The Three-Component Synthesis of 4-Sulfonyl-1,2,3-triazoles via a Sequential Aerobic Copper-Catalyzed Sulfonylation and Dimroth Cyclization

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Abstract: 4-Sulfonyl-1,2,3-triazole scaffolds possess promising bioactivities and applications as anion binders. However, these structures remain relatively unexplored and efficient synthetic procedures for their synthesis remain desirable. A practical room-temperature, aerobic copper-catalyzed three-component reaction of aromatic ketones, sodium sulfinates, and azides is reported. This procedure allows for facile access to 4-sulfonyl-1,5-disubstituted-1,2,3-triazoles in yields ranging from 34 to 89%. The reaction proceeds via a sequential aerobic copper(II)chloride-catalyzed oxidative sulfonylation and the Dimroth azide–enolate cyclization.

Keywords: 4-sulfonyl-1,2,3-triazoles; three-component tandem reaction; aerobic oxidation; copper-catalysis; C-H activation; Dimroth azide–enolate cyclization

1. Introduction

4-Sulfonyl-1,2,3-triazole scaffolds possess very promising bioactivities, which include antibacterial [1] and antifungal agents [2,3], as well as potent antagonists of neutrophil elastase (HLE) [4] and the human pregnane X receptor (hPXR) [5–7], as shown in Figure 1. Additionally, they have found application as (monomeric) anion binders [8]. However, despite their promising applications, these structures remain relatively unexplored, making efficient synthetic procedures towards these scaffolds starting from readily available starting materials desirable.

Figure 1. Examples of bioactive 4-sulfonyl triazoles.

Several methods for preparing 4-sulfonyl triazoles have been reported, each with their own drawbacks, as shown in Scheme 1. These routes include the non-catalyzed Huisgen azide–alkyne cycloadditions (AACs) of thio- or sulfonyl alkynes, which require high temperatures, long reaction times, and suffer from low yields and regioselectivity [4,9,10]. The metal catalyzed variants, of which the most notable are the IrAAC [11], RuAAC [12], and RhAAC [13], elegantly solve these issues. However, several limiting factors remain, such as the necessary multistep synthesis of the alkynyl sulfide [14–17] and sulfone starting materials [9,18–20], the use of stoichiometric oxidants for conversion of the thioether into a sulfone, and the high cost of the noble metal catalyst. The most prominent alternative to the AAC synthesis of 4-sulfonyl triazoles is the Dimroth azide–enolate cycloaddition.
of sulfonyl ketones [3,21–24]. While previously reported room temperature Dimroth cyclizations furnished 4-sulfonyl triazoles in good to high yields [3,22,23], the requirement of prior synthesis and isolation of the sulfonyl ketones reduces their sustainability and attractiveness [3,25–35]. Additionally, there are two alternative pathways, based on the Wolff triazole synthesis [36,37] and azide–alkene cycloaddition [38–40] that are both less attractive due to the use of unstable α-diazo-sulfonyl ketones, and the somewhat lower yields or availability of the starting materials.

Previous work

\[
\begin{align*}
\text{Scheme 1. Synthetic routes towards 4-sulfonyl-triazoles.}
\end{align*}
\]

In light of the above-mentioned limitations, we envisioned a multicomponent 4-sulfonyl-1,2,3-triazole synthesis that starts from readily available aromatic ketones, sodium sulfinates, and organic azides, via a one-pot oxidative sulfonylation and Dimroth cyclization sequence, as shown in Scheme 1. In order to increase the sustainability of the envisioned procedure, we wanted to avoid the use of stoichiometric oxidants such as hypervalent iodine [25], peroxides [41], copper salts [42,43], and silver salts [44,45] that are commonly used in oxidative coupling reactions, in favor of air as the terminal oxidant, which is environmentally benign and results only in formation of water as a side product [43,46,47]. Over the past decade, many catalysts have been developed that allow for aerobic/O\textsubscript{2} oxidative coupling of diverse substrates, with the significant focus being on palladium [48–51] and other noble metal catalysts [43,50,52–55]. However, copper catalysts are particularly interesting when compared to noble metal catalysts. Next to generally being inexpensive, readily available, and of low toxicity, they have great potential for catalyzing a broad range of reactions. Catalysis by natural copper-oxidases can serve as an example [46]. This is epitomized by the wide array of aerobic copper-catalyzed oxidative coupling reactions that have been reported to date [46,56,57].

2. Results and Discussion

As starting point for our three-component aerobic oxidative sulfonylation/Dimroth sequence, we utilized the reaction conditions reported by Lan et al. for the CuBr\textsubscript{2}-catalysed synthesis of α-alkyl ketosulfones, as shown in Table 1 and Table S1 [26]. While the original ligand-free procedure furnished the ketosulfones from α-unsubstituted acetophenone only in a low yield of 20%, it was expected that subsequent transformation of the in situ formed ketosulfone into the corresponding 1,2,3-triazole would result in a significantly improved yield. Pleasingly, when applying these reaction conditions, the corresponding 4-tosyl triazole 4a was obtained in 54% yield (Entry 1). Different copper salts, including CuI, Cu(OAc)\textsubscript{2}, Cu(OTf)\textsubscript{2}, and CuCl\textsubscript{2} were screened (Entries 1–5), and CuCl\textsubscript{2} was found to be superior, furnishing 4a in an isolated yield of 71%, and 72% upon repetition of the experiment (Entry 2). Next, different bases and solvents were evaluated, as well as a reduction in the equivalents of base (Entries 6–15, and Tables S16–S18). However, any
deviation from the standard conditions (Entry 2) resulted in a decreased yield. The amine base may perform a dual role, acting both as base and ligand. Pyridine and Et$_3$N (Entry 6 and 7) presumably are unreactive because they are both weaker bases and ligands than DBU, thereby not sufficiently deprotonating the enol and stabilizing the copper complex. Surprisingly, DBN results in a markedly lower yield than DBU (Entry 8), 52% versus 72%, which may be the result of it being too strongly coordinated to the copper and thereby hindering the formation of the copper-enolate. K$_2$CO$_3$ and KOtBu presumably are unreactive since they are both less soluble in DMSO and weaker ligands (Entry 9 and 10). Presumably, DMSO is superior since it is both a polar coordinating solvent as well as a mild oxidant.

Table 1. Optimization of reaction conditions.$^a$

| Entry | Catalyst | Base | Base pKaH | Solvent | Ligand | Yield (%)$^b$
|-------|----------|------|-----------|---------|--------|----------------|
| 1     | CuBr$_2$| DBU  | 12        | DMSO    | none   | 56 |
| 2     | CuCl$_2$| DBU  | 12        | DMSO    | none   | 71 (72) |
| 3     | CuI     | DBU  | 12        | DMSO    | none   | 47 |
| 4     | Cu(OAc)$_2$| DBU  | 12        | DMSO    | none   | 62 |
| 5     | Cu(OTf)$_2$| DBU  | 12        | DMSO    | none   | 64 |
| 6     | CuCl$_2$| Pyridine | 3.4    | DMSO    | none   | 0 |
| 7     | CuCl$_2$| Et$_3$N | 9      | DMSO    | none   | 0 |
| 8     | CuCl$_2$| DBN  | 13.4      | DMSO    | none   | 52 |
| 9     | CuCl$_2$| K$_2$CO$_3$ | 10.3   | DMSO    | none   | 0 |
| 10    | CuCl$_2$| KOtBu | 29.4     | DMSO    | none   | 0 |
| 11    | CuCl$_2$| DBU  | 12        | DCM     | none   | 0 |
| 12    | CuCl$_2$| DBU  | 12        | EtOAc   | none   | 0 |
| 13    | CuCl$_2$| DBU  | 12        | ACN     | none   | 7 |
| 14    | CuCl$_2$| DBU  | 12        | DMF     | none   | 24 |
| 15    | CuCl$_2$| DBU  | 12        | EtOH    | none   | 4 |
| 16    | CuCl$_2$| DBU  | 12        | DMSO    | TMEDA  | 81 |
| 17    | CuCl$_2$| DBU  | 12        | DMSO    | 2,2'-bipyridine | 67 |
| 18    | CuCl$_2$| DBU  | 12        | DMSO    | 1,10-phenanthrolone | 68 |
| 19    | CuCl$_2$| DBU  | 12        | DMSO    | Neocuproine | 58 |
| 20    | CuCl$_2$| DBU  | 12        | DMSO    | TMEDA  | 84$^d$ |
| 21    | CuCl$_2$| DBU  | 12        | DMSO    | TMEDA  | 77$^e$ |
| 22    | CuCl$_2$| DBU  | 12        | DMSO    | TMEDA  | 99$^f$ |
| 23    | CuCl$_2$| DBU  | 12        | DMSO    | TMEDA  | 50$^g$ |
| 24    | none    | DBU  | 12        | DMSO    | TMEDA  | Nr$^c$ |
| 25    | CuCl$_2$| DBU  | 12        | DMSO    | TMEDA  | <5$^h$ |

