Photoinduced ynamide structural reshuffling and functionalization

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The radical chemistry of ynamides has recently drawn the attention of synthetic organic chemists to the construction of various N-heterocyclic compounds. Nevertheless, the ynamide-radical chemistry remains a long-standing challenge for chemists due to its high reactivity, undesirable byproducts, severe inherent regio- and chemoselective problems. Importantly, the ynamide C(sp)-N bond fission remains an unsolved challenge. In this paper, we observe Photoinduced radical trigger regio- and chemoselective ynamide bond fission, structural reshuffling and functionalization of 2-alkynyl-ynamides to prepare synthetically inaccessible/challenging chalcogen-substituted indole derivatives with excellent step/atom economy. The key breakthroughs of this work includes, ynamide bond cleavage, divergent radical precursors, broad scope, easy to handle, larger-scale reactions, generation of multiple bonds (N-C(sp²), C(sp²)-C(sp²), C(sp²)-SO₂R/C-SR, and C-I/C-Se/C-H) in a few minutes without photocatalysts, metals, oxidants, additives. Control experiments and ¹³C-labeling experiments supporting the conclusion that sulfone radicals contribute to ynamide structural reshuffling processes via a radical pathway.
**Ynamides** are privileged alkyne precursors that bind to nitrogen atoms with an electron-withdrawing group, notably enhancing their stability. In addition, the electron-pushing ability of nitrogen atoms can easily polarize alkyne groups and activate triple bonds, thus realizing high regio- and chemoselectivity in organic transformations. Well-established strategies for ynamides include transition-metal-catalyzed (metal carbene)/Bronsted acid-mediated (keteniminium ion) intermediates, which are then trapped by various nucleophiles/electrophiles to yield various difunctionalization products, or N-heterocyclic compounds; these intermediates have been studied by various research groups (Liu, Hashmi, Ye, Sahoo, Gandon, and numerous other groups). In addition, metal/oxidant/photocatalyst-induced radical addition to the α/β-carbons of ynamides leads to a mixture of E/Z isomers in the products. Recently, professors Gandon, Sahoo and coworkers observed an intermolecular radical-triggered reactivity of alkynes vs. ynamides in yne-tethered ynamides with sulfur radicals under traditional reaction conditions. In 2020, Ye and coworkers reported intramolecular photoredox-catalyzed regioselective ketyl radical addition on the α-carbon of ynamide in ketyl-ynamide and radical Smiles rearrangement. Despite their advantages, these limited existing radical strategies require expensive metals/photocatalysts, oxidants, longer reaction times, harmful waste production, and a lack of atom economy. Importantly, selective intermolecular radical-triggered ynamide bond fission and structural reshuffling have remained unanswered challenges in ynamide chemistry until now. Structural reshuffling is a process involving multiple-bond fission and new bond formation for molecular skeleton reassembly. In 2020, Cui and coworkers reported unusual, ion-divergent intramolecular structural reshuffling of ynamides aided by lithium disopropylamide (LDA) to produce thiete sulfones, while the additional use of 1,3-dimethyltetrahydropropiridinum-2(1H)-one (DMPU) altered the process to produce propargyl sulfonamides. Very recently, Li and coworkers reported intramolecular ionic gold-catalyzed, 1,2-N-migration of ynamides via 1,1-carboalkoxylation in an atom-economical synthesis of tetrahydrofuran-fused 1,4-dihydroquinolines. In addition to ynamides, other types of well-known intramolecular ionic path structural rearrangements have been reported. Fax. 1 Previous literature and background for reaction development. a Simple ynamide in a metal/Lewis acid. b Simple ynamide in 1,2-radical additions. c Gandon and Sahoo work on yne-tethered ynamides with traditional radical generation. d Intramolecular ynamide structural reshuffling with metals via ionic mechanism. e In Intramolecular ynamide structural reshuffling with gold-catalyst. f Well-known intramolecular 1,3-bond activation with metals/Lewis acid for 1,3-migration via ionic path. g Our initial hypothesis on 2-alkynyl-ynamides. h Our photoinduced radical diversification strategy on 2-alkynyl-ynamides.
of substituted 2-alkynylanilines have been reported through the utilization of transition metal/Lewis acid-catalyzed cyclization/ migration. In this strategy, an alkynyl with metal (Pd, Pt, Rh, Ir, Au, Cu, Co)/Lewis acids first activated to induce the reaction, and simultaneous 1,3-migration occurs to produce straightforward implausible substituted indole derivatives (Fig. 1f)\(^3\), thus enabling access to chalcogen-substituted indoles derivatives (Fig. 1g (paths 1–4)).

