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Sulfur(IV)-Mediated Transformations: From Ylide Transfer to Metal-Free Arylation of Carbonyl Compounds

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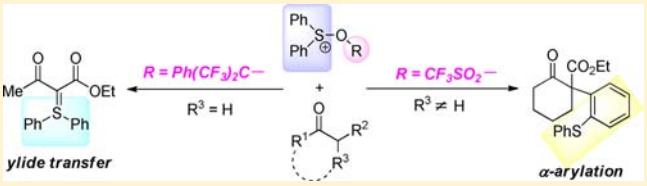
Supporting Information

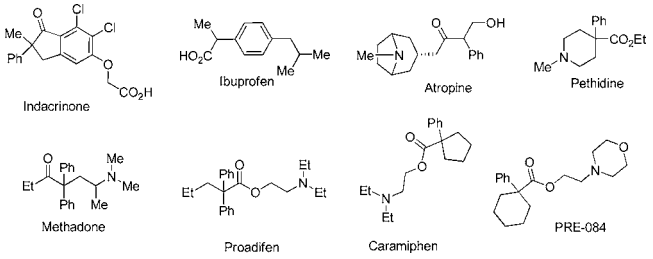
ABSTRACT: The development of a direct ylide transfer to carbonyl derivatives and of a sulfoxide-mediated arylation is presented from a unified perspective. Mechanistic studies (including density functional calculations) support a common reaction pathway and showcase how subtle changes in reactant properties can lead to disparate and seemingly unrelated reaction outcomes.



INTRODUCTION

α-Arylated carbonyl compounds are recurrent motifs and subunits in organic molecules with interesting biological activities (Scheme 1).[1] Arguably, the most-studied approaches

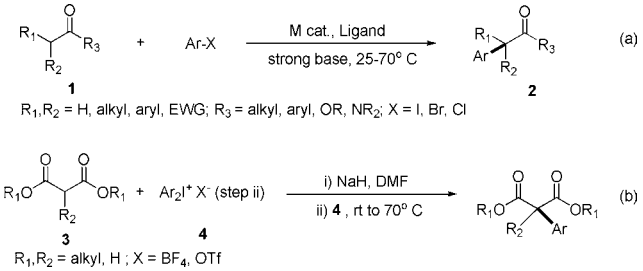
Scheme 1. Selected Biologically Active Compounds Bearing an α-Arylated Carbonyl Moiety



for their synthesis thus far have relied on noble transition-metal-catalyzed cross-coupling of enolates with aryl halides, aryl pseudohalides, or more-reactive reagents.[2] However, the high cost of most noble transition metal complexes, the necessity of careful exclusion of air and moisture during the reactions, and the possibility of contamination of the end-products by trace amounts of heavy metals represent potential drawbacks for industrial and pharmaceutical applications and have stimulated work toward the development of so-called "metal-free" arylations. Useful transition-metal-free α-arylation processes[3] typically entail stoichiometric reactions of enolate anions (or equivalents thereof) with electrophilic aromatic derivatives of Bi(V),[4] Pb(IV),[5] or I(III)[6] or with benzynes[7] as aryl donors (Scheme 2), the preparation of some of which involves multistep procedures. Although elegant organocatalytic approaches for the enantioselective α-arylation of carbonyl compounds have been recently reported,[8] the challenge of developing transition-metal-free direct arylations of carbonyl compounds remains alive within the synthetic community.

Martin's sulfurane **5** is a highly efficient dehydrating reagent for the direct conversion of alcohols to alkenes under mild

Scheme 2. Different Approaches to the α-Arylation of Carbonyl Compounds



conditions.[9] In their seminal studies toward the development of this reagent, Martin and co-workers found that adding *trans*-cyclohexane-1,2-diol **6a** to a solution of **5** afforded epoxide **7** in nearly quantitative yield (Scheme 3a). However, the reaction of *cis*-cyclohexane-1,2-diol **6b** with **5** gave cyclohexanone **8** and 2-arylcyclohexanone **9**, in 28% and 21% yields respectively (Scheme 3b). Since the direct reaction of **8** with **5** was found not to lead to **9**, product **9** may have resulted from sigmatropic rearrangement of hypothetical intermediate **10**, itself generated by two-fold ligand exchange followed by *trans*-elimination of diphenylsulfoxide and alcohol (R_FOH, Scheme 3b).[9e]

Inspired by this report, we speculated that a carbonyl compound with a more favorable enol content (such as β-keto ester **11a**) might be amenable to form an intermediate **13** akin to **10**, eventually rearranging to α-arylated product **12** (Scheme 4).

This simple yet conceptually appealing hypothesis led us to perform the reaction depicted in Scheme 5. As shown, admixing the β-keto ester **15a** with Martin's sulfurane **5** led to a single product in essentially quantitative yield. To our surprise, this was the sulfur ylide **16a** (curiously, isomeric to the anticipated α-arylated material **12**, R^1 = Me, R^2 = Et).[10]

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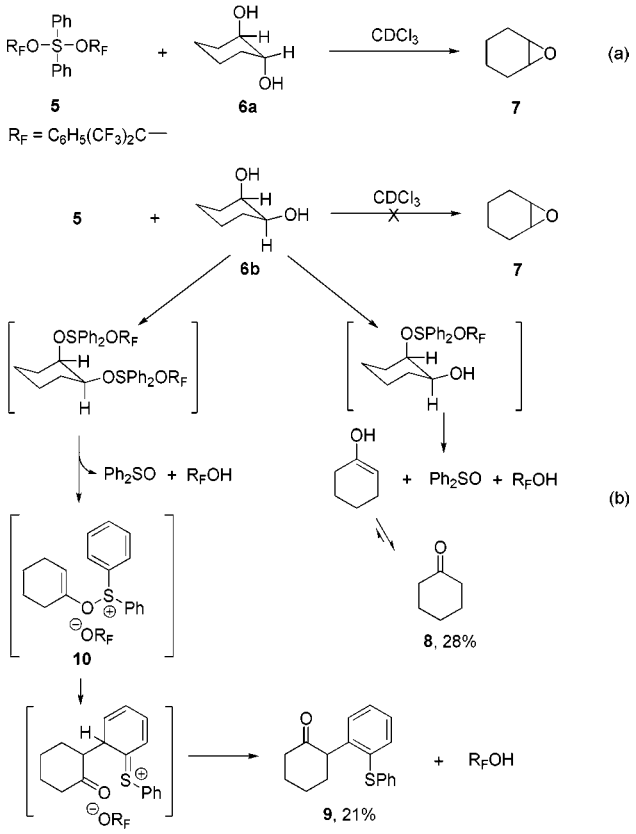
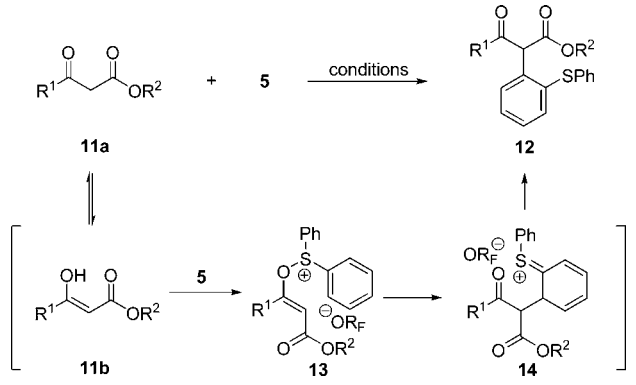
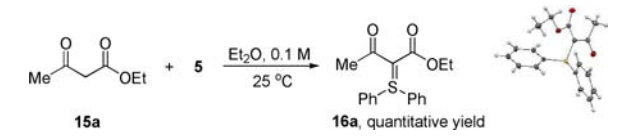
Scheme 3. Reaction of Martin's Sulfurane 5 with *cis*- and *trans*-Cyclohexane-1,2-diol



