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# Amidoalkylation of Sulfonylheteroarenes with Alkylamides through a Radical Chain Mechanism

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Dedication ((optional))

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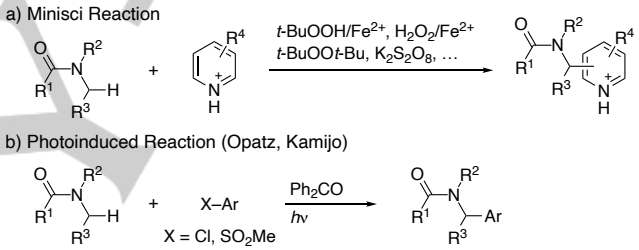
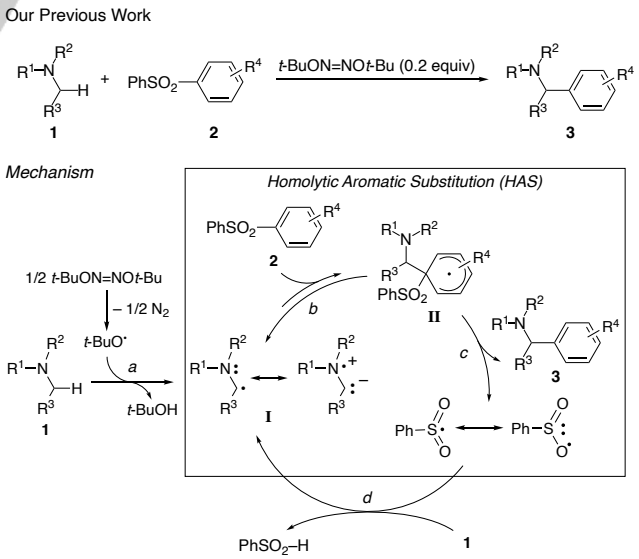
**Abstract:** In the presence of a substoichiometric amount of a *tert*-butoxy radical precursor and a base, alkylamides were found to be heteroarylated at their α-C–H bonds with sulfonylheteroarenes through homolytic aromatic substitution, where a radical chain is operative.

α-Heteroarylalkylamides are ubiquitous motifs in biologically active compounds used for medicinal chemistry and agrochemistry.[1] The Minisci reaction, a formal dehydrogenative coupling between alkylamides and protonated pyridine derivatives, readily gives α-heteroarylalkylamides (Scheme 1a).[2] The reaction proceeds through a homolytic aromatic substitution (HAS) mechanism consisting of a radical addition and a radical elimination. Here utilization of heteroarenes without prefunctionalization is beneficial, but it is intrinsically difficult that a particular C–H bond of the heteroarene is regioselectively substituted. The regioselectivity problem can be solved when a heteroatom radical is selectively eliminated from the heteroarene. In recent years, it has been reported that 2-chlorobenzazoles (X = Cl) or sulfonylheteroarenes (X = $SO_2Me$) are used for the photoinduced α-heteroarylation of alkylamides through HAS utilizing benzophenone as a photosensitizer, ensuring the regiochemistry on the aromatic rings (Scheme 1b).[3] In this context, we have recently reported that the direct α-arylation of alkylamines with sulfonylarenes proceeds through an HAS mechanism mediated by a substoichiometric amount of *t*-BuO$^\bullet$ precursor (Scheme 2).[4] The reaction starts with hydrogen abstraction from an alkylamine by *t*-BuO$^\bullet$, generated through homolysis of *t*-BuON=NO*t*-Bu, to give α-aminoalkyl radical **I**, which is stabilized by resonance with the lone pair on the nitrogen atom (step *a* in Scheme 2). After addition of **I** to a sulfonylarene (**2**) (step *b*), the resulting cyclohexadienyl radical (**II**) undergoes elimination to give α-arylalkylamine **3** and $PhSO_2^\bullet$ (step *c*). Hydrogen abstraction from **1** by the eliminated $PhSO_2^\bullet$ regenerates **I** to make a radical chain operative (step *d*).[5] Here the stabilities of $PhSO_2^\bullet$ and **I** are comparable, and thus both homolytic substitution of $PhSO_2^\bullet$ with **I** in steps *b* and *c* and hydrogen abstraction from **1** by $PhSO_2^\bullet$ to regenerate **I** in step *d* are feasible to achieve the radical chain.[6] Here we have found that, for the α-heteroarylation of alkylamides, $MeSO_2^\bullet$ instead of $PhSO_2^\bullet$ is suitable as a leaving radical to meet the requirements, and report the α-heteroarylation of alkylamides with methanesulfonylheteroarenes using a substoichiometric amount of a *tert*-butoxy radical precursor [Eq. (1)].




