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Research article

Aldehydes as reducing agents: Reductive alkylation of ketones

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ABSTRACT

Aldehydes are key building blocks in organic synthesis due to their high availability and diverse reactivity. However, their intrinsic reducing ability remains underutilized. Herein, we illustrate a possibility to use aldehydes as dual-purpose reagents in redox transformations: as alkylating agents and reductants. This concept is supported by a ruthenium-catalyzed reductive alkylation of ketones and other nucleophiles using aldehydes. This operationally simple protocol proceeds under neat conditions without any external reductants providing a convenient, selective and eco-friendly C—C and C—N bond formation protocol. The utility of the protocol was illustrated by the synthesis of pharmaceutically relevant scaffolds, including Nabumetone and a derivative of pregnenolone acetate. Mechanistic experiments along with DFT-calculations were conducted to investigate mechanism of this transformation.

1. Introduction

Due to the diverse reactivity profile, aldehydes are among the most useful synthetic equivalents in organic chemistry giving the way to a large number of bond-forming strategies [1–4]. Despite the high reactivity, many aldehydes are industrial multiton compounds. For instance, 6 million tons of butyraldehyde is manufactured per year [5]. Other aldehydes like acetaldehyde [6], citronellal [7], furfural [8], cinnamaldehyde [9], vanillin [10], and glucose are also available in multiton amounts and are applied in a variety of fields including food industry and manufacture of flavouring agents and plastics, dyes, and pharmaceuticals [11–15] (Scheme 1).

There are two principal modes of aldehyde reactivity (Scheme 2): being an electrophile in different addition reactions or being a substrate for oxidation. Electrophilic behavior [16] is widely applied starting from classical reactions, such as aldol condensation [17], Wittig olefination [18], Knoevenagel [19], Henry [20], Corey-Chaykovsky [21], reduction reactions [22–24] *etc.*, ending with state-of-the-art aldehyde transformations [25–28]. Such a diverse reactivity is based on high electrophilicity parameters *E* of aromatic (−19.5) and aliphatic (−18.7) [29] aldehydes.

Oxidative transformations of aldehydes are likewise common. For example, selective oxidation of aldehydes [30–32] is a crucial industrial reaction, often employed in the synthesis of carboxylic acids and related derivatives. However, despite the prospectively reducing ability of the aldehyde group, it is rarely used as reducing agent in chemical reaction. Only some examples are known, like well-established reduction silver (+1) [33] and copper (+2) cations leading to formation of silver metal and copper (+1) oxide. Finally, use of aldehydes as reducing agents (not as substrates, but as reagents) in organic transformations is underestimated and understudied [34,35].

Herein we demonstrate the possibility to combine two types of aldehyde reactivity in one reaction leading to the external reductant-free reductive addition of different nucleophiles to carbonyl compounds (Scheme 2).

The reductive addition reactions represent a highly important class of transformations, widely used in synthetic chemistry [3,36,37]. However, the classical approach relies on an external source of hydrogen atoms such as molecular hydrogen [38–42], hydrides [43–45], alcohols [46–48] and some more exotic examples [49–53] (Scheme 3).

