

Aromatic Substitution

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Hydrodehalogenation of Haloarenes by a Sodium Hydride–Iodide Composite

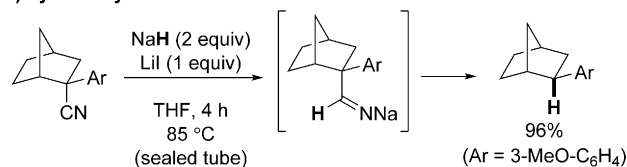
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Abstract: A simple protocol for hydrodebromination and -deiodination of halo(hetero)arenes was enabled by sodium hydride (NaH) in the presence of lithium iodide (LiI). Mechanistic studies showed that an unusual concerted nucleophilic aromatic substitution operates in the present process.

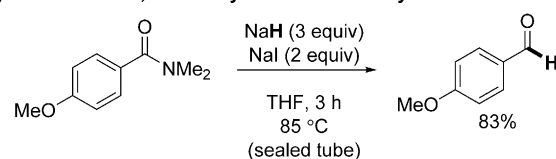
Among various reductive molecular transformations,^[1] hydrodehalogenation of organic halides has attracted much attention not only as a synthetic strategy^[2] but also from their potential use for detoxification of environmentally hazardous organic halides.^[3] Thus, various methodologies for the hydrodehalogenation have been developed,^[4] commonly employing halogen–metal exchange with highly reactive organolithium or -magnesium reagents under cryogenic reaction conditions,^[5] transition metal catalysis with hydride sources,^[6] and radical-mediated processes mainly with toxic tin hydrides.^[7] However, the typical reaction conditions for the established procedures cause some disadvantageous concerns in process efficiency, safety, operation, and cost. Recent developments in the use of organic super electron donors,^[8] photo-redox catalysis,^[9] sodium alcoholates as the organic chain reductant,^[10] and catechols as the hydrogen radical source^[11] for hydrodehalogenation under mild reaction conditions could compensate for such drawbacks.

We recently disclosed that sodium hydride (NaH) could act as a hydride donor in the hydrodeacylation of nitriles (Scheme 1 a) and hydride reduction of amides into aldehydes (Scheme 1 b) in the presence of LiI or NaI.^[12,13] This unprecedented and unique hydride donor reactivity of sodium hydride–iodide composite stimulated us to further explore development of new reductive transformation with the composite. Herein, we report use of sodium hydride–iodide composite to perform hydrodehalogenation of a wide range of bromo- and iodoarenes under mild reaction conditions (Scheme 1 c). The detailed mechanistic studies suggested that the present hydrodehalogenation proceeds via neither a radical nor a metal–halogen exchange pathway, but through a rather unusual concerted nucleophilic aromatic substitution mechanism.^[14,15]

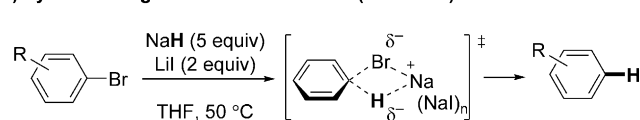
a) hydrodeacylation



b) reduction of N,N-dimethyl amides to aldehydes

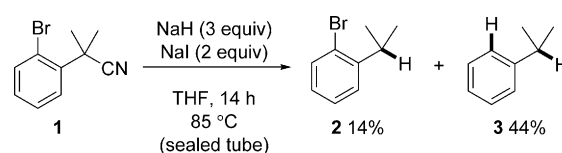


c) hydrodehalogenation of haloarenes (this work)



Scheme 1. Reductive molecular transformations by the sodium hydride–iodide composite.

While studying the substrate scope of the hydrodeacylation by the NaH–iodide composite, we found that the reaction of bromoaryl substrate **1** provided not only 2-bromocumene (**2**) in 14% yield but also cumene (**3**) in 44% yield (Scheme 2). It was tempting to assume that cumene (**3**) was formed through hydrodebromination by the NaH composite, and therefore, we explored the scope and limitation as well as the reaction mechanism of the process.^[16]

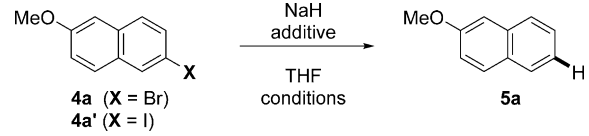


Scheme 2. Serendipitous observation of hydrodebromination during hydrodeacylation of **1**.

