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α-Arylation of Alkylamines with Sulfonylarenes through a Radical Chain Mechanism

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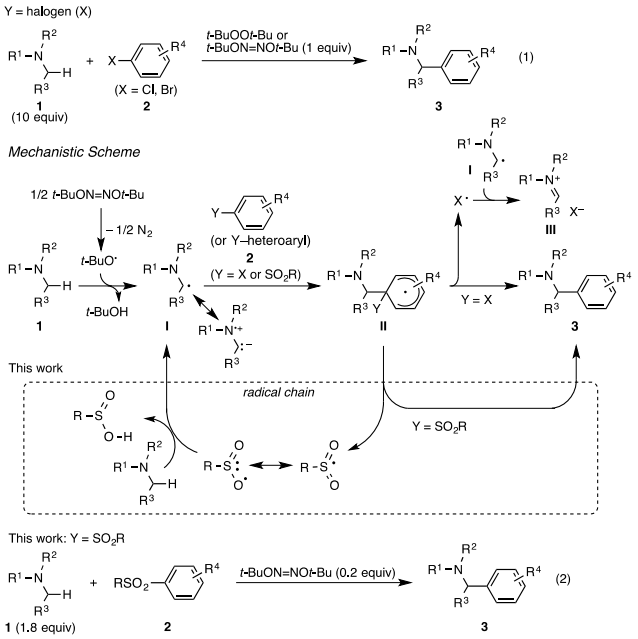
In the presence of a substoichiometric amount of a *tert*-butoxy radical precursor, the reaction of alkylamines with sulfonylarenes was found to give α-arylated alkylamines through homolytic aromatic substitution, where a radical chain is operative.

Many reports are available for α-arylation of alkylamines, reflecting its importance in organic synthesis. Methods to activate alkylamines getting ready for α-arylation are divided into three types: α-aminoalkyl anions, cations and radicals. The most popular method is utilization of the anions to obtain α-arylated secondary alkylamines representatively through a sequence consisting of acylation of a secondary alkylamine, deprotonation by butyllithium, transmetalation of the resulting α-(acylamino)alkyllithium with zinc chloride, the Negishi coupling with an aryl halide, and deacylation.[1] In contrast to the anion protocol, which requires a laborious process including acylation–deacylation, α-aminoalkyl cations, i.e. iminium salts, are available directly from alkylamines through facile 2e⁻ oxidation by the combination of a transition metal catalyst with an oxidant. The *in situ*-generated cationic species undergo electrophilic aromatic substitution with arenes but only with highly electron-rich ones such as indoles and pyrroles due to the low electrophilicity of the cationic species[2] α-Aminoalkyl radicals, which are also readily available through hydrogen abstraction from alkylamines by an oxy radical, have potential to undergo homolytic aromatic substitution (HAS), consisting of radical addition and radical elimination, to give α-arylation products.[3] In this context, we have recently reported that alkylamines (**1**: 10 equiv) react with aryl halides (**2**) having an electron-withdrawing group and/or a polycyclic structure in the presence of a stoichiometric amount (1 equiv) of a *tert*-butoxy radical precursor such as *t*-BuOO*t*-Bu and *t*-BuON=NO*t*-Bu to give α-arylation products (**3**) (eq. 1 in Scheme 1).[4,5] The reaction starts with homolysis of a *tert*-butoxy radical precursor to give *t*-BuO•, which abstracts an α-hydrogen from **1** (Scheme 1, middle). Addition of the resulting α-aminoalkyl radical (**I**) to **2** (Y = X) is followed by elimination of the halogen radical (X•) to give **3**.[6] Here X• does not undergo α-hydrogen abstraction that would make a radical chain to be operative. Instead, X• oxidizes another molecule of **I** to give an iminium halide (**III**), where 1 equivalent of **I** is sacrificed, and thus 2 equivalents of *t*-BuO• and an excess amount (2 equiv at least) of **1** are required.[7] The use of a leaving group that is sufficiently stable to leave as a radical and is sufficiently reactive in hydrogen abstraction from **1** makes it possible to promote the reaction through a radical chain mechanism and to reduce the amounts of the *t*-BuO• precursor



Scheme 1 α-Arylation of alkylamines through homolytic aromatic substitution (HAS).

