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Regiospecific Synthesis of 1,4-Diaryl-5-cyano-1,2,3-triazoles and Their Photoconversion to 2- or 3-Cyanoindoles

Brandon D. Nusser, Lucia E. Jenkins, Xinsong Lin, and Lei Zhu*

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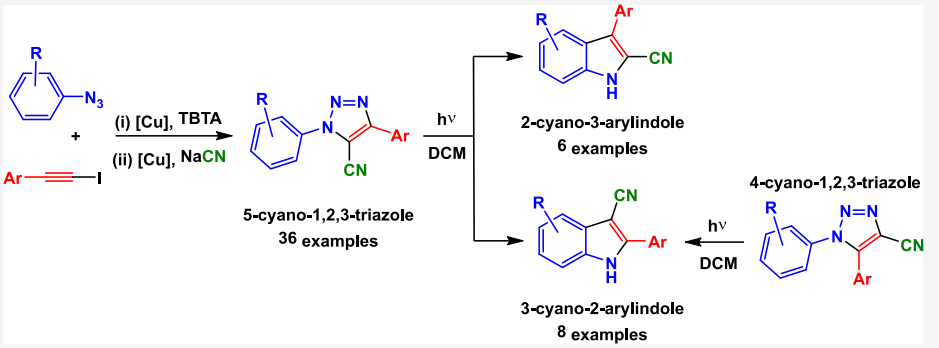


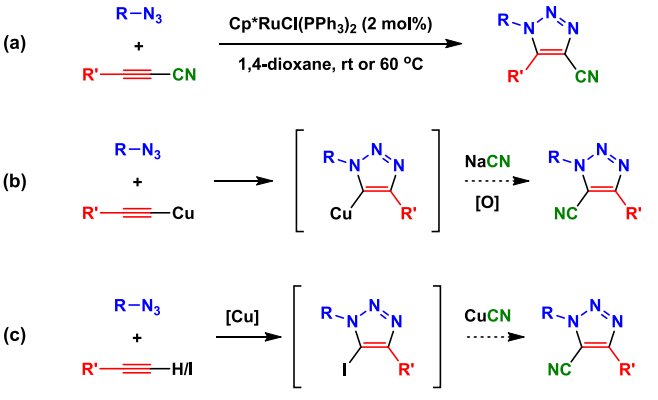
ABSTRACT: We report the synthesis of 1,4-diaryl-5-cyano-1,2,3-triazoles from azides and alkynes via two copper-mediated steps. Aryl-substituted cyanotriazoles are emissive in nonpolar solvents. When the N^1-aryl group is electron-donating, the photoconversion of a cyanotriazole to a cyanoindole is efficient. Each of the seven pairs of 4- and 5-cyanotriazole isomers is photoconverted to either distinctive cyanoindoles without rearrangement or a major cyanoindole product via the presumed common intermediate azirine. The resulting cyanoindoles appear to be stronger emitters in polar solvents than the parent cyanotriazoles.

INTRODUCTION

A main objective of organic chemistry is developing methods to create an ever-increasing number of molecular structures from a limited collection of building blocks from which interesting and perhaps useful properties arise. An example to illustrate this point is the suite of reactions starting from azides and alkynes to prepare substituted 1,2,3-triazoles with regiospecificity, as represented by the works from several landmark papers.[1,2] Our group has contributed to this effort,[3−7] from which a method of preparing 1,5-disubstituted-4-cyano-1,2,3-triazole (4-cyanotriazole from here on) was developed (Scheme 1a).[6] The selective synthesis of the complementary regioisomer 5-cyano-1,2,3-triazole (5-cyanotriazole from here on) from an azide and an alkyne has not been reported.

Two strategies were devised to access 5-cyanotriazoles from azides and alkynes. First, the coupling reaction between an azide and a copper(I) acetylide could be intercepted by a cyanide ion (Scheme 1b), which, after a redox maneuver, could afford the desired 5-cyanotriazole. This route mirrors a known synthesis of 5-alkynyltriazoles[7]: a cyanide ion ($N{\equiv}C^-$), which is similar in structure to an acetylide ($R{-}C{\equiv}C^-$), might undergo oxidative cross-coupling with copper(I) triazolide to result in 5-cyanotriazole. This strategy, however, is plagued by several side reactions that suppress the production of the target structure. For example, CuCN might instead undergo oxidative cross-coupling with copper(I) acetylide to produce 1-cyanoalkyne, which is unable to engage in the copper-catalyzed

Scheme 1. Formation of 4-Cyanotriazole (a)[6] and Two Strategies for Producing 5-Cyanotriazole (b,c)



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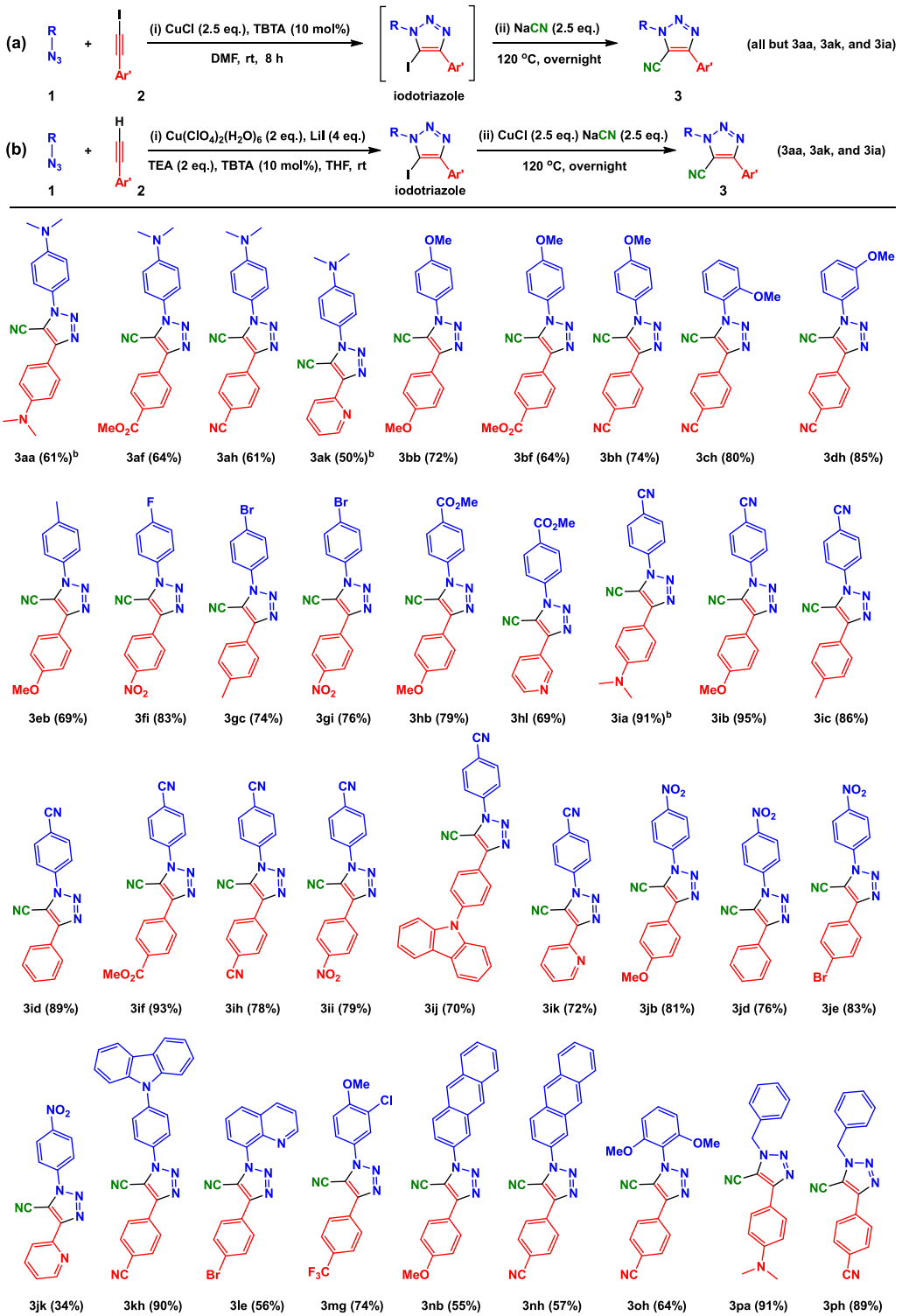
Scheme 2. Synthesis of 1,4-Diaryl-5-cyano-1,2,3-triazole from Azide and Iodoalkyne[a]



