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Polarity Reversal Catalysis in Radical Reductions of Halides by N-Heterocyclic Carbene Boranes

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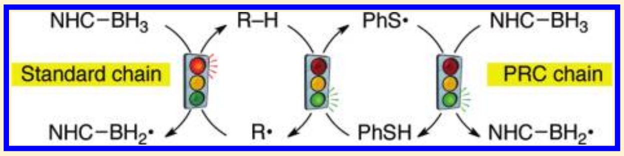
Ⓢ *Supporting Information*



ABSTRACT: Otherwise sluggish or completely ineffective radical reductions of alkyl and aryl halides by N-heterocyclic carbene boranes (NHC-boranes) are catalyzed by thiols. Reductions and reductive cyclizations with readily available 1,3-dimethylimidazol-2-ylidene borane and a water-soluble triazole relative are catalyzed by thiophenol and *tert*-dodecanethiol [$C_9H_{19}C(CH_3)_2SH$]. Rate constants for reaction of the phenylthiyl (PhS•) radical with two NHC-boranes have been measured to be ~10^8 M^{-1} s^{-1} by laser flash photolysis experiments. An analysis of the available evidence suggests the operation of polarity reversal catalysis.

■ INTRODUCTION

Reductive radical reactions and reaction cascades are commonly used in organic synthesis,[1] so the development of practical, efficient, and economical radical hydrogen transfer reagents is an important goal.[2] The use of organoboron reagents for radical hydrogen atom transfer reactions was pioneered by Roberts over 20 years ago.[3] This work was seminal because so little was then known about boryl radicals. However, the amine borane reagents ($R_3N{-}BH_3$) that emerged have seen sporadic use in radical chemistry because they are rather poor hydrogen atom donors[4] and because they thermally dissociate to give aggressive free boranes.[5] While boron-based hydrogen transfer chemistry has been fallow, other uses of boron reagents in radical chemistry have flourished.[6]

Recently, N-heterocyclic carbene boranes (NHC-boranes)[7] have revived the promise of boron-based radical hydrogen transfer reagents.[8] The second-generation reagent 1,3-dimethylimidazol-2-ylidene borane (diMe-Imd-BH$_3$, **1**; Figure 1)[8e] is a readily available and stable white solid that is easy to handle. It has good solubility in many solvents and does not dissociate on heating. It contains only hydrogen and second-row elements, has a low molecular weight (110 g/mol), and forms byproducts that are easy to separate from the target products. The triazole analogue, diMe-Tri-BH$_3$ (**2**), is generally similar to **1** but is also soluble in water.[8e,9]

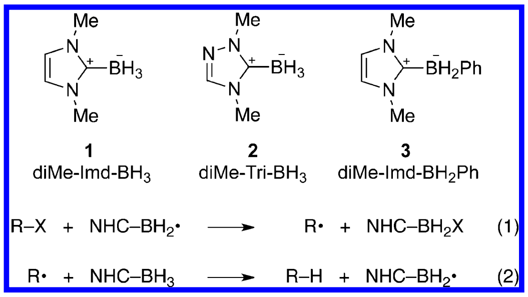


Figure 1. (top) Structures of NHC-borane radical hydrogen transfer reagents **1**–**3**. (bottom) Proposed propagation steps for chain reductions of halides.

Boranes **1** and **2** smoothly reduce xanthates [X = $OC(S)SCH_3$] and related functional groups.[8e] However, radical reductions of the all-important halides (X = Br, I) have been limited to alkyl precursors R that have electron-withdrawing groups near the halide.[8f] Simple alkyl halides such as adamantyl iodide and bromide have not been reduced efficiently, and aryl halides have been untouched by NHC-boranes.

The problem in alkyl halide reductions seems to be the hydrogen atom transfer (step 2 in Figure 1). Secondary alkyl radicals react with NHC-boranes with rate constants of only ~10^4 M^{-1} s^{-1}.[8c,e] In contrast, the rate constants for reactions of alkyl radicals with tin hydrides are 100–500 times larger.[10] The only successful halide reductions match electron-poor radicals with the "nucleophilic" hydrogen donor properties of NHC-boranes.[8f] This need for polarity matching is a significant limitation.

Problems with slow hydrogen transfer have been solved in silane reductions and other types of radical reactions by addition of a "polarity reversal catalyst", often a thiol or selenide.[11] Here we report that NHC-borane reductions are subject to polarity reversal catalysis with thiols. This catalysis significantly extends the scope and practicality of radical reductions by NHC-boranes.

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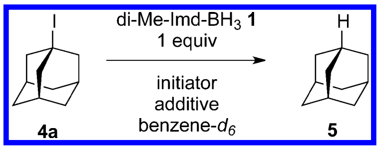
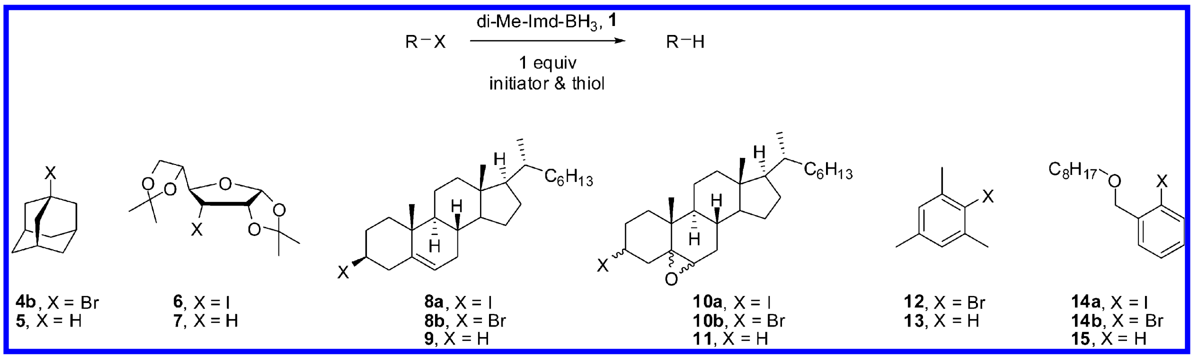
Table 1. Scouting Experiments with Adamantyl Iodide (4a), diMe-Imd-BH$_3$ (1), and Various Initiators, with and without Thiol Sources



entry	init	equiv	temp	5% PhSH	time	conv **4a**	yield of **5**[a]
1	AIBN	1	80 °C	no	5 h	65%	41%
2	AIBN	1	80 °C	yes	5 h	82%	49%
3	Et$_3$B	1	rt	no	5 h	62%	16%
4	Et$_3$B	0.5	rt	yes	2 h	76%	76%
5	TBHN	1	80 °C	no	5 h	86%	46%
6	TBHN	0.1	80 °C	yes	2 h	82%	82%
7	DTBP	1	$h\nu$[b]	no	1 h	39%	38%
8	DTBP	0.2	$h\nu$[b]	yes	1 h	99%	99%

[a] NMR yields determined using 1,3,5-trimethoxybenzene as an internal standard. [b] The NMR tube was warmed by the lamp to an estimated temperature of 50−60 °C.

Table 2. Preparative Reductions of Alkyl and Aryl Iodides and Bromides Catalyzed by Thiols



entry	substrate	conditions[a]	thiol	product	yield
1	**4b**	TBHN, 4 h	PhSH	**5**	97%[b]
2	**4b**	DTBP, 1 h	PhSH	**5**	92%[b]
3	**6**	Et$_3$B, 1 h	PhSH	**7**	82%
4	**6**	TBHN, 2 h	PhSH	**7**	79%
5	**6**	DTBP, 1 h	PhSH	**7**	79%
6	**8a**	TBHN, 2 h	TDT[c]	**9**	96%
7	**8a**	TBHN, 2 h	PhSH	**9**	81%[d]
8	**8b**	TBHN, 2 h	TDT[c]	**9**	95%
9	**8b**[e]	TBHN, 2 h	TDT[c]	**9**	95%
10	**8b**[f]	TBHN, 2 h	TDT[c]	**9**	90%
11	**10a**	TBHN, 3 h	TDT[c]	**11**	–
12	**10b**	TBHN, 3 h	TDT[c]	**11**	91%
13	**12**	TBHN, 3 h	TDT[c]	**13**	96%[b,g]
14	**14a**	TBHN, 3 h	PhSH	**15**	86%[b]
15	**14a**	DTBP, 7 h	PhSH	**15**	86%[b]
16	**14b**	TBHN, 3 h	PhSH	**15**	81%[b]
17	**14b**	DTBP, 7 h	PhSH	**15**	82%[b]

[a] Conditions: Et$_3$B (0.5 equiv), air, rt; TBHN (0.2 equiv), 80 °C; DTBP (0.2 equiv), $h\nu$ (50−60 °C). [b] NMR yield determined using 1,3,5-trimethoxybenzene as an internal standard. [c] TDT = *tert*-dodecanethiol. [d] diMe-Tri-BH$_3$ (**2**) was used in place of **1**; isolated yield after aqueous extraction. [e] In C$_6$H$_5$CF$_3$. [f] In C$_6$H$_5$CH$_3$. [g] 1.5 equiv of **1** was used.

■ RESULTS AND DISCUSSION

Discovery and Development of Thiol Catalysis. Thiols are powerful hydrogen atom donors that can suppress or interfere with radical chains as well as promote them. We selected adamantyl iodide (**4a**) for preliminary experiments because it resists ionic reduction[12] and is inefficiently reduced by NHC-boranes alone under radical conditions. Thus, it is ideal for quickly ascertaining whether thiols and NHC-boranes interact antagonistically or synergistically.

Table 1 summarizes selected scouting experiments in the reduction of **4a** by **1**. Little or no conversion occurred upon heating or irradiation of these reactants without an added initiator. Entries 1−8 are alternating pairs of experiments with standard initiators,[13] with and without 5 mol % thiophenol. Room-temperature experiments were conducted with triethylborane,[14] while azobis(isobutyronitrile) (AIBN) and di-*tert*-butyl hyponitrite (TBHN)[15] experiments were performed at 80 °C. Photolysis at 50−60 °C was used with di-*tert*-butyl peroxide. The conversions of iodide **4a** and yields of adamantane **5** were measured by ^{1}H NMR integration against an internal standard.

With AIBN (entries 1 and 2), the yields were moderate both without and with thiophenol (41 and 49%). However, under the other three sets of conditions, the addition of thiophenol significantly increased the yields (compare entry 3 with 4, 5 with 6, and 7 with 8). Furthermore, the percent conversions and yields were essentially the same when thiophenol was added (entries 4, 6, and 8), indicating a smooth radical chain. In contrast, the control experiments (especially entries 3 and 5), where the percent conversion exceeded the yield, indicated that other pathways were competing. One equivalent of initiator was used to maximize the conversion in the control experiments, but in the thiophenol experiments with TBHN and DTBP (entries 6 and 8), the amount of initiator was decreased to 10−20% while maintaining high yield and conversion.

^{11}B NMR experiments showed that the expected boron product (diMe-Imd-BH_2I) was formed cleanly with high conversions and yields in several of the reactions of **4a**. Additional experiments (see the Supporting Information) showed the importance of the combination of the NHC-borane and the thiol. Replacement of **1** with tetrabutylammonium cyanoborohydride (Bu_4NBH_3CN)[16] resulted in moderate conversions and yields in the reduction of **4a**, while triphenylphosphine borane[3d] and trimethylamine borane[4] gave very low conversion. The thiol could not be replaced by a phenol or catechol,[2c] and benzeneselenol[11d] gave inferior results to thiophenol. On the other hand, while pentadecanethiol ($C_{15}H_{31}SH$) did not match thiophenol, *tert*-dodecanethiol [$C_9H_{19}C(CH_3)_2SH$, TDT] performed at least as well and possibly better. TDT also has a weak odor, and it was used in several of the subsequent preparative experiments.

Table 2 summarizes the results of a series of preparative experiments under several of the conditions identified in Table 1. Yields for low-molecular-weight products such as adamantane and mesitylene were determined by ^{1}H NMR integration against an internal standard, while the larger products were isolated by flash chromatography.

Adamantyl bromide (**4b**) was reduced in yields comparable to those for the iodide **4a** with TBHN (97%) and DTBP (92%) (entries 1 and 2). In contrast, little conversion was observed with adamantyl chloride (see the Supporting Information).

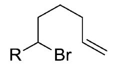
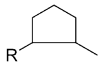
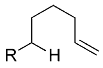
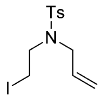
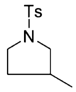
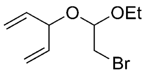
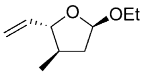
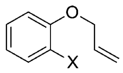
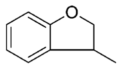
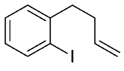
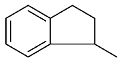
Glucose diacetonide **6** is a halide that can be reduced directly with **1**,[8f] but addition of thiophenol gave faster conversions and higher yields (67−81%; entries 3−5). Cholesterol iodide (**8a**) and bromide (**8b**) were not reduced by **1** alone, but both were cleanly reduced in the presence of thiophenol (96 and 95% yield; entries 6 and 8). The iodide was also reduced with the triazole borane **2**, after which the crude product was partitioned between ether and water and the ether phase was evaporated. This provided a good-quality sample of **9** in 81% yield, free of both thiophenyl- and boron-containing products (entry 7). A limitation was encountered in reductions of the derived epoxides **10a** and **10b**. Bromide **10b** was reduced cleanly with TBHN initiation (91%; entry 12), but the iodide gave a complex mixture (entry 11). This may be due to the Lewis acidity of the boron-derived product, diMe-Imd-BH_2I.[17]

In a major expansion of scope, aryl iodides and bromides are also reduced by **1** and PhSH. For example, reduction of mesityl bromide (**12**) under TBHN conditions give mesitylene (**13**) in 95% yield after 3 h (entry 13). Without the thiol, no mesitylene was formed. Aryl iodide **14a** and bromide **14b** were also cleanly reduced to **15** with TBHN and DTBP (81−86% yield; entries 14−17).

All of these reactions were conducted in benzene for consistency, but we expect that other solvents can also be used. Preferred alternatives to benzene in preparative chemistry include benzotrifluoride ($C_6H_5CF_3$)[18] and toluene. Reductions of **8b** in these two solvents gave about the same yield as the reduction in benzene (compare entries 8−10: C_6H_6, 95%; $C_6H_5CF_3$, 95%, $C_6H_5CF_3$, 90%).

Reductive cyclizations of both alkyl and aryl radicals derived from halides can also be catalyzed by thiols, as shown by the examples in Table 3. All of the yields reported in this table were obtained after flash chromatography. Cyclization of bromide **16** (0.2 M starting concentration) provided a mixture of cyclized product **17** and directly reduced product **18** in an 83/17 ratio in 90% yield (entry 1). The formation of significant amounts of **18** shows the effect of the thiol as a hydrogen donor (as **1** itself is not capable of intercepting the radical before cyclization). Compound **19**, the precursor of a more rapidly cyclizing alkyl radical, provided only the cyclized product **20** in 83% yield (entry 2). Stork−Ueno cyclization[19] of bromoacetal **21** gave cyclic acetal **22** in 76% yield (entry 3). In addition, aryl radical reactions could be conducted, as shown by the cyclizations of **23a**, **23b**, and **25** (80−83% yield; entries 4−6).

Table 3. Thiol-Catalyzed Radical 5-Exo-Trig Cyclizations of Halides with diMe-Imd-BH_3 1[a]

entry	substrate	product(s)	yield
1	 **16** R = $(CH_2)_5$-OBn	 **17** R = $(CH_2)_5$-OBn +  **18** R = $(CH_2)_5$-OBn	90% 83/17[b]
2	 **19**	 **20**	83%
3	 **21**	 **22**[c]	76%
4	 **23a**, X = I	 **24**	80%
5	**23b**, X = Br	**24**	83%
6	 **25**	 **26**	80%

[a] All used 0.2 M substrate under TBHN-initiated conditions: TBHN (20 mol %), **1** (1.1 equiv), TDT (5 mol %), 80 °C, 2 h. [b] **17**:**18** ratio. [c] 9/1 mixture of diastereomers; the major product is shown.

Mechanism of Thiol Catalysis. Figure 2 shows suggested propagation steps for these halide reductions. We focus the mechanistic analysis on alkyl radicals because currently no rate constants for reactions involving aryl radicals and NHC-

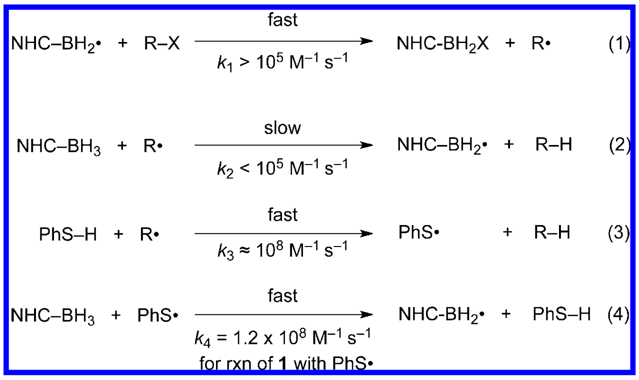


Figure 2. Suggested propagation steps with rate constants for alkyl radicals R●.

boranes are known. In the reaction without thiophenol, the carbene boryl radical NHC-BH_2● abstracts a halogen atom from RX to give an alkyl radical R● (step 1), which in turn abstracts a hydrogen atom from the precursor NHC-BH_3 (step 2). The measured rate constants k_1 for abstraction of bromine and iodine by NHC-boryl radicals[20] are 1−3 orders of magnitude larger than k_2 for hydrogen abstraction by alkyl radicals ($<1 \times 10^5$ M^{-1} s^{-1}).[8b,d] Thus, the slow hydrogen transfer step (step 2) presumably limits the chain propagation.

When thiophenol is added, this slow hydrogen transfer reaction is superseded by two fast reactions. First, thiophenol donates a hydrogen to the alkyl radical (step 3). Rate constants k_3 for this reaction are in the range $(0.7-1) \times 10^8$ M^{-1} s^{-1}.[21] We propose that the phenylthiyl radical PhS● next abstracts a hydrogen atom from NHC-borane **1** to give the starting radical R● and regenerate the thiophenol catalyst (step 4).

The thermodynamics of step 4 can be assessed on the basis of bond dissociation energies (BDEs). The experimental BDE of the S−H bond of thiophenol is ∼83 kcal/mol.[22] An estimate (from an Evans−Polyani relationship) places the BDE of an NHC-borane at ∼87 kcal/mol,[8d] which would mean that step 4 is endothermic. However, several calculations of the B−H BDEs of **1** and related NHC-boranes at the UB3LYP/6-31+G* level provide BDEs of 80−82 kcal/mol.[8c,20] At the same level, PhS−H is calculated to have a BDE of 79 kcal/mol, which would mean that step 4 is almost thermoneutral.

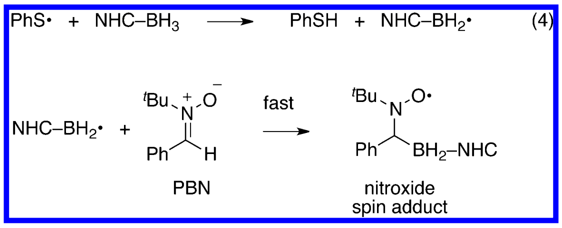
Thermochemistry aside, it is the rate of step 4 that dictates its importance.[23] Here, the polarity matching between the electrophilic thiyl radical and the NHC-borane is expected to lower the barrier of the forward and reverse reactions. Polarity effects are reflected by the difference between the electronegativities of the radicals involved in the hydrogen atom transfer reactions (PhS● and NHC-BH_2●). The Mulliken electronegativity (χ_M) of a radical is defined by eq 1:

$$\chi_M = \frac{\text{IP} + \text{EA}}{2} \tag{1}$$

The ionization potential (IP) and electron affinity (EA) for the PhS● and NHC-BH_2● radicals were calculated at the UB3LYP/6-31+G* level by optimization of the relevant radicals and ions (see the Supporting Information). Remarkably, PhS● and diMe-Imd-BH_2● were found to have χ_M = 5.33 and 2.72 eV, respectively. This large electronegativity difference anticipates polar effects in the hydrogen transfer reactions, in which PhS● is electrophilic and diMe-Imd-BH_2● is nucleophilic.

The viability of step 4 was first supported by electron spin resonance (ESR) spin-trapping experiments. Phenylthiyl radicals are conveniently produced by photolysis of diphenyl disulfide. In addition, NHC-boryl radicals produced by other means can add to the spin trap *N-tert*-butyl-*α*-phenylnitrone (PBN) to give a stable nitroxide spin adduct.[20] Thus, photolysis of PhSSPh, **1**, and PBN should product a nitroxide spin adduct, as shown in Scheme 1.

Scheme 1. Spin Trapping Provides Evidence for Hydrogen Transfer



The spin adduct was detected by ESR experiments, as shown in Figure 3. In a control experiment, **1** and PBN were irradiated in *tert*-butylbenzene in an ESR cavity, but no signal was observed. Irradiation of a mixture of PhSSPh, **1**, and PBN gave a strong signal of a spin adduct that was simulated with hyperfine coupling constants a_N = 15.4 G, a_H = 2.1 G, and a_B = 4.3 G. These values agree with previous data on NHC-boryl radical spin adducts with PBN.[9a,20] Accordingly, a photolytically generated PhS● radical abstracts hydrogen from **1**, and the resulting NHC-boryl radical adds to PBN.

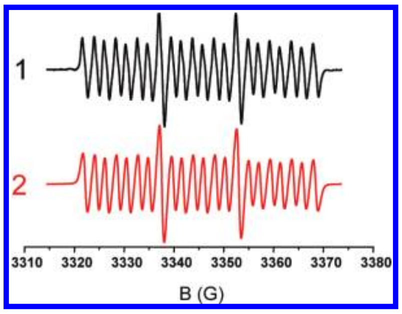


Figure 3. ESR spin-trapping spectra for PhSSPh/**1** in *tert*-butylbenzene: (1) experimental and (2) simulated spectra for the nitroxide spin adduct.

We next used laser flash photolysis (LFP) experiments to measure the rate constant for the reaction between phenylthiyl radical and diMe-Imd-BH_3 **1**. The phenylthiyl radical was again generated by irradiation of diphenyl disulfide and allowed to react with increasing concentrations of **1**. The results of these experiments are summarized in Figure 4. The rate constant for the reaction of PhS● with **1** was determined according to the classical Stern−Volmer equation (eq 2),

$$\frac{1}{\tau} = \frac{1}{\tau_0} + k_H[\mathbf{1}] \tag{2}$$

where k_H is the rate constant for hydrogen transfer and τ_0 is the PhS● lifetime in the absence of quencher. A plot of the reciprocal of the lifetime of the radical against the concentration of **1** provided the rate constant $k_4 = 1.2 \times 10^8$ M^{-1} s^{-1}. On the basis of the high values of k_3 and k_4, we conclude that thiophenol can behave as a catalyst for such reductions through the chain in Figure 2 that involves step 1 but bypasses the slow step 2 in favor of the fast steps 3 and 4. It is not currently clear

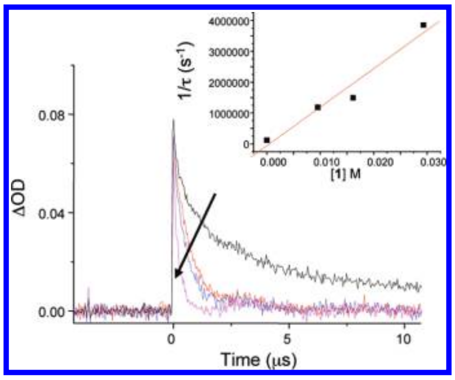


Figure 4. Decay of the PhS● signal at 480 nm in ethylbenzene/acetonitrile with increasing concentrations of **1**. The arrow shows that the thiyl lifetime decreases as the concentration of **1** increases. ΔOD is the change in optical density associated with the light excitation. Inset: the associated Stern–Volmer treatment.

whether step 4 is reversible. The reverse reaction certainly has a relatively high rate constant, but the concentration of PhSH is relatively low. The reaction in step 1 competes for NHC-BH_2●, and this reaction could well be faster than the reverse of step 4.[23]

We could not directly detect the formation of diMe-Imd-BH_2● in these experiments because its UV absorption overlaps with that of PhS●. Accordingly, we carried out complementary experiments with the *B*-phenyl-substituted analogue diMe-Imd-BH_2Ph (**3**) (Figure 1) because the UV–visible spectrum of its derived boryl radical is characterized by a strong red shift (λ_{max} = 550 and 350 nm for diMe-Imd-BHPh● and diMe-Imd-BH_2●, respectively).[18a] Indeed, on photolysis of PhSSPh and **3**, both PhS● and diMe-Imd-BHPh● were observed (Figure 5). This further supports the conclusion that PhS● and NHC-boranes react by hydrogen atom transfer.

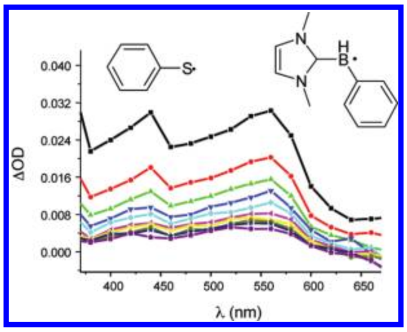


Figure 5. Transient spectra for PhS–SPh and diMe-Imd-BH_2Ph (**3**) in acetonitrile from 0.5 to 36.5 μs in 4.5 μs steps (represented as different colors).

A series of LFP experiments were conducted with different concentrations of **3**, and these data are shown in the Supporting Information. The results were analyzed by the usual Stern–Volmer treatment, which provided $k_H = 7 \times 10^7$ M^{-1} s^{-1} for the hydrogen abstraction reaction of PhS● from **3**. The small decrease in the rate constant relative to **1** caused by the phenyl substituent in **3** is in line with prior rate measurements with alkyl radicals[8e] and alkoxy radicals.[18a]

We also conducted a similar LFP experiment with triphenylphosphine borane (Ph_3P-BH_3) in place of the NHC-borane. However, this reagent did not quench the PhS● radical under the conditions of the experiment (see the Supporting Information). From this, we estimate that k_H for the reaction of PhS● with Ph_3P-BH_3 is at least 2 orders of magnitude smaller ($<10^6$ M^{-1} s^{-1}) than k_H for **1**. This is consistent with the earlier observation that Ph_3P-BH_3 and thiophenol do not reduce adamantyl iodide effectively.

CONCLUSIONS

In summary, we have developed several practical recipes for thiol-catalyzed reductive dehalogenations with convenient and readily available NHC-boranes. The use of thiols considerably expands the scope of reductions of alkyl halides and for the first time adds aryl halides as substrates for NHC-borane reductions. In the case of alkyl radicals, an analysis of available and new rate constants suggests that the thiol accelerates the radical hydrogen atom transfer reaction through polarity reversal catalysis. Rate constants for the reaction of the phenylthiyl radical with two NHC-boranes were measured to be $\sim10^8$ M^{-1} s^{-1} by laser flash photolysis experiments. These values are large for reactions that that are probably nearly thermoneutral, no doubt thanks to the favorable polarity effect. Thus, the scope of halide reductions by carbene boranes has been significantly expanded, and the basis for thiol catalysis has been placed on a firm mechanistic foundation.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Full details for all experiments and calculations and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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