In this work, we observe radical trigger regio- and chemoselective intermolecular ynamide C(sp)–N bond fission, structural reshuffling and functionalization producing synthetically inaccessible/challenging substituted indole derivatives (Fig. 1g, path 5).

We are utilizing 2-alkynyl-ynamides with divergent radical precursors to prepare chalcogen-substituted indoles derivatives via the formation of multiple bonds (N–C(sp)\(^2\), C(sp)\(^2\)–C(sp)\(^2\)), C(sp)\(^2\)–SO\(_2\)R/C–SR, and C–I/C–Se/C–H) in a rapid transformation that occurs under mild reaction conditions with excellent step/atom economy (Fig. 1h).

### Results

#### Screening of the reaction conditions.

We commenced our photoinduced radical-triggered regio- and chemoselective strategy on ynamides by using 4-methyl-N-(phenylethynyl)-N\(^2\)-(2-phenylethynyl)phenyl)benzenesulfonamide (\(1a\)) with 4-methylbenzenesulfonyl iodide (\(2a\)) as a model substrate in an acetone solvent under 40 W blue light-emitting diode (LED) light irradiation (Supplementary Figs. 1 and 7). To our delight, we observed radical-triggered ynamide bond fission, structural reshuffling and functionalization to produce a selective single isomer, (E)-3-(1-ido-2-phenyl-2-tosylovinyl)-2-phenyl-1-tosylindole (3), in 60% yield and trace amounts of (E)-2-phenyl-1-(2-phenyl-1-tosylindolyl-3-yl)-2-tosylovinyl 4-methylbenzenesulphonate (4) (Table 1, entry 1). An extensive solvent-screening process led to these optimized reaction conditions (Table 1, entries 1–10). Such conditions enabled the production of the desired product at maximum yields (85%) with dichloromethane (DCM) solvent within 3 min, without the formation of the compound (E)-2-phenyl-1-(2-phenyl-1-tosylindolyl-3-yl)-2-tosylovinyl 4-methylbenzenesulfonate (4). Encouraged by this finding, we altered the solvent molarity ratio from 0.05 to 0.1 M, but the subsequent reaction failed to improve the yields (Table 1, entry 11). Then, the equivalence of compound 2a was altered, but this failed to improve the yield (Table 1, entry 12). The reported methods revealed the high reactivation of sulfonyl iodides; thus, we carried out the reaction in the absence of a light source, but this reaction did not yield the desired product in a few minutes (Table 1, entry 13). The same reaction continued for 24 h, and compounds 3 and 4 were observed in 61/<15 yields (Table 1, entry 14). Next, we performed the reaction under a \(N\(_2\)\) atmosphere (Supplementary Figs. 2 and 3), which afforded the

| Entry | Radical initiator | Time (min) | Solvent | Yield 3/4 |
|-------|-------------------|------------|---------|-----------|
| 1     | Blue LED          | 5          | Acetone | 60/Trace  |
| 2     | Blue LED          | 5          | Toluene | 52/Trace  |
| 3     | Blue LED          | 5          | THF     | 43/Trace  |
| 4     | Blue LED          | 5          | DCM     | 83/Trace  |
| 5     | Blue LED          | 3          | DCM     | 85/<15    |
| 6     | Blue LED          | 5          | EtOH    | Trace/<   |
| 7     | Blue LED          | 5          | EIOH    | 35/<      |
| 8     | Blue LED          | 5          | DEC     | 58/Trace  |
| 9     | Blue LED          | 5          | DMSO    | N         |
| 10    | Blue LED          | 5          | MeCN    | 75/Trace  |
| 11\(^c\) | Blue LED    | 5          | DCM     | 72/<5    |
| 12\(^d\) | Blue LED    | 3          | DCM     | 79/Trace  |
| 13\(^e\) | Blue LED    | -          | DCM     | N         |
| 14\(^f\) | Blue LED    | 24 (h)    | DCM     | 61/<15    |
| 15\(^g\) | Blue LED    | 5          | DCM     | 81/<15   |
| 16\(^h\) | Blue LED    | -          | DCM     | /<15     |
| 17\(^i\) | Blue LED    | -          | DCM     | 80/<      |

