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para-Selective Alkylation of Sulfonylarenes by Cooperative Nickel/Aluminum Catalysis

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Supporting Information

ABSTRACT: A method for the *para*-selective alkylation of a variety of arenesulfonamides and aromatic sulfones with 1-alkenes by cooperative nickel/aluminum catalysis has been developed. Taking advantage of the sulfornyl functionality serving as a removable *ortho*-directing group, the reaction can be applied to facile access to 1,3-dialkyl-substitued benzenes.

Sulfonylarenes are key structural motifs in drugs such as Glibenclamide and Celecoxib (Figure 1), in organic

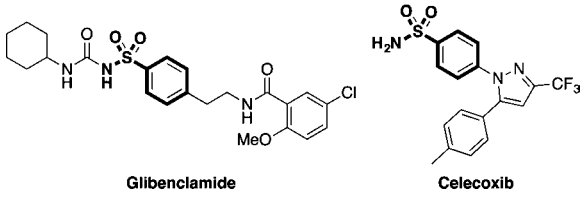
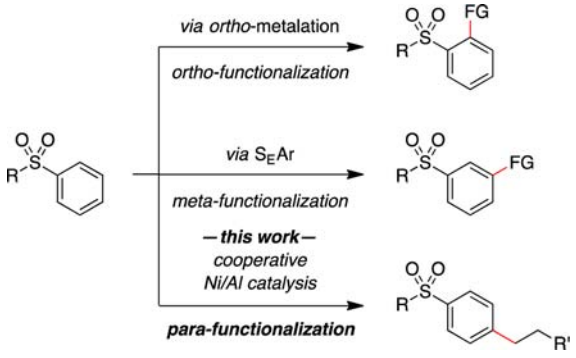


Figure 1. Examples of drugs containing sulfonylarenes.

materials,[1] dyes,[2] and surfactants.[3] In order to effectively synthesize these valuable compounds, regioselective methods for the C−H functionalization of aromatic sulfonyl compounds are required (Scheme 1). The *ortho*-functionalization of

Scheme 1. C−H Functionalization of Sulfonylarenes



sulfonylarenes can be accomplished via stoichiometric[4] and catalytic[5] *ortho*-metalations, while the functionalization of the *meta*-position can be achieved by aromatic electrophilic substitution reactions.[6] Sulfonyl groups on arenes can moreover be transformed into other functional groups or removed by transition metal catalysis.[7,8] In this context, sulfonylarenes play an important role as versatile intermediates in the synthesis of polysubstituted benzenes. Although the *para*-selective functionalization of *ortho*/*para*-oriented arenes,[9] some monosubstituted arenes in combination with bulky rhodium or iridium catalysts,[10] and arenes containing *para*-directing groups[11] has already been reported, the *para*-selective C−H functionalization of aromatic sulfonyl compounds still remains elusive. Herein, we report the first *para*-selective alkylation of benzenesulfonamides and aromatic sulfones using a cooperative catalytic approach based on nickel and aluminum.

We have recently reported the *para*-selective alkylation of aromatic carbonyl compounds by cooperative nickel/aluminum catalysis.[12] In order to achieve high regioselectivity, the combination of a nickel catalyst with a bulky *N*-heterocyclic carbene (NHC) ligand and a bulky aluminum Lewis acid is required. The alkylation reaction is accelerated by the coordination of substrate-bound carbonyl groups to the Lewis acid. These results prompted us to conduct unprecedented *para*-C−H functionalization reactions on aromatic sulfonyl compounds, as these should afford comparable adducts with aluminum and thus furnish activated substrates for subsequent nickel-catalyzed reactions.

Initially, we examined the reaction of a benzenesulfonamide with a 1-alkene under the same conditions as in the previous report (Table 1). Treatment of *N*,*N*-diethylbenzenesulfonamide (**1a**) with 1-octene (**2a**) in the presence of $Ni(cod)_2$ (10 mol %; cod = 1,5-cyclooctadiene), bulky NHC ligand **L** (10 mol %), and $(2,6\text{-}t\text{-}Bu_2\text{-}4\text{-}Me\text{-}C_6H_2O)_2AlMe$ (MAD; 40 mol %) at 150 °C for 18 h afforded a mixture of *para*- (**3aa**) and *meta*-alkylated benzenesulfonamides (**3′aa**) in 39% yield (*para*/*meta* = 94:6). Subsequently, we examined the scope of alkenes: vinylcyclohexane (**2b**), 3,3-dimethyl-1-butene (**2c**), and an alkene bearing a siloxy group (**2d**) proceeded *para*-selectively although 100 mol % MAD were required for the case with **2d**. Vinylsilanes such as 1,1,1,3,5,5,5-heptamethyl-3-vinyltrisiloxane (**2e**) are competent alkene substrates as in the case of the *para*-alkylation of aromatic carbonyl compounds. Unfortunately, cyclic alkenes and 1,1-disubstituted alkenes did not participate in the alkylation reaction (see Supporting Information).

