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Efficient indoles and anilines syntheses employing *tert*-butyl sulfinamide as ammonia surrogate

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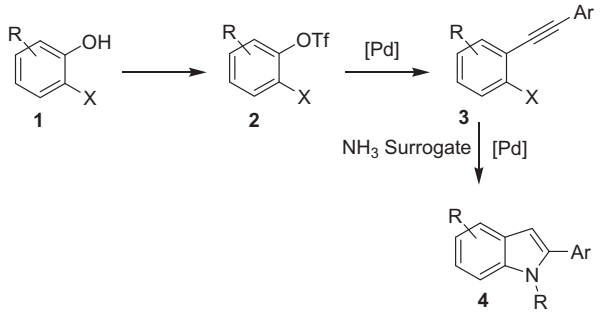
ABSTRACT

tert-Butyl sulfinamide is an ammonia equivalent for the palladium-catalyzed amination of aryl bromides and aryl chlorides. Using these amine derivatives, it has been observed that indoles and anilines with sensitive functional groups can be readily prepared. This surrogate has also been used for the synthesis of indoles from 2-halophenols using palladium catalyzed cross coupling reaction as the key step.

Heterocyclic compounds, particularly indole ring system is present in drug candidates having interesting biological activities and in numerous natural alkaloids that cover a wide range of structural types.[1] Consequently this plays a key role in the continued search for the development of new, efficient, and selective protocols for its construction.[2] In this context, palladium-catalyzed transformations for the synthesis of indole backbone, starting from *o*-alkynylanilines or derivatives[3] thereof as well as *o*-haloanilines,[4] have been studied intensively. *o*-Dihaloarenes or *o*-alkynylhaloarenes[5] also been used where dihalo compound was selectively converted into *o*-alkynylhaloarenes and then alkylamine or arylamines are used for C—N coupling reaction to yield *N*-substituted indole. However, much less attention has been paid to the use of *o*-halophenols although they are easily accessible from inexpensive starting materials. We focused our attention on the preparation of 2-substituted indoles from phenols containing an *ortho* halo group and 1-alkynes through an integrated process involving three basic steps: conversion of *o*-halophenols to triflate followed by Sonogashira reaction with 1-alkynes and then Buchwald coupling with suitable ammonia surrogates (Scheme 1).

Significant progress has been made in the development of transition metal catalyzed aminations of aryl halides.[6] As a result, a wide variety of secondary aryl amines can be prepared efficiently using this methodology. Thus, reactions have been conducted with ammonia surrogates. Allylamine was used as ammonia equivalent and the resulting allyl group from the resulting aryl alkyl amine was conveniently cleaved using methane sulfonic acid and palladium on carbon.[7] Benzophenone imine was frequently used as an effective ammonia equivalent. The coupling reactions with this imine are high yielding and can be performed under extremely mild reaction conditions and the resulting *N*-aryl imines can be cleaved using several orthogonal methods that are compatible with a variety of protecting groups.[8] Hartwig and Buchwald group



Scheme 1. Indole synthesis using *o*--halophenol.

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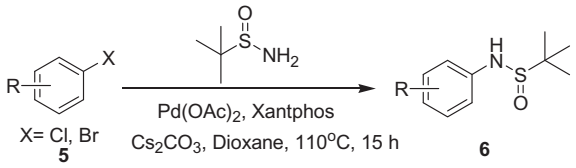
independently reported inexpensive silyl reagents such as (LiN-$(SiMe_3)_2$) and Ph_3SiNH_2 as ammonia equivalents for palladium catalyzed amination and the resulting aryl silylamine is easily deprotected.[9] Amidine hydrochloride has recently been used as an ammonia equivalent for copper-catalyzed couplings with aryl halide to prepare anilines.[10] Hydroxylamine *o*-benzyl ether as an ammonia equivalent in the catalytic amination of aryl halides has been reported.[11] Toluene sulfonamides have been used as ammonia surrogates for palladium-catalyzed aminations.[12] Very recently, ammonia itself has been used as an amine reagent for the palladium-catalyzed coupling of aryl halides to afford primary aryl amines.[13] Aqueous ammonia and ammonium chloride were used recently for the synthesis of primary aryl amines using copper as catalyst.[14] We recently reported SES-NH_2 and Teoc-NH_2 as ammonia surrogate.[15] Recently a group of scientists from Novartis used *tert*-butyl sulfinamide for copper-catalyzed coupling with 2-bromo pyridine.[16] In the search for other suitable and stable ammonia surrogates we found that *tert*-butyl sulfinamide as ammonia surrogate for the palladium-catalyzed amination (Scheme 2).

