Reduction of N,N-Dimethylcarboxamides to Aldehydes by Sodium Hydride-Iodide Composite

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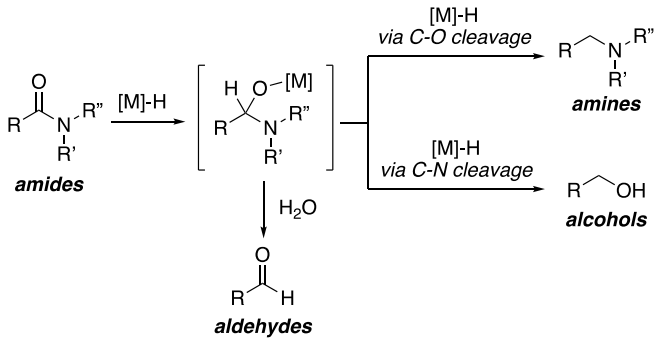
A new and concise protocol for selective reduction of N,N-dimethylamides into aldehydes was established using sodium hydride (NaH) in the presence of sodium iodide (NaI) under mild reaction conditions. The present protocol with the NaH-NaI composite allows for reduction of not only aromatic and heteroaromatic but also aliphatic N,N-dimethylamides with wide substituent compatibility. Retention of α-chirality in the reduction of α-enantioriched amides was accomplished. Use of sodium deuteride (NaD) offers a new step-economical alternative to prepare deuteriated aldehydes with high deuterium incorporation rate. The NaH-NaI composite exhibits unique chemoselectivity for reduction of N,N-dimethylamides over ketones.

Keywords: Amides • Aldehydes • Reduction • Sodium hydride • Iodide

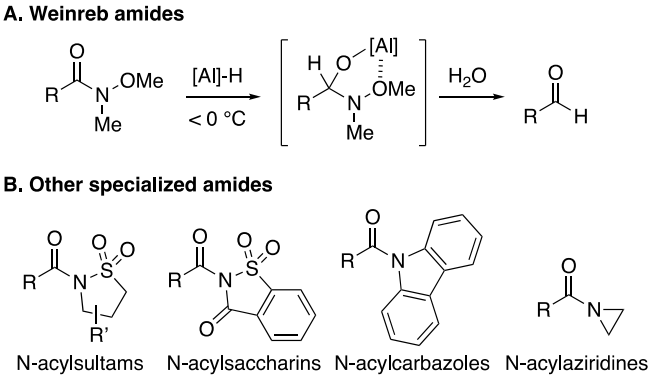
Introduction

Hydride reduction of carbonyl compounds is one of the most fundamental and important processes in organic synthesis[1-2]. Among various carbonyl compounds, bench-stable amides are used as a versatile precursor to be reduced into amines and alcohols as well as aldehydes (Scheme 1)[3-6]. Especially, to perform the efficient and selective reduction of amides into aldehydes, specific setups in the amide substituents, the reductants, and/or the reaction conditions are required to prevent fragmentation of transient tetrahedral metalated aminal intermediates, that results in over-reduction to amines or alcohols.



Scheme 1. Reduction of amides.