[a]a. TBTA: tris(benzyltriazolylmethyl)amine.[13] The first and second letters in a name are derived from its azide and iodoalkyne precursors (see structures in Charts S1 and S2), respectively; b. The yield was of a two-step sequence with the 5-iodotriazole intermediate isolated.

cycloaddition with an azide.[6] More concerning is the competitive protonation of the copper(I) triazolide intermediate to 5-protiotriazole, which was observed to have become the major product during attempts to implement the strategy illustrated in Scheme 1b. The lack of success in turning this idea into a practical method of synthesizing 5-cyanotriazole prompted us to explore the next option (Scheme 1c), which was to reach a 5-iodotriazole intermediate first,[4] followed by an in situ Rosenmund-von Braun reaction with CuCN[8] to arrive at the target regioisomer. 1-Aryl-5- (and 4-) cyanotriazoles have the potential to undergo photochemical conversion to 2- (or 3-) cyanoindoles.[9] In this article, a preliminary account of the latter transformation is also provided.

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RESULTS AND DISCUSSION

Cyanation of an aryl group can be achieved via the Rosenmund-von Braun-type copper-catalyzed substitution of an aryl halide by sodium or potassium cyanide.[8,10] The regiospecific synthesis of a 5-iodotriazole (from either a terminal alkyne or an iodoalkyne as shown in Scheme S1),[2,4] followed by cyanation shall deliver 5-cyanotriazole in a tandem (i.e., one-pot) operation. We elected to start the tandem sequence from the coupling reaction between an azide and an iodoalkyne (Scheme 2a). The latter could be prepared from its terminal alkyne precursor through several methods.[11] Starting this sequence from an iodoalkyne rather than a terminal alkyne alleviates safety concerns of heating reactive reagents involved in iodination, such as perchlorates that have been practiced by our group in 5-iodotriazole synthesis.[4,12] In addition, this method avoids the undesired 5-protiotriazole that might form in reactions starting from the corresponding terminal alkyne. Regarding the substrate scope, we focused on demonstrating the utility of this method in producing 1,4-diaryl-5-cyanotriazoles (Scheme 2) because of their potential to be fluorescent in both solution and solid phases. Though not extensively demonstrated, the reported procedure is expected to be effective for nonaryl azides. Two 5-cyanotriazoles prepared from benzyl azide are shown at the bottom of Scheme 2. It is helpful at this point to describe how the compounds are numbered in this article: compounds **1** and **2** are aryl azides (Chart S1) and iodoalkynes (Chart S2), respectively. Each individual compound also carries a letter from the alphabet for identification. Compounds **3** are 5-cyanotriazoles, compounds **4** are 4-cyanotriazoles, while compounds **5** and **6** are 2- and 3-cyanoindoles, respectively. The first and second letters in each name of compounds **3**−**6** are derived from their azide and iodoalkyne precursors, respectively.

The tandem sequence from an aryl azide and an iodoalkyne to a 5-cyanotriazole was tolerated by a number of functional groups included in the products shown in Scheme 2. The robustness of this method was derived from the efficiency of 5-iodotriazole formation from an azide and an iodoalkyne,[2] and the reliability of the Rosenmund-von Braun procedure in spite of high temperatures (120 °C or more).[8] The reaction was compatible with aryl halides (other than iodides, see compounds **3fi**, **3gc**, **3gi**, **3le**, and **3mg**), a testament to the selectivity of the Rosenmund-von Braun reaction for triazolyl iodides. The only compounds not prepared using the tandem sequence were those requiring the iodoalkyne with an *N*,*N*-dimethylanilinyl component (**2a** in Chart S2). This iodoalkyne was shown to be unstable. In such a case, 5-iodotriazole was first prepared using the procedure that started from the terminal alkyne,[4] followed by the Rosenmund-von Braun cyanation, to afford compounds **3aa** and **3ia** (Scheme 2b). The X-ray single crystal structures of 5-cyanotriazole **3ah** and its regioisomer 4-cyanotriazole **4ah** (for the purpose of demonstrating the contrasting regiochemistry), the latter obtained from a ruthenium(II)-catalyzed coupling reaction (Scheme 1a),[5] are shown in Figure 1.

Photoconversion of N^1-aryl-1,2,3-triazoles to indoles[9,14−17] is one of the several 1,2,3-triazole ring-opening reactions[18] that have thus far been reported. Others include the thermal denitrogenation of N^1-sulfonyltriazoles to metal-bound iminocarbenes,[19] pyrolysis of N^1-vinyltriazoles,[20] Dimroth rearrangement of 5-aminotriazoles,[21] and denitrogenative transformations of closely related benzotriazoles[22] and pyridotriazoles.[23] However, the photoreaction has not been studied in depth in terms of either applicability or mechanism. This lack of development could be attributed, in part, to the scarcity of methods of triazole synthesis until the advent of metal-catalyzed approaches.

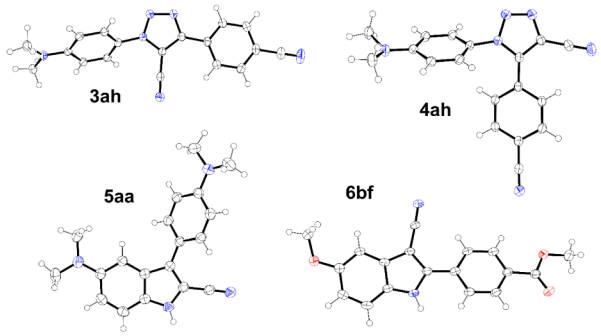

Figure 1. ORTEP views (50% probability ellipsoids) of the X-ray single crystal structures for confirming the regiochemistry of 5-cyanotriazole **3ah** (CCDC# 2252535), 4-cyanotriazole **4ah** (CCDC# 2309514), 2-cyanoindole **5aa** (CCDC# 2309515), and 3-cyanoindole **6bf** (CCDC# 2308319). Carbon and hydrogen are black; nitrogen is blue; oxygen is red.

