Aryl Sulfoxides from Allyl Sulfoxides via [2,3]-Sigmatropic Rearrangement and Domino Pd-Catalyzed Generation/Arylation of Sulfenate Anions
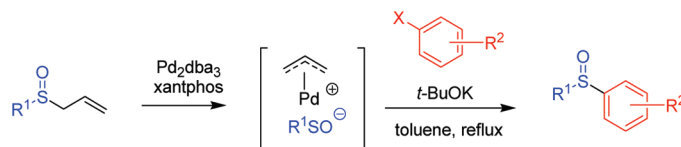
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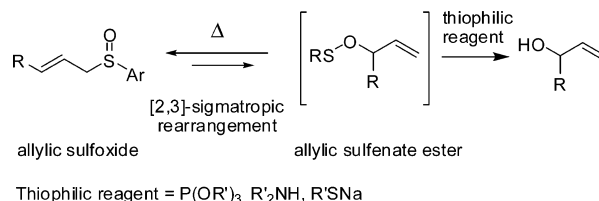
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ABSTRACT

Allylic sulfoxides, via [2,3]-sigmatropic rearrangement and oxidative addition of the resulting allylic sulfenate esters to Pd(0), are found to be excellent precursors of sulfenate anions. This hitherto unknown reactivity is applied in a new Pd(0)-catalyzed domino sequence involving sulfenate anion generation followed by arylation to afford aryl sulfoxides.

Since its first publication by Mislow in 1966,[1] the reversible [2,3]-sigmatropic rearrangement of allylic sulfoxides to allylic sulfenate esters (Mislow–Braverman–Evans rearrangement)[2] has been intensively studied.[3] Nevertheless, the only application of this rearrangement remains the preparation of allylic alcohols by addition of thiophilic reagents, such as phosphites, amines, or thiolate anions (Scheme 1).[4] On the other hand, the palladium-catalyzed arylation reaction

Scheme 1. Mislow–Braverman–Evans Rearrangement

allylic sulfoxide   allylic sulfenate ester

Thiophilic reagent = P(OR')₃, R'₂NH, R'SNa

represents a synthetic tool of the utmost importance for generating carbon–carbon and carbon–heteroatom bonds.[5] In particular, the use of sulfur-based nucleophiles,[6] such as thiolates (RS^-),[7] sulfenates (RSO^-),[8] and sulfinates (RSO_2^-)[9] allows the easy generation of the corresponding aryl thioethers, sulfoxides, and sulfones, respectively.

In view of the importance of many aryl sulfoxides in medicinal and pharmaceutical chemistry,[10] we decided to focus our attention on the development of new methods for

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the generation of sulfenate anions[11] and their application in palladium catalysis. In this regard, we recently described the synthesis of allylic and aromatic sulfoxides by palladium-catalyzed allylic alkylation[12] and arylation reaction[8] of sulfenate anions generated via β-sulfinyl esters enolate elimination,[13] under specifically developed biphasic conditions (Scheme 2).[14]
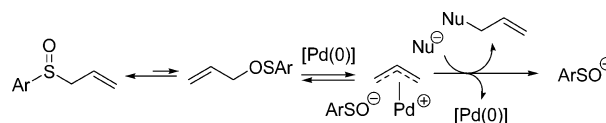
Scheme 2. Sulfenate Anions in Palladium Catalysis
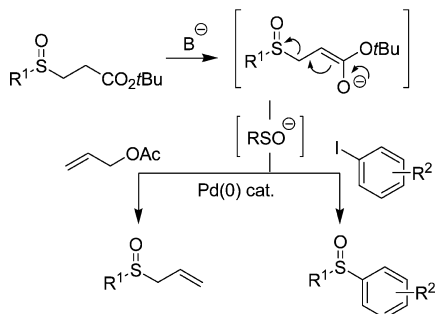
Given these last results, we speculated that, taking advantage of the known allylsulfoxide-to-allylsulfenate ester equilibrium,[1] sulfenate anions might be generated from the

corresponding allyl sulfoxides by treatment with catalytic amounts of a Pd(0) complex and an appropriate nucleophilic species, capable of trapping the transiently formed allyl moiety (Scheme 3).

Scheme 3. Hypothesis of Sulfenate Pd(0)-Catalyzed Anion Generation from Allyl Sulfoxides

Herein, we report our results on the conversion of allyl sulfoxides to aryl sulfoxides via a pseudodomino[15] palladium-catalyzed generation of sulfenate anions and in situ reaction with aryl halides.