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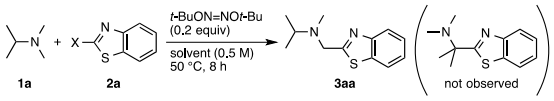
and the amine. We expected a sulfonyl radical to act as a leaving group that realizes a radical chain mechanism (Scheme 1, broken line box).[8] Here we report α-arylation of alkylamines (1.8 equiv) with sulfonylarenes in the presence of a substoichiometric amount (0.2 equiv) of *t*-BuON=NO*t*-Bu through a radical chain mechanism (eq. 2 in Scheme 1).

Treatment of 2-(benzenesulfonyl)benzothiazole (**2a**) with isopropyl(dimethyl)amine (**1a**: 1.2 equiv) and *t*-BuON=NO*t*-Bu (0.2 equiv) in methanol at 50 °C for 8 h gave (2-benzothiazolylmethyl)(isopropyl)(methyl)amine (**3aa**) in 75% yield with 80% conversion of **2a**, where a regioisomer, 2-(1-dimethylamino-1-methylethyl)benzothiazole, was not observed (Table 1, entry 1). The result that the yield of **3aa** exceeded the maximum amount (40%) of *t*-BuO• generation shows operation of a radical chain. The use of other solvents such as ethanol, 2-propanol, acetonitrile, dimethyl sulfoxide, 1,2-dichloroethane and benzene was less effective (entries 2–7). The yield was improved to 98% by the use of an increased amount (1.8 equiv) of **1a** (entry 8). On the other hand, the use of 2-chlorobenzothiazole (**2'a**) instead of **2a** drastically lowered the conversion and the yield, even with an increased amount (3.6 equiv) of **1a** (entries 9 and 10). The result that a high yield is accomplished with **2'a** by the use of 1 equiv of *t*-BuON=NO*t*-Bu (entry 11) shows that a radical chain does not work with chlorine as a leaving group.

Table 1 α-Arylation of isopropyl(dimethyl)amine (**1a**) with a 2-benzothiazolyl electrophile (**2a** or **2'a**) using *t*-BuON=NO*t*-Bu[a]

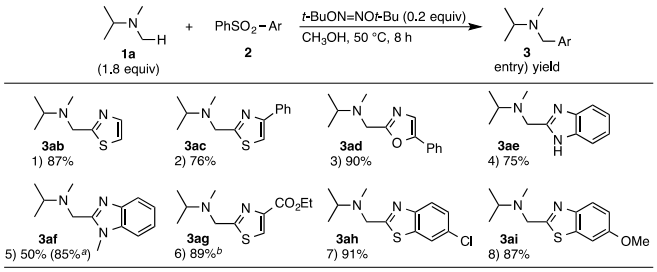


entry	X	**1a** (equiv)	solvent	conv. (%)[b]	yield (%)[b]
1	$PhSO_2$ (**2a**)	1.2	MeOH	80	75
2	$PhSO_2$ (**2a**)	1.2	EtOH	67	65
3	$PhSO_2$ (**2a**)	1.2	*i*-PrOH	63	54
4	$PhSO_2$ (**2a**)	1.2	MeCN	66	56
5	$PhSO_2$ (**2a**)	1.2	DMSO	18	18
6	$PhSO_2$ (**2a**)	1.2	$ClCH_2CH_2Cl$	67	65
7	$PhSO_2$ (**2a**)	1.2	C_6H_6	40	35
8	$PhSO_2$ (**2a**)	1.8	MeOH	98	98 (96)[c]
9	Cl (**2'a**)	1.8	MeOH	3	<1
10	Cl (**2'a**)	3.6	MeOH	20	11
11[d]	Cl (**2'a**)	3.6	MeOH	92	87

[a]The reaction was carried out under a nitrogen atmosphere at 50 °C for 8 h using a 2-benzothiazolyl electrophile (**2a** or **2'a**: 0.25 mmol), isopropyl(dimethyl)amine (**1a**) and *t*-BuON=NO*t*-Bu (0.050 mmol) in a solvent (0.5 mL). [b]Determined by GC. [c]The yield of the isolated product. [d] *t*-BuON=NO*t*-Bu (0.25 mmol) was used.