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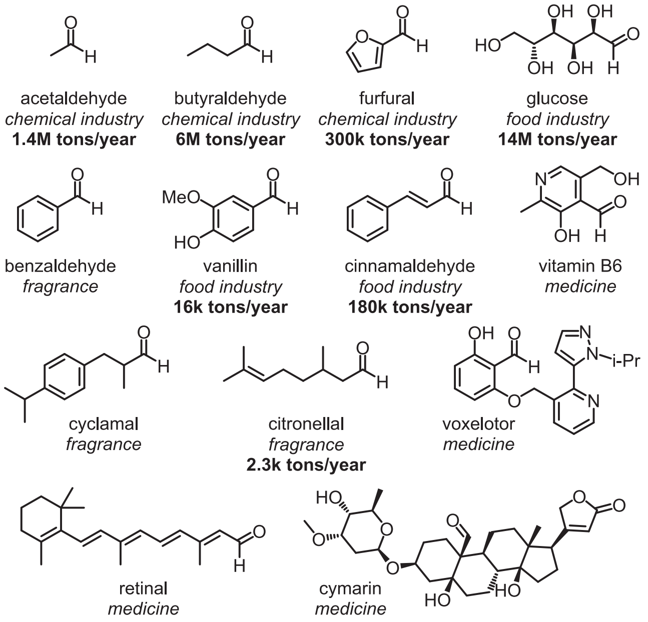
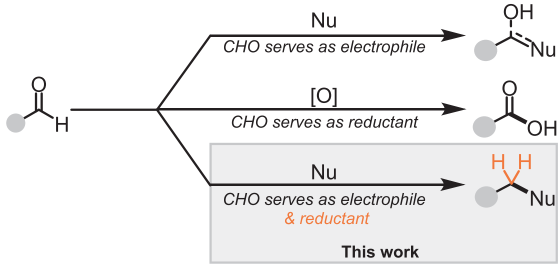
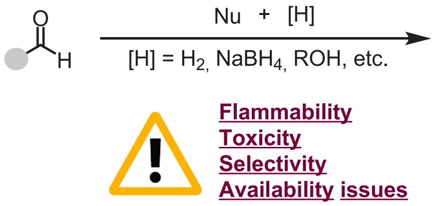


Scheme 1. Examples of important aldehydes in industry and medicine.



Scheme 2. Modes of aldehyde reactivity.



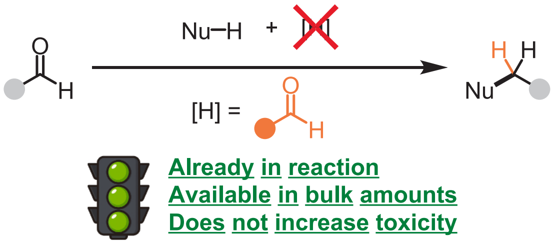
Scheme 3. Classical approach to the reductive addition: external reductant.

While each of external reducing system has benefits, they introduce practical disadvantages. Table 1 summarizes advantages and disadvantages of existing classical and state-of-the-art reducing agents [54]. Hydrogen (H_2/Pd) is a universal reducing agent for all kinds of chemistry, it often delivers high rates. However, its intrinsic problem (without catalyst tuning – just using a simple Pd/C catalyst) is over-reduction and competitive hydrogenolysis of the C—Nu bond [55]. Stoichiometric borohydrides such as $NaBH_4$ are broadly available and easy to handle. Yet they are typically nonselective (e.g. they could reduce aldehyde to alcohol) and generate inorganic by-products that complicate quench and extraction, increasing waste and unit operations. CO-based systems (e. g., CO/[Ru] [49,51,56,57]) enhance chemoselectivity and make workup easier. Nevertheless, carbon monoxide introduces acute toxicity and requires gas-handling hardware, which limits generality outside specialized settings. Alcohol donors (ROH) likewise tend to improve selectivity and operational simplicity, however, from a supply-chain perspective, they are frequently less accessible than the corresponding aldehydes. In many synthetic routes the alcohol is prepared from the aldehyde, so choosing the alcohol as a reductant can be logically and logistically circular when the aldehyde precursor is already available.

Table 1
Comparison of classical reducing systems.

[H]	H_2/Pd	$NaBH_4$	CO/[Ru]	ROH	RCHO
Selectivity	✗	✗	✓	✓	✓
Workup	✓	✗	✓	✓	✓
Flammability	🔥	✓	🔥	🔥	✓
Toxicity	✓	✗	✗	✓	✓
Availability	✗	✓	✗	±[a]	✓

[a] Accordingly to Sigma-Aldrich (sigmaaldrich.com) product catalog (accessed October 2025), approximately 812 benzaldehydes and 387 primary benzylic alcohols are listed as commercially available compounds [58].



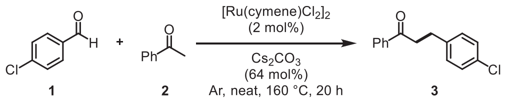
Scheme 4. This work. No external reductant is applied – Dual role of aldehyde as electrophile and reductant.

