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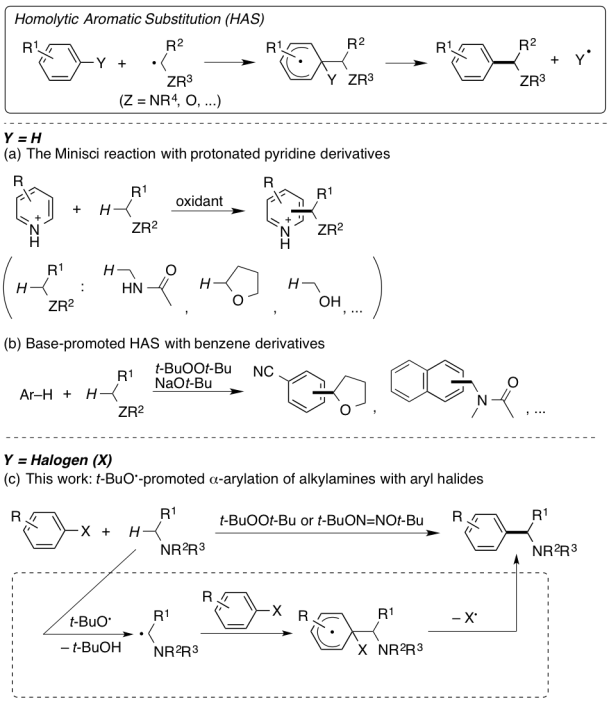
tert-Butoxy Radical-Promoted α-Arylation of Alkylamines with Aryl Halides

*Ryota Ueno, Yuko Ikeda and Eiji Shirakawa**

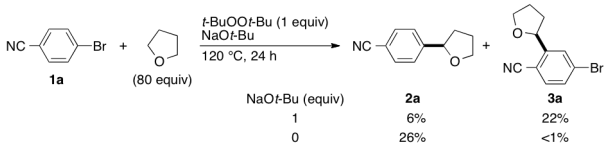
Abstract: *In the presence of a tert-butoxy radical precursor, the reaction of alkylamines with aryl halides was found to give α-arylated alkylamines through homolytic aromatic substitution of the halogen atoms.*

Homolytic aromatic substitution (HAS), consisting of addition of an aliphatic sp^3-carbon radical adjacent to a heteroatom to an aromatic compound (Ar–Y) followed by elimination of radical Y$^{\bullet}$, has high potential as a synthetic method to achieve α-arylation of heteroatom-containing aliphatic compounds (Scheme 1, top).[1] The most successful example is the Minisci reaction, which employs sp^3-carbon radicals adjacent to a heteroatom in combination with protonated pyridine derivatives to give α-pyridination products of amides, ethers and alcohols, H$^{\bullet}$ being leaving group Y$^{\bullet}$ here (Scheme 1, a).[2] The Minisci reaction utilizes readily available sp^3-carbon radicals generated through hydrogen abstraction from heteroatom-containing aliphatic compounds such as amides and ethers. However, the unfavorable aromaticity-breaking radical addition step requires high electrophilicity for aromatic compounds to facilitate the reaction with the nucleophilic sp^3-carbon radicals having a heteroatom at α-position. This requirement limits its scope essentially to protonated pyridine derivatives. In this context, we have recently reported that use of a strong base such as NaO*t*-Bu as a promoter reduces the limitation to expand the scope to benzene derivatives having electron-withdrawing groups and/or a polycyclic structure (Scheme 1, b).[3] The both methods, employing H$^{\bullet}$ as leaving group Y$^{\bullet}$, suffer from production of a mixture of regioisomers because selection of an optional C–H bond is intrinsically difficult. The regioselectivity problem can be solved by use of aryl halides [Y = halogen (X)], making the halogen atom to leave as the radical (X$^{\bullet}$).[4,5] Here we report α-arylation of alkylamines with aryl halides having an electron-withdrawing group and/or a polycyclic structure with the aid of a *tert*-butoxy radical precursor, where an HAS mechanism with X$^{\bullet}$ as a leaving group is operative.[6,7]



Scheme 1. α-Arylation of heteroatom-containing aliphatic compounds through homolytic aromatic substitution (HAS).

