Article

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Catalytic Sulfone Upgrading Reaction with Alcohols via Ru(II)

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Dedicated to Spinal Tap on the occasion of their 36th year reunion concert

ABSTRACT: Sulfones and sulfonamides with an α-CH bond can be easily alkylated by aliphatic alcohols to add the carbon skeleton of the alcohol via a one-step, Ru(II) catalyzed redox neutral reaction. The reaction requires a sub-stoichiometric amount of base and produces only water as a byproduct. A number of pharmaceutically relevant functional groups such as piperidine, morpholine, etc. are well tolerated under the reaction conditions to give higher value-added products in one step from widely available substrates. The reaction proceeds through a sulfone carbanion addition to an in-situ generated aldehyde formed via catalytic dehydrogenation and subsequent catalyst mediated replacement of the secondary alcohol by hydrogen.

Aliphatic sulfones are a class of valuable compounds used in the chemical industry and are a common functional group motif found in many drugs such as elitriptan and tinidazole.[1] Sulfonamides are a motif present in many antibiotics often as an aryl amide sulfone. The underreporting of hospital deaths due to resistant bacteria may eventually lead to a renaissance in the search for new antibiotic[2] sulfonamides with different carbon skeletons. Simple aliphatic sulfones such as dimethyl sulfone are primarily used as recyclable, high boiling solvents in the petroleum industry to extract valuable aromatic materials.[3] Recently, dialkyl and alkyl aryl sulfones have found use as electrolytes in lithium ion batteries.[4] Moreover, alkyl aryl sulfones are also often used in a C-C bond forming reaction, the Julia olefination (Figure 1, a), [5] which is characterized by its wide functional group tolerance, mild reaction conditions, and *E*-selectivity (as opposed to the Z selectivity in the potassium mediated Wittig coupling) for the products.

Traditionally, building the carbon skeleton of functionalized sulfones can be accomplished by modification of the readily available dimethyl sulfone or aryl alkyl sulfones by deprotonation with a strong base such as n-BuLi, and subsequent reaction with an alkyl halide. Alternatively, the sulfone can be made by the synthesis of an appropriate sulfide and its oxidation with peroxide or oxime. However, these approaches are multi-step and are not atom economical, generating large amount of waste products in the process. The highly desirable direct, one-step alkylation of readily available simple sulfones with alcohols generating only water as a by-product is currently unknown.

We recently reported a C-C bond forming reaction where sulfones were reacted with alcohols in a 2:1 ratio in the presence of the Gusev catalyst (^{Et}SNS-Ru, Figure 1, b)[6] to give diastereoselective cyclopropane products.[7] At low temperature, minor linear sulfone products that were the result of a 1:1 reaction could also be detected (Figure 1, c). Interestingly, this reactivity was in contrast to the olefination of sulfones with alcohols in the presence of a bipyridine Ru catalyst reported by the Milstein group (Figure 1, b).[8]

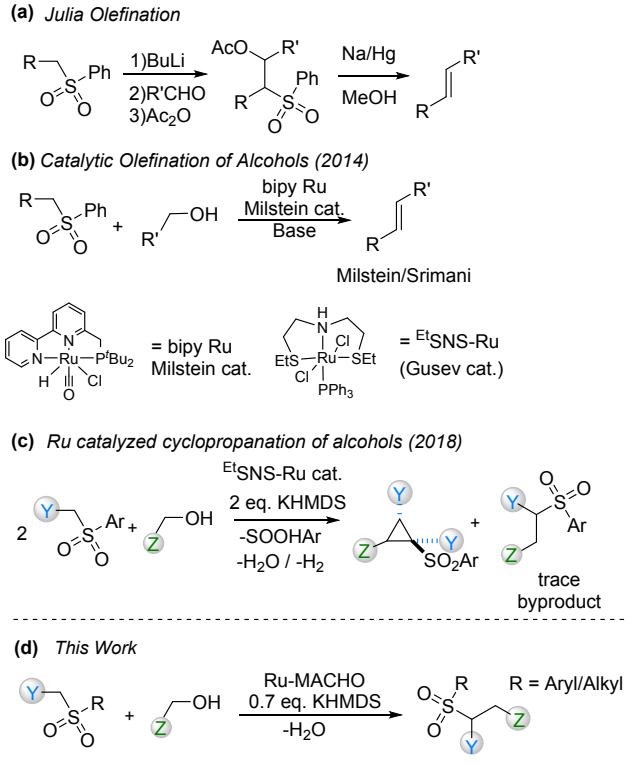


Figure 1. Reactivity of sulfones in Julia olefination and in Ru-catalyzed reactions.