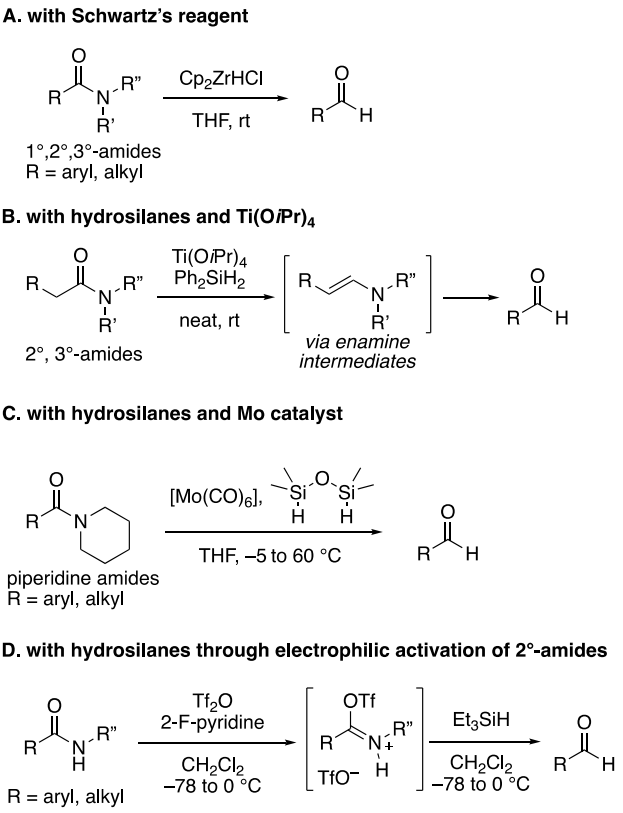
For this purpose, *N*-methoxy-*N*-methylamides (the Weinreb amides), that form stabilized tetrahedral five-membered-chelate intermediates[7-9], have typically been utilized with reactive hydride donors such as lithium aluminum hydride, diisobutylaluminium hydride, and Red-Al under cryogenic reaction conditions (commonly at < 0 °C) (Scheme 2A)[10]. There has also been reported use of tertiary amides having special substituents which reduce the electron-donating nature of the amide nitrogen onto the carbonyl group, including N-acylsultam[11], N-acylsaccharin[12], N-acyl carbazoles[13] and N-acylaziridines (Scheme 2B)[14-15].



Scheme 2. Special setups onto amides for reduction to aldehydes

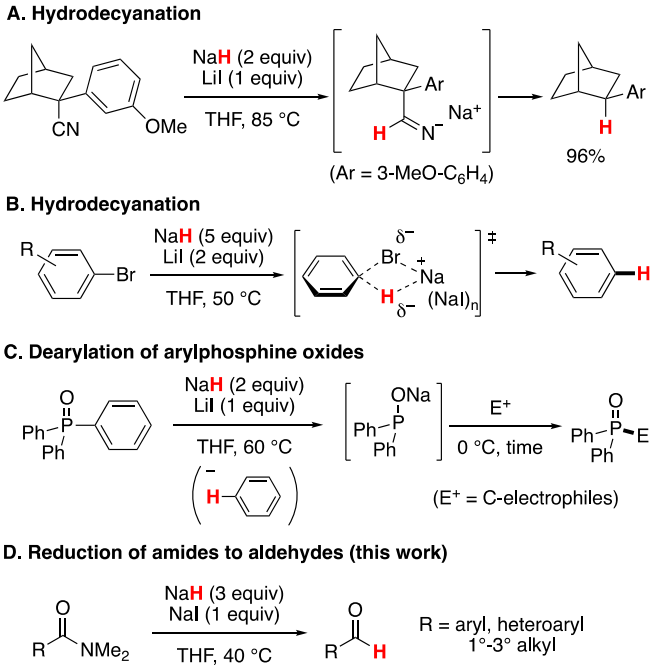
On the other hand, the reduction of simple N,N-dialkylamides to aldehydes needs use of modified hydride reagents such as $LiAlH_n(OEt)_{4-n}$ (n = 1 or 2)[16-17], disiamylborane[18], and lithium diisobutylpiperidinohydroaluminate[19]. It should be noted that the Schwartz's reagent [$Cp_2Zr(H)Cl$] is capable of reducing a variety of amides (primary, secondary, and tertiary) to the corresponding aldehydes under very mild reaction conditions with wide functional group compatibility (Scheme 3A)[20-22]. There have been reported several methods for reduction of amides to aldehydes using hydrosilanes with the aid of transition metals. Buchwald developed reduction of aliphatic amides into aldehydes by combined use of Ph_2SiH_2 and $Ti(OiPr)_4$, that proceeds via formation of an enamine intermediate (Scheme 3B)[23]. Therefore, racemization is observed in the reduction of α-enantioriched amides. Adolfsson disclosed versatile reduction of piperidine amides into aldehydes with 1,1,3,3-tetramethyldisiloxane catalyzed by $Mo(CO)_6$ (Scheme 3C)[24]. Temperature control is the key to enable selective formation of

