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Effective Recognition of Different Types of Amino Groups: From Aminobenzenesulfonamides to Amino-(*N*-alkyl)benzenesulfonamides via Iridium-Catalyzed *N*-Alkylation with Alcohols

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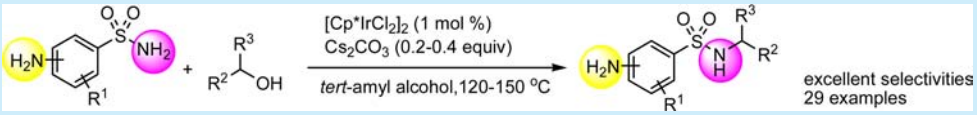
Supporting Information



ABSTRACT: A simple, highly efficient, and general strategy for the direct synthesis of amino-(*N*-alkyl)benzenesulfonamides has been accomplished via direct *N*-alkylation of aminobenzenesulfonamides bearing both different types of amino groups with alcohols as alkylating agents. Notably, this research exhibited the potential for the recognition of different types of amino groups in the *N*-alkylation of complex molecules with alcohols, facilitating the progress of the transition-metal-catalyzed "hydrogen autotransfer (or hydrogen-borrowing) process."

The *N*-alkylation of amines constitutes one of the most important C−N bond-forming reactions in organic synthesis. In recent years, much attention has been paid to the *N*-alkylation of amines with alcohols instead of alkyl halides as alkylating agents based on the "hydrogen autotransfer (or hydrogen-borrowing) process",[1] using ruthenium,[2] iridium,[3] or other transition metal catalysts.[4] In this process, alcohols are first dehydrogenated to form aldehydes, followed by the condensation between amines and the resulting aldehydes to afford imine intermediates, which are hydrogenated by metal hydride species generated in the dehydrogenative step of alcohols to produce *N*-alkylated amines. Such methodology is attractive due to the formation of water as the only byproduct. Despite these advances, most studies focus on the use of relatively simple reactants bearing a single amino group such as nucleophiles. From a synthetic point of view, effective recognition of different types of amino groups is crucial for the *N*-alkylation of complex molecules with alcohols, and it is apparently an extremely challenging subject.

Recently, we have reported a series of catalytic transformations with the activation of alcohols as electrophiles.[5] As part of our continuing interest in this field, we herein wish to demonstrate the *N*-alkylation of aminobenzenesulfonamides, which bear an amino group and a sulfamido group, with alcohols as alkylating agents, to amino-(*N*-alkyl)benzenesulfonamides based on the effective recognition of different types of amino groups. It should be pointed out that amino-(*N*-alkyl)benzenesulfonamides are important structural motifs in many natural products and other biologically active molecules and were also utilized as key synthetic intermediates.[6] Traditional methods for the synthesis of amino-(*N*-alkyl)-benzenesulfonamides suffer from including multistep reactions, the use of hazardous reagents, and the generation of a large amount of harmful byproducts.[6]

Our investigations began with the *N*-alkylation of *p*-aminobenzenesulfonamide (**1a**) with benzyl alcohol (**2a**) using commercially available $[Cp^*IrCl_2]_2$ (Cp* = pentamethylcyclopentadienyl) as a catalyst. Fujita, Yamaguchi and coworkers have demonstrated that such a complex is a highly efficient catalyst for the individual *N*-alkylation of amines[3a−c] and sulfonamides[3g,7] with alcohols to the corresponding *N*-alkylated products. The reaction of **1a** with **2a** proceeds in *tert*-amyl alcohol (1 mL) in the presence of $[Cp^*IrCl_2]_2$ (1 mol %) at 120 °C for 12 h, and none of the product was found (Table 1, entry 1). To our delight, when Na_2CO_3 (0.2 equiv) was used as an additive, the product **3aa** could be obtained, albeit in 10% yield (Table 1, entry 2). It was found that K_2CO_3 and Cs_2CO_3 have a more obvious effect on this reaction and the desired product **3aa** was obtained in 81% and 88% yields, respectively (Table 1, entries 3−4). A similar result was found when K_3PO_4 was added (Table 1, entry 5). Then, Cs_2CO_3 was chosen as the base for further research. Other transition metal catalysts, including $[Ir(cod)Cl]_2$ (cod = 1,5-cyclooctadienyl), $[Cp^*RhCl_2]_2$, and $[Ru(p\text{-cymene})Cl_2]_2$, were also examined, and the product **3aa** was isolated in ≤45% yields (Table 1, entries 6−8). Attempts to decrease the reaction temperature and reduce the amount of Cs_2CO_3 resulted in relatively low yields (Table 1, entries 9−10).

