Cross-Coupling Reactions

The Tertiary Sulfonamide as a Latent Directed-Metalation Group: Ni^0-Catalyzed Reductive Cleavage and Cross-Coupling Reactions of Aryl Sulfonamides with Grignard Reagents

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In the rich portfolio of transition-metal-catalyzed cross-coupling reactions that have been added to the synthetic chemist's repertoire during the last thirty years,[1] sulfur-based leaving groups of the organometallic coupling partners have been underdeveloped. Thus application of sulfur groups in modern cross-coupling chemistry has been largely neglected in favor of the highly successful and readily available halo,[2] triflate,[3] and, to some extent, *O*-carbamate[4] leaving groups in combination with various aryl metal partners. Exceptionally, Wenkert et al.[5] demonstrated coupling of sulfur derivatives in several oxidation states with RMgX reagents (**1**→**2**), our group[6,7] and Julia and co-workers[8] married the directed *ortho* metalation strategy with the Corriu–Kumada–Tamao reaction to allow access to 1,3-di- and 1,2,3-trisubstituted benzenes, (e.g., **3**→**4**), and Takei and co-workers[9] explored the cross-coupling of vinyl sulfones, and the coupling of aryl sulfonates (**5**→**6**) was recently reported (Scheme 1).[10]

Herein we report that tertiary aryl sulfonamides undergo Ni^0-catalyzed reductive cleavage with β-hydride donors (iPr$_2$Mg or iPrMgCl)[11] under especially mild conditions,

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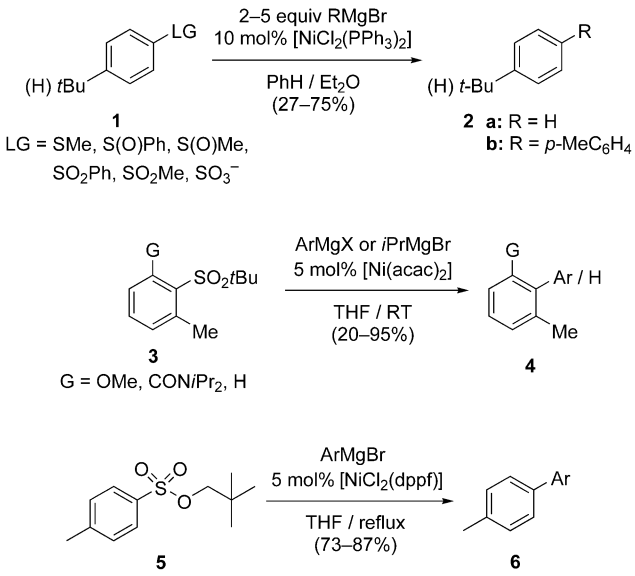


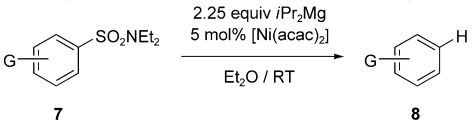
Scheme 1. Application of sulfur leaving groups in modern cross-coupling chemistry. acac = acetylacetonate; dppf = 1,1′-bis(diphenylphosphanyl)ferrocene.

(Tables 1 and 2) and cross-coupling with Grignard reagents (Table 3), thus presenting a new directed *ortho* metalation—connected methodology for the construction of polysubstituted aromatic and biaryl compounds. The hydrodesulfamoylation reaction establishes a latent quality to the powerful sulfonamide directed-metalation group[12] and thereby allows the construction of 1,3-disubstituted aromatic compounds (Table 2), which are unavailable by traditional electrophilic aromatic substitution protocols. The increasing prominence of aryl sulfonamides as commercial entities or lead-drug candidates[13] constitutes an appropriate backdrop in which this new chemistry may find application and extension.