During the course of the investigation on the α-arylation of ethers with arenes through the dehydrogenative coupling in (b) of Scheme 1,[3] we found that the reaction of 4-bromobenzonitrile (**1a**) with tetrahydrofuran (THF: 80 equiv) in the presence of *t*-BuOO*t*-Bu (1 equiv) and NaO*t*-Bu (1 equiv) at 120 °C for 24 h gave a dehydrobrominative coupling product, 4-(2-tetrahydrofuranyl)benzonitrile (**2a**: 6%), in addition to a dehydrogenative coupling product, 4-bromo-2-(2-tetrahydrofuranyl)benzonitrile (**3a**: 22%) (Scheme 2). The reaction in the absence of NaO*t*-Bu, which had been shown to be indispensable for the effective dehydrogenative coupling, gave **2a** exclusively but only in a low yield (26%). The eliminated bromine atom (Br$^{\bullet}$) is likely to be reduced to Br$^-$ by THF. We anticipated that alkylamines, which are more electron-rich than alkyl ethers, readily reduce Br$^{\bullet}$, or successively generated Br_2, to Br$^-$, and examined the α-arylation of alkylamines with aryl halides with the aid of *t*-BuOO*t*-Bu.



Scheme 2. The reaction of tetrahydrofuran with 4-bromobenzonitrile using *t*-BuOO*t*-Bu in the presence or absence of NaO*t*-Bu.

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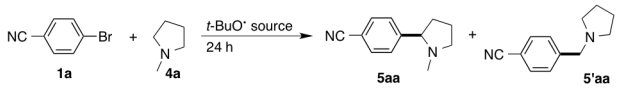
Treatment of 4-bromobenzonitrile (**1a**) with *N*-methylpyrrolidine (**4a**: 10 equiv) and *t*-BuOO*t*-Bu (1 equiv) at 120 °C for 24 h gave *N*-methyl-2-(4-cyanophenyl)pyrrolidine (**5aa**) and *N*-(4-cyanophenylmethyl)pyrrolidine (**5'aa**) (85:15) in 79% combined yield, where no dehydrogenative coupling products were observed (Table 1, entry 1).[8] The conversion and the yield were much lowered by use of a decreased amount (0.2 equiv) of *t*-BuOO*t*-Bu (Table 1, entry 2), showing that only a short radical chain is operative. No reaction took place in the absence of *t*-BuOO*t*-Bu or at a low temperature (60 °C) of which homolysis of *t*-BuOO*t*-Bu is negligible (Table 1, entries 3 and 4). The reaction using *t*-BuON=NO*t*-Bu, which undergoes much more facile homolysis than *t*-BuOO*t*-Bu to give *t*-BuO$^{\bullet}$,[9] at 60 °C scored a high yield with a high regioselectivity (Table 1, entry 5). These results show that the reaction proceeds at 60 °C when *t*-BuO$^{\bullet}$ is available. In the following investigation, we used the reaction conditions of entry 1 or 5 in Table 1 according to the combination of substrates.

Table 1: α-Arylation of *N*-methylpyrrolidine with 4-bromobenzonitrile using a *t*-BuO$^{\bullet}$ source.[a]

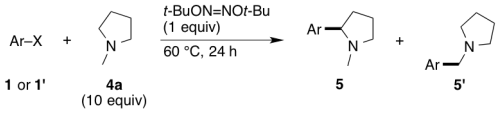


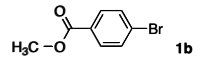
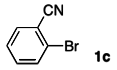
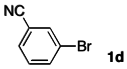
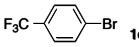
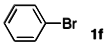
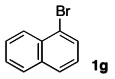
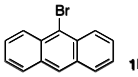
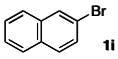
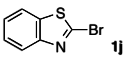
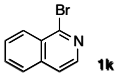
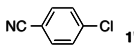
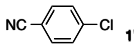
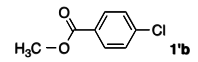
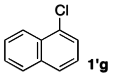
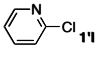
Entry	*t*-BuO$^{\bullet}$ source (equiv)	temp. (°C)	conv. of **1a** (%)[b]	yield of **5aa** + **5'aa** (%)[b]	**5aa**:**5'aa**[c]
1	*t*-BuOO*t*-Bu (1)	120	100	79	85:15
2	*t*-BuOO*t*-Bu (0.2)	120	37	35	79:21
3	none	120	<1	<1	—
4	*t*-BuOO*t*-Bu (1)	60	<1	<1	—
5	*t*-BuON=NO*t*-Bu (1)	60	99	98 (95)[d]	94:6