aldehydes over that of amines (–5 to 60 °C), in which unique chemoselectivity for the reduction of amides over other susceptible π-polar functional groups such as keto, formyl, and imine moieties was observed. On the other hand, transition-metal free reduction of secondary amides into aldehydes was reported by Charette (Scheme 3D)[25]. The process requires prior activation of amides with Tf_2O followed by reduction with Et_3SiH.



Scheme 3. Reduction of simple *N,N*-dialkylamides into aldehydes

Despite the recent progress, there is still ample room to develop methods for reducing simple amides into aldehydes, that can be conducted in operationally simple and cost-effective manners under milder reaction conditions. We recently disclosed that sodium hydride (NaH) could act as a hydride donor in the presence of NaI or LiI in THF, capable of performing a series of unprecedented hydride reduction such as hydrodecyanation of carbonitriles (Scheme 4A)[26-27], hydrodehalogenation of haloarenes (Scheme 4B)[28], and dearylation of arylphosphipne oxides[29] (Scheme 4C)[30-31]. In this context, we envisioned that use of the sodium hydride-iodide composite for the reduction of amides results in unique outcomes[1]. This article describes a full account on hydride reduction of amides to aldehydes by the sodium hydride-iodide composite with broad evaluation in scope and limitations (Scheme 4D).



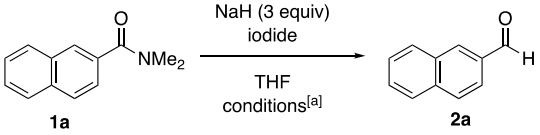
Scheme 4. Reduction by the NaH-I composite

Results and Discussion

Our preliminary investigation revealed that the reaction of *N,N*-dimethyl-2-naphthamide (**1a**) with NaH (3 equiv) and NaI (1 equiv) in THF at 85 °C (under sealed reaction conditions) completed within 1 h to give 2-naphthaldehyde (**2a**) in 90% yield as a sole product (Table 1, entry 1). Surprisingly, the transient tetrahedral hemiaminal intermediate could be kept stable even at high reaction temperature (85 °C), enabling selective formation of aldehyde **2a**. This unprecedented discovery stimulated us further to optimize the reaction conditions to render the reduction process more selective and versatile. Slower reaction rate was observed when the iodide additive was changed to LiI (entry 2). We found that with the NaH-NaI system, lowering of the reaction temperature to 40 °C could also complete the process and the yield of **2a** was improved to 93% (entry 3). Implementation of the reduction at 40 °C, despite longer reaction time required, is advantageous to make the process more selective (vide infra). Further lowering of the reaction temperature to 25 °C or the amount of NaI to 0.1 equivalent made the process incomplete even after 24 h (entries 4 and 5). It should be noted that use of NaH in the absence of iodide additives is not sufficient to drive the hydride reduction (entry 6).

[1] For our preliminary communications on reduction of simple amides onto aldehydes, see: ref. 26 and ref. 31.

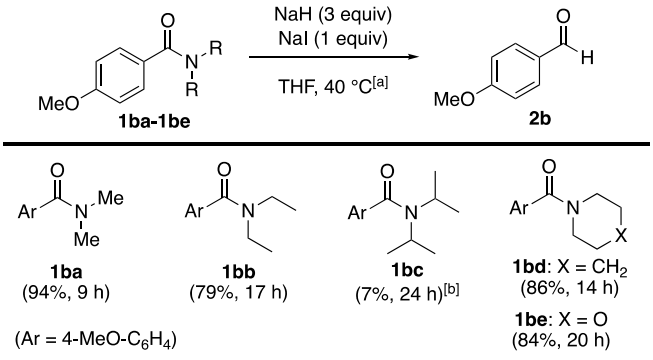
Table 1. Optimization of reaction conditions



