries 6 and 7). Moreover, the replacement of the R^3 group from aromatic to cyclopropyl prevents the competitive pathway that produced the ketones **11**, allowing the preparation of α-indolyl ketones **10** with good yields and selectivities (entries 11–15). An exception to this result was observed for the butyl-substituted **9k**, which led to the competitive formation of the ketone **12k**, which could be isolated and characterized (entry 11). Finally, in the case of **9p**, possessing a methyl group at the propargylic position, a lower yield of **10p** was obtained due to competitive double oxidation of the alkyne (entry 16).

Finally, related alkenyl-substituted secondary propargyl indoles **9q–y** were tested. Interestingly, α-indolyl cyclopentenones **13** were obtained in good to high yields using modified reaction conditions involving the use of *p*-TsOH as an additive to favor the formation of only one isomer of the final cyclopentenone. Various alkenyl groups are tolerated as alkyne substituents, and cyclopropyl and (hetero)aromatic groups can be located at the propargylic position R^2 (Scheme 6). The formation of cyclopentenones **13** seems to involve a Nazarov cyclization of likely intermediate di-alkenyl ketones **10q–y** (where R^4 = alkenyl, see Table 3), favored by the complementary action of the gold complex and the Brønsted acid.[32]

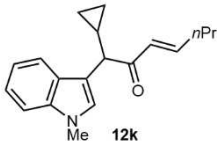
To account for the diversity of results obtained in the gold-catalyzed reactions of 3-propargyl indoles, in the presence of external oxidants, a plausible mechanistic proposal is outlined in Scheme 7. Considering our previous results for these reactions in the absence of oxidants, two different pathways can initially be proposed. In pathway *(a)*, an initial attack of the indole onto the activated alkyne would occur, producing an α,β-unsaturated gold carbene through a 1,2-indole migration. This pathway may be initially favored for tertiary propargyl indoles with relatively bulky groups at the propargylic positions due to the Thorpe-Ingold effect,[30] which postulates that increasing the size of two substituents on a tetrahedral center facilitates reactions between parts of the other two substituents. This seems to be the preferred evolution for the terminal tertiary propargyl indoles **1**, in which the intermediate gold carbene **A** is subsequently oxidized by the *N*-oxide,[32] or even the softer Ph_2SO,[27] leading to the α-indolylenals **3**. The Thorpe-Ingold effect is crucial, as demonstrated by the reaction of the less bulky dimethyl-substituted propargyl indole **1n**, which gave the tricyclic ketone **4n** via an initial regioselective attack of the *N*-oxide on the terminal alkyne. The evolution of **1n** could be switched by employing a softer oxidant such as Ph_2SO, allowing the selective formation and isolation of the aldehyde **3n**. Alterna-



Scheme 6. Tandem oxidation-indole migration-Nazarov cyclization of secondary alkenyl-substituted propargyl indoles **9q–y**. Synthesis of cyclopentenones **13**.

Table 3. Synthesis of α-(indol-3-yl)-α,β-unsaturated β-monosubstituted ketones **10**.[a]

