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3-Sulfonylindoles via Gold- or Silver-Catalyzed Cyclization—1,3-Sulfonyl Migration Sequences under Visible Light Irradiation

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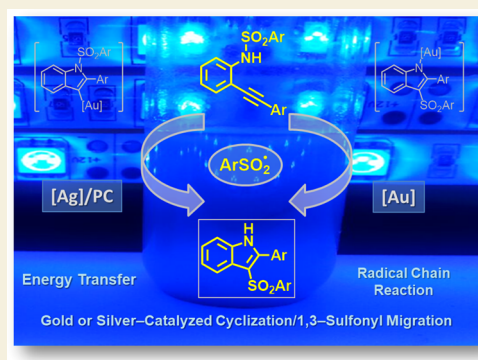


Article Recommendations



Supporting Information

ABSTRACT: A pathway for the synthesis of 3-sulfonylindoles has been devised. Upon blue LED irradiation, in the presence of a gold(I) or a silver(I) salt, *ortho*-alkynyl *N*-sulfonyl precursors readily undergo a 5-*endo-dig* cyclization concomitant with a 1,3-sulfonyl migration. While the gold-catalyzed reaction takes place in photocatalyst-free conditions, an iridium photocatalyst (Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆) is necessary with silver catalysis. Mechanistic studies featuring the generation of a sulfonyl radical support this dichotomy.



KEYWORDS: 1,3-sulfonyl migration, indole, gold(I) catalysis, silver(I) catalysis, photosensitization

1. INTRODUCTION

Indole structures are one of the most abundant skeletons in a wide variety of natural products, and they are also useful targets in drug discovery.^{1–4} Among them, 3-sulfonylindoles have raised continuous interest in the synthetic community, notably because of their biological activities and therapeutic values such as L-737,126 and congeners that are non-nucleoside inhibitors of HIV-1 reverse transcriptase.^{5–8} Other examples include 4-dialkylaminoethyl-3-sulfonyl-1*H*-indoles **I**, which are dual-action norepinephrine reuptake inhibitors (NRIs) and 5-HT_{2A} receptor antagonists,⁹ and 1-aminoalkyl-3-aryl-sulfonyl-1*H*-indoles **II** that act as human 5-HT₆ receptor ligands (Figure 1).^{10,11}

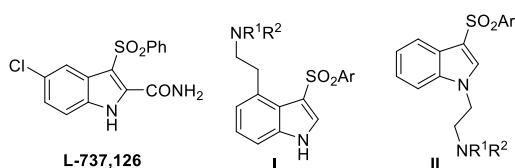


Figure 1. Examples of biologically active 3-sulfonylindole derivatives.

Several approaches have been devised toward these derivatives. While sulfonylation of preformed indole frameworks has been developed,^{12–14} a series of more convergent indole-forming processes have been investigated, notably the cascade annulation of acyclic precursors, to build the indole core and install the sulfonyl group. For instance, a general

metal-free reaction of 2-alkynyl-*N,N*-dialkylanilines with sulfonyl hydrazines as sulfonylating reagents in the presence of iodine and *tert*-butylhydroperoxide allowed the formation of 3-sulfonylindoles via a radical sulfonylation cascade process (Scheme 1a).¹⁵ A photoredox-catalyzed radical process starting from 2-alkynyl-azidoarenes and based on the oxidation of arylsulfinate anions by eosin Y as the photocatalyst under green light irradiation leads to the formation of alkyl-3-sulfonylindoles (Scheme 1b).^{16–18}

Readily accessible styryl azides β -substituted by sulfones gave 3-sulfonylindoles by catalysis with a rhodium(II) carboxylate complex. The reaction transits through a rhodium nitrene obtained by N₂ loss, enabling the C–N bond formation (Scheme 1c).¹⁹ The gold-catalyzed cyclization of 2-alkynyl-*N*-alkyl, *N*-tosyl anilines represents an interesting approach. Transiting via a quaternary ammonium intermediate, the cyclization process is followed by 1,3-migration of the sulfonyl group on the vinyl gold intermediate and allows the formation of the desired skeleton when the aromatic moiety is unsubstituted (Scheme 1d).^{20–22}

