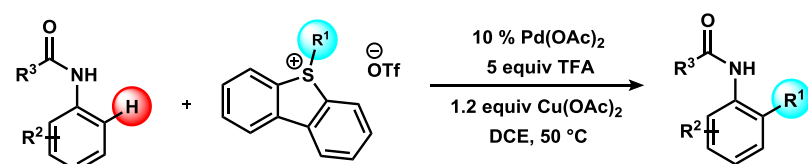


# Sulfonium Salts as Alkylating agents for Palladium Catalyzed Direct Alkylation of Anilides and Aromatic Ureas

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Supporting Information Placeholder



**ABSTRACT:** A novel method for the *ortho* alkylation of acetanilide and aromatic urea derivatives via C-H activation was developed. Alkyl dibenzothiophenium salts are considered to be new reagents for the palladium catalyzed C-H activation reaction, which enables the transfer of methyl and other alkyl groups from the sulfonium salt to the aniline derivatives under mild catalytic conditions.

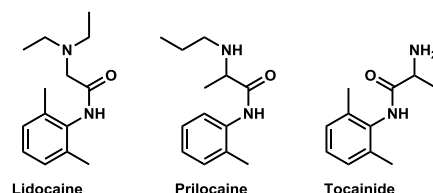
C-C bond forming reactions via aromatic C-H bond activation processes have been intensively studied during recent decades.<sup>1</sup> Although, several methods are described to evaluate C(sp<sup>2</sup>)-C(sp<sup>2</sup>) couplings on aromatic substrates, C-H activation based direct alkylations by alkyl group transfer are less explored in the field<sup>2</sup>. However, the presence of alkyl groups, especially, the ubiquitous methyl group in molecular scaffolds could have beneficial effects on biological properties.<sup>3</sup> For this reason, the expansion of available alkylation methodologies is an important task for organic syntheses with special regard to late stage functionalization approaches.

Amide functional groups are excellent moieties in guided C-H activation to functionalize aromatic C-H bonds. Taking advantage of the beneficial properties of this directing group, palladium catalyzed *ortho* functionalization of acetanilide derivatives under mild reaction conditions have been widely studied.<sup>4</sup> Supported by the use of aryl-boronic acids<sup>5b,c</sup> and -iodides<sup>5d,e</sup>, these methods enable the introduction of aryl groups into substrates. Alkenylation reactions have been studied in detail and developed by Leeuwen, Youn, Hii among other research groups.<sup>6</sup> Although, one of the earliest examples of C-H activation reactions described the direct alkylation of anilides using stoichiometric palladium,<sup>7</sup> the introduction of alkyl groups under catalytic conditions has remained a challenging task, especially under mild reaction conditions.<sup>8</sup> Existing alkylation methods often suffer from the loss of selectivity or byproduct formation, as chain isomerization in Friedel-Crafts or  $\beta$ -H-elimination in transi-

tion metal catalyzed coupling reactions. Additionally, to the best of our knowledge there is only one existing method for the *ortho* alkylation of aromatic ureas through direct C-H bond functionalization, considering both traditional and transition metal catalyzed methods.<sup>9</sup>

Aside from the utilization of acetanilides in academic research as suitable substrates for transition metal catalyzed C-H bond functionalizations, the aniline derivatives bearing a methyl group in the *ortho* position, such as Lidocaine, Prilocaine and Tocainide, have significant biological activities and medicinal applications as local anesthetics.

## Scheme 1. Biologically active *ortho*-methyl anilid derivatives

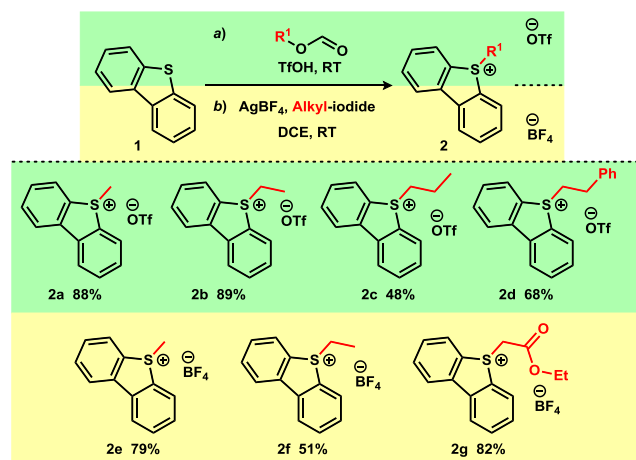


Electrophilic reagents, such as iodonium salts, are efficient coupling partners in C-H activation reactions.<sup>10</sup> We previously have demonstrated that a novel fluoroalkyl iodonium salt is an excellent alkyl source for C-H bond functionalization to alkylate indoles<sup>11</sup> and aniline derivatives.<sup>9, 12</sup> In our research program we focused to the expansion of the alkylations via C-H activation, which can be performed under mild conditions. To achieve this, we intended to use electrophilic alkyl sources, which could