Entry	Iodide (equiv)	Temp / °C	time (h)	Yield of 2a (%)[b]
1	NaI (1)	85	3	90
2	LiI (1)	85	6	89
3	NaI (1)	40	10	93
4	NaI (1)	25	24	(63)[c]
5	NaI (0.1)	40	24	(23)[d]
6	–	40	10	–[e]

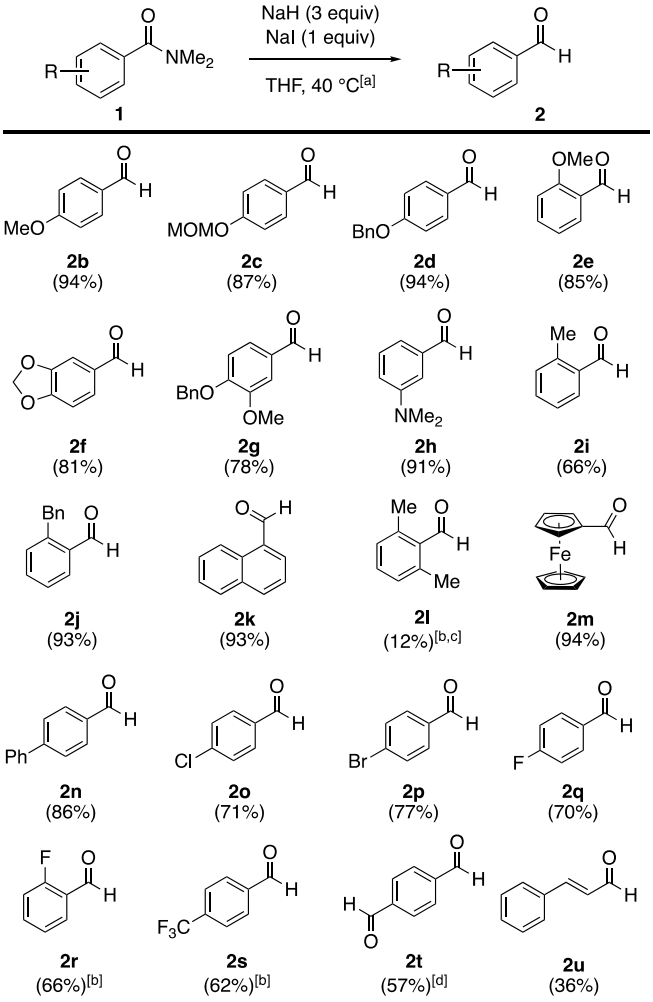
[a] The reactions were conducted using 0.5 mmol of amide **1a** in THF (0.2 M). [b] Isolated yields. [c] ^{1}H NMR yield based on the internal standard. **1a** was recovered in 36% yield. [d] ^{1}H NMR yield based on the internal standard. **1a** was recovered in 74% yield. [e] **1a** was recovered in >95% yield based on the internal standard.

Having optimized the reaction conditions, we next investigated the substituent effect of the amide nitrogen (Scheme 5). We found that as the steric demand increases, the reaction becomes more sluggish. The reduction of diisopropylamide **1bc** was not completed even after 24 h, providing only 7% yield of aldehyde **2b** with 70% recovery of **1bc**. Piperidine and morpholine amides **1bd** and **1be** showed similar reactivity as that of diethylamide **1bb**.



Scheme 5. Investigation of the substituent effect on the amide nitrogen. [a] The reactions were conducted using 0.5 mmol of amides **1** with 3 equiv of NaH and 1 equiv of NaI in THF (0.2 M) at 40 °C and isolated yields of anisaldehyde (**2b**) and the reaction time were noted above. [b] ^{1}H NMR yield based on the internal standard. **1bc** was recovered in 70% yield.