The reaction between phenyl allyl sulfoxide and *p*-iodoanisole to afford phenyl *p*-methoxyphenyl sulfoxide was chosen as a model reaction (Table 1). Preliminary experi-

Table 1. Optimization of the Reaction Conditions[a]

entry	catalytic system	nucleophile	solvent	yield (%)[b]
1	Pd$_2$dba$_3$/xantphos	AcOK	toluene	—[c]
2	"	HCO$_2$K	"	—[d]
3	"	t-BuOK	"	57
4	"	t-BuONa	"	34
5	"	Ph$_3$SiH	"	e
6	"	PMHS	"	—
7	"	Meldrum's acid sodium anion	"	—[f]
8	"	dibenzoylmethane sodium anion	"	14[g]
9	[Pd(C$_3$H$_5$)Cl]$_2$ xantphos	t-BuOK	"	37
10	Pd$_2$dba$_3$/xantphos[h]	"	"	52
11	Pd$_2$dba$_3$/xantphos	"	THF	35 [−]
12	"	"	CH$_3$CN	—[e]
13	"	"	DMF	31

[a] Reagents and reaction conditions: *p*-iodoanisole (1.2 equiv), allyl phenyl sulfoxide (1.0 equiv), Pd$_2$dba$_3$ or [Pd(C$_3$H$_5$)Cl]$_2$ (2 mol %), xantphos (5 mol %), nucleophile (2.0 equiv), 2 h at reflux. [b] Yields are given for isolated products. [c] Reagents were recovered unchanged. [d] Only anisole was observed in the crude product. [e] Complete degradation of the reaction mixture. [f] (E)-Phenylsulfinyl-1-propene (10%) was isolated. [g] (E)-Phenylsulfinyl-1-propene (46%) was isolated. [h] Addition of *n*-Bu$_4$NBr (2 equiv) as additive.

ments performed with potassium acetate or potassium formate as the nucleophilic reagents were disappointing. Indeed, with the former one the substrates were recovered unchanged (entry 1), whereas potassium formate brought

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about the reduction of *p*-iodoanisole into anisole. This latter result can be interpreted in terms of competitive reaction of the formate anion with the transiently formed arylpalladium(II) complex (entry 2). On the other hand, use of potassium *tert*-butoxide allowed generation of the corresponding aromatic sulfoxide in 57% yield (entry 3). Replacement of potassium *tert*-butoxide for sodium *tert*-butoxide did not increase the yield (entry 4). Use of triphenylsilane or poly(methylhydroxysiloxane) (PMHS) as the hydride source led to the complete degradation of the reaction mixture (entries 5 and 6). Use of carbanions derived from Meldrum's acid or dibenzoylmethane as the nucleophilic reagents gave poor results and afforded mainly the corresponding propenyl sulfoxide resulting from competitive isomerization of allylic starting sulfoxide (entries 7 and 8). Replacement of Pd_2dba_3 by $[Pd(C_3H_5)Cl]_2$ decreased the yield of the reaction (entry 9), whereas use of tetrabutylammonium bromide as an additive[9] did not affect the conversion (entry 10). The influence of solvent was next studied. Replacement of toluene by THF led to the formation of aryl sulfoxide in a poor 35% yield (entry 11). Use of acetonitrile brought about complete degradation of reaction mixture (entry 12), while DMF afforded results similar to those obtained in toluene (entry 13).

With the optimized reaction conditions in hand (Table 1, entry 3, and Table 2, entry 1), we next investigated the scope

Table 2. Scope of the Reaction[a]

entry	aryl halide	product	yield (%) [b]
1	I–C6H4–OMe	1a	57
2	I–C6H4–Me	1b	51
3	I–C6H4–NO2	1c	36
4	Br–C6H4–OMe	1a	56
5	Br–C6H4–Me	1b	44
6	Cl–C6H4–OMe	1a	- [c]

[a] Reagents and reaction conditions: aryl halide (1.2 equiv), allyl phenyl sulfoxide (1.0 equiv), Pd_2dba_3 (2 mol %), xantphos (5 mol %), *t*-BuOK (2.0 equiv), 2 h in toluene at reflux. [b] Yields are given for isolated products. [c] No reaction.

and limitations of this transformation by treating the phenyl sulfenate precursor with a variety of substituted aryl halides (Table 2). In the event, 4-iodotoluene afforded the corre-

Table 3. Scope of the Reaction[a]

entry	aryl halide / R^1	product	yield (%) [b]
1	I–C6H4–OMe; R^1 = *p*-Tol	2a	60
2	I–C6H4–OMe (meta); R^1 = *p*-Tol	2b	45
3	I–C6H4–OMe (ortho); R^1 = *p*-Tol	2c	15
4	I–C6H4–Me; R^1 = *p*-Tol	2d	47
5	I–C6H4–NO2; R^1 = *p*-Tol	2e	28
6	I–C6H4–CF3; R^1 = *p*-Tol	2f	44
7	I–C6H4–OMe; R^1 = 2-Naphthyl	3a	37
8	I–C6H4–Me; R^1 = 2–Naphthyl	3b	49
9	I–C6H4–OMe; R^1 = Benzyl	-	- [c]

[a] Reagents and reaction conditions: aryl halide (1.2 equiv), allyl sulfoxide (1.0 equiv), Pd_2dba_3 (2 mol %), xantphos (5 mol %), *t*-BuOK (2 equiv), 2 h in toluene at reflux. [b] Yields are given for isolated products. [c] Complete degradation of reaction mixture.

sponding sulfoxide **1b** in 51% yield (entry 2). Under the same conditions, *p*-iodonitrobenzene generated the sulfoxide **1c** in a poor 36% yield (entry 3). Reactions of 4-bromoanisole and 4-bromotoluene produced the corresponding sulfoxides **1a** and **1b** in 56% and 44% yield, respectively (entries 4

and 5). Such a positive result was somewhat surprising in light of the low reactivity of aryl bromides previously observed by us using β-sulfinylesters as the sulfenate precursors.[8] Indeed, 4-chloranisole did not allow generation of the expected aryl sulfoxide (entry 6).

The reaction was next studied using differently substituted allyl sulfoxides as the sulfenate anion source (Table 3). Starting from allyl tolyl sulfoxide as the sulfenate precursor, the reaction with *p*-iodoanisole afforded the corresponding sulfoxide **2a** in 60% yield (entry 1). The same reaction on *m*-iodoanisole produced the desired sulfoxide **2b** in 45% yield (entry 2). Conversely, under the same conditions, *o*-iodoanisole gave aryl sulfoxide **2c** in a poor 15% yield (entry 3), whereas 4-iodotoluene reacted with allyl *p*-tolyl sulfoxide to afford the symmetrical sulfoxide **2d** in 47% yield (entry 4). Electron-poor aryl iodides carrying *p*-NO$_2$ or *p*-CF$_3$ substituents on the aryl moiety led to the corresponding sulfoxides **2e** and **2f** in 28 and 44% yields, respectively (entries 5 and 6). Starting from the 2-naphthyl sulfenate precursor, the reaction with 4-iodoanisole afforded the corresponding arylation product **3a** in 37% yield (entry 7). Similarly, sulfoxide **3d** was isolated in 49% yield starting from 4-iodotoluene (entry 8). More disappointingly, the reaction between the benzyl sulfenate precursor and the electron-rich 4-iodoanisole brought about only the total degradation of the reaction mixture (entry 9).

A mechanistic proposal for the palladium-catalyzed sulfenate generation/arylation domino sequence is depicted in Scheme 4. First, oxidative addition of the allylsulfenate to Pd(0) is expected to give the corresponding η^3-allylpalladium(II) complex.[16] Trapping of the allyl moiety of the palladium complex by potassium *tert*-butoxide releases the sulfenate anion as well as Pd(0), which are both ready to enter the second catalytic cycle. Transmetalation between the sulfenate anion and the σ-arylpalladium(II) complex, in turn generated from oxidative addition of the aryl iodide to Pd(0) to the aryl iodide, gives, after reductive elimination, the corresponding aromatic sulfoxide. It should be noted that the role

(16) Involvement of the sulfenate ester in the oxidative addition process, although likely, is for the moment a matter of speculation.

Scheme 4. Proposed Mechanism
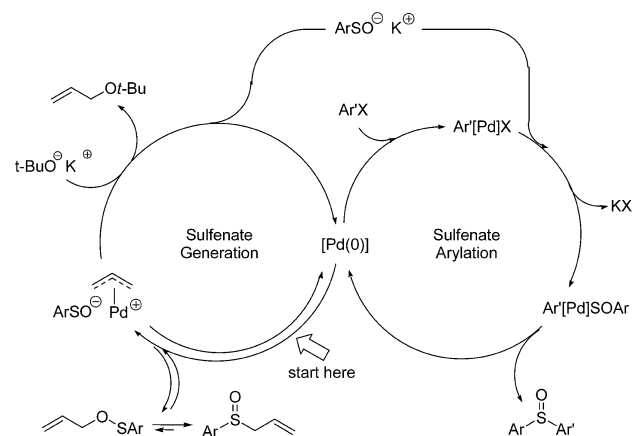
of potassium *tert*-butoxide is central in that it reacts irreversibly with the allyl moiety in the first catalytic cycle, thus generating the required sulfenate anion and Pd(0), yet it does not interfere in the second catalytic cycle.

In conclusion, we have reported the first palladium-catalyzed generation of sulfenate anions exploiting the Mislow−Braverman−Evans rearrangement and its application in a new pseudodomino sulfenate generation/arylation sequence to afford aromatic sulfoxides in synthetically useful yields. Vinylative and enantioselective variants of the present palladium-catalyzed sequences, as well as mechanistic studies, are presently under investigation and will be reported in due course.

Supporting Information Available: General procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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