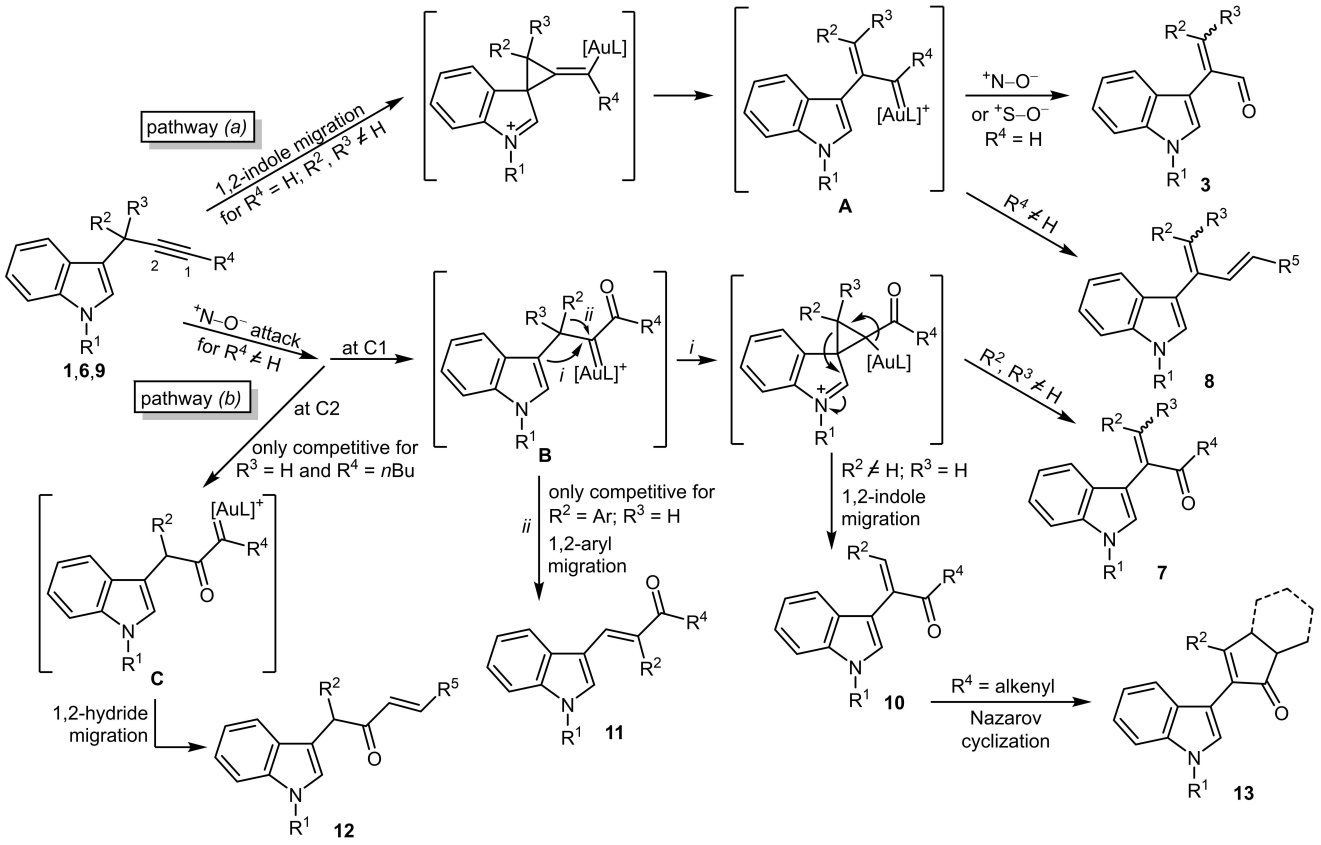
entry	**9**	R^1	R^2	R^3	R^4	**10**	yield [%][b]
1	**9a**	Me	H	4-$MeOC_6H_4$	*n*Bu	**10a**	60[c,d]
2	**9b**	H	H	4-$MeOC_6H_4$	*n*Bu	**10b**	56[c]
3	**9c**	Me	H	2-thienyl	*n*Bu	**10c**	56[d,e]
4	**9d**	Me	H	2-thienyl	*c*C_3H_5	**10d**	72[e]
5	**9e**	Me	H	2-thienyl	Ph	**10e**	68[e]
6	**9f**	Me	Me	2-thienyl	*n*Bu	**10f**	73[f]
7	**9g**	H	Ph	2-thienyl	*n*Bu	**10g**	72[f]
8	**9h**	Me	H	Ph	*n*Bu	**10h**	48[d,e]
9	**9i**	Me	H	Ph	*c*C_3H_5	**10i**	67[e]
10	**9j**	Me	H	Ph	Ph	**10j**	66[e]
11	**9k**	Me	H	*c*C_3H_5	*n*Bu	**10k**	53[d,g]
12	**9l**	Me	H	*c*C_3H_5	*c*C_3H_5	**10l**	71[g]
13	**9m**	Me	Me	*c*C_3H_5	*c*C_3H_5	**10m**	70[g]
14	**9n**	Me	H	*c*C_3H_5	Ph	**10n**	70[g]
15	**9o**	Me	H	*c*C_3H_5	3-Th	**10o**	69[g]
16	**9p**	Me	H	Me	Ph	**10p**	48[h]



