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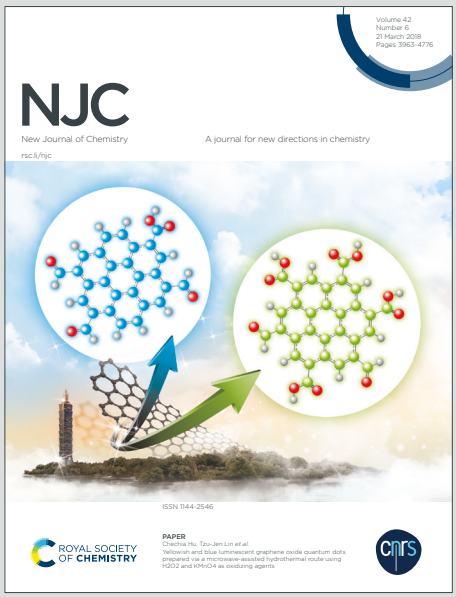

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COMMUNICATION

Chemoselective Reduction of Aldehyde via a Combination of $NaBH_4$ and Acetylacetone

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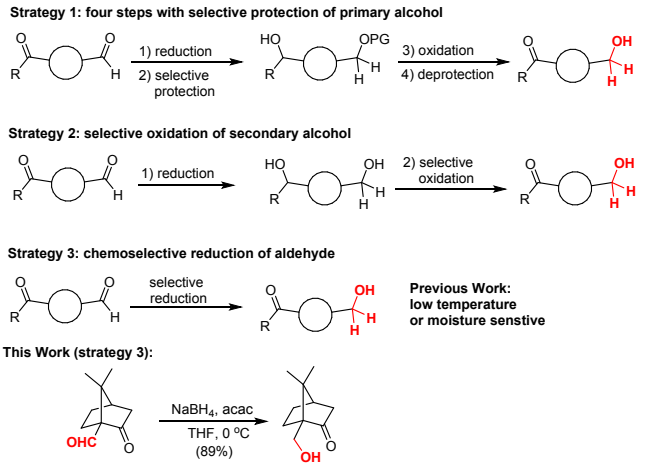
A bench-stable combination of $NaBH_4$-Acetylacetone was developed for the efficient chemoselective reduction of aldehydes in the presence of ketones. This method offers a useful synthetic protocol for distinguishing carbonyl reaction sites, and its synthetic utility is reflected by its moisture tolerance and high efficiency in a variety of complex settings.

Functional group transformation is important for the strategic execution in organic synthesis, and chemoselective functional transformation can facilitate to synthesis the desired product with minimal of redox manupulation.[1] Carbonyl group, as one of the most ubiquitous and important functional groups in the repertoire of organic chemistry, many of its various transformations have become trivial reaction in organic synthesis. Among the transformations, the reduction of carbonyl groups to alcohols is one of the most basic chemical transformations, and its significance is reflected in the many reagents that have been developed for this purpose,[2] such as $LiAlH_4$, $NaBH_4$, and DIBAL-H. Limitations in chemoselectivity[3] still exist, however, and in complex settings, such as the selective reduction of aldehydes in the presence of ketones and other functional groups can present a difficult challenge in many scenarios.

In this regard, several strategies have been developed to address this problem. For instance, global reduction of both aldehyde and ketone motifs followed by selective protection and oxidation of the so-formed diol. While this strategy can synthesis the desired product 'steadily', it will need four steps. The second strategy need selective oxidation of the secondary alcohol, which is not a trivial transformation considering the chemoselective.[4] Alternatively, a straight forward way to directly chemoselective reduce[5] the aldehyde would make the synthesis more efficiency. Several methods have been reported based on the tunable reactivity of borohydrides. For example, Ward has excellently shown[6] that aldehydes can be selectively reduced using CH_2Cl_2 and EtOH as co-solvents at −78°C, the excess $NaBH_4$ was quenched with distilled acetaldehyde. Toshima has also disclosed the combination of $NaBH_4$ with hexafluoroisopropanol to obtain the $NaBH(HFIP)_3$. While the method has been successfully applied in total syntheses,[7] this reagent is reported to be moisture sensitive when handling in the solid state. Several methods based on metal-catalyzed hydrogen transfer have also reported,[8] which show further potential application. In this regard, an aldehyde reduction method possessing both chemoselectivity and mild operability is still needed, and the formed primary alcohol can be further modified in natural product synthesis and biorthogonal chemistry. During a total synthesis project, we settled this chemoselective reduction challenge, taking inspiration from an earlier total synthesis project.[9]



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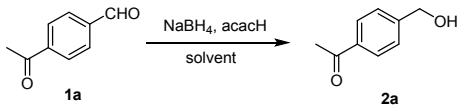
Scheme 1 Strategies for chemoselective reduction of aldehyde