In this work, some of the synthesized 5-cyanotriazoles were photoconverted to 2- or 3-cyanoindoles (Scheme 3). The reactivity of 5-cyanotriazole depends principally on three factors: (1) the absorptivity at the wavelength coverage of the irradiation source, (2) at least one of two *ortho* positions on N^1-aryl (the reaction site) is available for bond formation, and (3) the electronic property of the N^1-aryl substituent. Triazoles carrying electron-donating aryl groups at the N^1 position are particularly reactive.[17] An N^1-aryl-5-cyanotriazole (e.g., **3ah**) that has a relatively high absorptivity under a given irradiation source (e.g., 390 nm LED) and also carries an electron-donating N^1-aryl group (e.g., *N*,*N*-dimethylanilinyl) undergoes photoconversion to a cyanoindole with high efficiency. Besides these intrinsic properties of a 5-cyanotriazole substrate, the selection of solvent is crucial: dichloromethane (as opposed to acetonitrile,[9,15,16] and in fewer cases, benzene[14] and isopropanol,[16] in which triazole photodenitrogenation has been reported) afforded the best outcome in terms of time and yield. The photooxidation of the *N*,*N*-dimethylamino group could be a significant side reaction.[24] Therefore, the relevant reaction mixture was deoxygenated via three freeze−pump−thaw cycles to ensure clean photoconversion to indole.

The regiochemical distinction between 2- and 3-cyanoindoles was characterized based on the diagnostic ^{13}C chemical shift value of C3 (80−90 ppm) in 3-cyanoindole. The reliability of this diagnostic tool is supported by both calculations and precedents[25] (see a detailed description in the Supporting Information). Furthermore, the regiochemical assignment is corroborated with the available single-crystal X-ray structures (**5aa** and **6bf** in Figure 1). Some 5-cyanotriazoles (e.g., **3aa**, **3af**, **3ah**, and **3ia**) afforded 2-cyanoindoles upon photodenitrogenation, while others (e.g., **3bf**, **3bh**, and **3ch**) produced 3-cyanoindoles, necessarily via a rearrangement process (see cyanoindole structures in frames (a) and (b) of Scheme 3).

The postulated mechanism of photoconversion of 5-cyanotriazole to 2- or 3-cyanoindole is shown in Scheme 4. The excitation of 5-cyanotriazole (lower left) triggers the N1−

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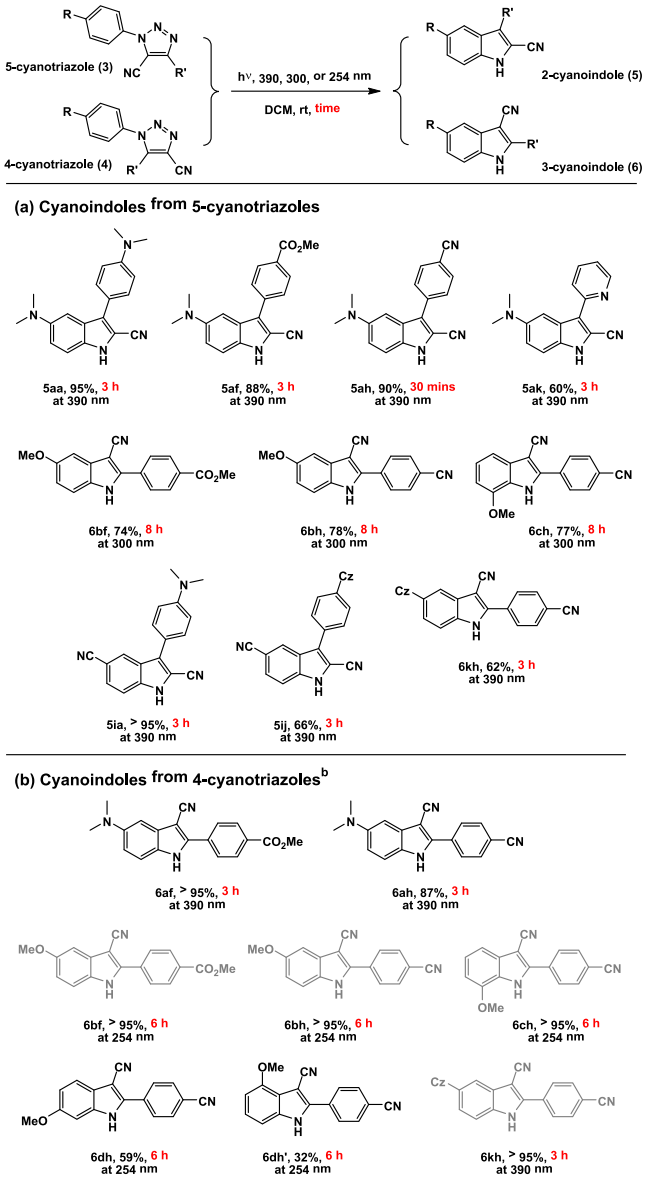
Scheme 3. Photodenitrogenation of N^1-Aryl-4/5-cyano-1,2,3-triazole to 2- or 3-Cyanoindole[a]



[a]Cz = *N*-carbazolyl; b. See the structures of 4-cyanotriazole precursors in Chart S3. Structures in gray (4 compounds) were also prepared from their 5-cyanotriazole precursors; see frame (a) above.

N2 bond cleavage to result in a diazo intermediate (Step 1), which may move irreversibly forward by ejecting molecular nitrogen to form an iminocarbene (Step 2). The chemistry following the N_2 ejection has only been discussed in relevant works in the ground states.[9,16,26,27] Iminocarbene is expected to undergo cyclization to afford 2-cyano preindole (Step 3), which tautomerizes to afford the isolable 2-cyanoindole (Step 6). The cyano-substituted iminocarbene may cyclize in a different way to form azirine (Step 4). Step 4 is depicted as irreversible based on the conclusion by Mitchell and Rees that in an azirine, the C−N bond carrying an electron-withdrawing group, e.g., cyano, breaks in preference to the other one to revert back to iminocarbene.[9] The bond that breaks in azirine is colored red in Scheme 4. We note that azirine was postulated to be the intermediate in the pyrolysis and photolysis of triazoles in the early works on this topic[26,27] but has not since been directly observed during these reactions. The C−N bond marked in red in the postulated azirine structure would break to afford the isomeric iminocarbene (Step 4'), thus leading to rearrangement.

The observed regiochemistry of cyanoindole formation, to a large extent, depends on the likelihood of azirine involvement. We realized that if an azirine is a necessary intermediate in this transformation, the reaction starting from either 5-cyanotriazole or the isomeric 4-cyanotriazole would result in the same cyanoindole product(s). The counterfactual of this scenario arrives at the following: if two distinct cyanoindoles were produced from two isomeric triazoles without rearrangement, then azirine could not be a shared intermediate. For this reason, we prepared seven 4-cyanotriazoles (structures are shown in Chart S3) that were regioisomers of seven of the 5-cyanotriazoles in Scheme 2 using the ruthenium(II)-catalyzed method (Scheme 1a),[6] and subjected them to photoirradiation. Only 3-cyanoindoles were afforded without rearrangement (Scheme 3, frame (b)). The contrasting regioselectivity of cyanoindole formation starting from different pairs of regioisomeric cyanotriazoles is represented in the reactions shown in Scheme 5.