Table 1 summarizes the initial results of the Ni-catalyzed hydrodesulfamoylation reaction of substituted tertiary aryl sulfonamides, **7**→**8**.[14] Several qualitative trends in the screened aryl sulfonamides deserve attention. The reaction is very sensitive to both steric and electronic effects. Large *ortho* substituents (Table 1, entries 7, 11, 14) and *para*-substituted electron-donating groups (Table 1, entries 8, 13) promote lower yields. Groups *ortho* to the sulfonamide that are capable of metal coordination[15] (Table 1, entry 9) appear to enhance the yield significantly, which may also be used to overcome inhibitory effects of electron-donating substituents (compare Table 1, entries 8 and 13 with Table 2, entries 4 and 2, respectively).

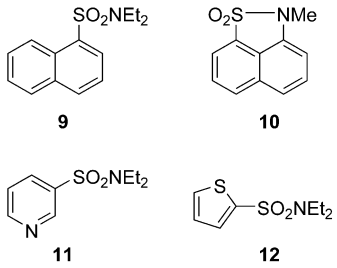
As a further test of scope, cyclic and other aryl and heteroaryl sulfonamides were subjected to the representative hydrodesulfamoylation conditions (Scheme 2). Thus *N*,*N*-diethyl-1-naphthalenesulfonamide (**9**) furnished naphthalene in moderate yield (59%) while the *N*-methyl-1,8-naphthalene sultam (**10**) afforded the reductive SO_2 extrusion product, *N*-methyl-1-naphthylamine in 43% yield.[16] *N*,*N*-Diethylpyridinesulfonamide (**11**) gave pyridine in 29% yield (complete consumption of starting material) while the corresponding 2-thiophenesulfonamide (**12**) was quantitatively recovered.

Table 1: Ni^0-catalyzed reduction of monosubstituted aryl sulfonamides.



Entry	7	G	8	Yield [%][a]
1	**a**	H	**a**	(74)
2	**b**	2-Me	**b**	(74)
3	**c**	3-Me	**b**	(94)
4	**d**	4-Me	**b**	(56)
5	**e**	2-$CONEt_2$	**c**	60(64)
6	**f**	4-$CONEt_2$	**c**	58(67
7	**g**	2-N(Me)Ph	**d**	53
8	**h**	4-N(Me)Ph	**d**	18
9	**i**	2-OMe	**e**	(97)
10	**j**	2-OCH_2Ph	**f**	68
11	**k**	2-O*i*-Pr	**g**	59
12	**l**	3-OMe	**e**	(91)
13	**m**	4-OMe	**e**	(18)
14	**n**	2-TMS	**h**	(48)
15	**o**	4-TMS	**h**	(76)
16	**p**	2-(*p*-MeO-C_6H_4)	**i**	90
17	**q**	4-(*p*-MeO-C_6H_4)	**i**	85

[a] Values in parenthesis indicate yields determined by GC analysis. TMS = trimethylsilyl.

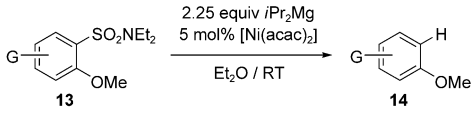


Scheme 2. Heteroaryl sulfonamides and sultams for the hydrodesulfamoylation reaction.

To develop a new combined directed *ortho* metalation–hydrodesulfamoylation route to *meta*-substituted aromatic compounds that overrides the standard electrophilic substitution approach, a selected group of aryl sulfonamides, readily available from inexpensive commercial entities, was tested (**13**→**14**, Table 2). Thus, prototypes of 1,3-dioxygenated (Table 2, entries 2, 8, 9) and 3-aminoanisole (Table 2, entry 4) were obtained in modest to good yields. Additional synthetic advantage is gained by the availability of products that originate from Negishi cross-coupling[17] (Table 2, entry 7) and Buchwald–Hartwig C–N coupling[18] (Table 2, entry 4) regimens.