We initiated our investigations by examining suitable conditions for the palladium catalyzed coupling of *tert*-butyl sulfinamide with aryl bromides. Preliminary studies showed that $Pd(OAc)_2$-Xantphos-Cs_2CO_3 catalyst system in 1,4-dioxane at 110 °C for 15 h gives excellent isolated yields of corresponding sulfonamide derivatives. Aryl bromides with various functional groups such as cyano, ester, aldehyde and methoxy reacted under the above optimized conditions without undergoing any other side reactions (Table 1).[17] Having been successful with aryl bromides, we next extended this reaction to aryl chlorides. Aryl chloride bond activation is an industrially important field of research due to the lower cost of aryl chlorides compared to aryl bromides and aryl iodides.[18] We used the same reaction conditions for the coupling of *tert*-butyl sulfinamide with aryl chlorides. The reaction worked well with aryl chlorides possessing different substituents such as cyano, ester, keto, and aldehyde, and the yields obtained were more than 80% in most cases (Table 2).

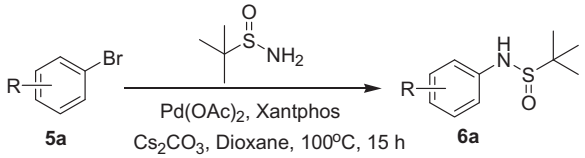
tert-Butyl sulfinamide products were very stable and could be used for further transformations without affecting the sulfinamide group. The sulfinamide group was cleaved selectively by treating with etherial HCl solution for 15 min without affecting other functional groups to yield anilines in excellent yield.[19] Thus, we established *tert*-butyl sulfinamide as an excellent ammonia surrogate for the aryl amination reaction.

We extended our work to utilize this new ammonia surrogate for the synthesis of indoles. To the best of our knowledge, the commercially available 2-halophenols have not been used for the general synthesis of indoles. Recently Ackermann et al. used carbamic acid *tert*-butyl ester as amine surrogate followed by deprotection of Boc group to get free N—H indoles.[20] Therefore, we explored this synthetic approach, as illustrated in Scheme 1, by starting with *o*-bromo phenol, **1**. Phenol triflate **2** was prepared by treating with Tf_2O and Et_3N in CH_2Cl_2 at 0 °C coupled with 1-aryl-alkynes under standard Sonogashira cross-coupling conditions.[21] The resulting *o*-alkynylbromoarene **3** was isolated and coupled with *tert*-butyl sulfinamide by using the above-mentioned conditions to yield



Scheme 2. *tert*-Butyl sulfinamide as an ammonia surrogate in the palladium catalyzed coupling of aryl halides.

Table 1
tert-Butyl sulfinamide as an ammonia surrogate in the palladium catalyzed coupling of aryl bromides[a]