We commenced optimization of the reaction conditions for the hydrodebromination using 2-bromo-6-methoxynaphthalene (**4a**) (Table 1). The reaction of **4a** with NaH (5 equiv) in THF was completed within 12 h even at 60 °C when NaI (2 equiv) was used as an additive, to afford 2-methoxynaphthalene (**5a**) in good yield (entry 1). Use of LiI instead of NaI rendered the process smoother, completing the process within 6 h (entry 2), while lowering the amounts of NaH and LiI slowed down the reaction rate (entry 3). Furthermore, the reaction temperature could be lowered to 40–50 °C without

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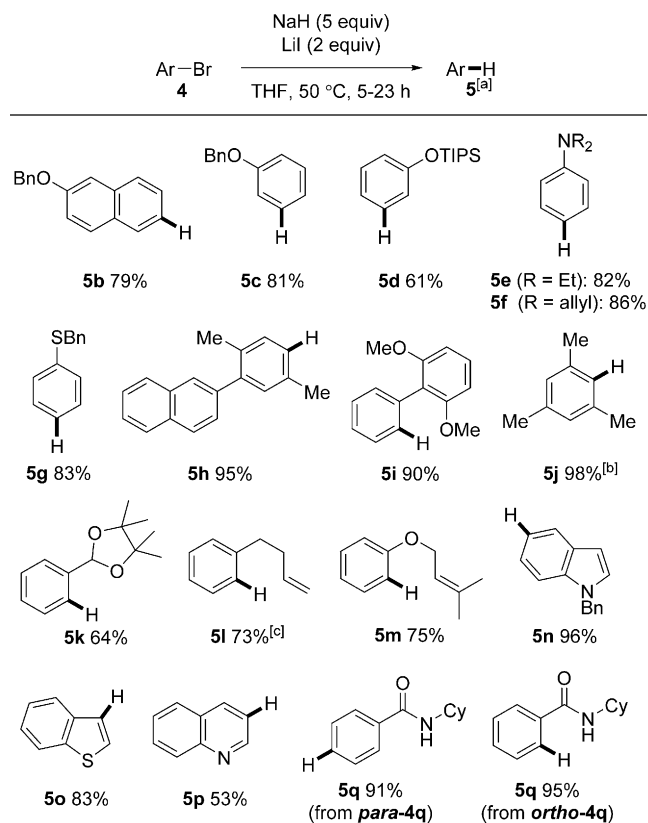
Table 1: Optimization of reaction conditions for hydrodehalogenation of **4a** and **4a'**.^[a]


Entry	X	NaH (equiv)	Additive (equiv)	T [°C]	t [h]	Yield of 5a [%] ^[b]
1	Br	5	NaI (2)	60	12	91
2	Br	5	LiI (2)	60	6	89
3	Br	3	LiI (1)	60	10	90
4	Br	5	LiI (2)	50	7	89 (81) ^[c]
5	Br	5	LiI (2)	40	10	89
6	Br	5	LiI (2)	24	16	33 ^[d]
7	Br	5	–	50	10	4 ^[e]
8	I	5	NaI (2)	30	10	85 (75) ^[c]
9	I	5	LiI (2)	30	10	61
10	I	5	–	30	10	0 ^[e]

[a] The reactions were conducted using 0.5 mmol of **4a** or **4a'** in THF (2.5 mL). [b] ¹H NMR yields. [c] Isolated yield of **5a**. [d] Recovery of **4a** in 63% yield. [e] Recovery of **4a** or **4a'** in more than 90% yield.

diminishment of the yields of **5a** (entries 4 and 5), although the reaction at room temperature (24°C) became sluggish (entry 6). It should be noted that NaH alone is not sufficient to drive the hydrodebromination (entry 7), indicating that this unique hydride donor reactivity is conferred on the NaH–iodide composite. Employment of more reactive iodide **4a'** allowed the reaction to reach full conversion even at 30°C (entries 8 and 9). Similarly, almost no reaction of **4a'** occurred without iodide additive (entry 10).

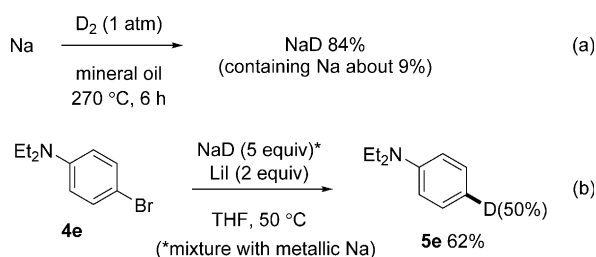
Under the optimized reaction conditions (Table 1, entry 4), we next investigated the substrate scope of hydrodebromination using various bromoarenes **4** (Scheme 3). As electron-donating substituents, benzyloxy (for **5b** and **5c**) and silyloxy (for **5d**) as well as dialkyl amino (for **5e** and **5f**) and benzylthioxy (for **5g**) moieties could be tolerated, and the corresponding reduced arenes were obtained in 61–86% yields. Sterically hindered bromoarenes having *ortho*-methyl (for **5h**) and *ortho*-aryl (for **5i**) groups could be reduced smoothly. It should be worthy of note that hydrodebromination of 2-bromomesitylene (**4j**) worked very nicely to give mesitylene (**5j**) in quantitative yield, suggesting that benzyne is unlikely involved as an intermediate in the present hydrodebromination. The acetal moiety could be kept intact during the reduction process (for **5k**). Bromoarenes **4l** and **4m** having *ortho*-butenyl and *ortho*-*O*-allyl tethers, respectively, gave **5l** and **5m** while keeping the alkenyl moieties intact.^[17] These results suggest that an aryl radical intermediate may not be involved in the reaction pathway. Hydrodebromination of 5-bromoindole **4n** and 3-bromobenzothiophene (**4o**) proceeded smoothly to give the corresponding heteroarenes **5n** and **5o** in high yields, whereas the reduction of 3-bromoquinoline (**4p**) afforded a moderate yield of **5p** (53% yield). Although the NaH–iodide composite could reduce tertiary amides to the corresponding aldehydes,^[12a] interestingly, secondary amides could be kept intact because the amide anion generated through deprotonation by NaH is



