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Coupling of Sulfoxonium Ylides with Arynes: A Direct Synthesis of Prochiral Aryl Ketosulfoxonium Ylides and Its Application in the Preparation of α-Aryl Ketones

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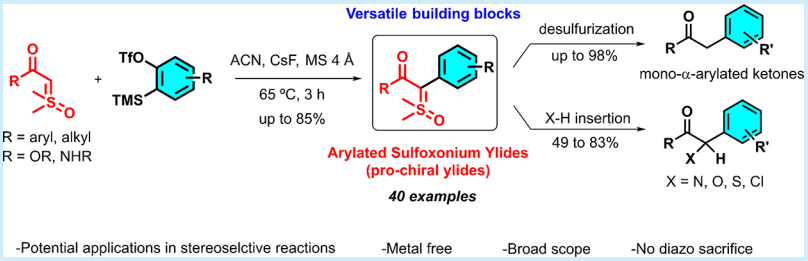
Supporting Information



ABSTRACT: A general, mild, and versatile synthesis of the challenging α-aryl-β-ketosulfoxonium ylides has been developed for the first time, substituting traditional methods starting from diazo compounds. The arylation of easily accessible β-ketosulfoxonium ylides using aryne chemistry allowed the preparation of a large scope of the pro-chiral ylides in very good yields (40 examples; up to 85%). As applications, these ylides were smoothly converted into α-aryl ketones after desulfurization in good yields (up to 98%) as well as in other important derivatives.

Sulfonium and sulfoxonium ylides[1,2] have played significant roles in organic synthesis as important building blocks in total synthesis,[3−9] chemical materials,[10−12] and pharmaceuticals,[13−15] among others.[16,17] These ylides have also proven to be alternative metallocarbene surrogates to diazo compounds,[18] having many reactions in common such as insertion,[19−21] cyclopropanation,[21] epoxidation,[22] aziridination,[23] dimerizations,[24] and Wolff[24,25] and Stevens rearrangements.[26,27] Furthermore, when compared with diazo compounds, these ylides are generally crystalline solids, more stable, have already been used in industrial scales,[15] and are easier/safer to prepare (since they do not involve the use of potentially explosive compounds such as azides, diazomethane, and its derivatives).[28]

Over many years, sulfoxonium ylides have received less attention compared to sulfonium ylides. However, in the past few years, this class of compounds has resurfaced as a powerful and versatile synthetic tool in the arsenal of organic chemists. Two examples are the seminal work of Baldwin[20] in metal-catalyzed N−H insertion reactions and from Mangion[19,29] at Merck, where β-ketosulfoxonium ylides were applied as diazo carbonyl surrogates. Since these contributions, this type of ylide has been employed in several important and new transformations that explore its ambiphilic behavior. Formation of C−C, C−N, C−O, and C−halogen bonds, synthesis of naphthols,[30] indoles,[13] and pyrroles,[13] cross-coupling reactions,[31,32] and synthesis of difunctionalized haloketones,[33] among others,[34−43] are some of the very recent examples (Figure 1).

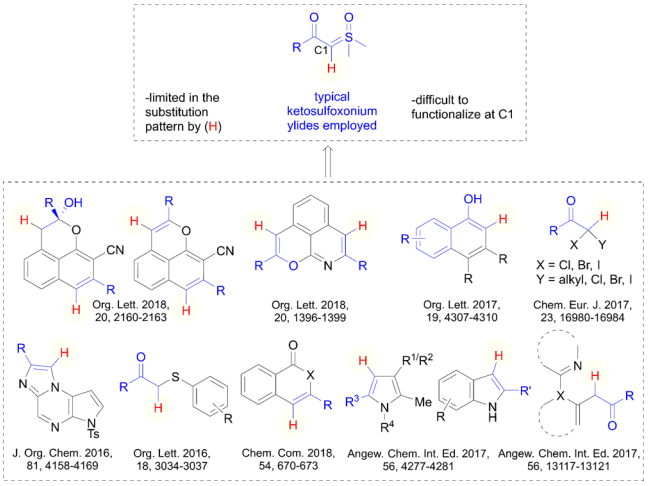


Figure 1. Sulfur ylides as diazo compound surrogates in different reactions with limited substitution patterns.