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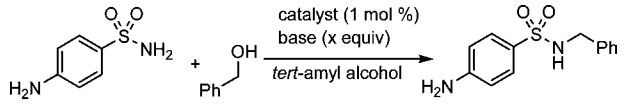
Table 1. *N*-Alkylation of *p*-Aminobenzenesulfonamide (1a) with Benzyl Alcohol (2a) under Various Conditions[a]



1a 2a 3aa

entry	catalyst	base	*x*	*T* (°C)	yield[b] (%)
1	$[Cp^*IrCl_2]_2$	–	0.2	120	0
2	$[Cp^*IrCl_2]_2$	Na_2CO_3	0.2	120	10
3	$[Cp^*IrCl_2]_2$	K_2CO_3	0.2	120	81
4	**$[Cp^*IrCl_2]_2$**	**Cs_2CO_3**	**0.2**	**120**	**88**
5	$[Cp^*IrCl_2]_2$	K_3PO_4	0.2	120	85
6	$[Ir(cod)Cl]_2$	Cs_2CO_3	0.2	120	<5
7	$[Cp^*RhCl_2]_2$	Cs_2CO_3	0.2	120	26
8	$[Ru(p\text{-cymene})Cl_2]_2$	Cs_2CO_3	0.2	120	45
9	$[Cp^*IrCl_2]_2$	Cs_2CO_3	0.1	120	77
10	$[Cp^*IrCl_2]_2$	Cs_2CO_3	0.2	110	79

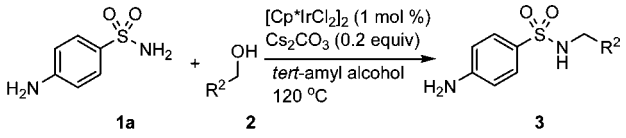
[a]Reactions conditions: **1a** (1 mmol), **2a** (1.2 mmol), catalyst (1 mol %), base (*x* equiv), *tert*-amyl alcohol (1 mL), 12 h. [b]Isolated yield.

With the optimal reaction conditions in hand (Table 1, entry 4), the *N*-alkylation of **1a** with a variety of benzylic alcohols **2** was evaluated and these results are summarized in Scheme 1. Reactions with benzylic alcohols bearing an electron-donating substituent, such as the methyl, isopropyl, and methoxy group, gave the desired products **3ab**–**3ae** in 80–86% yields. When benzylic alcohols bearing one or two halide atoms, such as chlorine, dichlorine, and bromine, were used as alkylating agents, the corresponding products **3af**–**3aj** were isolated in 83–92% yields. This catalytic system was also applied to benzylic alcohols bearing a strong electron-withdrawing substituent, such as the trifluoromethyl and trifluoromethoxy group, affording the desired product **3ak** and **3al** in 85% and 90% yields, respectively. Furthermore, transformations of 1-naphthalenemethanol, 2-thiophenemethanol, and ferrocenemethanol proceeded smoothly, and the corresponding products **3am**–**3ao** were obtained in 74–87% yields.

