We present a highly regio- and chemoselective Csp³–H arylation of benzylamines mediated by synergy of single electron transfer (SET) and hydrogen atom transfer (HAT) catalysis. Under well-precedented SET catalysis alone, the arylation reaction of \( \text{N,N-dimethylbenzylamine} \) proceeded via aminium radical cation formation and selectively targeted the \( \text{N-methyl} \) group. In contrast, addition of \( \text{PhC(O)SH} \) as a HAT catalyst precursor completely switched the regioselectivity to Csp³–H arylation at the \( \text{N-benzylic} \) position. Measurement of oxidation potentials indicated that the conjugate base of \( \text{PhC(O)SH} \) is oxidized in preference to the substrate amine. The discovery of the thioicarboxylate as a novel HAT catalyst allowed for the selective generation of the sulfur-centered radical, so that the \( \text{N-benzyl} \) selectivity was achieved by overriding the inherent \( \text{N-methyl} \) and/or \( \text{N-methylene} \) selectivity under SET catalysis conditions. While visible light-driven \( \alpha-C-H \) functionalization of amines has mostly been demonstrated with aniline derivatives and tetrahydroisoquinolines (THIQs), our method is applicable to a variety of primary, secondary and tertiary benzylamines for efficient \( \text{N-benzylic C-H arylation} \). Functional group tolerance was high, and various 1,1-diarylmethylamines, including an \( \alpha,\alpha,\alpha \)-trisubstituted amine, were obtained in good to excellent yield (up to 98%). Importantly, the reaction is applicable to late-stage functionalization of pharmaceuticals.

Nucleophilic addition of an aryl nucleophile to an imine or an iminium ion is a commonly used strategy to construct the 1,1-diarylmethylamine core. On the other hand, recent work has explored direct benzylic Csp³–H arylation of amine derivatives (Scheme 1). Li and co-workers reported an oxidative cross-
Elegant methodologies using transition metal-catalyzed C–H activation have also been disclosed, though in these cases, deprotonation of an unprotected N-alkyl benzylamines is still a challenging subject. To our knowledge, there is no general and selective method available for N-benzylic C–H arylation. Herein, we report a regio- and chemoselective C–H functionalization of benzylamines via redox-neutral SET and HAT synergistic catalysis (Scheme 1E).

The distinct features of the present reaction are listed below: (1) in addition to well-studied aniline-type compounds, various unprotected N-alkyl benzylamines are available in this reaction. (2) Since PhC(O)SH is easily deprotonated and converted to the corresponding sulfur-centered radical, single electron oxidation of the amine substrates is blocked effectively. SET/HAT synergistic catalysis enables excellent N-benzyl selectivity in preference to inherent N-methyl and N-methylene selectivity observed under SET catalysis conditions. (3) Due to the efficient generation of the HAT catalyst, as little as 1 mol% of PhC(O)SH is sufficient. In addition, an excess amount of starting amine is not required in our reaction. (4) The chemoselectivity is high, and the late-stage functionalization of pharmaceutical drugs was demonstrated successfully.

Results and discussion

According to the reported reaction conditions of photoredox catalysis via an aminium radical cation intermediate,11 we began with the reaction of N,N-dimethyldimethylamine (1a) with terephthalonitrile expecting that the most stable (benzylic and 2') a-amino radical would be generated (Scheme 2). With Ir(ppy)$_3$ (1 mol%) as a photoredox catalyst and K$_2$HPO$_4$ as base, the reaction afforded two compounds, 2a and 3a, in excellent mass balance (95%), though a long reaction time (12 h) was required for completion. Contrary to our expectation, the major product was not 2a but 3a, which is derived from the thermodynamically less stable non-benzylic and 1' a-amino radical.17

While the origin of this regioselectivity is unclear at this point, we think that the kinetic acidity in terms of steric and electronic factors are crucial. Thus, deprotonation of amine radical cations to give a-amino radicals might be accelerated by the overlap of the breaking C$_3^\alpha$–H bond orbital with the SOMO orbital on the amonium radical cation.18,19 These

![Scheme 2 C$_3^\alpha$–H arylation of N,N-dimethyldimethylamine under photoredox catalysis.](image-url)
results suggested that well-precedented SET catalysis is not applicable and distinct reaction conditions should be devised for achieving the targeted N-benzylic transformation.