The α-arylation of isopropyl(dimethyl)amine (**1a**: 1.8 equiv) in the presence of 0.2 equiv of *t*-BuON=NO*t*-Bu is applicable to various 2-benzenesulfonylazoles including benzannulated ones (Table 2). Non- or phenyl-substituted thiazoles, oxazoles and benzimidazoles underwent the coupling in high yields (entries 1–4). The reaction of sterically hindered *N*-methylbenzimidazole resulted in a moderate yield (50%) under the standard conditions but the use of twice amounts of *t*-BuON=NO*t*-Bu and **1a** improved the yield to 85% (entry 5). (Benzo)thiazoles having an electron-withdrawing or -donating group also participated in the α-arylation in high yields (entries 6–8).[9]

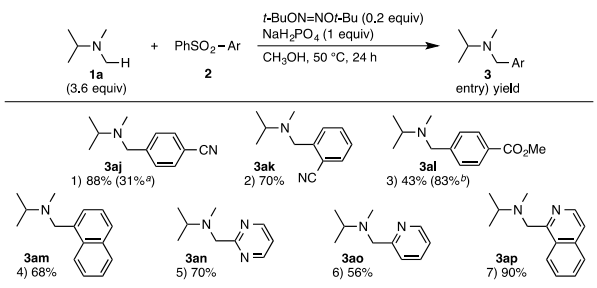
Table 2 α-Arylation of isopropyl(dimethyl)amine with sulfonylarenes.



[a]*t*-BuON=NO*t*-Bu (0.4 equiv) and **1a** (3.6 equiv) were used. [b]Ethanol was used instead of methanol.

The reaction is also applicable to six-membered aromatic sulfones, though some modification of the reaction conditions is required (Table 3). The reaction of 4-(benzenesulfonyl)-benzonitrile (**2j**) with isopropyl(dimethyl)amine (**1a**: 1.8 equiv) under the conditions employed in Table 2 gave the α-arylation product (**3aj**) at a methyl group of **1a** only in 31% yield with 39% conversion of **1a** (entry 1). In contrast, the use of the twice amount (3.6 equiv) of the amine and addition of NaH_2PO_4 (1 equiv) largely improved the yield of **3aj** to 88% with 90% conversion of **1a** (entry 1).[10] Other sulfonylbenzenes having an electron-withdrawing group participated in the α-arylation (entries 2 and 3). No substitution takes place on the phenyl group of the benzenesulfonyl moiety in all the sulfonylarenes (**2**) that undergo α-arylation, showing that the nucleophilic character of α-aminoalkyl radicals (**I** in Scheme 1), due to the carboanionic resonance structure as shown in Scheme 1, favors electrophilic aromatic rings as reaction partners in the aromaticity-breaking radical addition step.[11] However, 1-(benzenesulfonyl)-naphthalene participated in the α-arylation with no aid of an electron-withdrawing group because radical intermediate **II** (in Scheme 1), which is both benzylic and allylic, is relatively stable (entry 4). π-Deficient N-heterocycles such as pyrimidine, pyridine and isoquinoline also participated in the α-arylation in moderate to high yields (entries 5–7).

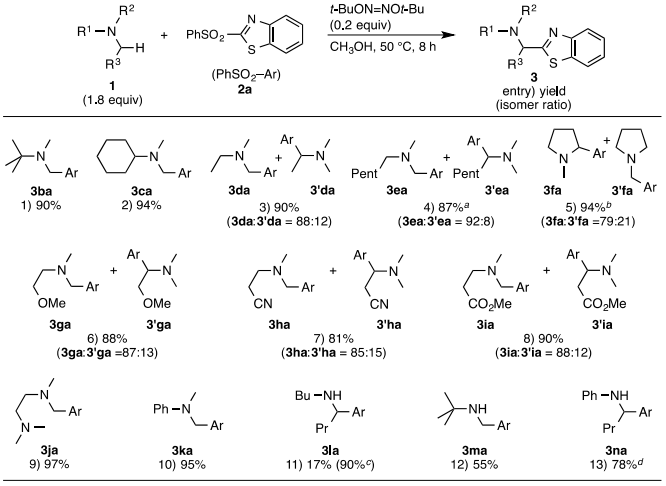
Table 3 α-Arylation of isopropyl(dimethyl)amine with sulfonylbenzene or sulfonylpyridine derivatives.



[a]**1a** (1.8 equiv) was used without NaH_2PO_4. [b]*t*-BuON=NO*t*-Bu (0.4 equiv) and **1a** (5 equiv) were used.

