Palladium-Catalyzed Aromatic Sulfonylation: A New Catalytic Domino Process Exploiting in situ Generated Sulfinate Anions

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Received 3 September 2011

Dedicated to Dr. Christian Bruneau on the occasion of his 60th birthday

Abstract: Allylic sulfones are excellent precursors of aryl sulfones via a new Pd-catalyzed domino sequence involving in situ generation of sulfinate anions and subsequent cross-coupling with aryl iodides or bromides.

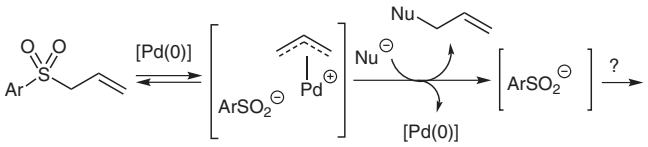
Key words: sulfones, sulfinate anions, catalysis, palladium, domino reaction

Aromatic sulfones[1] are compounds of considerable interest embedding a number of positive features such as stability, crystallinity, chromophoric activity,[2] as well as antibacterial, antifungal, and antitumor activities.[3] Classical strategies to access these compounds rely on the oxidation of aryl thioethers, electrophilic aromatic substitution on sulfonyl halides, reaction of organometallic reagents with sulfonate esters, and arylation of sulfinate anions.[4] With regard to the last method, transition-metal-catalyzed allylic[5] and aromatic[6] sulfonylations recently appeared as an interesting method to generate the corresponding allyl and aryl sulfones.

We recently reported that, under palladium catalysis, allyl sulfoxides can generate sulfenate anions, which can in turn be easily cross-coupled to afford aryl sulfoxides.[7,8] In this communication we report a successful extension, from sulfoxides to sulfones, of our Pd-catalyzed allyl-to-aryl conversion domino process.

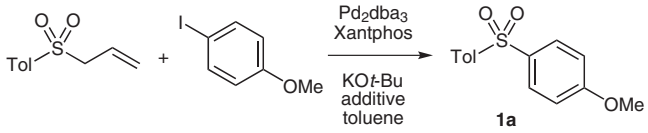
Accordingly, we envisaged to generate the required sulfinate anion via oxidative addition of an allylic sulfone onto a Pd(0) complex.[9] Subsequent nucleophilic interception of the thus formed η^3-allyl palladium complex is then expected to trigger the sulfinate anion release, which may in turn be further reacted in a palladium-catalyzed arylation reaction (Scheme 1).

The palladium-catalyzed sulfonylation reaction between allyl *p*-tolyl sulfone and 4-iodoanisole was chosen as the model reaction. The Pd_2dba_3/Xantphos combination, already described as an efficient catalytic system for sulfur-based nucleophiles[10] and specifically for sulfinate anions,[6] was selected as the catalytic system. As to the intercepting nucleophile, we selected potassium *tert*-butoxide, as it showed to be a competent nucleophile in our previous study[7] (Table 1).



Scheme 1 Hypothesis of Pd(0)-catalyzed sulfinate anion generation from allyl sulfones

Table 1 Optimization of the Pd-Catalyzed Aromatic Sulfonylation[a]



Entry	Additive	Temp (°C)	Yield (%)[b]
1	–	80	–
2	*n*-Bu_4NCl	80	–
3	*n*-Bu_4NBr	80	65
4	*n*-Bu_4NHSO_4	80	15
5	*n*-Bu_4NBr	reflux	88

[a] Reagents and conditions: 4-iodoanisole (1.2 equiv), allyl *p*-tolyl sulfone (1.0 equiv), Pd_2dba_3 (2 mol%), Xantphos (5 mol%), additive (if used, 2.0 equiv), KO*t*-Bu (2.0 equiv).
[b] Yields are given for isolated products.

Preliminary experiments performed in toluene at 80 °C according to our preceding studies of arylic sulfinylation, in the absence (Table 1, entry 1) or in the presence (Table 1, entry 2) of an overstoichiometric amount of

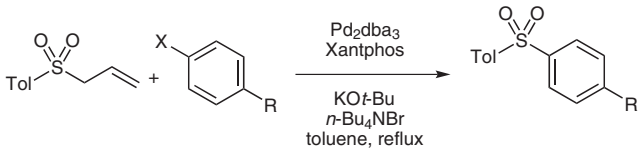
SYNLETT 2011, No. 20, pp 2943–2946
Advanced online publication: 11.11.2011
DOI: 10.1055/s-0031-1289880; Art ID: B17111ST

n-Bu_4NCl, led to total degradation of the substrates. The latter result is surprising if we consider the efficiency of *n*-Bu_4NCl as additive in couplings previously described by some of us,[6] and could be due to the generation of an unreactive dimeric $[Pd(\eta^3\text{-allyl})Cl]_2$ complex. Satisfyingly, replacement of *n*-Bu_4NCl with *n*-Bu_4NBr allowed the desired aromatic sulfonylation to take place, affording the expected anisyl-tolyl sulfone in 65% yield (Table 1, entry 3). Switch to *n*-Bu_4NHSO_4 as additive gave a much poorer result (15% yield, Table 1, entry 4), whereas heating the reaction mixture at reflux of toluene for eight hours raised the yield of sulfone to 88% (Table 1, entry 5). It is worthy to note that after one hour reaction the allylic sulfone is totally consumed, whereas the formation of the aromatic sulfone is still rising. This observation suggests that, as mechanistically required (see later), the rate of sulfinate generation is higher than that of sulfinate arylation, and that such anions may accumulate at the entrance of the arylation catalytic cycle.