**Scheme 1.** Previous works on the direct α-heteroarylation of alkylamides through homolytic aromatic substitution (HAS).




**Scheme 2.** Direct α-arylation of alkylamines with benzenesulfonylarenes through a radical chain mechanism involving HAS.

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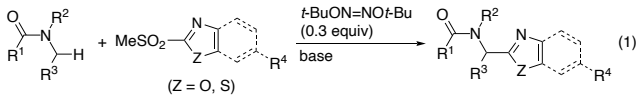
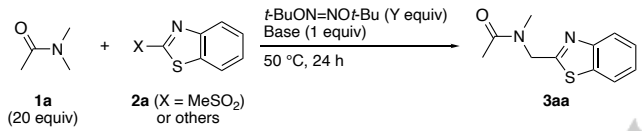
This Work




We first examined α-heteroarylation of *N*,*N*-dimethylacetamide (**1a**: DMA) under the conditions that we employed in the α-arylation of alkylamines with benzenesulfonylarenes. Thus, treatment of 2-(benzenesulfonyl)benzothiazole with DMA (20 equiv) as a substrate and a solvent in the presence of *t*-BuON=NO*t*-Bu (0.2 equiv) at 50 °C for 24 h gave *N*-(2-benzothiazolylmethyl)-*N*-methylacetamide (**3aa**) but only in 26% yield (Table 1, entry 1). The use of the $MeSO_2$ derivative (**2a**) instead of the $PhSO_2$ one scored a comparable yield (entry 2). Addition of $KHCO_3$ (1 equiv) as a neutralizer for co-produced sulfinic acid increased the yield of **3aa** with **2a** but not with the benzenesulfonyl derivative (entries 3 and 4). The result, using **2a,** that the yield of **3aa** exceeded the maximum amount (40%) of *t*-BuO• generation shows operation of a radical chain. The reaction of 2-halobenzothiazoles (X = Cl, Br) resulted in low yields (entries 5 and 6). As for the reaction using 2-benzenesulfonyl- and 2-chlorobenzothiazoles, the use of a stoichiometric amount of *t*-BuON=NO*t*-Bu increased the conversions and yields (entries 7 and 8 *vs*. entries 4 and 5), showing that some problem lies in the operation of a radical chain with these heteroaryl electrophiles.[6,7] Other bases, weaker or stronger than $KHCO_3$, are less effective (entries 9–13).[8] Especially, $NaHCO_3$ The yield was improved to 81% by the use of a slightly increased amount (0.3 equiv) of *t*-BuON=NO*t*-Bu (entry 14). The reaction also proceeded under an air atmosphere or a nitrogen atmosphere by use of a nitrogen balloon instead of a glove box (entries 15 and 16).

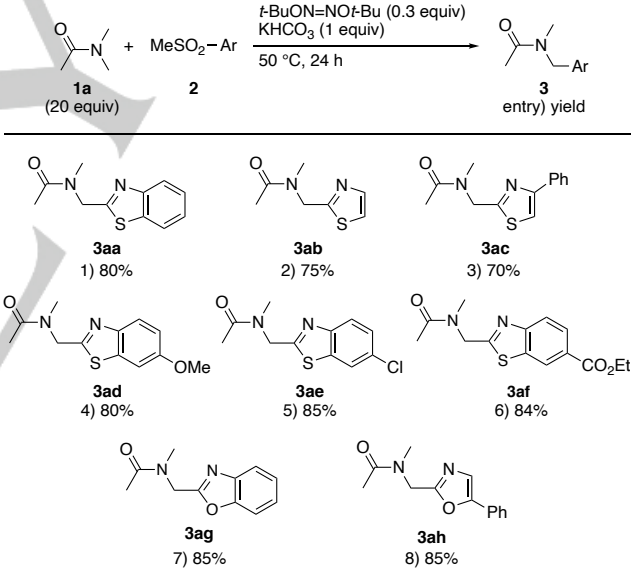
**Table 1.** α-Heteroarylation of *N*,*N*-dimethylacetamide (**1a**) with a 2-benzothiazolyl electrophile using *t*-BuON=NO*t*-Bu.[a]