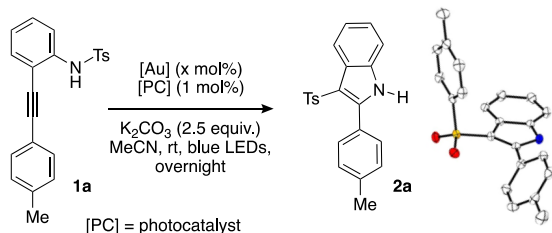
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Table 1. Optimization of Reaction Conditions Using Photoinduced Au(I) Dual Catalysis^a

ORTEP drawn with the thermal ellipsoids at 50% level

entry	catalyst (mol %)	[PC] (1 mol %)	yield of 2a (%) ^b
1	(<i>p</i> -CF ₃ C ₆ H ₄) ₃ PAuCl (10)	[Ir-F]	43
2	(<i>p</i> -CF ₃ C ₆ H ₄) ₃ PAuCl (5)	[Ir-F]	40
3	(<i>p</i> -CF ₃ C ₆ H ₄) ₃ PAuCl (10)	none	57
4	(<i>p</i> -CF ₃ C ₆ H ₄) ₃ PAuCl (5)	none	41
5	Ph ₃ PAuCl (10)	none	37
6	none	[Ir-F]	NR

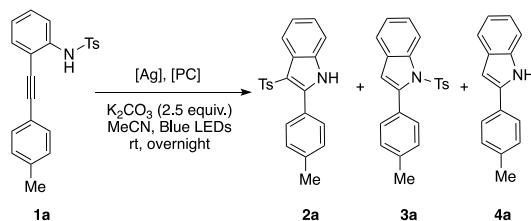
^a**1** (0.2 mmol), gold catalyst [Au], photocatalyst [PC], K₂CO₃ (2.5 equiv), degassed solvent (3 mL), and overnight stirring; [Ir-F] = Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆. ^bIsolated yield; 20–30% of **1a** was recovered.

In the course of our studies on gold(I) catalysis under visible light irradiation,^{23–35} we now report the reactivity of 2-alkynyl-*N*-tosyl anilines in the presence of gold(I) and silver(I) salts to provide an expedient access to 2-aryl-3-sulfonyl-NH-indoles (Scheme 1e). This study stems from the

observation of an intriguing faint fluorescent blue spot on the crude product TLCs of some of the recently reported gold(I)-catalyzed alkylation reactions of 2-alkynyl-*N*-tosyl anilines under visible light irradiation.²⁵ These spots significantly gained in intensity when the reactions were conducted without an alkyne partner and aroused our interest. Structural identification concluded the formation of 3-sulfonylindole derivatives **2**. These compounds, to the best of our knowledge, have never been obtained from NH-tosyl anilines through a 1,3-migration of the sulfonyl³⁶ group, and this is what we wish to develop in this study.