Note: It is necessary to use freshly prepared 4-methylbenzenesulfonyl iodide in all the reactions. Compound 4 formation can be inhibited by carefully monitoring the reaction time.  
*Reaction conditions, unless otherwise noted: 1a (0.10 mmol), 2a (0.11 mmol), and DCM (0.05 M) were stirred at 28 °C (The fluctuation depends on local atmosphere) under irradiation with a 40 W Kessil blue LED lamp (Kessil A160WE Tuna Blue controllable LED aquarium light, \(\lambda_{max} = 462 \text{ nm} \) flanked by a second peak at \(\lambda = 382 \text{ nm} \); more information can be found at Kessil.com) and cooled with a fan, and the reaction mixtures were placed 8.5 cm from the LED light; 50% intensity of blue light was used.  
\(^a\) Isolated yields.  
\(^b\) 0.1 M DCM was used.  
\(^c\) 1.5 equiv of 2a was used.  
\(^d\) Stirred at room temperature in the absence of a light source for 24 h.  
\(^e\) Stirred under nitrogen atmosphere.  
\(^f\) Stirred at 28 °C under heating in absence of light source.  
\(^g\) 40 W PR160L-456 nm blue LED lamp was used (no second emission peak at <400 nm).  
\(^h\) 1.5 equiv of 2a was used.
expected desired product in 81% yield (Table 1, entry 15). From these findings, we believe there is no oxygen role in the reaction. The probable reason could be the spontaneous decomposition ability of the weak –SO₂–I bond in 4-methylbenzenesulfonyl iodide to generate an arylsulfonyl radical and iodine radical at room temperature in the absence of light irradiation or any additives.³⁴–³⁵. The reaction tested with traditional heating at 28 °C (Supplementary Figs. 5 and 6) failed to produce product 3 (Table 1, entry 16) (both starting material visible on TLC).

Next, a blue LED light source which has no second emission peak <400 nm also produced product 3 in 80% yield (Table 1, entry 17) (Supplementary Figs. 4 and 8). According to our observations, the reaction speed and conversion is greatly enhanced by irradiation with visible light; an added advantage is that the reaction also gives a higher final conversion in a shorter reaction time.⁵⁻⁶,⁶⁰–⁶⁴. Additionally, reaction time monitoring, solvent molarity, and the use of freshly prepared sulfonyl iodide are vital to inhibit compound 4 formation in this rapid transformation. The molecular structures of the products E isomers (Fig. 2), 30 (Fig. 2a), and 34 (Fig. 2b) were unambiguously confirmed by X-ray crystallography (CCDC numbers: 3 (2084458), 4 (2084457)).

