Sulfonamides as *N*-centered radical precursors for C–N coupling reactions to generate amidines

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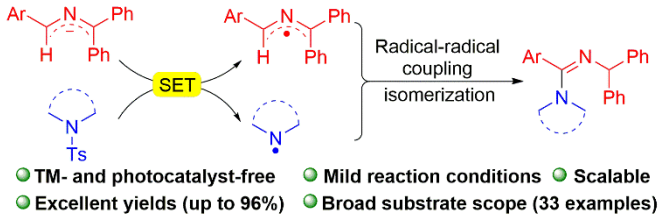


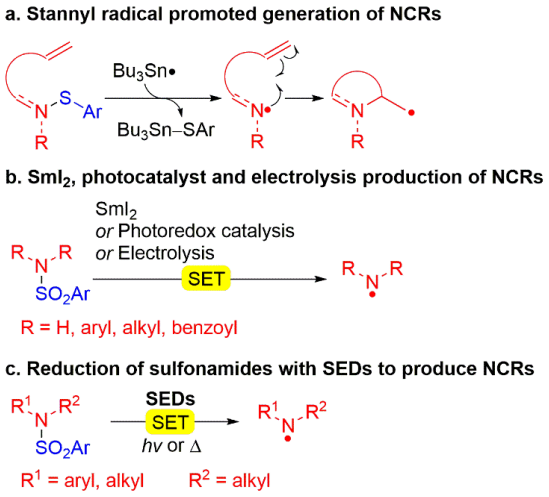
ABSTRACT: Nitrogen-centered radicals (NCRs) are valuable intermediates for the construction of C−N bonds. Traditional methods for the generation of NCRs employ toxic radical initiators, transition-metal catalysts, photocatalysts or organometallic reagents. Herein, we report a novel strategy for generation of NCRs toward the construction of C–N bonds under transition-metal-free conditions. Thus, super electron donors (SED) 2-azaallyl anions undergo SET with sulfonamides, forming aminyl radicals (R_2N•, R = alkyl) and culminating in the generation of amidines bearing various functional groups (33 examples, up to 96% yield). Broad substrate scope and gram-scale telescoped preparation demonstrate the practicality of this method. Radical clock and EPR experiments support the proposed radical coupling pathway between the generated *N*-centered radical and the C-centered 2-azaallyl radical.

The pervasive nature of nitrogen atoms in medications and biologically active compounds has inspired countless investigations into the generation of C–N bonds. Most of these approaches have historically revolved around 2-electron pathways, often catalyzed by transition metals. For example, chemists have developed palladium- and copper-catalyzed processes to construct C(sp^2)–N bonds, including the Buchwald–Hartwig reaction, Ullmann amination and Chan–Lam amination. Recently, however, there has been renewed interest in harnessing reactive nitrogen-centered radicals as viable synthetic intermediates for C–N bond construction.[1] Nitrogen-centered radicals (NCRs) can be generated by the cleavage of N−X bonds (X = Cl, N, O, S, H) or by the addition of a radical to an unsaturated nitrogen group.[1b, 2]

In the case of S–N bonded precursors to NCRs, initial strategies for cleavage of these bonds were reagent heavy. In the 1990's, Zard, Bowman and others pioneered the cleavage of various N−S bonds with stannyl radicals to generate NCRs that cyclized to *N*-heterocycles (Scheme 1a).[3] More recently single electron transfer (SET) has emerged as a powerful means of generating radicals.[4]