2. RESULTS AND DISCUSSION

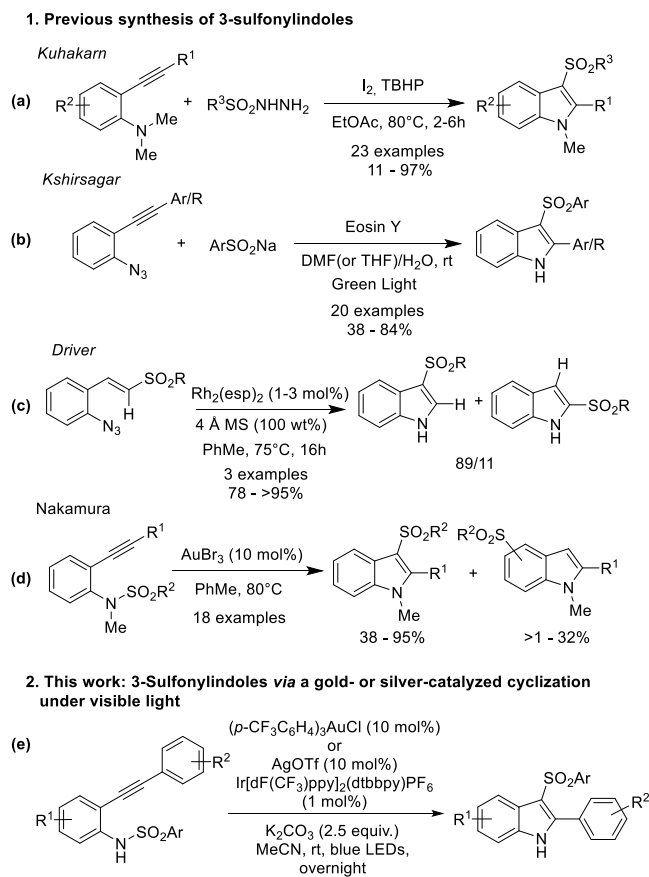
Our investigation for the synthesis of 3-sulfonylindole derivatives **2** began by using *N*-tosyl alkynylaniline **1a** as the model substrate in the presence of a photocatalyst and a gold(I) catalyst. Thus, we submitted **1a** to 10 mol % of (*p*-CF₃C₆H₄)₃PAuCl in the presence of 1 mol % of Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ and 2.5 equiv of K₂CO₃ under blue LED irradiation. These conditions delivered 3-sulfonylindole **2a** in a moderate 43% yield (Table 1, entry 1) accompanied by the recovered starting material **1a** (around 30%). A lower catalytic amount of Au(I) catalysts resulted in a lower yield of **2a** (entry 2). Importantly, the photocatalyst-free conditions could also afford **2a** in a better yield (entry 3). The loading and the nature of Au(I) bear some impact on the reaction outcomes, as using 5 mol % of (*p*-CF₃C₆H₄)₃PAuCl or 10 mol % of Ph₃PAuCl gave **2a** in 41% or 37% yield, respectively (entries 4 and 5). A final control experiment revealed that the reaction is not operative using only Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ without the Au(I) catalyst (entry 6). The structure of **2a** was secured by X-ray diffraction.³⁷

Table 2. Optimization of Reaction Conditions Using Photoinduced Ag(I) Dual Catalysis^a

entry	[Ag] (mol %)	[PC] (mol %)	solvent	yield of 2a (%) ^b
1 ^c	AgOTf (10)	[Ir-F] (1)	MeCN	65 (4a , 17)
2 ^c	AgOTf (10)	[Ir-F] (5)	MeCN	47 (4a , 17)
3	AgOTf (5)	[Ir-F] (1)	MeCN	35 (4a , 15)
4	AgBF ₄ (10)	[Ir-F] (1)	MeCN	35 (4a , 14)
5	Ag ₂ CO ₃ (10)	[Ir-F] (1)	MeCN	50 (4a , 20)
6 ^c	AgOTf (10)	Ru(bpy) ₃ (PF ₆) ₂ (5)	MeCN	8 (3a , 58)
7 ^c	AgOTf (10)	<i>fac</i> -Ir(ppy) ₃ (1)	MeCN	56 (4a , 19)
8 ^c	AgOTf (10)	eosin Y (1)	MeCN	18 (3a , 62)
9 ^c	AgOTf (10)	4CzIPN (1)	MeCN	24 (3a , 76)
10 ^c	AgOTf (10)	benzophenone (1)	MeCN	16 (3a , 24; 4a , 20)
11	AgOTf (10)	[Ir-F] (1)	MeOH	^d
12	AgOTf (10)	[Ir-F] (1)	DCE	35 (4a , 20)
13	AgOTf (10)	none	MeCN	0 (3a , 82)
14	none	[Ir-F] (1)	MeCN	NR
15 ^e	AgOTf (10)	[Ir-F] (1)	MeCN	NR
16 ^f	AgOTf (10)	[Ir-F] (1)	MeCN	0 (3a , 78)

^a**1** (0.2 mmol), silver catalyst [Ag], photocatalyst [PC], K₂CO₃ (2.5 equiv), degassed solvent (3 mL), and stirring overnight; [Ir-F] = Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆. ^bIsolated yields. ^cDetermined by ¹H NMR by using 1,3,5-trimethoxybenzene as an internal standard. ^dComplex mixture. ^eWithout K₂CO₃. ^fNo light.