Scheme 4. Initial Design of a Transition-Metal-Free Process for the α-Arylation of Carbonyl Compounds



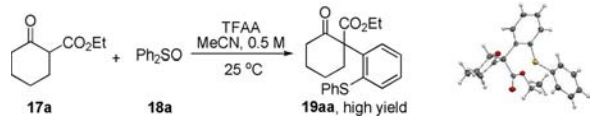
Scheme 5. Direct Ylide Transfer to β-Keto Ester 15a



This fortuitous observation paved the way for a series of studies involving tetravalent sulfur(IV) compounds that eventually led to a sulfoxide-mediated α-arylation of carbonyl compounds (Scheme 6).[11]

Herein, we recount the development of these apparently unrelated transformations from a unified perspective, along with more-recent results that significantly extend the scope and

Scheme 6. Diphenylsulfoxide-Mediated Arylation of 17a



synthetic utility of both procedures. In addition, NMR and DFT mechanistic studies that shed light on the subtle yet intricate connections between sulfur-mediated ylide transfer and arylation are presented.

RESULTS AND DISCUSSION

Ylide Transfer to Carbonyl Compounds and Heteroaromatics. Sulfonium ylides have been extensively employed in the preparation of small rings and the construcion of more-complex structures.[12] Nevertheless, standard methodology available for preparation of sulfonium and sulfoxonium ylides is still essentially the same that was introduced more than 40 years ago.[13]

During our preliminary investigations toward the direct α-arylation of carbonyl compounds (*vide supra*), we found Martin's sulfurane **5** to be an excellent ylide-transfer agent. Treatment of a solution of **5** (in different solvents) with ethyl acetoacetate **15a** invariably led to the corresponding sulfonium ylide in quantitative yields upon stirring at room temperature for half an hour.[14]

Reaction Scope of the Ylide Transfer to Activated Carbonyl Compounds. With optimal conditions in hand, the reaction scope was examined by varying the electron-withdrawing groups adjacent to the activated methylene. In the event, a broad range of substrates were tolerated, and the ylide products were obtained in good to excellent yields (Table 1). Diverse keto esters reacted smoothly with **5** (entries 1−4, 11, and 13). The phosphonate ester depicted in entry 11 also undergoes ylide transfer in quantitative yield. The reactions of acyclic and cyclic diketones bearing aromatic or aliphatic substituents gave the corresponding ylides in good to quantitative yields (entries 5−7, 12),and dimethyl malonate, malononitrile,and Meldrum's acid were viable substrates for this reaction (entries 10, 14, and 15). It is interesting to note the failure of acetophone (entry 18) in generating any ylide product, for its α-cyano and α-bromo derivatives reacted well (entries 16 and 17). These results suggest the existence of a window of pK_a values that defines reactivity toward ylide formation by sulfurane **5**. Given that the pK_a value of acetophenone is commonly estimated to be ca. 24.7 (DMSO),[15] this can roughly be taken as an upper limit for reactivity in the current transformation.

Phenylacetate derivatives reacted successfully with **5**, leading to the corresponding ylides in good isolated yields (entries 19 and 20). Unmodified ethyl (2-phenylacetate), for which pK_a = 23.6 is tabulated,[16] led to no ylide product. This is in agreement with the aforementioned pK_a-window hypothesis (result not shown; compare with the use of the *p*-nitro derivative, entry 19) and further refines its upper border value.

Reaction Scope of Heteroaromatics. Having delineated an ylide transfer to carbonyl compounds, we looked for other substrate classes that might be amenable to this transformation. Indoles and pyrroles are important heterocycles that are often found in natural products and drug candidates, and are reportedly capable of binding to a variety of receptors with high affinity.[17] We hypothesized that the ylide-transfer ability of

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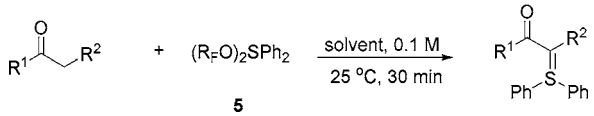
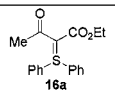
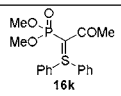
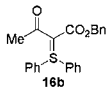
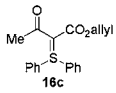
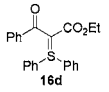
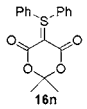
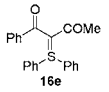
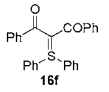
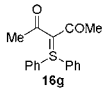
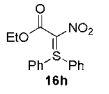
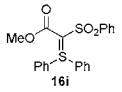
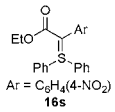
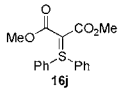
Table 1. Direct Ylide Transfer to Active Methylene Compounds[a]



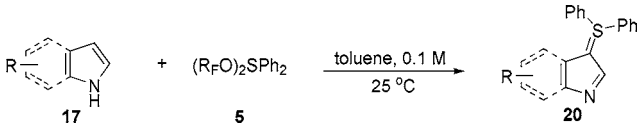
Entry	Product	Yield (%)	Entry	Product	Yield (%)
1	 16a	99	11	 16k	99
2	 16b	88	12	 16l	57
3	 16c	74	13	 16m	73
4	 16d	88	14[b]	 16n	88
5	 16e	99	15	 16o	90
6	 16f	99	16	 16p	99
7	 16g	99	17[c]	 16q	76
8	 16h	98	18	 16r	0
9	 16i	99	19	 Ar = C6H4(4-NO2) 16s	69
10	 16j	85	20	 16t	74

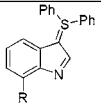
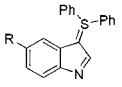
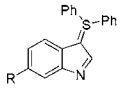
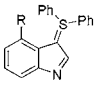
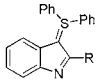
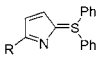
[a]Yields refer to pure, isolated compounds. All reactions were run in diethyl ether using 1.5 equiv of **5** unless mentioned otherwise. [b]Solvent was chloroform. [c]Solvent was dichloromethane.

sulfurane **5** might be amenable to "Friedel–Crafts-like" dearomatisation of indoles and pyrroles.