Table 1. Optimization of Reaction Conditions[a]



1a 2a

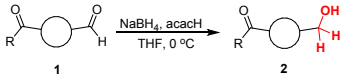
Entry	Solvent	Reaction time	Yield (%)
1	CH_2Cl_2	12 h	67
2	EtOAc	16 h	37
3	Toluene	24 h	70
4	1,4-dioxane	40 min	77
5	CH_3CN	10 min	93
6	$CHCl_3$	22 h	78
7	THF	5 min	85
8	THF[b]	5 min	81
9	**THF (0 °C)**	**12 min**	**95**
10	THF/acetone (10:1)	12 min	80
11	THF[c]	24 h	43

[a]Reaction conditions: **1a** (1.0 mmol), $NaBH_4$ (1.25 mmol), acetylacetone (1.0 mmol) in dry solvent at r.t [b]Commercial available THF was used. [c]$NaBH(OAc)_3$ (2 mmol) was used instead of $NaBH_4$ and acetylacetone.

Sodium borohydride ($NaBH_4$) which was first synthesized by Schlesinger and H. C. Brown,[10] have become the most common used reagent for carbonyl reduction, however the used condition ($NaBH_4$ in MeOH or EtOH) can not differentiate between aldehyde and ketone. So several modifications to decrease the reactivity of $NaBH_4$ were reported. For example, sodium triacetoxyborohydride ($NaBH(OAc)_3$),[11] with the B-H bond being stabilized by the steric and electron-withdrawing effects of the acetoxy groups, acts as a mild and widely used reducing reagent. This strategy has been applied to prepare both $NaBH(OAc)_3$ and $NaBH(OCH(CF_3)_2)_3$, but their reactivities are deactivated significantly, thus both reagents require higher temperatures and/or long reaction times to reduce aldehydes. Herein, we report an efficient chemoselective aldehyde reduction approach enabled by a novel bench-stable combination with a mixture of $NaBH_4$ and a bidentate ligand acetylacetone.

Initially, the preparation of the combination was simply accessed by mixing $NaBH_4$ (1.25 equiv) and acetylacetone (1.0 equiv) in THF at 0 °C. After stirring for 2 hs, the reaction solvent was evaporated to obtain a white powder which is stable in open air. [12] Then we start to test the reactivity of this combination with 4-acetylbenzaldehyde (**1a**) as the substrate. As shown in Table **1**, solvent effect seemed to be rather significant in this process. Dichloromethane and EtOAc only gave moderate yields with long reaction time (entry 1 and 2). Toluene provided a better yield while a further decreased reaction efficiency (entry 3). 1,4-dioxane, by contrast, proved to be a much more efficient solvent, dramatically reducing the reaction time to 40 mins (entry 4). To pursue a more efficient protocol, the screening of other solvents that might facilitate this transformation was further conducted. Among the tested solvents, acetonitrile (CH_3CN) and THF outweighed others in terms of yield and reaction time (entry 5 and 7). Lowering the reaction temperature to 0°C further increased the yield to 95% (entry 9). It should be noted that wet THF or even a THF/acetone mixture as the solvent allowed smooth reduction, showcasing the mildness of the condition. $NaBH(OAc)_3$ was also test for the selective reduction, the product **2a** only isolated in 43% yield after 24 h (entry 11).

Table 2. Superior Reduction Selectivity of Aldehyde to Ketone Motif[a]