The formation of cyanoindoles **5ah** and **6ah** from their respective triazole precursors (**3ah** and **4ah** in Scheme 5a) suggests one of the two scenarios − either there is no azirine formation in the photodenitrogenation of both cyanotriazoles (i.e., Steps 4 or 4' are absent in Scheme 4, or Steps 5 and 5′ are operative to skip iminocarbene and azirine entirely), or only one cyanotriazole of the pair is converted to azirine after denitrogenation but does not continue further to form the isomeric iminocarbene. In order to explain the conversion of the cyanotriazole pair of **3bh** and **4bh** to a single cyanoindole **6bh** (Scheme 5b), the only condition is that one of the triazoles (5-cyanotriazole **3bh**, to be specific) needs to be converted to azirine, in which the original C−N bond is then broken to arrive at the isomeric iminocarbene. The biased ring-opening of the presumed cyano-substituted azirine (illustrated in Scheme 4 by an irreversible Step 4 and a reversible Step 4') is consistent with the conclusion by Mitchell and Rees, in which the C−N bond of an azirine is favored to break if the bond carries an electron-withdrawing substituent (e.g., a cyano group).[9,27] Relating substrate structures to the likelihood of these scenarios is an ongoing research topic in our laboratory, the results of which will be reported in due course.

From this initial set of observations, we found that (1) 2-cyanoindoles **5** were obtained as the sole or major regioisomers from 5-cyanotriazoles **3** that carried *N*,*N*-dimethylanilinyl at either the N^1- or the C^4-position. 3-Cyanoindoles **6** were the major regioisomers from photoconverting the rest of the 5-cyanotriazoles **3**. (2) Photodenitrogenation of 4-cyanotriazoles **4** delivered 3-cyanoindoles **6** as the sole products. (3) The denitrogenative photoconversion of triazole to indole does not have to go through the azirine intermediate that may trigger a rearrangement, as evidenced by the two pairs of reactions shown in Scheme 5. The continuation on the topic of triazole photochemistry by our group after this report will include (1) the expansion of the scope of 4-cyanotriazole photoconversion as a method for preparing 3-cyanoindoles, which are attractive synthetic targets,[25,28] and (2) the quest for a mechanistic model with predictive power of the regioselectivity of triazole photoconversion to indole.

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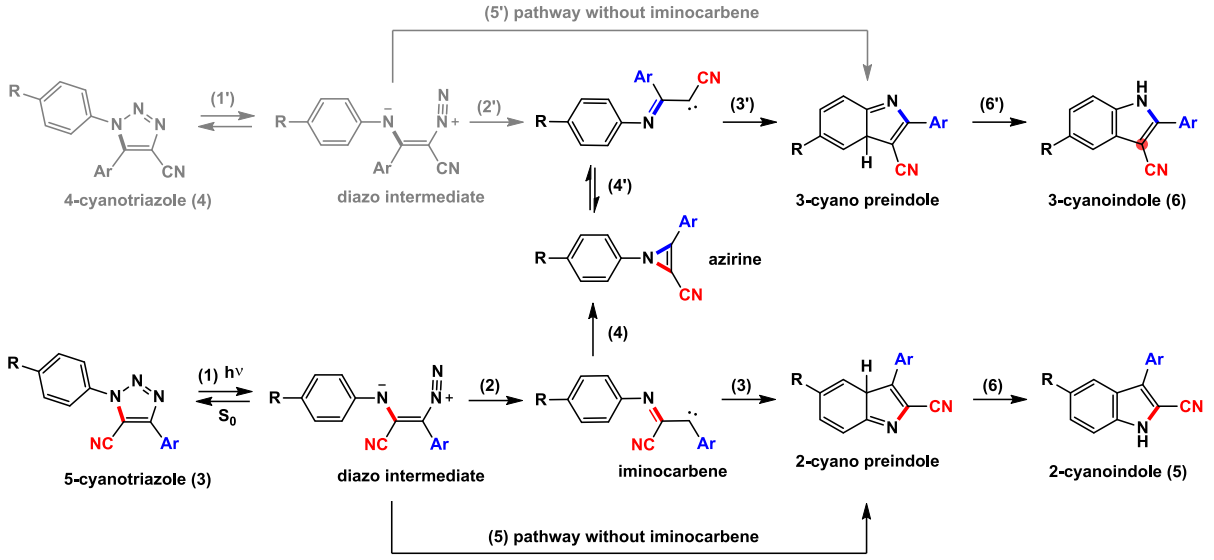
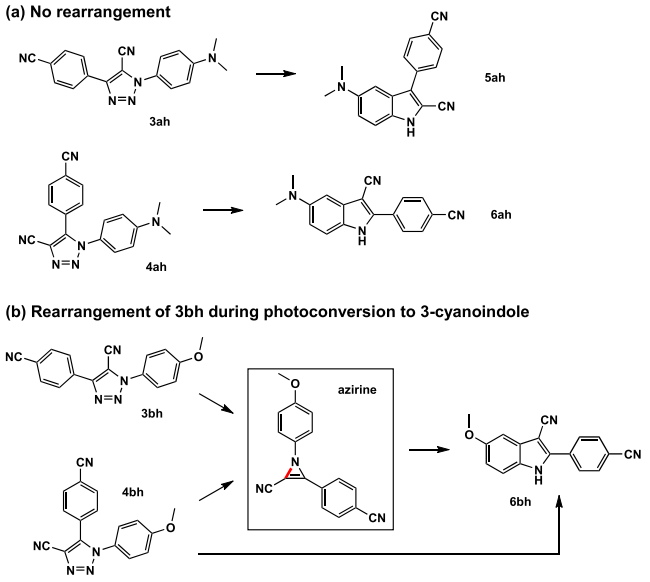
Scheme 4. A Mechanistic Sketch of Photodenitrogenation of Cyanotriazole to Cyanoindole[a]



[a]The red C−N bond in 2-cyanoindole (lower right) is carried over from the starting 5-cyanotriazole (lower left), while the blue C−N bond in 3-cyanoindole (upper right) results from a rearrangement through azirine. The engagement of the 4-cyanotriazole isomer (upper left) in this scheme is depicted in gray. The red-highlighted carbon in 3-cyanoindole has a characteristic ^{13}C chemical shift in the range of 80−90 ppm.

Scheme 5. Photoconversion of N^1-Aryltriazole to Indole (a) without and (b) with Rearrangement[a]



[a]In (b), the C−N bond of the azirine that carries the electron-withdrawing cyano group (marked in red) breaks, which is consistent with the conclusion by Mitchell and Rees,[9] and determines the regiochemistry of the observed 3-cyanoindole product.

The cyano group at the 5-position of a triazole shifts the lowest energy absorption band of the unsubstituted analogue (5-protiotriazole) to a longer wavelength that may breach the visible region (e.g., see the spectrum of **3ah** in Figure S4). As such, the utility of the triazole core structure as a photochemical precursor is elevated because glass-based optics and (near) visible excitation sources are now compatible. The installation of the cyano group did not appear to negatively impact the emission properties of its protiotriazole analog. As an example, the solvent-sensitive emission of **3ah** was similar to that of its reported protiotriazole analogue,[17] and the emission quantum yield in each solvent was respectable (Figure 2a). After photodenitrogenation of **3ah**, the resulting 2-cyanoindole

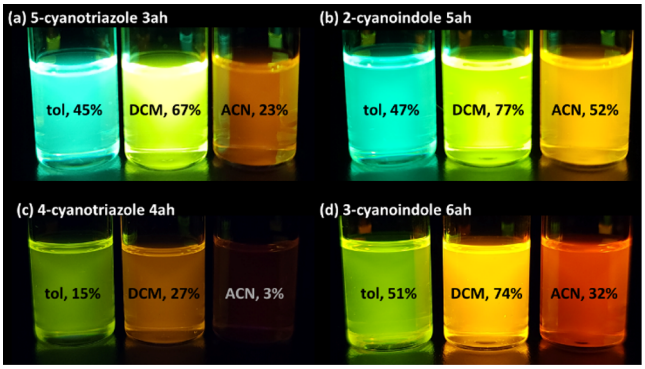


Figure 2. Emission colors of (a) 5-cyanotriazole **3ah**, (b) 2-cyanoindole **5ah**, (c) 4-cyanotriazole **4ah**, and (d) 3-cyanoindole **6ah** in, from left to right in each frame, toluene, dichloromethane, and acetonitrile. Emission quantum yields are given in the figure. Concentrations were 25 μM (for acquiring emission images) and 5 μM (for acquiring emission quantum yields).

