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Metal-Catalyzed Reactivity Reversal in the Sulfonylation Reaction of α-Allenols: Controlled Synthesis of 4-(Arylsulfonyl)-2,5-Dihydrofurans

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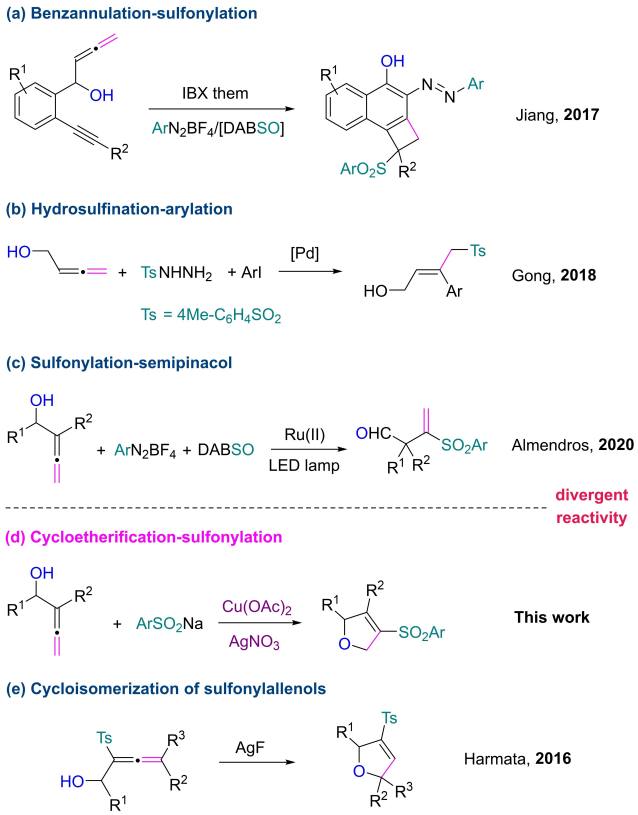
Abstract: The synergy between metal catalysis and radical chemistry allows to surpass previous limitations of the reactions between allenols and sulfonylating reagents. Considering that previous studies of the reactivity of the allenol moiety with sulfonylating reagents have been limited to addition and rearrangement reactions lacking cyclization, we decided to modify the protocol for achieving a catalytic cyclization/functionalization. In this way, we accomplished a copper-catalyzed cascade cycloetherification/sulfonylation for the controlled preparation of 4-(arylsulfonyl)-2,5-dihydrofurans from allenols and sulfinates involving *in situ*-generated sulfur-centered radicals. The generality of our strategy was illustrated using various methyl- and phenyl-substituted allenes.

Keywords: allenes; copper; oxycyclization; radicals; sulfones

The competent formation of products bearing distinct scaffolds from a common precursor, namely, divergent synthesis constitutes a powerful tool for generating molecular diversity.[1–4] In this way, a collection of structurally diversified molecules can be attained through judicious choice of the reaction conditions. The cumulated 1,2-diene (allene) moiety exhibits higher reactivity compared to naked alkenes, showing fascinating reactivity patterns.[5–18] However, allenes bear three different reactive sites for potential functionalization, making difficult the reactivity control in a selective transformation. The pharmacological properties of sulfones, joined to the utilization of these compounds as useful building blocks for the construction of other types of molecules, stimulate the investigation of novel protocols for the preparation of compounds bearing the sulfone group.[19–24]

Taking into account that the dihydrofuran ring is a recurrent motif in several natural products and pharmaceuticals, the combination of both pharmacophores in a same nucleus may be of interest. Metal-catalyzed cascade cycloetherification/sulfonylation across an allenol is a direct and attractive strategy that fulfils the step and atom economy criteria. However, it is a challenging task and has not been reported to date. The reactions of allenols with sulfonylating reagents have been limited to addition and rearrangement reactions lacking oxycyclization (Scheme 1a–c).[25–27] The copper-catalyzed methodology developed in the present contribution provided a novel possibility for the reaction between allenols and sulfonylating reagents, using inexpensive and very stable starting materials for the preparation of (arylsulfonyl)-2,5-dihydrofurans by sulfocycloetherification of allenols (Scheme 1d). The synergy between metal catalysis and radical chemistry allows surpassing previous limitations of the reactions between allenols and sulfonylating reagents. It should be mentioned that the only report available in the literature for the preparation of sulfonyl-dihydrofurans from allenes deals with the silver-catalyzed cycloisomerization of sulfonylallenols,

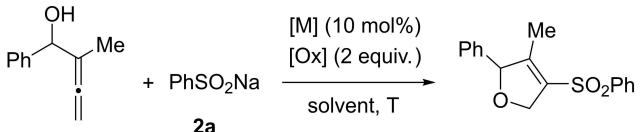


Scheme 1. Reactions of allenols with sulfonylating reagents.