$^a$ Reaction conditions: Acetophenone 1 (0.50 mmol), sodium p-toluene sulfinate 2 (1.00 mmol), DBU (1.00 mmol), catalyst (20%) in DMSO (3 mL) under air atmosphere. $^b$ Isolated yield. $^c$ n.r. = no reaction. $^d$ DMSO (2 mL). $^e$ DMSO (1 mL). $^f$ CuCl$_2$/TMEDA (10 mol%), DMSO (2 mL). $^g$ CuCl$_2$/TMEDA (5 mol%), DMSO (2 mL). $^h$ Reaction under argon atmosphere. The entry highlighted in bold corresponds to the optimized conditions.

Subsequently, different tertiary amine ligands were screened, including TMEDA, 2,2'-bipyridine, 1,10-phenanthroline, and neocuproine (Entries 16–19). Primary and secondary amine ligands were excluded due to the risk of α-amination [58], and phosphine ligands were excluded due to their susceptibility to oxidative degradation [51]. Out of the evaluated amine ligands, TMEDA proved to be the superior with a yield of 81% (Entry 16). Finally, the catalyst loading and solvent volume were varied and an optimal loading of 10 mol% CuCl$_2$/TMEDA and 2 mL volume of DMSO was found, resulting in a yield of
89% (Entry 28). As final control experiments, reactions were set up under the optimized conditions in either absence of CuCl₂ (Entry 29) or under argon atmosphere (Entry 30), which resulted in no reaction and in less than 5% of triazole being formed.

With the optimized conditions in hand, we set out to explore the substrate scope for this reaction and investigated various acetophenone derivatives, sodium sulfinates, and organic azides, as shown in Scheme 2. For the reaction of acetophenone derivatives 1a–j with sodium p-toluene sulinate 2a and phenyl azide 3a, the yields of triazoles 4a–j varied from high to low. The reactions of electron-deficient acetophenones progressed at similar or faster rates yet resulted in lower yields. The 4-tosyl triazoles derived from p-trifluoromethyl substituted 4b, p-fluoro substituted 4c, and α-bromo substituted 4d acetophenone were obtained in yields of 55 (4b), 73 (4c), and 64% (4d). The reduced yields compared to 4a can be in part explained by the occurrence of Regitz diazo transfer, as observed previously for cyclic sulfonyl ketones [24] and evidenced by the observation of nitrogen evolution from the reaction mixture and the presence of a minor quantity of aniline in the crude mixture, as determined by GC/MS. However, no other product from this side-reaction could be isolated. The presence of donating substituents resulted in a reduced reaction rate and concomitantly reduced yields. The p-methyl and p-methoxy substituted triazoles 4e and 4f were obtained in yields of 51% and 34% after 48 h. Next, the influence of steric hindrance was investigated and the expected negative correlation between steric hindrance and product yields was observed. The α-methyl and 1-naphthyl triazoles 4g and 4h give reduced yields in comparison to their less sterically hindered counterparts, the p-methyl and 2-naphthyl triazoles 4e and 4i, 36% (4g) versus 51% (4e) and 60% (4h) versus 71% (4i).

Several aliphatic ketones including acetone, pinacolone, and trifluoromethyl acetone were screened without success, as expected.

**Scheme 2.** Substrate scope for three-component 4-sulfonyl triazole synthesis. a Reaction conditions: Acetophenone 1 (0.50 mmol), sodium sulfinate 2 (1.00 mmol), DBU (1.00 mmol), CuCl₂/TMEDA (10%) in DMSO (2 mL) under air atmosphere. b 24 h. c 48 h. d 35 °C. Ts = p-toluene sulfonyl.
A plausible reason for the limitations of the reaction scope for ketones is given in the final paragraph, after discussing the reaction mechanism.

Pleasingly, 4-methyl sulfinate triazole 4j was furnished in a good yield of 85%. However, in the case of the p-chlorophenyl sulfonyl triazole 4k, a yield of only 51% was obtained. Finally, the scope in azide was evaluated and both for phenyl azides with electron-withdrawing and donating groups, good yields of 74% (4l) and 64% (4m) were obtained. Regrettably, sterically hindered azides were unreactive and no triazole 4n formed. Benzyl azide performed far less effectively and furnished the triazole 4o in 18% yield, along with 45% of sulfonyl ketone 5a.

A plausible reason for the limitations of the reaction scope for azides is given in the final paragraph, after discussing the reaction mechanism.

In order to gain more insight into the mechanism, several control experiments were performed. In the absence of CuCl₂ no reaction occurred, and under argon atmosphere less than 5% of product formed, as shown in Table S1 (Entry 32–33), which shows that the copper salt is required for catalyzing the reaction and oxygen is needed for catalytic turnover. Addition of four equivalents of TEMPO completely inhibited the reaction, as shown in Scheme 3a. From the control reaction in the presence of 1,1-diphenylethylene (DPE) 6, a radical trapping reagent, the sulfonyltriazole 4a, could be isolated in a reduced yield of 39% and the yield of the radical trapping product 7 was rather low, 4%, as shown in Scheme 3b. These results indicate involvement of both free radicals and alternative mechanisms, such as via oxidative chlorination or via an organometallic intermediate.

Phenacyl chloride 8 is a possible reaction intermediate, considering that the halogena-
tion of the carbonyl α-position by stoichiometric copper halides, as well as diverse aerobic copper-catalyzed oxidative halogenations, have been reported [46,59,60]. From the reaction of 8 under standard conditions in presence and absence of the copper catalyst, triazole 4a was obtained in yields of 11% and 45%, as shown in Scheme 4c. This indicates that 8 may be an intermediate in the oxidative sulfonylation, although, it shows that there must be alternative operative pathways. However, it should be noted that 8 was not isolated from or observed in the reaction mixture. Additionally, the reported copper-catalyzed oxidative halogenation reactions generally take place under (Lewis) acidic conditions, which raise the Cu(II) reduction potential and consequently promote single-electron transfer SET reactivity.
Conversely, basic conditions and stronger ligands stabilize both Cu(II) and Cu(III), or lower the Cu(II) reduction potential, which reduces SET reactivity and favors the formation of organometallic intermediates \[46,61\].

Scheme 4. Proposed mechanism for three-component reaction for (a) oxidative sulfonylation via Cu(III)-intermediate, (b) oxidative sulfonylation via Cu(II)-intermediate, (c) generation of sulfonyl radical, and (d) enolate/azide cycloaddition.

The intermediacy of the sulfonyl ketone \(5\) is supported by the observation of the NMR characteristic peak in the crude reaction mixture at reduced reaction times. When the oxidative sulfonylation was performed in absence of azide good yields of phenacyl sulfones \(5a\) and \(5b\) were obtained, as shown in Scheme 3d, which proves its intermediacy. Advantageously, this shows that the presented methodology can also be used for the synthesis of sulfonyl ketones in good yield.

Based on the reaction outcomes and literature reports \[26,27,46,62–67\], three plausible mechanisms are considered, as shown in Scheme 4, two of which are analogous to those described by Lan et al. (Scheme 4a pathway A and Scheme 4b) \[26\]. First, DBU deprotonates the acetophenone \(1\), and the resulting enolate exchanges chloride at Cu(II),
forming intermediate I1. Next, there are two possible pathways, as shown in Scheme 4a. Via pathway A, the free sulfonyl radical SR2 is formed through oxidation of the sulfinate 2 by Cu(II), oxygen, or DMSO via a SET mechanism [63–67], as shown in Scheme 4b, and then undergoes oxidative addition to the Cu(II) complex, forming Cu(III)-intermediate I3 [26,27,66]. Via pathway B, ligand exchange of the chloride for sulfinate results in the formation of Cu(II)-intermediate I2. This intermediate can then be oxidized via SET by CuCl2, or by oxygen or DMSO, resulting in the formation of Cu(III)-intermediate I3. Reductive elimination of I3 results in the formation of sulfonyl ketone 5 and Cu(I)Cl. Finally, oxidation of Cu(I) by oxygen or DMSO regenerates the Cu(II)-catalyst [26,27,46,62,66].