To take advantage of the mechanistic implications of the above results, the cross-coupling of aryl sulfonamides with Grignard reagents was studied (**7**→**15**, Table 3). Screening of catalysts led to optimization using the $[Ni(acac)_2]$–bidentate phosphane ligand (dppp) combination, although higher temperatures were required to achieve efficient coupling.[19] Electronic effects appear to have little influence on the yields of products (Table 3, entries 3, 7, and 9) while comparison of *ortho* and *para* substituents shows consistently lower yields

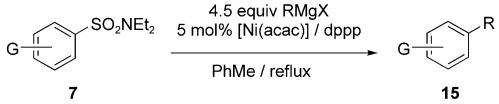
Table 2: Ni^0-catalyzed reduction of di- and trisubstituted aryl sulfonamides.



Entry	13	G	14	Yield [%][a]
1	**a**	4-TMS	**a**	91
2	**b**	4-OMe	**b**	(87)
3	**c**	4-Me	**c**	(80)
4	**d**	4-N(Me)Ph	**d**	77
5	**e**	4-NBn_2	**e**	10
6	**f**	4-Cl	**f**	63
7	**g**	6-(*p*-MeO-C_6H_4)	**g**	89
8	**h**	6-OMe	**h**	(54)
9	**i**	6-OMe, 4-TMS	**i**	53(60)

[a] Values in parenthesis indicate yields determined by GC analysis.

Table 3: Ni^0-catalyzed cross-coupling of aryl sulfonamides.

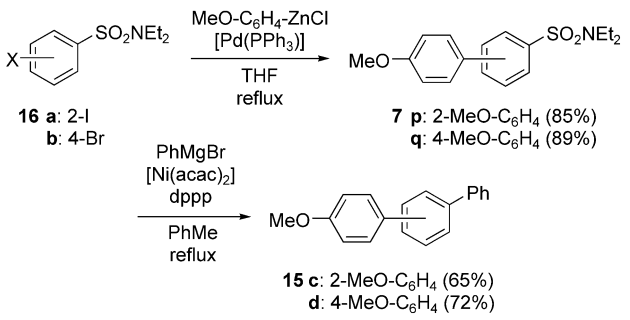


Entry	7	G	R	15	Yield [%][a]
1	**i**	2-OMe	Me	**a**	(60)
2	**i**	2-OMe	Ph	**b**	52
3	**m**	4-OMe	Ph	**i**	79
4	**p**	2-(*p*-MeO-C_6H_4)	Ph	**c**	65
5	**q**	4-(*p*-MeO-C_6H_4)	Ph	**d**	72
6	**b**	2-Me	Ph	**e**	(69)
7	**d**	4-Me	Ph	**f**	(80)
8	**n**	2-TMS	Ph	**g**	(73)
9	**o**	4-TMS	Ph	**h**	(84)

[a] Values in parenthesis indicate yields determined by GC analysis.

for the former with the exception of the OMe group (Table 3, entries 2 vs. 3, 6 vs. 7, 8 vs. 9).

To demonstrate the iterative cross-coupling potential, haloaryl sulfonamides (Scheme 3, **16a**,**b**) were subjected to Negishi cross-coupling to afford biaryl compounds **7p**,**q** which, upon sulfonamide–PhMgBr coupling, furnished teraryls **15c**,**d** in good overall yields. Further regioselective polyaryl construction by taking advantage of the directed



Scheme 3. Iterative Negishi/Kumada cross-coupling of haloaryl sulfonamides to furnish teraryls. dppp = propane-l,3-diylbis(diphenylphosphane).

ortho metalation potential of **7p**,**q** followed by the above modular coupling approach may be envisaged.

The established oxidative addition into the C–S bond[20] for most oxidation states of sulfur, including sulfonates[5,8,9] suggest a similar mechanistic path for the aryl sulfonamide–Grignard desulfamoylation and cross-coupling reactions. Reduction of *N*,*N*-diethyl-2,6-dimethoxy-4-trimethylsilylbenzenesulfonamide (Table 2, entry 9) with [D_7]*i*PrMgBr afforded 1,3-dimethoxy-5-trimethylsilylbenzene (85% [D] by GC–MS, ^{1}H- and ^{2}H NMR) supports the proposed mechanism. These results, in combination with regiospecific cross-coupling of aryl sulfonamides with aryl Grignard reagents (Table 3), suggest that the aryl sulfonamide cross-coupling reaction proceeds predominantly through the catalytic cycle proposed for the Corriu–Kumada–Tamao reaction.[11]

