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Lewis Base−Boryl Radicals Enabled the Desulfurizative Reduction and Annulation of Thioamides

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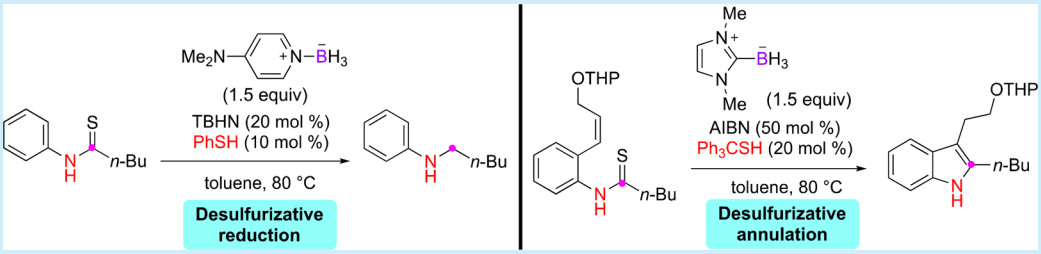
Supporting Information



ABSTRACT: A new protocol for radical transformations of thioamides promoted by Lewis base−boryl radicals is reported. The desulfurizative reduction to access organic amines was enabled utilizing 4-dimethylaminopyridine−BH_3 as the boryl radical precursor and PhSH as the polarity reversal catalyst. Alternatively, the chain process for unsaturated thioamides was switched to an annulation reaction using *N*-heterocyclic carbene−BH_3 as the boryl radical precursor and sterically bulky Ph_3CSH as the catalyst, allowing for the construction of *N*-heterocyclic and carbocyclic skeletons.

Nitrogen-containing molecules are ubiquitous in natural products, bioactive compounds, pharmaceuticals, and functional materials.[1] Thioamides are among the most privileged synthetic precursors to access these molecules, owing to their easy accessibility and versatile chemical reactivity.[2] Thus, a variety of synthetic transformations of thioamides have been developed.[2] For example, the reductive desulfurization of thioamides has shown great utility in preparing organic amines.[2a] The classical reduction methods include Raney nickel hydrogenolysis,[3] $LiAlH_4$ reduction,[4] Zn/HCl reduction,[5] the hydride reduction of thioimonium salts,[6] and the transition-metal-catalyzed reduction with hydrosilanes.[7] However, these approaches often suffer from defects such as harsh reaction conditions, modest functional group compatibility, or operational inconvenience. In addition, since the pioneering work by Bachi[8] and Fukuyama,[9] the radical annulation of unsaturated thioamides has been widely explored and proven to be competent in the synthesis of a range of important indole alkaloids,[10] such as catharanthine,[11] vinblastine,[12] and strychnine.[13] However, the general necessity for large excess amounts of toxic organotin reagents limits its application. Thus, the development of eco-friendly, practical, and broadly applicable methods that can solve the aforementioned issues and enhance the utility of thioamides is highly desirable.

Our idea to develop new approaches for the conversion of thioamides into nitrogen-containing molecules was inspired by recent advances in the chemistry of Lewis base−boryl radicals.[14] For example, Fensterbank, Lacôte, Malacria, and Curran discovered that *N*-heterocyclic carbene (NHC)−boryl radicals could be generated by hydrogen atom abstraction from the corresponding readily available NHC−BH_3 complexes.[15] Notably, these NHC−boryl radical species have shown versatile reactivity to enable a range of radical reactions, including the radical reduction of xanthates,[15,16] organic halides,[17] and nitriles,[18] polymerization of alkenes,[19] homolytic substitution of disulfides,[20] and borylative radical cyclization of 1,5-diynes.[21] In addition, Lalevée and Blanchard disclosed that pyridine−boryl radicals could also induce the radical reduction of organic halides.[22] Given these developments and our interest in exploring new transformations of Lewis base−boryl radicals (LB−BH_2•),[23] we surmised that if a LB−BH_2• could react with thioamides to generate α-thioaminoalkyl radical intermediates, the following reductive desulfurization would afford amines (Scheme 1). Furthermore, an intramolecular cyclization could be envisioned to construct *N*-heterocyclic or carbocyclic frameworks by the introduction of an intramolecular unsaturated moiety at a proper position onto the substrate.

Scheme 1. Reaction Design: Lewis Base-Boryl Radicals Promoted Desulfurizative Reduction and Cyclization of Thioamides

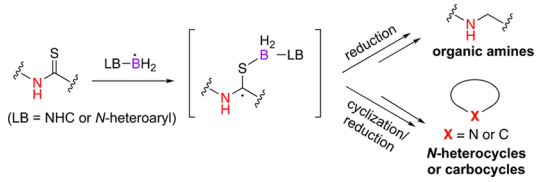


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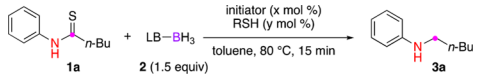
Table 1. Optimization of Reaction Conditions for the Reduction Reaction[a]



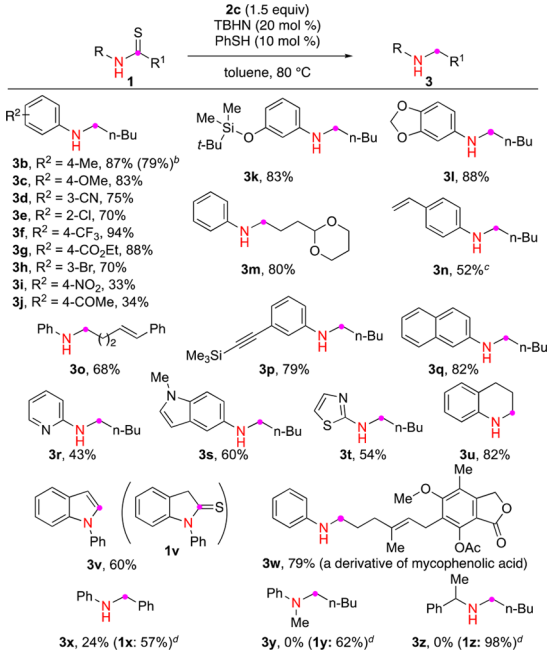
entry	LB–BH_3 (**2**)	initiator (x mol %)	RSH (y mol %)	**3a** yield (%)[b]
1[c]	NHC–BH_3 (**2a**)	AIBN (50)	-	32 (30)[d]
2	**2a**	AIBN (50)	PhSH (20)	68
3	**2a**	TBHN (50)	PhSH (20)	70
4[c]	**2a**	AIBN (50)	$C_9H_{19}C(CH_3)_2SH$ (20)	44 (52)[d]
5[c]	**2a**	AIBN (50)	Ph_3CSH (20)	49 (50)[d]
6[c]	pyridine–BH_3 (**2b**)	AIBN (50)	PhSH (20)	25 (73)[d]
7	DMAP–BH_3 (**2c**)	AIBN (50)	PhSH (20)	70 (26)[d]
8	**2c**	TBHN (50)	PhSH (20)	98
9	**2c**	TBHN (20)	PhSH (10)	97[e]
10[f]	**2c**	Et_3B (50)/O_2	PhSH (10)	95[e]
11[g]	**2c**	-	-	0 (98)[d]

[a]Unless otherwise noted, the reactions were carried out on a 0.3–0.5 mmol scale of **1a** with 1.5 equiv of LB–BH_3 (**2**) in the presence of an initiator (x mol %) and RSH (y mol %) in toluene (0.1 M) under a nitrogen atmosphere. [b]NMR yield using tetrachloroethane as an internal standard. [c]The reaction was performed for 15 h. [d]Recovery yield of **1a** is shown in parentheses. [e]Isolated yield. [f]The reaction was run at 40 °C under an air atmosphere. [g]The reaction was performed for 5 h.

We began our study by testing the reduction of *N*-phenylpentanethioamide (**1a**) using 1,3-dimethylimidazol-2-ylidene–BH_3 (NHC–BH_3, **2a**) as the boryl radical precursor and hydrogen atom donor. As expected, the reaction proceeded smoothly in the presence of 2,2-azobis(isobutyronitrile) (AIBN) as the radical initiator, giving *N*-pentylaniline (**3a**) in a 32% yield (Table 1, entry 1). The addition of a thiol as an additive, which might act as a polarity reversal catalyst,[17b,24] was beneficial to increase the yield (entries 2–5). Further screening of Lewis base–boryl radical precursors revealed that the employment of pyridine–BH_3 (**2b**) diminished the yield (entry 6),[25] while 4-dimethylaminopyridine–BH_3 (DMAP–BH_3, **2c**) was as efficient as **2a** (entry 7). Switching the radical initiator to di-*tert*-butyl hyponitrite (TBHN) led to a quantitative isolated yield of **3a** (entry 8). Reducing the amount of TBHN to 20 mol % and PhSH to 10 mol % maintained a good yield (entry 9). Moreover, a comparable result was obtained when Et_3B/O_2 was utilized as the radical initiator (entry 10). No reaction occurred in the absence of a radical initiator (entry 11), supporting a radical reaction mechanism rather than an ionic pathway through hydride reduction in the initiation step of this transformation.

With the optimized reaction conditions in hand, the scope of this radical desulfurization of thioamides was examined next (Scheme 2). Various *N*-alkylanilines **3** were afforded in good yields with the tolerance of a wide range of functional groups (for **3b–g**). The 1 mmol scale reaction of **1b** afforded **3b** in 79% yield. A susceptible bromine substituent (for **3h**), which could be easily reduced by an NHC–radical,[17] remained intact in the reaction conditions. However, the presence of a nitro group (for **3i**) and ketone moiety (for **3j**) interfered with the reduction, resulting in diminished yields. Remarkably, some acid-labile functional groups, such as silyl ether (for **3k**) and acetals (for **3l** and **3m**), were compatible, which could complement the classic metal/acid promoted reduction protocols.[2a] It is noteworthy that the introduction of an alkene or alkyne moiety onto the thioamides did not retard the reactions, giving the corresponding amines (for **3n–p**) in good yields. A range of *N*-pentylarylamines bearing naphthyl (for **3q**), pyridine (for **3r**), indole (for **3s**), and thiazole (for **3t**) motifs could be produced in high yields. The present method allowed a facile access to a tetrahydroquinoline scaffold (for **3u**). The reaction of **1v** led to indole **3v** in a 60% yield, probably via a fast aromatization step instead of the further hydride reduction reaction. The synthetic utility of this method was demonstrated by the quick modification of a drug molecule. Treatment of **1w**, which was prepared from mycophenolic acid[26] through a condensation and thionation sequence, with **2c** under the optimized reaction conditions afforded **3w** in 79% yield. The reduction of benzothioamide **1x** (R^1 = Ph) became sluggish, leading to *N*-benylaniline **3x** in a 24% yield along with a 57% recovery of **1x**. In addition, no reduced product was detected when tertiary thioamide **1y** and *N*-alkylthioamide **1z** were employed.

Scheme 2. Substrate Scope for the Radical Reduction of Thioamides 1[a]



[a]Unless otherwise noted, the reactions were carried out on a 0.3–0.5 mmol scale of **1** with 1.5 equiv of **2c** in the presence of TBHN (20 mol %) and PhSH (10 mol %) in toluene (0.1 M) under a nitrogen atmosphere. [b]One mmol scale of **1b** was used. [c]The reaction was run at 40 °C using Et_3B/O_2 as the initiator. [d]Recovery yield of **1** is shown in parentheses.

To verify the radical nature of the process, a radical probe experiment was conducted (Scheme 3a). Thioamide **1a′** bearing a cyclopropyl radical clock was reduced to *N*-butylaniline **3a′**, supporting the existence of cyclopropylmethyl radical intermediate **A** in the reaction sequence.[27] Based on this observation and previous findings for NHC–boryl[28] and DMAP–boryl radical[22] chemistry, a plausible mechanism for the reduction of thioamide **1a** is outlined in Scheme 3b. In the initiation step, Lewis base–boryl radical **II** or **III** is generated by hydrogen atom abstraction from **2a**[28] or **2c**,[22] respectively. The addition of **II** or **III** to the C=S bond of thioamide **1a** gives an α-

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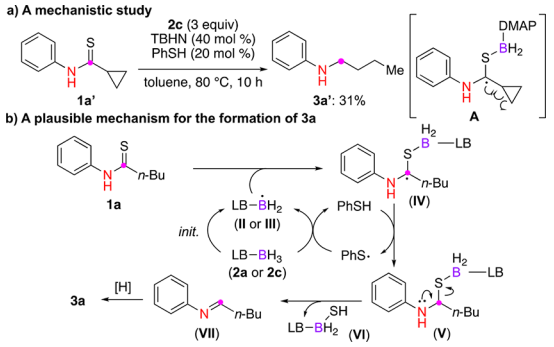
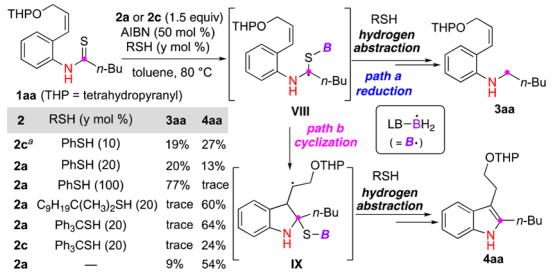
Scheme 3. Mechanistic Study and a Plausible Mechanism for the Formation of 3a



thioaminoalkyl radical **IV**, which abstracts a hydrogen atom from PhSH to afford the intermediate **V**. The subsequent elimination of **VI** and hydride reduction of the resulting *N*-phenylimine **VII** provides aniline **3a**. Control experiments showed that the thermal reduction of imine **VII** with **2a** or **2c** could afford **3a** in 32% or 75% yield, respectively.[29] The radical chain reaction was propagated by the hydrogen abstraction of PhS• from **2a** or **2c** to regenerate PhSH and **II** or **III**. In this reaction sequence, the use of 1.5 equiv of **2c** is sufficient to enable both radical (**IV** to **V**) and ionic (**VII** to **3a**) reduction reactions, suggesting that more than one of the B–H bonds of **2c** were presumably used.

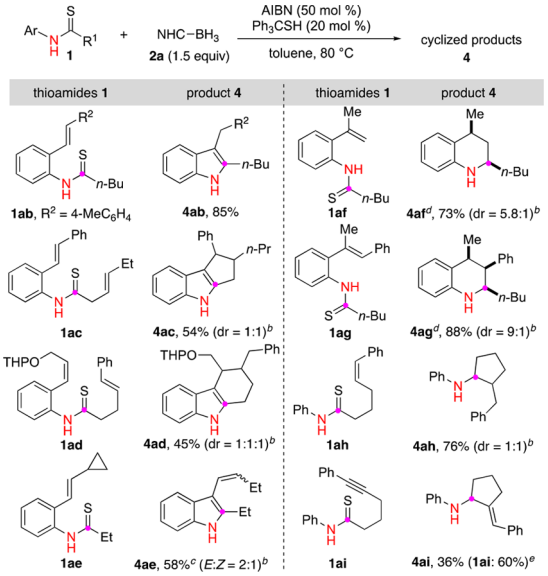
Next, we turned our attention to examine the radical annulation reactions of unsaturated thioamides, in which the generated α-thioaminoalkyl radicals might be trapped by an intramolecular C–C unsaturated bond, leading to a series of *N*-heterocyclic and even carbocyclic frameworks.[30] However, using the standard reaction conditions for the reductive desulfurization, the reaction of 2-alkenylthioanilide **1aa** with **2a** or **2c** provided a mixture of reduced aniline **3aa** and cyclized indole **4aa** in low selectivity and moderate combined yields (Scheme 4).[31] Employment of 100 mol % of PhSH as the additive led to the predominant formation of amine **3aa**, while only a trace amount of indole **4aa** was detected. We reasoned that the choice of a sterically hindered thiol catalyst may decrease the reaction rate of hydrogen atom transfer to intermediate **VIII** (*path a, reduction*), thus making the intramolecular cyclization (*path b*) favorable to form intermediate **IX**. To our delight, when bulky *tert*-dodecanethiol or triphenylmethanethiol was utilized as the catalyst, **4aa** was isolated in 60% or 64% yield, respectively. However, the combination of **2c** and *tert*-dodecanethiol resulted in a messy reaction with the formation of **4aa** in only 24% yield. It should be noted that the reaction with **2a** in the absence of a thiol catalyst provided **3aa** and **4aa** in 9% and 54% yields, respectively.