In the third pathway, as shown in Scheme 4b, the sulfonyl radical SR2 reacts with copper enolate I4 with formation of a benzylic ketyl radical I5. Oxidation of the ketyl radical I5 by Cu(II) via an intramolecular SET process forms the ketosulfone 5 and Cu(I)Cl, which is reoxidized by oxygen to regenerate the active copper(II) catalyst [46,62–67]. The sulfonyl ketone 5 can undergo DBU Bronsted-basic and/or CuCl2 Lewis-acidic mediated Dimroth enolate/azide cycloaddition, forming the 4-sulfonyl triazole 4.

The reason why the reaction scope is limited to aromatic ketones can be explained by the reaction mechanisms shown in Scheme 4, in which the first step involves the formation of a (copper-) enolate. The observation that the reaction times increase for more electron-rich aromatic ketones indicates that this deprotonation may be the rate limiting step. This fact would explain why acetone and pinacolone are unreactive since these are less acidic than acetophenone by at least 1.8 orders of magnitude. On the other hand, 1,1,1-trifluoroacetone, while more acidic, may be unreactive due to its high tendency to form hydrates with water [68]. The reason for the reduced yields of 1,2,3-triazole 4o from the reaction with benzyl azide are intrinsic to the Dimroth azide–enolate cycloaddition, which was defined by L’abbé in 1971 as “the condensation of organic azides with active methylene compounds in the presence of an equimolar amount of organic or inorganic base leading to highly substituted 1,2,3-triazoles in a regioselective manner” [69,70]. The reaction mechanism involves either a stepwise concerted [3+2] cycloaddition or a stepwise addition of the enolate to the azide with formation of an N1-triazenyl ion intermediate. The rate of this cycloaddition depends on the stabilization of this ion [71]. For this reason, aromatic azides with electron-donating groups are expected to react more slowly than those with withdrawing substituents, and benzyl azides and aliphatic azides are expected to react more slowly than their aromatic counterparts.

3. Materials and Methods

3.1. General Information

All chemicals were purchased from Acros Organics (Geel, Belgium), Merck (Darmstadt, Germany), Alfa Aesar (Kandel, Germany), Fluorochem (Hadfield, UK), and TCI Europe (Zwijndrecht, Belgium) and used as received. For column chromatography, 70–230 mesh silica 60 (Acros, Geel, Belgium) was used as the stationary phase. NMR data were recorded using a Bruker AV 400 MHz (Bruker (Biospin), Kontich, Belgium) and chemical shifts (δ) were reported in parts per million (ppm) referenced to tetramethylsilane (1H), or the internal (NMR) solvent signal (13C) as internal standards [72]. High-resolution mass spectra were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA, USA). Samples were infused at 3 µL/min and spectra were obtained in positive ionization mode with a resolution of 15,000 (FWHM—full width at half maximum) using leucine enkephalin as a lock mass. Melting points (not corrected) were determined using a Reichert Thermovar apparatus. GC/MS were measured on a Thermo Finnigan Interscience Trace™ GC gas chromatograph (Waltham, Massachusetts, USA) coupled to a Thermo Scientific ITQ 900™ mass spectrometer (Waltham, Massachusetts, USA) in full-scan EI (electron ionization) mode. Phenyl azide (3a), 4-bromophenyl azide (3b), 4-methoxyphenyl azide (3c), and benzyl azide (3d) were prepared according to literature procedures [40,73].
FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for compounds: 4a, 4b, 4c, 4d, 4e, 4f, 4g, 4h, 4i, 4j, 4k, 4l, 4m, 4o, 5a, 5b.

3.2. General Procedure and Characterization Data

To a 10 mL round bottom flask, acetophenone 1a–j (0.50 mmol), DMSO (dry, 2 mL), sodium sulfinate 2a–c (1.00 mmol, 2 eq.), DBU (150 µL, 1.00 mmol, 2 eq.), TMEDA (8 µL, 0.05 mmol, 10 mol%), and azide 3a–e (0.75 mmol, 1.5 eq.) were added sequentially. The reaction was initiated by addition of CuCl2 (6.7 mg, 10 mol%). After stirring open vessel for 24 or 48 h at 25 °C, 5 mL EtOAc and 3 mL NH2Cl were added and the mixture was transferred to a separation funnel along with 20 mL EtOAc. Then, 3 mL H2O was added in order to break the suspension. The organic phase was collected and following two more extractions (2 × 25 mL EtOAc), washed with brine, dried over Na2SO4, and concentrated in vacuo. Flash chromatography with ethyl acetate/petroleum ether 10–60% as eluent afforded the title products as off-white and white solids.

1,5-Diphenyl-4-[(4-methylphenyl)sulfonyl]-1H-1,2,3-triazole (4a), Prepared according to the general procedure using acetophenone 1a (60 mg, 0.50 mmol), sodium p-toluenesulfinate 2a (178 mg, 1.00 mmol), and phenyl azide 3a (83 µL, 0.75 mmol). Reaction time was 24 h. Flash chromatography using EtOAc/petroleum ether 10–40% yielded 4a (170 mg, 0.453 mmol, 89%) as a white solid; mp 175–177 °C. 1H-NMR (400 MHz, CDCl3): δ (ppm) 7.82–7.71 (app. d, J = 8.3 Hz, 2H), 7.50–7.43 (m, 1H), 7.43–7.30 (m, 5H), 7.30–7.17 (m, 6H), 2.39 (s, 3H). 13C-NMR (101 MHz, CDCl3): δ (ppm) 163.9 (d, J = 252.3 Hz), 146.3, 145.4, 137.4, 137.1, 135.2, 132.5 (q, J = 33.1 Hz), 131.2, 130.3, 129.8, 128.4, 125.3 (q, J = 3.6 Hz), 125.3, 123.6 (q, J = 272.7 Hz), 218. 15F-NMR (377 MHz, CDCl3): δ (ppm)–63.00 Hz. HRMS (ESI-Q-TOF): m/z [M + H]+ calcd. for C21H17N3O2S1: 376.11141; found: 376.1113.

1-Phenyl-4-[(4-methylphenyl)sulfonyl]-5-(4-trifluoromethylphenyl)-1H-1,2,3-triazole (4b), Prepared according to the general procedure using 4c-[(trifluoromethyl)acetophenone 1b (94 mg, 0.50 mmol), sodium p-toluenesulfinate 2a (178 mg, 1.00 mmol), and phenyl azide 3a (83 µL, 0.75 mmol). Reaction time was 24 h. Flash chromatography using EtOAc/petroleum ether 10–40% yielded 4b (122 mg, 0.275 mmol, 55%) as an off-white solid; mp 208–210 °C. 1H-NMR (400 MHz, CDCl3): δ (ppm) 7.82–7.71 (app. d, J = 8.1 Hz, 2H), 7.71–7.60 (app. d, J = 8.1 Hz, 2H), 7.50–7.34 (m, 5H), 7.33–7.27 (app. d, J = 8.0 Hz, 2H), 7.24–7.16 (app. d, J = 7.7, 2H), 2.42 (s, 3H). 13C-NMR (101 MHz, CDCl3): δ (ppm) 146.8, 145.4, 137.4, 137.1, 135.2, 132.5 (q, J = 33.1 Hz), 131.2, 130.3, 129.8, 128.4, 125.7 (q, J = 3.6 Hz), 125.3, 123.6 (q, J = 272.7 Hz), 218. 15F-NMR (377 MHz, CDCl3): δ (ppm)–63.00 Hz. HRMS (ESI-Q-TOF): m/z [M + H]+ calcd. for C21H16F3N3O2S1: 444.09879; found: 444.0987.