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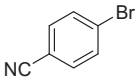
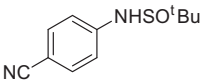
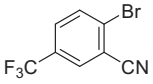
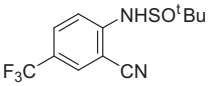
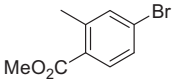
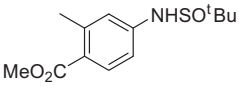
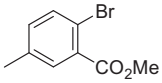
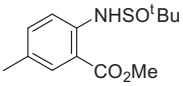
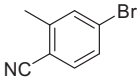
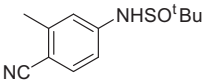
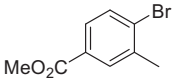
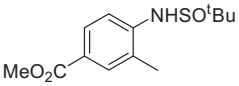
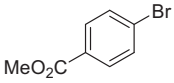
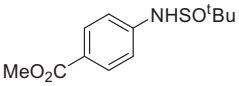
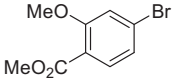
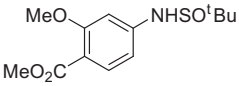
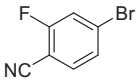
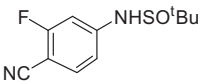
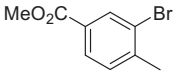
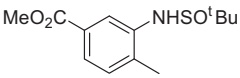
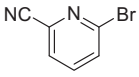
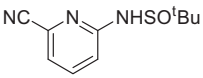
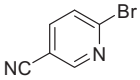
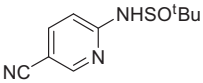
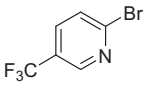
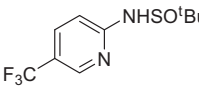
1			97
2			94
3			96
4			98
5			97 (93)
6			97
7			98
8			96
9			94 (92)
10			95 (96)
11			94 (90)
12			92
13			89

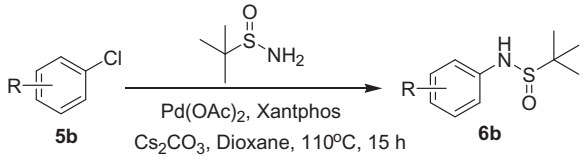
[a] *Reaction conditions:* Aryl bromide (1 mmol), *tert*-butyl sulfinamide (1.2 mmol), $Pd(OAc)_2$ (0.03 mmol), Xantphos (0.06 mmol), Cs_2CO_3 (2.0 mmol) 1,4-dioxane (3 ml), Schlenk tube, 100 °C, 15 h.

[b] Isolated yield. Yield given in the parentheses is deprotected yield obtained from the amination product. *Deprotection conditions:* Aminated product (1 mmol), 4 M HCl (5 mmol), 1,4-dioxane (3 ml), rt, 15 min.

2-arylsubstituted indoles, **4** directly (Table 3). Sulfinamide group was deprotected during the reaction conditions to form free N—H indole.

In conclusion, we have reported the synthesis of several sulfinated aryl aniline syntheses from aryl bromides and arylchlorides from *tert*-butyl sulfinamide. The *tert*-butyl sulfinyl group can be

Table 2
tert-Butyl sulfinamide as an ammonia surrogate in the palladium catalyzed coupling of aryl chlorides[a]