As depicted in Table 2, this reaction appears to be fairly general. Indoles bearing a notable scope of substituents ranging from electron-donating to electron-neutral and strong electron-withdrawing were tolerated. The actual location of the substituents on the indole system had only a negligible effect on the efficiency of the transfer (entries 1–12). In addition, pyrrole and its derivatives also performed competently in this

Table 2. Direct Ylide Transfer to Indoles and Pyrroles[a]



Entry	Product	Yield (%)	Entry	Product	Yield (%)
					
1	**20a**, R = Et	95	9	**20i**, R = OMe	94
2	**20b**, R = NO_2	99	10	**20j**, R = CO_2Me	99
					
3	**20c**, R = Me	99	11	**20k**, R = Me	90
4	**20d**, R = Cl	99	12	**20l**, R = Br	99
					
5	**20e**, R = H	99	13	**20m**, R = H	99
6	**20f**, R = Me	99	14	**20n**, R = Et	52
7	**20g**, R = Ph	99	15	**20o**, R = CO_2Me	83[b]
8	**20h**, R = CO_2Et	99			

[a]Yields refer to pure, isolated compounds. All reactions were run in toluene using 1.5 equiv of **5** unless mentioned otherwise. [b]16% of the 4-sulfonium ylide **20o′** was also obtained (not shown), and the structure of the major regioisomer (depicted) was confirmed by X-ray.

reaction. As might be expected, pyrrole 2-sulfonium ylide was obtained as the exclusive regioisomer (entry 13). Other derivatives bearing alkyl and carboxyl functionalities also afforded the corresponding sulfonium ylides in good yields (entries 14 and 15). Interestingly, the presence of an ester substituent led to the production of small amounts of the 4-sulfonium ylide isomer (entry 15), likely a result of that substituent's *meta*-directing ability.

Sulfoxide-Mediated α-Arylation of Carbonyl Compounds. Having serendipitously uncovered the ylide-transfer reaction, several lateral observations made during this study prompted us to explore it further. For one, the use of a substituted (cyclic) keto ester under various conditions resulted in the formation of multiple products with rapid consumption

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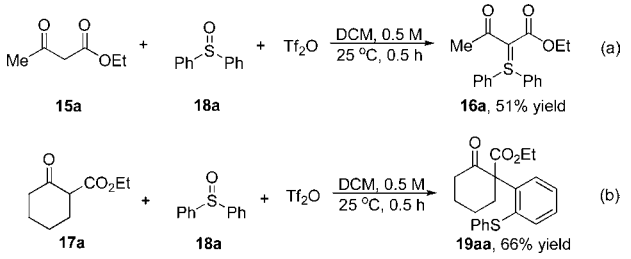
of sulfurane **5**. In addition, the relatively high cost of this reagent stimulated a search for surrogates.[18]

Inspired by prior reports,[19] treatment of a mixture of ethyl acetoacetate and diphenylsulfoxide with 2.0 equiv of triflic anhydride led to the corresponding sulfonium ylide **16a** in moderate 51% isolated yield along with several additional, highly polar compounds (Scheme 7a). However, and to our

Scheme 7. Different Reactivities of Substituted and Unsubstituted β-Keto Esters



surprise, when ethyl 2-oxocyclohexanecarboxylate **17a** was exposed to similar conditions, the α-arylated keto ester **19aa** was isolated in 66% yield, and its structure was unambiguously confirmed by single-crystal X-ray analysis (Scheme 7b; see Scheme 6 for the X-ray structure).

Reaction Scope of Activated Carbonyl Compounds. After optimizing conditions for what amounts to a "transition-metal-free" arylation (see Supporting Information for details), we sought to examine the scope of this transformation. As it turned out, triflic anhydride was not always the best activating agent (method A), and eventually TFAA (method B) was found to be a more general solution in the majority of cases (Table 3).

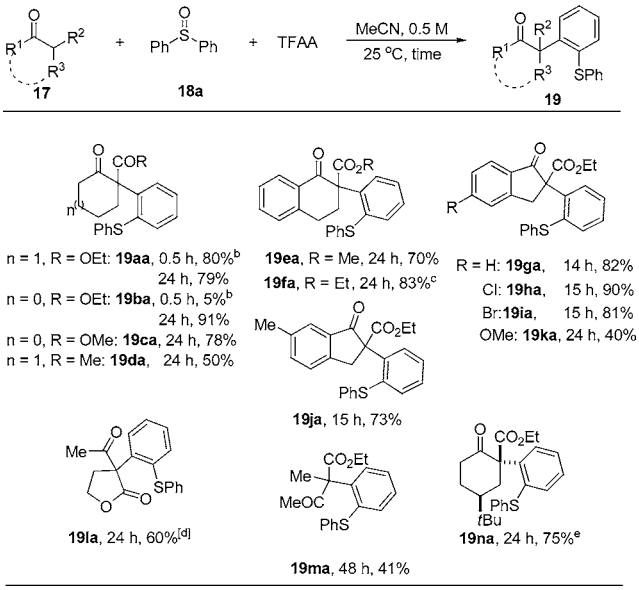
In addition to six-membered cyclic β-keto esters, five-membered substrates bearing different ester groups afforded the corresponding arylated products in very good yields under similar conditions (entries 1−6, and entry 14). When an acyclic β-keto ester (entry 15) was employed, a slower reaction resulted. This process also displayed high levels of diastereoselectivity, as a keto ester derived from 4-*tert*-butylcyclohexanone generated the arylated counterpart in 75% yield with a 9:1 diastereomer ratio (entry 16). This interesting diastereoselection (in favor of the axially disposed aryl stereoisomer) is consistent with hypothetical C−C bond formation from a pseudoaxial trajectory in a half-chair intermediate (*vide infra*).

Reaction Scope of Sulfoxides. After testing different activated carbonyl compounds, we turned our attention to the effects of different sulfoxide reagents. As shown in Scheme 8, by employing sulfoxides with different electronic properties the corresponding products could be obtained in moderate yields.

Scheme 8 also details the results of competition experiments performed. As shown, the reaction of a slight excess of keto ester **17a** with equimolar amounts of an electron-rich (di-*p*-tolylsulfoxide **18b**) and an electron-poor (di-(*p*-chlorophenyl)-sulfoxide **18c**) sulfoxide afforded the tolylsulfanyl-arylated **19ab** as the only product of reaction.

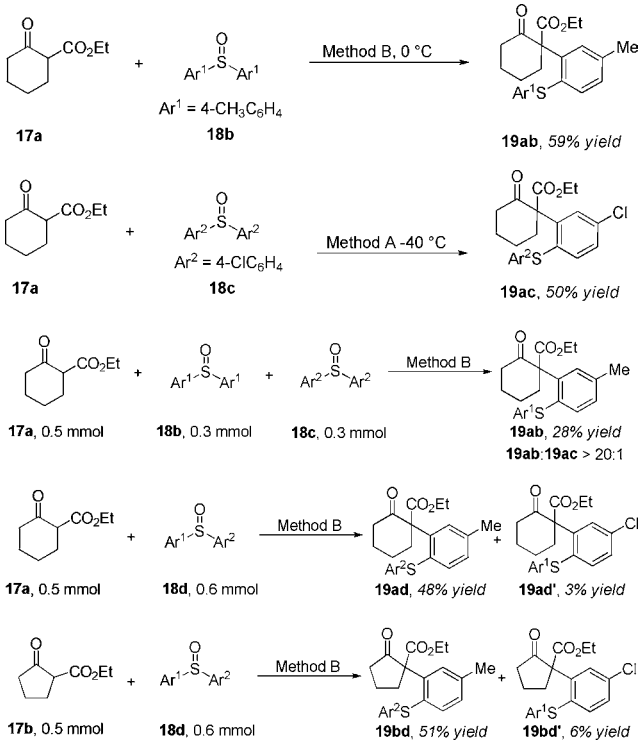
Furthermore, the use of an unsymmetrical sulfoxide, simultaneously bearing *p*-tolyl and *p*-chlorophenyl residues, resulted in a highly regioselective transfer of the *p*-tolyl fragment with less than 6% yields of the alternative products. The strongly regioselective preference for transferring the most

Table 3. Direct Arylation of Carbonyl Compounds with Diphenylsulfoxide[a]



[a]Method A: 1.5 equiv of Tf_2O, 1.2 equiv of sulfoxide **18**, CH_2Cl_2, 0.5M, 25 °C. Method B: 1.5 equiv of TFAA, 1.2 equiv of sulfoxide **18a**, MeCN, 0.5 M, 25 °C. Method B was applied in most cases unless mentioned. [b]Method A was employed. [c]Based on recovered starting material (34% of **17f** was recovered). [d]The reaction was run at 0 °C. [e]Combined yield with a d.r. of 9:1 (was determined by GC).