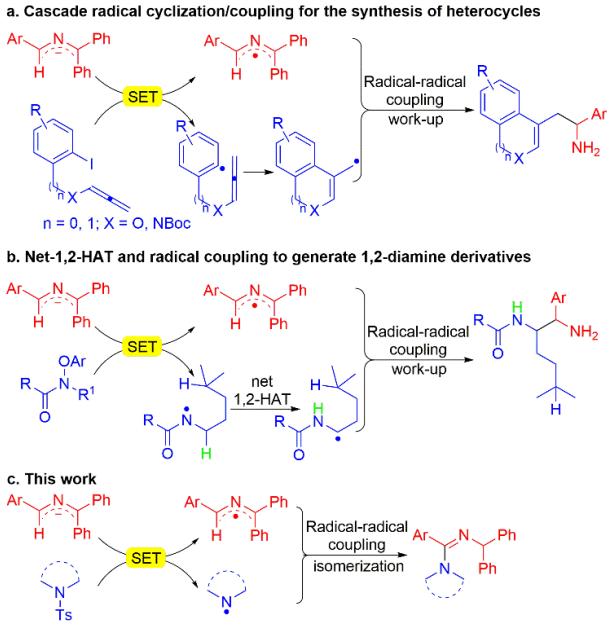
Some SET methods, such as SmI_2 mediated electron transfer,[5] photoredox catalysis,[6] and electrochemical methods,[7] have been successfully applied to induce S–N bond cleavage to produce NCRs (Scheme 1b). Recently, Murphy and co-workers introduced neutral organic super-electron-donors (SEDs)[8] ($E_{1/2}$ = –1.20 ~ –1.70 V vs SCE) to generate NCRs via photoactivated or thermally induced reductive cleavage of sulfonamides (Scheme 1c).[9] It is noteworthy that although sulfonamides have typical reduction potentials of –2.3 V vs SCE, their reduction can be achieved by electron transfer from molecules with less negative redox potentials due to the relatively low-energy LUMO of the arene sulfonyl unit.[9-10]

Scheme 1. The formation of NCRs by S–N bond cleavage



Our team has been interested in radical-radical cross-coupling reactions, which are largely dependent on the generation of persistent radicals.[11] We found that 2-azaallyl radicals behaved as persistent radicals and undergo highly chemo selective radical-radical cross-coupling to construct new C–C bonds.[12] For example, a cascade radical cyclization/intermolecular coupling reaction of 2-azaallyl anions for the synthesis of medicinally relevant heterocycles was introduced (Scheme 2a).[13] In the context of NCRs, we reported that amidyl radicals were generated by SET between 2-azaallyl anions and *N*-aryloxy amides. Under basic conditions, the amidyl radical underwent α-C–H deprotonation and net-1,2-HAT to form C–centered radicals, which coupled with 2-azaallyl radicals to generate 1,2-diamine derivatives (Scheme 2b).[14]

Scheme 2. Application of 2-azaallyl anions in our previous works

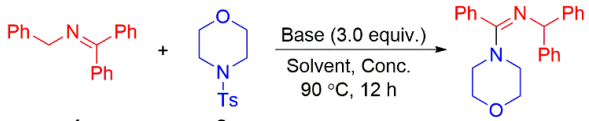


Based on our past studies, we ponder the application of the SED character of 2-azaallyl anions to cleavage S–N bonds to generate NCRs (R_2N•) (Scheme 2c). We hypothesized that 2-azaallyl anions and *N,N*-dialkyl *p*-toluenesulfonamides would undergo an SET process to generate 2-azaallyl radicals and *N,N*-dialkyl NCRs. Intermolecular radical-radical coupling between these open shelled species is followed by isomerization of the carbon-nitrogen double bond leading to the overall formation of amidines.

Herein, we describe a novel approach for the transition-metal-free construction of C–N bonds by coupling of 2-azaallyl anions with sulfonamides, which led to the formation of amidines bearing various functional groups (33 examples, up to 96% yield). Amidines are valuable intermediates for the synthesis of *N*-heterocycles and possess important pharmacological activities. Their synthesis, however, remains challenging. Mechanistic studies (radical clock and EPR experiments) provide insight into these radical C–N cross-coupling reactions.

We selected 4-tosylmorpholine **2a** as the model substrate, which was easily synthesized by reaction of morpholine with 4-methylbenzenesulfonyl chloride (95% yield, see Supporting Information). At the outset, we explored the reaction optimization using *N,N*-dialkyl *p*-toluenesulfonamide **2a** and *N*-benzyl ketimine **1a** as coupling partners with $NaN(SiMe_3)_2$ (3.0 equiv.) in DME at 90 °C for 12 h. The coupling/isomerization product **3aa** was attained in 18% assay yield (AY, as determined by ^{1}H NMR integration against an internal standard, Table 1, entry 1).