In contrast, aldehydes are indispensable and inherently present in such transformations as key reactants, meaning that their dual function as both alkylating agents and reductants introduces no additional hazard, logistical barrier, or cost. This feature is especially valuable when other reductants – particularly exotic, expensive, or sensitive ones – may be inaccessible to researchers or impractical for routine use. We hypothesized that aldehydes could play a dual role in alkylation reaction of ketones with aldehydes. Herein, we disclose the way for alkylating nucleophiles with aldehydes as electrophiles and reductants at the same time (Scheme 4). This concept was illustrated by the reductive addition of five different nucleophiles.

2. Results and discussion

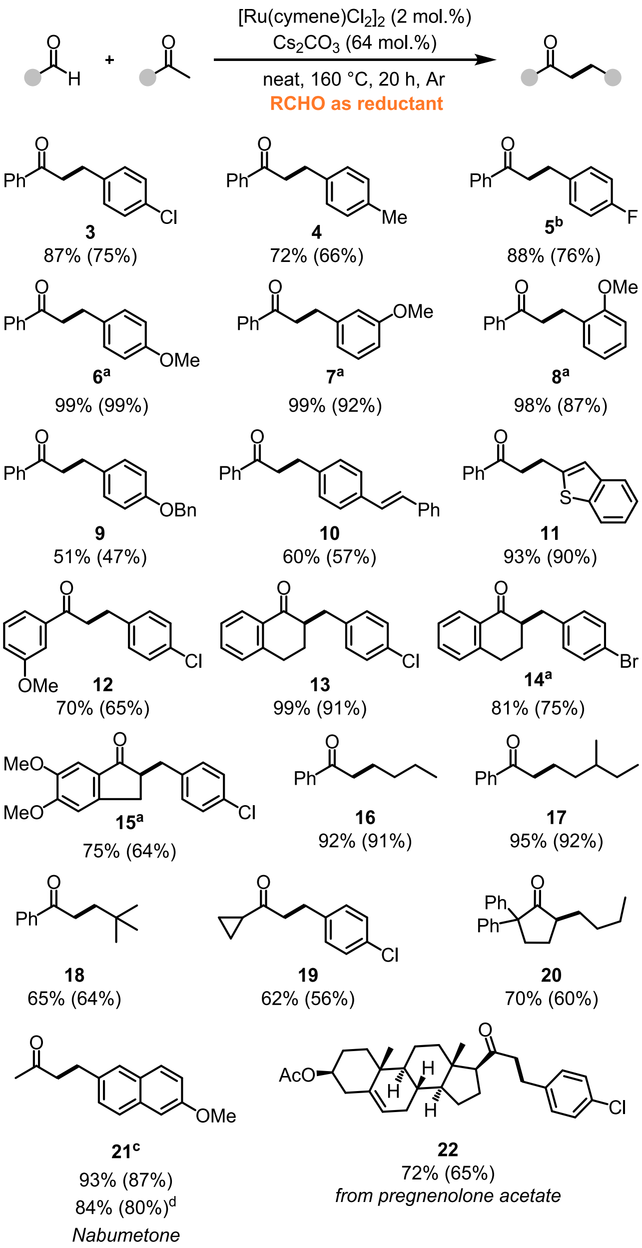
Our investigation started from conditions optimization for the reductive alkylation of ketones by aldehyde – important C—C bond

Table 2
Selected optimization results.



Entry[a]	Deviation from standard conditions	Yield of **3**[b], %
1	**None**	**87 (75)**[c]
2	1 equiv. of **1**	17
3	5 % of catalyst	75
4	1 % of catalyst	61
5	1 h [d]	56
6	K_2CO_3, 1 h [d]	33
7	NaOAc, DIPEA, DABCO or CsF, 1 h [d]	0

[a] 0.16 mmol scale, **1** (3 equiv.), **2** (1 equiv.). [b]Yields were determined by GC with external standard. [c]Isolated yield is given in parentheses. [d]8 mol% [Ru(cymene)Cl_2]$_2$, 48 mol% of base, 1 h. Full optimization data is provided in ESI.