5ah was arguably a stronger emitter (Figure 2b). Unlike its cyanotriazole precursor, the emission quantum yield of **5ah** did not diminish in acetonitrile, a polar solvent, making it a promising candidate for labeling and imaging purposes in polar environments. We also obtained emission quantum yields of 4-cyanotriazole **4ah** and the photoconverted product 3-cyanoindole **6ah** (Figure 2c,d). It is notable that the emission of 4-cyanotriazole **4ah** was almost quenched in acetonitrile, while its 3-cyanoindole photoproduct **6ah** retained a high emission quantum yield. More thorough photophysical characterizations of 2- and 3-cyanoindoles that were derived from diaryl-substituted cyanotriazoles will be reported in an upcoming account.

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CONCLUSION

In summary, a method of the regiospecific synthesis of 5-cyanotriazoles is described. The tandem 5-iodotriazole formation followed by the Rosenmund-von Braun cyanation tolerates a wide range of functional groups to deliver 5-cyanotriazoles in yields of 50−95% (except **3jk** with 34%). This method complements our previously reported synthesis of 4-cyanotriazoles.[6] Both regioisomers, when substituted with aryl groups at the two remaining positions, may undergo photodenitrogenation to form 2- or 3-cyanoindoles. The photodenitrogenation proceeds rapidly with minimal by-products in dichloromethane, which is an improvement over the previously reported examples of photoconverting triazoles to indoles. The reigning mechanistic model[9] invokes azirine as an intermediate by which rearrangement occurs to produce two isomeric indoles. We found that the regioselectivity of this photoconversion varies depending on the substrate structure. In certain cases, no rearrangement occurs in the sense that the regiochemistry of the cyanoindole product is determined by that of the starting cyanotriazole. While in other cases, both 4- and 5-cyanotriazole regioisomers yield the same major 3-cyanoindole product. Clearly, the mechanism of this photoreaction is more nuanced than that portrayed in the literature. The photoconversions of 4-cyanotriazoles exclusively result in 3-cyanoindoles. Both cyanotriazoles and cyanoindoles can be highly emissive fluorophores. The expansion of the synthetic utility of cyanotriazole photoconversion to cyanoindole and the applications of cyanotriazoles and cyanoindoles as fluorescent labels will be reported in due course.

EXPERIMENTAL SECTION

1. Materials and General Methods. Reagents and solvents were used as received from various commercial sources. Dichloromethane (DCM) used in the photochemical reaction was dried and then distilled from calcium hydride. Thin-layer chromatography (TLC) was performed on silica gel 60 F254 plates. Flash column chromatography was performed using 40−63 μm (230−400 mesh) silica gel. ^{1}H and ^{13}C{^{1}H} NMR spectra were acquired at 500/600 and 125/150 MHz, respectively. Chemical shifts are reported in δ (ppm) values relative to the residual internal $CHCl_3$ (δ_H 7.26, δ_C 77.2) or DMSO-d_5 (δ_H 2.50, δ_C 39.5). High-resolution mass spectra of the reported organic compounds were obtained at the Mass Spectrometry Laboratory at Florida State University. Absorption spectra were recorded on a Cary 100 spectrophotometer. Absolute emission quantum yields were measured on a Hamamatsu Quantaurus-QY instrument. X-ray single crystal structures were collected using a Rigaku XtaLAB Synergy-S diffractometer equipped with a HyPix-6000HE Hybrid Photon Counting (HPC) detector and dual Mo and Cu microfocus sealed X-ray sources as well as a low-temperature Oxford Cryosystem 800 at 150 K. All aryl azides (compounds **1** in Chart S1) used in this work have been reported,[29] while all but one (**2j**) iodoalkynes (compounds **2** in Chart S2) used in this work have been reported.[30] Ligand TBTA was prepared based on our previously reported procedure.[5] **CAUTION!** Low molecular weight organic and inorganic azides are potentially explosive. Appropriate protective measures should always be applied when handling these chemicals.

2. General Procedure for 5-Cyanotriazoles (Compounds 3 Except 3aa and 3ia). To an oven-dried 15 mL pressure tube equipped with a magnetic stir bar, an iodoalkyne (0.2 mmol), an azide (0.2 mmol), TBTA (11 mg, 0.02 mmol), CuCl (50 mg, 0.5 mmol), and DMF (1.0 mL) were added in this order. The pressure tube was capped, and the reaction mixture was stirred at rt for 8 h. NaCN (25 mg, 0.5 mmol) was then added, and the reaction mixture was maintained at 120 °C in an oil bath overnight. The reaction mixture was allowed to cool to rt, quenched with ammonium hydroxide (28−30 w/w%, 10 mL), diluted with ethyl acetate (30 mL), and separated. The organic phase was washed first with saturated ammonium chloride (2 × 30 mL) and then with a saturated sodium chloride solution (1 × 30 mL), followed by drying over anhydrous sodium sulfate. TLC analysis was carried out during the drying stage using an eluent of hexanes/ethyl acetate (3:1, v/v). After the solvent was removed in vacuo, the concentrate was typically chromatographed on a silica column using an increasing gradient of ethyl acetate (up to 50%) in hexanes. The eluting solvent used in both TLC and the column may vary depending on the structure of the product.

3. The Two-Step Procedure to Prepare 5-Cyanotriazoles (Compounds 3aa, 3ak, and 3ia). Step (i) − the preparation of 5-iodotriazole. To a 50 mL round-bottom flask equipped with a magnetic stir bar, an azide (1 mmol), THF (5 mL), LiI (536 mg, 4 mmol), copper(II) perchlorate hexahydrate (740 mg, 2 mmol), triethylamine (TEA, 280 μL, 2 mmol), TBTA (53 mg, 10 mol %), and a terminal alkyne (1 mmol) were added in this order. The reaction mixture was stirred for 3 h at rt. The mixture was quenched with ammonium hydroxide (30 mL, 28−30 w/w%) and filtered. The filtrate was first washed with water (3 × 15 mL) and then with chilled (in an ice water bath) ethyl acetate. The recovered material was verified to be the intended 5-iodotriazole, and it was used directly in the next step.

Step (ii) − the preparation of 5-cyanotriazole. To an oven-dried 15 mL pressure tube equipped with a magnetic stir bar, 5-iodotriazole (0.2 mmol from Step (i), CuCl (50 mg, 0.5 mmol), NaCN (25 mg, 0.5 mmol), and DMF (1.0 mL) were added, respectively. The pressure tube was capped, and the reaction mixture was maintained at 120 °C in an oil bath overnight. The reaction mixture was allowed to cool to rt, quenched with ammonium hydroxide (30 mL, 28−30 w/w %), diluted with ethyl acetate (30 mL), washed first with saturated ammonium chloride (2 × 30 mL) and then with a saturated sodium chloride solution (1 × 30 mL), and dried over anhydrous sodium sulfate. TLC analysis was carried out during the drying stage using an eluent of hexanes and ethyl acetate in a 3:1 ratio. After the solvent was removed in vacuo, the concentrate was typically chromatographed on a silica column using an increasing gradient of ethyl acetate (up to 50%) in hexanes. The eluting solvent used in both TLC and the column may vary depending on the structure of the product.