12k

[a] *Reaction conditions*: **9** (0.5 mmol), $[Au]^+$ (5 mol%), DCE (2.5 mL), RT, 2 h.
[b] Yield of the isolated product referred to the corresponding propargyl indole **9**.
[c] *rr* **10**/**11** ~ 3.5/1. **11a** was isolated in 18% yield.
[d] Trace to minor amounts of ketones **12** were observed in the crude reaction mixtures. **12k** was isolated in 20% yield.
[e] *rr* **10**/**11** ~ 4.5–7/1.
[f] *rr* **10**/**11** > 12/1.
[g] *rr* **10**/**11** > 20/1.
[h] Carried out with $IPrAuNTf_2$. The *E*/*Z* ratio was 8/1.

tively, if the oxidation of the activated alkyne is the first step, pathway *(b)*, an initial regioselectivity issue arises as the alkyne lacks direct electronic perturbation. Gratifyingly, both steric differences between the substituents of the triple bond, the oxygen atom is preferentially delivered to the less hindered alkyne end, and electronic delocalization in the case of aryl alkynes or enynes, favor the regioselective generation of the α-oxo gold carbene intermediate **B**. In the case of tertiary substrates **6**, the subsequent indole attack to the highly electrophilic carbene is again strongly favored by the Thorpe-Ingold effect, generating a new gold intermediate, which undergoes elimination with concurrent indole migration leading to ketones **7**. Butadienyl indoles **8** have in some cases been obtained from internal tertiary propargyl indoles **6**, when indole migration takes place before the oxidation. For secondary substrates **9**, the attack of the *N*-oxide was initially more challenging due to less difference in steric hindrance at either end of the alkyne. Gratifyingly, the use of alkynes substituted with phenyl, alkenyl or cyclopropyl groups resulted in a regioselective *N*-oxide attack, likely due to electronic delocalization. The corresponding intermediate α-oxo gold carbene **B** (R^3 = H) can again evolve by indole attack and subsequent cyclopropane ring-opening to give the parent α,β-unsaturated ketones **10**. Regioisomeric ketones **11** would arise from an alternative 1,2-(hetero)aryl migration in **B**, a process that it is competitive only for R^2 = (Het)Ar, but not for R^2 = *c*C_3H_5. On the other hand, for alkyl-substituted alkynes **9a**, **c**, **h**, **k**, a competitive *N*-oxide attack on the internal carbon of the triple bond leads to the regioisomeric α-oxo gold carbene **C** that evolves via 1,2-hydride migration to ketones **12**. Finally, for alkenyl-substituted propargylindoles **9q–y**, the delivery of the oxy-



Scheme 7. Mechanistic proposal for the synthesis of aldehydes **3**, ketones **7** and **10**–**13**, and dienes **8**.

gen atom was again regioselective, affording the corresponding carbene species **B** (R^4 = alkenyl). In this case, the related α-indolyl ketones **10**, generated by formal indole migration, are dialkenyl ketones that undergo a subsequent Nazarov cyclization to cyclopentenones **13**.

Conclusion

The different reactivity of 3-propargyl indoles towards *N*-oxides under gold catalysis has been investigated. The choice of substrate, oxidant and catalytic system is crucial in favoring one path over all the possible ways, enabling the formation of α-indol-3-yl α,β-unsaturated carbonyl compounds. The different substituents at the alkyne or the propargylic position could facilitate or hinder the formation of the desired α,β-unsaturated carbonyls, giving rise to alternative byproducts. However, the different reactivity patterns can be modulated by selecting adequate catalysts and oxidants directing the reaction to the formation of α-indol-3-yl α,β-unsaturated ketones, or aldehydes. The side products observed suggest that alternative reaction mechanisms operate for terminal and internal alkynes affording gold carbenes at the different C-atoms of the starting alkyne. Initial 1,2-indole migration followed by oxidation seems to be the predominant reaction pathway for terminal alkynes, whereas by employing internal 3-propargyl indoles, an initial attack of the *N*-oxides followed by the alkyne oxidation and the 1,2-indole migration is expected. In addition, the substituents at the propargylic position also play a decisive role in the reaction requiring different gold catalysts when employing propargyl indoles, bearing a secondary center instead of a tertiary carbon at the propargylic position. Remarkably, the reaction can be applied to the design of more elaborated tandem reactions. In this sense, when alkenyl-substituted alkynes are employed, the initially generated divinyl ketones could be engaged in a subsequent Nazarov cyclization, affording a variety of α-indolyl cyclopentenones, expanding the diverse range of indol-3-yl α,β-unsaturated carbonyl compounds that can be accessed by applying the developed methods.