1-Phenyl-4-[(4-methylphenyl)sulfonyl]-5-(4-fluorophenyl)-1H-1,2,3-triazole (4c), Prepared according to the general procedure using 4f-[(fluorophenyl)acetophenone 1c (68 mg, 0.49 mmol), sodium p-toluenesulfinate 2a (178 mg, 1.00 mmol), and phenyl azide 3a (83 µL, 0.75 mmol). Reaction time was 24 h. Flash chromatography using EtOAc/petroleum ether 10–40% yielded 4c (122 mg, 0.359 mmol, 73%) as an off-white solid; mp 170–172 °C. 1H-NMR (400 MHz, CDCl3): δ (ppm) 7.83–7.70 (app. d, J = 8.2 Hz, 2H), 7.47–7.33 (m, 3 H), 7.32–7.24 (app. t, J = 3.5 Hz), 7.20–7.13 (m, 3H), 7.60–7.55 (m, 3H), 7.47–7.34 (m, 4H), 7.33–7.18 (m, 6 H), 2.42 (s, 3H). 13C-NMR (101 MHz, CDCl3): δ (ppm) 163.9 (d, J = 252.3 Hz), 146.3, 145.1, 137.7, 137.6, 135.3, 132.7 (d, J = 8.8 Hz), 130.1, 129.9, 129.8, 128.5, 125.4 (d, J = 3.5 Hz), 116.0 (d, J = 22.2 Hz), 218. 15F-NMR (377 MHz, CDCl3): δ (ppm)–108.69 Hz. HRMS (ESI-Q-TOF): m/z [M + H]+ calcd. for C21H16F4N3O2S1: 494.09879; found: 494.0987.

1-Phenyl-4-[(4-methylphenyl)sulfonyl]-5-(3-bromomethylphenyl)-1H-1,2,3-triazole (4d), Prepared according to the general procedure using 4i-bromoacetophenone 1d (100 mg, 0.500 mmol), sodium p-toluenesulfinate 2a (178 mg, 1.00 mmol), and phenyl azide 3a (83 µL, 0.75 mmol). Reaction time was 24 h. Flash chromatography using EtOAc/petroleum ether 10–40% yielded 4d (145 mg, 0.319 mmol, 64%) as an off-white solid; mp 158–160 °C. 1H-NMR (400 MHz, CDCl3): δ (ppm) 7.85–7.75 (app. d, J = 8.2 Hz, 2H), 7.63–7.55 (app. d, J = 7.9 Hz, 1H), 7.47–7.34 (m, 4H), 7.33–7.18 (m, 6, H), 2.42 (s, 3H). 13C-NMR (101 MHz, CDCl3): δ
1-Phenyl-4-[(4-methylphenyl)sulfonyl]-5-(2-naphtyl)-1H-1,2,3-triazole (125.0, 124.3, 124.2, 122.0, 21.6. HRMS (ESI-Q-TOF): m/z [M + H]+ calcd. for C21H18Br1N3O2S1: 454.0218; found: 454.0216.

1-Phenyl-4-[(4-methylphenyl)sulfonyl]-5-(1-naphtyl)-1H-1,2,3-triazole (131.0, 130.6, 129.8, 129.5, 128.2, 126.13, 124.3, 124.1, 21.8, 19.7. HRMS (ESI-Q-TOF):

1-Phenyl-4-[(4-methylphenyl)sulfonyl]-5-(4-methoxyphenyl)-1H-1,2,3-triazole (114.2, 55.4, 21.7. HRMS (ESI-Q-TOF):

1-Phenyl-4-[(4-methylphenyl)sulfonyl]-5-(4-methylphenyl)-1H-1,2,3-triazole (126.4, 125.2, 122.5, 21.8. HRMS (ESI-Q-TOF): m/z [M + H]+ calcd. for C21H18Br1N3O2S1: 454.0218; found: 454.0216.

1-Phenyl-4-[(4-methylphenyl)sulfonyl]-5-(4-methoxyphenyl)-1H-1,2,3-triazole (111.2, 111.0, 137.5, 137.0, 135.7, 135.4, 133.7, 133.4, 130.22, 130.20, 130.0, 129.7, 129.2, 128.3, 126.4, 125.2, 122.5, 21.8. HRMS (ESI-Q-TOF): m/z [M + H]+ calcd. for C21H18Br1N3O2S1: 454.0218; found: 454.0216.

1-Phenyl-4-[(4-methylphenyl)sulfonyl]-5-(1-naphtyl)-1H-1,2,3-triazole (131.0, 130.6, 129.8, 129.5, 128.2, 126.13, 124.3, 124.1, 21.8, 19.7. HRMS (ESI-Q-TOF): m/z [M + H]+ calcd. for C21H18Br1N3O2S1: 454.0218; found: 454.0216.

1-Phenyl-4-[(4-methylphenyl)sulfonyl]-5-(4-methoxyphenyl)-1H-1,2,3-triazole (114.2, 55.4, 21.7. HRMS (ESI-Q-TOF):

1-Phenyl-4-[(4-methylphenyl)sulfonyl]-5-(4-methylphenyl)-1H-1,2,3-triazole (126.4, 125.2, 122.5, 21.8. HRMS (ESI-Q-TOF): m/z [M + H]+ calcd. for C21H18Br1N3O2S1: 454.0218; found: 454.0216.

1-Phenyl-4-[(4-methylphenyl)sulfonyl]-5-(4-methoxyphenyl)-1H-1,2,3-triazole (111.2, 111.0, 137.5, 137.0, 135.7, 135.4, 133.7, 133.4, 130.22, 130.20, 130.0, 129.7, 129.2, 128.3, 126.4, 125.2, 122.5, 21.8. HRMS (ESI-Q-TOF): m/z [M + H]+ calcd. for C21H18Br1N3O2S1: 454.0218; found: 454.0216.

1-Phenyl-4-[(4-methylphenyl)sulfonyl]-5-(1-naphtyl)-1H-1,2,3-triazole (131.0, 130.6, 129.8, 129.5, 128.2, 126.13, 124.3, 124.1, 21.8, 19.7. HRMS (ESI-Q-TOF): m/z [M + H]+ calcd. for C21H18Br1N3O2S1: 454.0218; found: 454.0216.

1-Phenyl-4-[(4-methylphenyl)sulfonyl]-5-(4-methoxyphenyl)-1H-1,2,3-triazole (114.2, 55.4, 21.7. HRMS (ESI-Q-TOF):

1-Phenyl-4-[(4-methylphenyl)sulfonyl]-5-(4-methylphenyl)-1H-1,2,3-triazole (126.4, 125.2, 122.5, 21.8. HRMS (ESI-Q-TOF): m/z [M + H]+ calcd. for C21H18Br1N3O2S1: 454.0218; found: 454.0216.

1-Phenyl-4-[(4-methylphenyl)sulfonyl]-5-(1-naphtyl)-1H-1,2,3-triazole (131.0, 130.6, 129.8, 129.5, 128.2, 126.13, 124.3, 124.1, 21.8, 19.7. HRMS (ESI-Q-TOF): m/z [M + H]+ calcd. for C21H18Br1N3O2S1: 454.0218; found: 454.0216.
1,5-Diphenyl-4-methylsulfonyl-1H-1,2,3-triazole (4j), Prepared according to the general procedure using acetonophene 1a (60 mg, 0.50 mmol), sodium methanesulfinate 2b (110 mg, 1.00 mmol), and phenyl azide 3a (83 μL, 0.75 mmol). Reaction time was 24 h. Flash chromatography using EtOAc/petroleum ether 10–60% yielded 4j (127 mg, 0.424 mmol, 85%) as a white solid; mp 155–157 °C. 1H-NMR (400 MHz, CDCl3): δ (ppm) 7.52–7.32 (m, 8H), 7.32–7.20 (app. d, J = 7.46 Hz, 2H), 2.34 (s, 3H). 13C-NMR (101 MHz, CDCl3): δ (ppm) 145.3, 139.7, 139.0, 135.4, 134.5, 130.6, 130.5, 130.0, 129.7, 129.5, 128.8, 125.2, 124.2. HRMS (ESI-Q-TOF): m/z [M + H]+ calc. for C19H14BrN3O2S1: 454.02198; found: 454.0222.

1,5-Diphenyl-4-[(4-chlorophenyl)sulfonyl]-1H-1,2,3-triazole (4l), Prepared according to the general procedure using acetonophene 1a (60 mg, 0.50 mmol), sodium 4-chlorophenylsulfinate 3a (198 mg, 0.75 mmol), and phenyl azide 3a (83 μL, 0.75 mmol). Reaction time was 24 h. Flash chromatography using EtOAc/petroleum ether 10–40% yielded 4l (167 mg, 0.368 mmol, 74%) as an off-white solid; mp 149–151 °C. 1H-NMR (400 MHz, CDCl3): δ (ppm) 7.90–7.74 (app. d, J = 8.3 Hz), 7.63–7.32 (m, 8H), 7.32–7.13 (m, 4H). 13C-NMR (101 MHz, CDCl3): δ (ppm) 145.6, 140.7, 139.2, 139.0, 135.4, 130.7, 130.5, 130.0, 129.7, 129.5, 128.9, 125.2, 124.2. HRMS (ESI-Q-TOF): m/z [M + H]+ calc. for C20H14ClN3O2S1: 396.05679; found: 396.0558.