[a] The reaction was carried out under a nitrogen atmosphere for 24 h using 4-bromobenzonitrile (**1a**: 0.25 mmol), *N*-methylpyrrolidine (**4a**: 2.5 mmol) and *t*-BuO$^{\bullet}$ source. [b] Determined by ^{1}H NMR. [c] Determined by GC and confirmed by ^{1}H NMR. [d] The yield of the isolated product.

The α-arylation of *N*-methylpyrrolidine (**4a**) using *t*-BuON=NO*t*-Bu at 60 °C for 24 h was applied to various aryl bromides (Table 2). Bromobenzenes having a conjugating electron-withdrawing group such as cyano and methoxycarbonyl at *para* or *ortho* underwent the reaction in high yields, whereas a cyano group at *meta* position or an inductively electron-withdrawing trifluoromethyl group at *para* position did not work effectively as a promoting substituent (Table 2, entries 1–4; Table 1, Entry 5). These results show that the radical addition to monocyclic aryl halides has a character of nucleophilic conjugate addition.[10] Besides this type, another mode to accept addition of an α-aminoalkyl radical is available when aryl halides have a polycyclic structure. Nonsubstituted bromobenzene (**1f**) was unreactive toward **4a**, whereas 1-naphthyl and 9-anthryl bromides participated in the coupling without the aid of a conjugating electron-withdrawing group (Table 2, entries 5–7). The radical addition step is advantageous for these polycyclic aromatics over monocyclic ones because the loss of aromaticity upon addition is less severe. However, the yield was much lower with 2-bromonaphthalene than with 1-bromonaphthalene (Table 2, entries 6 and 8), due to the difference in the stability of the intermediates after the radical addition: just a benzylic radical for the former and a benzylic as well as an allylic radical for the latter. Heteroaryl bromides also participated in the α-arylation (Table 2, entries 9 and 10). The reaction is applicable also to aryl chlorides, though a high temperature is required. For example, the yield in the reaction of 4-chlorobenzonitrile (**1'a**) was improved from 57% to 88% by raising the temperature from 60 °C to 120 °C using *t*-BuOO*t*-Bu instead of *t*-BuON=NO*t*-Bu (Table 2, entries 11 and 12).[11] Other aryl chlorides underwent the α-arylation with **4a** under these conditions (Table 2, entries 13–15).

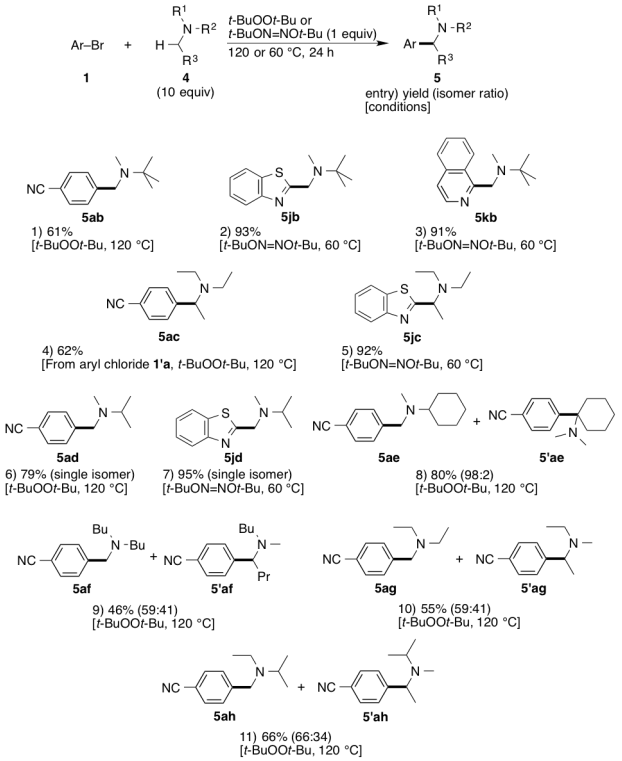
Table 2: α-Arylation of *N*-methylpyrrolidine with aryl halides.[a]