Various tertiary alkylamines are applicable to the α-arylation (Table 4). *tert*-Butyl(dimethyl)amine (**1b**) and cyclohexyl(dimethyl)amine (**1c**) were α-arylated with 2-(benzenesulfonyl)benzothiazole (**2a**) exclusively at a methyl group in high yields (entries 1 and 2). Dimethyl(*n*-alkyl)amines underwent the arylation at a methyl group in high preference to the primary alkyl group probably due to the steric reason (entries 3 and 4). However, this does not hold true for *N*-methylpyrrolidine (**1f**), the five-membered primary alkyl group of which gives an exceptionally stable alkyl radical with a relatively compact size (entry 5).[12,13] Functional groups such as methoxy, cyano, methoxycarbonyl and dimethylamino on dimethyl(alkyl)amines are tolerated (entries 6–9). Rather surprisingly, the arylation of *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA: **1j**) took place exclusively at a methyl group in a high yield, being free from diarylation (entry 9).[14] *N*,*N*-Dimethylaniline (**1k**) also participated in the α-arylation in a high yield (entry 10). The reaction of dibutylamine (**1l**) resulted in a low yield (17%) under the standard conditions but the use of an increased amount (1 equiv) of *t*-BuON=NO*t*-Bu improved the yield to 90% (entry11), showing that a radical chain is not operative. This observation is likely to be ascribed to high α-C–H bond dissociation energies of secondary amines compared with the corresponding tertiary amines,[15] preventing hydrogen abstraction by $PhSO_2^{\bullet}$. Secondary amines having a relatively low α-C–H bond dissociation energy such as *tert*-butyl(methyl)amine (**1m**) and *N*-butylaniline (**1n**) underwent the α-arylation in moderate yields even by the use of 0.2 equiv of *t*-BuON=NO*t*-Bu (entries 12 and 13).[15] The α-arylation of primary alkylamines is accomplished through a sequence consisting of *tert*-butyldimethylsilylation of primary alkylamines, the α-arylation and desilylation with an aqueous work-up (Table 5). α-Benzothiazolylation products of primary alkylamines including those having a functional group such as alkoxy, amino and ester were obtained in high yields.

Table 4 α-Arylation of tertiary and secondary alkylamines with 2-(benzenesulfonyl)benzothiazole.



[a]The reaction time = 24 h. [b]2-(Methanesulfonyl)benzothiazole was used instead of **2a**. [c]*t*-BuON=NO*t*-Bu (1 equiv) was used. [d]Methanol/1,2-dichloroethane (1:1, 0.5 mL) was used instead of methanol (0.5 mL).

Table 5 α-Arylation of primary alkylamines through *tert*-butyldimethylsilyl protection–deprotection.

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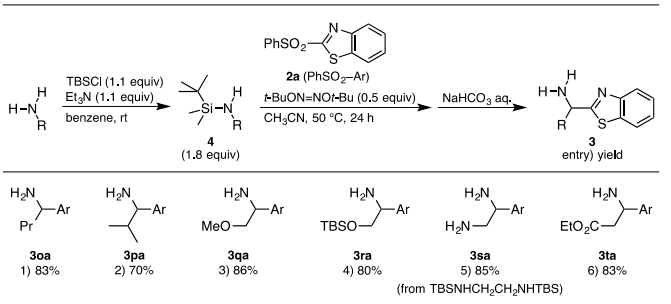
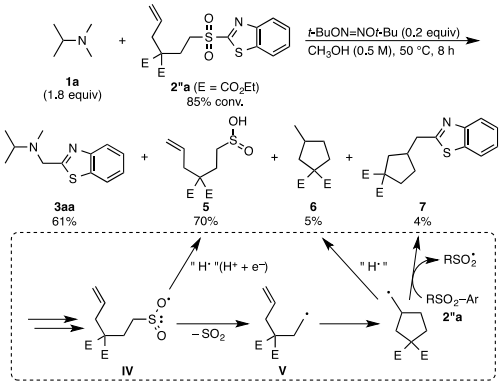
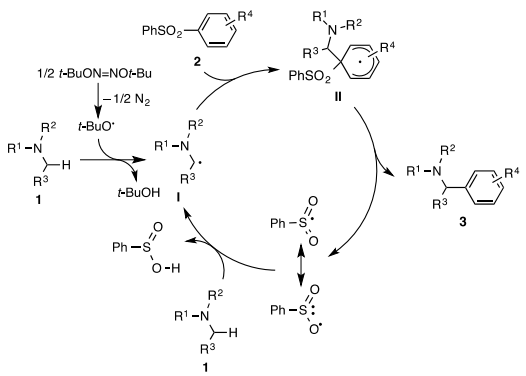