Scheme 8. Results Obtained Using Other Diarylsulfoxides as Aryl Donors



electron-rich aromatic is a notable feature of this sulfoxide-mediated arylation (*vide infra*).

Particularly enticing was the prospect of employing arylalkyl-sulfoxides as donors, since these formally contain a single equivalent of the aryl donor moiety. However, from the onset

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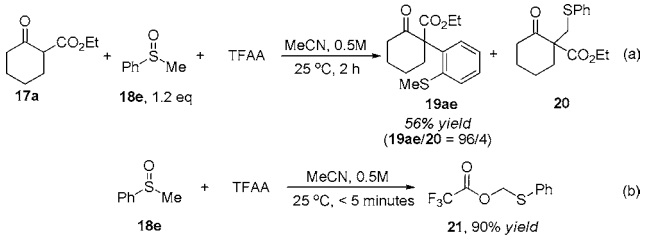
we were aware that sulfoxides bearing alkyl residues are prone to the well-known Pummerer rearrangement, an internal redox process that amounts to sulfoxide reduction with concomitant α-oxidation.[20] Nevertheless, we probed phenylmethylsulfoxide under our optimized protocol and observed full conversion within 2 h. Strikingly, arylated product **19ae** was still obtained as the major adduct of the reaction, together with traces of the "normal" Pummerer product **20** detected in the reaction mixture (Scheme 9a). This result is all the more noteworthy

Scheme 9. Evaluation of Reactivity of Phenylmethylsulfoxide



taking into account that exposure of sulfoxide to the action of TFAA almost instantaneously generates the trifluoroacetate **21** in very high yield (Scheme 9b). Importantly, mixing α-acyloxysulfide **21** with the β-keto ester substrate **17a**, under the reaction conditions, leads only to a very slow reaction producing **20**. The obtention of product **19ae** in detriment of its isomer **20**, from only 1.2 equiv of phenylmethylsulfoxide and in spite of the rapid conversion of the latter into acetate in a "background" process strongly suggests that the mechanism of these arylations is fundamentally different from the classical Pummerer reaction (*vide infra*).

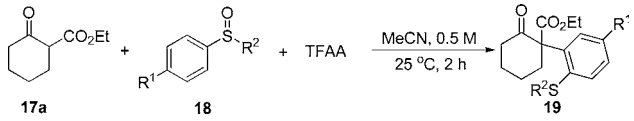
Encouraged by these observations, we further explored other alkyl aryl sufoxides as aryl donors. As demonstrated in Table 4, increasing the length of the alkyl chain did not affect the reaction efficiency (entries 1 and 2). The aryl moiety could also be modified, and the corresponding arylated products were isolated in moderate yields (entries 4–6).

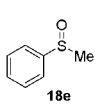
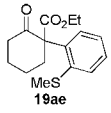
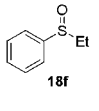
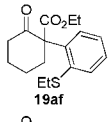
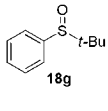
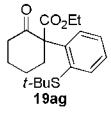
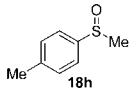
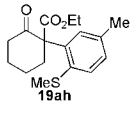
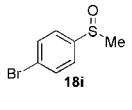
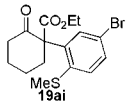
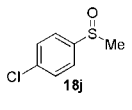
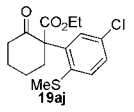
Given the intrinsic nature of the "background" Pummerer reaction of arylalkylsulfoxides, it was reasonable to assume that the introduction of a tertiary alkyl residue in the sulfoxide might shut this competitive process down and favor the arylation pathway. To our surprise, when sulfoxide **18g** bearing a *tert*-butyl group was employed (Table 4, entry 3), only the sulfenylated product **22** could be isolated from the reaction mixture (Scheme 10). This is likely a consequence of loss of a *tert*-butyl cation from the activated sulfoxide and concomitant generation of phenylsulfanyl trifluoroacetate, an electrophilic sulfenylating reagent.[21]

Arylation of Simple Carbonyl Derivatives. The challenge of transposing the α-arylation methodology described in the preceding paragraphs to simple carbonyl derivatives such as ketones and aldehydes is perhaps best expressed by the recalcitrance of cyclohexanone, for which arylated product **9** was obtained in only 9% yield after 20 h at room temperature (Scheme 11). Curiously, the main side product of this reaction was diphenyl sulfide.[22−24]

In face of this setback, we probed a wide range of reaction conditions and cyclohexanone derivatives, eventually finding that a direct arylation of enol silanes under modified conditions was possible.[25] We then examined the potential of this novel transformation (Table 5). Gratifyingly, the reaction of silyl enol ethers bearing an α-disposed methyl group proceeded

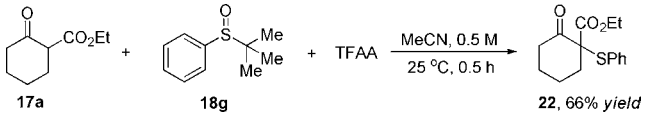
Table 4. Scope of Arylalkylsulfoxides in the Arylation Reaction[a]



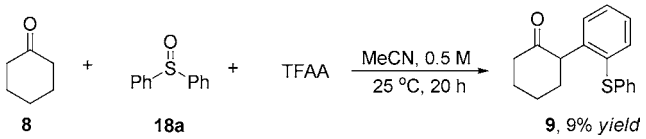
Entry	Sulfoxide	Product	Yield (%)[b]
1	 18e	 19ae	56
2	 18f	 19af	57
3	 18g	 19ag	0
4	 18h	 19ah	48
5	 18i	 19ai	45
6	 18j	 19aj	44

[a]1.5 equiv of TFAA, 1.2 equiv of sulfoxide were employed. [b]Yields refer to pure, isolated products.

Scheme 10. Reaction of Keto Ester 17a with *tert*-Butylphenylsulfoxide 18f



Scheme 11. Initial Attempt on Direct Arylation of Cyclohexanone



smoothly, giving the corresponding products in high yield (entry 2). Furthermore, the silylenol ether derived from acetaldehyde was also a viable substrate, providing the corresponding 2-arylacetaldehyde (entry 3). To the best of our knowledge, this represents the first example of metal-free α-arylation of simple aldehyde derivatives.[26] The arylation of enol silanes with two identical β,β-terminal substituents afforded the desired arylated aldehydes (entries 4–6). The scope was further extended to substrates carrying two different sub-

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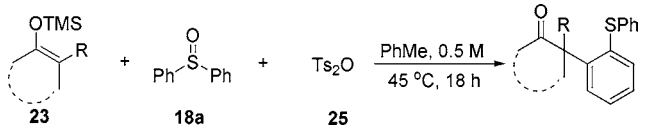
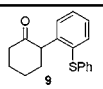
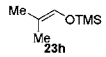
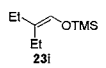
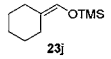
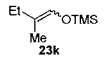
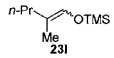
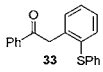
Table 5. Arylation of Silyl Enol Ethers with Diphenylsulfoxide[a]



23 18a 25

Entry	Substrate	Product	Yield (%)[b]
1	 23a	 9	65
2	 23f	 26	64
3	 23g	 27	33
4	 23h	 28	73
5	 23i	 29	46
6	 23j	 30	43
7	 23k	 31	63
8	 23l	 32	40
9	 23m	 33	0

[a]The reaction was run in 0.5 mmol scale, and the concentration was 0.5 M. [b]Isolated yield after column chromatography.

stituents at the terminal position of the double bond (entries 7 and 8). It is noteworthy that these arylations provide aldehydes with an all-carbon quaternary center in moderate to good yields. However, when the enol ether derived from acetophenone was subjected to the current system, no arylated product was isolated (entry 9).