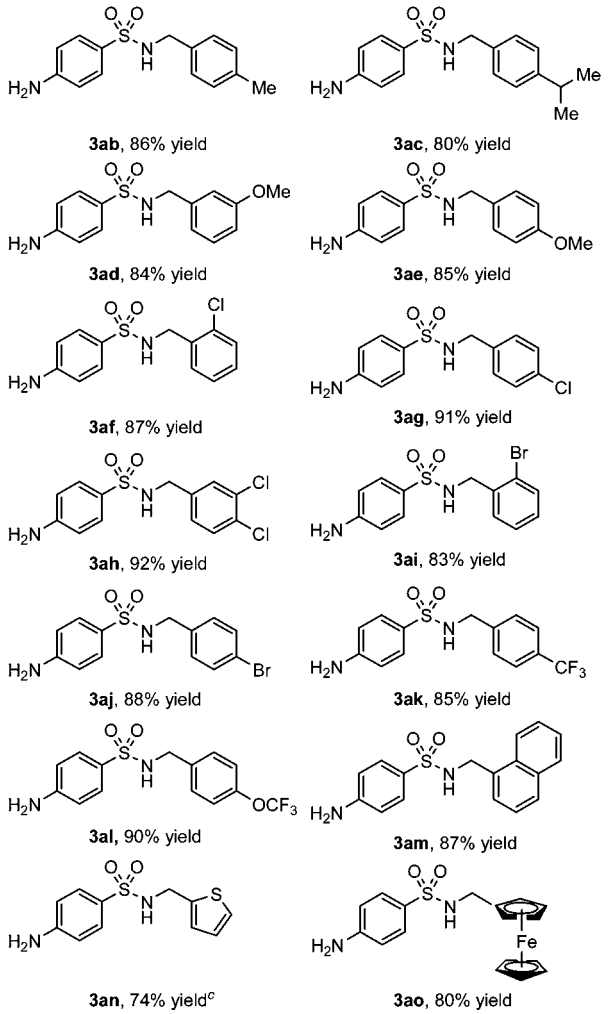
As shown in Scheme 2, reactions of **1a** with a series of aliphatic alcohols were then examined. When linear alcohols, such as 1-butanol, 1-hexanol, and 1-octanol, were used as reagents, the corresponding products **3ap**–**3ar** were obtained in 78–84% yields. Transformations of branched-chain alcohols, such as 3-methylbutan-1-ol, 2-ethylhexan-1-ol, and cyclohexylmethanol, afforded the desired products **3as**–**3au** in 80–85% yields. For secondary alcohols with high steric hindrance, such as cyclopentanol and cyclohexanol, the corresponding products **3av** and **3aw** could be successfully obtained in 50% and 56% yields, respectively, although an elevated reaction temperature (150 °C) and prolonged reaction time (24 h) were required.

To further expand the scope of the reaction, the *N*-alkylation of a range of aminobenzenesulfonamides **1** with **2a** was investigated (Scheme 3). Reactions of *p*-aminobenzenesulfonamides bearing one or two substituents, such as bromine, dibromine, and dichlorine, gave the desired products **3ba**–**3da** in 82%–86% yields. Transformations of *m*-aminobenzenesulfonamide and *m*-aminobenznenesulfonamide bearing a substituent afforded the corresponding products **3ea** and **3fa** in 83% and 79% yields, respectively. In the case of *o*-aminobenzenesulfonamide, the desired product **3ga** was also obtained in 76% yield.

Scheme 1. *N*-Alkylation of *p*-Aminobenzenesulfonamide (1a) with a Variety of Benzylic Alcohols (2)[a,b]



1a 2 3



[a]Reactions conditions: **1a** (1 mmol), **2** (1.2 mmol), $[Cp^*IrCl_2]_2$ (1 mol %), Cs_2CO_3 (0.2 equiv), *tert*-amyl alcohol (1 mL), 120 °C, 12 h. [b]Isolated yield. [c]Cs_2CO_3 (0.4 equiv).

As a representative example, the structure of product **3ag** was confirmed by single-crystal X-ray crystallography (see Figure 1 in Supporting Information). It is noteworthy that in all cases, apart from the desired amino-(*N*-alkyl)benzenesulfonamides, only a trace of isomer *N*-alkylaminobenzenesulfonamides was detected. In addition, the minor *N*-alkylamino-(*N*-alkyl)-benzenesulfonamides as byproducts (<5% yield) were observed in some cases.

A possible mechanism was proposed for iridium-catalyzed *N*-alkylation of aminobenzenesulfonamides with alcohols (Scheme 4). The initial step involves the formation of an alkoxo iridium species **A** by the reaction of $[Cp^*IrCl_2]_2$ with alcohols under the acceleration of a base. Accompanied by the *β*-hydrogen elimination of an alkoxo iridium species **A**, an iridium hydride species coordinated with an aldehyde or ketone **B** was generated.[8] Similar to the oxygen atom on the carbonyl group, one of the oxygen atoms on the sulfoamino group could

