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Transition-metal-free direct amination of simple arenes with sulfonyl azides

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ABSTRACT

A metal-free green protocol has been developed for amination of simple arenes using arylsulfonyl azides via a nitrene transfer process under solvent free conditions at 130 °C releasing N_2 gas as the sole by-product.

Nitrogen-containing compounds are broadly present in natural products and synthetic intermediates. Aryl amines are very important key components displaying important chemical, biological, and medicinal properties.[1] Therefore efforts are continuously driven toward the development of efficient reactions to carry out C–N bond formation over arene molecules. Particularly, the Cu and Pd mediated N-arylation of aryl(pseudo)halides is extensively reported. However, it suffers from the drawbacks of using prefunctionalized arene and formation of unnecessary by-products.[2] Amination through C–H activation of arenes (inner-sphere mechanism)[3] has received special attention as the process does not require prefunctionalized arene. Though transition metal catalyzed C–H bond offers notable advantages in terms of reaction conditions and selectivity, substrate scope is rather limited. The nature of aminating source is crucial in these reactions. Parent amines can be used in the presence of external oxidants.[4] The use of preactivated amino precursors like halogenated amine[5] allows an external oxidant-free method for the amination. However, the generation of stoichiometric byproducts from the use of oxidants and bases cannot be avoided under these conditions. Use of organic azides [6] provides another oxidant-free method that releases nitrogen gas as the only by-product. Nitrene insertion reaction (outer sphere mechanism) is an alternative tool for introducing a functional group in the presence of a transition metal catalyst.[3f,7] Nitrene-transfer process is successfully applied for sp^3 C–H bonds at aliphatic, benzylic or allylic positions.[7] Organic azides are widely used for transition-metal catalyzed intermolecular C–H amination of sp^3 C–H bonds.[8] However, most of them are based on nitrene insertion reaction at allylic and benzylic positions.[8a–k] Recently, a number of azide mediated sp^2 C–H amination, particularly in arene systems have been reported in the presence of various catalytic systems.[6,8k,9] These chelation-guided direct C–N bond formation reactions occur in the absence of external oxidants. Literature using azides as nitrene precursor for sp^2 C–H activation is very rare.[10] While intramolecular case is limited to arene C–H activation,[10a,c,d,f,g] intermolecular sp^2 C–H activation is confined to acyl C–H bond.[10h–j]

This field of oxidative C–H activation process has been boosted by the advent of several metal free protocols.[11] Efforts are continuously being devoted for metal free oxidative amination process using various aminating agents.[12] Ayyangar and co-workers reported the generation of sulfonyl nitrene from azides via thermolysis process. These reports mainly revealed the formation of azepines.[13] Although the synthesis of sulfonanilde from benzene has been reported during the course of such reactions, the amination process of arene is not explored widely and is very limited. Here we wish to report an intermolecular metal free nitrene transfer to arene C–H bond using arylsulfonyl azide as the source of nitrogen.

Initially, our study focused on the C–H amination process of mesitylene as a model substrate with different arylsulfonyl azides as the nitrene source. To evaluate the scope of the azides, we used 4-methylbenzenesulfonyl azide (Scheme 1, **2a**, 0.3 mmol) with 0.5 mL of mesitylene (Scheme 1, **1a**) at 80 °C. The reaction was allowed to run for 24 h.

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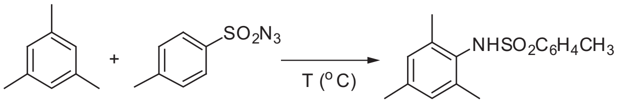
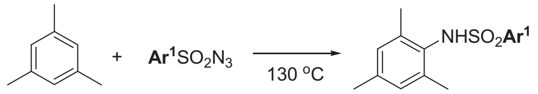


1a **2a** **3a**

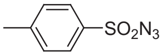
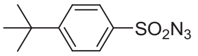
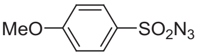
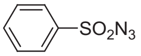
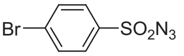
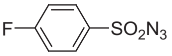
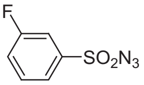
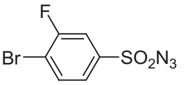
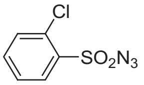
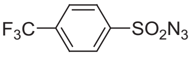
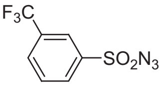
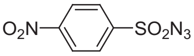
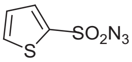
Scheme 1.