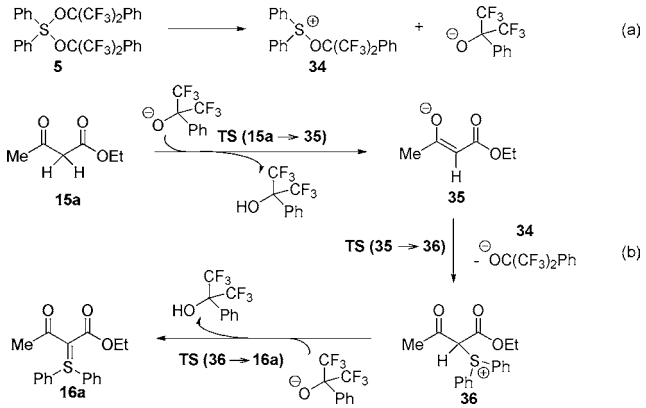
Mechanistic Theoretical Studies. We performed density functional theory (DFT) calculations to gain more insight into the mechanisms of ylide transfer and α-arylation. Ethyl acetoacetate **15a** and the cyclic β-keto ester **17a** were taken as model substrates for these two reactions, respectively.

Computational Methods. All stationary points were optimized without any constraints in the solvent phase at the B3LYP/6-31+G** level of theory.[27] Solvation effects were treated by the polarizable continuum model (PCM) with acetonitrile as solvent (dielectric constant 36.64).[28] All calculations were performed with the Gaussian09 quantum chemical programs.[29] The optimized stationary points were characterized as local minima or transition structures by harmonic force constant analysis, and intrinsic reaction coordinate (IRC) calculations were performed to verify the transition state structures.[30]

Empirical dispersion corrections for the B3LYP functional were included using single-point B3LYP-D/6-31+G** energy calculations.[31] Gibbs free energies were in all cases computed by adding to the single-point energies both zero-point vibrational energies and thermal corrections (300 K) obtained at the level of theory employed in the geometry optimization (B3LYP/6-31+G** in the solvent phase). Relative free energies are reported for all relevant stationary points at the following two DFT levels: B3LYP-I, from solvent-phase geometry optimizations [PCM/B3LYP/6-31+G**], and B3LYP-II, solvent-phase dispersion-corrected single-point calculations at solvent-phase optimized geometries [PCM/B3LYP-D/6-31+G**//PCM/B3LYP/6-31+G**]. The relative free energies are always given with respect to the separated reactants. Comparison between the B3LYP-I and B3LYP-II results reveals the effects of dispersion on the computed energies.

DFT Results for Ylide Transfer. The proposed mechanistic pathway for ylide transfer to ethyl acetoacetate **15a** in the presence of Martin's sulfurane **5** is shown in Scheme 12. The

Scheme 12. Proposed Mechanism for Ylide Transfer to Substrate 15a



reaction is expected to begin with proton abstraction from **15a** by the $^{-}OC(CF_3)_2Ph$ anion, formed reversibly upon solubilization of sulfurane **5**.[32] The resulting enolate **35** can directly attack the sulfonium ion **34** in an S_N2 fashion, with concomitant expulsion of $^{-}OC(CF_3)_2Ph$, which acts as the base for the final proton abstraction from the intermediate sulfonium ion **36**.

The computed transition states **TS(15a→35)** and **TS(36→16a)** have geometries that are typical for an essentially collinear proton transfer.[33] Therefore only the transition state for nucleophilic addition of the enolate **35** to the sulfonium ion **34** is shown in Figure 1. The optimized geometry of **TS(35→36)** exhibits a very long incipient C···S bond (enolate–sulfonium ion, 3.91 Å), with a CSO angle of 160°. The approach of **34** on top of **35** (see Figure 1) is hindered by the two phenyl rings of **34**, so that the two molecules are kept apart and interact only weakly at **TS(35→36)**. The low imaginary frequency of 28*i* cm^{-1} also indicates a very feeble interaction between the enolate and sulfonium ions at **TS(35→36)**.[34]

The relative free energies computed at the B3LYP-I and B3LYP-II levels are collected in Figure 2 for all relevant species and transition states. At B3LYP-I, the initial complexation between **15a** and $^{-}OC(CF_3)_2Ph$, which affords a suitable

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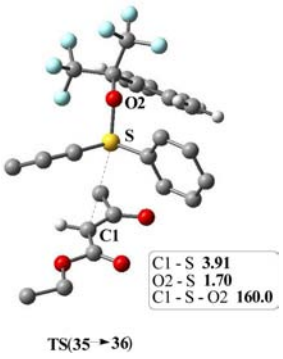


Figure 1. Optimized geometry of the transition state for nucleophilic attack **TS(35→36)** in the proposed mechanism for ylide transfer. Relevant bond distances (Å) and angles (°) are given. For clarity, only selected hydrogen atoms are shown.

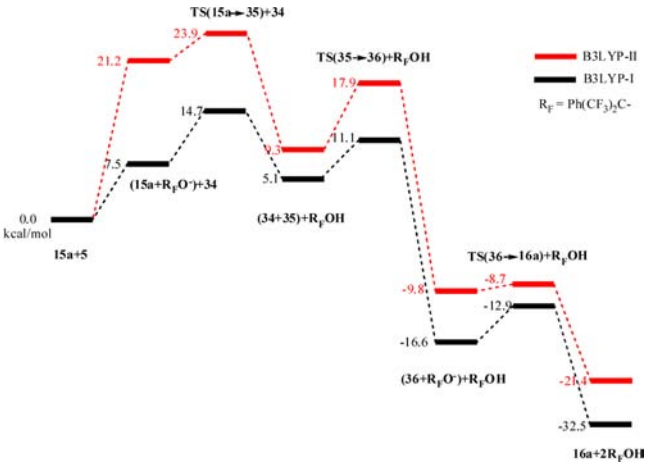


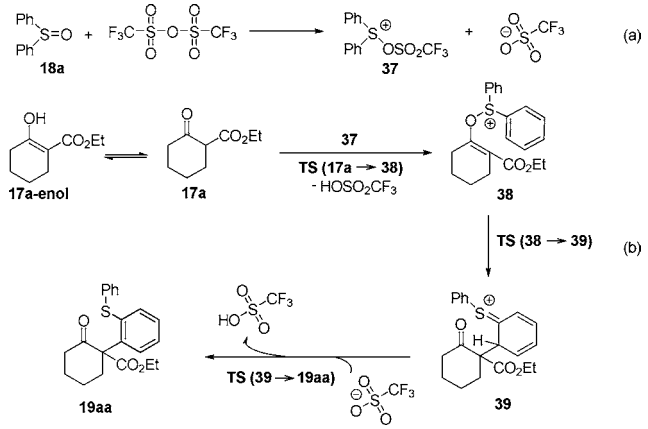
Figure 2. Relative free energies (in kcal/mol) of intermediates and transition states computed at the B3LYP-I and B3LYP-II levels for the pathway shown in Scheme 12. Entries in parentheses such as (**34**+**35**) denote complexes between the two moieties.