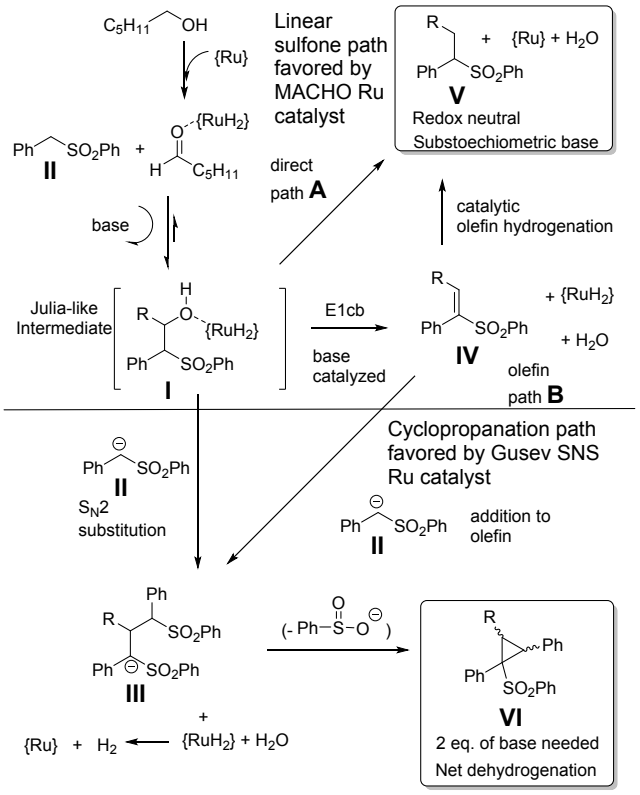
In this paper, we report the optimization of the linear sulfone reaction that when carried out with a different catalyst, lower temperature, and a sub-stoichiometric amount of base, results in almost full conversion of the starting sulfone to the alkylated product, with suppression of the cyclopropanation reaction (Figure 1, d). In effect, starting from common and commercially available sulfones and alcohols, the hereby described protocol is a one-step, and atom economical method of synthesizing more complex sulfones. This one-step approach reduces the number of intermediate isolation steps, eliminates the need to use expensive base or oxidants, and decreases the amount of generated hazardous waste.

We were able to obtain linear sulfones directly from alcohols in good to excellent yields, with the only byproduct being water, as hydrogen gas produced during the reaction is used in the overall redox-neutral transformation (Figure 1, d / Scheme 1). The new sulfone alkylation method is an excellent, fast, clean, and selective way to produce novel solvents for the petrochemical industry, electrolyte components for batteries, reactive partners in the Julia olefination reaction, and it provides a short route to generate a large library of potential drug-like fragments for screening. There have been recent reports of Ru and Mn catalyzed dehydroxylative alcohol additions to the β-carbon of other functionalized substrates,[9] however with sulfones the reaction has to be performed under milder conditions to avoid the outcome of cyclopropanation[7] or sulfone elimination to form the olefin.[8]

In order to optimize the reaction, we considered a plausible mechanism suggested in the earlier cyclopropanation report based on a number of stoichiometric experiments (Scheme 1) performed previously.[7] These experiments did not suggest an olefin intermediate **IV** in cyclopropanation; however, its presence could not be conclusively ruled out. It could also be a viable intermediate for linear sulfone synthesis, where hydrogenation of an intermediate vinyl sulfone by a Ru dihydride complex would be reminiscent of the hydrogen borrowing chemistry developed by the Williams group. [10] Since the product proved to be catalyst dependent, it may be that a different pathway is operative in each case.