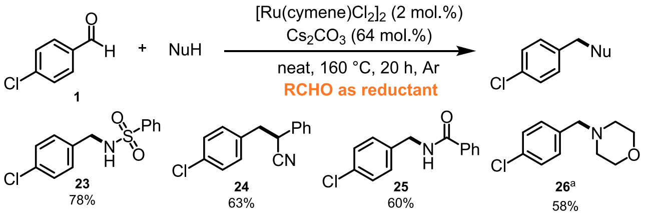
Scheme 5. Scope of alkylation of ketones using aldehydes as reductants. 0.4 mmol scale, aldehyde (3 equiv.), ketone (1 equiv.). yields were determined by NMR with internal standard; isolated yields given in parentheses. [a]48 h. [b]4 mol.% of [Ru(cymene)Cl_2]$_2$. [c]60 equiv. of acetone. [d]5 mmol scale.

forming strategy, useful in the pharmaceutical chemistry [36,49,51] in the benchmark reaction between 4-chlorobenzaldehyde and acetophenone (Table 2). Full optimization details are provided in ESI. Optimal conditions imply the simple [Ru(cymene)Cl_2]$_2$ [59] catalyst without any ligands, along with Cs_2CO_3 as a base under solvent-free conditions. Reducing aldehyde amount from 3 to 1 equivalent (Entry 2) significantly decreased the yield to 17 %, emphasizing the dual role of aldehyde – as electrophile and reductant. Increasing the catalyst amount to 5 mol% (Entry 3) unexpectedly lowered the yield to 75 %. Conversely, decreasing the catalyst concentration to 1 mol% (Entry 4) led to insufficient catalytic activity, reducing the yield significantly to 61 %.