Importantly, many of these reactions are fruitless when the equivalent sulfonium ylide or diazo carbonyl are employed in place of sulfoxonium ylides, showing that these three classes of compounds (though similar) can also have distinct behavior. Regardless of the appearance of these new methodologies, the limitation of the substitution pattern in the ylide center (only

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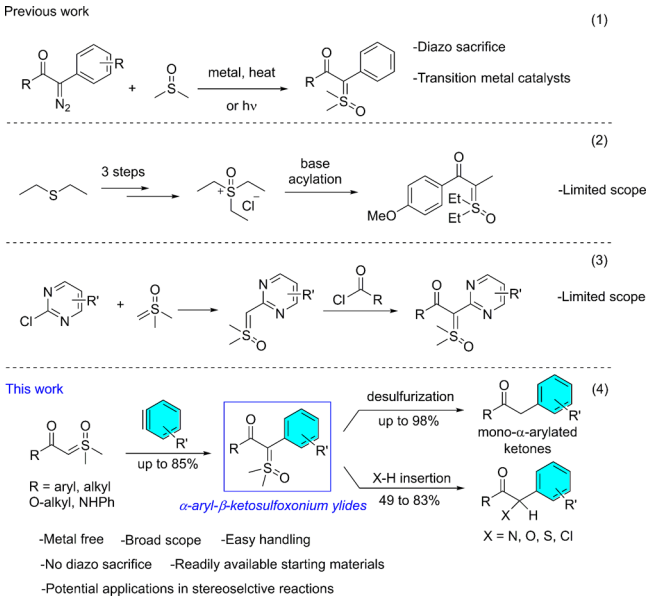
H in C1) (Figure 1) is still a drawback. For example, it reduces the product scope of the method and does not permit asymmetric versions in many cases.[31,32] These limitations are directly associated with the absence of specific methodologies that offer substitution in the α-position of ylides (direct synthesis of pro-chiral ylides), and that is why the respective diazo equivalents have gained far more attention in organic synthesis.[44−47] To the best of our knowledge, prochiral ketosulfoxonium ylides, containing either alkyl or aryl groups in the α-position, can be better synthesized with the intermediacy of diazo compounds (sulfoxide insertions catalyzed by metals, light or heat)[48,49] (Scheme 1, eq 1). This is in some way a paradox since the idea to employ sulfur ylides is to avoid the use of diazo compounds in similar transformations.[19,29]

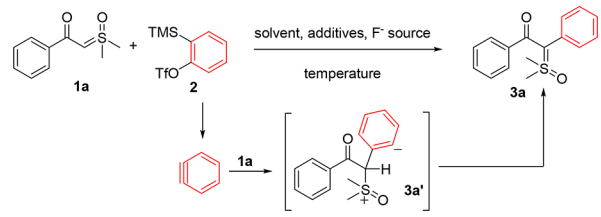
Scheme 1. Methodologies for the Synthesis of Prochiral β-Ketosulfoxonium Ylides



Prochiral α-alkylketosulfoxonium ylides could be prepared via a multistep protocol involving alkylation of thioethers, followed by oxidation[50] (that fails in many substrates, including the ones with benzyl substituents that could provide the desired α-aryl-ketosulfoxonium ylides) and acylation (Scheme 1, eq 2). However, only one example is demonstrated.[31] Another less general method that also leads to this kind of sulfoxonium ylide is the reaction of the expensive 2- or 4-chloropyrimidines with dimethylsulfoxonium methylide to afford, after nucleophilic substitution and acylation, α-pyrimidinyl-β-ketosulfoxonium ylides[51,52] (Scheme 1, eq 3). Unfortunately, this method is restricted only to pyrimidines as substituents. In view of the comments above, a method that permits the direct alkylation or arylation of easily accessible β-ketosulfoxonium ylides is highly desired. In the case of the challenging arylation of β-ketosulfoxonium ylides, one of the many possible applications is the synthesis of α-arylated ketones.[51,52] Monoarylation of ketones in a regio- and chemoselective fashion is still challenging and is limited to ketone substrates with no competitive enolization or functionality.[53,54] In general, ketones with bulky substituents at one of the α-carbons are employed to guarantee high degrees of regioselectivity.[55−58]