**Substrate scope.** With the optimized standard reaction conditions in hand, we focused on the feasibility of the reaction substrate scope as depicted in Fig. 3, a broad range of substituted 2-alkynyl-ynamides (1) were compatible with this transformation to produce the corresponding (E)-3-(1-iodo-2-phenyl-2-tosylvinyl)-2-phenyl-1-tosylindole 3–26 with yields ranging from 29% to 88%. Various 2-alkynyl-ynamides 1 (R = Ar) were initially screened, and the reaction produced the desired inaccessible chalcogen-substituted indole derivatives 3–9 in high yields (64–85%) in a few minutes. Long-chain aliphatic and electron- withdrawing groups in the para position smoothly tolerated the reaction and produced the desired products. Moreover, this reaction was also carried out with 2-alkynyl-ynamides 1 (R¹ = aromatic) with electron-donating groups p-Me–Ph, p-OMe–Ph, and 3,4-di-OMe–Ph, smoothly producing the desired products (10–12) in efficiently high yields without affecting the functionality. Similarly, 2-alkynyl-ynamides 1 (R¹ = aliphatic) with an n-butyl group compatible under standard reaction conditions produced the desired product (13) in good yields (74%). In addition, we were surprised to find that a highly strained cyclopropane ring was readily converted to the desired product in an excellent yield of 82%. This supports the importance of the mild reaction of our divergent radical strategy on the 2-alkynyl-ynamides because cyclopropane is very delicate in the radical homolytic bond fission process. The molecular structure of product 14 was unambiguously confirmed by X-ray crystallography (CCDC number: 14 (2084459)). Importantly, unprotected propan-1-ol gave the desired product (15) albeit in low yield (29%) due to the freely available –OH group in the radical reaction under photoirradiation. Next, various 2-alkynyl-ynamides 1 (R² = Ar) were studied, and the reactions gave the desired products in moderate to excellent yields of 35–83%. Initially, the electron-donating groups p-Me–Ph (16), p-ethyl–Ph (17), m-OMe–Ph (18) and p-OMe–Ph (19) were found to be compatible with the preparation of the desired products in excellent yields (63–83%) without affecting the substituents in the reaction transformation. To our surprise, highly substituted 3,4-5-OMe–Ph (20) produced the desired product with a moderate yield of 47%. Importantly, 2-alkynyl-ynamides 1 (R² = Ar) with electron-withdrawing substituents m-NO₂–Ph (21), p-COO–Me–Ph (22), and p-COMe–Ph (23) were compatible with the preparation of the desired products in good yields (42–64%). Additionally, 2,4-di-Cl-Ph (24) substitutions were also compatible for the preparation of the desired product, which was isolated with a mixture of E/Z isomers (52:48) in moderate yield (43%). The reaction with the product having naphthyl functionality (25) gave a mixture of E/Z isomers (81:19) in moderate yield (55%). Notably, the heterocyclic moiety was smoothly converted to the desired product (26) in low yield (53%) with a mixture of E/Z isomers (76:24), and the probable reason might be the deactivation of the alkyne in ynamide. Next, the R² = –CH₂CH₂Ph group was introduced and treated under standard reaction conditions, and the desired product (27) was obtained in moderate yield (59%). This result shows that electronic factors have no effect on the product regioselectivity and chemoselectivity in 2-alkynyl-ynamides. Next, the scope of radical precursor reagents sulfonyl iodides/sulfonyl hydrazides (2) was tested with 2-alkynyl-ynamides 1 to equip the corresponding inaccessible chalcogen-substituted indole derivatives 28–42 with yields ranging from 40% to 90%. Benzene sulfonyl iodide smoothly produced the desired product (28) with an excellent yield of 88%. Due to difficulties in the synthesis/isolation of sulfonyl iodides, a slight modification of the radical precursors was used for the photo-induced radical transformations (sulfonyl iodides were replaced by sulfonyl hydrazides in the presence of oxidizing agents). The reaction proceeded smoothly to give the desired product in the presence of sulfonyl halogens/sulfonyl hydrazide with a series of substituents on the aryl moiety containing electron-donating/drawing groups, such as p-Oe-Ph (29) and p-tert-butyl (30), to give chalcogen-substituted indole derivatives in 71–82% yield. A series of aryl groups with electron-withdrawing groups, p-F–Ph (31), p-Cl–Ph (32), p-Br–Ph (33), p-I–Ph (34), o-NO₂–Ph (35), and p-CF₃–Ph (36), produced the desired products in good yields of 53–78%. Our reactions were compatible with highly substituted 2,4,5-tri–Cl–Ph sulfonylhydrazine to give desired product 37 in 40% yield. In addition, a series of aliphatic functionalities (methyl (38), ethyl (39)) in compound 2 smoothly generated the desired products in good yields (54–60%). The strained cyclopropane ring was also compatible with the preparation of the corresponding product (40) in excellent yield (77%). The bulky naphthyl (41) moiety smoothly delivered the substituted indole derivatives in excellent yield (90%). Most importantly, the heterocyclic moiety (42) smoothly produced the desired product with a moderate yield of 63%. For all of the above products (except R¹ = an aliphatic group), we observe a very broad signal and no sharp peaks (in the case of R¹ = an aromatic group, a broad peak is observed at ~7.8 ppm) in the ¹H NMR spectra. We hypothesized that bulky iodine could affect the neighboring aromatic protons so that the orthoprotomers may broaden (Supplementary Fig. 9).

To demonstrate the scope and usefulness of our method, we chose to study different starting materials of 2-alkynyl-ynamides (1) and sulfonyl halogens (2), as shown in Fig. 4a. Various N-protecting groups (N-SO₂–Ph (1w), 4-chloro-N-(phenylethynyl)-N-(2-(phenylethynyl)phenyl)benzenesulfonamide (1x), and N-SO₂–Et (1y)) with 4-methylbenzenesulfonyl iodide (2a) smoothly afforded desired products 43–45 in 72–77% yield. Next, sulfonyl bromides (2ca) gave the desired products (46 and 47) in 20–52% yield under standard reaction conditions. However, 4-toluene sulfonyl chloride (S17) failed to give the desired product under optimized reaction conditions. The reason for the low reactivity of the sulfonyl bromides/chlorides is due to the relative strength of the sulfone–halogen bond.⁵⁻⁶,⁶⁴ The UV–vis absorption spectra of sulfonyl iodide 2a in various solvents (DCM, MeCN, and THF in 10⁻²–10⁻⁵ M) were measured (Supplementary Figs. 13–24). In more concentrated solutions better absorption in each of these solvents was observed in the blue LED area (our actual reaction condition is even more concentrated than the samples used for
Fig. 3 Substrate scope for the 2-alkynyl-ynamides, sulfonyl iodide, and sulfonyl hydrazides. Reaction conditions: 1 (0.10 mmol), 2 (sulfonyl iodides (0.11 mmol)), and DCM (0.05 M) were stirred at 28 °C under irradiation with a 40 W Kessil blue LED lamp (Kessil A160WE Tuna Blue, λ<sub>max</sub> = 462 nm flanked by a second peak at λ = 382 nm) and cooled with a fan, and reaction vessels were placed ~8.5 cm from the LED light for irradiation with a 40 W Kessil blue LED lamp for 2–10 min; isolated yields, a major E isomer was formed. *Mixtures of E/Z isomers were formed (E/Z ratios were determined based on indole 4-position aromatic C–H protons in 1H NMR. Notes: (1) Freshly prepared sulfonyl iodide was used, and the reaction was carefully monitored. (2) Most of the sulfonyl iodides were unstable during synthesis (or) at room temperature. 2b (0.10 mmol), 2 (sulfonyl hydrazide) (1.5 equiv), I<sub>2</sub> (0.5 equiv), aq. 70% tert-butyl hydroperoxide (TBHP) (3.0 equiv), and DCM (0.05 M) were stirred at 28 °C under irradiation with a 40 W Kessil blue LED lamp (Kessil A160WE Tuna Blue, λ<sub>max</sub> = 462 nm flanked by a second peak at λ = 382 nm) and cooled with a fan, and reaction vessels were placed ~8.5 cm from the LED light for irradiation with a 40 W Kessil blue LED lamp for 10–30 min; isolated yields. *4-(tert-butyl)benzenesulfonyl iodide was used. *Naphthalene-1-sulfonyl iodide was used.