have high reactivity for mild functionalizations. Unfortunately, alkyl-iodonium salts are not stable enough to this purpose, therefore the design of novel alternative reagents was necessary. Considering the properties of onium salts, alkylsulfonium salts could provide an alternative solution. However, only trifluoromethylations have been developed yet with these type of onium reagents by Yu<sup>13</sup> and Shi<sup>14</sup> using Umemoto's reagent<sup>15</sup> for the *ortho* functionalization of aromatic amide and phenylpyridine derivatives.

For the synthesis of the sulfonium salts, we used two approaches (Scheme 2). The alkylation of dibenzothio-*phene* can be performed with formate-esters in strong acidic media<sup>16</sup> or with alkyl iodide in the presence of silver tetrafluoroborate.<sup>17</sup> Weakly coordinating anions are important in C-H activation therefore we prepared the salts with BF<sub>4</sub><sup>-</sup> and triflate counterions. In comparison, the acid induced method, using esters, is cheaper and seemed to be more robust, hence we used it for gram scale preparation of the salts (2 to 50 mmol scales).

**Scheme 2. Synthesis of alkylsulfonium salts with formate esters or silver tetrafluoroborate**



Reaction conditions: a) 1 equiv of **1**, 2 equiv of formate ester, 6 equiv of triflic acid. b) 1 equiv of **1**, 1 equiv of AgBF<sub>4</sub>, 3-6 equiv of alkyl iodide in dichloroethane. Isolated yields.

Parallel to the synthesis of alkylsulfonium salts we optimized the reaction parameters necessary for the efficient *ortho* methylation of anilides. On the basis of our earlier studies on the C-H activation of anilide derivatives we chose palladium acetate as catalyst and trifluoroacetic acid as additive for the initial studies. First, we compared the conversions of the reaction of 3'-methylacetanilide and *S*-methyl-dibenzothiophenium triflate in different solvents. We found that in polar solvents the reaction did not work, but less polar, non-protic solvents such as toluene, DCM, DCE were suitable for the transformation (Table 1, entries 1-7). Regarding the catalyst loading, the conversion of the reaction changed proportionally to the amount of palladium (entries 8-9). Additionally, the presence of 5 equiv acid was found to be necessary for the complete suppression of the formation of *N*-alkylated byproduct. As a further development of the coupling we probed the effect of copper acetate because of its general use as an additive for palladium catalyzed C-H activa-

tion.<sup>18</sup> To our delight, a significant increase of the conversion was observed (98%, Table 1, Entry 10).<sup>19</sup>

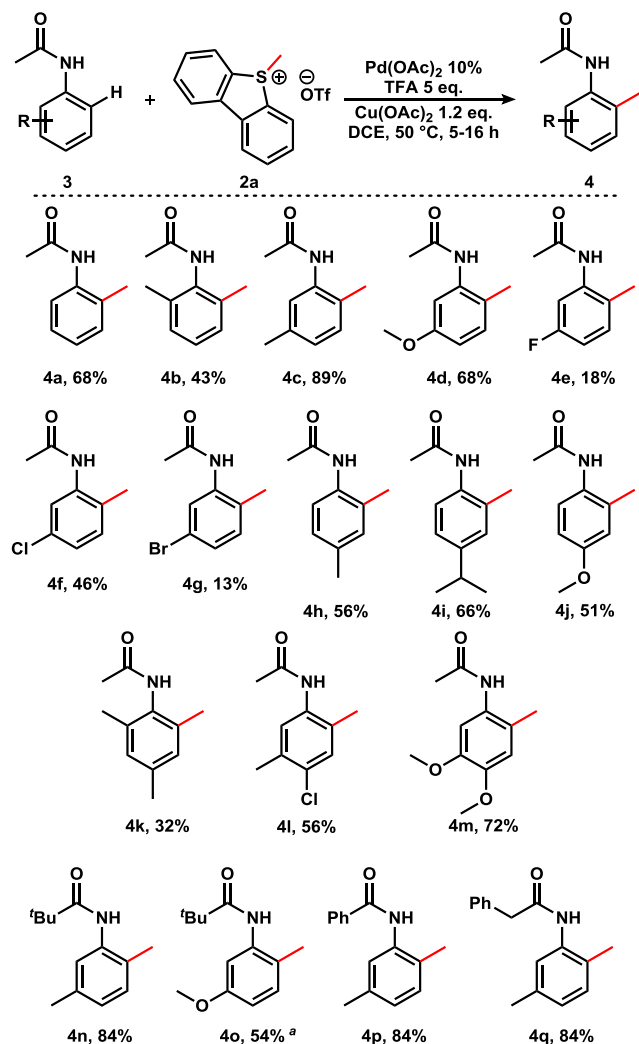
**Table 1. Optimization studies<sup>a</sup>**