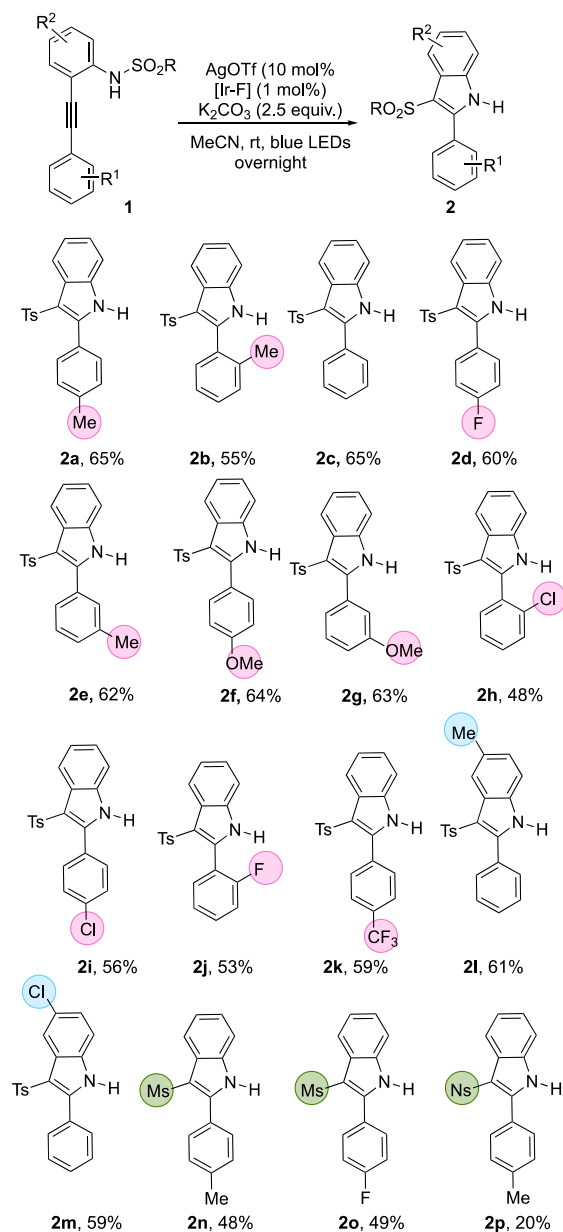
Scheme 1. Synthetic Approaches to 3-Sulfonylindoles



We next examined the possibility of running this type of transformation with more economical noble metal salts, and we focused on Ag(I) catalysis.^{38,39} Silver salts are indeed also known to efficiently catalyze the cyclization of 2-alkynyl-*N*-sulfonyl derivatives.^{40,41}

First, we investigated the effect of the ratio of silver (AgOTf) and photocatalyst Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ under basic conditions (Table 2, entries 1–3). When the reaction was carried out in the presence of AgOTf (10 mol %)/ Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (1 mol %), disubstituted indole **2a** was obtained in 65% isolated yield (entry 1) along with desulfonylated indole **4a**. Lower yields of the product **2a** were obtained when a larger amount of Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5 mol %, entry 2) or a smaller amount of AgOTf (5 mol %, entry 3) was used. As the silver catalyst plays a crucial role in the transformation of 3-alkynyl-*N*-tosyl aniline **1a**, the catalytic activity of other silver salts such as AgBF₄ and Ag₂CO₃ was evaluated (entries 4 and 5). Both exhibited a low reactivity, giving the desired C3-tosyl indole **2a** in 35% and 50% yields, respectively, accompanied by **4a**. Other photocatalysts (e.g., Ru(bpy)₃(PF₆)₂, *fac*-Ir(ppy)₃, eosin Y, 4CzIPN, and benzophenone) were also tested (entries 6–10). However, none of them have outperformed Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆. In addition, the nature of the solvent was also examined. MeOH gave an intractable mixture, and DCE was not effective for this reaction (entries 11 and 12). Some control experiments were carried out. When the reaction was performed without a photocatalyst, 1,3-sulfonyl migration did not occur, and *N*-tosyl alkynylaniline **1a** was converted into *N*-tosyl indole **3a** in 82% yield (entry 13). No reaction took