UV–vis measurement). In case of sulfonyl bromide 2ca, marginal absorption in the blue LED area in various concentrations (10<sup>−2</sup>–10<sup>−3</sup> M in DCM) was observed (Supplementary Figs. 25–28). Next, we changed the reaction time from minutes to hours under the optimized reaction conditions in Fig. 4b. Sulfonyl iodides (2b and 2c) and sulfonyl hydrazides (2.5 equiv) (2be and 2be) produced desired products 28 and 30 in a short time under both reaction conditions. In parallel, we performed the
**Fig. 4 Miscellaneous reactions.**

**a** Substrate scope for the sulfonamides in 2-alkynyl-ynamides and sulfonyl halogens

**b** Sulfonyl iodide/sulfonyl hydrazide under longer reaction time

**C** Reaction of homopropargyl tethered ynamide

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same reactions with extended reaction times and observed undesired products 48 and 49 in low yields in addition to the expected major products (28 and 30). We hypothesized that the formation of the side products was due to the in situ formation of sulfonic acid from sulfonyl iodides or sulfonyl hydrazides. To validate our hypothesis, we used compound 3 as a starting material and treated it with p-toluenesulfonic acid monohydride under optimized reaction conditions. To our surprise, the iodine product (3) replaced by the −OTs product (4) was formed in moderate yield. Note that when we used 4-toluenesulfonyl bromide as a radical source, product 4 did not form in the reaction due to the bond energy (C(sp)^2−Br) in compound 46 being higher than the C(sp)^2−I bond energy in compound 3 (Supplementary Fig. 10). Next, we extended our methodology by using propargyl-linked ynamide (1aa) under optimized reaction conditions (Fig. 4c) and produced 2-(iodo(phenyl)methylene)-3-phenyl-1,4-ditosyl-2,5-dihydropyrrole as product (50) in 23% yield. The molecular structure of product 50 was unambiguously confirmed by X-ray crystallography (CCDC number: 50 (210787)). However, we did not observe cleavage of the C(sp)−N bond of ynamide because propargylamide alkynes are more reactive than ynamide29,30. The reaction of homopropargyl tethered ynamide (1ab) in thin layer chromatography (TLC) showed multiple spots, probably due to the lower stability of starting material 1ab (spontaneous decomposition in the presence of water (trace amount) within 2−3 days yielded hydration products with ynamide alkynes), and the formed product can easily isomerize into various products. In accordance with these
was unambiguously confirmed by X-ray crystallography (CCDC number: 51 (2084460)). Next, the reaction was used to—test 2-alkynyl-ynamide 1 (R = aromatic) with electron donating and electron-withdrawing groups p-Me–Ph (56), p-OMe–Ph (57), and 3,4-di-OMe–Ph (58), and the desired products were produced in efficiently good yields (40–70%) without affecting the functionality. Notably, the n-butyl group (59) and strained cyclopropane (60) smoothly produced the desired products in moderate yields of 38–74%. Next, we tested various 2-alkynyl-ynamides 1 (R = Ar) with electron-donating and electron-withdrawing groups, such as p-Me–Ph (61), p-ethyl–Ph (62), m-OMe–Ph (63), m-NO2–Ph (64), p-COOH–Ph (65), and p-COMe–Ph (66), which produced the desired products in low to moderate yields (25–69%). Next, we used various selenosulfonate radical precursors with electron-donating withdrawing groups –Ph (67), p-COMe–Ph (68), p-Cl–Ph (69), p-F–Ph (70) and heterocyclic groups (71) compatible with the sulfone moiety to produce the desired products in moderate yields (20–69%). Modifications of the selenium moiety with groups such as p-Me–Ph (72), p-F–Ph (73), m-Cl–Ph (74), and n-pentyl (75) groups smoothly produced the desired products in 18–59% yield.