| Entry | X | Y | Base | Conv. [%][b] | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | $PhSO_2$ | 0.2 | none | 26 | 26 |
| 2 | $MeSO_2$ | 0.2 | none | 31 | 31 |
| 3 | $MeSO_2$ | 0.2 | $KHCO_3$ | 79 | 71 |
| 4 | $PhSO_2$ | 0.2 | $KHCO_3$ | 30 | 28 |
| 5 | Cl | 0.2 | $KHCO_3$ | 40 | 37 |
| 6 | Br | 0.2 | $KHCO_3$ | 22 | 20 |
| 7 | $PhSO_2$ | 1.0 | $KHCO_3$ | >99 | 96 |
| 8 | Cl | 3.0 | $KHCO_3$ | 89 | 80 |
| 9 | $MeSO_2$ | 0.2 | NaOAc | 38 | 38 |
| 10 | $MeSO_2$ | 0.2 | $NaHCO_3$ | 60 | 53 |
| 11 | $MeSO_2$ | 0.2 | $K_2HPO_4$ | 40 | 37 |
| 12 | $MeSO_2$ | 0.2 | $K_2CO_3$ | 40 | 38 |
| 13 | $MeSO_2$ | 0.2 | $K_3PO_4$ | 81 | 46 |
| 14 | $MeSO_2$ | 0.3 | $KHCO_3$ | 90 | 81 (80)[c] |
| 15[d] | $MeSO_2$ | 0.3 | $KHCO_3$ | 89 | 80 |
| 16[e] | $MeSO_2$ | 0.3 | $KHCO_3$ | 83 | 75 |

[a] The reaction was carried out under a nitrogen atmosphere using a glove box at 50 °C for 24 h using a 2-benzothiazolyl electrophile (**2a** or others: 0.25 mmol), *N*,*N*-dimethylacetamide (**1a**: 5.0 mmol), *t*-BuON=NO*t*-Bu and a base (0.25 mmol). [b] Determined by GC. [c] The yield of the isolated product. [d] The reaction was carried out under an air atmosphere. [e] The reaction was carried out under a nitrogen atmosphere using a nitrogen balloon.

The α-heteroarylation of DMA (**1a**: 20 equiv) using 0.3 equivalent of *t*-BuON=NO*t*-Bu is applicable to diverse 2-(methanesulfonyl)azoles (Scheme 3). In addition to 2-(methanesulfonyl)benzothiazole (**2a**), monocyclic 2-(methanesulfonyl)thiazoles reacted with **1a** to give the corresponding heteroarylation products (entries 1–3). 2-(Methanesulfonyl)benzothiazoles having an electron-donating or -withdrawing group also participated in the α-heteroarylation in high yields (entries 4–6). 2-(Acetylaminomethyl)oxazoles are also obtained in high yields (entries 7 and 8).




**Scheme 3.** α-Heteroarylation of *N*,*N*-dimethylacetamide (**1a**) with 2-(methanesulfonyl)azoles.

Various tertiary alkylamides are α-heteroarylated with 2-(methanesulfonyl)benzothiazole (**2a**) (Scheme 4). *N*,*N*-Diethylacetamide (**1b**) was α-heteroarylated in a high yield (entry 1). *N*-Ethyl-*N*-methylacetamide (**1c**) underwent the heteroarylation preferentially at the methyl group over the linear alkyl group but with a low selectivity (entry 2). On the other hand, the heteroarylation of *N*-methylated cyclic alkylamides, ureas and carbamates took place mainly at a cyclic alkyl group over a methyl group (entries 3–6). The regioselectivity between methyl group and a linear or cyclic alkyl group as a primary alkyl group is determined essentially in the hydrogen abstraction step and the step of addition of an α-acylaminoalkyl radical to a