Entry	Pd(OAc) <sub>2</sub> mol %	solvent	GC-yield %
1	7.5	MeOH	0%
2	7.5	MeCN	0%
3	7.5	acetone	0%
4	7.5	EtOAc	53%
5	7.5	toluene	79%
6	7.5	DCM	76%
7	7.5	DCE	81%
8	5	DCE	70%
9	10	DCE	86%
10	7.5	DCE	98% <sup>b</sup>

<sup>a</sup> Reaction conditions: 1 eq. of **3** (0.05 mmol), 1.2 equiv of **2**, Pd(OAc)<sub>2</sub> 5-10 mol%, TFA 5 equiv, solvent 0.5 mL. Yields determined by GC analysis. <sup>b</sup> 1.2 equiv of Cu(OAc)<sub>2</sub> was used as additive

Under the optimized reaction conditions, we explored the substrate scope of the alkylation. First, acetanilide derivatives were methylated with *S*-methyl-dibenzothiophenium salt. The simple 2'-methylacetanilide (**4a**) was isolated in 68% yield. Substituents at the *ortho*, *meta* and *para* positions are tolerated and the appropriate products **4b-4j** were isolated in 13-89 % yield range. Although the methylation took place more efficiently in the presence of electron donating functional groups, the F and Br substituted aromatic products (**4e** and **4g**) were obtained only in poor yields. Similarly to the monosubstituted substrates, electron rich anilines equipped with two substituents on the aryl ring were *ortho* methylated and products **4k-m** were prepared in 32-72 % yield. As a general reactivity pattern, electron rich rings favor the coupling, but the presence of electron donating groups in *para* position to the amide directing group can lead the formation of dimethylated side-products. Therefore, these reactions gave moderate yields of products **4h-j** after separation and purification. As a limitation, the presence of electron withdrawing groups (acetyl, nitro) on the aromatic ring did not allow for functionalization. Polar functional groups (amine, free OH) on the acetyl directing moiety were not tolerated as well (not shown). At the same time, sterically hindered anilides can be transformed easily. Bulky groups on the directing amide group had no deleterious effect on the methylation and products **4n-q** were isolated in good 75-84% yield.

### Scheme 3. Methylation of acetanilide derivatives



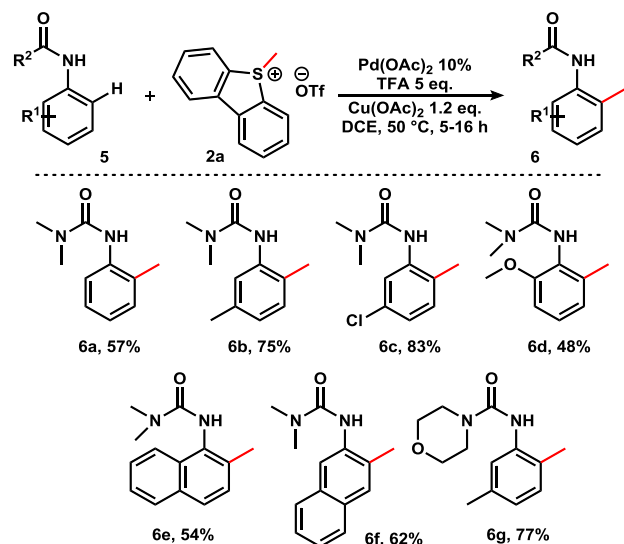
Reaction conditions: 1 equiv of **3** (1 mmol), 1.2 equiv of **2**, Pd(OAc)<sub>2</sub> 10 mol%, TFA 5 eq., Cu(OAc)<sub>2</sub>·H<sub>2</sub>O 1.2 equiv, in 10 mL DCE at 50 °C. Isolated yields. <sup>a</sup>: conversion, based on NMR measurement; product was isolated as a mixture of the SM and **4o** (ratio SM:**4o** is 46:54).