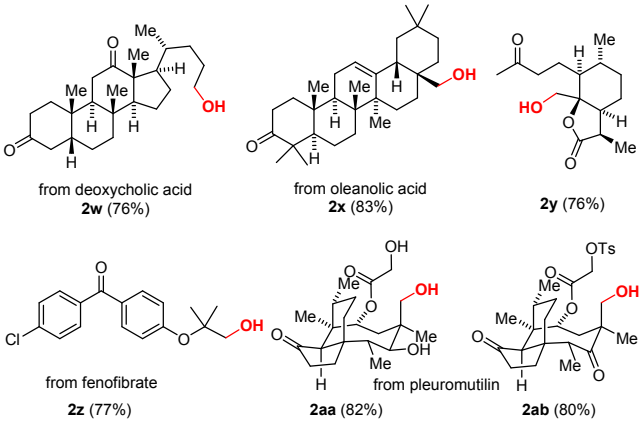
1 2

Entry	1	2	Time (min)	Yield (%)
1	**1b** R = Et	**2b** R = Et	12	76
2	**1c** R = *n*-Bu	**2c** R = *n*-Bu	15	92
3	**1d** R = Ph	**2d** R = Ph	3	86
4	**1e**	**2e**	25	94
5	**1f**	**2f**	20	85
6	**1g**	**2g**	10	65
7	**1h**	**2h**	15	73
8	**1i** R = Me	**2i** R = Me	15	87 (83)[b]
9	**1j** R = Et	**2j** R = Et	20	80
10	**1k** R = *n*-Bu	**2k** R = *n*-Bu	30	81
11	**1l** R = Ph	**2l** R = Ph	20	83
12	**1m** R = Me	**2m** R = Me	20	67
13	**1n** R = Et	**2n** R = Et	15	75
14	**1o** R = *n*-Bu	**2o** R = *n*-Bu	70	74
15	**1p** R = Ph	**2p** R = Ph	80	95
16	**1q**	**2q**	8	81 (32)[c]
17	**1r**	**2r**	10	84 (32)[c]
18	**1s**	**2s**	25	97 (19)[c]
19	**1t**	**2t**	25	83 (39)[c]
20	**1u**	**2u**	13	91 (0)[c]
21	**1v**	**2v**	5	89

[a]Reaction conditions: **1a to 1v** (1.0 mmol), $NaBH_4$ (1.25 mmol), acetylacetone (1.0 mmol) in dry THF at 0 °C. [b]1.0 g scale. [c]Reaction conditions: **1q to 1u** (1.0 mmol), $NaBH_4$ (1.0 mmol) in MeOH at 0 °C.

With the optimized conditions established, efforts began to evaluate the substrate scope. Several aromatic aldehydes (**1b** to **1g**) were prepared form 4-(hydroxymethyl)benzaldehyde through Grignard addition and global oxidation while aliphatic aldehyde substrates (**1i** to **1p**) were synthesized rapidly in three steps from the corresponding 10-undecenoid acid and ethyl chrysanthemumate (cis/trans mixture) through Weinreb amide formation, Grignard addition followed by ozonolysis (For details, see Supporting Information). Then these substrates were submitted to the above reaction conditions. As compiled in Table **2**, the superior selectivity toward the aldehyde motif to the ketone group was shown in cases of aromatic as well as aliphatic ones. In each case, the desired selective aldehyde reduction products were isolated in satisfactory yields ranging from 67% to 97%. Notably, substrates with labile functional groups such as aldimine (**1s**), succinimide derivatives 1**t** and **1u** (for the preparation of these substrates, see Supporting Information), also underwent the anticipated reduction (entry 18-20). The disulfide aldehyde substrate **1q** can be reduced efficiently in 81% yield while $NaBH_4$/MeOH will reduce the "fragile"disulfide bond. Meanwhile, selective reduction in the presence of tetrazole **1r** also worked well (84% yield) while in $NaBH_4$/MeOH condition, only 1-phenyl-1,2,3,4-tetrazole resulting from C-S bond cleavage was isolated.[13] Furthermore, this approach was conducted on a 1.0 g gram scale, furnishing the desired product **2i** in 83% yield (87% yield when in 1 mmol). During the study, we also found that under reaction condition, the monosubstituted conjugated ketone **1g** underwent both selective reduction and 1,4-reduction.[14] Substrates (**1h**, **1v**) from chiral terpene (limonene and camphor) also works well under the reduction condition (entry 7 and 21).

Table 3 Selective reduction of complex molecules



[a]Reaction conditions: **1w to 1ab** (1.0 mmol), $NaBH_4$ (1.25 mmol), acetylacetone (1.0 mmol) in dry THF at 0 °C.

The synthetic utility of this protocol further illustrated through complex molecule applications. As shown in Table **3**, several substrates derived from natural products and clinical medicines were submitted to the above optimized reaction conditions. For example, **1x** and **1y** served as excellent examples as the structure possess sterically hindered aldehydes groups, and the formed alcohol was isolated in good yield. In the case of **1w**, aldehyde was selective reduced in the presence of two ketone groups. Substrates (**1z**, **1aa** and **1ab**) from fenofibrate (a drug used for primary hypercholesterolemia or mixed dyslipidemia) and pleuromutilin (a tricyclic diterpene fungal metabolite as starting material for further antibiotic development) also yielded the corresponding primary alcohols in good yield. In this regard, this representative structural elaboration demonstrated that the developed sequence may provide facile access to a focused library of an array of structural analogues.

Conclusions

In summary, a convenient, highly efficient, and chemoselective reduction of aldehyde carbonyl moiety to primary alcohols enabled by a bench-stable solid through combination of $NaBH_4$ and acetylacetone is reported. The diversity of substrates, the high degree of compatibility with common organic functional groups, as well as the operability and stability of the reducing reagent raised the prospect of its applications in the pharmaceutical industry, general organic synthesis and natural product modification. Application in natural product total synthesis is actively pursued and will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgement

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