Entry	**1**	yield of **5** + **5'** [%][b]	**5**:**5'**[c]
1	 **1b**	78	93:7
2	 **1c**	83	79:21
3	 **1d**	16[d]	77:23
4	 **1e**	3[d]	78:22
5	 **1f**	<1[d]	—
6	 **1g**	88	90:10
7	 **1h**	81	88:12
8	 **1i**	22[d]	88:12
9	 **1j**	95	82:18
10	 **1k**	85	83:17
11	 **1'a**	57	94:6
12[e]	 **1'a**	88	85:15
13[e]	 **1'b**	70	90:10
14[e]	 **1'g**	80	85:15
15[e,f]	 **1'l**	53	95:5

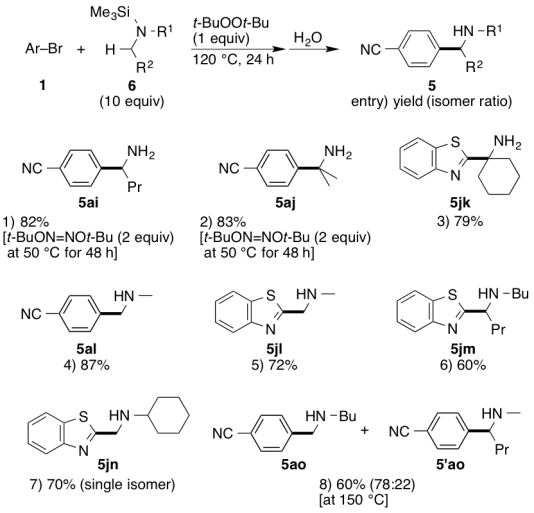
[a] The reaction was carried out under a nitrogen atmosphere for 24 h using an aryl halide (**1** or **1'**: 0.25 mmol), *N*-methylpyrrolidine (**4a**: 2.5 mmol) and *t*-BuON=NO*t*-Bu (0.25 mmol). [b] The yield of the isolated products. [c] Determined by GC and confirmed by ^{1}H NMR. [d] Determined by ^{1}H NMR. [e] *t*-BuOO*t*-Bu was used instead of *t*-BuON=NO*t*-Bu at 120 °C. [f] *t*-BuOO*t*-Bu (2 equiv) was used.

Acyclic trialkylamines were also employed (Scheme 3). *tert*-Butyl(dimethyl)amine (**4b**) and triethylamine (**4c**) underwent the α-arylation with aryl and heteroaryl halides in moderate to high yields (Scheme 3, entries 1–5). Dimethyl(*sec*-alkyl)amines (**4d** and **4e**) were arylated at a methyl group in high preference to the secondary alkyl group (Scheme 3, entries 6–8). Preference for methyl over primary alkyl groups was observed but in low selectivities (Scheme 3, entries 9–11). The regioselectivity in the α-arylation of dissymmetric alkylamines is well-understood, considering the regioselectivity of the hydrogen abstraction as well as the rates in which the resulting radicals add to an aryl halide. In the hydrogen abstraction step, the steric factor, which favors the reaction order of methyl > primary >> secondary, seems to slightly surpass the electronic factor, which depends on the stability of the resulting radicals in order of secondary > primary > methyl. The same tendencies of the steric and electronic factors are likely to be operative in the addition step, where the electronic factor seems to slightly surpass the steric factor. As a consequence, the steric factor in the both steps makes secondary alkyl groups less reactive, whereas methyl and primary alkyl groups show similar reactivities due to the conflicting reaction orders in the steric and electronic factors. This does not hold true for *N*-methylpyrrolidine (**4a** in Tables 1 and 2), the five-membered primary alkyl group of which gives an exceptionally stable alkyl radical,[12] making it electronically favored in both the hydrogen abstraction and the addition steps.