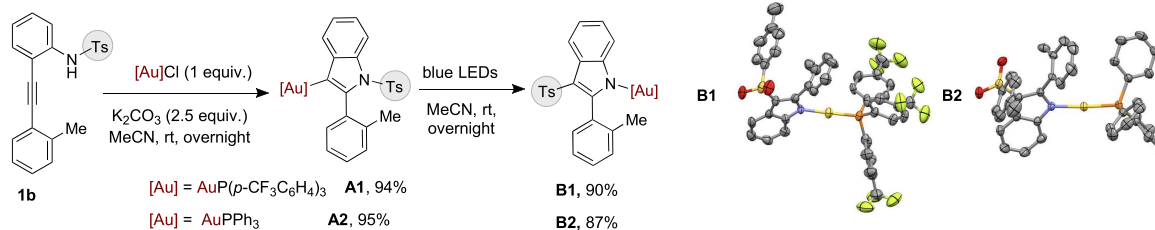
Table 3. Scope of the Reaction



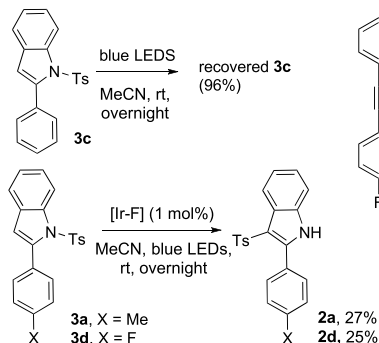
place in the absence of a silver salt or without a base (entries 14 and 15). In addition, when the reaction was carried out without blue LED irradiation, only 78% of *N*-tosyl indole **3a** was obtained (entry 16). These results indicate that the silver salt, the base, and the photocatalyst are necessary for this transformation. Thus, the use of 10 mol % of AgOTf in combination with 1 mol % of Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ and excess of K₂CO₃ in MeCN kept overnight appeared as the optimal reaction conditions, and the latter conditions were used in our further investigations.

Based on the optimization of the reaction conditions and the mechanistic investigations, we examined the scope of this transformation. Several 2,3-disubstituted indoles **2b–2p** have been synthesized from 3-alkynyl-*N*-tosyl, -mesyl, or -nosyl anilines, in 20–65% yields (Table 3). Of note, the reaction of precursor **1d** could also be run on a larger scale (1 mmol), giving product **2d** in 50% yield after crystallization. The tosyl substrates provided better yields compared to mesyl (**2n**, **2o**)

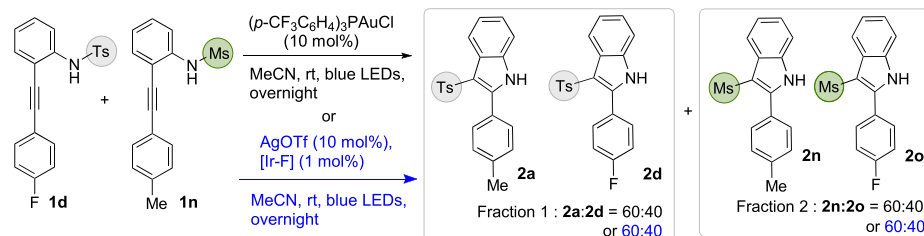
Scheme 2. Mechanistic Investigations

(a) Formation of vinylgold complexes **A** and indolyl complexes **B** (ORTEPs drawn with the thermal ellipsoids at 50% level)