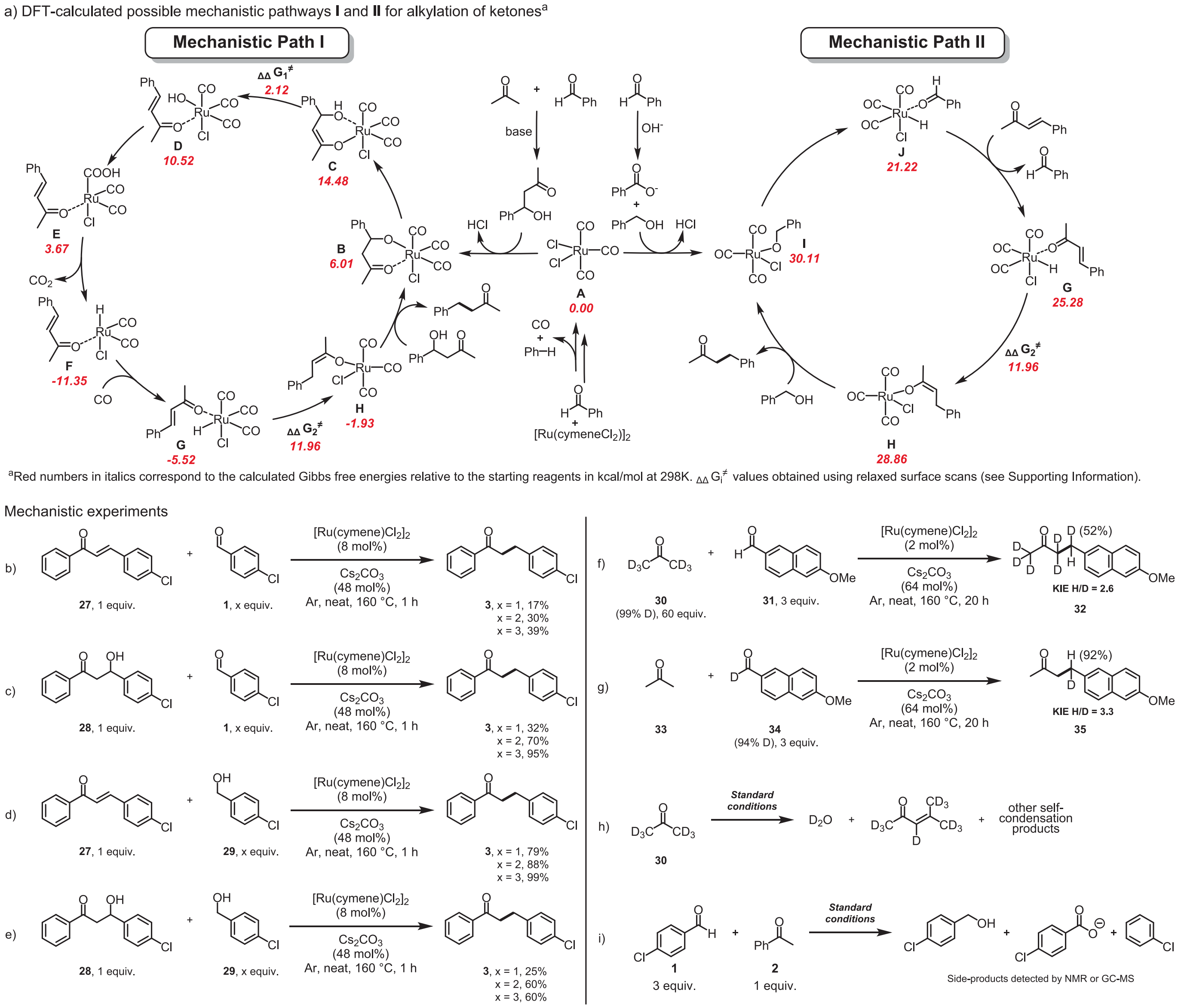
The base choice significantly influenced the reaction outcome. Replacing Cs_2CO_3 with K_2CO_3 under similar conditions (Entry 5 vs 6) reduced the yield to 42 %, reflecting the unique solubility and coordinating characteristics of base critical to the reaction outcome. Other bases tested (Entry 7), including NaOAc, DIPEA, DABCO, and CsF, failed to yield the desired product, due to their insufficient basicity and weaker coordination ability. The reaction was performed in various solvents (see ESI); however, the method remains effective even under neat conditions, which makes it attractive from the perspective of process E-factors (~3 for synthesis of compound **3**).

With the optimized conditions in hand, we switched to the substrate scope investigations (Scheme 5). Reductive alkylation reaction of ketones using aldehydes as alkylating agent and reductant was conducted with different combinations of ketones and aldehydes – reaction proceeded with primary aromatic ketones (**3**–**12**), secondary aromatic ketones and aromatic aldehydes (**13**–**15**); aromatic ketones and aliphatic aldehydes (**16**–**18**); secondary aliphatic ketone and aliphatic aldehyde (**20**); primary aliphatic ketones and aromatic aldehydes (**19, 21, 22**).

We found that relatively electron-rich aldehydes are less active than electron-neutral or electron-deficient aldehydes in this process, for example **9** vs. **5**, however this issue could be solved using prolonged reaction as it was shown in examples **6**–**8**. Electron-deficient benzo[b]thiophene-2-carboxaldehyde yielded product **11** in a better yield, which



Scheme 6. Usage of other N- and C-nucleophiles. 0.4 mmol scale, 1 equiv. of nucleophile, 3 equiv. of **1**, 2 mol.% of $[Ru(cymene)Cl_2]_2$, 64 mol% of Cs_2CO_3, 160 °C, Ar atmosphere, neat, 20 h; isolated yields. [a] 5 mol.% of $[Ru(cymene)Cl_2]_2$, 16 mol% of Cs_2CO_3.



[a] Red numbers in italics correspond to the calculated Gibbs free energies relative to the starting reagents in kcal/mol at 298K. $\Delta\Delta G_i^{\neq}$ values obtained using relaxed surface scans (see Supporting Information).

