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Palladium-catalyzed arylation of sulfonyl CH-acids

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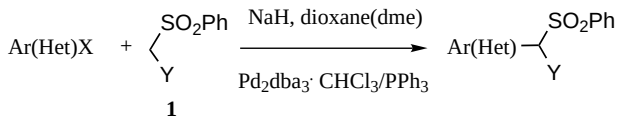
Abstract—A method for the palladium-catalyzed monoarylation of a series of functionalized sulfones by aryl halides is described. The reaction proceeds in the presence of 2 mol% of $Pd_2dba_3{\cdot}CHCl_3$ (dba = dibenzylideneacetone), PPh_3 and NaH as a base, only with relatively strong CH-acids and gives monoarylated products in moderate to high yields.

Sulfones are an important type of organic synthon, widely used in the total synthesis of useful organic compounds such as natural products and bioactive substances.[1] The auxiliary sulfonyl group enables the deprotonation of a neighboring carbon atom and the resulting carbanions can enter into various transformations after which the group can be removed by reductive desulfonylation.[1b] Several synthetic routes to (arylmethyl)-sulfones have been reported, but these are not of general applicability and involve complex multi-step procedures.[1c]

Here we report on the synthesis of α-functionalized arylmethylphenylsulfones by palladium-catalyzed arylation of the related phenylmethylsulfones with aryl halides. We followed a synthetic approach based on the palladium-catalyzed arylation of CH-acids. It is known that α-functionalized nitriles, YCH_2CN,[2] can be monoarylated by a Pd-catalyzed reaction with a conventional PPh_3 ligand. However, in the majority of cases including the arylation of ketones[3] and many other CH-acids such as amides,[4] diethyl malonate,[5a,b] cyclic 1,3-diketones,[5b] nitroalkanes[5b] and esters,[5c,d] the reactions demand the application of a Pd-catalyst with bidentate or specific bulky, electron-rich phosphines.

We have found that the compounds **1a–d** react smoothly with various aryl, heteroaryl and vinyl halides in the presence of the catalyst-Pd_2dba_3/3 PPh_3 and NaH as the base.

The above mentioned conditions were developed in the investigation of the reaction of **1a** with *p*-bromobenzotrifluoride (dioxane, 70°C). It was found that sodium hydride was a suitable base. When *t*-BuOK was used, a side reaction leading to biaryl formation was observed, and the yield of the main product decreased. Weaker bases (K_3PO_4, Cs_2CO_3) turned out to be ineffective. It is necessary to use at least a twofold excess of the base. A number of phosphines (PPh_3, dppf, BINAP, xanphos) have similar effectiveness, therefore, we used the common triphenylphosphine as the ligand. Pd_2dba_3 was used as a palladium source because other sources such as $PdCl_2$, and $[Pd_2(\mu\text{-}Cl)_2(o\text{-dimethylaminomethylphenyl})_2]$ turned out to be less effective.



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1a: Y=CO_2Et **1c**: Y=COPh
1b: Y=SO_2Ph **1d**: Y=NO_2

We performed the reaction of **1b** and **1a** with various aryl, heteroaryl and vinyl halides[6] using the optimized conditions above. The reaction proceeds smoothly with aryl bromides and iodides both with electron-donating and electron-withdrawing substituents and results in high to moderate yields of the monoarylated products.

The reaction with the aryl chloride stopped with incomplete conversion and led to a low yield of the product (Table 1, entry 10). This result was the same even when we used donating and bulky phosphines such as PCy_3 and 2-di-*t*-butylphosphinobiphenyl which are efficient in other reactions of aryl chlorides.[5b] Heterocyclic bromides (Table 1, entries 4, 5 and 13) also undergo this reaction and give monoarylated products in moderate to high yields. A vinylation reaction of **1a** with β-bromostyrene also proceeds under the above mentioned conditions (Table 1, entry 14). To the best of our knowledge, this is the first example of intermolecular vinylation of CH-acids.

Keywords: palladium; sulfones; CH-acids; catalysis; aryl halides; arylation; carbanions.