which already bear the sulfone functionality in the starting material (Scheme 1e).[28,29]

We initiated this research using allenol **1a** and sodium benzenesulfinate **2a** as model substrates to determine convenient reaction conditions for the tandem sequence. After some experimentation, we identified $Cu(OAc)_2$ and $AgNO_3$ as the salts of choice for this transformation. Different catalysts ($CuCl_2$, CuOAc and $FeCl_2$) as well as various oxidants such as Ag_2CO_3, AgOAc, $K_2S_2O_8$, TBPB (*tert*-butyl peroxybenzoate), and O_2 were found to be less effective than the $Cu(OAc)_2$-$AgNO_3$ couple. The reaction did not proceed at rt regardless of the amount of copper-based catalyst, and the required cycloetherification/sulfonylation product **3a** was best obtained at 100 °C. Among the solvents surveyed, acetonitrile turned out to be the best; consequently, the reaction was carried out in a sealed tube. The most efficient reaction conditions were established using 10 mol% of $Cu(OAc)_2$ and 200 mol% of $AgNO_3$ with a ratio **1a**/**2a** of 1:2, providing functionalized dihydrofuran **3a** in a reasonable 68% yield (Table 1). Worthy of note, no rearranged acyclic product was observed, and heterocycle **3a** was formed with total selectivity. The suppression of the semipinacol rearrangement could be ascribed to the coordination ability of the copper with the allene moiety, which should facilitate an initial oxycyclization. Next, the scope of the above sequence was studied through modification of the carbinol core. As depicted in Scheme 2, the formation of 4-(sulfonyl)-2,5-dihydrofurans tolerates the presence of both elec-

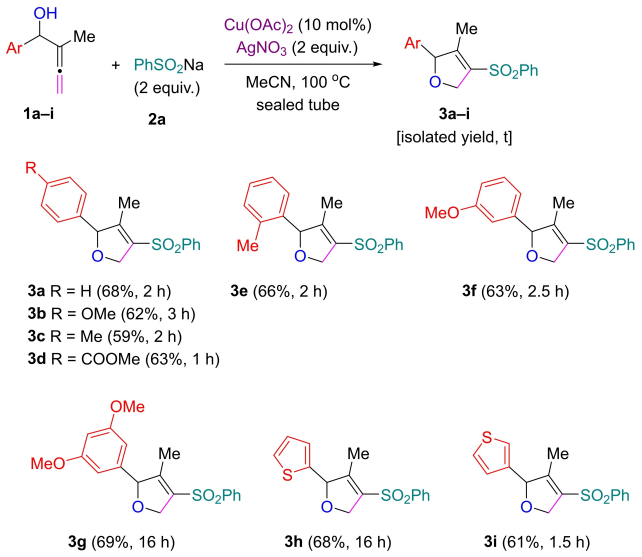
Table 1. Cycloetherification/sulfonylation of allenol **1a** under modified copper-catalyzed conditions.



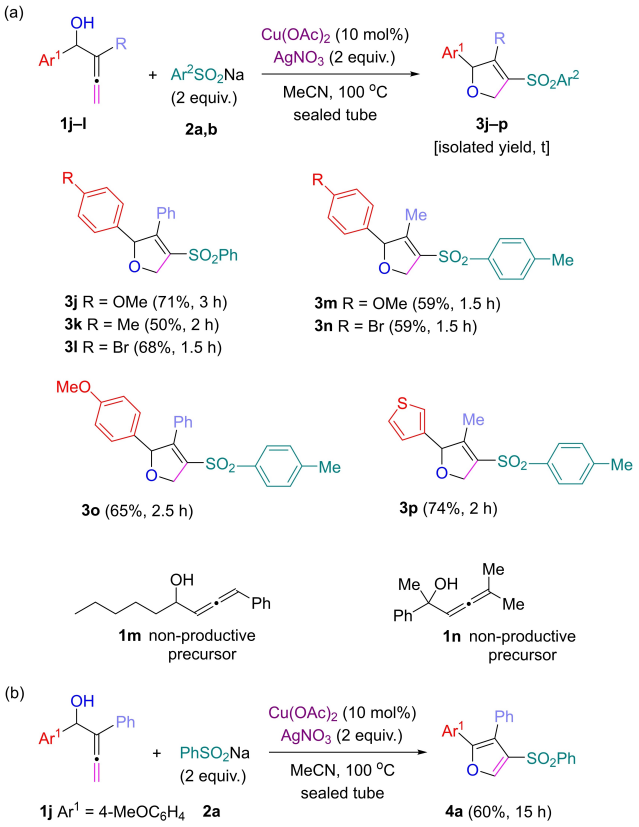
1a **2a** **3a**

entry	catalyst	oxidant	solvent	T (°C)	time (h)[a]	yield (%)[b]
1	CuOAc	$AgNO_3$	MeCN	100	3	45
2	$Cu(OAc)_2$	$AgNO_3$	MeCN	100	2	68
3	$CuCl_2$	$AgNO_3$	MeCN	100	3	37
4	$FeCl_2$	$AgNO_3$	MeCN	100	3	trace
5	$Cu(OAc)_2$	Ag_2CO_3	MeCN	100	2	49
6	$Cu(OAc)_2$	AgOAc	MeCN	100	2	46
7	$Cu(OAc)_2$	$K_2S_2O_8$	MeCN	100	3	trace
8	$Cu(OAc)_2$	$AgNO_3$	DMF	100	2.5	51
9	$Cu(OAc)_2$	$AgNO_3$	DCE	100	3	trace
10	$Cu(OAc)_2$	$AgNO_3$	THF	100	3	21
11	$Cu(OAc)_2$	$AgNO_3$	MeCN	40	3	trace
12	$Cu(OAc)_2$	TBPB	MeCN	100	3	18
13	$Cu(OAc)_2$	O_2	MeCN	100	3	trace

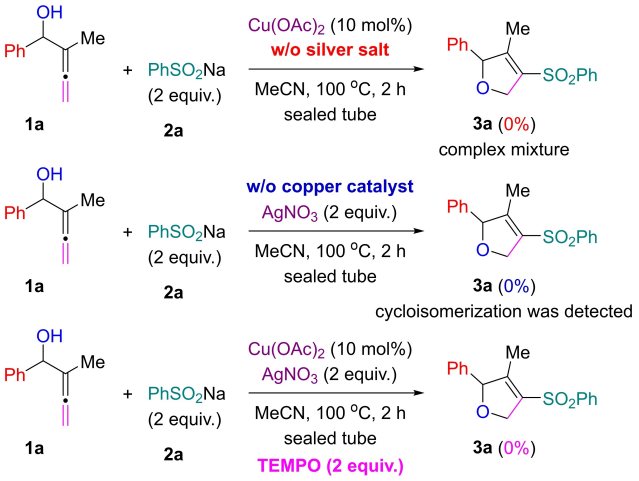
[a] The experiments were performed in a sealed tube using **1a** (0.15 mmol), **2a** (0.30 mmol), oxidant (200 mol%) and catalyst (10 mol%) in the specified solvent (1 mL). Reaction progress was followed by TLC.
[b] Yield of pure, isolated product with correct analytical and spectral data.



Scheme 2. Cooperative copper-silver catalyzed cycloetherification/sulfonylation of allenes **1 a–i** with benzenesulfinate **2 a**.



Scheme 3. Cooperative copper-silver catalyzed cycloetherification/sulfonylation of allenes **1 j–l** with benzenesulfinates **2 a**,**b**.



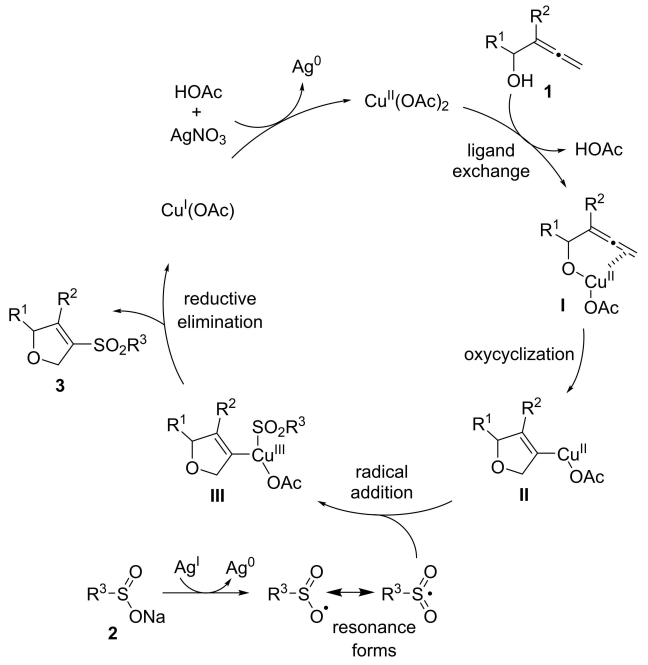
Scheme 4. Control experiments.

tron-withdrawing (CO_2Me) as well as electron-donating (Me and MeO) substituents at the aryl moiety in **1**. Besides, the tandem sequence is amenable to different arene substitution patterns such as *ortho*- *meta*-, and *para*-subtitution. The reaction did also smoothly proceed in allenol-tethered π-excedent heterocyclic scaffolds such as thiophenes **1 h**,**i** but not in allene precursors having the π-deficient pyridine nucleus.