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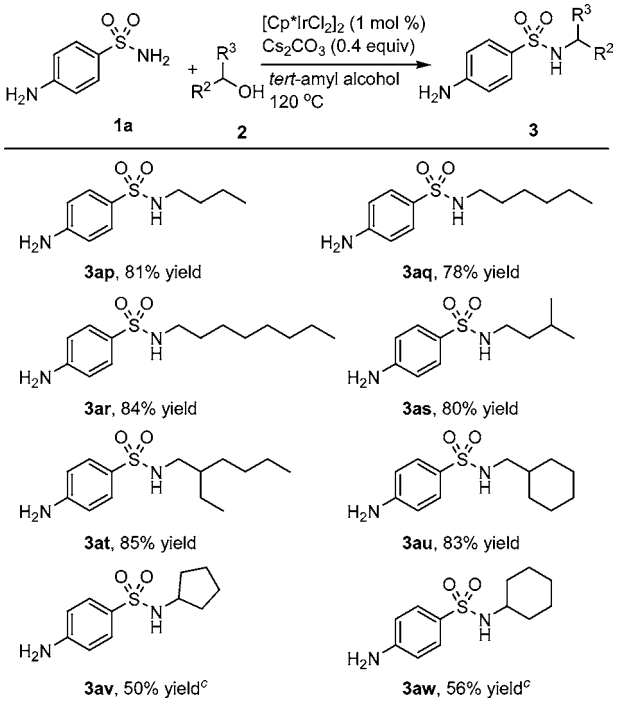
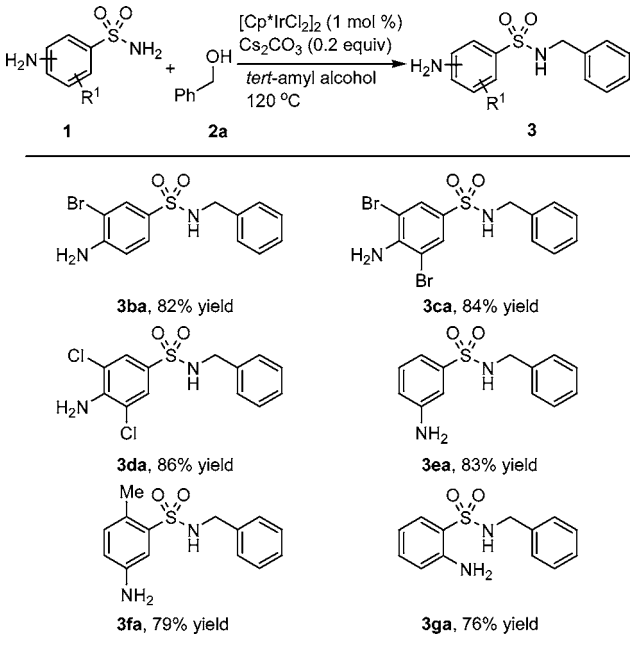
Scheme 2. *N*-Alkylation of *p*-Aminobenzenesulfonamide (1a) with a Series of Aliphatic Alcohols (2)[a,b]



[a]Reactions conditions: **1a** (1 mmol), **2** (2 mmol), $[Cp^*IrCl_2]_2$ (1 mol %), Cs_2CO_3 (0.4 equiv), *tert*-amyl alcohol (1 mL), 120 °C, 12 h. [b]Isolated yield. [c]150 °C, 24 h.

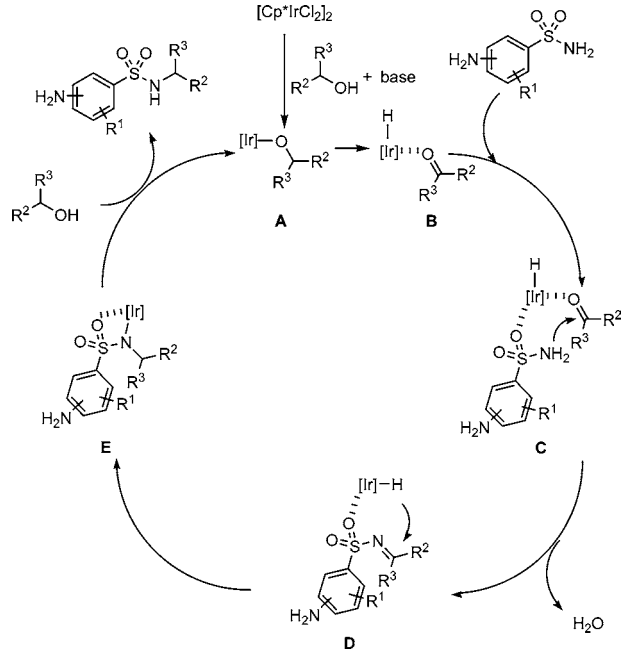
Scheme 3. *N*-Alkylation of Aminobenzenesulfonamides (1) with Benzyl Alcohol (2a)[a,b]