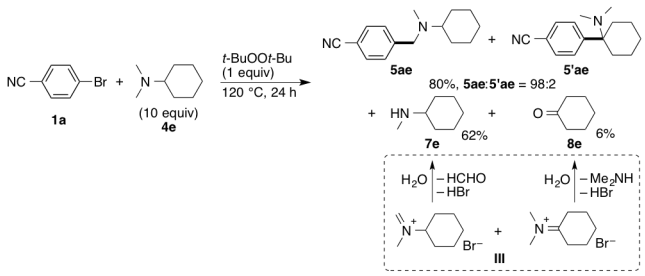
Scheme 3. α-Arylation of acyclic tertiary alkylamines.

Although no α-arylation took place with primary and secondary alkylamines,[13] trimethylsilylated ones reacted with aryl bromides (**1**) to give the corresponding desilylated α-arylation products after aqueous work-up (Scheme 4). The resonance effect by the β-silyl group is likely to facilitate formation of the radical intermediates and enhance the reactivities toward aryl bromides with increased nucleophilicities.[14] Primary amines such as butyl, isopropyl and cyclohexylamines were subjected to the silyl protection–α-arylation–deprotection protocol to give the corresponding α-arylated primary alkylamines (Scheme 4, entries 1–3). The protocol is applicable also to secondary alkylamines (Scheme 4, entries 4–8). The arylation of cyclohexyl(methyl)(trimethylsilyl)amine (**6n**) took place exclusively at the methyl group (Scheme 4, entry 7). The selectivity of methyl over a primary alkyl was high in the reaction of butyl(methyl)(trimethylsilyl)amine (**6o**) compared with dibutyl(methyl)amine (**4f**) (Scheme 4, entry 8; *cf*. Scheme 3, entry 9).



Scheme 4. α-Arylation of trimethylsilylamines to give α-arylated primary and secondary alkylamines.

In order to elucidate the stoichiometry of the α-arylation, we pursued the products derived from an alkylamine (Scheme 5). In the reaction of 4-bromobenzonitrile (**1a)** with cyclohexyl(dimethyl)amine (**4e**) (*cf*. Scheme 3, entry 8), cyclohexyl(methyl)amine (**7e**) and cyclohexanone (**8e**) were obtained in 62% and 6% yields, respectively. Products **7e** and **8e** are most likely to be obtained through hydrolysis of methylidene- and cyclohexylidene-containing iminium bromides (Scheme 5, **III**), respectively, showing that an extra equivalent of the alkylamine is consumed to reduce X$^{\bullet}$ into X^{-}.



Scheme 5. Elucidation of the stoichiometry of the α-arylation of alkylamines.

On the basis of these results, the α-arylation of alkylamines with aryl halides is likely to proceed through the mechanism we initially expected (Scheme 6). Homolysis of *t*-BuOO*t*-Bu or *t*-BuON=NO*t*-Bu

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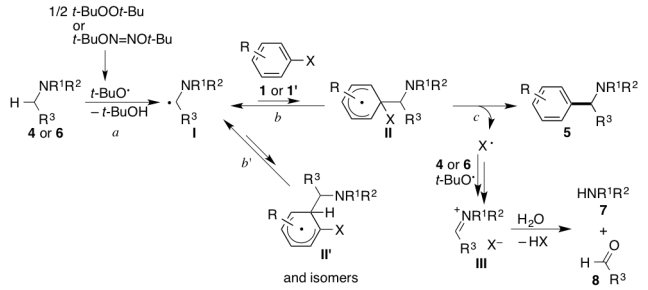
gives *t*-BuO•, which abstracts a hydrogen atom from a carbon–hydrogen bond adjacent to the nitrogen atom of an alkylamine (**4** or **6**) (Scheme 6, step *a*). The resulting α-aminoalkyl radical (**I**) adds to an aryl halide (**1** or **1'**) to give cyclohexadienyl radical intermediate **II** (Scheme 6, step *b*). Although attack of **I** toward **1**/**1'** takes place also on carbon atoms having a hydrogen atom (Scheme 6, step *b'*), the addition products such as **II'** do nothing but going back to **I** and **1**/**1'** as the radical addition step is reversible and its equilibrium lies far to **I**. Elimination of the halogen radical (X•) gives α-arylation product **5** (Scheme 6, step *c*). Although it is unclear how the eliminated X•, or the successively generated X_2, is reduced into X^-, alkylamine **4**/**6** accept two electron oxidation directly or indirectly by X• and *t*-BuO• to give iminium halides **III**, which are converted into the corresponding dealkylated amine (**7**) and aldehyde/ketone (**8**) by aqueous workup.[15]



Scheme 6. A plausible mechanism.