Following our previous work47, we treated 2-alkynyl-ynamides (1) under visible-light irradiation with thiol acting as a radical precursor (Supplementary Table 1). We focused on the feasibility of the substrate scope of the reaction, as depicted in Fig. 6. In this transformation, a series of substituted 2-alkynyl-ynamides (1) were compatible with equipping the corresponding mixture of (E/Z)-2-phenyl-3-(2-phenyl-2-(phenylthio)vinyl)-1-tosylindole derivatives in low to moderate yields with electron-donating/writhing groups –Ph (76), p-Cl–Ph (77), and p-Br–Ph (78). The ratio of the E and Z mixture in the products changes with the substituents. In the case of compound 1 (R = C1 or Br), we exclusively observed the Z isomer in product 77 or the major Z isomer in product 78 (E/Z, 10:90). We believe that the radical intermediate (E) formed in the mechanism affects the formation of the single isomer (Supplementary Fig. 54).76 The molecular structure of product 76 was unambiguously confirmed by X-ray crystallography (CCDC number: 76 (2084461)). Next, the reaction was also applied to 2-alkynyl-ynamides 1 (R = aromatic), where the electron-donating groups p-Me–Ph (79) and p-OMe–Ph (80) produced the desired products in moderate yields of 44–50% with a mixture of E/Z ratios (47:53 and 17:83). Most importantly, various aromatic thiolos containing electron-donating/electron-withdrawing groups P-Me–Ph (81), m-OMe–Ph (82), p-OMe–Ph (83), o-Br–Ph (84), and p-Br–Ph (85) produced the desired products in moderate yields of 38–53%. In all cases, we observed the formation of a mixture of E/Z isomers. According to our experimental observations, the electron-withdrawing group at R gave good selectivity (Z) compared to other substituents, either in ynamide or thiol moieties.

**Fig. 6** Substrate scope of 2-alkynyl-ynamides and aromatic thiols.

Reaction conditions: 2-alkynyl-ynamides (0.1 mmol), aromatic thiol (0.25 mmol), and MeCN (0.1 M) were stirred at 28 °C under irradiation with a 40 W Kessil blue LED for 4–7 h in air; isolated yields of the mixture of E and Z isomers were reported, and E/Z ratios were determined based on alkenes protons in 1H NMR. *E*/*Z* isomer was formed.