Table 1. Optimization of coupling of ketimine 1a and 4-tosylmorpholine 2a[a]



1a (2.0 equiv.) **2a** (1.0 equiv.) **3aa**

entry	solvent	base	Conc./M	**3aa** (%)[b]
1	DME	$NaN(SiMe_3)_2$	0.1	18
2	CPME	$NaN(SiMe_3)_2$	0.1	23
3	MTBE	$NaN(SiMe_3)_2$	0.1	9
4	THF	$NaN(SiMe_3)_2$	0.1	19
5	1,4-dioxane	$NaN(SiMe_3)_2$	0.1	18
6	Toluene	$NaN(SiMe_3)_2$	0.1	7
7	Acetonitrile	$NaN(SiMe_3)_2$	0.1	0
8	DMF	$NaN(SiMe_3)_2$	0.1	0
9	DMSO	$NaN(SiMe_3)_2$	0.1	0
10	CPME	$LiN(SiMe_3)_2$	0.1	0
11	CPME	$KN(SiMe_3)_2$	0.1	85
12	CPME	LiO^{t}Bu	0.1	0
13	CPME	NaO^{t}Bu	0.1	0
14	CPME	KO^{t}Bu	0.1	32
15[c]	CPME	$KN(SiMe_3)_2$	0.1	62
16[d]	CPME	$KN(SiMe_3)_2$	0.1	84
17	CPME	$KN(SiMe_3)_2$	0.2	95 (92)[e]
18	CPME	$KN(SiMe_3)_2$	0.05	84

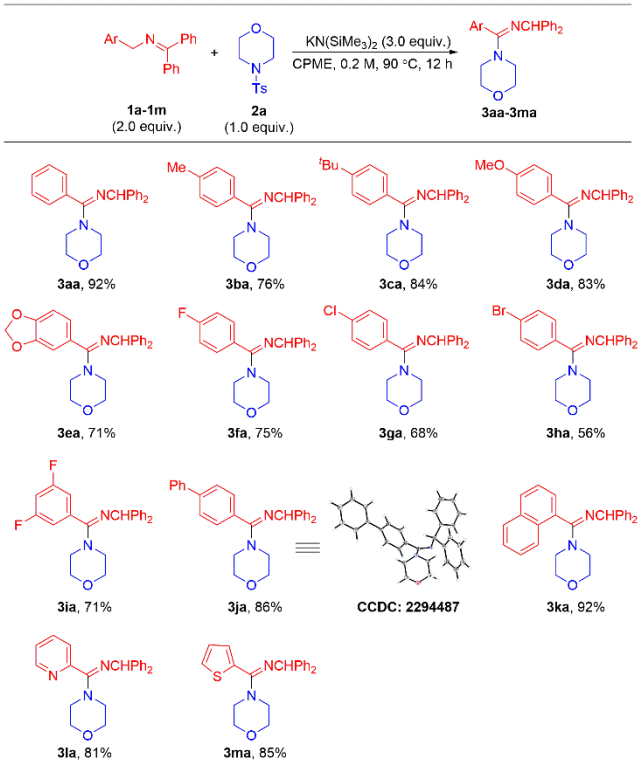
[a]Reactions conducted on a 0.1 mmol scale. [b]Assay yields determined by ^{1}H NMR spectroscopy of the crude reaction mixture using $C_2H_2Cl_4$ as an internal standard. [c]80 °C. [d]100 °C. [e]Isolated yield after chromatographic purification.

Our previous studies revealed that solvents play an important role in the chemistry of 2-azaallyl anions, because they coordinate to the main group cation of the 2-azaallyl anion ($[HPhC{=}{-}{-}N{=}{-}{-}CPh_2]M(sol)_n$), thus modulating its reactivity.[15] Therefore, a range of solvents, including CPME, MTBE, THF, 1,4-dioxane, toluene, acetonitrile, DMF, and DMSO, were tested (entries 2–9). Among them, CPME provided the target compound **3aa** in 23% AY, while other solvents led to lower AY or no reaction. The deprotonation of *N*-benzyl ketimines to form 2-azaallyl anions is mediated by base.[16] We, therefore, conducted a careful survey of various bases [$LiN(SiMe_3)_2$, $KN(SiMe_3)_2$, LiO^{t}Bu, NaO^{t}Bu and KO^{t}Bu, entries 10–14] in CPME. We were pleased to find that $KN(SiMe_3)_2$ and KO^{t}Bu afforded product **3aa** in 85% and 32% AY, respectively. Other bases did not result in the desired product.

Lowering the temperature resulted in a decrease in the AY of **3aa** (62%, entry 15), while increasing the temperature did not affect the AY (84%, entry 16). Concentration also plays an important role in radical–radical coupling reactions. Increasing the concentration from 0.1 M to 0.2 M resulted in up to 95% AY, with 92% isolated yield (entry 17). Also formed was 4-methylbenzenesulfinic acid in 90% isolated yield. Similarly, conducting the reaction at 0.05 M afforded 84% AY (entry 18).

Based on this optimization exercise, the standard conditions for the synthesis of amidines are those in entry 17 of Table 1.

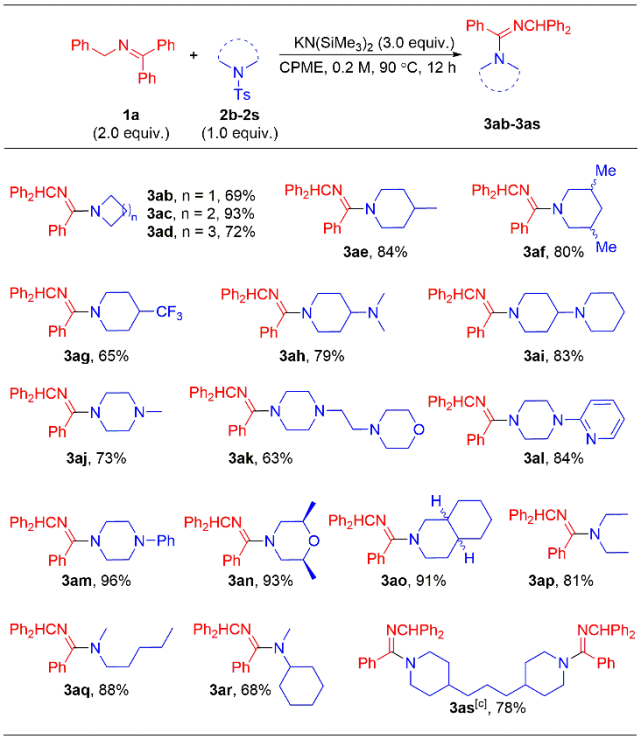
Scheme 3. Scope of Ketimines[a, b]



[a]Reactions were conducted on a 0.4 mmol scale using 2.0 equiv. ketimine, 1.0 equiv. **2a** and 3.0 equiv. $KN(SiMe_3)_2$ at 0.2 M and 90 °C. [b]Isolated yields after chromatographic purification.

With the optimized conditions in hand (Table 1, entry 17), we explored the scope of *N*-benzyl ketimines **1**. In order to better characterize the products, the reactions were conducted on 0.4 mmol scale. As shown in Scheme 3, ketimines bearing various electron-rich and electron-deficient Ar groups provided good to excellent yields under the optimized conditions. Electron-donating substituents, such as 4-Me, 4-^{t}Bu, 4-OMe and 3,4-methylenedioxy groups generated amidine products **3ba**, **3ca**, **3da** and **3ea** in 76%, 84%, 83% and 71% yields, respectively. *N*-benzyl ketimines possessing electronegative and electron-withdrawing substituents on the benzyl, such as 4-F, 4-Cl, 4-Br and 3,5-di-F, were also suitable coupling partners, delivering products **3fa**, **3ga**, **3ha**, and **3ia** in 75%, 68%, 56%, and 71% yields, respectively. Next, a ketimine containing a biphenyl group produced **3ja** in 86% yield. Crystals were obtained of product **3ja** and the structure confirmed by X-ray crystallography (see Supporting Information for details). An *N*-benzyl ketimine with a sterically hindered substituent, such as a 1-naphthyl group, was also suitable coupling partner, leading to product **3ka** in 92% yield. Notably, medicinally relevant heterocyclic ketimines bearing a 2-pyridyl and 2-thiophenyl were also competent coupling partners, furnishing products **3la** and **3ma** in 81% and 85% yields. For ketimines bearing 4-CF_3, 3-pyridyl, 4-pyridyl or 2-furanyl group, no product was observed (see the Supporting Information for details).

Scheme 4. Scope of dialkyl *p*-toluenesulfonamides[a,b]



[a]Reactions were conducted on a 0.4 mmol scale using 2.0 equiv. ketimine **1a**, 1.0 equiv. dialkyl *p*-toluenesulfonamides, and 3.0 equiv. $KN(SiMe_3)_2$ at 0.2 M and 90 °C. [b]Isolated yields after chromatographic purification. [c]Using 4.0 equiv. ketimine **1a** and 6.0 equiv. $KN(SiMe_3)_2$ for **3as**.

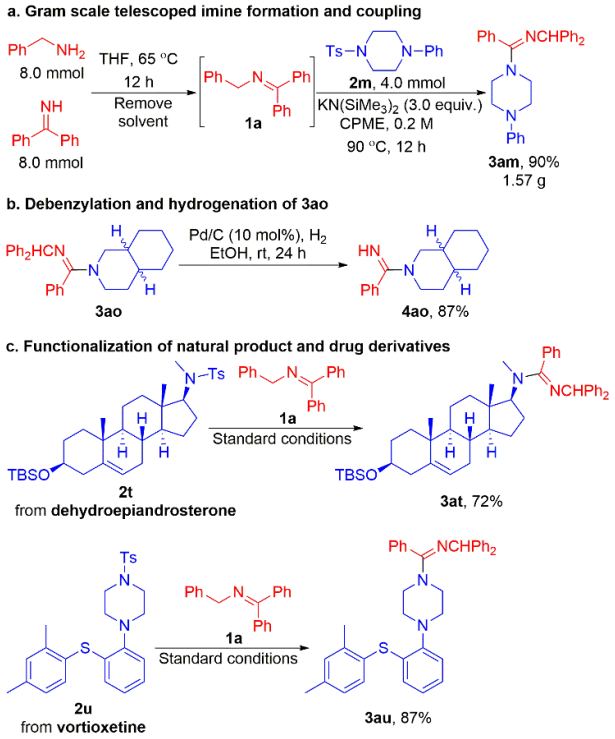
We next focused our attention on the scope of substituted dialkyl sulfonamides **2**. As shown in Scheme 4 under the standard conditions *p*-toluenesulfonamides bearing different ring systems such as azetidine, pyrrolidine and piperidine reacted smoothly with *N*-benzyl ketimine **1a**, affording products **3ab**, **3ac** and **3ad** in 69%, 93% and 72% yields, respectively. Moreover, substituted piperidines possessing 4-Me, 3,5-di-Me, 4-CF_3, 4-dimethylamino and 4-piperidyl groups were coupled with ketimine **1a** to generate products **3ae**–**3ai** in 65–84% yields. When substituted piperazines bearing 4-Me, 4-(2-ethyl)morpholine, 4-pyridin-2-yl and 4-phenyl groups were employed as coupling partners with **1a** products **3aj**–**3am** were afforded in good to excellent yields (63–96%).

The *meso* sulfonamide 2,6-dimethyl-4-tosylmorpholine was a suitable substrate, delivering the corresponding product **3an** in 93% yield. 2-Tosyldecahydroisoquinoline reacted with ketimine **1a** to provide product **3ao** in 91% yield. Finally, acyclic dialkyl-*p*-toluenesulfonamides were also competent substrates, furnishing products **3ap**–**3ar** in 68–88% yields. Notably, this method could successfully achieve double-intermolecular radical coupling with 2-azaallyl radicals. The 1,3-bis(1-tosylpiperidin-4-yl)propane was prepared and coupled using 4.0 equiv. of ketimine **1a** leading to diamidine product **3as** in 78% yield. However, *p*-toluenesulfonamides bearing monoalkyl, acyl, monoaryl or diaryl group led to no reaction (see the Supporting Information for details).

To test the scalability of this method, we explored the telescoping of this reaction on gram-scale. Treatment of the benzyl amine with benzophenone imine in THF at 65 °C for 12 h was followed by removal of the solvent under reduced pressure