In conclusion, we have disclosed α-arylation of tertiary alkylamines or silylated primary and secondary alkylamines with aryl halides utilizing a *t*-BuO• source. The reaction proceeds through chemoselective homolytic aromatic substitution, where halogen atoms (Br and Cl) act as leaving groups.

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Keywords: α-arylation• alkylamines• aryl halides • radical mechanism • *t*-BuO• source

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[2] For selected examples, see: a) G. P. Gardini, F. Minisci, G. Palla, A. Arnone, R. Galli, *Tetrahedron Lett.* **1971**, 59–62. b) A. Arnone, M. Cecere, R. Galli, F. Minisci, M. Perchinunno, O. Porta, G. Gardini, *Gazz. Chim. Ital.* **1973**, *103*, 13–29. For reviews, see: c) F. Minisci, *Synthesis* **1973**, 1–24; d) F. Minisci, E. Vismara, F. Fontana, *Heterocycles* **1989**, *28*, 489–519.

[3] R. Ueno, E. Shirakawa, *Org. Biomol. Chem.* **2014**, *12*, 7469–7473.

[4] For reviews on HAS with a halogen leaving group, see: a) J. G. Traynham, *Chem. Rev.* **1979**, *79*, 323–330; b) M. Tiecco, *Acc. Chem. Res.* **1980**, *13*, 51–57; c) M. Tiecco, *Pure Appl. Chem.* **1981**, *53*, 239–258.

[5] For example, the reaction of bromobenzene (6.2 equiv) with cyclohexane (5 equiv) in the presence of *t*-BuOO*t*-Bu (1 equiv) gives a mixture of cyclohexylbenzene and bromo(cyclohexyl)benzenes (1:5). J. R. Shelton, C. W. Uzelmeier, *J. Am. Chem. Soc.* **1966**, *88*, 5222–5228.

[6] Several research groups have recently reported the α-arylation of heteroatom-containing aliphatic compounds with heteroaryl halides under photoredox catalysis. Although an HAS mechanism is considered to be operative, how the elimination of the halogen atom proceeds is not clarified. The reaction requires a rather complicated photoredox system and the scope of aryl halides is limited to heteroaryl chlorides containing more than two heteroatoms on the aromatic ring. a) A. Singh, A. Arora, J. D. Weaver, *Org. Lett.* **2013**, *15*, 5390–5393; b) C. K. Prier, D. W. C. MacMillan, *Chem. Sci.* **2014**, *5*, 4173–4178; c) A. Lipp, G. Lahm, T. Opatz, *J. Org. Chem.* **2016**, *81*, 4890–4897. As a similar example under photoredox catalysis, α-arylation of alkylamines with benzonitriles having an electron-withdrawing group has been reported, where the proposed mechanism includes single electron reduction of a benzonitrile to give the corresponding anion radical, which undergoes coupling with α-aminoalkyl radical, and the following elimination of cyanide (CN^-) gives the α-arylation product. d) A. McNally, C. K. Prier, D. W. C. MacMillan, *Science* **2011**, *334*, 1114–1117. Recently, α-arylation of alkylamines with aryl halides using a photoredox and nickel catalyst has been reported, where an α-aminoalkyl radical was transformed into an α-aminoalkyl nickel species to undergo the cross-coupling reaction with an aryl halide. e) D. T. Ahneman, A. G. Doyle, *Chem. Sci.* **2016**, *7*, 7002–7006. For a related example, see: f) D. R. Heitz, J. C. Tellis, G. A. Molander, *J. Am. Chem. Soc.* **2016**, *138*, 12715–12718.

[7] α-Arylation of secondary alkylamines is achieved e.g., through acylation of a secondary amine, deprotonation by butyllithium, transmetalation of the resulting α-(acylamino)alkyllithium with $ZnCl_2$, the Negishi coupling with a heteroaryl halide, and deacylation. a) K. R. Campos, A. Klapars, J. H. Waldman, P. G. Dormer, C.-Y. Chen, *J. Am. Chem. Soc.* **2006**, *128*, 3538–3539. For a review, see: b) E. A. Mitchell, A. Pœeschiulli, N. Lefevre, L. Meerpoel, B. U. W. Maes, *Chem. Eur. J.* **2012**, *18*, 10092–10142.