(b) Control and crossover experiments

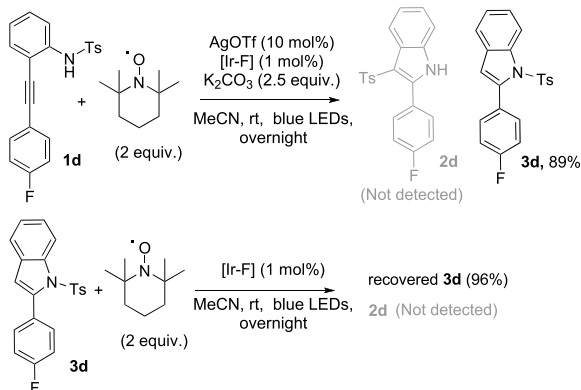
Reactivity of *N*-tosylindoles **3**

Scrambling of the sulfonyl groups

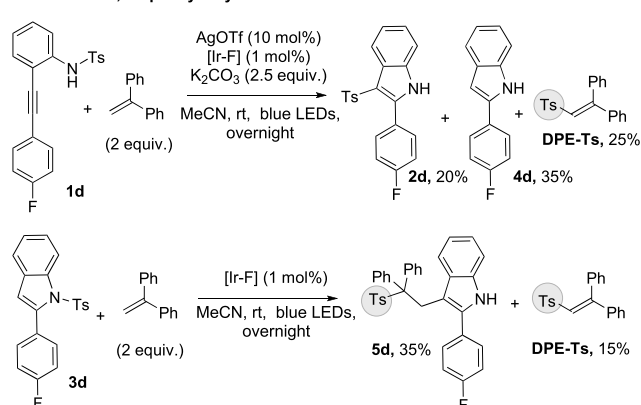


(c) Probing the intervention of sulfonyl radicals and mechanism proposal

Reactions with TEMPO



Reactions with 1,1-diphenylethylene

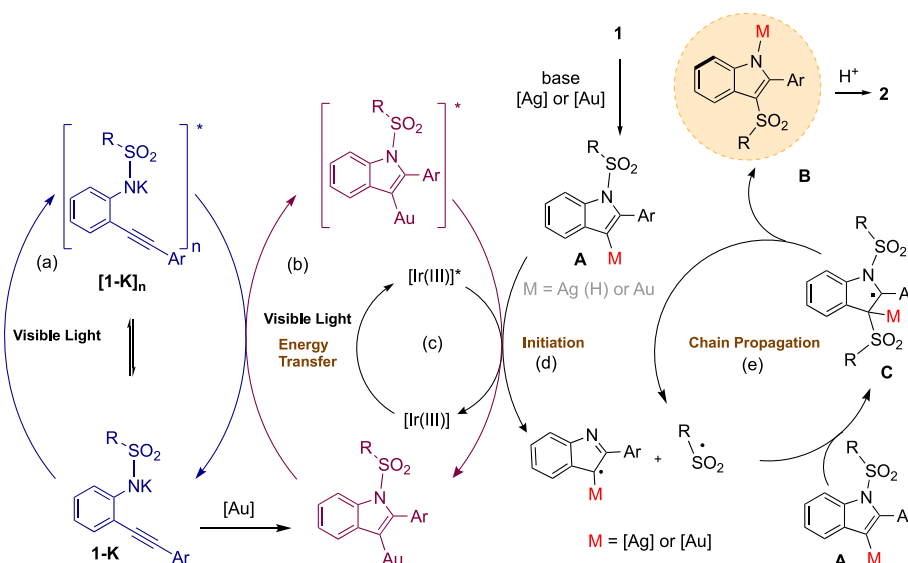


and nosyl (**2p**) precursors. Precursors featuring either a *para* electron-donating group (–Me, –OMe) or an electron-withdrawing group (–F, –Cl, –CF₃) on the 2-alkynylaryl moiety were found to be compatible, affording the corresponding cyclization–migration products **2b–2k** in 48–65% yields. Of note, –Me or –Cl group on the aniline aryl moiety did not affect the yield of the reaction (**2l**, **2m**). However, reactions with 2-alkynylanilines (R = Ph, R₂ = H) bearing an alkyl chain (pentyl or 1-chlorobutyl) at the alkyne terminal position gave only the cyclo-isomerization products in 88% yield in both cases without 1,3-sulfonyl migration.

This difference of reactivity between the photosensitizer-free gold catalysis and the dual Ag/Ir catalysis was puzzling. In order to gain some insights into this reaction, we first prepared indolyl–gold complexes **A1** and **A2** through a stoichiometric reaction between the related Ts-aniline substrate **1b** and (*p*-CF₃C₆H₄)₃PAuCl or Ph₃PAuCl in the presence of 2.5 equiv of K₂CO₃. Both complexes **A1** and **A2** proved to be highly stable and could be isolated in more than