We considered that a HAT strategy might alter the regioselectivity (Scheme 3). A significant determinant of the selectivity of a HAT process is the C–H bond dissociation energy (BDE). Since BDE is directly associated with the stability of the radical products, a large difference between N-methyl C–H and N-benzylic C–H BDEs should be anticipated. According to the previous studies,39,40 we expected that sulfur-centered radicals would be HAT agents of choice for selective activation of the N-benzylic group. Importantly, however, in order to avoid direct single electron oxidation of N-benzylamine 1a leading to SET catalysis pathway (Scheme 3, right), the sulfur-centered radical precursor should have a lower anodic peak potential than that of N-benzylamine 1a. For this purpose, we envisaged that the anion of a sulfur atom would undergo more facile oxidation than a typical thiol such as cysteine ($E_{1/2} = +0.85$ V vs. SCE for cysteine in CH$_3$CN, p$_K_a = 9.35$ for cysteine methyl ester)$^{23}$ and that a more acidic sulfur compound would be more favorable. Therefore, we selected thiocarboxylic acid 4, whose conjugate base could be generated with a weak base (p$_K_a = 3.2$ for thioacetic acid).$^{25}$ The negatively charged, electron-rich thio-carboxylate species 5 might undergo SET oxidation much faster than the substrate amine, thereby affording the sulfur-centered radical 6 preferentially (Scheme 3, left). This scenario would lead to regioselective C–H activation at the N-benzylic position by overriding the natural N-methyl selectivity observed in Scheme 2.

To validate our working hypothesis, we measured the oxidation potentials of potassium thiobenzoate (PhC(O)SK) and three N-benzylamines by cyclic voltammetry (CV) in DMA (Fig. 2; see ESI† for potentials vs. SCE and further CV studies). Gratifyingly, PhC(O)SK was found to have a less positive anodic peak potential ($E_{p_{ox}} (6/5) = +0.80$ V vs. Ag/AgCl in DMA) than all the amine compounds examined, even when compared to the aniline-type N-benzyl tetrahydroquinoline (THQ) ($E_{p_{ox}} = +0.97$ V vs. Ag/AgCl in DMA). Therefore, thermodynamics predicted that selective oxidation of the thiobenzoate anion would occur even in the presence of the reducing amine substrates. Furthermore, CV revealed that oxidation of PhC(O)SK by [IrIV(ppy)$_3$]$^+$ ($E_{1/2} (\text{IrIV}/\text{IrIII}) = +0.96$ V vs. Ag/AgCl in DMA) was exergonic, while oxidation of the amines was always endergonic. According to these data, a faster reaction profile is expected compared to the reaction shown in Scheme 2.

With the promising CV results in mind, we revisited benzyl C–H arylation of N,N-dimethylbenzylamine (1a) in the presence of PhC(O)SH (4) and other HAT catalyst precursors (Table 1). The arylation proceeded in 91% yield at the benzyl position with excellent regioselectivity (r.r. > 20 : 1, entry 2), which is consistent with the idea of a mechanistic switchover from SET catalysis to SET/HAT synergistic catalysis. It should be noted that the reaction reached completion within 1 h (entry 3), compared to 12 h required when PhC(O)SH was absent (entry 1). This rate-acceleration might be due to exergonic SET oxidation of the thio-carboxylate and a favorable difference in BDE between PhC(O)S–H (87.4 kcal mol$^{-1}$)$^{24}$ and the targeted N-benzylic C–H bond (84.9 kcal mol$^{-1}$).$^{24}$ Precatalysts 10 and 11 gave 2a with excellent N-benzyl selectivity. However, the yields were much lower even in the presence of 20 mol% of HAT catalysts (entries 4, 5). We assume that these less acidic thioils are not deprotonated under the reaction conditions, and thus SET oxidation might not be efficient compared to the case of PhC(O)SK ($E_{1/2} = +0.85$ V vs. SCE for cysteine in CH$_3$CN,$^{22}$ $E_{p_{ox}} (6/5) = +0.65$ V vs. SCE in CH$_3$CN; see ESI†). Considering the p$_K_a$ values of the HAT precatalysts, 12 was also examined as a more acidic thiol (entry 6). However, almost no reaction was observed, probably because the generated thiyl radical would be less reactive in the subsequent HAT process (S–H BDE of TolSH = 77–83 kcal mol$^{-1}$) with HAT with alkylamines at the α position to the nitrogen. Given its accessible oxidation potential ($E_{p_{ox}} = +0.69$ V vs. SCE in
Table 1  Screening of conditions for benzylic Csp³–H arylation of N,N-dimethylbenzylamine