But its progress was found to be disappointing and trace amount of C–H aminated product **3a** (Scheme 1) was detected through GC–MS. Changing the temperature to 120 °C, 40% of the product **3a** was isolated. The product was characterized through NMR spectral data. Further increasing the temperature to 130 °C, the product yield increased to 67% within a period of 12 h. These observations lead us to believe that the temperature is very crucial for the amination process. To our delight, all the reactions were found to be effective under solvent free conditions.[14]

Table 1
Reactions of different azides with mesitylene[a]



1a **2a-m** **3a-m**

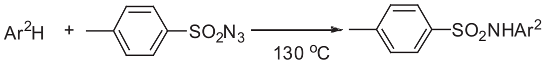
Entry	$Ar^1SO_2N_3$ (**2a–m**)	Products (**3a–m**)	Yield[b] (%)
1	 **2a**	**3a**	67
2	 **2b**	**3b**	78
3	 **2c**	**3c**	76
4	 **2d**	**3d**	83
5	 **2e**	**3e**	80
6	 **2f**	**3f**	86
7	 **2g**	**3g**	85
8	 **2h**	**3h**	80
9	 **2i**	**3i**	89
10	 **2j**	**3j**	96
11	 **2k**	**3k**	89
12	 **2l**	**3l**	86
13	 **2m**	**3m**	88

[a] Reaction condition: **1a** (0.5 mL), **2a-m** (0.3 mmol), 130 °C, 12 h.
[b] Isolated yield.

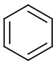
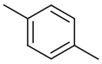
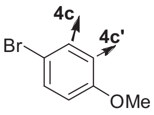
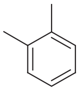
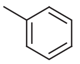
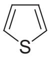
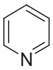
After successful investigation with TsN_3, we extended the C–H amination of mesitylene with various sulfonyl azides (Table 1, **2a**–**m**). It was observed that, the substituents on the aromatic ring of azides have slight impact on the nitrene transfer process. Electron withdrawing substituents were found to be effective in terms of yields of the reaction (entries 5–12, 80–96% yield) in comparison with electron donating substituents (entries 1–3, 67–80% yield). The azide, **2m** bearing heteroarene group also facilitates the nitrene transfer to mesitylene effectively under the reaction conditions and 88% of the aminated product (**3m**) was isolated.

We also observed the efficacy of the nitrene transfer process with different arenes (Table 2). For this purpose we have chosen TsN_3 as the suitable precursor and all the reactions were carried out at 130 °C under solvent free conditions. Although the arenes (Table 2, entries 1–5) were aminated under the standard condition, selectivity was found to be poor with unsymmetrical arenes (Table 2, entries 3–5), leading to the formation of regiomers, as detected via ^{1}H NMR spectral data. The isomers were found to be non-separable and isolated as a mixture. While 1-bromo-4-methoxybenzene (Table 2, entry 3) provided 1:1 *ortho* product (**4c**:**4c′**, 75% combined yield), *ortho*-xylene provided 1:1 2,3-dimethyl-*N*-tosylbenzenamine and 3,4-dimethyl-*N*-tosylbenzenamine products (**4d**:**4d′**, 78% combined yield) and toluene provided 1:1 *N*-(2-methylphenyl)-4-methylbenzenesulfonamide and *N*-(4-methylphenyl)-4-methylbenzenesulfonamide products (**4e**:**4e′**, 80% combined yield). We have not detected formation of over aminated product with any kind of arene under the reaction conditions. However, with heteroarenes, the scope of the nitrene transfer process is limited (Table 2, entries 6 and 7). While with thiophene, trace amount of aminated product was detected, with

Table 2
Amination of different arenes with TsN_3[a]



2a 4a-g

Entry	Ar^2H	Product (**4a–g**)	Yield[b] (%)
1		**4a**	76
2		**4b**	53
3		**4c**:**4c′** (1:1)[c]	75[d,e]
4		**4d**:**4d′** (1:1)[c]	78[d]
5		**4e**:**4e′** (1:1)[c]	80[d]
6		**4f**	Trace
7		**4g**	–

[a] Reaction condition: Arene (0.5 mL), TsN_3 (0.3 mmol), 130 °C, 12 h.
[b] Isolated yield.
[c] Ratio determined from ^{1}H NMR integration.
[d] Combined yield.
[e] **4c**:**4c′** can be isolated by performing thin layer chromatography twice.

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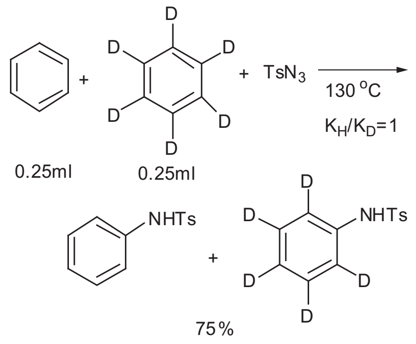

Scheme 2. Isotope effect.

pyridine, this approach did not lead to the formation of the desired product.

The mechanism of this reaction is not clear. The kinetic isotope effect ($k_H/k_D = 1.0$) was determined by an intermolecular competition experiment, indicating that the cleavage of C–H bond in this amination is not included in the rate-determining step (Scheme 2).

In conclusion, we have developed an efficient nitrene transfer process to arenes using azides under metal free conditions. Various sulfonyl azides were found to be effective under the protocol. While unsymmetrical arenes provided regiomeric mixture of aminated products, heteroarene could not be carried out for amination.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.02.009.

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14. Using a solid arene, for example, dimethoxybenzene, 1,3,5-trimethoxybenzene or 1,2,4,5-tetramethylbenzene with TsN_3 in the presence of different solvents like DCE, DMSO and DMF, the reaction failed.

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