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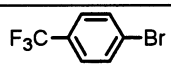
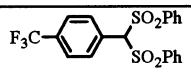
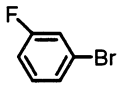
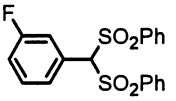
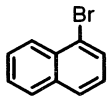
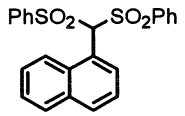
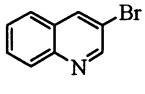
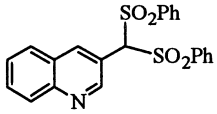
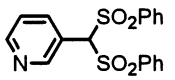
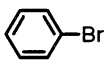
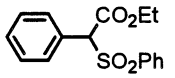
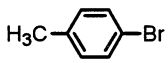
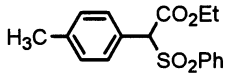
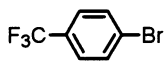
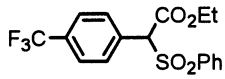
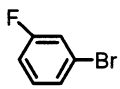
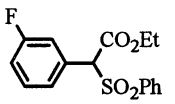
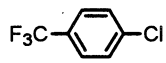
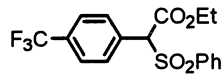
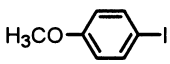
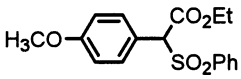
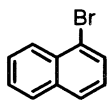
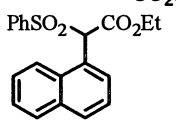
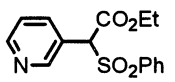
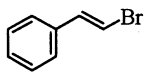
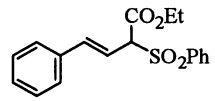
Table 1. Palladium-catalyzed arylation of bis-(phenylsulfonyl)methane and ethylphenylsulfonylacetate[a]

Entry	Aryl halide	Time (h)	Product[b]	Conversion (%) of Ar(Het)X	Yield (%)[c]
1		3		100	85
2		4		100	81
3		6		100	77
4		6		100	76
5		5		97	90
6		9		100	72
7		8		91	74
8		3		100	83
9		4		100	64
10		27		75	25
11		3		100	71
12		12		85	62
13		6		94	51
14		7		100	42[d]

(a) The reactions were carried out with 0.5 mmol of aryl halide, 0.65 mmol of CH-acid, 2 mol % of $Pd_2dba_3 \cdot CHCl_3$ (4 mol % Pd), 12 mol % PPh_3, 1.5 mmol NaH in 4 ml of dioxane at 70°C under positive argon pressure.
(b) Entries 1-5 CH-acid = $(PhSO_2)CH_2$, entries 6-14 CH-acid = $PhSO_2CH_2CO_2Et$.
(c) The yields are of pure isolated compounds, purified by column chromatography on silica gel 40-100 μm. All of the substances were characterized by elemental analysis, and ^1H NMR and IR spectroscopy.
(d) The position and configuration of the double bond in the product did not change.

The reaction was found to be accompanied by a side process resulting in aryl halide reduction to the corresponding arene, reducing the yield of the main product. The competition between these processes depends on the sulfones used:

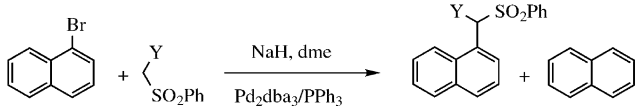
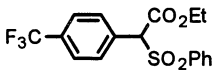
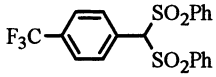
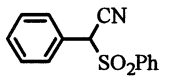
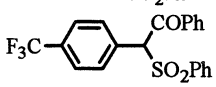
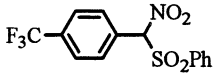
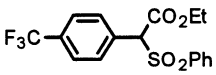


Table 2. Palladium-catalyzed reactions of *p*-bromobenzotrifluoride and α-functionalized phenylmethylsulfones[a]