<table>
<thead>
<tr>
<th>Entry</th>
<th>HAT cat.</th>
<th>P.C.</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>2a : 3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1†</td>
<td>—</td>
<td>15</td>
<td>12</td>
<td>95</td>
<td>1 : 8.5</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>15</td>
<td>12</td>
<td>91</td>
<td>&gt;20 : 1</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>15</td>
<td>1</td>
<td>93</td>
<td>&gt;20 : 1</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>15</td>
<td>1</td>
<td>23</td>
<td>&gt;20 : 1</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>15</td>
<td>1</td>
<td>12</td>
<td>1 : 2</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>15</td>
<td>1</td>
<td>Trace</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>15</td>
<td>1</td>
<td>Trace</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>14</td>
<td>15</td>
<td>1</td>
<td>12</td>
<td>&gt;20 : 1</td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>16</td>
<td>1</td>
<td>42</td>
<td>&gt;20 : 1</td>
</tr>
<tr>
<td>10</td>
<td>4</td>
<td>17</td>
<td>1</td>
<td>No reaction</td>
<td>—</td>
</tr>
<tr>
<td>11†‡</td>
<td>4</td>
<td>15</td>
<td>2</td>
<td>90 (87)†</td>
<td>&gt;20 : 1</td>
</tr>
<tr>
<td>12†‡</td>
<td>4</td>
<td>15</td>
<td>2</td>
<td>72</td>
<td>&gt;20 : 1</td>
</tr>
</tbody>
</table>

* The reactions were run on 0.2 mmol scale. † Yield and regioisomeric ratio were determined by 1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. ‡ Data from Scheme 3. § 1 mol% of PhC(O)SH and 0.5 mol% of Ir(ppy)₃ were used on a 1 mmol scale. ¶ 2 equiv. of N,N-dimethylbenzylamine was used. † Isolated yield. ‡ 1 equiv. of N,N-dimethylbenzylamine was used. P.C.: photocatalyst.

CH₃CN),[28] DABCO would undergo SET oxidation selectively over 1a. However, when PhC(O)SK was replaced with DABCO, the reaction did not proceed (entry 7). The reason is not clear at present, but back electron transfer processes such as quenching of the DABCO radical cation by arene radical anion might be sufficiently rapid to interfere with the HAT process.[26] When PhC(O)SK was replaced with quinuclidine, the product was formed in only very low yield with low regioselectivity (entry 8), probably because the strong reactivity of quinuclidine radical cation (N⁻–H BDE of quinuclidine = 100 kcal mol⁻¹)[32] cannot effectively differentiate between the C–H bonds at the N-methyl and N-benzyl positions. These results strongly indicate the superiority of PhC(O)SK for the selective N-benzyl arylation over other HAT catalysts.

We also examined other photoredox catalysts. When [Ir(ppy)₂dtbbpy]PF₆ was used, the product was obtained in a lower yield (entry 9). In this case, reductive quenching of [IrIII⁺] (E₁/₂ (IrIII/IrII) = +0.66 V vs. SCE in CH₃CN)[34] from the thiacarboxylate (Eox = +0.65 V vs. SCE in CH₃CN) is plausible. Since the subsequent SET process between [Ir²⁺] (E₁/₂ (IrII/IrI) = −1.51 V vs. SCE in CH₃CN)[36] and terephthalonitrile (Ered = −1.61 V vs. SCE in CH₃CN)[37] is thermodynamically disfavored, the reaction might be retarded. On the other hand, the reaction did not proceed with Ru(bpy)₃Cl₂ (entry 10). Considering the redox potential after the favorable reductive quenching of [RuII⁺] (E₁/₂ (RuII/RuI) = +0.77 V vs. SCE in CH₃CN) by PhC(O)SK, SET from [Ru⁺] (E₁/₂ (RuIV/RuI) = −1.33 V vs. SCE in CH₃CN) to terephthalonitrile (Econd = −1.61 V vs. SCE in CH₃CN) is energetically unfavorable. Gratifyingly, we succeeded in decreasing the amount of the catalysts. When we used 0.5 mol% of Ir(ppy)₃ and as little as 1 mol% of PhC(O)SH, the reaction proceeded without difficulty to give 2a in 90% yield (entry 11). In contrast, the reaction using 1 mol% of 11 resulted in lower yield and regioselectivity (31% yield, benzyl/Me = 5.2 : 1). Moreover, a stoichiometric amount of 1a was sufficient to produce 2a in good yield (entry 12), in contrast to most of the preceding examples in which a large excess amount of amine substrate (at least three equivalents of starting amines) was generally needed to achieve good yields. A control experiment confirmed that the reaction does not occur in the dark (see ES†).