At the conclusion of the current work, we spiked a typical catalytic reaction with a β-hydroxy alkyl sulfone or a vinyl sulfone in different amounts. The results of these experiments, that do favor the olefin pathway and the formation of **IV** in linear sulfone synthesis, are summarized in the SI with a discussion. We thus believe that the reaction proceeds via **IV** and olefin path **B**, however the other pathway could not be conclusively be ruled out (Scheme 1). Recent work by the Maji group on the manganese catalyzed synthesis of vinyl sulfones by the cross-coupling of phenyl benzyl sulfones and benzylic alcohols also argues for the intermediacy of vinyl sulfone, even though the conditions are harsher than those used in the current work and the catalyst identity is different. [11]

Regardless of the exact pathway, the initial step of the reaction is the same in both the linear and cyclopropyl product synthesis. It involves the dehydrogenation of the alcohol to the intermediate aldehyde that is rapidly captured by an anionic sulfone to give **I**. We hypothesized that unlike cyclopropanation, where the Ru complex is only responsible for dehydrogenation, the synthesis of the linear byproduct would require the catalyst to subsequently react with the unobserved intermediate (i.e. add an H_2 equivalent to olefin **IV** to give **V** before the alternative pathway to give intermediate **III** and eventually product **VI** could occur), meaning that one of the first possible screening parameters was to find a dehydrogenation catalyst capable of this further transformation (Figure 2).



Scheme 1. Suggested mechanism.

Phenyl methyl sulfone and 1-butanol were chosen for the model reaction, as the cyclopropane byproduct would be very similar in polarity and would be impossible to separate by regular chromatography. A large ratio of the desired linear product over cyclopropane had to be obtained. In the previous report, less linear product was observed at higher temperatures with the Gusev commercially available catalyst, [6] so the screen for a competent catalyst was carried out at a lower 90°C (Table 1). As expected, the two major products, a linear sulfone and a cyclopropane, were obtained with a ratio and yield highly dependent on the catalyst. In practice, another minor byproduct that was obtained was the double alkylation product, which however could be separated by chromatography (see SI for full optimization tables). We

quickly identified commercially available MACHO-Cl and MACHO-BH_4 as competent catalysts in linear sulfone formation providing higher yields of the desired linear sulfone product when compared to Ru amine PNN or modified Gusev catalysts ^{Me}SNS-Ru-X (reported as more active in alcohol dehydrogenation than the original). [12] Potassium bis(trimethylsilyl)amide (KHMDS) was used as a base to give high yield even in sub-stoichiometric amounts (0.5-0.75 equiv, entries 6-14), although KO^{t}Bu also gave good results (entries 15-16). The olefin elimination product obtained by Milstein/Srimani in earlier work, [8] was not seen in initial experiments with larger aliphatic alcohols (i.e. heptene that would be obtained from hexanol was not observed).

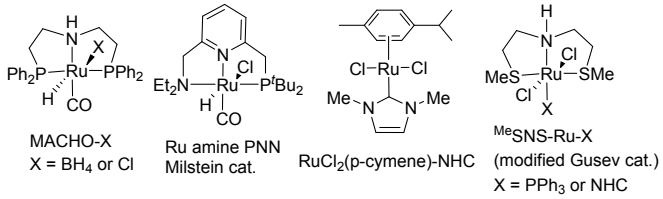
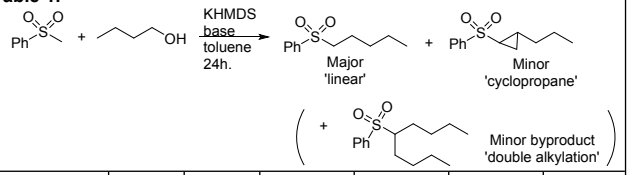


Figure 2. Catalysts tested for linear sulfone formation (See SI for full table). [12-13] Both MACHO catalysts gave interchangeable activity.

Table 1.



Entry/ Catalyst	mol%[a]	T °C	KHMDS (mol %)	Conc. [M] [b]	Ratio[c]	Yield %[d]
1.SNS-Ru	2	90	70	0.125	--	18
2.Ru PNN	2	90	70	0.125	--	12
3.MACHO	2	90	70	0.125	--	90
4.MACHO	1	90	120	0.125	17	73
5.MACHO	1	90	100	0.125	46	87
6.MACHO	1	90	70	0.125	60	91
7.MACHO	1	90	50	0.125	96	82
8.MACHO	1	80	75	0.125	60	91
9.MACHO	1	100	75	0.125	60	88
10.MACHO	3	90	75	0.125	103	88
11.MACHO	1	90	75	0.2	38	83
12.MACHO	1	90	75	0.1	85	73
13.MACHO	1	90	75	0.05	150	78
14.MACHO	2	90	75	0.05	202	85
15.MACHO	0.01	95[f]	100[e]	1.3	14	35
16.MACHO	0.05	90[g]	100[e]	1.2	147	76

For full optimization tables see SI. [a] mol percent catalyst based on starting sulfone; SNS-Ru-PPh_3, Ru-aminePNN, and MACHO-BH_4 used in entries [b] Initial concentration of phenyl methyl sulfone in toluene in M [c] ratio of linear over cyclopropane product (-- means undetermined); double alkylation minor product not included [d] Yield of linear sulfone product determined by GC/FID against internal standard mesitylene [e] KO^{t}Bu used instead of KHMDS [f] 72 h. reaction time; 3 eq. butanol [g] 48 h reaction time; 3 eq. butanol

For the more large-scale applications with a specific and well optimized substrate, we were able to demonstrate a TON of 3500 with cheap base KO^{t}Bu and a catalyst loading of 0.01 mol% after three days of reaction time. Full conversion could be reached with 0.05 mol% catalyst after three days of reaction time (1520 TON based on product yield).

Overall the screening results were consistent with the proposed mechanism of Scheme 1. The relative ratio of a linear sulfone to cyclopropane was a function of the amount of a base, catalyst loading and substrate concentration. Lowering the amount of base suppressed cyclopropanation (entries 4-7), with the yield only being sacrificed below 70 mol% of base. Decreasing concentration of the substrate suppresses the bimolecular reaction of **I** with **II** which leads to cyclopropane (entries 11-14). Increasing the amount of catalyst accelerates the

rate of the catalyzed transformation of **I** to **V** (Entries, 9,10,14), giving a higher ratio for the linear product; however, it's a trade-off as in practice less catalyst use is desirable. Finally, temperatures of 100°C or below did not have a large effect on yields or the ratio. 90°C was used in subsequent reactions for most substrates. Ultimately, we deemed a ratio of >60 of linear to cyclopropane to be acceptable as it would mean less than 1% of a difficult to separate impurity in our isolated products for the most difficult substrates.

Using optimized conditions, we then demonstrated the scope of substrates demonstrating selective linear sulfone formation from various substituted alcohols and dialkyl or alkyl aryl sulfones. Thus, a large variety of primary alcohols and sulfones could be coupled at a concentration of 0.05 M with a 1-2 mol% catalyst loading, giving excellent isolated yields for many of the products (Figure 3).

Entries 1-17 (Figure 3) represent aliphatic alcohols coupled with primary sulfones, which give secondary aromatic alkyl sulfones that can find potential use as an electrolyte or solvent. All of these relatively simple compounds are either not described in the literature or are cost/time prohibitive to make for the purpose of screening for such applications by previous methods. These products, including the moieties obtained from aromatic alcohols (Entries 29-30), can also all be used subsequently in Julia coupling reactions.

Thus, we believe that our protocol for the synthesis of secondary sulfones can address the lack of reagent availability, which is a significant bottleneck in the Julia olefination. Julia coupling reagents are typically prepared from the coupling of an aryl thiol with an alkyl halide. The resulting sulfide subsequently has to be oxidized to a sulfone (often with a non-trivial amount of oxone or a large excess of hydrogen peroxide and tungsten catalyst.[14] Our method allows for the synthesis of Julia coupling partners in one step as very pure reagents.