[a]Reactions conditions: **1** (1 mmol), **2a** (1.2 mmol), $[Cp^*IrCl_2]_2$ (1 mol %), Cs_2CO_3 (0.2 equiv), *tert*-amyl alcohol (1 mL), 120 °C, 12 h. [b]Isolated yield.

also be coordinated to the iridium atom and thus a species **C** was formed. The condensation between the resulting aldehyde or ketone and the sulfonamide group rather than the amino group of aminobenzenesulfonamide occurred more easily due

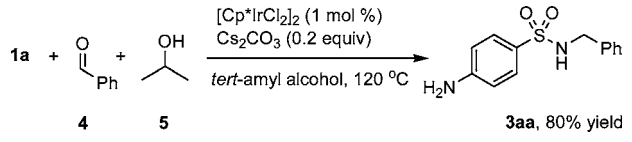
Scheme 4. Proposed Reaction Mechanism



to the spatial distance, and thus the species **D** was generated. Then, the addition of iridium hydride into the C=N bond of sulfonimine afforded the amido-iridium species **E**. Finally, the catalytically active alkoxo iridium species **A** was regenerated and the amino-(*N*-alkyl)benzenesulfonamide was released via the amido−alkoxo exhange reaction between **E** and alcohol.[9] On the basis of previous reports,[10] dinuclear iridium complexes are speculated to be catalytically important species.

Furthermore, the reaction of aminobenzenesulfonamide (**1a**) and benzylaldehyde (**4**) in the presence of 2-propanol (**5**) as a hydrogen source under catalytic conditions was investigated. As outlined in Scheme 5, the reaction was carried out in the

Scheme 5. Reaction of *p*-Aminobenzenesulfonamide (1a), Benzylaldehyde (4), and 2-Propanol (5)



presence of $[Cp^*IrCl_2]_2/Cs_2CO_3$ at 120 °C for 12 h to give the product **3aa** in 80% yield. Apparently, accompanied by the dehydrogenation of 2-propanol, iridium hydride species could be generated. In the presence of the resulting iridium hydride species, the condensation between **1a** and **4** afforded the unsaturated sulfonamide (this corresponds to **D** in Scheme 4), which underwent the transfer hydrogenation from iridium hydride to give the desired product **3aa**. This experiment strongly supported the proposed mechanism shown in Scheme 4.

To demonstrate the practicality of this strategy, the direct synthesis of a biologically active molecule C-7280948 (the histone arginine methyltransferase PRMT1 Inhibitor) via the regisoelective *N*-alkylation of *p*-aminobenzenesulfonamide (**1a**) with 2-phenylethanol (**6**) was undertaken. As shown in Scheme 6, the reaction was performed in the presence of $[Cp^*IrCl_2]_2$ (1 mol %)/KOH (1 equiv) at 120 °C for 12 h to afford the desired

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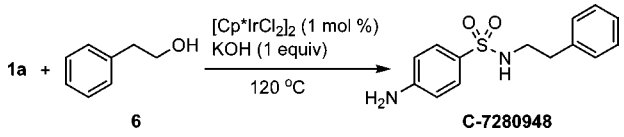
Scheme 6. Synthesis of Biologically Active Molecule



product in 80% yield. The new route exhibited obvious advantages over the previous multistep synthesis of C-7280948.[6a]

In summary, we have demonstrated a simple, highly efficient, and general strategy for direct synthesis of amino-(*N*-alkyl)benzenesulfonamides via iridium-catalyzed *N*-alkylation of aminobenzenesulfonamides bearing both different types of amino groups with alcohols as alkylating agents. Notably, this research exhibited the potential for the recognition of different types of amino groups in the *N*-alkylation of complex molecules with alcohols, facilitating the progress of the transition-metal-catalyzed "hydrogen autotransfer (or hydrogen-borrowing) process".

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and a CIF file giving crystallographic data for product **3ag**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00824.

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Notes

The authors declare no competing financial interest.

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