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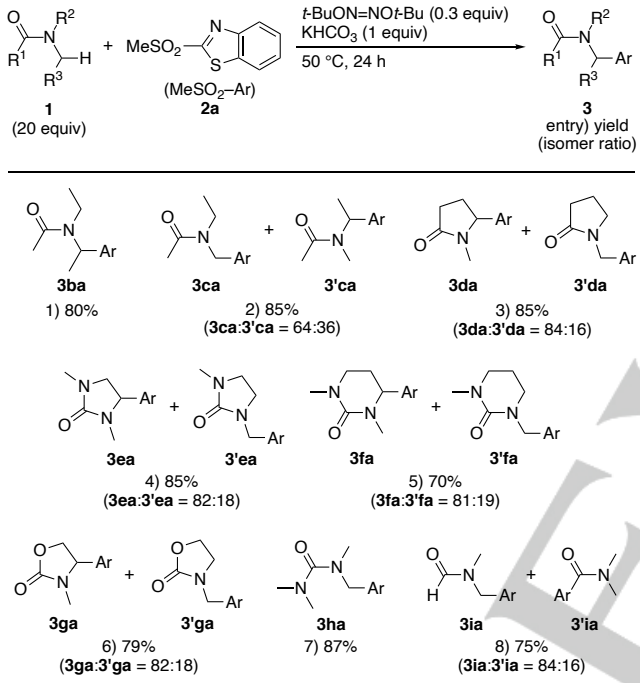
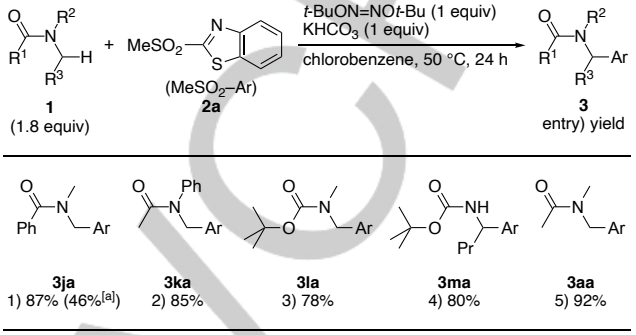
sulfonylheteroarene. In both steps, the electronic factor favors the reaction at a primary alkyl group because the stability and the nucleophilicity are higher with an α-amino primary alkyl radical, whereas the steric factor favors the reaction at the less hindered methyl group. High selectivities for the cyclic alkyl group observed in the reaction of the cyclic amides are likely to be ascribed to the enhanced electronic factor due to the stereoelectronic effect derived from the cyclic structure[9] and the reduced steric hinderance due to the binding effect again derived from the cyclic structure. *N*,*N*,*N*',*N*'-Tetramethylurea (**1h**) participated in the α-heteroarylation in a high yield (entry 7). In the reaction of *N*,*N*-dimethylformamide (**1i**), heteroarylation at a methyl group on nitrogen is preferred over the formyl group, which also accepts hydrogen abstraction (entry 8).