4. Photochemistry (Compounds 5 and 6). (i) General procedure. The absorption spectrum of a given cyanotriazole was first collected to determine which light source (390 nm LEDs, or 300- or 254 nm in a Rayonet photoreactor) was appropriate for the photochemical reaction (see spectra in Figure S5). To a 50 mL Schlenk tube (Pyrex or quartz, depending on the chosen light source) equipped with a magnetic stir bar, cyanotriazole (0.1 mmol) was added. The reaction vessel was evacuated for 5 min and refilled with argon, and calcium hydride-dried DCM (30 mL) was added via an oven-dried syringe. The reaction mixture was irradiated. The lamp, irradiation time, or need for a quartz container are noted in the entries of characterization of each indole product in the Supporting Information. If 390 nm LEDs (Kessil, 52 W maximum power) were applied, the reaction was placed 2 in. from the source between two LEDs. The reaction was then washed with deionized water (1× 20 mL) and dried over anhydrous sodium sulfate. TLC analysis was carried out during the drying stage. After the solvent was removed in vacuo, the crude product was typically purified on a silica column using an increasing gradient of ethyl acetate in hexanes as the eluent. The eluting solvent used in both TLC and the column may vary depending on the structure of the product.

(ii) Photochemistry of cyanotriazoles with the N^1-(*N*,*N*-dimethyl)-anilinyl group. (*N*,*N*-Dimethyl)aniline-derived compounds tend to undergo photochemical oxidation of the *N*-substituted methyl groups.[24] Therefore, a more stringent deoxygenation procedure was carried out before the photochemical reactions of these compounds. To a 50 mL Schlenk tube equipped with a magnetic stir bar, cyanotriazole (0.1 mmol) and DCM (30 mL) were added. The solution was freeze−pump−thawed three times for 15 min per cycle. The vessel was backfilled with argon. The reaction mixture was irradiated (light source and reaction time are specified in the

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J. Org. Chem. 2024, 89, 12610−12618

characterization entries). The reaction mixture was then washed with deionized water (20 mL) and dried over anhydrous sodium sulfate. TLC analysis was carried out during the drying stage. The crude product was typically purified on a silica column with an increasing gradient of ethyl acetate in hexanes as the eluent. The eluting solvent used in both TLC and the column may vary depending on the structure of the product.

■ ASSOCIATED CONTENT

Data Availability Statement

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

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c01533.

Stepwise synthesis of 5-cyanotriazole (Scheme S1); azides and 1-iodoalkynes used in this work (Charts S1 and S2); regiochemical assignment of cyanoindole; aromatic regions of $^{13}C\{^{1}H\}$ NMR spectra (Figure S1); correlations between calculated chemical shift values and experimental chemical shifts (Figure S2); aromatic regions of HMBC spectra (Figure S3); structures of 4-cyanotriazoles (Chart S3); absorption spectra (Figures S4 and S5); emission colors of 5-cyanotriazole and 2-cyanoindole (Figure S6); synthetic procedures and characterization data; X-ray single-crystal data and structure refinement (Tables S1−S4); copies of ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of reported compounds (Figures S7−S66) (PDF)

Accession Codes

CCDC 2252535, 2308319, and 2309514−2309515 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 336 033.

■ AUTHOR INFORMATION

Corresponding Author

Lei Zhu − *Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida 32306-4390, United States;* orcid.org/0000-0001-8962-3666; Email: lzhu@fsu.edu

Authors

Brandon D. Nusser − *Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida 32306-4390, United States*

Lucia E. Jenkins − *Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida 32306-4390, United States*

Xinsong Lin − *Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida 32306-4390, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.4c01533

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Tornøe, C. W.; Christensen, C.; Meldal, M. Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides. *J. Org. Chem.* **2002**, *67* (9), 3057−3064. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective "Ligation" of Azides and Terminal Alkynes. *Angew. Chem., Int. Ed.* **2002**, *41* (14), 2596−2599. (c) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. Ruthenium-Catalyzed Cycloaddition of Alkynes and Organic Azides. *J. Am. Chem. Soc.* **2005**, *127* (46), 15998−15999. (d) Angell, Y.; Burgess, K. Base Dependence in Copper-Catalyzed Huisgen Reactions: Efficient Formation of Bistriazoles. *Angew. Chem., Int. Ed.* **2007**, *46* (20), 3649−3651. (e) Worrell, B. T.; Ellery, S. P.; Fokin, V. V. Copper(I)-Catalyzed Cycloaddition of Bismuth(III) Acetylides with Organic Azides: Synthesis of Stable Triazole Anion Equivalents. *Angew. Chem., Int. Ed. Engl.* **2013**, *52*, 13037−13041. (f) Gutiérrez-González, A.; Destito, P.; Couceiro, J. R.; Pérez-González, C.; López, F.; Mascareñas, J. L. Bioorthogonal Azide−Thioalkyne Cycloaddition Catalyzed by Photoactivatable Ruthenium(II) Complexes. *Angew. Chem., Int. Ed.* **2021**, *60* (29), 16059−16066. (g) Wu, Y.-M.; Deng, J.; Li, Y.; Chen, Q.-Y. Regiospecific Synthesis of 1,4,5-Trisubstituted-1,2,3-triazole via One-Pot Reaction Promoted by Copper(I) Salt. *Synthesis* **2005**, *2005*, 1314−1318.

(2) Hein, J. E.; Tripp, J. C.; Krasnova, L. B.; Sharpless, K. B.; Fokin, V. V. Copper(I)-Catalyzed Cycloaddition of Organic Azides and 1-Iodoalkynes. *Angew. Chem., Int. Ed.* **2009**, *48* (43), 8018−8021.

(3) Kuang, G.-C.; Michaels, H. A.; Simmons, J. T.; Clark, R. J.; Zhu, L. Chelation-Assisted, Copper(II)-Acetate-Accelerated Azide−Alkyne Cycloaddition. *J. Org. Chem.* **2010**, *75* (19), 6540−6548.

(4) Brotherton, W. S.; Clark, R. J.; Zhu, L. Synthesis of 5-Iodo-1,4-disubstituted-1,2,3-triazoles Mediated by in situ Generated Copper(I) Catalyst and Electrophilic Triiodide Ion. *J. Org. Chem.* **2012**, *77* (15), 6443−6455.

(5) Brassard, C. J.; Zhang, X.; Brewer, C. R.; Liu, P.; Clark, R. J.; Zhu, L. Cu(II)-Catalyzed Oxidative Formation of 5,5′-Bistriazoles. *J. Org. Chem.* **2016**, *81* (24), 12091−12105.

(6) Liu, P.; Clark, R. J.; Zhu, L. Synthesis of 1-Cyanoalkynes and Their Ruthenium(II)-Catalyzed Cycloaddition with Organic Azides to Afford 4-Cyano-1,2,3-triazoles. *J. Org. Chem.* **2018**, *83*, 5092−5103.