1-Methyl-1-(4-methoxyphenyl)-4-[(4-methylphenyl)sulfonyl]-1H-1,2,3-triazole (4d), Prepared according to the general procedure using acetophenone 1a (60 mg, 0.50 mmol), sodium 4-methoxyphenyl sulfinate 2a (178 mg, 1.00 mmol), and benzyl azide 3b (149 mg, 0.750 mmol). Reaction time was 24 h. Flash chromatography using EtOAc/petroleum ether 10–40% yielded 4d (167 mg, 0.368 mmol, 74%) as a pale brown solid; mp 192–194 °C. 1H-NMR (400 MHz, CDCl3): δ (ppm) 7.82–7.73 (app. d, J = 8.3 Hz, 2H), 7.48–7.35 (m, 2H), 7.35–7.24 (m, 4H), 7.24–7.15 (m, 2H), 3.79 (s, 3H), 2.40 (s, 3H). 13C-NMR (101 MHz, CDCl3): δ (ppm) 145.6, 140.7, 139.2, 139.0, 135.4, 130.7, 130.5, 130.0, 129.7, 129.5, 128.9, 128.0, 126.6, 124.14, 121.12, 21.8. HRMS (ESI-Q-TOF): m/z [M + H]+ calc. for C21H16BrN3O2S1: 454.02198; found: 454.0222.

1-Methyl-1-(4-bromophenyl)-4-[(4-methylphenyl)sulfonyl]-1H-1,2,3-triazole (4f), Prepared according to the general procedure using acetophenone 1a (60 mg, 0.50 mmol), sodium p-toluene sulfinate 2b (110 mg, 1.00 mmol), and benzyl azide 3b (149 mg, 0.750 mmol). Reaction time was 24 h. Flash chromatography using EtOAc/petroleum ether 10–40% yielded 4f (167 mg, 0.368 mmol, 74%) as an off-white solid; mp 194–196 °C. 1H-NMR (400 MHz, CDCl3): δ (ppm) 7.82–7.73 (app. d, J = 8.3 Hz, 2H), 7.48–7.38 (m, 2H), 7.38–7.24 (m, 4H), 7.17–7.07 (app d, J = 8.8 Hz, 2H), 2.41 (s, 3H). 13C-NMR (101 MHz, CDCl3): δ (ppm) 145.6, 140.7, 139.0, 135.4, 130.7, 130.5, 130.0, 129.7, 129.5, 128.9, 128.0, 126.6, 124.14, 121.12, 21.8. HRMS (ESI-Q-TOF): m/z [M + H]+ calc. for C21H16BrN3O2S1: 454.02198; found: 454.0222.

1-Methyl-1-[(4-methylphenyl)sulfonyl]-5-(4-chlorophenyl)-1H-1,2,3-triazole (4o), Prepared according to the general procedure using acetonophene 1a (60 mg, 0.50 mmol), sodium p-toluene sulfinate 2a (178 mg, 1.00 mmol), and benzyl azide 3d (94 mL, 0.75 mmol). Reaction temperature was 35 °C and reaction time was 24 h. Flash chromatography using EtOAc/petroleum ether 10–40% yielded 4o (35 mg, 0.090 mmol, 18%) as an off-white semi-solid. 1H-NMR (400 MHz, CDCl3): δ (ppm) 7.74–7.67 (app. d, J = 8.32, 2H), 7.57–7.51 (m, 1H), 7.48–7.42 (m, 2H), 7.28–7.20 (m, 5H), 7.18–7.12 (m, 2H), 6.98–6.92 (m, 2H), 5.33 (s, 2H), 2.39 (s, 3H). 13C-NMR (101 MHz, CDCl3): δ (ppm) 145.6, 144.8, 139.0, 130.7, 134.0, 130.5, 130.0, 129.8, 128.8, 128.2, 127.9, 124.5, 52.7, 21.8. HRMS (ESI-Q-TOF): m/z [M + H]+ calc. for C22H19BrN3O2S1: 390.12706; found: 390.1270.
3.3. Procedures for Mechanistic Studies

3.3.1. Procedure A: Reaction under Argon Atmosphere

To a flame dried, Ar-flushed 10 mL Schlenck tube, sodium p-toluene sulfinate 2a (178 mg, 1.00 mmol, 2 eq.) and CuCl\(_2\) (6.7 mg, 10 mol%) were added. After evacuating and filling with argon three times, DMSO (dry, 2 mL), DBU (150 \(\mu\)L, 1.00 mmol, 2 eq.), TMEDA (15 \(\mu\)L, 0.05 mmol, 10 mol%) and phenyl azide 3a (83 \(\mu\)L, 0.75 mmol, 1.5 eq.) and acetophenone 1a (60 mg, 58 \(\mu\)L, 0.50 mmol) were added sequentially. After stirring for 24 h at 25 °C, 5 mL EtOAc and 3 mL NH\(_3\)Cl were added and the mixture was transferred to a separation funnel along with 20 mL EtOAc. Then, 3 mL H\(_2\)O was added in order to break the suspension. The organic phase was collected and following two more extractions (2 \(\times\) 25 mL EtOAc), washed with brine, dried over Na\(_2\)SO\(_4\), and concentrated in vacuo. TLC, \(^1\)H-NMR, and GC/MS showed only a trace of triazole 4a.

3.3.2. Procedure B: Reaction in Presence of TEMPO

To a 10 mL round bottom flask, acetophenone 1a (60 mg, 0.50 mmol), DMSO (dry, 2 mL), p-toluene sulfinate 2a (178 mg, 1.00 mmol, 2 eq.), DBU (150 \(\mu\)L, 1.00 mmol, 2 eq.), TMEDA (15 \(\mu\)L, 0.05 mmol, 10 mol phenyl), azide 3a (83 \(\mu\)L, 0.75 mmol, 1.5 eq.), and TEMPO (312 mg, 2 mmol, 4 eq.) were added sequentially. The reaction was initiated by addition of CuCl\(_2\) (6.7 mg, 10 mol%). After stirring the open vessel for 24 h at 25 °C, 5 mL EtOAc and 3 mL NH\(_3\)Cl were added and the mixture was transferred to a separation funnel along with 20 mL EtOAc. Then, 3 mL H\(_2\)O was added in order to break the suspension. The organic phase was collected and following two more extractions (2 \(\times\) 25 mL EtOAc), washed with brine, dried over Na\(_2\)SO\(_4\), and concentrated in vacuo. TLC, \(^1\)H-NMR, and GC/MS showed no triazole 4a or sulfonyl ketone 5a.

3.3.3. Procedure C: Reaction of 1,1-Diphenylethylene (DPE)

To a 10 mL round bottom flask, acetophenone 1a (60 mg, 0.50 mmol), DMSO (dry, 2 mL), p-toluene sulfinate 2a (1.00 mmol, 2 eq.), DBU (150 \(\mu\)L, 1.00 mmol, 2 eq.), TMEDA (15 \(\mu\)L, 0.05 mmol, 10 mol%), phenyl azide 3a (83 \(\mu\)L, 0.75 mmol, 1.5 eq.), and DPE (180 mg, 1.00 mmol, 2 eq.) were added sequentially. The reaction was initiated by addition of CuCl\(_2\) (6.7 mg, 10 mol%). After stirring the open vessel for 24 h at 25 °C, 5 mL EtOAc and 3 mL NH\(_3\)Cl were added and the mixture was transferred to a separation funnel along with 20 mL EtOAc. Then, 3 mL H\(_2\)O was added in order to break the suspension. The organic phase was collected and following two more extractions (2 \(\times\) 25 mL EtOAc), washed with brine, dried over Na\(_2\)SO\(_4\), and concentrated in vacuo. Flash chromatography with ethyl acetate/petroleum ether 10–40% as eluent afforded triazole 4a (73 mg, 0.194 mmol, 39%) and radical trapping product 7 (14 mg, 0.0419 mmol, 4%). \(^1\)H-NMR for 7 was in accordance with the literature.