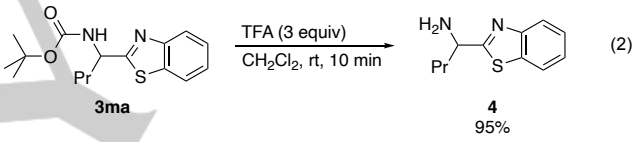



**Scheme 4.** α-Heteroarylation of tertiary alkylamides with 2-(methanesulfonyl)benzothiazole (**2a**).

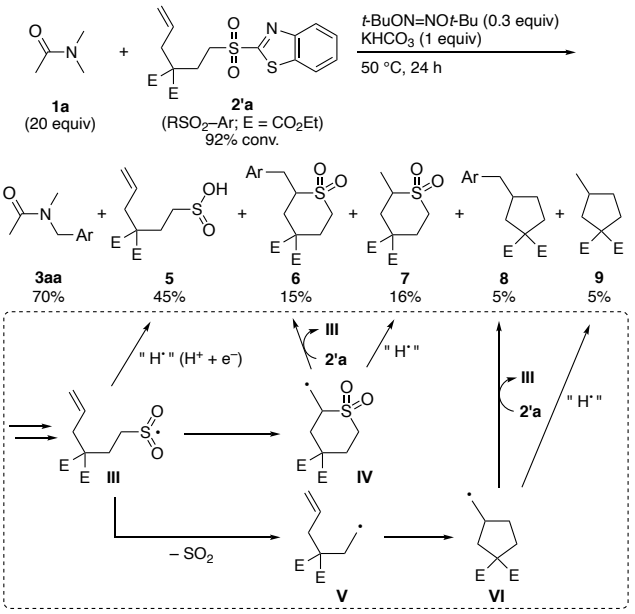
The amount of alkylamides can be reduced from 20 equivalents to 1.8 by the use of chlorobenzene as a solvent, though a stoichiometric amount (1 equiv) of *t*-BuON=NO*t*-Bu is required for high yields (Scheme 5). This protocol is beneficial especially for alkylamides that are solids and/or expensive. The α-heteroarylation of *N*,*N*-dimethylbenzamide (**1j**: 1.8 equiv) with **2a** in the presence of *t*-BuON=NO*t*-Bu (1 equiv) and $KHCO_3$ (1 equiv) in chlorobenzene gave the α-heteroarylation product (**3ja**) in 87% yield (entry 1). With a substoichiometric amount (0.3 equiv) of *t*-BuON=NO*t*-Bu, **3ja** was obtained only in 46% yield (49% conv. of **2a**), showing that an efficient radical chain is not operative, a probable reason of which is discussed later in the mechanism section. *N*-Methylacetanilide also underwent the α-heteroarylation (entry 2). *N*-Alkylated carbamates such as *tert*-butyl *N*,*N*-dimethylcarbamate (**1l**) and *tert*-butyl *N*-butylcarbamate (**1m**) were heteroarylated in high yields (entries 3 and 4). Deprotection of *tert*-butoxycarbonyl group of **3ma** with trifluoroacetic acid (TFA) in $CH_2Cl_2$ gave the corresponding α-heteroarylated butylamine (**4**) [Eq. (2)]. DMA is heteroarylated in a high yield compared with the reaction under the previous conditions (entry 5 *vs*. entry 14 of Table 1). Under these conditions, no further α-heteroarylation of the α-heteroarylated alkylamides took place in all entries in Scheme 5, as in the case of Scheme 4, even though a lower amount of amides **1** and a higher amount of the *tert*-butoxy radical precursor are used.




**Scheme 5.** α-Heteroarylation of alkylamides with 2-(methanesulfonyl)benzothiazole (**2a**) in chlorobenzene. [a] 0.3 equiv of *t*-BuON=NO*t*-Bu was used.



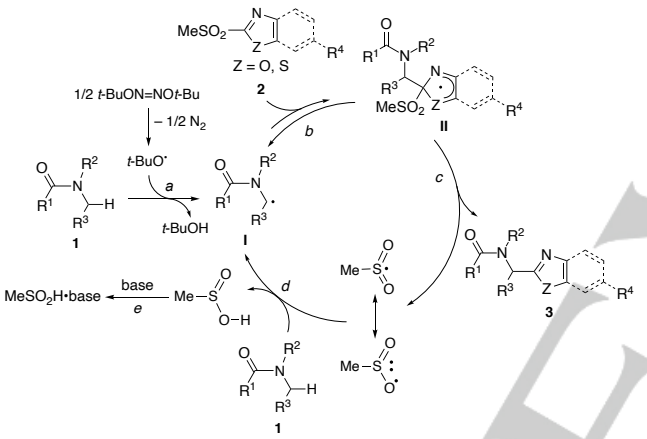

To gain insight into the reaction mechanism, a radical clock experiment was conducted. The reaction of 2-[3,3-bis(ethoxycarbonyl)-5-hexene-1-sulfonyl]benzothiazole (**2'a**) with DMA (**1a**) as a substrate and a solvent gave certain amounts of cyclization products (**6**–**9**) derived from the alkanesulfonyl moiety of **2'a** in addition to the normal α-heteroarylation product (**3aa**) and 3,3-bis(ethoxycarbonyl)-5-hexene-1-sulfinic acid (**5**)




**Scheme 6.** Proof of the involvement of sulfonyl radicals as leaving groups.

(Scheme 6). All the cyclization products (**6**–**9**) are highly likely to be produced from 3,3-bis(ethoxycarbonyl)-5-hexene-1-sulfonyl radical (**III**). Sulfonylradical **III** cyclizes, as it stands[10] and after decomposition to alkyl radical **V** with elimination of $SO_2$,[11] to give alkyl radicals **IV** and **VI**, which undergo HAS with **2'a** giving **6**/**8** and hydrogen abstraction giving **7**/**9**. The result shows that alkanesulfonyl radicals are involved as leaving groups in the α-heteroarylation.