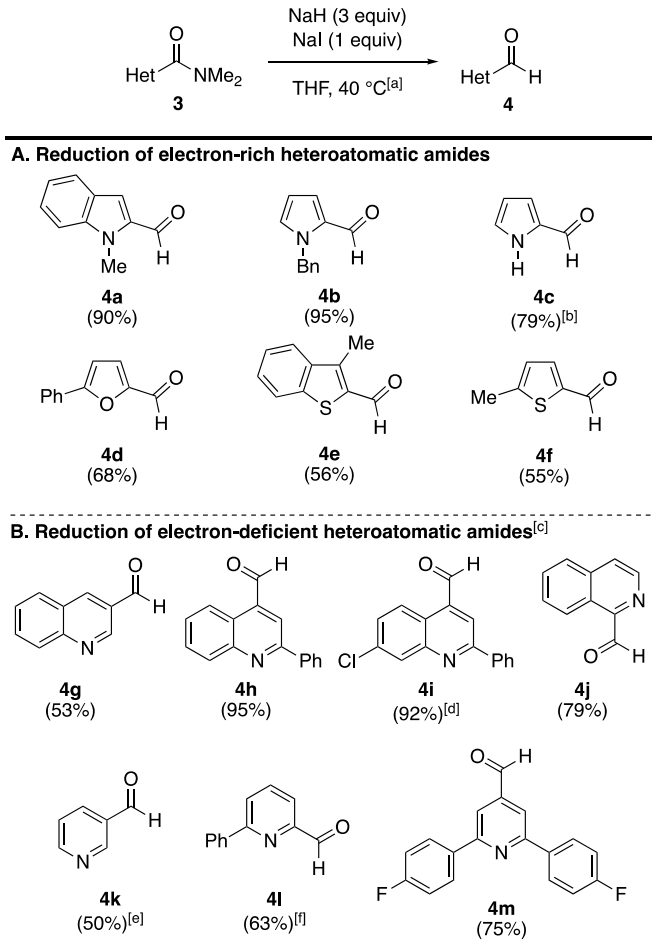
Reduction of various aromatic *N,N*-dimethylamides was next examined (Scheme 6). As electron-donating substituents, methoxy, methoxymethoxy (MOMO-), benzyloxy, and methylenedioxy as well as dimethylamino moieties could be tolerated, and the corresponding aldehydes were obtained in 78-94% yields (for **2b**-**2h**). Sterically hindered benzamides having *ortho*-methyl (for **2i**) and *ortho*-benzyl (for **2j**) groups as well as 1-naphthamide **1k** could be reduced smoothly, while reduction of 2,6-dimethylbenzamide **1l** became sluggish. Synthesis of ferrocenecarboxaldehyde (**2m**) was achieved in 93% yield. It should be worthy of note that the present reaction conditions allowed for chemoselective reduction of amides into benzaldehydes keeping C-halogen bonds intact (for **2o**-**2r**). Reduction of electron-deficient amides **1s** and **1t** also worked well, while that of α,β-unsaturated amide **1u** performed in moderate efficiency.



Scheme 6. Reduction of aromatic amides. [a] Unless otherwise stated, the reactions were conducted using 0.5 mmol of amides **1** with 3 equiv of NaH and 1 equiv of NaI in THF (0.2 M) at 40 °C and isolated yields of aldehydes **2** were noted above. [b] ^{1}H NMR yield with the aid of internal standard. [c] **1l** was recovered in 81% yield based on the internal standard. [d] The reaction was conducted using N^1,N^1,N^4,N^4-tetramethylterephthalamide (**1t**) with 5 equiv of NaH and 2 equiv of NaI at 85 °C.