orientation of the $^{-}OC(CF_3)_2Ph$ anion for the subsequent proton transfer, is endoergic by 7.5 kcal/mol. The proton abstraction from **15a** requires an additional energy of 7.2 kcal/mol. The overall free energy barrier for this step is thus 14.7 kcal/mol, rendering it the rate-limiting step of the reaction. The free energy barriers for the following two steps (relative to the corresponding intermediates) are smaller: 6.0 kcal/mol for the nucleophilic addition of enolate **35** to the sulfonium ion **34** via **TS(35→36)**, and 3.7 kcal/mol for the final proton abstraction from intermediate **36** to furnish ylide **16a**. The thermodynamic stability of product **16a** (ΔG = −32.5 kcal/mol) ensures complete conversion of **15a** to **16a**.

The B3LYP-II relative free energies (Figure 2) differ from the B3LYP-I values by the inclusion of dispersion corrections, which tend to stabilize more compact structures. The relative free energies in Figure 2 refer to the separated reactants (**15a** and **5**), one of which (**5**) is strongly favored by the dispersion corrections, and therefore the B3LYP-II values for the other species in Figure 2 are consistently higher those from B3LYP-I. As a result, the free energies of the transition states (involving fragments of **5**) rise by 4−9 kcal/mol, but the overall mechanistic scenario remains the same.

DFT Results for Arylation. It is well established that the treatment of a sulfoxide with TFAA (or Tf_2O) should lead to the formation of an activated intermediate such as **37**.[35] The proposed mechanistic route for the arylation of **17a** in the presence of activated diphenylsulfoxide **18a** is given in Scheme 13. The optimized transition state geometries are shown below in Figure 3, and the free energy profiles obtained at the B3LYP-I and B3LYP-II levels are presented in Figure 4.

Scheme 13. Proposed Mechanism for the Sulfoxide-Mediated α-Arylation of β-Keto Ester 17a



As initial step of the reaction, we considered the generation of an enolate through direct deprotonation of substrate **17a** or its enol tautomer by the anion $^{-}OSO_2CF_3$ generated during sulfoxide activation. However, compounding the large pK_a gap between both species (for **17a**, p$K_a \approx 14$; for TfOH, pK_a = −15) is the fact that the barrier computed for this process is prohibitively high (36.6 kcal/mol).[36] IRC calculations indicate that the anion $^{-}OSO_2CF_3$ may not be able to retain the abstracted proton but rather transfer it back to the carbonyl oxygen of substrate **17a**, thus effectively only assisting in keto−enol tautomerization.[37]

In a more likely scenario, the sulfonium ion **37** generated through activation of sulfoxide **18a** with triflic anhydride may assist the deprotonation of substrate **17a**. One may envision that the cationic sulfur of **37** coordinates to the carbonyl oxygen of **17a** while the anion $^{-}OSO_2CF_3$ is simultaneously engaged in proton abstraction. The optimized geometry of the transition state for this concerted process, **TS(17a→38)**, is depicted in Figure 3. Characteristic features are the lengths of the breaking CH bond (1.32 Å), the forming OH bond (1.31 Å), and the coordinating SO bond (1.77 Å) as well as the large $Ph_2S^{+}\cdots{}^{-}OSO_2CF_3$ distance (3.56 Å) between the separating fragments. This reaction step generates an O-sulfenylated enolate **38** which undergoes a formal sigmatropic rearrangement (**TS (38→39)**) and subsequent proton loss **TS(39→19aa)** to form the observed product. The optimized geometry of transition state **TS(38→39)** exhibits a boat-like structure with simultaneous cleavage of the O1···S bond and formation of the C1···C2 bond (Figure 3). C−C bond formation takes place between the central α-carbon atom (C1) of the enolate system and the *ortho*-carbon atom (C2) of one of the phenyl rings.

The relevant distances for O1···S (breaking bond) and C1···C2 (forming bond) are 2.85 and 2.49 Å, respectively. Inspection of the frontier molecular orbitals reveals an unexpected electronic structure for **TS(38→39)**. The highest occupied molecular orbital (HOMO) shows a distinct orbital

dx.doi.org/10.1021/ja4017683 | J. Am. Chem. Soc. 2013, 135, 7312−7323

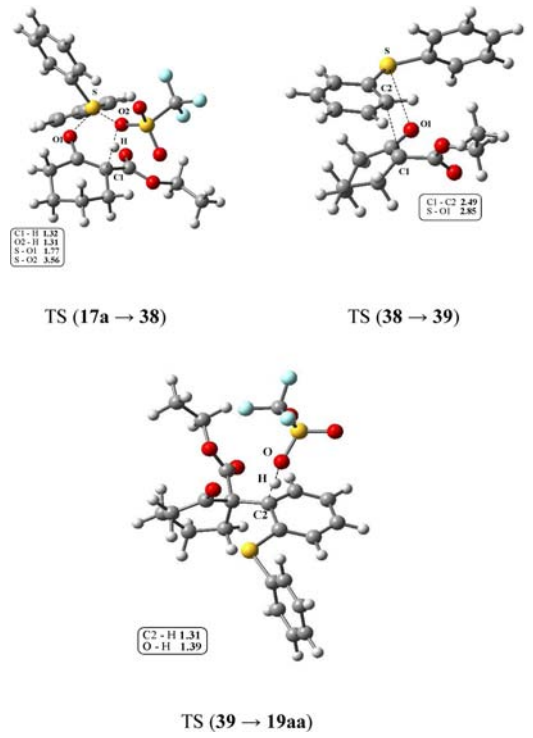


Figure 3. Optimized geometries of the transition states for the conversions **17a→38**, **38→39**, and **39→19aa**. Selected distances are given in Å.

disconnection at the C(*ipso*)−C(*ortho*) bond of the reacting phenyl ring, and none of the occupied orbitals has a closed loop of interacting atomic orbitals along the six-membered ring that contains the breaking and forming bonds. By contrast, the lowest unoccupied molecular orbital (LUMO) is mainly located at the C(*ipso*)−C(*ortho*) bond of the reacting phenyl ring and has a shape that allows its participation in the formation of the new σ-bond. This MO analysis thus suggests that the conversion **38→39** should best be described as an intramolecular nucleophilic addition rather than a sigmatropic rearrangement.[38−42] The transition state **TS(39→19aa)** for the final proton abstraction has the expected structure (Figure 3): the O···H···C2 moiety is essentially linear, the breaking C2···H bond is stretched (1.31 Å), and the forming O···H bond is still rather long (1.39 Å), indicating an early transition state.