With the optimal reaction conditions identified (Table 1, entry 11), we turned our attention to the substrate scope of the SET/HAT synergistic catalysis for Csp³–H arylation of N-benzylamines (Table 2). N,N-Dimethylbenzylamine derivatives with varying electronic properties were well tolerated, and the highest-yielding, which is consistent with the polarity effects.[31] However, para-ester-substituent retarded the reaction and the corresponding arylated product was not obtained, suggesting that strongly electron withdrawing groups are not suitable for this reaction. Compared to the para-methyl-substituted derivative (2f), the ortho-methyl-substituted derivative gave 2g in a lower yield (75%), probably due to the steric interaction. Similarly, the reaction of the starting benzylamine was much faster than that of the dibenzylamine, so that over-reaction of the products was not observed. Nevertheless, we found that treating sterically congested 1h under the reaction conditions successfully afforded α,α,α-trisubstituted amine 2h in good yield (74%). Different substituted groups on the nitrogen atom did not prohibit the reaction, since ethyl groups (2i), aliphatic cyclic substituents (2j, 2k), and heteroatom-bearing cyclic substituents (2l, 2m) performed equally well under the reaction conditions. N-Methyl THIQ provided 2n in 94% yield as an expected regioisomer.[33] Notably, secondary and primary amines having no protective group were also applicable, affording 20 and 2p in 98% and 98% yield, respectively. These are relatively difficult substrates for SET catalysis due to their more positive anodic peak potentials, and so have been less well studied in the literature. Glycine derivative 1q underwent selective N-benzyl functionalization to afford 2q in 97% yield. Moreover, heterocyclic aromatic derivatives were tolerated, providing the corresponding arylated products 2r–2t. Aside from terephthalonitrile, 4-cyanopyridine derivatives and 1-cyanoisquinoline reacted in a regioselective manner, providing 2u–2y in good to excellent yields. When cyanobenzenes bearing different para-electron-withdrawing groups were examined, the reaction proceeded with excellent...
Table 2 Substrate scope for benzylic Csp3–H arylation of N-benzylamines

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield</th>
<th>Regioselectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>6%</td>
<td>C1/C2 = 1 : 1</td>
</tr>
<tr>
<td>1c</td>
<td>90%</td>
<td>C1/C2 = 1 : 1</td>
</tr>
<tr>
<td>1d</td>
<td>67%</td>
<td>C1/C2 = 1 : 1</td>
</tr>
<tr>
<td>1e</td>
<td>61%</td>
<td>C1/C2 = 1 : 1</td>
</tr>
<tr>
<td>1f</td>
<td>56%</td>
<td>C1/C2 = 1 : 1</td>
</tr>
<tr>
<td>1g</td>
<td>93%</td>
<td>C1/C2 = 1 : 1</td>
</tr>
</tbody>
</table>

Arylation of 1j under SET conditions.

Synergistic catalysis that can outcompete the inherent N-methyl and/or N-methylene selectivity observed under SET catalysis conditions.

An interesting phenomenon was observed when comparing cyclic N-benzyllamine-type substrates. Treatment of N-benzylinol (1aa) under our reaction conditions resulted mainly in N-benzyl arylation. Nonetheless, under photocatalyst-mediated SET catalysis alone, the regioselectivity was inverted completely from the N-benzyl position to the cyclic N-methylene position (90% yield, C1/C2 = 1 : 6.7). In contrast, N-benzyltetrahydroquinoline (1ab) reacted under our conditions to give the cyclic N-methylene-arylated product 2ab with high regioselectivity (C1/C2 = 1 : 17). We postulate that the increase in steric repulsion around the N-benzyl position in moving from the 5- to the 6-membered ring system may be responsible. However, on the other hand, N-benzyltetrahydrobenzoazepine (1ac) gave a 1.1 : 1 mixture of the C1/C2 regioisomers. The origin of the regioselectivity remains unclear at this point, but we assume that the conformational flexibility within the nitrogen atom-containing ring is important to achieve orbital overlap of the n-orbital on the nitrogen atom with the σ* orbital of the breaking C–H bond, which should have an impact on the BDE.

Next, we evaluated the chemoselectivity of our reaction in more detail. For substrate 1ad, exclusive N-benzyl functionalization occurred in the presence of the benzylic alcohol (Scheme 5A), reflecting the difference in C–H BDEs between the benzylic alcohol side (C–H BDE of benzylic alcohol = 87.5 kcal mol\(^{-1}\))\(^{14}\) and the N-benzyl group (C–H BDE of N,N-dimethylbenzylamine = 84.9 kcal mol\(^{-1}\)).\(^{24}\) An intramolecular competitive experiment with 1ae targeted the N-benzyllamine side to produce 2ae in 71% yield (Scheme 5B). We next examined the reaction of a more challenging substrate (Scheme 5C). The C–H arylation reaction of 1af occurred only at the N-benzyl position, even though the BDEs of both N-benzylic C–H bond and N-allylic C–H bond are reported to be close (ca. 85 kcal mol\(^{-1}\) and 83 kcal mol\(^{-1}\), respectively).\(^{24}\) The yield was only moderate due to competitive reactions at the C–C double bond, but no arylation product at the N-allylic position was detected in this reaction. Moreover, we conducted an intramolecular competition experiment using 1b and 1c (1 : 1). In this case, the reaction mainly proceeded with 1b bearing an electron-donating group, which is indicative of a polarity matching effect (Scheme 5D).\(^{31}\)

To confirm the synthetic utility of our SET/HAT synergistic catalysis, we evaluated its efficiency in late-stage functionalization. When treated in a 1 : 1 ratio, donepezil and 7 underwent regio- and chemoselective coupling reaction smoothly to give 1,1-diarylmethyamine 2ag in good yield (74%). Further, even with more complex clodipogrel, C–H arylation at the endocyclic...
N-benzylic position proceeded regioselectively, furnishing 2ah in 96% yield. These examples clearly demonstrate that the present reaction is applicable to late-stage derivatization of structurally complex bioactive compounds, and thus should be useful to facilitate structure–activity-relationship studies.

All reactions were conducted on 1 mmol scale and isolated yields are shown. Chemo- and regioselectivity were determined by 1H NMR analysis.

Finally, on the basis of the observed selectivity and CV measurements, we propose the catalytic cycle shown in Scheme 6. fac-Tris(2-phenylpyridinato)iridium(III) [IrIII(ppy)3]15 is excited by photo-irradiation (blue LED, 425 nm) and [IrIII(ppy)3]+ (18) is generated. This reductant [Ir(ppy)3]* (18) (E1/2 (IrIV/IrIII) = −1.73 V vs. SCE in CH3CN) undergoes SET to electron-deficient arene 20 to afford radical anion intermediate 21 along with [IrIII(ppy)3]+ (19). Subsequently, [IrIII(ppy)3]+ (19) (E1/2 (IrIV/IrIII) = +0.77 V vs. SCE in CH3CN) performs SET oxidation of the electron-rich PhC(O)SK (Epox (6/5) = +0.65 V vs. SCE in CH3CN, see ESI†), which outcompetes SET oxidation of the amine substrate leading to the different reaction pathway. The generated sulfur-centered radical 6 regioselectively undergoes SET oxidation of the 3/C14 amine substrates was suppressed effectively due to the favorable oxidation of PhC(O)SK, and the resulting sulfur radical abstracts C–H bonds selectively to give N-benzylic radicals. The excellent regio- and chemoselectivity enables the late-stage N-benzylic arylation of pharmaceuticals with reactive functional groups. Further studies including N-methyl selective functionalization are underway in our laboratory.

Conclusions

In conclusion, we have developed a highly regio- and chemo-selective Csp3–H arylation of a variety of benzylamine derivatives by employing SET/HAT synergistic catalysis. Under SET catalysis alone, Csp3–H arylation of benzylamines proceeded at the N-methyl and/or cyclic N-methylene positions through an aminium radical cation intermediate. In contrast, synergistic SET and HAT catalysis inverts the regioselectivity. The reaction was completed within 2 h in the presence of as little as 0.5 mol% of the Ir complex and 1 mol% of PhC(O)SH as a HAT catalyst, and various 1,1-diarylmethylamines were obtained in good to excellent yields (56–98%). Importantly, high yields were achieved even when a stoichiometric amount of the benzylamine substrate was employed. From a mechanistic viewpoint, the use of PhC(O)SH as a HAT catalyst precursor is the key to success: SET oxidation of the 3° amine substrates was suppressed effectively due to the favorable oxidation of PhC(O)SK, and the resulting sulfur radical abstracts C–H bonds selectively to give N-benzylic radicals. The excellent regio- and chemoselectivity enables the late-stage N-benzylic arylation of pharmaceuticals with reactive functional groups. Further studies including N-methyl selective functionalization are underway in our laboratory.
Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references


11 A. McNally, C. K. Prier and D. W. C. MacMillan, Science, 2011, 334, 1114–1117. In this report, a pyrrolidine derivative was examined as a single example of an aliphatic amine substrate.


19 The detail of the N-methyl selective arylation under SET catalysis conditions will be reported separately in due course.