Herein, we describe the direct synthesis of α-aryl-β-ketosulfoxonium ylides through the coupling of simple and easily prepared β-ketosulfoxonium ylides with arynes. The arylated ylides are also rapidly transformed into α-aryl ketones after desulfurization as well as in some α-carbonyl derivatives (Scheme 1, eq 4). Our optimization studies began with the use of ylide **1a** and the benzyne precursor **2** as standard substrates under various conditions (Table 1). Initially, equimolar

Table 1. Reaction Optimization[a]



entry	solvent	F⁻ source	additives	yield (%)
1	CH_3CN	CsF	none	55
2	CH_3CN	CsF	Cs_2CO_3	61
3	THF	CsF	Cs_2CO_3	42
4	DME	CsF	Cs_2CO_3	39
5[b]	CH_3CN	CsF	Cs_2CO_3	traces
6[c]	CH_3CN	CsF	Cs_2CO_3	40
7[d]	CH_3CN	KF	18-crown-6	54
8[e]	CH_3CN	TBAF	Cs_2CO_3	32%
9[f]	CH_3CN	CsF	Cs_2CO_3, MS 4 Å	63
10[f,g]	CH_3CN	CsF	Cs_2CO_3, MS 4 Å	traces
11[f,h]	CH_3CN	CsF	Cs_2CO_3, MS 4 Å	57
12[f,i]	CH_3CN	CsF	Cs_2CO_3, MS 4 Å	30%
13[f,j]	CH_3CN	CsF	Cs_2CO_3, MS 4 Å	61
14[f,j]	CH_3CN	CsF	MS 4 Å	70

[a]All reactions were performed using 0.127 mmol of **1a** and 0.127 mmol of **2** in 1 mL of solvent, 4 equiv of CsF, and 3 equiv of Cs_2CO_3 and at a temperature of 65 °C, unless otherwise indicated. [b]At 25 °C. [c]At 110 °C in microwave reactor. [d]Using 2 equiv of 18-crown-6 and 3 equiv of KF. [e]Using 2 equiv of TBAF. [f]25 mg of MS 4 Å. [g]Using 1.5 equiv of **2** and addition of **1a** over 3 h. [h]Using 1.5 equiv of **2** over 24 h addition. [i]0.127 mmol of **3a** as starting ylide and 1.5 equiv of **2**. This reaction led to a complex mixture. [j]1.5 equiv of **2** added in three portions with 3 h of reaction.

proportions of starting materials were used under classic conditions to generate arynes.[59,60] This includes acetonitrile (CH_3CN) as the solvent, CsF as the fluoride source, and a temperature of 65 °C. This first condition was enough to provide our desired product **3a** in 55% yield (Table 1, entry 1). However, total consumption of ylide **1a** was not observed, which made the purification of compound **3a** difficult. Efforts were then focused to optimize the yield of reaction and the total consumption of **1a**.