According to the relative free energies computed at the B3LYP-I level (Figure 4), the initial association of **17a** and **37** is endoergic by 9.2 kcal/mol, largely because of the entropic penalty for complexation. The subsequent generation of intermediate **38** requires another 8.5 kcal/mol of activation, and the transition state **TS(17a→38)** is the highest point on the free energy profile (17.7 kcal/mol). The following two steps are rather facile, with free energy barriers (relative to the preceding intermediate) of 10.1 kcal/mol for the rearrangement via **TS(38→39)** and 5.1 kcal/mol for the final proton transfer via **TS(39→19aa)**. Both the overall and the individual barriers are fairly small so that the overall **17a→38→39→19aa** conversion is predicted to proceed smoothly. The overall free energy of reaction is −32.0 kcal/mol, indicative of a large thermodynamic driving force for this α-arylation reaction. Procter and co-workers reported a conceptually related nucleophilic allylation of activated sulfoxides by allyl silanes,[42] which may proceed through a similar mechanistic rationale.

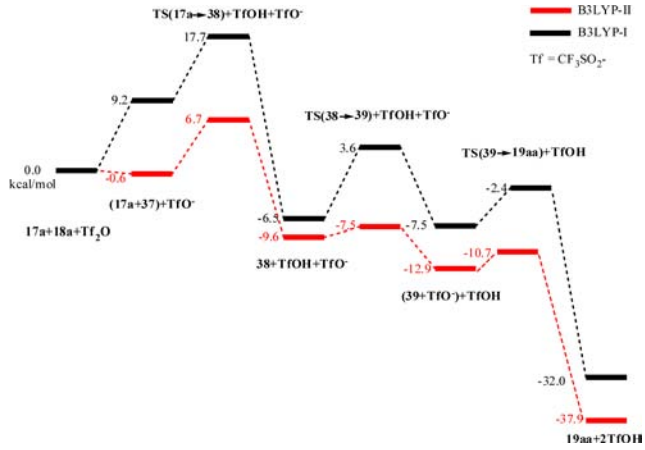


Figure 4. Relative free energies (in kcal/mol) of intermediates and transition states computed at the B3LYP-I and B3LYP-II levels for the pathway shown in Scheme 13. Entries in parentheses such as (**17a** +**37**) denote complexes between the two moieties.

The B3LYP-II relative free energies (Figure 4) differ from the B3LYP-I values by the inclusion of dispersion corrections, which generally tend to favor compact structures. Since the separated reactants, **17a+18a+Tf_2O**, are taken as reference system in Figure 4, it is clear that the relative free energies for the other species will generally be lower for B3LYP-II than for B3LYP-I (typically by about 10 kcal/mol). The overall mechanistic scenario, however, remains the same. The transition state **TS(17a→38)** continues to be the highest point on the free energy profile (now at 6.7 kcal/mol), and the computed barriers are even smaller than in the B3LYP-I case, since the dispersion corrections stabilize the transition states more than the less compact intermediates. It should be emphasized that the B3LYP-II values come from single-point calculations (without geometry reoptimization) and may thus be expected to underestimate the actual barriers.

Finally, we have studied the reaction between **17a** and the unsymmetrically substituted sulfoxide **18d** (cf. Scheme 8) bearing one electron-rich (4-Me) and one electron-poor (4-Cl) aryl ring, focusing on the two distinct transition states for the internal nucleophilic addition step (i.e., corresponding to **TS(17a→38)** in Figures 3 and 4). In accord with the experimental results, we find that the arylation process clearly favors the electron-rich over the electron-poor aryl ring, with the difference in the computed free energies of the two transition states amounting to 3.7 (3.2) kcal/mol at the B3LYP-I (B3LYP-II) level. Arylation involves the formation of a C−C bond between the substrate (C1) and one of the sulfoxide aryl rings (C2), see Figure 3. According to natural bond orbital analysis for the two transition states, C1 has a small positive charge, while C2 carries a substantial negative charge that is larger when C2 resides in the electron-rich (4-Me) rather than the electron-poor (4-Cl) aryl ring. In the former case, the electrostatic interaction between C1 and C2 is therefore stronger, which contributes to the observed preference for arylation.

Comment on Differences between the Computed Pathways. One key distinction is the proton affinity of the anions that are initially generated (Schemes 12a and 13a). Judging from the gas-phase B3LYP values, the proton affinity of $^{-}OC(CF_3)_2Ph$ is about 40 kcal/mol higher than that of $^{-}OSO_2CF_3$. Hence, $^{-}OC(CF_3)_2Ph$ is able to deprotonate

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substrate **15a** and form the corresponding enolate **35**. Nucleophilic attack of **35** at the sulfonium ion **34** yields the C-sulfenylated intermediate **36**, which is more stable than the alternative O-sulfenylated intermediate by 19.0 kcal/mol (B3LYP-I, thermodynamic control) and is then easily deprotonated to give the ylide product **16a** (see Scheme 12 and Figure 2). By contrast, the weaker base $^{-}OSO_2CF_3$ is not able to deprotonate substrate **17a**. The only viable pathway that we have found involves deprotonation with assistance of the sulfonium ion 37 and formation of the O-sulfenylated intermediate **38**. The latter may, in principle, undergo a 1,3-sulfur migration to the C1-sulfenylated intermediate, which is more stable than **38** by 15.6 kcal/mol (B3LYP-I) but obviously cannot lead to ylide formation as it lacks a C1−H bond. Moreover, the barrier for the 1,3-sulfur migration is estimated (B3LYP-I) to be about 5 kcal/mol higher than that for the competing rearrangement (**38**→**39**), all of which are factors conspiring to favor the arylation pathway (see Scheme 13 and Figure 4).

NMR Investigation. An NMR kinetic and mechanistic study was also undertaken on the arylation reaction. Figure 5

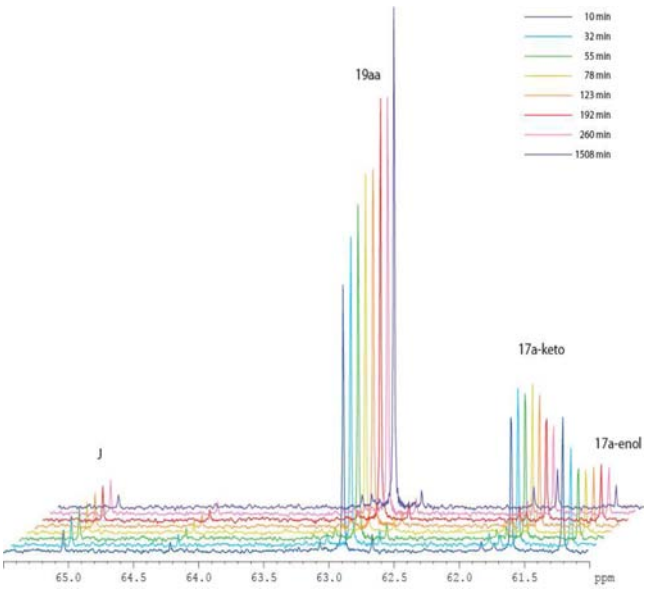
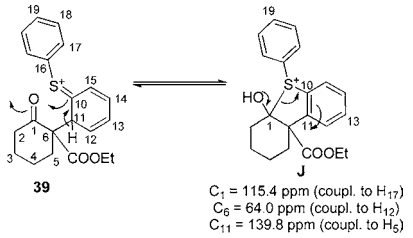


Figure 5. Time evolution of the carbon methylene region of the ethyl ester group of **17** during the arylation process.

shows the time evolution of the ^{13}C signal intensity of the methylene group in the keto ester (**17a**),[45] the enol ester (**17a-enol**), and the product (**19aa**) in the reaction depicted in Scheme 6. Interestingly, a stable intermediate species (**J**) can also be detected. It becomes apparent from inspection of Figure 5 that the enol curve declines more sharply than the corresponding keto curve. The keto and enol forms are in exchange (k_1, $k_{-1} \ll 100\ s^{-1}$) at room temperature with keto formation being about 3 times as fast as the reverse enol formation ([enol]/[keto] = k_{-1}/k_1 = 0.77/0.23 = 3.3). One can thus conclude that it is the keto form that reacts with the activated sulfoxide since that form will tend to accumulate upstream to the rate-limiting step. This is in agreement with the model proposed in Scheme 13.