On the basis of the above experimental results and our previous report,[4] the α-heteroarylation of alkylamides is likely to proceed through the mechanism shown in Scheme 7. Thus, the reaction is initiated by hydrogen abstraction from an alkylamide (**1**) by *t*-BuO$^{\bullet}$ generated through homolysis of *t*-BuON=NO*t*-Bu (step *a*). The resulting α-(acylamino)alkyl radical (**I**) adds to a methanesulfonylheteroarene (**2**) (step *b*), followed by elimination of $MeSO_2^{\bullet}$ from **II** to give the α-heteroarylation product (**3**) (step *c*). Finally, $MeSO_2^{\bullet}$ undergoes hydrogen abstraction from **1** to regenerate **I** (step *d*). Step *d* is likely to be thermodynamically unfavorable,[7] and thus an excess amount of **1** are required to step forward.[12]




**Scheme 7.** A plausible mechanism.

In conclusion, we have expanded the substrate scope of nitrogen-containing aliphatic compounds to alkylamides in the α-arylation with sulfonylarenes by tuning the sulfonyl radical leaving group.

## Acknowledgements

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**Keywords:** α-heteroarylation • alkylamides • sulfonylheteroarenes • radical mechanism • *t*-BuO$^{\bullet}$ source

[1] For examples of biologically active compounds: a) F. Ferrigno, I. Biancofiore, S. Malancona, S. Ponzi, G. Paonessa, R. Graziani, A. Bresciani, N. Gennari, A. Di Marco, M. Kaiser, V. Summa, S. Harper, J. M. Ontoria, *Bioorg. Med. Chem. Lett.* **2018**, *28*, 3689–3692; b) K. E. Sexton, S. Barrett, K. Bridgwood, M. Carroll, D. Dettling, D. Du, S. Fakhoury, V. Fedij, L.-Y. Hu, C. Kostlan, D. Pocalyko, N. Raheja, Y. Smith, V. Shanmugasundaram, K. Wade, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5230–5233; c) N. Desroy, F. Moreau, S. Briet, G. L. Fralliec, S. Floquet, L. Durant, V. Vongsouthi, V. Gerusz, A. Denis, S. Escaich, *Bioorg. Med. Chem.* **2009**, *17*, 1276–1289; d) M. Ikeguchi, M. Sawaki, H. Nakayama, H. Kikugawa, H. Yoshii, *Pest Manag. Sci.* **2004**, *60*, 981–991.

[2] For an early example, see: a) G. P. Gardini, F. Minisci, G. Palla, *Tetrahedron Lett.* **1971**, *12*, 59–62. For reviews, see: b) F. Minisci, *Synthesis* **1973**, 1–24; c) F. Minisci, E. Vismara, F. Fontana, *Heterocycles* **1989**, *28*, 489–519; d) R. S. J. Proctor, R. J. Phipps, *Angew. Chem. Int. Ed.* **2019**, *58*, 13666–13699; *Angew. Chem.* **2019**, *131*, 13802–13837. For examples of of the Minisci reaction under a photoredox catalysis, see: e) Y. Zhang, K. B. Teuscher, H. Ji, *Chem. Sci.* **2016**, *7*, 2111–2118; f) J. Dong, Q. Xia, X. Lv, C. Yan, H. Song, Y. Liu, Q. Wang, *Org. Lett.* **2018**, *20*, 5661–5665. For benzothiazoles: g) J. Wang, J. Li, J. Huang, Q. Zhu, *J. Org. Chem.* **2016**, *81*, 3017–3022.

[3] For recent examples of alkylation of 2-chlorobenzazoles and alkane(arene)sulfonylheteroarenes, see: a) A. Lipp, G. Lahm, T. Opatz, *J. Org. Chem.* **2016**, *81*, 4890–4897; b) S. Kamijo, K. Kamijo, T. Murafuji, *J. Org. Chem.* **2017**, *82*, 2664–2671; c) S. Kamijo, K. Kamijo, T. Murafuji, *Synthesis* **2019**, *51*, 3859–3864; d) N. P. Ramirez, T. Lana-Villarreal, J. C. Gonzalez-Gomez, *Eur. J. Org. Chem.* **2020**, 1539–1550.