**Larger scale synthesis and product synthetic transformations.**

To demonstrate the robustness of our diversified radical strategy (Fig. 7), we performed larger-scale reactions of 4-methyl-N-(phenylethynyl)-N-(2-(phenylethynyl)phenyl)benzenesulfonamide 1a (1.0 g of TsI (2a)), 0.25 g of Se-phenyl 4-methylbenzenesulfonylamine (2a), and 0.25 g of benzenethiol (2ae) that underwent smooth transformations to produce the desired products in good yields (3 (74%), 51 (60%), and 76 (46%) without affecting the quality of the starting material (Fig. 7a). The active C–I bond in the synthesized products was further transformed into the corresponding derivatives, such as p-tolylboronic acid (526) (Suzuki reaction), producing the expected product in a good yield of 61% (eq 1, Fig. 7b). Most importantly, under basic...
Mechanistic studies. To gain insights into this reaction mechanism, we conducted several control experiments to form products 3, 51 in Fig. 8 and 76 in Supplementary Figs. 52–54. First, we conducted radical-trapping experiments using (2,2,6,6-tetramethylpiperidin-1-yl)oxadionyl 89 (TEMPO), ethene-1,1-diylidibenzene (90), and butylated hydroxytoluene 91 (BHT) as radical scavengers under standard conditions (Fig. 8a). The TEMPO and ethene-1,1-diylidibenzene radical scavengers completely shut down the desired product formation in the reaction. When we used ethene-1,1-diylidibenzene, sulfone radical-trapping product 92 was observed in 15% yield. The product was confirmed by $^1$H nuclear magnetic resonance (NMR), $^{13}$C NMR, and high-resolution mass spectrometry (HRMS) (Supplementary Fig. 49). The above reactions suggest that radical operation is involved in this transformation. However, in the case of the radical scavenger BHT, the desired product was observed in 55% yields with extended reaction times. The probable reason for this result could be the low reactivity of BHT compared to that of 4-methyl-N-(phenylethynyl)-N-(2-phenylethynyl)benzenesulfonamide (1a). To determine the importance of the alkynyl group in 2-alkynyl-ynamides (1), we performed a reaction with simple ynamide 93 (Fig. 8b). Surprisingly, this reaction did not produce the expected ynamide bond-fission product (94); instead, a regioselective α,β-addition product (94a) was observed in 58% yield. The molecular structure of product 94a was unambiguously confirmed by X-ray crystallography (CCDC number: 94a (2084462)); this reveals the importance of the 2-alkynyl moiety in 2-alkynyl-ynamides (1) for successful transformations. Next, experiments were conducted by using simple ynamide (93) and 4-methyl-N-(phenylethynyl)-N-(2-phenylethynyl)phenylbenzenesulfonamide (1a) to compare the reactivities (ynamide 1a is more reactive than ynamide 93) and produce the particular desired product (3) at 64% yields (Fig. 8c). We speculated that the 2-alkynyl moiety in 4-methyl-N-(phenylethynyl)-N-(2-phenylethynyl)phenylbenzenesulfonamide (1a) acts as a directing group in this regio- and chemoselective radical cascade process. Most importantly, to identify the in situ reshuffling groups in these transformations (Ph, alkynyl or sulfone), we synthesized $^{13}$C-labeled 4-methyl-N-(phenylethynyl)-N-(2-phenylethynyl)phenylbenzenesulfonamide (1a) and treated it under standard reaction conditions to produce the $^{13}$C-labeled desired products (3) at a higher yield (79%) (Fig. 8d) (Supplementary Fig. 178). This synthesis realizes the first sulfone radical addition to the α-carbon of ynamide and then intramolecular alkynyl migration via the expulsion of sulfone radicals and the simultaneous addition of available sulfone radicals to the β $^{13}$C-labeled alkyl group. To determine the importance of the electron-withdrawing group in the 2-alkynyl-ynamides (1), we replaced −Ts (aromatic) with the −Ms (aliphatic) group (1z) and treated it under standard reaction conditions to produce the desired product (95) at an excellent yield (80%) (Fig. 8e). The molecular structure of product 95 was unambiguously confirmed by X-ray crystallography (CCDC number: 95 (2084463)). These results

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**Fig. 7 Larger scale and product synthetic transformations.** a Reactions on a larger scale by using 1a with radical precursors 2a, 2da, and 2ea. b Synthetic transformations of the product 3.
suggest that sulfone derivatives (aliphatic or aromatic) may not be involved in the alkyne migration process, but they will exert a strong influence on ynamide stabilization and isomerization. Despite our attempts, we were not able to synthesize other protection groups in compound 1. The nature of the alkyne migration step was investigated via a crossover experiment with ynamides 1a and simple ynamide with 2a and simple ynamide with 2a. d 13C-labeled experiment to identify the in situ reshuffling groups in the transformations with help of 1a with 2a. The importance of the electron-withdrawing group in the 2-alkynyl-ynamides by replacing N-Ts with N-Ms in ynamide. d Intermolecular or intramolecular alkyne migration was investigated via a crossover experiments. g The carbon-linker length effect was tested by using compounds S22 and 2a. h Reaction tested by using intermediate 2-phenyl-3-(phenylethenyl)-1-tosylindole (87) with 2a under standard condition.
(2-iodo-2-phenylvinyl)sulfonyl)-4-methylbenzene) was observed in this transformation, 4-methyl-reaction intermediates in the reaction. Next, we utilized 4-methylynamide bond Ynamide (standard conditions, the compounds 4-methyl-irradiation, but the expected 2-phenyl-1-tosylindole product (were treated under standard reaction conditions and expected to not form, con
phenyl)benzenesulfonamide (2-(phenylethynyl)phenyl)benzenesulfonamide (1a), UV–vis absorption was not observed (Supplementary Figs. 45–48), which suggests that blue LED light only activate the radical precursors but not ynamides (1).

Based on the results of the above control experiment, previous1,11,37–40,47,54–64,69,70 reports and our own research experience41, a plausible mechanism is depicted in Fig. 9 for compounds 3', 51 and 76 (Supplementary Fig. 55). Blue LED light activate the radical precursor 2a (TsI) to the excited state 2a'. Then homolytic bond fission of excited state 2a' to generate sulfone (a) and iodine (b) radicals57. The generated reactive sulfone radical (a) triggers regio- and chemoselectively on the α-carbon of isomerized ynamide intermediate A, producing nitrogen-center radical-cation intermediate B and then inducing selective 5-endo-dig cyclization with an alkyl to generate key reactive intermediate C. The nucleophilic β-carbon of ynamide pushes electrons toward nitrogen cations via C(sp)–N bond fission to generate key intermediate D. Simultaneously, intramolecular migration and insertion of 1-methyl-4-((phenylethynyl)-2-13C)sulfonyl)benzene (99') by discharging sulfone radicals via Ts-C(sp) homolytic bond fission68,71,72 generates another key intermediate E. Finally, liberated radical sulfone addition to the β-carbon of the alkylene produces vinyl radical intermediate F. The available second radical source (iodine radical selenium) binds with intermediate F to produce the final product (3'/51).