Of particular interest is the detection of an intermediate species (**J**) that forms early during the reaction, reaches a maximum after 4−5 h and declines to zero when the reaction is completed (cf. leftmost peak in Figure 5). This species was characterized by low-temperature (−20 °C) NMR correlation experiments. The quaternary carbon at position C_6 (see Scheme 14 for numbering) with a chemical shift of 63.8 ppm

Scheme 14. NMR Assignment of Late-Stage Intermediate J and Plausible Mechanism for Its Reversible Formation



correlates through 3-bond coupling to an aromatic proton (H_{12}), implying that the bond to the *ortho*-position is already formed. This is therefore a late-stage intermediate, and the attached carbon is fully aromatic as revealed by six aromatic carbon shifts in the benzene ring, two of which are substituted. However, this species distinguishes itself from the actual product by the following observations: (a) chemical shifts in the aromatic rings suggest a positive charge at the sulfur, and (b) C_1 has a peculiar ^{13}C chemical shift of 115.4 ppm which surprisingly presents a very weak coupling correlation to the free phenyl ring (H_{17}). This information can only be reconciled with a structure where sulfur is covalently attached to the cyclohexane ring through C_1. From a mechanistic standpoint, it would appear that **J** and the short-lived, dearomatized intermediate **39** (Scheme 13) are related through a straightforward bond reorganization as shown in Scheme 14.

Taken together, the kinetic NMR data can be fit to the reaction model shown in Figure 6, which closely resembles that

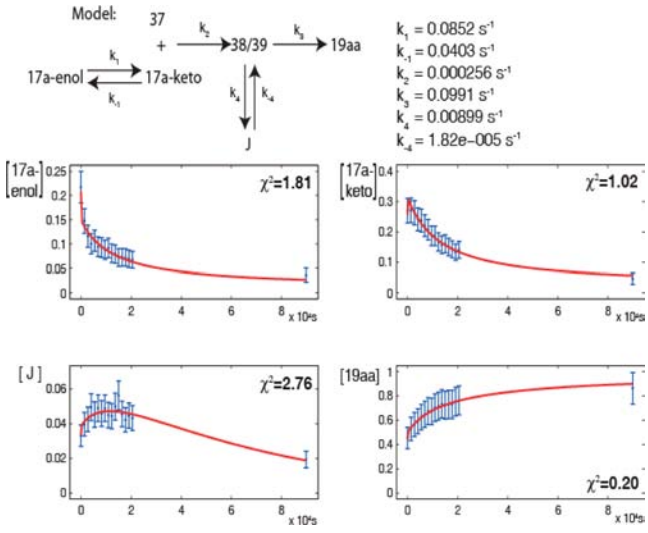


Figure 6. Kinetic profile for the direct arylation reaction.

of Scheme 13. The slow tautomeric interconversion between the keto (**17a**) and enol (**17a-enol**) forms is driven by the rate constants k_1 and k_{-1}. In comparison, the encounter of **17a** with the activated sulfoxide **37** to form an invisible intermediate **38**/**39** is slower and represents the rate determining step. This intermediate, or group of rapidly interconverting intermediates, are invisible to NMR and cannot be further characterized by

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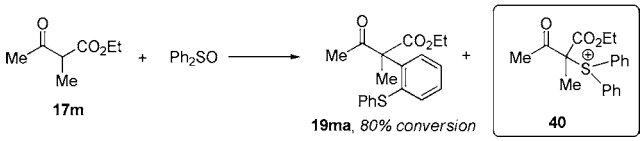
this method. However, two seemingly competing isomerization reactions (with similar rates) take place from this intermediate, one leading to a relatively stable five-membered ring (**J**), the other leading to the end product (**19aa**).

In an attempt to identify similar intermediates and kinetic curves in the slower reaction starting from the acyclic β-keto ester **17m** and forming the α-arylated carbonyl compound **19ma**, a side-product **40** was fortuitously encountered (Scheme 15). The structure of **40**, isomeric with **19ma** and

Scheme 15. Interception of an "Interrupted Ylide-Transfer" Intermediate 40



corresponding to ca. 20% of the converted material, was assigned by NMR. The low-field shifted ^{13}C signals in the *ortho*- and *para*-positions of the aromatic rings in agreement with a positively charged sulfur center, while the quaternary ^{13}C of 84.1 ppm reveals the location of sulfur at the α-position. The structure of **40** is suggestive of an "interrupted ylide-transfer" process.[46]

Summary of the Mechanistic Findings. Our combined mechanistic analysis highlights a clear analogy between the ylide-transfer and arylation processes, both proceeding through very similar cationic electrophilic S(IV) species. It would thus appear that the basicity of the counteranion (a trifluoromethylated alkoxide versus triflate) accompanying the S(IV) species is crucial. On one hand, high basicity leads to deprotonation of the dicarbonyl substrates. On the other hand, the lower basicity of triflate and its inability to mediate direct proton abstraction mandates the adoption of a different mechanistic route, where the S(IV) electrophile serves as an interesting "organic Lewis acid"[47] to enable deprotonation (by triflate).

The conjugate base of the dicarbonyl substrate appears to have a preference for C−S bond formation, ultimately leading to an energetically favored ylide-transfer process. Conversely, the S(IV)-assisted deprotonation intrinsically generates an O−S bound intermediate, from which the sequence of events eventually leading to arylation is energetically downhill. The detection of minor amounts of C−S bound species even in cases where arylation is ultimately favored, consistent with the observation of low yields of ylide transfer on unsubstituted active methylene compounds (cf. Scheme 7a), suggests that pathways may exist for migration of sulfur from O to C but that their efficiency is, in any case, lower than that of the main reaction manifolds observed.[48]

CONCLUSION

In summary, we have developed an ensemble of sulfur(IV)-mediated transformations that yield very diverse products (as are sulfonium ylides and α-arylated carbonyl derivatives), yet proceed by tightly interconnected pathways. A useful pK_a threshold of ca. 23 has been established for ylide transfers employing Martin's sulfurane, and the scope of α-arylation mediated by activated sulfoxides has been extended to silyl enol ethers. Particularly interesting is the inference that the cationic sulfur(IV) species which are intermediates in these reactions are prone to react with enolizable carbonyls at either C or O, depending on both structural factors and counteranion basicity. In-depth mechanistic insight has been acquired by NMR structural and kinetic analysis as well as DFT calculations, highlighting *inter alia* an intriguing role for sulfonium ions as mediators for deprotonation and allowing the identification of hidden pathways that interconnect ylide transfer and carbonyl arylation. The transformations reported herein should find growing synthetic utility among the community.

ASSOCIATED CONTENT

Supporting Information

Optimized Cartesian coordinates (B3LYP-I) and total energies (B3LYP-I, B3LYP-II) of all computed stationary points, plots of relevant frontier molecular orbitals, complete ref 29, and experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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