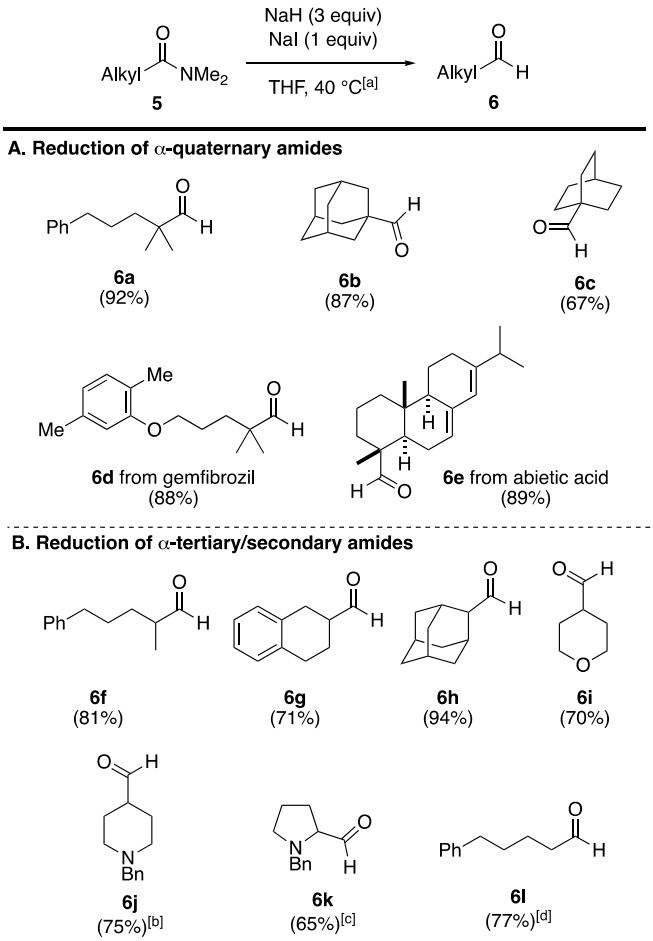
We then shifted our attention to the reduction of heteroaromatic amides (Scheme 7). Various electron-rich 5-membered heteroaromatic substrates were first screened (Scheme 7A). Reduction of *N*-methyl-2-indolecarboxamide **3a** and *N*-benzyl-2-pyrrolecarboxamide **3b** gave the corresponding aldehydes in excellent yields. *N*-Unprotected 2-pyrrolecarboxamide **3c** could be reduced in good yield, while use of 5 equivalents of NaH was required to complete the process. Other electron-rich heteroaromatic amides based on furan, thiophene, and benzothiophene could be

converted into the corresponding aldehydes in good to moderate yields (for **4d**-**4f**). On the other hand, electron-deficient 6-membered-ring aromatic heterocycles are susceptible to the conventional hydride reductants. In this regard, use of the NaH-NaI composite is advantageous as quinoline and pyridine scaffolds were tolerated during the amide reduction. Various quinoline and pyridinecarboxamides were reduced to the corresponding aldehydes in good to moderate yields. Nevertheless, this protocol is capable of reducing 7-chloro-2-phenylquinoline-4-carboxamide (**3i**) to 7-chloro-2-phenylquinoline-4-carboxaldehyde (**4i**), which is a key intermediate for supplying a quinolone-based anti-cancer agent[32].



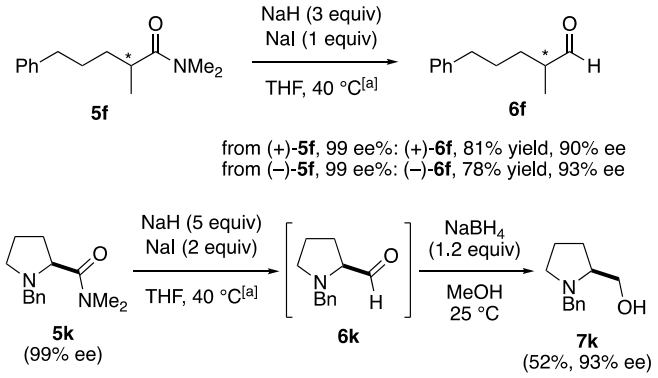
Scheme 7. Reduction of heteroaromatic amides. [a] Unless otherwise stated, the reactions were conducted using 0.3-0.5 mmol of amides **3** with 3 equiv of NaH and 1 equiv of NaI at 40 °C in THF (0.2 M) and isolated yields of aldehydes **4** were noted above. [b] The reaction was conducted using 5 equiv of NaH and 2 equiv of NaI in THF (0.1 M). [c] The reactions were quenched by pouring the reaction mixture into pH7 phosphate buffer solution (see the Supporting Information for details). [d] The reaction was conducted using 1 g (3.2 mmol) of **1i**. [e] ^{1}H NMR yield based on the internal standard. [f] The reaction was conducted using 3 equiv of NaH and 2 equiv of NaI.