With the optimized reaction conditions in hand, the scope and limitations of this transformation were studied, reacting allyl *p*-tolylsulfone with a variety of substituted aryl halides (Table 2). In the event, 4-iodotoluene afforded the corresponding sulfone **1b** in 66% yield (Table 2, entry 2), whereas the electron-poor 4-trifluoromethyl iodobenzene gave the aryl sulfone **1c** in a meager 16% yield, and 4-nitro iodobenzene gave only degradation products (Table 2, entry 4).

Aryl bromides could be successfully used as partners. Indeed, 4-bromoanisole and 4-bromotoluene gave the corresponding sulfones **1a** and **1b** in 48% and 52% yield, respectively (Table 2, entries 5 and 6). On the other hand, 4-chloroanisole did not allow the desired coupling to take place (Table 2, entry 7).

Table 2 Scope of the Pd-Catalyzed Aromatic Sulfonylation[a]

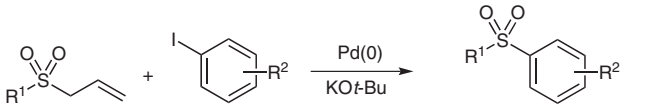


Entry	X	R	Product	Yield (%)[b]
1	I	OMe	**1a**	88
2	I	Me	**1b**	66
3	I	CF_3	**1c**	16
4	I	NO_2	–	–[c]
5	Br	OMe	**1a**	48
6	Br	Me	**1b**	52
7	Cl	OMe	–	–[c]

[a] Reaction conditions: aryl halide (1.2 equiv), allyl *p*-tolyl sulfone (1.0 equiv), Pd_2dba_3 (2 mol%), Xantphos (5 mol%), KO*t*-Bu (2.0 equiv), 16 h, toluene, reflux.
[b] Yields are given for isolated products.
[c] No reaction.

The reaction was next studied using differently substituted allyl sulfones as the sulfinate anion source and various aryl iodides (Table 3). Starting from allyl *p*-tolyl sulfone, the reaction with *m*-iodoanisole afforded sulfone **2b** in 55% yield (Table 3, entry 2), to compare with 88% yield previously obtained with *p*-iodoanisole (Table 3, entry 1). Under the same reaction conditions *o*-iodoanisole did not allow the generation of the expected sulfone (Table 3, entry 3). This suggests that the present coupling is very sensitive to steric hindrance in the vicinity of the aryl halide reacting center. Starting from allyl *p*-anisyl sulfone as sulfonylating agent reaction with 4-iodo toluene afforded the corresponding arylation product **1a** in 40% yield (Table 3, entry 4).

Table 3 Scope of the Reaction[a]