Secondary sulfones are compatible with alcohols under the reaction conditions, and the wide functional group tolerance of the reaction allows for the synthesis of a number of diverse small molecules (Entries 18-24) that can be further functionalized: i.e. the sulfone moiety can be removed by Mg reduction[15] or employed in a coupling reaction recently discovered by the Crudden group.[16] Although the reaction environment is strongly basic, the protocol is compatible with a number of functional groups that include fluorines, hindered olefins, morpholine and ether (Entry 6, 7, 12, 13, 17, 23).

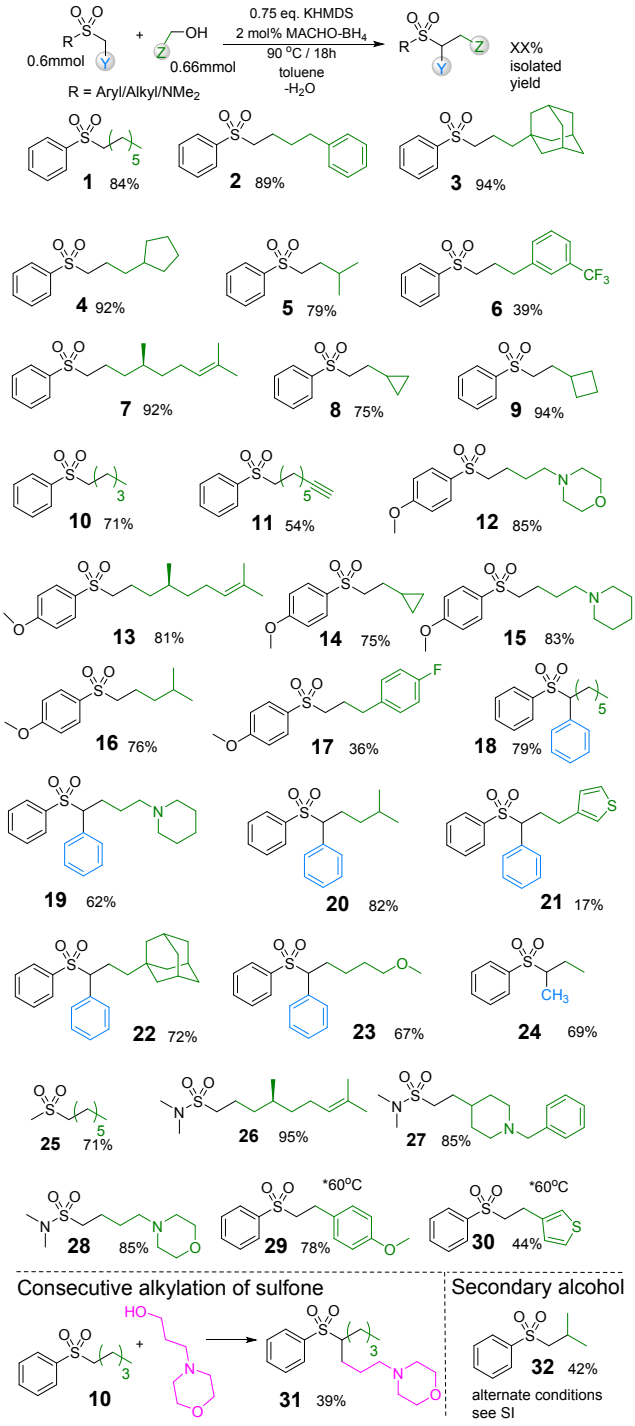
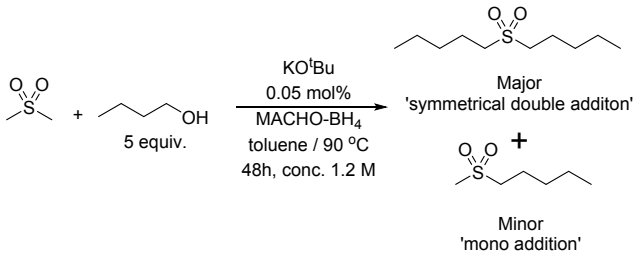


Figure 3. Substrate scope under the optimized conditions

Functionalized sulfones were also tested and found to be compatible with a wide range of substrates to give methoxy (Entries 12-17). Importantly, medicinally relevant sulfonamides often gave much larger isolated yields of pure product than many of the sulfones (Entries 26-28). Simple sulfones such as dimethyl sulfone were also easily modified (Entry 25), displaying symmetrical double functionalization in the presence of several equivalents of alcohol and a low catalyst loading (Scheme 2; TON~2000 in total; no cyclopropane; not isolated).