Scheme 4. Competitive Reduction and Annulation Reactions of Unsaturated Thioamides



2	RSH (y mol %)	3aa	4aa
2c[a]	PhSH (10)	19%	27%
2a	PhSH (20)	20%	13%
2a	PhSH (100)	77%	trace
2a	$C_9H_{19}C(CH_3)_2SH$ (20)	trace	60%
2a	Ph_3CSH (20)	trace	64%
2c	Ph_3CSH (20)	trace	24%
2a	—	9%	54%

Table 2. Substrate Scope for the Radical Annulation of Thioamides 1[a]



[a]Unless otherwise noted, the reactions were carried out on a 0.3–0.5 mmol scale of **1** with 1.5 equiv of **2a** in the presence of AIBN (50 mol %) and Ph_3CSH (20 mol %) in toluene (0.1 M) under a nitrogen atmosphere. [b]The ratio was determined by the analysis of ^1H NMR of the crude reaction mixture. [c]NMR yield. [d]The major diastereomer was depicted. [e]Recovery yield of **1** is shown in parentheses.

As depicted in Table 2, the radical annulation process proceeded nicely to assemble a range of *N*-heterocyclic and carbocyclic skeletons. Remarkably, this procedure was found to be robust for the construction of 2,3-substituted indoles (for **4ab–4ad**). In particular, 2,3-fused indoles (for **4ac** and **4ad**) could be formed through a cascade comprised of two successive cyclization steps, albeit with moderate yields and diastereoselectivity. Notably, the reaction of **1ae** tethering a cyclopropyl substituent afforded cyclopropane ring-opening product **4ae**, which could further prove the radical cyclization mechanism. For the reactions of **1af** and **1ag**, where the internal carbon of the alkene moiety was blocked by an alkyl substituent, a 6-*endo*-*trig* cyclization took place to give tetrahydroquinolines (for **4af** and **4ag**) in good yields. Eventually, *N*-cyclopentylanilines **4ah** and **4ai** could be accessed from the reactions of hex-5-enethioamide **1ah** and hex-5-ynethioamide **1ai**, respectively.

In conclusion, we have developed Lewis base–boryl radicals induced desulfurizative reduction and annulation of thioamides. The reduction reaction could be achieved using DMAP–BH_3 as the boryl radical precursor and PhSH as the polarity reversal catalyst, while the combination of NHC–BH_3 and Ph_3CSH was required to make the cyclization feasible. As DMAP– and NHC–BH_3 complexes are readily accessible, bench stable, and nontoxic, we expect that these protocols will provide a new platform enabling the efficient synthesis of a variety of nitrogen-containing molecules from readily available thioamides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03201.

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Detailed experimental procedures and characterization of new compounds (PDF)

Accession Codes

CCDC 1574325 and 1574329 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, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(29) For the detailed results, see Supporting Information. For a related work, see: Horn, M.; Mayr, H.; Lacôte, E.; Merling, E.; Deaner, J.; Wells, S.; McFadden, T.; Curran, D. P. *Org. Lett.* **2012**, *14*, 82.

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(31) For the detailed optimization of reaction conditions and the reaction mechanism, see Supporting Information.

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