3.3.4. Procedure D: Reaction of Phenacyl Chloride under Standard Conditions

To a 10 mL round bottom flask, phenacyl chloride 8 (77 mg, 0.50 mmol), DMSO (dry, 2 mL), p-toluene sulfinate 2a (1.00 mmol, 2 eq.), DBU (150 \(\mu\)L, 1.00 mmol, 2 eq.), TMEDA (15 \(\mu\)L, 0.05 mmol, 10 mol%), and phenyl azide 3a (83 \(\mu\)L, 0.75 mmol, 1.5 eq.) were added sequentially. The reaction was initiated by addition of CuCl\(_2\) (6.7 mg, 10 mol%). After stirring the open vessel for 24 h at 25 °C, 5 mL EtOAc and 3 mL NH\(_3\)Cl were added and the mixture was transferred to a separation funnel along with 20 mL EtOAc. Then, 3 mL H\(_2\)O was added in order to break the suspension. The organic phase was collected and following two more extractions (2 \(\times\) 25 mL EtOAc), washed with brine, dried over Na\(_2\)SO\(_4\), and concentrated in vacuo. Flash chromatography with ethyl acetate/petroleum ether 10–40% as eluent afforded triazole 4a (19 mg, 0.05 mmol, 10%).
3.3.5. Procedure E: Reaction of Phenacyl Chloride under Copper-Free Conditions

To a 10 mL round bottom flask, phenacyl chloride 8 (77 mg, 0.50 mmol), DMSO (dry, 2 mL), p-toluene sulfinylate 2a (1.00 mmol, 2 eq.), DBU (150 µL, 1.00 mmol, 2 eq.), TMEDA (15 µL, 0.05 mmol, 10 mol%), and phenyl azide 3a (83 µL, 0.75 mmol, 1.5 eq.) were added sequentially. After stirring the open vessel for 24 h at 25 °C, 5 mL EtOAc and 3 mL NH₃Cl were added and the mixture was transferred to a separation funnel along with 20 mL EtOAc. Then, 3 mL H₂O was added in order to break the suspension. The organic phase was collected and following two more extractions (2 × 25 mL EtOAc), washed with brine, dried over Na₂SO₄, and concentrated in vacuo. Flash chromatography with ethyl acetate/petroleum ether 10–40% as eluent afforded triazole 4a (75 mg, 0.20 mmol, 40%).

3.3.6. Procedure F: Reaction of Acetophenone (1a) in Absence of Azide towards Ketosulfones 5a and 5b

To a 10 mL round bottom flask, acetophenone 1a,b (0.50 mmol), DMSO (dry, 2 mL), sodium p-toluenesulfinate 2a (178 mg, 1.00 mmol, 2eq), DBU (150 µL, 1.00 mmol, 2 eq.), and TMEDA (15 µL, 0.050 mmol, 10 mol%) were added sequentially. The reaction was initiated by addition of CuCl₂ (6.7 mg, 10 mol%). After stirring the open vessel for 24 h at 25 °C, 5 mL EtOAc and 3 mL NH₃Cl were added and the mixture was transferred to a separation funnel along with 20 mL EtOAc. Then, 3 mL H₂O was added in order to break the suspension. The organic phase was collected and following two more extractions (2 × 25 mL EtOAc), washed with brine, dried over Na₂SO₄, and concentrated in vacuo. Flash chromatography with ethyl acetate/petroleum ether 10–30% as eluent afforded the title products as white solids.

1-Phenyl-2-(toluene-4-sulfonyl)ethane (5a, Known compound [74,75]). Prepared according to the general procedure using acetophenone 1a (60 mg, 0.50 mmol). Reaction time was 24 h. Flash chromatography using EtOAc/petroleum ether 10–30% yielded 5a (89 mg, 0.324 mmol, 65%) as a white solid; mp 105–106 °C (Lit. mp 105–106 °C [75]). ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 8.03–7.87 (app. d, J = 7.2 Hz, 2H), 7.83–7.70 (app. d, J = 6.8 Hz, 2H), 7.67–7.56 (m, 1H), 7.54–7.42 (m, 2H), 7.38–7.26 (app. d, J = 6.8 Hz, 2H), 4.72 (s, 2H), 2.43 (s, 3H). ¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 188.3, 145.5, 135.88, 135.87, 134.4, 129.9, 128.9, 128.7, 63.7, 21.8.

1-(4-Trifluoromethylphenyl)-2-(toluene-4-sulfonyl)ethane (5b, known compound [27]). Prepared according to the general procedure using 4’-(trifluoromethyl)acetophenone 1b (94 mg, 0.50 mmol). Reaction time was 24 h. Flash chromatography using EtOAc/petroleum ether 10–30% yielded 5b (113 mg, 0.330 mmol, 65%) as a white solid; mp 136–137 °C: 365.04299; found: 365.0427.

4. Conclusions

In conclusion, we have developed an efficient Cu-catalyzed three-component synthesis of 4-sulfonyl triazoles from aromatic ketones, azides, and sodium sulfinites, with air oxygen as terminal oxidant, operating at room temperature. This reaction involves a sequential oxidative sulfonylation of aromatic ketones/Dimroth cyclization. Preliminary mechanistic investigations indicate that both sulfonyl free radicals and organometallic Cu(III)-intermediates are involved.

Supplementary Materials: The following are available online. Table S1: Optimization of reaction conditions, copies and primary NMR FID files of the ¹H, ¹⁹F, and ¹³C-NMR spectra.

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References

1. Narsimha, S.; Battula, K.S.; Reddy, N.V. Microwave-Assisted One-Pot Synthesis of Benzo[d]Thiazole Containing 1,2,3-Triazoles by Using Organo Catalytic Reaction and Their Antibacterial Activity. Heterocycl. Lett. 2017, 7, 1139–1146.

2. Gonzalez-Calderon, D.; Mejia-Dionicio, M.G.; Morales-Reza, M.A.; Ramirez-Villalva, A.; Morales-Rodriguez, M.; Jaueregui-Rodriguez, B.; Diaz-Torres, E.; Gonzalez-Romero, C.; Fuentes-Benites, A. Azide-Enolate 1,3-Dipolar Cycloaddition in the Synthesis of Novel Triazole-Based Miconazole Analogues as Promising Antifungal Agents. Eur. J. Med. Chem. 2016, 112, 60–65. [CrossRef]

3. Ramírez-Villalva, A.; González-Calderón, D.; Rojas-García, R.I.; González-Romero, C.; Tamariz-Mascaruía, J.; Morales-Rodriguez, M.; Zavala-Segovia, N.; Fuentes-Benítes, A. Synthesis and Antifungal Activity of Novel Oxazolidin-2-One-Linked 1,2,3-Triazole Derivatives. MedChemComm 2017, 2, 2258–2262. [CrossRef]

4. Hlasta, D.J.; Ackerman, J.H. Steric Effects on the Regioselectivity of an Azide-Alkyne Dipolar Cycloaddition Reaction: The Synthesis of Human Leukocyte Elastase Inhibitors. J. Org. Chem. 1994, 59, 6184–6189. [CrossRef]

5. Lin, W.; Wang, Y.-M.; Chai, S.C.; Lv, L.; Zheng, J.; Wu, J.; Zhang, Q.; Wang, Y.-D.; Griffin, P.R.; Chen, T. SPA70 Is a Potent Antagonist of Human Pregnane X Receptor. Nat. Commun. 2017, 8, 741. [CrossRef]

6. Li, L.; Welch, M.A.; Li, Z.; Mackowiak, B.; Heyward, S.; Swaan, P.W.; Wang, H. Mechanistic Insights of Phenobarbital-Mediated Activation of Human but Not Mouse Pregnane X Receptor. Mol. Pharmacol. 2019, 96, 345–354. [CrossRef]

7. Huber, A.D.; Wright, W.C.; Lin, W.; Majumder, K.; Low, J.A.; Wu, J.; Buchman, C.D.; Pintel, D.J.; Chen, T. Mutation of a Single Amino Acid of Pregnane X Receptor Switches an Antagonist to Agonist by Altering AF-2 Helix Positioning. Cell. Mol. Life Sci. 2020. [CrossRef]