Beside anilide derivatives we aimed to explore the *ortho* methylation of aromatic ureas for the first time. We found that *N,N*-dimethylamino and morpholino urea functions behave as excellent directing groups for the palladium catalyzed C-H activation.

The alkylations with the methylbenzothienophenium salt took place with similar efficiency to the anilides (Scheme 4) under optimized catalytic conditions. Substituted phenyl ureas and naphthylureas were successfully methylated in the *ortho* position leading to products **6a-g**, which were isolated in 48-83% yield.

Finally, we studied the extension of the alkylation method beyond methyl group transfer. Reactions were carried out under the optimized conditions with the previously prepared *S*-alkyl sulfonium salts. We found that the *ortho* alkylation of anilides and aromatic ureas can be achieved under mild reaction conditions (Scheme 5).

### Scheme 4. Methylation of aromatic ureas

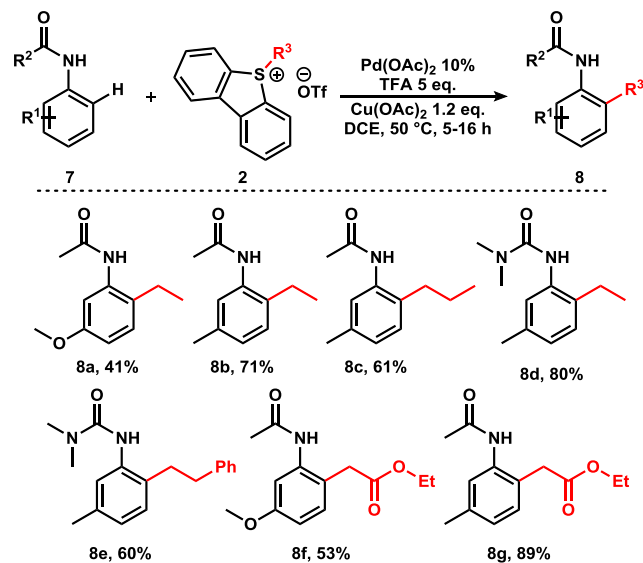


Reaction conditions: 1 equiv of **3** (1 mmol), 1.2 equiv of **2**, Pd(OAc)<sub>2</sub> 10 mol%, TFA 5 equiv, Cu(OAc)<sub>2</sub>·H<sub>2</sub>O 1.2 equiv, in 10 mL DCE at 50 °C. Isolated yields.

Ethyl, propyl, phenethyl and carboxymethylene groups were introduced into *ortho* position to the directing group. 2'-Alkylacetanilides **8a-c,f,g** were isolated in 41-89% yield, while 2'-alkylurea derivatives **8d,e** were obtained in 60-80% respectively.

To increase the efficiency of the procedure, dibenzothiophene, the precursor of the alkylating agents, was recovered by isolation from the reaction mixture of **4c**, **k**, **6a**, **d**, and dibenzothiophene was recovered in a range of 70-99% efficiency.

### Scheme 5. Different alkyl groups



Reaction conditions: 1 equiv of **3** (1 mmol), 1.2 equiv of **2**, Pd(OAc)<sub>2</sub> 10 mol%, TFA 5 equiv, Cu(OAc)<sub>2</sub>·H<sub>2</sub>O 1.2 equiv, in 10 mL DCE at 50 °C. Isolated yields.

In summary, we have developed a new and efficient catalytic method for the direct alkylation of aromatic

amide and urea derivatives with the utilization of palladium catalyzed C-H activation under mild reaction condition. We demonstrated that *S*-alkyl-dibenzothiophenium salts are suitable alkylating reagents for the C-H activation. Additionally, with the aid of this reagent the alkylation of aromatic ureas can be achieved for the first time. The prepared sulfonium salts are considered to be new reagents in such transformations and hence hopefully their applicability could open new reaction paths in the field of transition metal catalyzed C-H activation.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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### Notes

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