Scheme 3. Substrate scope for the hydrodebromination of bromoarenes **4**. [a] The reactions were conducted using 0.5 mmol of **4** in THF (2.5 mL) and isolated yields of **5** were noted above unless otherwise stated. [b] GC yield. [c] ¹H NMR yield. Bn = benzyl; TIPS = triisopropylsilyl; Cy = cyclohexyl.

inert toward hydride reduction by the NaH–iodide composite. Taking advantage of this unique reactivity pattern, selective reduction of bromo-*N*-cyclohexylbenzamides *para*-**4q** and *ortho*-**4q** could be achieved, which afforded debrominated **5q** in excellent yields.

To investigate the reaction mechanism, especially how the hydrogen is installed during the hydrodehalogenation process, several deuterium labelling experiments were conducted. Incorporation of deuterium was not observed at all in the reactions of **4a** in THF-D₈ or with D₂O quench (see the Supporting Information (SI)), implying that single-electron reduction of aryl bromides by NaH^[18] should not be involved in the present process. Rather, NaH in the composite state functions as a hydrogen atom donor in the reduction process, most probably via nucleophilic aromatic substitution. To prove this hypothesis, we prepared sodium deuteride (NaD) from metallic Na and D₂ gas following the reported procedure (Scheme 4a).^[19] Treatment of Na dispersion in mineral oil with D₂ gas (1 atm) at 270°C afforded NaD containing metallic Na (ca. 9%), which was characterized by solid-state NMR (²³Na and ²H) spectroscopy as well as powder X-ray diffraction. The hydrodebromination of **4e** by this NaD sample resulted in deuterium incorporation of 50% in the reduced product **5e** (Scheme 4b), which unambiguously exemplified the role of NaH as the hydrogen donor.^[20]



Scheme 4. Preparation of NaD and a deuterium labelling experiment.

Our recent work on materials characterization of the NaH–iodide composite indicated that a smaller nanometric unit of NaH dispersed on NaI might be produced by solvothermal treatment of NaH with NaI or LiI in THF, giving rise to unique hydride donor reactivity.^[12b] On this basis, to better understand the reaction mechanism of the present hydrodehalogenation, DFT calculations were performed for a model reaction of bromobenzene with a single molecule of NaH,^[21] using Gaussian09 software.^[22] The bulk solvent effect of THF was described with an implicit model, and two molecules of THF were included explicitly. A highly exothermic pathway having a single transition state (**TS-I**) for concerted nucleophilic aromatic substitution was obtained (Figure 1). The barrier for the reaction was not very high

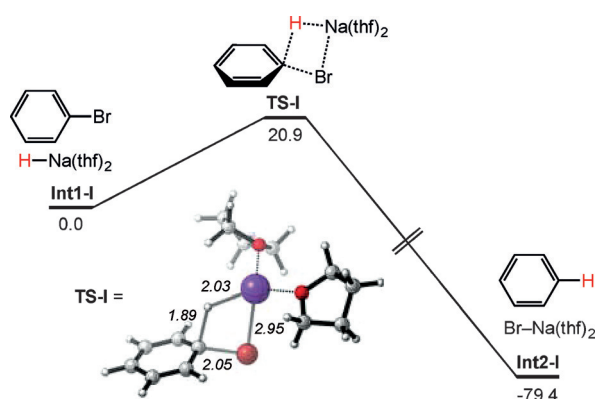


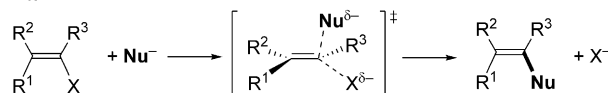
Figure 1. Free energy profile for hydrodehalogenation of bromobenzene by a single molecule of NaH in THF (in kcal mol^{-1}), determined at the B3LYP(SCRF)-D3(B)/def2-TZVP//B3LYP/def2-TZVP level. Key bond distances are indicated in Å.