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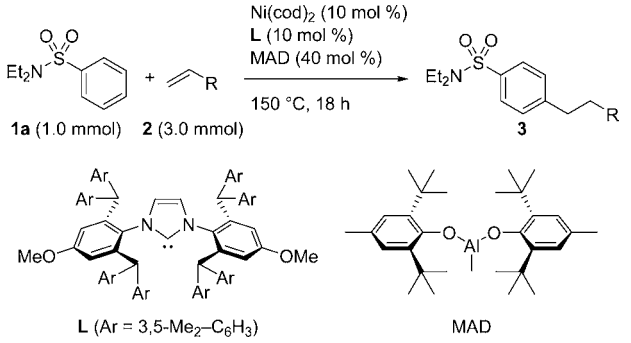
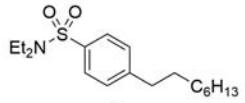
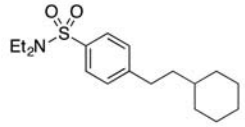
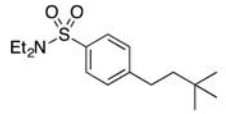
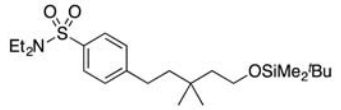
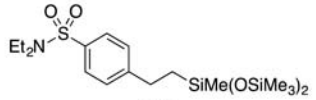
Table 1. Alkylation of *N,N*-Diethylbenzenesulfonamide (1a) with Alkenes by Cooperative Ni/Al Catalysis

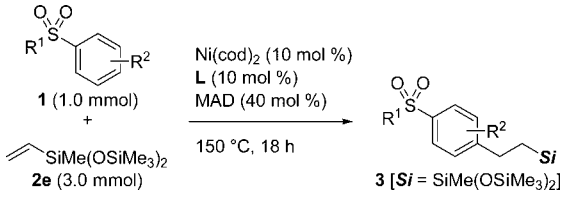


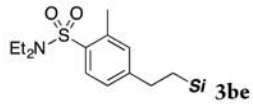
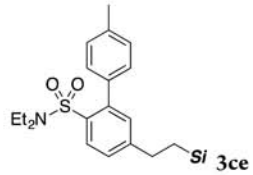
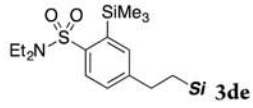
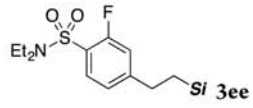
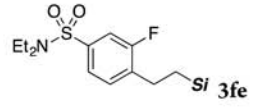
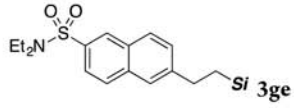
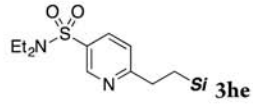
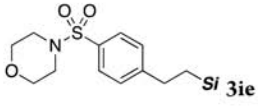
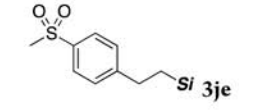
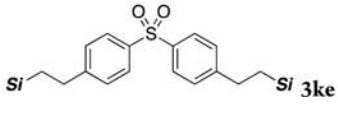
entry	3	yield (%)	3/others[a]
1[b]	 **3aa**	39	94:6
2[b]	 **3ab**	42	93:7
3[c]	 **3ac**	66	96:4
4[d]	 **3ad**	83	97:3
5	 **3ae**	77	96:4

[a]Determined by GC. [b]5.0 mmol of **2** was used. [c]Reaction run in toluene (1.0 mL) at 120 °C. [d]100 mol % of MAD was used.

We then investigated the scope of aromatic sulfonyl compounds using **2e** as a coupling partner (Table 2). The corresponding alkylated products were obtained in excellent selectivity for the 2-methyl- and 2-(*para*-tolyl)benzenesulfonamides **1b** and **1c**, respectively (entry 2). A fluoro substituent did not affect the alkylation irrespective of its position (entries 3 and 4), while a bulky trimethylsilyl group at the *ortho*-position was detrimental to both the yield and regioselectivity (entry 5), most likely on account of the steric repulsion between the trimethylsilyl group and the nickel catalyst. Conversely, no alkylation was observed for 3-(*p*-tolyl)-*N,N*-diethylbenzenesulfoamide (see Supporting Information for further details about unsuccessful examples). Interestingly, selectivity toward C6 was observed for the alkylation of 2-naphthalene sulfonamide (**1g**; entry 6). Although we have already reported the C4-selective alkylation of nonsubstituted