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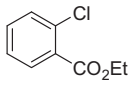
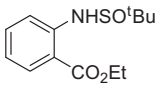
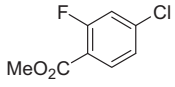
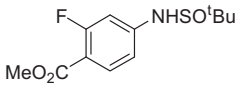
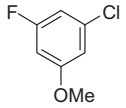
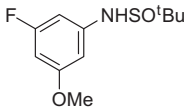
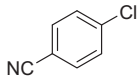
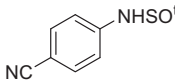
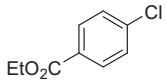
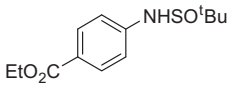
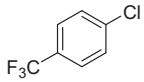
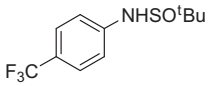
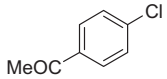
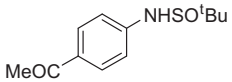
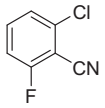
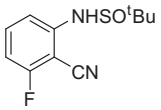
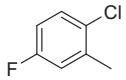
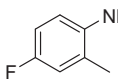
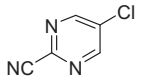
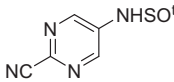
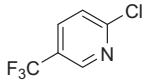
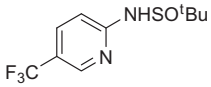
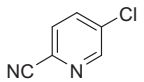
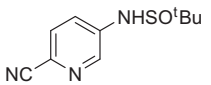
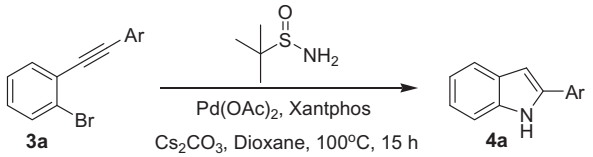
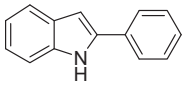
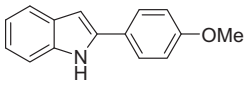
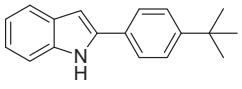
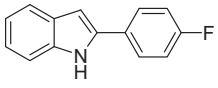
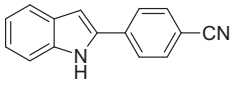
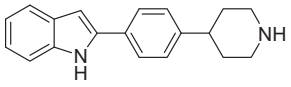
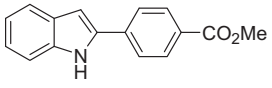
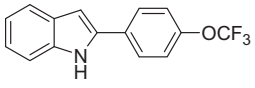
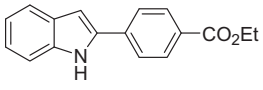
1			96
2			94
3			88
4			93 (95)
5			97
6			93
7			94
8			90
9			70 (96)
10			83 (79)
11			84
12			78

[a] *Reaction conditions:* Aryl chloride (1 mmol), *tert*-butyl sulfinamide (1.2 mmol), $Pd(OAc)_2$ (0.03 mmol), Xantphos (0.06 mmol), Cs_2CO_3 (2.0 mmol) 1,4-dioxane (3 ml), Schlenk tube, 110 °C, 15 h.
[b] Isolated yield. Yield given in the parentheses is deprotected yield obtained from the amination product. *Deprotection conditions:* Aminated product (1 mmol), 4 M HCl (5 mmol), 1,4-dioxane (3 ml), rt, 15 min.

selectively cleaved without affecting other functional groups establishes *tert*-butyl sulfinamide as an excellent ammonia surrogate for aryl amination reaction. Moreover, utilizing this surrogate, a general and efficient approach for the synthesis of indoles from *o*-halophenol is presented.

Table 3
Palladium-catalyzed indole synthesis employing *tert*-butyl sulfinamide as an ammonia surrogate[a]



Entry	Product	Yield (%)[b]
1		90
2		88
3		71
4		82
5		86
6		72
7		80
8		86
9		83

[a] *Reaction conditions:* *o*-Alkynylbromoarene (1 mmol), *tert*-butyl sulfinamide (1.2 mmol), $Pd(OAc)_2$ (0.03 mmol), Xantphos (0.06 mmol), Cs_2CO_3 (2.0 mmol) 1,4-dioxane (3 ml), Schlenk tube, 100 °C, 15 h.
[b] Isolated yield.

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Supplementary data

Supplementary data associated (experimental and analytical data for new compounds) with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.075.

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17. General procedure: An oven-dried resealable Schlenk tube was charged with $Pd(OAc)_2$ (0.03 mmol), Xantphos (0.06 mmol), *tert*-butyl sulfinamide (1.2 mmol), and Cs_2CO_3 (2.0 mmol). The Schlenk tube was evacuated and back-filled with argon. Aryl halide (1.0 mmol) and dioxane (3 ml) were added and the Schlenk tube was then sealed with a Teflon screw cap and placed in a preheated oil bath at 100 °C for 15 h for aryl bromides and 110 °C for aryl chlorides. After cooling the reaction mixture to room temperature, water was added and the reaction mixture was extracted with ethyl acetate (2×10 ml). The combined organic layer was washed with brine (20 ml), dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by flash chromatography on silica gel (30% ethylacetate in *n*-hexane). (see Supplementary data).
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