8. Álvarez-Pérez, M.; Velado, M.; García-Puentes, D.; Sáez, E.; Vicent, C.; Fernández de la Pradilla, R.; Viso, A.; de la Torre, M.C.; Sierra, M.A. Sulfur Groups Improve the Performance of Triazole- and Triazolium-Based Interaction Units in Anion Binding. J. Org. Chem. 2017, 82, 3341–3346. [CrossRef]

9. Gao, D.; Zhai, H.; Parvez, M.; Back, T.G. 1,3-Dipolar Cycloadditions of Acetylenic Sulfones in Solution and on Solid Supports. J. Org. Chem. 2008, 73, 8057–8068. [CrossRef]

10. Salameh, B.A.; Cumpstey, I.; Sundin, A.; Leffler, H.; Nilsson, U.J. 1H-1,2,3-Triazol-1-Yl Thiodigalactoside Derivatives as High Affinity Galectin-3 Inhibitors. Bioorg. Med. Chem. 2010, 18, 5367–5378. [CrossRef]

11. Ding, S.; Jia, G.; Sun, J. Iridium-Catalyzed Intermolecular Azide—Alkyne Cycloaddition of Internal Thioalkynes under Mild Conditions. Angew. Chem. Int. Ed. 2014, 53, 1877–1880. [CrossRef]

12. Destito, P.; Couceiro, J.R.; Faustino, H.; López, F.; Mascareñas, J.L. Ruthenium-Catalyzed Azide—Thioalkyne Cycloadditions in Aqueous Media: A Mild, Orthogonal, and Biocompatible Chemical Ligation. Angew. Chem. Int. Ed. 2017, 56, 10766–10770. [CrossRef]

13. Song, W.; Zheng, N.; Li, M.; Dong, K.; Li, J.; Ullah, K.; Zheng, Y. Regiodivergent Rhodium(I)-Catalyzed Azide—Alkyne Cycloaddition (RhAAC) to Access Either Fully Substituted Sulfonyl-1,2,3-Triazoles under Mild Conditions. Org. Lett. 2018, 20, 6705–6709. [CrossRef]

14. Braga, A.L.; Reckziegel, A.; Menezes, P.H.; Stefani, H.A. Alkynyl Sulfoxides and Selenides from Alkynyl Bromides and Diorganoyl Chalcogenides Promoted by Copper(I) Iodide. Tetrahedron Lett. 1993, 34, 393–394. [CrossRef]

15. Reeves, J.T.; Camara, K.; Han, Z.S.; Xu, Y.; Lee, H.; Busacca, C.A.; Senanayake, C.H. The Reaction of Grignard Reagents with Bunte Salts: A Thiol-Free Synthesis of Sulfoxides. Org. Lett. 2014, 16, 1196–1199. [CrossRef] [PubMed]
16. Frei, R.; Wodrich, M.D.; Hari, D.P.; Borin, P.-A.; Chauvier, C.; Waser, J. Fast and Highly Chemoselective Alkynylation of Thiol
with Hypervalent Iodine Reagents Enabled Through a Low Energy Barrier Concerted Mechanism. J. Am. Chem. Soc. 2014, 136, 16563–16573. [CrossRef]

17. Gao, W.-C.; Shang, Y.-Z.; Chang, H.-H.; Li, X.; Wei, W.-L.; Yu, X.-Z.; Zhou, R. N-Alkynylthio Phthalimide: A Shelf-Stable
Alkynylthio Transfer Reagent for the Synthesis of Alkynyl Thioethers. Org. Lett. 2019, 21, 6021–6024. [CrossRef]

18. Hammert, D.J.; Moran, W.J. Improving Alkynyl(Aryl)iodonium Salts: 2-Anisyl as a Superior Aryl Group. Org. Biomol. Chem. 2014, 12, 4156–4162. [CrossRef]

19. Chen, P.; Zhu, C.; Zhu, R.; Wu, W.; Jiang, H. MnO2-Promoted Oxidative Radical Sulfonylation of Haloalkynes with Sulfonyl Hydrazides: C(Sp)-S Bond Formation towards Alkynyl Sulfones. Chem. Asian J. 2017, 12, 1875–1878. [CrossRef]

20. Singh, R.; Allam, B.K.; Singh, N.; Kumari, K.; Singh, S.K.; Singh, K.N. A Direct Metal-Free Decarboxylative Sulfono Functionalization (DSF) of Cinnamic Acids to α,β-Unsaturated Phenyl Sulfones. Org. Lett. 2015, 17, 2656–2659. [CrossRef]

21. Pokhodylo, N.T.; Matiychuk, V.S.; Obushak, M.D. (Arylsulfonyl)Acetones and -Acetonitriles: New Activated Methylenic Building
Blocks for Synthesis of 1,2,3-Triazoles. Synthesis Stuttgart. 2009, 2321–2323. [CrossRef]

22. Saraiva, M.T.; Costa, G.P.; Seus, N.; Schumacher, R.F.; Perin, G.; Paixão, M.W.; Luque, R.; Alves, D. Room-Temperature
Organocatalytic Cycloaddition of Azides with β-Keto Sulfones: Toward Sulfonyl-1,2,3-Triazoles. Org. Lett. 2015, 17, 6206–6209. [CrossRef]

23. Ahamad, S.; Kumar, A.; Kant, R.; Mohanan, K. Metal-Free Three-Component Assembly of Fully Substituted 1,2,3-Triazoles. Asian J. Org. Chem. 2013, 8, 1698–1703. [CrossRef]

24. Safrygin, A.; Dar’in, D.; Kantin, G.; Krasavin, M. α-Diazo-β-Oxosulfones as Partners in the Wolff 1,2,3-Triazole Synthesis and the
Wolff Rearrangement in the Presence of Aromatic Amines. Eur. J. Org. Chem. 2019, 2019, 4721–4724. [CrossRef]

25. Farrington, A.; Hough, L. A New Entry to Triazoles from Carboxydrates. Chem. Commun. 1965, 219–220. [CrossRef]

26. Farrington, A.; Hough, L. A Fused Pyrrolidotriazole Derivative from Bis(Ethylsulphonyl)-(2,3-O-Isopropylidene-4-O-
Methanesulphonyl-α-D-Lyxopyranosyl)Methane. Carbohydr. Res. 1974, 38, 107–115. [CrossRef]

27. Thomas, J.; John, J.; Parekh, N.; Dehaen, W. A Metal-Free Three-Component Reaction for the Regioselective Synthesis of
1,4,5-Trisubstituted 1,2,3-Triazoles. Chem. Rev. 2015, 155, 10155–10159. [CrossRef]

28. Zhou, L.; Yi, H.; Zhu, L.; Qi, X.; Jiang, H.; Liu, C.; Feng, Y.; Lan, Y.; Lei, A. Tuning the Reactivity of Radical through a Triplet
Diradical Cu(II) Intermediate in Radical Oxidative Cross-Coupling. Sci. Rep. 2015, 5, 15934. [CrossRef] [PubMed]

29. Fu, H.; Wang, S.-S.; Li, Y.-M. Copper-Mediated Oxidative Radical Addition/Cyclization Cascade: Synthesis of Trifluoromethylated
and Sulfonated Quinoline-2,4(1H,3H)-Diones. Adv. Synth. Catal. 2016, 358, 3616–3626. [CrossRef]
43. Funes-Ardoiz, I.; Maseras, F. Oxidative Coupling Mechanisms: Current State of Understanding. ACS Catal. 2018, 8, 1161–1172. [CrossRef]

44. Choi, H.; Min, M.; Peng, Q.; Kang, D.; Paton, R.S.; Hong, S. Unraveling Innate Substrate Control in Site-Selective Palladium-Catalyzed C–H Heterocycle Functionalization. Chem. Sci. 2016, 7, 3900–3909. [CrossRef]

45. Itahara, T.; Ikeda, M.; Sakakibara, T. Alkenylation of 1-Acylindoles with Olefins Bearing Electron-Withdrawing Substituents and Palladium Acetate. J. Chem. Soc. Perkin Trans. 1 1983, 1361–1363. [CrossRef]

46. McCann, S.D.; Stahl, S.S. Copper-Catalyzed Aerobic Oxidations of Organic Molecules: Pathways for Two-Electron Oxidation with a Four-Electron Oxidant and a One-Electron Redox-Active Catalyst. Accounts Chem. Res. 2015, 48, 1756–1766. [CrossRef]

47. Lei, A.; Shi, W.; Liu, C.; Zhang, H.; He, C. Oxidative Cross-Coupling Reactions; Wiley Hoboken, NJ, USA, 2016; pp. 1–9. [CrossRef]