Entry	CH-acid	pK_a[b]	Product	Time (h)	Conversion of Ar(Het)X (%)	Yield (%)[c]
1	$PhSO_2Me$	29.0	-	5	12	0[d]
2	$PhSO_2CH_2C_6F_5$	-	-	5	13	0
3	$PhSO_2CH_2CO_2Et$	-		3	100	83
4	$PhSO_2CH_2SO_2Ph$	12.2		3	100	85
5	$PhSO_2CH_2CN$	12.0		5	-	82[e]
6	$PhSO_2CH_2COPh$	11.4		4.5	100	30
7	$PhSO_2CH_2NO_2$	7.1		4.5	100	72
8		-	-	8	18	0
9	$PhSO_2CH(Me)CO_2Et$	-	-	8	17	0

(a) The reactions were carried out with 0.5 mmol of aryl halide, 0.65 mmol of CH-acid, 2 mol % of $Pd_2dba_3{\cdot}CHCl_3$ (4 mol % Pd), 12 mol % PPh_3, 1.5 mmol NaH in 4 ml of dimethoxyethane at 70°C under positive argon pressure.
(b) pKa in DMSO.[8]
(c) The yields of isolated compounds, purified by column chromatography on silica gel 40-100 μm. All of the substances were characterized by elemental analysis, and ^1H NMR and IR spectroscopy.
(d) The reaction did not proceed when *n*-BuLi was used as the base.
(e) This reaction with bromobenzene has been reported previously.[2d]

We have also observed the reduction of aryl bromides in the absence of the CH-acids.[7]

In order to clarify the scope of the method we performed the palladium-catalyzed reaction of *p*-bromobenzotrifluoride with a number of α-functionalized phenylmethylsulfones with a wide pK_a range.

The results shown in Table 2 prompted us to consider the following reaction features: Firstly, weak CH-acids being the precursors of highly nucleophilic carbanions are unreactive (Table 2, entries 1 and 2). It is noteworthy that the reaction does not proceed even when *n*-BuLi was used as the base and the CH-acid was completely transformed to the corresponding carbanions; Secondly, the reaction proceeds only in the case of relatively strong CH-acids. The most notable is the arylation of the strong CH-acid **1d** ($pK_a = 7.1$) (Table 2, entry 7), the anion of which is apparently a very weak nucleophile; Thirdly, the reactions proceed as a selective monoarylation of CH-acids. The CH-acids containing a tertiary α-carbon were demonstrated to be inactive in the reaction (Table 2, entries 8 and 9). This is an essential difference from the results reported with the donating bulky phosphines, when both mono- and diarylation of CH-acids were possible.[9]

Thus, in this report we suggest a method of functionalized (arylmethyl)sulfone synthesis based on palladium catalyzed arylation of strongly CH-acidic sulfones. In our opinion, the unusual dependence of the CH-acid reactivity on the pK_a could be related to the mechanism of the reaction which is a subject of our present studies.

Acknowledgements

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3. See for example: (a) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740; (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382–12383; (c) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108–11109.
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6. **Typical procedure for the reaction of aryl or heteroaryl halides and sulfones.** A mixture of ethylphenylsulfonylacetate (148 mg, 0.65 mmol), NaH (1.5 mmol), *p*-bromobenzotrifluoride (112 mg, 0.5 mmol), $Pd_2dba_3{\cdot}CHCl_3$ (10.4 mg, 2 mol%) and PPh_3 (15.8 mg) in dioxane (4 ml), purged with argon, was placed into an argon filled reactor. The reaction mixture was degassed by several freeze–pump–thaw cycles and the reactor was filled with argon. The reaction was carried out with stirring at 70°C under positive argon pressure. After 3 h, GLC showed the absence of the starting *p*-bromobenzotrifluoride. The reaction mixture was cooled to room temperature, mixed with brine, extracted with ether three times (30 ml), and the extract was evaporated. The residue was chromatographed on silica gel 40–100 μm, eluting with light petroleum ether:ethyl acetate mixture (v/v 4:1), to give 153 mg (83%) of ethyl(*p*-trifluoromethylphenyl)phenylsulfonylacetate (mp = 95–96°C). All substances were purified by column chromatography on silica gel 40–100 μm and were characterized by elemental analysis, and ^1H NMR and IR spectroscopy.
7. The reduction of aryl halides by sodium hydride in the absence of palladium complexes has been reported: Nelson, R. B.; Gribble, G. W. *J. Org. Chem.* **1974**, *39*, 1425–1426.
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