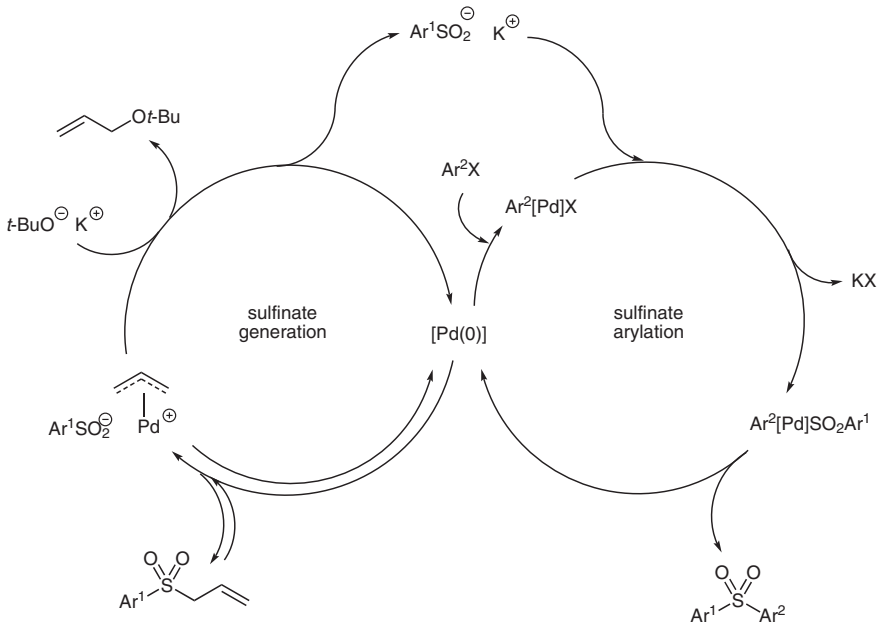


Entry	R^1	R^2		Yield (%)[b]
1	4-MeC_6H_4	4-MeO	**1a**	88
2	4-MeC_6H_4	3-MeO	**2b**	55
3	4-MeC_6H_4	2-MeO	–	–
4	4-$MeOC_6H_4$	4-Me	**1a**	40
5	4-$MeOC_6H_4$	4-MeO	**2d**	37
6	4-$O_2NC_6H_4$	4-Me	**2e**	21
7	4-$O_2NC_6H_4$	4-MeO	–	–
8	2-naphthyl	4-Me	**3a**	60
9	2-naphthyl	4-MeO	**3b**	61
10	Bn	4-MeO	–	–[c]

[a] Reaction conditions: aryl halide (1.2 equiv), allyl sulfoxide (1.0 equiv), Pd_2dba_3 (2 mol%), Xantphos (5 mol%), KO*t*-Bu (2.0 equiv), 16 h, toluene, reflux.
[b] Yields are given for isolated products.
[c] Complete degradation of the reaction mixture.

Similarly, symmetrical sulfone **2d** was isolated in 37% yield when starting from 4-iodoanisole (Table 3, entry 5), whereas starting from allyl 4-nitrophenyl sulfone and 4-iodotoluene, sulfone **2e** was obtained in a poor 21% yield (Table 3, entry 6). Under the same reaction conditions, 4-iodoanisole did not afford the expected sulfone (Table 3, entry 7). Starting from the 2-naphthyl sulfinate precursor, reaction with 4-iodotoluene and 4-iodoanisole afforded the corresponding arylation products **3a** and **3b** in 60% and 61% yield, respectively (Table 3, entries 8 and 9). Rather disappointingly, reaction between the benzyl sulfinate precursor and 4-iodoanisole brought about only total degradation of the reaction mixture (Table 3, entry 10).[11]

A mechanistic proposal for the palladium-catalyzed sulfinate generation–arylation pseudo-domino[12] catalytic se-



Scheme 2 Proposed mechanism

quence is depicted in Scheme 2. First, oxidative addition of the allylic sulfone to Pd(0) is expected to afford the corresponding η^3-allylpalladium(II) complex.

Interception of the allyl moiety of the palladium complex by potassium *tert*-butoxide liberates the sulfinate anion as well as Pd(0), which are both set to enter the second catalytic cycle.

Halide-to-sulfinate ligand exchange on the σ-arylpalladium(II) complex in turn generated from oxidative addition of the aryl iodide to Pd(0) gives, after reductive elimination, the corresponding aromatic sulfone. It should be noted that the task of potassium *tert*-butoxide is essential in that it irreversibly intercepts the allyl ligand in the first catalytic cycle thereby generating the required sulfinate anion and Pd(0), yet, not perturbing the second catalytic cycle.[13]

Inspection of this mechanism reveals that such a pseudo-domino process can only be successful if the oxidative addition of the allyl sulfone to the Pd(0) complex is faster than that associated to the aryl halide. Indeed, otherwise, the second catalytic cycle (sulfinate arylation) would probably stall at the irreversibly generated σ-arylpalladium(II) complex stage and no spare Pd(0) complex would be available to feed the first catalytic cycle (sulfinate generation). Such analysis is in full accord with the experimental finding that in the case of **1a** (Table 1) the rate of sulfinate generation was found to be higher than that of sulfinate arylation, and with the fact that electron-poor aryl halides, which are associated to a fast oxidative addition, did not afford satisfactory results (Table 2, entries 3 and 4).

In conclusion, we have reported the first pseudo-domino sequence involving the palladium-catalyzed generation of sulfinate anions followed by their arylation to afford aromatic sulfones. Studies to elucidate the details of the reaction mechanism of this aromatic sulfonylation are presently under investigation and will be reported in due course.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This work is the fruit of a collaborative project from COST, Action D40 'Innovative Catalysis: New Processes and Selectivities'.

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(13) **Representative Experimental Procedure for the Domino Palladium-Catalyzed Generation–Arylation of Sulfinate Anions**

To a solution of tris(dibenzylideneacetone)dipalladium (2 mol%) in toluene (500 μL) was added Xantphos ligand (5 mol%). The solution was stirred at r.t. for 5 min. Then, a solution of allyl sulfone (0.30 mmol in 1.0 mL of toluene, 1 equiv), a solution of aryl halide (0.36 mmol in 500 L of toluene, 1.2 equiv.), TBAB (0.60 mmol, 2 equiv), and KO*t*-Bu (0.60 mmol, 2 equiv) were successively added. The resulting system was stirred at reflux for 16 h. Then, after cooling to r.t., a sat. aq NH_4Cl solution (3 mL) were added, and the aqueous phase was extracted three times with CH_2Cl_2. The collected organic layers were dried over anhyd $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography.