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Accessing Aliphatic Amines in C−C Cross-Couplings by Visible Light/Nickel Dual Catalysis

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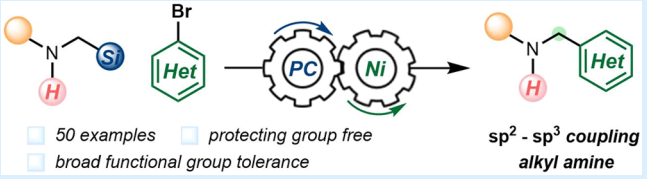
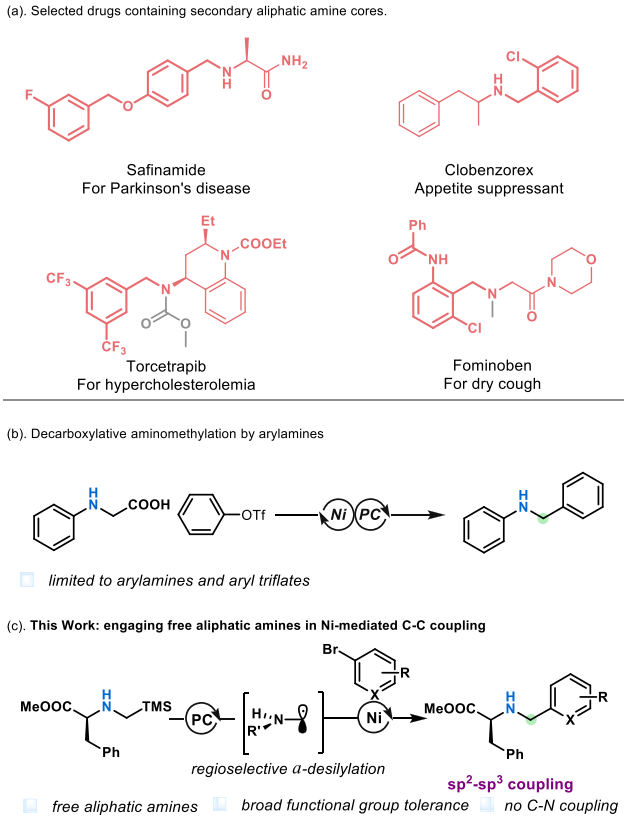
ABSTRACT: A general aminoalkylation of aryl halides was developed, overcoming intolerance of free amines in nickel-mediated C−C coupling. This transformation features broad functional group tolerance and high efficiency. Taking advantage of the fast desilylation of α-silylamines upon single-electron transfer (SET) facilitated by carbonate, α-amino radicals are generated regioselectively, which then engage in nickel-mediated C−C coupling. The reaction displays high chemoselectivity for C−C over C−N bond formation. Highly functionalized pharmacophores and peptides are also amenable.



Amines are prevalent structural motifs in natural products, agrochemicals, and pharmaceuticals.[1] Among them, secondary arylmethylamines are abundantly represented in numerous bioactive molecules. A survey of marketed drugs shows that a significant number of arylmethylamines are either secondary amines or derivatives thereof via simple substitution (Scheme 1a). Classical syntheses of such amines include nucleophilic displacement,[2] reductive amination,[3] and reduction of aryl nitriles.[4] These strategies suffer from competing reactions in polyfunctional substrates and remain in large part inapplicable in such situations. Although transition-metal-catalyzed cross-couplings offer alternative pathways for amine synthesis, they typically rely on elevated temperatures as well as the need for protecting group strategies for Lewis basic handles.[5]

Scheme 1. Representative Drug Molecules Containing Arylmethylamine Scaffolds and Free Aliphatic Amine Syntheses by Transition-Metal-Mediated C−C Couplings



In recent years, the emergence of Ni/photoredox dual catalysis has enabled the assembly of challenging C(sp^2)−C(sp^3) bonds under extremely mild conditions in the presence of delicate functional groups.[6] Through single-electron transfer (SET), radical precursors undergo reductive or oxidative fragmentation to generate alkyl radicals that can be harnessed through Ni-catalyzed cross-couplings. Based on this strategy, we sought to develop a complementary approach to construct arylmethylamines through the intermediacy of easily accessible α-aminomethyl radicals in conjunction with commercially abundant (het)aryl halides.