Considering that intermediate **3a′** is formed after ylide attack to the aryne, we thought that the addition of base could help the 1,3-hydrogen migration step (see the scheme of Table 1). Therefore, when cesium carbonate was used as base, a slight increase in yield was observed (Table 1, entry 2). Subsequently, other solvents such as tetrahydrofuran (THF) and dimethoxyethane (DME) were tested without increasing the yield (Table 1, entries 3 and 4). Lower and higher reaction temperatures from the optimum 65 °C provided compound **3a** in traces and 40% yield, respectively (Table 1, entries 5 and 6). Other sources of fluoride ions were also explored without any

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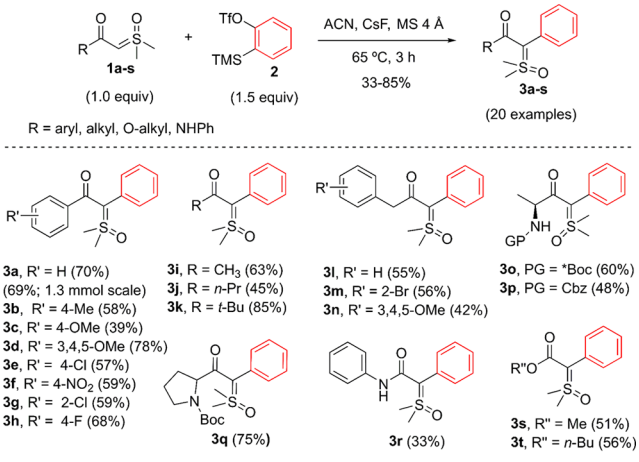
improvement in the reaction performance (Table 1, entries 7 and 8) along with difficulty in the purification process. Next, the use of molecular sieves (4 Å) was evaluated, observing a slight increase in the yield (Table 1, entry 9). Surprisingly, the use of excess of **2** (1.5 equiv) furnished only a trace amount of the product with the slow addition of ylide **1a** (Table 1, entry 10). Contrary to the previous entry, the slow addition of **2** to ylide **1a** (Table 1, entry 11) furnished a similar yield when compared to our best conditions (see entry 9). Results in Table 1, entries 10 and 11, indicate that the product might undergo degradation in the presence of excess aryne left in the reaction medium. To prove it, a control experiment using ylide **3a** (our product) was carried out in the presence of **2** (conditions of entry 9), resulting in a complex mixture of products (Table 1, entry 12). Compound **2** was then added in three portions, providing **3a** in 61% yield with total consumption of **1a** (Table 1, entry 13). As controlled and slow generation of benzyne is the key to reaction success and believing that Cs_2CO_3 also helps in promoting its in situ generation,[61] we next repeated our best conditions in the absence of the base (aiming a slower benzyne formation). In this case, the desired product **3a** was obtained in 70% yield (Table 1, entry 14).

After the optimization studies, we next evaluated the scope of the reaction using **2** in the presence of different ylides (Scheme 2). Ylides with various aromatic substituents

Scheme 2. Scope of Ylide Starting Material



containing electron-donating and -withdrawing groups are well tolerated (**3a**–**h**). It is worth mentioning that ylide **3h**, obtained in 68% yield, is the same ylide used by Vaitla in the formal synthesis of atorvastatin (prepared through a rhodium-catalyzed sulfoxide insertion from a α-diazoketone).[13] Although without success, the preparation of ylide **3h** was also investigated from iodonium ylide chemistry, showing the importance of these types of prochiral arylated sulfoxonium ylides.[62] Alkyls groups, including *t*-Bu and benzyl substituents, smoothly led to desired ylides (**3i**–**n**) in good yields. Similarly, amino acid derivatives with different protecting groups were well tolerated (**3o**–**q**) without loss of the respective stereogenic center (**3o**). Derivatives of esters and amides also led to the formation of the respective ylides **3r**–**t** in good yields. Synthesis of **3a** on a 10-fold scale (1.3 mmol) did not change the yield (69%).

We next investigated the scope of the reaction by varying the aryne precursors (Figure 2).