Involvement of sulfonyl radicals as leaving groups is strongly supported by the following result. The reaction of 2-[3,3-bis(ethoxycarbonyl)-5-hexenesulfonyl]benzothiazole (**2"a**) with isopropyl(dimethyl)amine (**1a**) under the standard conditions gives certain amounts of cyclized products (**6** and **7**) in addition to the α-arylation product (**3aa**) and 3,3-bis(ethoxycarbonyl)-5-hexenesulfinic acid (**5**) (Scheme 2).[16] A part of 3,3-bis(ethoxycarbonyl)-5-hexenesulfonyl radical (**IV**), generated upon HAS, is considered to decompose into SO_2 and 3,3-bis(ethoxycarbonyl)-5-hexenyl radical (**V**), which, after cyclization, undergoes hydrogen abstraction and HAS on **2"a** to give **6** and **7**, respectively.



Scheme 2 Involvement of sulfonyl radicals as leaving groups.

On the basis of the above result as well as the operation of a radical chain derived from the observation that just a substoichiometric amount of a *tert*-butoxy radical precursor



Scheme 3 A plausible mechanism.

works, the α-arylation is likely to proceed through the mechanism we initially expected (Scheme 3). Homolysis of *t*-BuON=NO*t*-Bu gives *t*-BuO•, which undergoes hydrogen abstraction from a carbon atom adjacent to the nitrogen atom of an alkylamine (**1**). Addition of the resulting α-aminoalkyl radical (**I**) to a benzenesulfonylarene (**2**) is followed by elimination of $PhSO_2$• to give the corresponding α-arylation product (**3**). Finally, $PhSO_2$• undergoes hydrogen abstraction from **1** to regenerate α-aminoalkyl radical **I**.[17]

In conclusion, we have developed α-arylation of alkylamines with sulfonylarenes through homolytic aromatic substitution just by the use of a substoichiometric amount of a *tert*-butoxy radical precursor and methanol as a solvent. Compared with the previous related method using aryl halides, remarkable reduction of the amounts of the *tert*-butoxy radical precursor and the amine has been accomplished by making a radical chain operative.

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Notes and references

1 For an early example, see: (a) K. R. Campos, A. Klapars, J. H. Waldman, P. G. Dormer and C.-Y. Chen, *J. Am. Chem. Soc.*, 2006, **128**, 3538. For a review, see: (b) E. A. Mitchell, A. Peschiulli, N. Lefevre, L.Meerpoel and B. U. W. Maes, *Chem. Eur. J.*, 2012, **18**, 10092.

2 For an example, see: (a) Z. Li and C.-J. Li, *J. Am. Chem. Soc.*, 2005, **127**, 6968. For a review, see: (b) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 74.

3 One of the most important reactions utilizing HAS with a sp^3-carbon radical adjacent to a hetroatom (N, O, S, ...) is the Minisci reaction, where α-arylation of heteroatom-containing aliphatic compounds such as amides, ethers and sulfides with pyridine derivatives takes place in the presence of a stoichiometric amount of an oxidant, "H•" acting as a leaving group. For reviews, see: (a) F. Minisci, *Synthesis*, 1973, 1; (b) F. Minisci, E. Vismara and F. Fontana, *Heterocycles*, 1989, **28**, 489. For a recent example, giving α-arylation products of alkylamides with benzothiazole derivatives, see: (c) J. Wang, J. Li, J. Huang and Q. Zhu, *J. Org. Chem.*, 2016, **81**, 3017.

4 R. Ueno, Y. Ikeda and E. Shirakawa, *Eur. J. Org. Chem.*, 2017, 4188.

5 There is an emerging area on the photoredox catalysis that accomplishes the α-arylation of heteroatom-containing aliphatic compounds with heteroaryl electrophiles under photoredox catalysis, where an HAS mechanism is considered to be operative. For the reaction of aryl halides, see: (a) A. Singh, A. Arora and J. D. Weaver, *Org. Lett.*, 2013, **15**, 5390; (b) C. K. Prier and D. W. C. MacMillan, *Chem. Sci.*, 2014, **5**, 4173; (c) A. Lipp, G. Lahm and T. Opatz, *J. Org. Chem.*, 2016, **81**, 4890. For aryl cyanides, see: (d) A. McNally, C. K. Prier and D. W. C. MacMillan, *Science*, 2011, **334**, 1114. For the reaction of 2- or 4-(methanesulfonyl)pyrimidine, see: (e) S. Kamijo, K. Kamijo and T. Murafuji, *J. Org. Chem*,. 2017, **82**, 2664. For the α-arylation in combination with a nickel catalysis, see: (f) D. T. Ahneman and A. G. Doyle, *Chem. Sci.*, 2016, **7**, 7002; (g) Y.-Y. Gui, L.-L. Liao, L. Sun, Z. Zhang, J.-H. Ye, G. Shen, Z.-P. Lu, W.-J. Zhou and D.-G. Yu, *Chem. Commun.*, 2017, **53**, 1192.