Experimental Section

General Procedure for the Synthesis of Aldehydes 3 (Table 1)

$IPrAuNTf_2$ (5 mol%, 0.025 mmol, 21.6 mg) was dissolved in DCE (1 mL) and the resulting solution was stirred for 5 min at

RT. A solution of 3,5-dichloropyridine *N*-oxide (**2a**) (0.55 mmol, 90.2 mg) in DCE (0.5 mL) and a solution of the corresponding 3-propargylindole **1** (0.5 mmol) in DCE (1 mL) were subsequently added. The reaction mixture was stirred at RT for 30 min (until complete disappearance of the starting material as determined by GC-MS or TLC) The mixture was filtered through a short pad of silica gel and celite using a mixture of hexane/EtOAc (5/1) and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography using mixtures of hexane/EtOAc as eluents to afford the corresponding aldehydes **3**. Characterization data and NMR spectra are presented in the Supporting Information.

General Procedure for the Synthesis of Ketones 7 (Table 2)

$IPrAuNTf_2$ (5 mol%, 0.025 mmol, 21.6 mg) (Catalyst A) or $[2,4\text{-}(t\text{Bu})_2C_6H_3O]_3PAuNTf_2$ [5 mol%, obtained from mixing $[2,4\text{-}(t\text{Bu})_2C_6H_3O]_3PAuCl$ (0.025 mmol, 22 mg) and $AgNTf_2$ (0.025 mmol, 9.7 mg)] (Catalyst B) was dissolved in DCE (1 mL) and the resulting solution was stirred for 5 min at RT. A solution of 3,5-dichloropyridine *N*-oxide (**2a**) (1 mmol, 164 mg) in DCE (0.5 mL) and a solution of the corresponding 3-propargylindole **6** (0.5 mmol) in DCE (1 mL) were subsequently added. The reaction mixture was stirred at RT for 3 h (until complete disappearance of the starting material as determined by GC-MS or TLC). The mixture was filtered through a short pad of silica gel and celite using a mixture of hexane/EtOAc (5/1), and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography using mixtures of hexane/EtOAc as eluents to afford the corresponding ketones **7** and, in some cases, dienes **8**. Characterization data and NMR spectra are presented in the Supporting Information.

General Procedure for the Synthesis of Cyclopentenones 13 (Scheme 6)

$[2,4\text{-}(t\text{Bu})_2C_6H_3O]_3PAuSbF_6$ [5 mol%, obtained from mixing $[2,4\text{-}(t\text{Bu})_2C_6H_3O]_3PAuCl$ (0.025 mmol, 22 mg) and $AgSbF_6$ (0.025 mmol, 8.6 mg)] was dissolved in DCE (1 mL) and it was stirred for 5 min at RT. A solution of 3,5-dichloropyridine *N*-oxide (**2a**) (1 mmol, 164 mg) in DCE (0.5 mL), a solution of *p*-TsOH (0.5 mmol, 95 mg) in DCE (0.5 mL) and a solution of the corresponding 3-propargylindole **9q–y** (0.5 mmol) in DCE (1 mL) were subsequently added. The reaction mixture was stirred for 2 h (until complete disappearance of the starting material as determined by GC-MS or TLC). The mixture was filtered through a short pad of silica gel and celite using a mixture of hexane/EtOAc (5/1), and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography using mixtures of hexane/EtOAc as eluents to afford the corresponding cyclopentenones **13**. Characterization data and NMR spectra are presented in the Supporting Information.

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[32] In the absence of *p*-TsOH a mixture of two regioisomeric α,β-cyclopentenones **13 q** and **13'q** was obtained. See Supporting Information for further details.

[33] For examples of the oxidation of gold carbenes by *N*-oxides, see: a) W. Yuan, X. Dong, Y. Wei, M. Shi, *Chem. Eur. J.* **2012**, *18*, 10501–10505; b) T. Groβ, P. Metz, *Chem. Eur. J.* **2013**, *19*, 14787–14790.