We next turned our attention to the reduction of aliphatic amides (Scheme 8). Amides having an α-quaternary carbon are suitable substrates for the reduction (Scheme 8A), including the ones derived from drug molecule, gemfibrozil (for **6d**) and natural product, abietic acid (for **6e**). We also found that the reduction of α-tertiary amides having one enolizable proton gave the corresponding aldehydes in good yields, emphasizing the mild reaction conditions and functional group tolerance of the NaH-NaI system (Scheme 8B). The method is compatible with aldehydes based on aliphatic heterocycles such as tetrahydropyran **6i**, piperidine **6j** which is used for production of donepezil hydrochloride, an *anti*-Alzheimer drug[33], and pyrrolidine **6k**. We also note that our reaction conditions were optimal for the reduction of α-secondary amide **5l**.



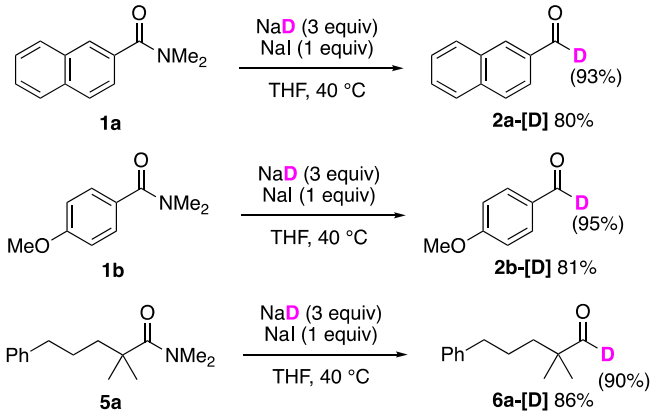
Scheme 8. Reduction of aliphatic amides. [a] Unless otherwise stated, the reactions were conducted using 0.5 mmol of amides **5** with 3 equiv of NaH and 1 equiv of NaI at 40 °C in THF (0.2 M) and isolated yields of aldehydes **6** were noted above. [b] The reaction was conducted using 1 g (4.1 mmol) of **5j** at 60 °C. [c] The reaction was conducted using 5 equiv of NaH and 2 equiv. [d] The reaction was quenched by pouring the reaction mixture into pH7 phosphate buffer solution (see the Supporting Information for details).

It is particularly worthy to note that the current protocol is amenable to reduce α-enantioriched amides **5f** and **5k** in good yields and selectivity to afford the corresponding aldehydes in high ee (**6k** was further converted into alcohol **7k** for the purpose to measure the ee by the Mosher method) (Scheme 9).



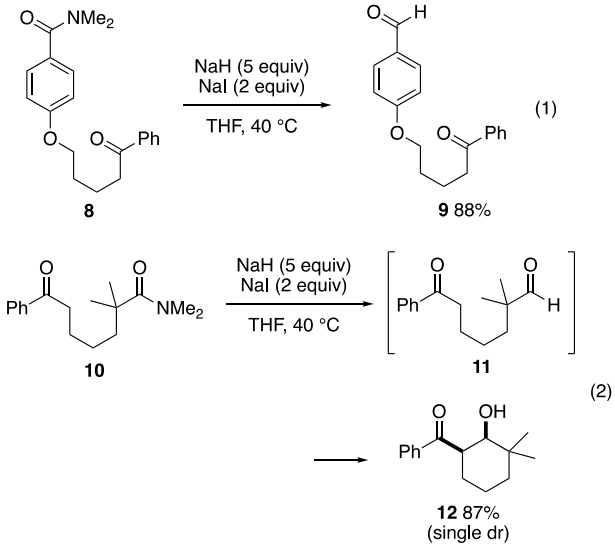
Scheme 9. Reduction of α-enantioriched amides. [a] The reactions were quenched by pouring the reaction mixture into pH7 phosphate buffer solution to prevent undesired epimerization (see the Supporting Information for details).