6 Addition does not always take place at the carbon atom connected to the halogen but the intermediates after addition to elsewhere inevitably go back to the original state.

7 The production of certain amounts of the corresponding secondary amine and ketone derived from the iminium halides (**III** in Scheme 1) is confirmed. See ref. 4.

8 Sulfonyl radicals are reported to act as leaving groups in HAS but they do not undergo hydrogen abstraction to regenerate the radicals attacking the aromatic ring. For an early examples, see: (a) M. Fiorentino, L. Testaferri, M. Tiecco and L. Troisi, *J. C. S., Chem. Comm.*, 1977, 316. For a review, see: (b) M. Tiecco, *Acc. Chem. Res.*, 1980, **13**, 51. See also ref. 5e.

9 In the reaction of **1a** with **2g** having an ethyl ester moiety in methanol (*cf*. Table 2, entry 6), α-arylation was accompanied by ester exchange to give **3ag** and the corresponding methyl ester with 76:24 ratio in 93% total yield.

10 The use of other bases such as Na_2HPO_4, KH_2PO_4, $NaHCO_3$, Na_2CO_3 and NaOAc resulted in lower yields. The reaction of 2-(benzenesulfonyl)benzothiazole (**2a**) with isopropyl(dimethyl)amine (**1a**) under these conditions (Table 3) gave a slightly lower yield (93%) of **3aa** than the reaction under the reaction conditions employed in Table 2. NaH_2PO_4 possibly convert sulfinic acid, generated upon hydrogen abstraction from an amine by a sulfonyl radical, into the sulfinate to eliminate it from the equilibrium, though it is unclear why such a role is not required in the reaction of sulfonylazoles such as **2a**.

11 This requirement for the aromatic rings as reaction partners is strict: benzenesulfonylarenes ($PhSO_2$–Ar), Ar of which is phenyl, 4-methoxyphenyl, 2-thienyl, 2-pyrrolyl, 2-indolyl, 1-methyl-5-pyrazolyl or 1-methyl-2-imidazolyl, gave alpha-arylation products of isopropyl(dimethyl)amine (**1a**) in <10% yield, <1% in most cases, under the conditions of Table 2 or 3.

12 For discussion on the radical structures and stabilization energies of alkylamines including pyrrolidine, see: D. D. M. Wayner, K. B. Clark, A. Rauk, D. Yu and D. A. Armstrong, *J. Am. Chem. Soc.*, 1997, **119**, 8925.

13 The yield of the α-arylation products by the use of 2-bezenesufonylbenzothiazole (**2a**), instead of the 2-methansulfonyl derivative, was lower (65%, **3fa**:**3'fa** = 77:23) due to coproduction of benzothiazole (26% yield) through reduction of **2a**.

14 The homogeneity of the reaction mixture looked low with this combination of the substrates compared with other combinations. A possible reason that no diarylation takes place is that low solubility of monoarylation product **3ja** drives itself out of the reaction mixture.

15 The bond dissociation energies of a C–H bond of a methyl group in methylamines are reported as follows (kcal/mol): Me_2NH (94.2), Me_3N (93.2), *t*-$BuNMe_2$ (90.0), $PhNMe_2$ (91.7). Y.-R. Luo in *Comprehensive Handbook of Chemical Bond Energies*; CRC Press: Boca Raton, 2007; chap. 3.6, pp 102–105.

16 For an example of the use of 3,3-bis(ethoxycarbonyl)-5-hexenesulfonyl radical for a radical clock experiment, see: D. Crich and D. Grant, *Tetrahedron Lett.*, 2008, **49**, 2999.

17 Addition of TEMPO (1 equiv) to the reaction mixture of isopropyl(dimethyl)amine (**1a**) and 2-(benzenesulfonyl)benzothiazole (**2a**) under the conditions of entry 8 of Table 1 completely inhibited the α-arylation with no conversion of **2a**.