(7) Liu, P.; Brassard, C. J.; Lee, J. P.; Zhu, L. Cu^{II}-Catalyzed Oxidative Formation of 5-Alkynyltriazoles. *Chem. - Asian J.* **2020**, *15*, 380−390.

(8) Huang, C.; Qu, J.; Qi, J.; Yan, M.; Xu, G. Dicyanostilbene-Derived Two-Photon Fluorescence Probe for Free Zinc Ions in Live Cells and Tissues with a Large Two-Photon Action Cross Section. *Org. Lett.* **2011**, *13* (6), 1462−1465.

(9) Mitchell, G.; Rees, C. W. Photolysis of 1-aryl −1,2,3-triazoles; rearrangement via 1H-azirines. *J. Chem. Soc., Perkin Trans.* **1987**, *1*, 413−422.

(10) (a) Bragg, R. A.; Bushby, N.; Ericsson, C.; Kingston, L. P.; Ji, H.; Elmore, C. S. The synthesis of tritium, carbon-14 and stable isotope labelled selective estrogen receptor degraders. *J. Labelled*

Compd. Rad. **2016**, *59* (11), 454−461. (b) Schareina, T.; Beller, M. Copper-Catalyzed Cyanations of Aryl Halides and Related Compounds, *Copper-Mediated Cross-Coupling Reactions*, John Wiley & Sons, Inc., 2013, pp. 313−334. (c) Tseng, H.-W.; Liu, J.-Q.; Chen, Y.-A.; Chao, C.-M.; Liu, K.-M.; Chen, C.-L.; Lin, T.-C.; Hung, C.-H.; Chou, Y.-L.; Lin, T.-C.; et al. Harnessing Excited-State Intramolecular Proton-Transfer Reaction via a Series of Amino-Type Hydrogen-Bonding Molecules. *J. Phys. Chem. Lett.* **2015**, *6* (8), 1477−1486.

(11) (a) Amatore, C.; Blart, E.; Genet, J. P.; Jutand, A.; Lemaire-Audoire, S.; Savignac, M. New synthetic applications of water-soluble acetate Pd/TPPTS catalyst generated in situ. Evidence for a true Pd(0) species intermediate. *J. Org. Chem.* **1995**, *60* (21), 6829−6839. (b) Mo, Z.-Y.; Zhang, Y.-Z.; Huang, G.-B.; Wang, X.-Y.; Pan, Y.-M.; Tang, H.-T. Electrochemical Sulfonylation of Alkynes with Sulfonyl Hydrazides: A Metal- and Oxidant-Free Protocol for the Synthesis of Alkynyl Sulfones. *Adv. Synth. Catal.* **2020**, *362* (11), 2160−2167. (c) Reddy, K. R.; Venkateshwar, M.; Maheswari, C. U.; Kumar, P. S. Mild and efficient oxy-iodination of alkynes and phenols with potassium iodide and tert-butyl hydroperoxide. *Tetrahedron Lett.* **2010**, *51*, 2170−2173.

(12) (a) Barsoum, D. N.; Brassard, C. J.; Deeb, J. H. A.; Okashah, N.; Sreenath, K.; Simmons, J. T.; Zhu, L. Synthesis of 5-iodo-1,2,3-triazoles from organic azides and terminal alkynes − ligand acceleration effect, substrate scope, and mechanistic insights. *Synthesis* **2013**, *45*, 2372−2386. (b) Barsoum, D. N.; Okashah, N.; Zhang, X.; Zhu, L. Mechanism of Copper(I)-Catalyzed 5-Iodo-1,2,3-triazole Formation from Azide and Terminal Alkyne. *J. Org. Chem.* **2015**, *80* (19), 9542−9551.

(13) (a) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. Polytriazoles as Copper(I)-Stabilizing Ligands in Catalysis. *Org. Lett.* **2004**, *6* (17), 2853−2855. (b) Michaels, H. A.; Zhu, L. Ligand-Assisted, Copper(II) Acetate-Accelerated Azide−Alkyne Cycloaddition. *Chem. - Asian J.* **2011**, *6*, 2825−2834.

(14) Burgess, E. M.; Carithers, R.; McCullagh, L. Photochemical decomposition of 1H-1,2,3-triazole derivatives. *J. Am. Chem. Soc.* **1968**, *90* (7), 1923−1924.

(15) Wender, P. A.; Cooper, C. B. Indole synthesis based on triazole photochemistry: Total synthesis of 7-methoxymitosene. *Tetrahedron Lett.* **1987**, *28* (49), 6125−6128.

(16) Alimi, I.; Remy, R.; Bochet, C. G. Photochemical C−H Activation: Generation of Indole and Carbazole Libraries, and First Total Synthesis of Clausenawalline D. *Eur. J. Org. Chem.* **2017**, *2017* (22), 3197−3210.

(17) Nusser, B. D.; Accardo, J. V.; Zhu, L. Luminescence and Stability of 1,4,5-Triaryl-1,2,3-Triazoles. *ChemPhysChem* **2023**, *24*, No. e202300209.

(18) (a) Akter, M.; Rupa, K.; Anbarasan, P. 1,2,3-Triazole and Its Analogues: New Surrogates for Diazo Compounds. *Chem. Rev.* **2022**, *122* (15), 13108−13205. (b) Li, W.; Zhang, J. Synthesis of Heterocycles through Denitrogenative Cyclization of Triazoles and Benzotriazoles. *Chem. - Eur. J.* **2020**, *26* (52), 11931−11945.

(19) (a) Davies, H. M. L.; Alford, J. S. Reactions of metallocarbenes derived from N-sulfonyl-1,2,3-triazoles. *Chem. Soc. Rev.* **2014**, *43* (15), 5151−5162. (b) Das, S. K.; Roy, S.; Chattopadhyay, B. Transition-Metal-Catalyzed Denitrogenative Annulation to Access High-Valued N-Heterocycles. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202210912.

(20) Su, Y.; Petersen, J. L.; Gregg, T. L.; Shi, X. Ambient Benzotriazole Ring Opening through Intermolecular Radical Addition to Vinyltriazole. *Org. Lett.* **2015**, *17* (5), 1208−1211.

(21) (a) Gilchrist, T. L.; Gymer, G. E. 1,2,3-Triazoles. In *Advances in Heterocyclic Chemistry*, Katritzky, A. R.; Boulton, A. J., Ed.; Academic Press, 1974, Vol. *16*, pp. 3385. (b) Ogata, V.; Takagi, K.; Hayashi, E. Photochemical Dimroth Rearrangement of 1,4-Diphenyl-5-amino- and 4-Phenyl-5-anilino-1,2,3-triazoles. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2505−2506.

(22) (a) Wang, Y.; Wang, Z.; Tang, Y. Renaissance of Ring-Opening Chemistry of Benzotriazoles: New Wine in an Old Bottle. *Chem. Rec.* **2020**, *20*, 693−709. (b) Wang, Y.; Wu, Y.; Li, Y.; Tang, Y. Denitrogenative Suzuki and carbonylative Suzuki coupling reactions of benzotriazoles with boronic acids. *Chem. Sci.* **2017**, *8*, 3852−3857. (c) Teders, M.; Pitzer, L.; Buss, S.; Glorius, F. Regioselective Synthesis of 2-Substituted Indoles from Benzotriazoles and Alkynes by Photoinitiated Denitrogenation. *ACS Catal.* **2017**, *7* (6), 4053−4056. (d) Li, J.; Wang, S.; Zhao, J.; Li, P. Visible Light-Promoted Radical-Mediated Ring-Opening/Cyclization of Vinyl Benzotriazoles: An Alternative Approach to Phenanthridines. *Org. Lett.* **2022**, *24*, 5977−5981.