90%. They were then dissolved in MeCN and submitted to blue LED irradiation. The evolution of **A1** in these conditions was confirmed by ³¹P NMR (δ_{A1} = 44.7 ppm). Interestingly, a new peak appeared at the chemical shift of 33 ppm (**Scheme 2a**). This new NMR peak corresponded to the formation of the indolyl (*p*-CF₃C₆H₄)₃P–Au–N gold(I) complex **B1** that was isolated in 90% yield and fully characterized by X-ray diffraction analysis.⁴² Similarly, complex **A2** was obtained from Ph₃PAuCl and further isomerized to the Au–indolyl complex **B2** (**Scheme 2a**).^{43,44} Additionally, we could consolidate a *one-pot* reaction from **1b** under blue LED irradiation, delivering indolyl–gold complexes **B1** in 82% yield and **B2** in 76% yield (see **Supporting Information**, Section 5.1). The reactivity of **B1** was examined under different conditions. It was found that this gold complex is stable toward an electrophilic species such as iodomethane and also to the exposure to 1 mol % of Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆. However, the stability of **B1** was slightly affected by an acidic medium, as the formation of 3-tosyl indole **2b** was observed

Scheme 3. Mechanism Proposal



after filtration through a short pad of silica gel, a **B1/2b** mixture in a 66/34 ratio being formed (see [Supporting Information](#), Sections 5.1 and 5.2).

To be consistent with the gold-related study, we tried to isolate vinyl silver intermediates presumably resulting from the stoichiometric reactions with AgOTf. Unfortunately, as mentioned in the literature, these putative intermediates proved to be reluctant to isolation.⁴⁵ Additional mechanistic investigations were therefore based on several control experiments. First, the stability of *N*-tosyl indole derivatives **3** under blue LED irradiation was probed. No reaction occurred when *N*-tosyl indole **3c** was irradiated overnight ([Scheme 2b](#)). In contrast, among complex mixtures, marginal 1,3-sulfonyl migration was observed from **3a** or **3d** in the presence of 1 mol % [Ir-F] (27% of indole **2a** and 25% of indole **2d**).

In addition, to find out if the migration of the sulfonyl group occurs in an intramolecular or intermolecular fashion, crossover experiments were run with *N*-tosyl aniline **1d** and *N*-mesylaniline **1n** in the presence of (*p*-CF₃C₆H₄)₃PAuCl (10 mol %) (black pathway, [Scheme 2b](#)). We observed the formation of a mixture of the four products **2a**, **2d**, **2n**, and **2o**. We isolated two fractions containing a mixture of unseparated sulfonylindole products in 60:40 and 60:40 ratio for **2a:2d** and **2n:2o**. Similarly, the silver-catalyzed reaction (blue pathway) provided comparable outcomes. Overall, these findings clearly evidenced the scrambling of the sulfonyl groups in these reactions and were suggestive of the intervention of sulfonyl radicals.

To probe the radical character of the sulfonyl migration,⁴⁶ a reaction was performed from **1d** under standard dual catalysis conditions in the presence of 2 equiv of TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) as the radical scavenger; the desired product **2d** was not observed; only *N*-tosyl indole **3d** (89%) and the starting product were obtained ([Scheme 2c](#)). Moreover, when *N*-tosyl indole **3d** was irradiated in the presence of 1 mol % of Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ and 2 equiv of TEMPO, only **3d** was recovered. Similar experiments were performed using 1,1-diphenylethylene as it is a more versatile radical scavenger, which does not affect the catalytic activities of transition metals.⁴⁷ Thus, precursor **1d** was

engaged in the silver catalysis reaction conditions in the presence of 2 equiv of 1,1-diphenylethylene. In addition to **2d** (20%) and **4d** (35%), **DPE-Ts** adduct, resulting from the addition of the tosyl radical⁴⁸ to 1,1-diphenylethylene, was isolated in 25% yield ([Scheme 2c](#)). Starting from *N*-tosyl indole **3d** in the presence of 1 mol % of Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆, **DPE-Ts** was isolated in 15% yield as well as the unexpected product **5d** in 35% yield ([Scheme 2c](#) and [Supporting Information](#), Sections 4 and 5).