To date, nickel-mediated aminomethylations of aryl halides remain limited to tertiary amines[7] or amines bearing electron-withdrawing protecting groups.[6b,8] The only similar route to

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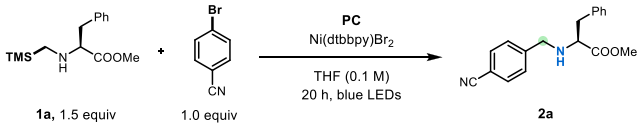
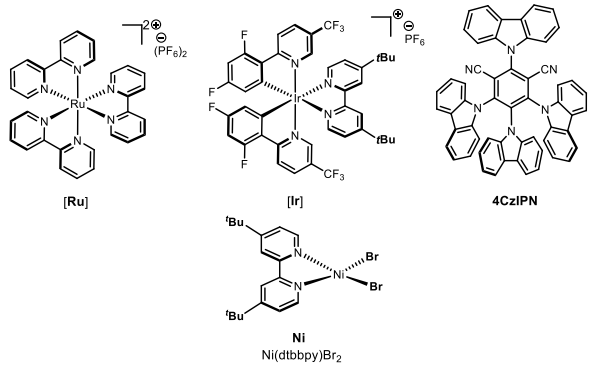
Table 1. Optimization and Control Studies[a]



1a, 1.5 equiv 1.0 equiv 2a

entry	[PC]	mol % [PC]/[Ni]	additive	yield (%)[b]
1	[**Ru**]	3:10	–	0
2	[**Ir**]	3:10	–	trace
3	**4CzIPN**	3:10	–	trace
4	**4CzIPN**	3:10	K_2CO_3 (3 equiv)	15
5	**4CzIPN**	5:2	K_2CO_3 (3 equiv)	99
6[c]	–	–	K_2CO_3 (3 equiv)	0
7[d]	**4CzIPN**	–	K_2CO_3 (3 equiv)	0
8[e]	**4CzIPN**	5:2	K_2CO_3 (3 equiv)	0

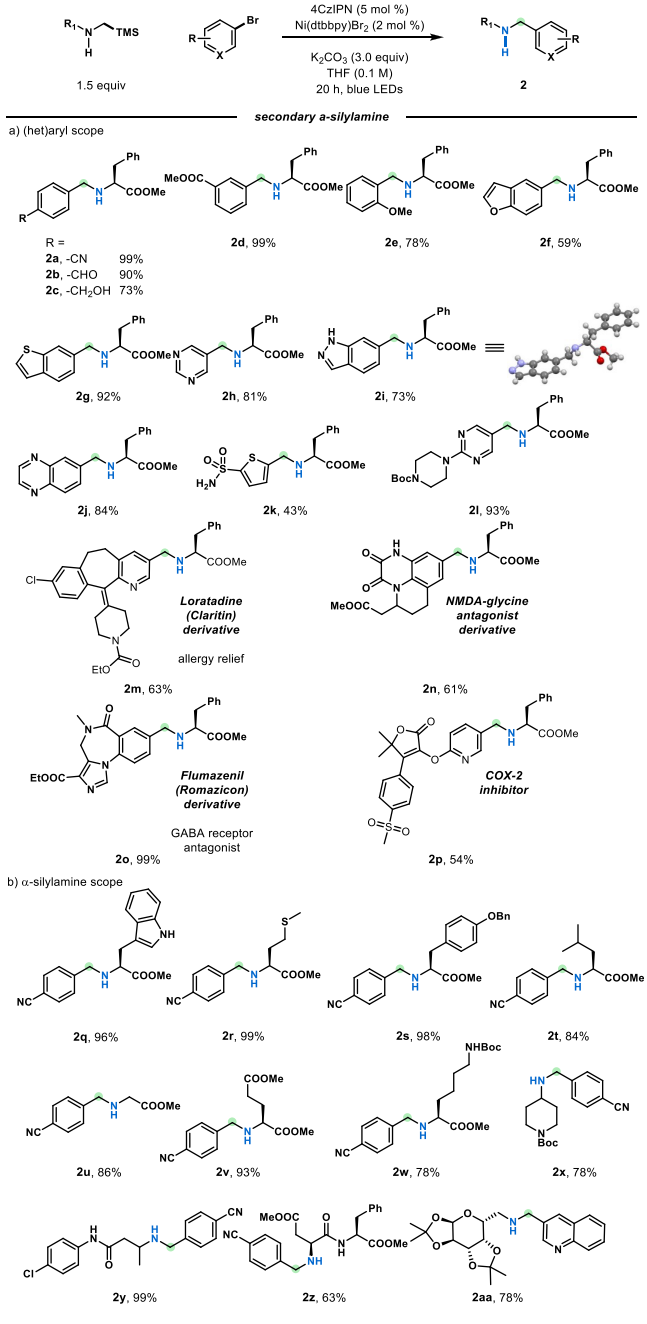
[a]Performed with α-silylamine **1a** (1.5 equiv), *para*-bromobenzonitrile (0.1 mmol) in THF (0.1 M) under blue LED irradiation at rt for 20 h. 3 mol % photocatalyst [**PC**] and 10 mol % [**Ni**] are added when the [**PC**]/[**Ni**] ratio is 3:10, while 5 mol % [**PC**] and 2 mol % [**Ni**] are added when the [**PC**]/[**Ni**] ratio is 5:2. [b]Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. [c]No [**PC**]. [d]No [**Ni**]. [e]No light.



unprotected secondary amines was reported by the Rueping group, but was restricted to the use of secondary *N*-phenyl amino acids with the decidedly less readily available triflate electrophiles (Scheme 1b).[9] Thus, engaging protecting group-free aliphatic amines in nickel-mediated C−C coupling with aryl and heteroaryl halides remains elusive. This challenge presumably stems from facile C−N couplings[10] and/or hydrodehalogenation of aryl halides.[11] To address these limitations, we turned our attention to α-silylamines because of the kinetically favorable alkyl radical generation event taking place by regioselective α-desilylation upon SET.[12] Additionally, secondary α-silylamines can be easily prepared from commodity chemicals (primary amines) by a simple alkylation reaction of halomethyltrimethylsilane or reductive amination of aldehydes or ketones with aminomethylsilane. Herein, we describe a protocol that successfully realizes the cross-coupling between secondary aliphatic amines in conjunction with (het)aryl halides through Ni/photoredox dual catalysis featuring high functional group tolerance and broad substrate scope (Scheme 1c).

To test the proposal, methyl ((trimethylsilyl)methyl)-L-phenylalaninate **1a**, which bears a free amino group, was reacted with *para*-bromobenzonitrile under conditions similar to those reported previously by our group.[7b] Unfortunately, no desired arylated product **2a** was detected, and only hydrodehalogenated arene was observed (Table 1, entry 1). This demonstrates the challenge in adapting free amines in C−C

Scheme 2. Scope of Secondary α-Silylamines and (Het)aryl Bromides[a,b]



[a]All values correspond to isolated yields after purification. [b]Unless otherwise noted, reactions were performed using aryl bromide (1 equiv, 0.3 mmol), α-silylamine (1.5 equiv, 0.45 mmol), 4CzIPN (5 mol %, 0.015 mmol), Ni(dtbbpy)Br_2 (2 mol %, 0.006 mmol), and K_2CO_3 (3 equiv, 0.9 mmol) in THF (0.1 M) at rt for 20 h with blue LEDs (~10 W) irradiation.

cross-couplings. Although the more oxidative [**Ir**] and **4CzIPN** photocatalysts also provided virtually no product (entries 2 and 3), the inclusion of a base, K_2CO_3, afforded the desired product in 15% yield (entry 4). We reason that K_2CO_3 facilitates the α-desilylation of **1a** upon SET and also sequesters the Lewis acid byproduct TMSBr.[13] Encouraged by this result, a modulation of the ratio of photocatalyst and nickel catalyst showed that a ratio featuring a high loading of photocatalyst is critical, and a satisfactory yield is then achieved

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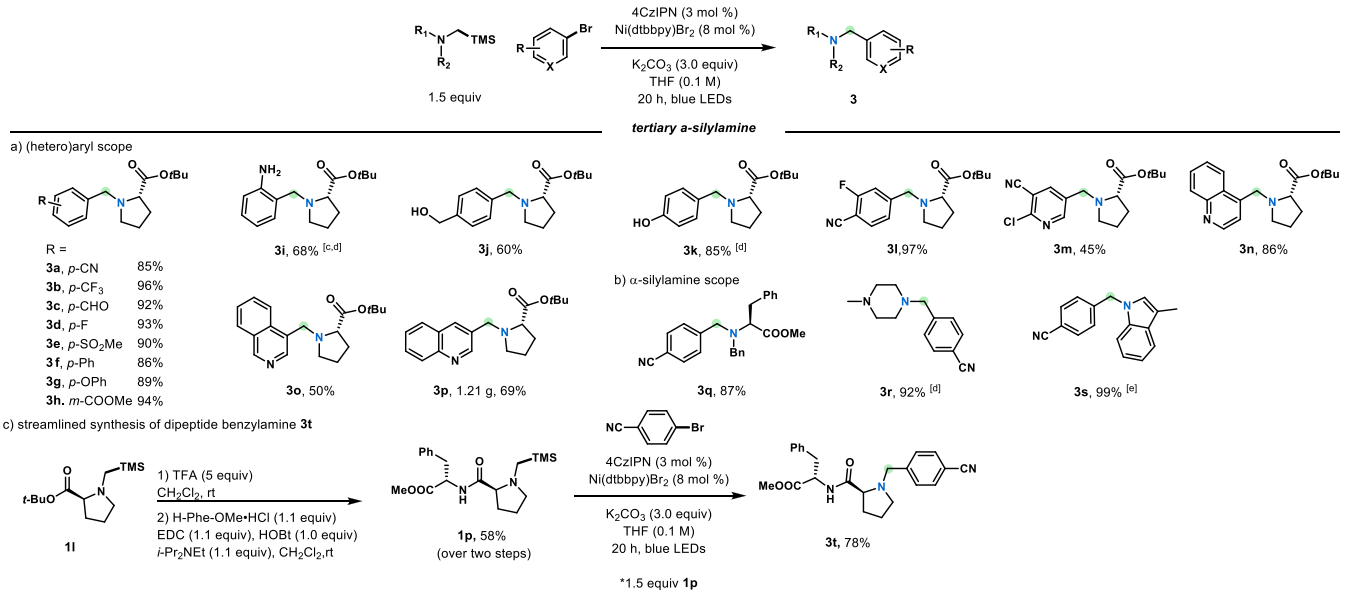
Scheme 3. Scope of Tertiary α-Silylamines and (Het)aryl Bromides[a,b]



[a]All values correspond to isolated yields after purification. [b]Unless otherwise noted, reactions were performed using aryl bromide (1 equiv, 0.3 mmol), α-silylamine (1.5 equiv, 0.45 mmol), 4CzIPN (3 mol %, 0.009 mmol), $Ni(dtbbpy)Br_2$ (8 mol %, 0.024 mmol), K_2CO_3 (3 equiv, 0.9 mmol) in THF (0.1 M) at rt for 20 h with blue LED (~10 W) irradiation. [c]Reactions were performed using aryl iodides. [d]Reactions were performed using two blue Kessil lamps (30 W) with a shortened reaction time (6 h). [e]NMP (0.1 M) was used instead of THF (0.1 M).

(entry 5). Furthermore, control studies showcased that all reaction parameters are necessary for effective aminomethylation (entries 6 to 8), and there is no erosion of the stereochemical integrity (see Supporting Information for details). Notably, neither starting material **1a** nor product **2a** appears to undergo C−N coupling with aryl halide, demonstrating the high chemoselectivity of this method.

Having established feasible cross-coupling conditions, the substrate scope of this aminomethylation process was evaluated (Scheme 2). The electron density on the aryl ring was demonstrated to have little to no effect on the coupling efficiency (**2a**−**e**), and *meta*- (**2d**) and *ortho* (**2e**)-substituted substrates also exhibited good coupling efficiency. Meanwhile, an unprotected alcohol group is well tolerated (**2c**), resisting silylation during the reaction process.[14] The scope of the reaction with regard to heteroaryl halides was next explored, permitting access to materials that otherwise would require use of the less commercially available benzyl halides (for *N*-alkylation approaches) or heteroaryl aldehydes (for reductive amination). A wide variety of heteroaryl cores are incorporated in good yields without the need of protection, including an indazole (**2i**). Additionally, heteroaryl-based pharmacophores (**2m**−**p**) including the antihistamine Loratadine (**2m**) and GABA receptor antagonist Flumazenil (**2o**) display excellent reactivity. Electron-rich heteroaryl systems (**2f**, **2g**) serve as competent substrates despite what must be a slower oxidative addition.[15] Notably, a primary sulfonamide (**2k**), which contains a polar acidic group, is accommodated, showing that multiple polar functional groups can be introduced by this method. With respect to the scope of secondary α-silylamines, amino acid based organosilanes including tyrosine (**2s**), glutamate (**2v**), and *N*-Boc-lysine (**2w**) afford the desired aminomethyl subunits without compromising yields. Furthermore, the oxidation-labile methionine residue (**2r**) is amenable to this cross-coupling reaction. No protecting group is necessary for the indole moiety of tryptophan (**2q**). The scope has been further extended to more nucleophilic amines (**2x**, **2y**, **2aa**). Because of the mild nature of Ni/photoredox dual catalysis, the protocol is applicable to complex amine systems including the dipeptide aspartame methyl ester (**2z**). Finally, as part of our ongoing efforts to develop synthetic tools to incorporate saccharide derivatives into complex molecular fragments,[16] this protocol was extended to the aminomethylation of aryl bromides with a pyranose moiety (**2aa**), prepared via reductive amination from the corresponding glycosyl aldehyde and commercially available aminomethylsilane.

With a broad scope based on a secondary α-amino radical, we next applied the developed method to the construction of tertiary amines. In fact, a significant improvement in reaction efficiency and functional group tolerance was observed over that of a protocol previously developed in the group (Scheme 3).[7b] Not only was a considerable improvement on yields achieved, but substrates with polar functional groups including amines (**3i**) and alcohols (**3j**, **3k**) were successfully accommodated. Additionally, instead of using (hetero)aryl iodides, the less expensive and more readily available (hetero)aryl bromides delivered the products in excellent yields (**3m**−**p**). The scope of the α-silylamines was not limited to aliphatic amines (**3q**, **3r**), but could be extended to an indole derivative as well (**3s**).

Another important feature of α-silylamine precursors is their ease of modification. To demonstrate this, a streamlined synthesis of dipeptide benzylamine **3t** starting from proline-derived organosilane **1l** was carried out (Scheme 3c).[12d] Deprotection of **1l** with TFA followed by peptide coupling afforded intermediate **1p** with good efficiency. Under standard arylation conditions, the corresponding tertiary amine **3t** was obtained without compromising the yield. As such, the modular nature of this cross-coupling allows rapid access to structurally diverse α-aminoalkyl radicals, delivering unique

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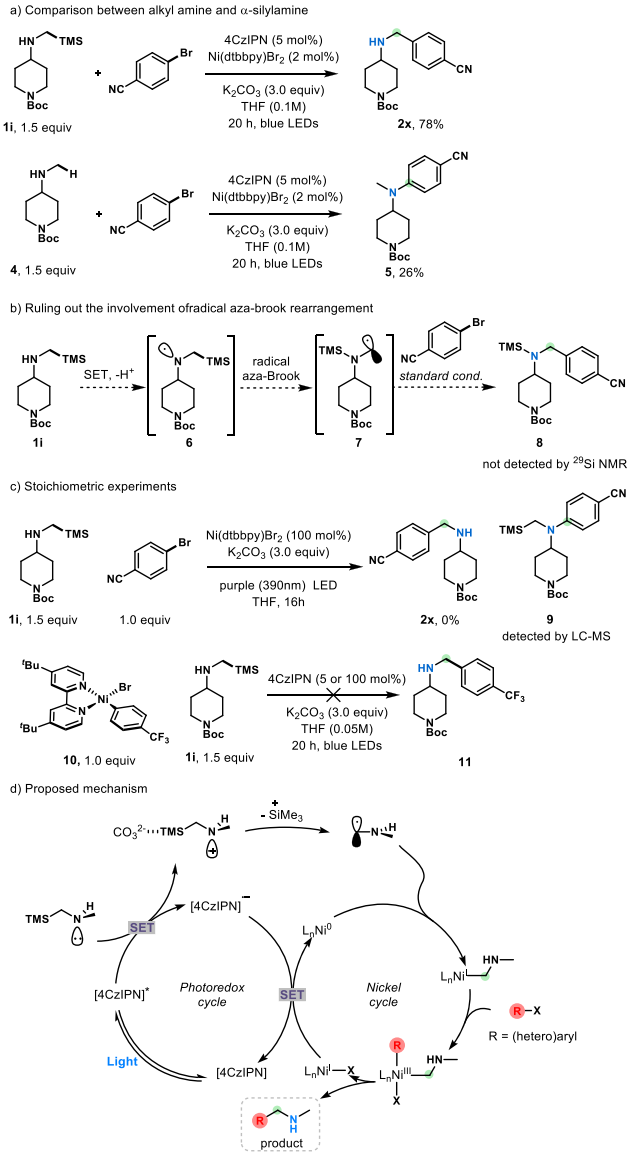
Scheme 4. Mechanistic Studies



synthetic disconnections in the design of peptide−drug conjugates in pharmaceutical settings.

To gain insight into the mechanism of this Ni/photoredox process involving free aliphatic amino groups, a series of experiments were performed. First, the reactivity difference between an α-silylamine **1i** and a secondary alkylamine **4** was evaluated (Scheme 4a), because both of them are known to generate α-amino radicals under SET.[17] Under the standard conditions for cross-coupling developed herein, the α-silylamine delivered the C−C coupling product **2x**, while the corresponding alkylamine underwent C−N coupling to an aniline **5**. We reasoned the mechanism for this C−N coupling is similar to what was proposed by the MacMillan group.[18] This divergent reaction pathway indicates that the rate difference between α-desilylation and α-deprotonation plays an important role, and the kinetically faster α-desilylation process favors C−C coupling overall. Additionally, α-silylamines are reportedly capable of undergoing a radical aza-Brook rearrangement under SET oxidation, generating α-silylamino methyl radical **7**.[19] Consequently, an experiment was conducted to explore this possibility. Because silylamines are prone to hydrolyze into hydroamines during workup, the crude mixture was directly monitored by ^{29}Si NMR (Scheme 4b). Results showed that there was no silylamine **8** present in the crude reaction mixture, thus ensuring no radical aza-Brook rearrangement is occurring. Although control studies have precluded the possibility of direct radical substitution of aryl halide by α-amino radical, the role of the nickel catalyst is still unclear. In a stoichiometric experiment, the nickel catalyst is found to be capable of oxidizing **1i** under 390 nm light irradiation, which aligns with results previously communicated by Miyake.[10c] However, only trace conversion of **1i** was detected under 456 nm light irradiation. Because the nickel catalyst can oxidize **1i** under 390 nm irradiation, aminomethylation in the absence of a photocatalyst under purple light irradiation was examined (Scheme 4c). In the stoichiometric experiment with a nickel catalyst, **1i**, and *para*-bromobenzonitrile, no formation of the C−C coupling product **2x** was observed, while a small amount of the C−N coupling product **9** was found. This indicates that the nickel species is not a competent oxidant in this system, and thus, an energy-transfer pathway is ruled out. Also, Stern−Volmer quenching studies demonstrate that **1i** can efficiently quench excited state **4CzIPN** (see Supporting Information), indicating the oxidation of α-silylamines by photocatalyst. Furthermore, a stoichiometric experiment using a Ni(II)-aryl halide complex **10** with **1i** does not yield any desired C−C coupling product **11**, excluding the possibility of oxidative addition of aryl halide to Ni(0) (Scheme 4c).

Based on these results, a dual photoredox/nickel-catalyzed process is proposed (Scheme 4d). First, blue LED irradiation enables the excitation of **4CzIPN**, which then oxidizes an α-silylamine via SET. The facile α-desilylation facilitated by carbonate promotes the generation of an α-amino radical, which could then be intercepted by Ni(0), yielding an alkyl-Ni(I) species, with subsequent oxidative addition of an aryl halide. The resulting Ni(III) complex readily undergoes reductive elimination, offering the C−C coupled product and Ni(I). Finally, SET from the reduced form of **4CzIPN** to the Ni(I) regenerates the ground state **4CzIPN** and Ni(0) for the next catalytic cycle.

In conclusion, a user-friendly and versatile route toward the aminomethylation of functionalized (het)aryl halides under mild reaction conditions is reported. This protocol features a protecting-group-free synthetic strategy for the preparation of secondary arylmethylamines. This aminomethylation can be further extended to the synthesis of tertiary amines. The commercial availability of (het)aryl halides as well as the low, uniform oxidation potentials of α-silylamines allow the incorporation of diverse radical architectures from commodity chemicals while retaining high functional group tolerance.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01207.

Experimental details and data (PDF)

Accession Codes

CCDC 2075097 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cam-

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Notes

The authors declare no competing financial interest.

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