The usefulness of the oxycyclization/sulfonylation sequence between methyl-substituted allenols **1 a–i** and sodium benzenesulfinate **2 a** was also extended to phenyl-substituted allenols **1 j–l** and sodium arenesulfinate **2 b**. When the same reaction conditions utilized for the cyclization/functionalization in Scheme 2 were adapted to precursors **1 j–l** and **2 b**, the required 4-(sulfonyl)-2,5-dihydrofurans **3 j–p** were conveniently obtained (Scheme 3a). The reactions of 1-phenylnona-1,2-dien-4-ol **1 m**, a 1,3-disubstituted allenol, and 5-methyl-2-phenylhexa-3,4-dien-2-ol **1 n**, a 1,3,3-trisubstituted allenol, were messy and did not produce the target sulfonyl-dihydrofurans (Scheme 3a). Interestingly, fully aromatic furan **4 a** could be obtained after exposure of the appropriate starting materials to the reaction conditions but under prolonged reaction times (Scheme 3b).

Control experiments were carried out with the aim of clarifying the reaction path. Dihydrofuran product **3 a** was not observed when allenol **1 a** and benzenesulfinate **2 a** were exposed to the standard reaction conditions in the absence either the copper catalyst or the silver salt (Scheme 4). A radical-trapping experiment was also performed; the reaction between **1 a** and **2 a** was completely inhibited in the presence of the radical scavenger TEMPO (Scheme 4), suggesting the radical nature of the sequence.

A plausible mechanism is postulated in Scheme 5. The reaction is initiated by substitution of the proton in allenols **1** with copper(II) acetate to generate a copper alkoxide, which *via* coordination with the terminal allene double bond affords complex **I**. Next, 5-*endo*-



Scheme 5. Mechanistic proposal for the copper-catalyzed preparation of 4-(arylsulfonyl)-2,5-dihydrofurans **3**.

trig-oxycupration by nucleophilic attack of the allenolic oxygen atom should form cupradihydrofuran species **II**. Simultaneously, sodium sulfinates **2** suffer oxidation by silver(I) nitrate giving rise to a sulfur-centered radical which reacted with alkenylcopper(II) species **II** resulting in $PhSO_2$-functionalized alkenylcopper(III) complex **III**. Further reductive elimination releases oxacycles **3** along with copper(I) acetate. Final oxidation of copper(I) acetate to copper(II) acetate promoted by silver(I) nitrate closes the copper catalytic cycle.

In conclusion, we have developed a copper-catalyzed selective preparation of 4-(arylsulfonyl)-2,5-dihydrofurans from allenols and sulfinates involving the sequential formation of C–O and C–S bonds via sulfone radicals generated *in situ.* Considering that previous studies of the reactivity of the allenol moiety with sulfonylating reagents have been limited to addition and rearrangement reactions lacking cyclization, our divergent strategy may be valuable for the catalytic and synthetic community.

Experimental Section

Typical Procedure for the Copper-Catalyzed Reaction of α-Allenic Alcohols; Synthesis of 4-(Arylsulfonyl)-2,5-Dihydrofuran 3 b

$Cu(OAc)_2$ (3.3 mg, 0.018 mmol), sodium salt **2** (59.1 mg, 0.36 mmol) and $AgNO_3$ (61.2 mg, 0.36 mmol) were added to a solution of allenol **1 b** (34.8 mg, 0.18 mmol) in acetonitrile (2 mL). The reaction mixture was stirred at 100 °C in a sealed tube until the starting material disappeared as indicated by TLC. The reaction mixture was cooled to room temperature, was extracted with ethyl acetate (3 × 2 mL), and the ethyl acetate layer was separated from the aqueous layer. The organic extract was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. After chromatography of the residue using *n*-hexane/ethyl acetate (7:1) as eluent, compound **3 b** (37 mg, 62%) was obtained as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.95 (m, 2H), 7.69 (m, 1H), 7.61 (m, 2H), 7.10 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.57 (t, J = 4.5 Hz, 1H), 4.97 (m, 1H), 4.82 (ddq, J = 9.6, 3.9, 2.1 Hz, 1H), 3.81 (s, 3H), 1.94 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ 160.1, 150.9, 140.8, 133.8, 132.0, 130.9, 129.5 (2 C), 128.5 (2 C), 127.2 (2 C), 114.2 (2 C), 92.8, 74.6, 55.3, 11.4; IR ($CHCl_3$, cm^{-1}): ν 1324, 995. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{19}O_4S$ 331.09986; Found 331.10036.

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