[4] Y. Ikeda, R. Ueno, Y. Akai, E. Shirakawa, *Chem. Commun.* **2018**, *54*, 10471–10474.

[5] We had reported, before ref. [4], the direct α-arylation of alkylamines with aryl halides utilizing a stoichiometric amount of a *tert*-butoxy radical precursor. The radical chain is not operative because the eliminated halo radical oxidizes the α-aminoalkyl radical (**I** in Scheme 1) to give the corresponding iminium halide rather than undergoes hydrogen atom abstraction from the amine. R. Ueno, Y. Ikeda, E. Shirakawa, *Eur. J. Org. Chem.* **2017**, 4188–4193.

[6] We have also reported the direct α-arylation of alcohols with aryl chlorides (and bromides) by the use of a substoichiometric amount of a *tert*-butoxy radical precursor. Here the radical chain is operative because the stabilities of halo radicals and α-hydroxyalkyl radicals are comparable. K. Aoki, K. Yonekura, Y. Ikeda, R. Ueno, E. Shirakawa, *Adv. Synth. Catal.* **2020**, *362*, 2200–2204.

[7] The Gibbs free energy values ΔG (kcal/mol) at 298 K for the reaction of a sulfonyl radical with DMA are estimated by DFT calculations using (U)B3LYP/6-311+G(d,p) to be +8.6 and +7.9 for $PhSO_2^{\bullet}$ and $MeSO_2^{\bullet}$, respectively, whereas that of the reaction of $PhSO_2^{\bullet}$ with isopropyldimethylamine is estimated to be +6.2 kcal/mol.

[8] The p$K_a$ values of the conjugated acids of $KHCO_3$, $K_2HPO_4$, $K_2CO_3$ and $K_3PO_4$ are reported to be 6.4, 7.2, 10.3 and 12.7, respectively. a) J. W. B. Fyfe, E. Valverde, C. P. Seath, A. R. Kennedy, J. M. Redmond, N. A. Anderson, A. J. B. Watson, *Chem. Eur. J.* **2015**, *21*, 8951–8964. The p$K_a$ value of $MeSO_2H$ is reported to be 2.3. b) F. Wudl, D. A. Lightner, D. J. Cram, *J. Am. Chem. Soc.* **1967**, *89*, 4099–4101.

[9] For discussion on the radical structures and stabilization energies of cyclic alkylamines such as pyrrolidine, see: D. D. M. Wayner, K. B. Clark, A. Rauk, D. Yu, D. A. Armstrong, *J. Am. Chem. Soc.* **1997**, *119*, 8925–8932.

[10] Alkanesulfonyl radicals having an alkene moiety, such as 4-pentenesulfonyl radical, are reported to undergo the intramolecular cyclization reaction. A. Tsimelzon, R. Braslau, *J. Org. Chem.* **2005**, *70*, 10854–10859.

[11] Methanesulfonyl radical is reported to decompose into $SO_2$ and methyl radical but a high temperature is required. S. Kim, H.-J. Song, T.-L. Choi, J.-Y. Yoon, *Angew. Chem. Int. Ed.* **2001**, *40*, 2524–2526; *Angew. Chem.* **2001**, *113*, 2592–2594.

[12] Considering the operation of a radical chain, we propose the mechanism shown in Scheme 7. However, another mechanism may be operative, considering the report that sulfinic acids are good hydrogen atom donors with alkyl radicals: M. Griesser, J.-P. R. Chauvin, D. A. Pratt, *Chem. Sci.* **2018**, *9*, 7218–7229.

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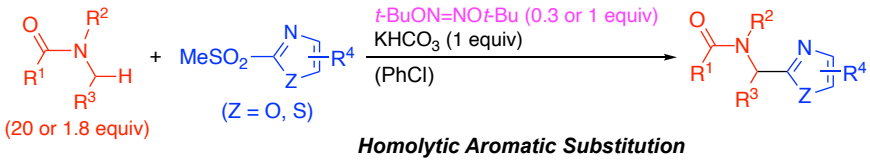


***Homolytic Aromatic Substitution***

The direct α-heteroarylation of alkylamides through a radical chain mechanism involving homolytic aromatic substitution (HAS) was accomplished using methanesulfonylheteroarenes and *t*-BuON=NO*t*-Bu as arylating reagents and a *tert*-butoxy radical precursor, respectively.