(23) (a) Yadagiri, D.; Rivas, M.; Gevorgyan, V. Denitrogenative Transformations of Pyridotriazoles and Related Compounds: Synthesis of N-Containing Heterocyclic Compounds and Beyond. *J. Org. Chem.* **2020**, *85* (17), 11030−11046. (b) Filippov, I. P.; Titov, G. D.; Rostovskii, N. V. Recent Advances in Denitrogenative Reactions of Pyridotriazoles. *Synthesis* **2020**, *52* (23), 3564−3576. (c) Wang, E.; Luo, J.; Zhang, L.; Zhang, J.; Jiang, Y. Copper-Catalyzed Oxidative [3 + 2] Cycloaddition of Enamines and Pyridotriazoles toward Indolizines. *Org. Lett.* **2024**, *26*, 1249−1254.

(24) Yang, S.; Li, P.; Wang, Z.; Wang, L. Photoinduced Oxidative Formylation of N,N-Dimethylanilines with Molecular Oxygen without External Photocatalyst. *Org. Lett.* **2017**, *19* (13), 3386−3389.

(25) (a) Subba Reddy, B. V.; Begum, Z.; Reddy, J. Y.; Yadav, J. S. Pd(OAc)2-catalyzed C−H activation of indoles: a facile synthesis of 3-cyanoindoles. *Tetrahedron Lett.* **2010**, *51* (25), 3334−3336. (b) Yuen, O. Y.; Choy, P. Y.; Chow, W. K.; Wong, W. T.; Kwong, F. Y. Synthesis of 3-Cyanoindole Derivatives Mediated by Copper(I) Iodide Using Benzyl Cyanide. *J. Org. Chem.* **2013**, *78* (7), 3374−3378. (c) Zhang, L.; Wen, Q.; Jin, J.; Wang, C.; Lu, P.; Wang, Y. Cyanation of indoles with benzyl cyanide as the cyanide anion surrogate. *Tetrahedron* **2013**, *69*, 4236−4240.

(26) Gilchrist, T. L.; Rees, C. W.; Thomas, C. Reactive intermediates. Part XXV. Investigation of the pyrolysis of 1,4- and 1,5-diphenyl-1,2,3-triazoles by use of 13C-labelled compounds. *J. Chem. Soc., Perkin Trans.* **1975**, *1*, 8−11.

(27) Mitchell, G.; Rees, C. W. 1H-azirines as intermediates in the photolysis of 1,2,3-triazoles. *J. Chem. Soc., Chem. Commun.* **1986**, 399−401.

(28) (a) Chaitanya, M.; Anbarasan, P. Rhodium Catalyzed C2-Selective Cyanation of Indoles and Pyrroles. *J. Org. Chem.* **2015**, *80* (7), 3695−3700. (b) Zhao, M.; Zhang, W.; Shen, Z. Cu-Catalyzed Cyanation of Indoles with Acetonitrile as a Cyano Source. *J. Org. Chem.* **2015**, *80* (17), 8868−8873. (c) Li, B.; Zhang, B.; Zhang, X.; Fan, X. Synthesis of 3-Cyano-1H-indoles and Their 2′-Deoxyribonucleoside Derivatives through One-Pot Cascade Reactions. *J. Org. Chem.* **2016**, *81* (20), 9530−9538. (d) Zeidan, N.; Bognar, S.; Lee, S.; Lautens, M. Palladium-Catalyzed Synthesis of 2-Cyanoindoles from 2-gem-Dihalovinylanilines. *Org. Lett.* **2017**, *19* (19), 5058−5061. (e) Wu, J.; Liu, J.; Zhou, K.; He, Z.; Wang, Q.; Wu, F.; Miao, T.; Qian, J.; Shi, Q. Efficient construction of diverse 3-cyanoindoles under novel tandem catalysis. *Chem. Commun.* **2020**, *56* (83), 12660−12663. (f) Sterligov, G. K.; Ageshina, A. A.; Rzhevskiy, S. A.; Shurupova, O. V.; Topchiy, M. A.; Minaeva, L. I.; Asachenko, A. F. One-Pot Modified Madelung Synthesis of 3-Tosyl- and 3-Cyano-1,2-disubstituted Indoles. *ACS Omega* **2022**, *7* (43), 38505−38511.

(29) (a) Babin, V.; Sallustrau, A.; Loreau, O.; Caillé, F.; Goudet, A.; Cahuzac, H.; Del Vecchio, A.; Taran, F.; Audisio, D. A general procedure for carbon isotope labeling of linear urea derivatives with carbon dioxide. *Chem. Commun.* **2021**, *57* (54), 6680−6683. (b) Dou, Y.; Gu, X.; Ying, S.; Zhu, S.; Yu, S.; Shen, W.; Zhu, Q. A novel lysosome-targeted fluorogenic probe based on 5-triazole-quinoline for the rapid detection of hydrogen sulfide in living cells. *Org. Biomol. Chem.* **2018**, *16* (5), 712−716. (c) Chainikova, E. M.; Khursan, S. L.; Yusupova, A. R.; Teregulova, A. N.; Abdullin, M. F.; Lobov, A. N.; Safiullin, R. L. Ortho-Cyclization in Asymmetrically Substituted Arylnitroso Oxides. *J. Org. Chem.* **2020**, *85* (16), 10813−10822. (d) Chen, L.-J.; Kuo, C.-J.; Liang, C.-F. Synthesis of Aryl Amides from Acyl-Bunte Salts and Aryl Azides. *J. Org. Chem.* **2023**, *88* (15), 10501−10507. (e) Biswas, B.; Venkateswarulu, M.; Gaur, P.; Sharma, Y.; Sinha, S.; Ghosh, S. Triggered emission for rapid detection of

https://doi.org/10.1021/acs.joc.4c01533
J. Org. Chem. 2024, 89, 12610−12618

hydrogen sulfide chaperoned by large Stokes shift. *J. Photochem. Photobiol. A Chem.* **2019**, *371*, 264−270.
(30) (a) Liu, X.; Chen, G.; Li, C.; Liu, P. Chloramine Salt Mediated Oxidative Halogenation of Terminal Alkynes with KI or NaBr: Practical Synthesis of 1-Bromoalkynes and 1-Iodoalkynes. *Synlett* **2018**, *29* (15), 2051−2055. (b) Rao, D. S.; Reddy, T. R.; Kashyap, S. Chemoselective and stereospecific iodination of alkynes using sulfonium iodate(i) salt. *Org. Biomol. Chem.* **2018**, *16* (9), 1508−1518. (c) Ferris, T.; Carroll, L.; Mease, R. C.; Spivey, A. C.; Aboagye, E. O. Iodination of terminal alkynes using KI/$CuSO_4$ − A facile method with potential for radio-iodination. *Tetrahedron Lett.* **2019**, *60* (13), 936−939. (d) Dumele, O.; Wu, D.; Trapp, N.; Goroff, N.; Diederich, F. Halogen Bonding of (Iodoethynyl)benzene Derivatives in Solution. *Org. Lett.* **2014**, *16* (18), 4722−4725.

https://doi.org/10.1021/acs.joc.4c01533
J. Org. Chem. 2024, 89, 12610−12618