In conclusion, a new Ni^0-catalyzed aryl sulfonamide–Grignard reagent reaction has been developed, which provides reductive desulfamoylation (Et_2O, room temperature) and cross-coupling (toluene/reflux)[21] processes of synthetic interest. The former reaction, paralleling the work of Julia and co-workers[8] on aryl-*tert*-butyl sulfones, allows the powerful sulfonamide directed-metalation group to act in a latent capacity, thus providing a route to aromatic compounds with 1,3-substitution patterns (Table 2) which are in opposition to those available, usually as mixtures, by classical electrophilic aromatic substitution chemistry. The cross-coupling process represents a new variant of the Corriu–Kumada–Tamao protocol but enjoys the advantage of the directed *ortho* metalation connection (Table 3).[22] Although the sensitivity of the reaction to both electronic and steric effects somewhat constrains functional-group flexibility, the enhancing, unprecedented *ortho* coordination group effect bodes well for further synthetic utility.[23]

Experimental Section

Representative Procedure for Desulfamoylation: *i*Pr_2Mg (5.4 mL, 0.65 M in *t*BuOMe, 3.6 mmol) was added to a solution of **7q** (510 mg, 1.6 mmol) and [Ni(acac)$_2$] (20.0 mg, 0.08 mmol) in a mixture of Et_2O (20 mL) and *t*BuOMe (15 mL) at room temperature, and the reaction mixture was stirred for 8 h. The reaction mixture was cooled in an ice bath and quenched with saturated aqueous NH_4Cl solution, partitioned between Et_2O and H_2O, and the organic layer was extracted twice with Et_2O. The combined organic layer was washed twice with saturated aqueous NH_4Cl solution, and then once with H_2O, and once with brine. The solution was dried (Na_2SO_4), and the solvent was removed in vacuo to give **8i**[24] (249 mg, 85%) as a colorless solid after column chromatography (20:1 hexane/EtOAc). M.p. 82–83 °C (hexane); ^{1}H NMR (200 MHz): δ = 7.58–7.22 (m, 6H), 6.97 (d, 2H, J = 8.9 Hz), 3.84 ppm (s, 3H); ^{13}C NMR (50.3 MHz): δ = 159.2, 140.8, 133.8, 128.7, 128.1, 126.7, 126.6, 114.2, 55.3 ppm; LRMS (EI): *m*/*z* (%): 184 [M^+] (100), 169 [M – 15] (60), 141 (61), 115 (37).

Representative Procedure for Cross-Coupling: PhMgBr (1.33 mL, 3.0 M in Et_2O, 4.0 mmol) was added to a solution of **7p** (319 mg, 1.0 mmol), [Ni(acac)$_2$] (13.0 mg, 0.05 mmol), and dppp (13.0 mg, 0.10 mmol) in toluene (10 mL), and the reaction mixture was heated at reflux for 6 h. The reaction mixture was cooled in an ice bath, quenched with saturated aqueous NH_4Cl solution, partitioned between EtOAc and H_2O, and the organic components were extracted twice with EtOAc. The combined organic layer was washed twice with saturated aqueous NH_4Cl solution, once with H_2O, and once with brine. The solution was dried (Na_2SO_4), and the

solvent was removed in vacuo to give **15c**[25] (168 mg, 65%) as a colorless oil after chromatography (50:1 hexane/Et_2O). ^{1}H NMR (200 MHz): $\delta = 7.62$–7.50 (m, 4H), 7.45–7.30 (m, 4H), 7.21 (d, 2H, $J = 8.9$ Hz), 6.90 (d, 2H, $J = 8.9$ Hz), 3.89 ppm (s, 3H); ^{13}C NMR (50.3 MHz): $\delta = 159.0$, 142.4, 141.1, 140.8, 134.6, 131.6, 131.3, 131.2, 130.5, 129.4, 128.5, 128.1, 127.7, 127.4, 127.0, 114.0, 55.7 ppm.

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