The reduction of aromatic amides **1a** and **1b** by NaD[2] resulted in formation of the corresponding deuterated aromatic aldehydes **2a-[D]** and **2b-[D]** with high deuterium incorporation rate of 93 % and 95%, respectively (Scheme 10). Similarly the reduction of aliphatic amide **5a** afforded 90% deuterium incorporation in **6a-[D]**. These results unambiguously support that sodium hydride is acting as a hydride donor. Moreover, this protocol provides a direct and concise method to supply deuterated aldehydes with high deuterium incorporation rate, given the fact that existing methods involve use of expensive reagents and/or require multistep routes for their preparation (Scheme 10)[34-39].



Scheme 10. Deuterium labeling experiments.

We found that the NaH-NaI composite shows unprecedented chemoselectivity for reduction of amide over ketone[3]. The reaction of benzamide **8** having a tethered keto group with the NaH-NaI composite proceeded smoothly to give benzaldehyde **9** in 88% yield keeping the keto moiety intact (Scheme 11-1). The reduction of keto amide **10** exclusively afforded keto aldehyde **11**, which spontaneously cyclized to 2-hydroxycyclohexyl phenyl ketone **12**.



Scheme 11. Chemoselective reduction of amides.

Conclusions

We have developed a new and concise protocol for selective reduction of N,N-dimethyl amides into aldehydes using the NaH-NaI composite under mild reaction conditions. The protocol is capable of reducing variety of amides ranging from aromatic and heteroaromatic amides to α-enantioriched aliphatic amides with retention of enantiomeric excess. Use of sodium deuteride (NaD) offers a new step-economical alternative to prepare deuterated aldehydes with high deuterium incorporation rate. The method exhibits unique chemoselectivity for reduction of amides over other carbonyl functions such as ketones. Further investigation of the reactivity of NaH-iodide composites to develop other types of hydride reduction processes is ongoing in our laboratory.

Supplementary Material

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/MS-number.

Acknowledgements

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[2] Sodium deuteride (NaD) was prepared by following the reported procedure (treatment of Na dispersion in mineral oil with D_2 gas (1 atm) at 270 °C). The prepared NaD contained metallic Na (ca. 3 %), which was characterized by solid state NMR (^{23}Na and ^{2}H) spectroscopy as well as powder X-ray diffraction. For details, see the Supporting Information.

[3] The chemoselective reduction of amides over esters was enabled only when t-Bu ester was used as the ester moiety. Methyl and isopropyl esters were partially converted into carboxylates probably due to the presence of NaOH in NaH, that somehow hampered reduction of amides. For details, see the Supporting Information.

Author Contribution Statement

G.H.C., D.Y.O., and *S.C.* designed the studies. *G.H.C., D.Y.O.,* and Z.Y. performed the experiments. *G.H.C.* and *S.C.* wrote the manuscript.

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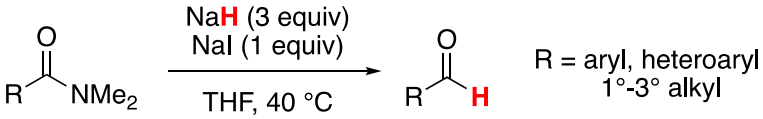

- concise synthetic protocol
- retention of α-chirality
- concise and efficient deuterium incorporation using NaD
- chemoselective reduction of amides over ketones