Scheme 2. Dimethyl sulfone symmetrical substitution

Such products may find use as electrolyte materials. Finally, we alkylated one of our products, sulfone **10**, to make compound **31**. Secondary alkyl sulfones are poorly reactive species, perhaps due to sterics, however we were able to obtain a 39% isolated yield of the morpholine modified product. With primary sulfones, β branched alcohols are well tolerated (entry 5, 8), which is in contrast with the cyclopropanation reaction.

Interestingly, some benzylic alcohols which were previously reported by Milstein to undergo Ru-catalyzed olefination (Figure 1) could be alkylated to give a linear sulfone as a major product. , Since benzylic alcohols are known to be dehydrogenated under milder conditions by Ru catalysts,[17] to achieve this selective transformation we used a much lower reaction temperature of 60°C in order to suppress undesired olefination. However, the selectivity of reaction is highly dependent on electronic properties of the benzylic alcohol, with unsubstituted and electron-poor substrates giving low yields of desired product and showing a higher fraction of styrene (Figure 4).

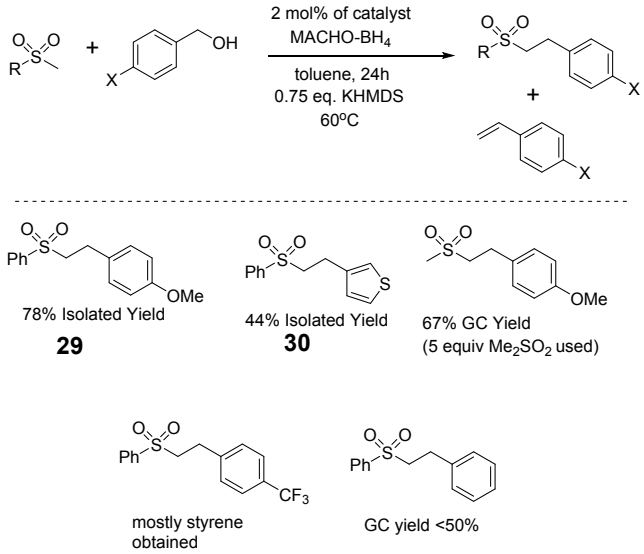


Figure 4. Aromatic alcohol reactivity

In conclusion, we discovered and developed a novel, catalytic sulfone and alcohol coupling reaction that does not rely on utilizing halogen substrates which are usually more expensive and leave behind halogenated waste. By utilizing readily available alcohols, we can prepare a broad range of linear sulfone products with the only waste byproduct being water. Many of our products are liquids at ambient conditions, and they, along with the dimethyl sulfone derivatives might find use as solvents or electrolytes or as potential drug candidates in fragment screening assays. The obtained linear sulfones can also be further utilized in the Julia olefination, removing a major bottleneck in the utilization of this coupling reaction.

ASSOCIATED CONTENT

Supporting Information. A file of experimental information including catalytic procedures, all NMR and HRMS characterization, mechanistic experiments, and a discussion of substrates not included in the main text, is available.

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Author Contributions

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

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SYNOPSIS TOC

Sulfones and sulfonamides with an α-CH bond can be easily alkylated by aliphatic alcohols to add the carbon skeleton of the alcohol via a one-step, Ru(II) catalyzed redox neutral reaction. The reaction requires a sub-stoichiometric amount of base and produces only water as a byproduct. A number of pharmaceutically relevant functional groups such as piperidine, morpholine, etc. are well tolerated under the reaction conditions to afford value-added products in one step from widely available substrates.