In summary, we developed a robust approach for photo-induced divergent radical-triggered regio- and chemoselective
ynamide bond fission, skeletal reshuffling, and functionalization of 2-alkynyl-ynamides under mild reaction conditions. These photoinduced radical transformations on ynamides include the ynamide C(sp)–N bond fission, featuring divergent radical precursors and a very short reaction time. Such transformations are atom economic, have mild reaction conditions and are easy to handle, and their reaction procedures are simple. E-isomers are observed in the products of the iodine and selenium derivatives, a mixture of E/Z isomers are observed in the thio derivatives, and a broad substrate scope is achieved. Additionally, there is no need for expensive photocatalysts/metals, oxidants, or additives, and there is high scalability for the synthesis of inaccessible/highly challenging indole derivatives. Moreover, the control experiments and 13C-labeled studies provide further support regarding the viability of the proposed mechanism. The 13C-labeled studies revealed that the reaction presumably proceeds in situ with sulfone reshuffling from the α-carbon to the β-carbon in ynamides. Moreover, the products bearing active C=C bonds can be easily converted to essential derivatives, which cannot be achieved through known synthetic methods.

Methods

General procedure for the synthesis of (E)-3-(1-iodo/bromo-2-phenyl-2-tosylvinyl)-2-phenyl-1-tosylindole derivatives (3, 5-27, 28, 30, 41-43 and 98). An oven-dried screw-capped, 8 mL vial equipped with a magnetic stir bar was charged with ynamide (0.10 mmol, 1.0 equiv), sulfonil iodide/sulfonil bromide (0.11 mmol, 1.1 equiv), and DCM (0.05 M) solvent was added. The resulting solution was stirred up to starting material completion (2–10 min) at 28 °C under a blue LED light (the reaction mixture vial cooled with a fan, and the reaction mixtures were placed ~8.5 cm from the blue LED light). After that, the crude reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed, and concentrated. The crude material was purified by flash column chromatography to give the corresponding product.

General procedure for synthesis of (E)-3-(1-iodo-2-(4-methoxyphenyl)sulfonyl)-2-phenyl-1-tosylindole derivatives (29, 31-40 and 42). An oven-dried screw-capped 8 mL vial equipped with a magnetic stir bar was charged with ynamide (0.10 mmol, 1.0 equiv) sulfonyl iodide/sulfonyl bromide (0.15 mmol, 1.5 equiv) in DCM (0.05 M), I2 (0.05 mmol, 0.5 equiv), aq. 70% TBHP (0.30 mmol, 3.0 equiv) was added. The resulting solution was stirred up to starting material completion (30 min) at 28 °C under a blue LED light (the reaction mixture vial cooled with a fan, and the reaction mixtures were placed ~8.5 cm from the blue LED light). After that, the crude reaction mixture was diluted with water and extracted with DCM. The organic layer was dried over Na2SO4, filtered, and concentrated. The crude material was purified by flash column chromatography to give the corresponding product.

General procedure for synthesis of (E)-2-phenyl-3-(2-phenyl-1-(phenylselanyl)-2-tosylvinyl)-1-tosylindole derivatives (51-75). An oven-dried screw-capped, 8 mL vial equipped with a magnetic stir bar was charged with ynamide (0.10 mmol, 1.0 equiv), selenosulfonates (0.11 mmol, 1.1 equiv), and DCM (0.05 M) solvent was added. The resulting solution was stirred up to starting material completion (10–30 min) at 28 °C under a blue LED light (the reaction mixture vial cooled with a fan, and the reaction mixtures were placed ~8.5 cm from the blue LED light). After that, the crude reaction mixture was diluted with water and extracted with DCM. The organic layer was dried over Na2SO4, filtered, and concentrated. The crude material was purified by flash column chromatography to give the corresponding product.

Data availability

All data generated and analyzed during this study are included in this article and its Supplementary Information, and also available from the corresponding author. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Center (CCDC), under deposition numbers CCDC numbers: 3 (2884458), 4 (2884457), 14 (2884458), 50 (2107787), 51 (2084460), 76 (2884461), 94a (2884462), 95 (2884463), 97a (2084593). These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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