Based on these mechanistic investigations and our precedent studies,²⁵ it seems reasonable to assume a preliminary formation of a vinyl metal (gold or silver) intermediate **A** resulting from the cyclization of the TsN amide anion on the π -activated alkyne by a metal salt (gold/silver). In the case of gold activation, the stable vinyl gold intermediate **A** would reach an excited state by direct irradiation, as in [Scheme 2a](#), or by energy transfer (EnT) from the excited state of potassium amide aggregate [**1a-K**] (cycles (a) and (b) of [Scheme 3](#)), as in the alkylation reaction,²⁵ and undergo homolytic cleavage of the N–SO₂Tol bond to generate in situ an indolyl radical and a sulfonyl radical (initiation (d)).⁴⁹ Such EnT-driven homolytic cleavage has been, for instance, reported for the photoinduced rearrangement of vinyl tosylates to β -ketosulfones.⁵⁰ In our case, the sulfonyl radical would be added in position 3 of another vinyl gold species (intermediate **C**) and trigger β -elimination of another sulfonyl radical, which propagates a radical chain process (cycle (e)). This also generates an imine intermediate⁵¹ that would tautomerize and give the previously isolated indolyl N–Au species **B** ([Scheme 2a](#)). Protonation liberates the final 3-sulfonylindole **2** and regenerates the gold catalyst.

In the case of photo/Ag(I) dual catalysis, we assumed that an energy transfer would occur from the photoexcited [Ir(III)*] to the vinyl silver intermediate **A** (cycle (c)), leading to the homolytic cleavage of the N–SO₂ bond and chain radical isomerization. As before, protonation would deliver the final product **2**. Alternatively, the unstabilized vinyl silver intermediate undergoes protodesilveration, giving an indole intermediate of type **3** which could also undergo 1,3-sulfonyl migration to give product **2** in the presence of 1 mol

% of Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆, as in Scheme 2b. However, the 1,3-sulfonyl migration on these intermediates would be less efficient, giving rise to products like 4a, as in Table 2.

In conclusion, an expedient access to valuable 3-sulfonylindoles has been devised. Starting from *ortho*-alkynyl-*N*-sulfonyl anilines 1, gold(I)- or silver(I)-triggered cyclization, concomitant with a light-induced 1,3-sulfonyl migration, leads to the desired scaffolds. Mechanistic studies are consistent with the generation via photoexcitation of a sulfonyl radical which propagates the 1,3-sulfonyl migration process. These findings confirm the vast opportunities of the practice of organometallic catalysis under visible light irradiation.

3. EXPERIMENTAL DETAILS

3.1. General 1,3-Sulfonyl Migration Procedure

[Au] or [Ag] complex (5 or 10 mol %), Ir[dF(CF₃)ppy]₂(dtbbpy)-PF₆ ([Ir-F]) (0 or 1 mol %), K₂CO₃ (2.5 equiv), and *o*-alkynyl-*N*-tosyl aniline derivatives 1 (0.2 mmol, 1.0 equiv) were introduced in a Schlenk tube equipped with a magnetic stirring bar and dissolved in dry MeCN (3 mL). The mixture was degassed using three freeze–pump–thaw cycles and purged with argon and then irradiated with blue LED light for 16 h (unless mentioned). The stirring speed is equal to or more than 1200 rpm. The reaction was quenched with EtOAc (5 mL) and 2 M HCl solution (5 mL). The solution was extracted with EtOAc (3 × 5 mL). The combined organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the desired product 2.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online supplementary material.

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsorginorgau.2c00034>.

General procedures, experimental details, characterization, and spectral data for all new compounds and crystal data and structural refinement for compounds B1, B2, and 2a (PDF)

Accession Codes

CCDC 2176539 and 2176567–2176568 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/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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<https://pubs.acs.org/10.1021/acsorginorgau.2c00034>

Author Contributions

F.Z., W.H., and M.B.M. ran all the experiments and provided all analytical data for the newly synthesized compounds. C.O., V.M.M., and L.F. supervised the work and wrote the manuscript. CRediT: Fen Zhao investigation (supporting), methodology (supporting); Wided Hagui investigation (supporting), methodology (supporting); María Ballarín-Marión investigation (supporting), methodology (supporting); Cyril Ollivier supervision (lead), writing-review & editing (lead); Virginie Mouriès-Mansuy supervision (lead), writing-original draft (lead); Louis Fensterbank supervision (lead), writing-original draft (lead).

Notes

The authors declare no competing financial interest.

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■ DEDICATION

To Mukund Sibi in celebration of his 70th birthday.

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