(20.9 kcal mol^{-1}), indicating that NaH, especially in a fragment state, is reactive toward an aromatic bromide. Moreover, the Hammett plot of $\log(k_X/k_H)$ versus σ showed a linear correlation with a positive ρ value of 0.47 (see the SI). This trend supports the concerted nucleophilic aromatic substitution mechanism via a rate-determining transition state having a partial negative charge (δ^-) (**TS-I** in Figure 1) without formation of a charged Meisenheimer complex, which is involved as an intermediate in typical aromatic substitution reactions proceeding via an addition–elimination mechanism.^[23]

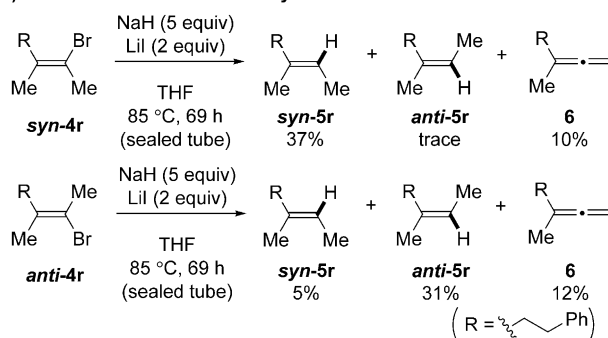
The predicted concerted nucleophilic aromatic substitution reaction in the hydrodehalogenation is initiated by the

interaction between the hydride and the π^* orbital of the aromatic ring. An analogous concerted substitution reaction at the vinylic carbon through the hydride attack onto the π^* orbital ($S_NV\pi$) should result in retention of the stereo-configuration of the haloalkenes (Scheme 5a).^[24] We thus

a) $S_NV\pi$ pathway with retention of the configuration



b) reactions of bromoalkenes *syn*- and *anti*-4r



Scheme 5. Hydrodebromination of bromoalkenes **4r**.

investigated the hydrodebromination of bromoalkenes **syn-4r** and **anti-4r** (Scheme 5b).^[25] The reduction of **syn-4r** at 85 °C afforded **syn-5r** in 37% yield. Similarly, the reduction of **anti-4r** delivered **anti-5r** in 31% yield along with a small amount of **syn-5r**. As expected, in both cases, reduction of the C–Br bond proceeded mostly with retention of the configuration. It is noted that both of the reactions also produced allene **6** via an elimination reaction.

DFT calculations of a model reaction of 2-bromo-3-methyl-2-butene with NaH provided **TS-II** for concerted vinylic substitution that involves attack of the hydride on the π^* orbital ($S_NV\pi$) (Figure 2); the barrier for this reaction was again not very high. An alternative pathway, in which the hydride attacks the σ^* orbital of the C–Br bond ($S_NV\sigma$), could

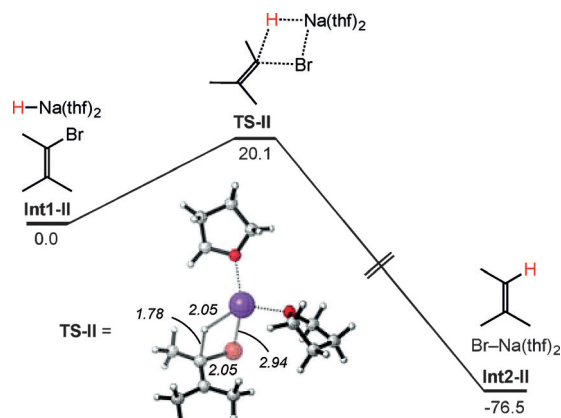


Figure 2. Free energy profiles for hydrodehalogenation of 2-bromo-3-methyl-2-butene by a single molecule of NaH in THF (in kcal mol^{-1}), determined at the B3LYP(SCRF)-D3(B)/def2-TZVP//B3LYP/def2-TZVP level.

not be obtained. When calculations were performed without adding two explicit THF molecules, the transition state for the $S_NV\sigma$ pathway could be located; however the barrier for this process was higher than that for the $S_NV\pi$ pathway by about 8 kcal mol^{-1} (see the SI). These results suggest that the $S_NV\pi$ pathway should be the dominant one for this process and are well consistent with the stereochemical outcomes in the hydrodebromination of *syn*- and *anti*-**4r** (Scheme 5).

This work demonstrated a new reactivity of sodium hydride in hydrodehalogenation of haloarenes that proceeds via a concerted nucleophilic aromatic substitution pathway. We are currently working to explore other types of reductive molecular transformations with the NaH–iodide composite.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: DFT calculations · haloarenes · hydrodehalogenation · reduction · sodium hydride

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bearing the C–H bond on the same side of the phenethyl group and vice versa for the *anti*-isomer.

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