[8] The reaction of **1a** with a reduced amount (2 equiv) of **4a** resulted in a much lower yield (19%, **5aa**:**5'aa** = 84:16) with a low conversion (28%) of **1a** under the conditions of entry 1 of Table 1.

[9] H. Kiefer, T. G. Traylor, *Tetrahedron Lett.* **1966**, 6163–6168.

[10] Aryl halides having an electron-donating group such as 4-bromoanisole did not participate in the α-arylation at all.

[11] Use of *t*-BuON=NO*t*-Bu (1 equiv) at 120 °C in the reaction of 4-chlorobenzonitrile (**1'a**) with *N*-methylpyrrolidine (**4a**: 10 equiv) scored a lower yield of **5aa** and **5'aa** (64%, 88:12), probably because supply of *t*-BuO• through homolysis is too fast mismatching other steps.

[12] Facility in generating the corresponding radical from pyrrolidine compared with structurally similar compounds is discussed on the basis of stereoelectronic effect by the lone pair on the nitrogen atom. a) D. Griller, J. A. Howard, P. R. Marriott, J. C. Scaiano, *J. Am. Chem. Soc.* **1981**, *103*, 619–623. For discussion on the radical structures and stabilization energies of alkylamines including pyrrolidine, see: b) D. D. M. Wayner, K. B. Clark, A. Rauk, D. Yu, D. A. Armstrong, *J. Am. Chem. Soc.* **1997**, *119*, 8925–8932.

[13] The reaction of butylamine or diethylamine (10 equiv) with 4-bromobenzonitrile (**1a**: 1 equiv) in the presence of *t*-BuON=NO*t*-Bu (1 equiv) at 60 °C for 24 h gave no α-arylated products with no consumption of **1a**.

[14] N. Auner, R. Walsh, J. Westrup, *J. Chem. Soc., Chem. Commun.* **1986**, 207–208.

[15] The possibility that the halogen atom (X) undergoes elimination in a form of X^- after single electron reduction of cyclohexadienyl radical **II** by α-aminoalkyl radical **I**, giving α-arylation products **5** and iminium salts **III**, cannot be excluded. A similar mechanism has been proposed in the reduction of alkyl halides into alkanes using α-aminoalkyl radicals. a) J. Lalevée, J. P. Fouassier, N. Blanchard, K. U. Ingold, *Chem. Phys. Lett.* **2011**, *511*, 156–158. In the reaction of dihalobenzenes (X–C_6H_4–X') with dibenzylmercury giving $PhCH_2$–C_6H_4–X' through an HAS mechanism, benzyl radical, which is generated in situ and acts as the radical attacking X–C_6H_4–X', is considered to work also as a single electron reductant toward X-substituted cyclohexadienyl radicals to give $PhCH_2$–C_6H_4–X' and $PhCH_2X$. b) R. Henriquez, D. C. Nonhebel, *Tetrahedron* **1993**, *49*, 6497–6500.

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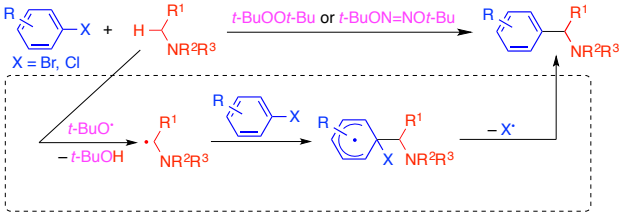

Just adding a *tert*-butoxy radical precursor, alkylamines react with aryl halides to give α-arylalkylamines. The reaction proceeds through chemoselective homolytic aromatic substitution of the halogen atom (Br or Cl) by an α-aminoalkyl radical.

α-Arylation of Alkylamines

*Ryota Ueno, Yuko Ikeda and Eiji Shirakawa**

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***tert*-Butoxy Radical-Promoted α-Arylation of Alkylamines with Aryl Halides**