Symmetrical aryne precursors such as **4** and **11** led to the formation of a single product (**11**, as a racemic mixture of atropisomers **12**–**14**).[63] Furthermore, ortho-substituted aryne precursors **15**, **17**, **21**, and **26** (having methoxy, fused aromatic ring and Br substituents) led to the formation of single regioisomers with addition at the meta carbon. This agrees with predictive models.[64−67] On the other hand, aryne precursor **18** afforded regioisomers in equal proportions, showing a weak or no effect of the distant methoxy groups as well as a little effect in terms of the volume of the nucleophile used. In the case of the *N*-tosyl-3-azacyclohexene[68] **33**, pyridinium precursor[69] **31**, and the new type of aryne precursor[70] **9**, only the latter two provided the desired product (although in low yield: **32** and **10**, with 5% and 26% yield, respectively). For these cases, the decomposition of the respective aryne precursors and recovery of the starting ylide were observed.

It is important to highlight that the reactions described in this work employing sulfoxonium ylides cannot be performed efficiently using sulfonium ylides or diazo ketones. For example, the first results in the formation of thioanisole derivatives by insertion into the C−S σ-bond.[71] The second gives indazoles by a [3 + 2]-cycloaddition reaction on the diazo moiety.[72]

As an application of this methodology, some of these ylides were subjected to a desulfurization reaction (Scheme 3) using Raney-Ni in refluxing 2-propanol.[73,74] This provided the respective monoarylated ketones (**35**–**45**) in good yields (up to 98%). In general, all of the substrates are well tolerated except for ylide **3g** where an inseparable mixture of desired product along with dehalogenation product of **35** was obtained in approximately a 1:1 ratio. This two-step approach for the synthesis of monoarylated ketones from β-ketosulfoxonium ylides not only competes with the methodologies already reported in the literature but also constitutes one of the few that involves arynes in its synthesis.[75,76]

To illustrate the synthetic utilities of these new types of ylide substrates in the α-heterofunctionalization of carbonyl compounds, we performed some known transformations (that are carried out with diazo compounds[77] as well as with simpler sulfoxonium ylides)[13,19,29,34,78] (Scheme 4). For example, O−H, S−H, N−H, and Cl−H insertions are some of the classic transformations that can be made with diazo compounds and some sulfur ylides and were extrapolated for ylide **3a**. The acyloin, α-keto thio, amino, and chloro derivatives **46**–**50** were obtained in good yields, showing the possible applications in the formation of new stereocenters with great potential in asymmetric versions for this kind of substrate.

In conclusion, we have developed the first general and versatile synthesis of a range of α-aryl-β-ketosulfoxonium ylides, starting from the readily available β-ketosulfoxonium ylides that is operationally simple and does not need to pass through the intermediacy of diazo compounds. Additionally, the desulfurization of representative arylated ylides successfully afforded the respective α-aryl ketones. Moreover, we also demonstrated that these ylides can be readily diversified to other important carbonyl compounds of choice, using classical reactions from the literature, and thus exhibiting its great potential as substitute for diazo compounds not only in reactions involving metallocarbenes but also in polar reactions.