48. McCann, S.D.; Stahl, S.S. Copper-Catalyzed Aerobic Oxidations of Organic Molecules: Pathways for Two-Electron Oxidation with a Four-Electron Oxidant and a One-Electron Redox-Active Catalyst. Accounts Chem. Res. 2015, 48, 1756–1766. [CrossRef]

49. Gligorich, K.M.; Sigman, M.S. Recent Advancements and Challenges of PalladiumII-Catalyzed Oxidation Reactions with Molecular Oxygen as the Sole Oxidant. Chem. Commun. 2009, 3854–3867. [CrossRef]

50. Guizar, N.; Schweitzer-Chaput, B.; Klussmann, M. Oxidative Coupling Reactions for the Functionalisation of C–H Bonds Using Oxygen. Catal. Sci. Technol. 2014, 4, 2781–2796. [CrossRef]

51. Wang, D.; Weinstein, A.B.; White, P.B.; Stahl, S.S. Ligand-Promoted Palladium-Catalyzed Aerobic Oxidation Reactions. Chem. Rev. 2018, 118, 2636–2679. [CrossRef]

52. Zhu, B.; Lazaro, M.; Trethew, B.G.; Angelici, R.J. Aerobic Oxidation of Amines to Imines Catalyzed by Bulk Gold Powder and by Alumina-Supported Gold. J. Catal. 2008, 260, 1–6. [CrossRef]

53. Ackermann, L.; Wang, L.; Lygin, A.V. Ruthenium-Catalyzed Aerobic Oxidative Coupling of Alkynes with 2-Aryl-Substituted Pyrroles. Chem. Sci. 2012, 3, 177–180. [CrossRef]

54. Matsushita, M.; Kamata, K.; Yamaguchi, K.; Mizuno, N. Heterogeneously Catalyzed Aerobic Oxidative Biaryl Coupling of 2-Naphthols and Substituted Phenols in Water. J. Am. Chem. Soc. 2005, 127, 6632–6640. [CrossRef] [PubMed]

55. Jiang, B.; Feng, Y.; Ison, E.A. Mechanistic Investigations of the Iridium(III)-Catalyzed Aerobic Oxidation of Primary and Secondary Alcohols. J. Am. Chem. Soc. 2008, 130, 14462–14464. [CrossRef] [PubMed]

56. Wang, J.; Wang, X.; Niu, Z.-Q.; Wang, J.; Zhang, M.; Li, J.-H. Copper Nitrate–Catalyzed Aerobic Oxidation of Alcohols. J. Org. Chem. 2015, 80, 11602–11609. [CrossRef] [PubMed]

57. Campbell, A.N.; Stahl, S.S. Overcoming the “Oxidant Problem”: Strategies to Use O2 as the Oxidant in Organometallic C–H Oxidation Reactions Catalyzed by Pd (and Cu). Accounts Chem. Res. 2012, 45, 851–863. [CrossRef]

58. Wu, K.; Huang, Z.; Qi, X.; Li, Y.; Zhang, G.; Liu, C.; Yi, H.; Meng, L.; Bunel, E.E.; Miller, J.T.; et al. Copper-Catalyzed Aerobic Oxidative Coupling: From Ketone and Diamine to Pyrazine. Sci. Adv. 2015, 1, e1500656. [CrossRef]

59. Wang, J.; Wang, X.; Niu, Z.-Q.; Wang, J.; Zhang, M.; Li, J.-H. Copper Nitrate–Catalyzed α-Bromination of Aryl Ketones with Hydrobromic Acid. Synth. Commun. 2016, 46, 165–168. [CrossRef]

60. Su, P.; Fan, C.; Yu, H.; Wang, W.; Jia, X.; Rao, Q.; Fu, C.; Zhang, D.; Huang, B.; Pan, C.; et al. Synthesis of Ti-Al Binary Oxides and Their Catalytic Application for C-H Halogenation of Phenols, Aldehydes and Ketones. Mol. Catal. 2019, 475, 110460. [CrossRef]

61. Suess, A.M.; Ertem, M.Z.; Cramer, C.J.; Stahl, S.S. Divergence between Organometallic and Single-Electron-Transfer Mechanisms in Copper(II)-Mediated Aerobic C–H Oxidation. J. Am. Chem. Soc. 2013, 135, 9797–9804. [CrossRef]

62. Wendlandt, A.E.; Suess, A.M.; Stahl, S.S. Copper-Catalyzed Aerobic Oxidative C–H Functionalizations: Trends and Mechanistic Insights. Angew. Chem. Int. Ed. 2015, 54, 11062–11087. [CrossRef] [PubMed]

63. Nishida, A.; Hamada, T.; Yonemitsu, O. Hydrolysis of Tosyl Esters Initiated by an Electron Transfer from Photoexcited Electron-Rich Aromatic Compounds. J. Org. Chem. 1988, 53, 3386–3387. [CrossRef]

64. Tang, X.; Huang, L.; Qi, C.; Wu, X.; Wu, W.; Jiang, H. Copper-Catalyzed Sulfinamides Formation from Sodium Sulfonates and Amines. Chem. Commun. 2013, 49, 6102–6104. [CrossRef] [PubMed]

65. Jiang, Q.; Shi, W.; Liu, C.; Zhang, H.; He, C. Oxidative Cross-Coupling Reactions; Wiley Hoboken, NJ, USA, 2016; pp. 1–9. [CrossRef]

66. Rao, W.-H.; Jiang, L.-L.; Liu, X.-M.; Chen, M.-J.; Chen, F.-Y.; Jiang, X.; Zhao, J.-X.; Zou, G.-D.; Zhou, Y.-Q.; Tang, L. Copper(II)-Catalyzed Alkene Aminosulfonylation with Sodium Sulfonates for the Synthesis of Sulfonylated Pyridylcarbinols. Org. Lett. 2019, 21, 2890–2893. [CrossRef]

67. Wang, Y.; Ding, J.; Zhao, J.; Sun, W.; Lian, C.; Chen, C.; Zhu, B. Iminyl Radical-Promoted Imino Sulfonylation, Imino Cyanogeneration and Imino Thiocyanation of γ,δ-Unsaturated Oxime Esters: Synthesis of Versatile Functionalized Pyrrolines. Org. Chem. Front. 2019, 6, 2240–2244. [CrossRef]

68. Buschmann, H.-J.; Feldner, H.-K.; Knoche, W. The Reverse Rehydration of Carbonyl Compounds in Aqueous Solution. Part I, The Keto/Gem-Diol Equilibrium. Ber. Bunsenges. Phys. Chem. 1980, 84, 41–44. [CrossRef]

69. L’abbé, G. Dimroth Reaction. Ind. Chim. Belge 1971, 36, 3–10.

70. John, J.; Thomas, J.; Dehaen, W. Organocatalytic Routes toward Substituted 1,2,3-Triazoles. Chem. Commun. 2015, 51, 10797–10806. [CrossRef]

71. Ramachary, D.B.; Shashank, A.B.; Karthik, S. An Organocatalytic Azide–Aldehyde [3+2] Cycloaddition: High-Yielding Regioselective Synthesis of 1,4-Disubstituted 1,2,3-Triazoles. Angew. Chem. Int. Ed. 2014, 53, 10420–10424. [CrossRef]
72. Gottlieb, H.E.; Kotlyar, V.; Nudelman, A. NMR Chemical Shifts of Common Laboratory Solvents as Trace Impurities. J. Org. Chem. 1997, 62, 7512-7515. [CrossRef] [PubMed]

73. Campbell-Verduyn, L.S.; Mirfeizi, L.; Dierckx, R.A.; Elsinga, P.H.; Feringa, B.L. Phosphoramidite Accelerated Copper(i)-Catalyzed [3+2] Cycloadditions of Azides and Alkynes. Chem. Commun. 2009, 2139–2141. [CrossRef] [PubMed]

74. Lai, C.; Xi, C.; Jiang, Y.; Hua, R. One-Pot Approach for the Regioselective Synthesis of β-Keto Sulfones Based on Acid-Catalyzed Reaction of Sulfonyl Chlorides with Arylacetylenes and Water. Tetrahedron Lett. 2005, 46, 513–515. [CrossRef]

75. Qian, H.; Huang, X. Solid-Phase Synthesis of β-Keto Sulfones. Synthesis Stuttgart. 2006, 1934–1936. [CrossRef]