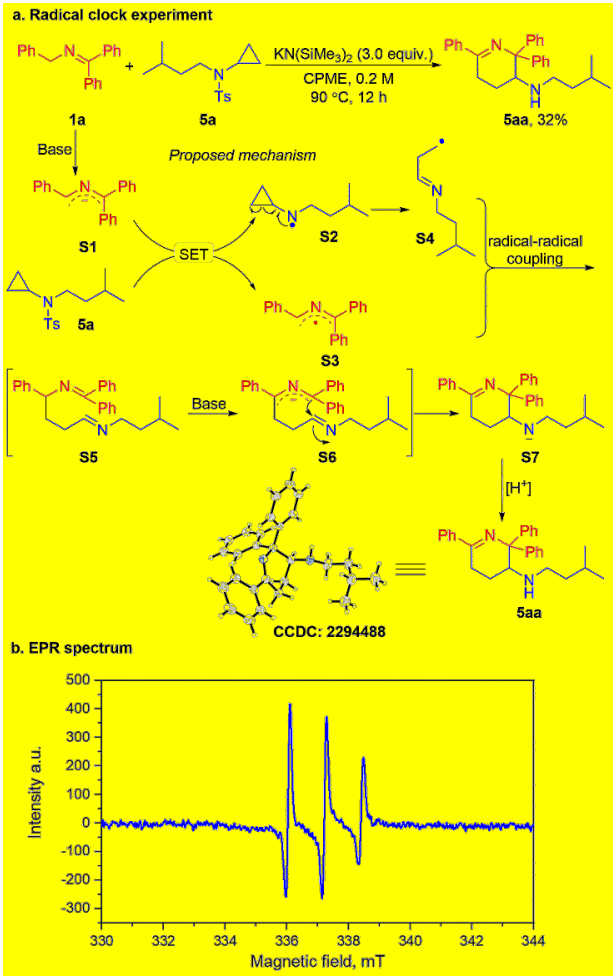
providing *N*-benzyl ketimine **1a**. The unpurified **1a** was coupled with 1-phenyl-4-tosylpiperazine **2m** following the standard conditions and afforded 1.57 g of **3am** in 90% yield (Scheme 5a). Deprotection of product **3ao** proceeded under catalytic hydrogenolysis with Pd/C, delivering amidine **4ao** in 87% yield (Scheme 5b). The versatility of the coupling reaction was further demonstrated by functionalization of more complex molecules. Thus, dehydroepiandrosterone, a naturally occurring steroid, was converted to the sulfonamide and reacted with ketimine **1a** under the standard conditions to generate **3at** in 72% yield. Similarly, the drug vortioxetine, used in treating depression, was transformed into the sulfonamide and then coupled with ketimine **1a** to produce **3au** in 87% yield (Scheme 5c).

Scheme 5 Synthetic applications



To obtain insight into the reaction pathway, we carried out a series of experiments. First, radical-clock-containing cyclopropyl sulfonamide **5a** was prepared to probe the presence of radical intermediates in the coupling reaction (Scheme 6a, see the Supporting Information for details). The reaction of the radical clock **5a** with ketimine **1a** under the standard conditions provided the ring-opened product **5aa** in 32% yield. The structure of compound **5aa** was confirmed by X-ray crystallography. A proposed mechanism for the formation of **5aa** is illustrated in Scheme 6a. The relatively low-energy LUMO of the arene fragment of **5a** facilitates SET from the 2-azaallyl anion **S1** ($E_{1/2}$ = −1.11 V vs SCE)[15] to produce NCR **S2** and 2-azaallyl radical **S3**. Radical **S2** is expected to undergo cyclopropane ring-opening to generate the alkyl radical **S4**. Intermediate **S4** undergoes an intermolecular radical-radical coupling with the 2-azaallyl radical **S3** to form acyclic **S5**. Intermediate **S5** undergoes deprotonation to form the 2-azaallyl anion **S6**, which adds to the aldimine to afford the amide **S7**. Protonation of **S7** leads to **5aa**.

Scheme 6. Mechanistic studies



To further substantiate radical intermediates in this reaction, electron paramagnetic resonance (EPR) experiments employing phenyl *N*-*tert*-butylnitrone (PBN) as the radical spin trap were performed (Scheme 6b, see the Supporting Information for details). The resulting EPR signal (g = 2.0088, A_N = 14.1 G, A_H = 2.3 G) is similar to the previously reported data for PBN trapped nitrogen-centered radicals.[17] Taken together, these results suggest that the coupling reaction proceeds through an NCR intermediate.

In summary, amidines are valuable functional groups in synthesis and in the pharmaceutical industry. Herein, we have advanced a novel strategy for the construction of C–N bonds by radical-radical coupling and translocation of the double bond to produce amidine derivatives. Unlike past advances, this C–N coupling reaction relies on the application of SED 2-azaallyl anions that reduced *p*-toluenesulfenamides to NCRs (R_2N•). Broad substrate scope is found in the coupling reaction and a gram-scale telescoped preparation demonstrated the practicality of this method. Mechanistically, radical clock and EPR experiments provided support for a radical coupling pathway. It is noteworthy that this approach enables the formation of C–N bonds by simply combining base and solvent without the addition of highly toxic reagents, transition-metal catalysts or photocatalysts, which enhances its attractiveness for applications in the pharmaceutical industry and in academics.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

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

Experimental procedures, characterization data, X-ray structures, and NMR spectra (PDF)

Accession Codes

CCDC 2294487 and 2294488 contain 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 Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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