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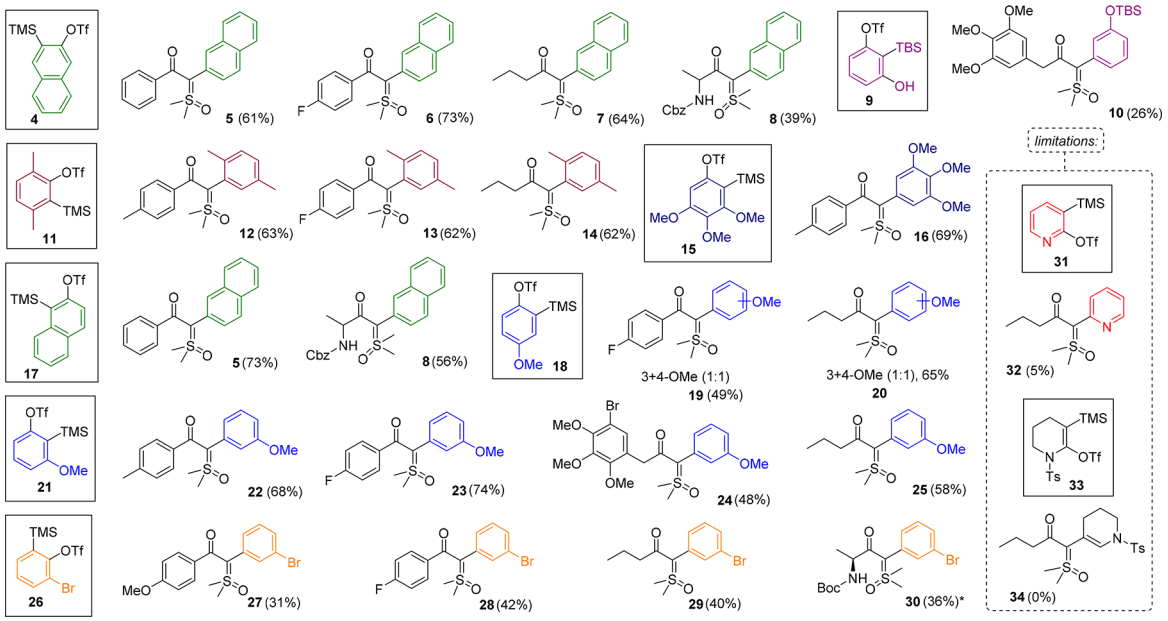
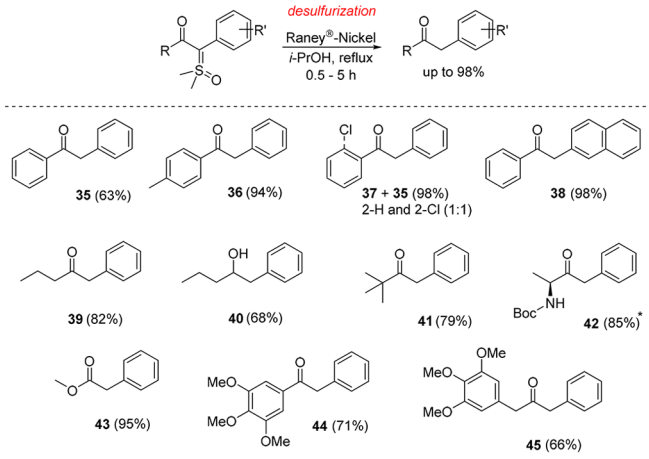
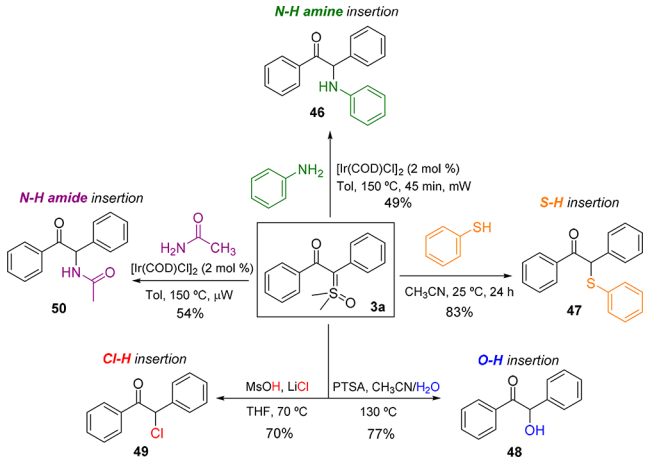


Figure 2. Aryne scope in β-ketosulfoxonium arylation.

Scheme 3. Scope of Desulfurization Reaction of α-Aryl-β-ketosulfoxonium Ylides



Scheme 4. Different α-Carbonyl Heterofunctionalizations for the Ylide 3a



We believe that this methodology will open new paths to the reactivity and use of arylketosulfoxonium ylides in stereoselective functionalization of α-carbonyl compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03126.

Experimental procedures, cNMR spectra, and other analysis data for the compounds (PDF)

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Notes

The authors declare no competing financial interest.

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