Table 2. Alkylation of Sulfonylarenes with 2e by Cooperative Ni/Al Catalysis



entry	3	yield (%)	3/others[a]
1	 **3be**	78	99:1
2[b]	 **3ce**	67	>99:1
3	 **3de**	23[c]	73:27
4[b]	 **3ee**	40	98:2
5[d]	 **3fe**	68	>99:1
6	 **3ge**	67	74:26
7	 **3he**	41	98:2
8	 **3ie**	45	96:4
9	 **3je**	67	96:4
10	 **3ke**	79	93:7

[a]Determined by GC. [b]20 mol % of $Ni(cod)_2$ and **L** were used. [c]**1d** was recovered by column chromatography in 50% yield. [d]Reaction run in toluene (1.0 mL) at 120 °C for 2.5 h.

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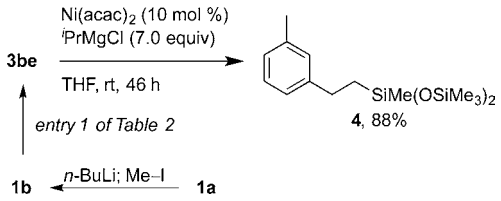
pyridine under similar conditions,[13] 3-pyridinesulfonamide (**1h**) afforded the corresponding C6-alkylated pyridine (**3he**; entry 7). In addition, morpholino(phenyl)methanone (**1i**) furnished the corresponding alkylated product in good selectivity (entry 8). This catalytic system also exhibited similar reactivity for the alkylation of aromatic sulfones. For example, methyl phenyl sulfone (**1j**) afforded the respective *para*-alkylated sulfone in good yield (entry 9). For diphenyl sulfone (**1k**), a dialkylation was observed to generate 4,4′-dialkyldiphenylsulfone (**3ke**; entry 10). Unfortunately, methyl phenyl sulfoxide did not afford any alkylation products.

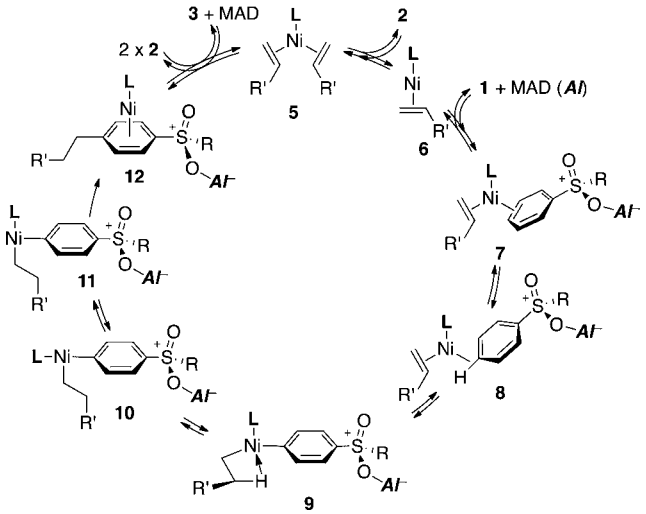
The aminosulfonyl group of **3be** could be removed by a known nickel-catalyzed method[8] to afford the corresponding 1,3-disubstituted benzene **4** in good yield (Scheme 2). As **1b** could be obtained *via ortho*-lithiation[8] followed by methylation with iodomethane, the overall process represents an example of the synthesis of 1,3-disubsituted benzenes through the combination of the newly developed *para*-alkylation reaction demonstrated herein with known transformations of arenesulfonamides.

Scheme 2. Synthesis of 1,3-Disubstituted Benzenes



A plausible reaction mechanism for the transformation is outlined in Scheme 3 based on that for the *para*-alkylation of benzamides supported by DFT studies.[12] Bis(alkene)nickel(0) complex **5** undergoes ligand exchange with a sulfonylarene/MAD adduct to form σ-complex **8** through alkene-ligated nickel(0) **6** and π-complex **7**. The C−H bond is cleaved, and alkyl(aryl)nickel(II) complex **9** is formed through concerted ligand-to-ligand hydrogen transfer.[14,15] A geometrical isomerization generates T-shaped nickel(II) complex **11** via its isomer **10** before reductive elimination forging the C−C bond. The aluminum catalyst would play key roles in both acceleration and regiocontrol of the C−H activation step as in the case of benzamides.

Scheme 3. A Plausible Mechanism for the *para*-Selective Alkylation of Sulfonylarenes



In summary, we have developed a method for the *para*-selective alkylation of benzenesulfonamides and aromatic sulfones based on cooperative nickel/aluminum catalysis. Combined with conventional methods, the controlled functionalization of selected C−H bonds in benzenesulfonamides is now possible.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03741.

Experimental procedures and characterization data of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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