Scheme 7. Mechanistic considerations.

additionally confirms the positive impact of electron-withdrawing group in aldehydes.

Noteworthy, despite aliphatic aldehydes (*i.e.* butyraldehyde) being prone to conduct self-condensation reaction under basic thermal conditions [60], they could be used as reductants and alkylating agents (**16**–**18**, **20**). Moderate drop of yield in case of pivaldehyde (**18**) is related to steric hindrance of *tert*-butyl group. The power of this approach was illustrated by preparation of anti-inflammatory drug Nabumetone **21,** noteworthy, its synthesis was scaled up for gram-scale. Moreover, derivatization of natural pregnenolone acetate giving product **22** is available. Overall, the developed protocol showed functional group tolerance to relatively labile OBn (**9**), C=C (**10, 22**), C-Br (**14**), C-Cl (**3, 12, 13, 19, 22**), OAc (**22**), and cyclopropyl (**19**). Moreover, the process was not inhibited by sulfur-containing (**11**) groups [61].

To further develop the suggested idea of using aldehydes as a reducing agent we have expanded the reaction scope by another four N-and C-nucleophiles. We have additionally demonstrated the possibility of aldehydes utilization in reductive amidation (**23**, **25**), reductive Knoevenagel addition (**24**) and reductive amination (**26**) (Scheme 6). In all these cases aldehydes serve in a dual role – reducing agent and electrophile. Further investigations of different nucleophiles alkylation are ongoing.

Several mechanistic investigations were carried out (Scheme 7). We assume that the real catalytically active species in this process is ruthenium chlorocarbonyl complex, modelled as $[Ru(CO)_3Cl_2]$ (**A**) for simplicity, which can form CO via its dissociation. However, other similar complexes may occur (like $[Ru(CO)_3Cl_3]^-$), which formation in the reaction mixture was observed by IR-spectroscopy (see ESI). Formation of such species and carbon monoxide could be explained by several times occurring Tsuji-Wilkinson decarbonylation reaction [62,63] of aldehydes with $[Ru(cymene)Cl_2]_2$. Overall, according to our observations [64–68], this catalytic system should be considered as 'cocktail-type' [69,70], *i.e.* containing a plenty of ruthenium species with different catalytic activity.

We propose two distinct mechanistic pathways operating concurrently, path **I** and path **II** (Scheme 7). Their feasibility was assessed by DFT calculations at the PBE/TZVP (QZVP on Ru atom) level of theory using solvent model density with acetone in Orca 6.0 software [71] (see ESI). Reaction of benzaldehyde with acetone was chosen as a model reaction to reduce computational cost. Path **I** is based on the previous work of our group [49]. Reaction of benzaldehyde with acetone provides formation of aldol which forms a complex **B**. Enolization of **B** to **C** allows elimination of the aldol OH group, forming a new double bond and furnishing the hydroxo-ruthenium specie **D** with a very low barrier ($_{\Delta\Delta}G_{1}^{\neq}$ = 2.1 kcal/mol). Next the migratory insertion of the hydroxyl group into the CO ligand leads to the carboxyl complex **E**. Rearrangement of **E** to hydride **G** occurs with release of CO_2. Further hydride-transfer and product release closes this catalytic cycle. The overall formation of complex **G** from complex **D** is the part of classical ruthenium catalyzed water–gas shift reaction and was recently well studied experimentally and theoretically [65,66,72].

Path **II** is based on disproportionation of aldehyde in the presence of base, which provides formation of carboxylate-anion and primary alcohol. Further coordination of alcohol to complex **A** gives complex **I,** which then undergoes β-hydride elimination [73] to give **J**. Ligand exchange from aldehyde to enone forms a complex **G**, where the key step of hydrogen transfer occurs with transition state $_{\Delta\Delta}G_{2}^{\neq}$ 11.96 kcal/mol, providing enolate complex **H**. Protonation of enolate with free alcohol forms product and encloses the catalytic cycle leading to formation of the initial complex **I**.

Mechanistic experiments supporting theoretical studies were carried out. It has been found that both enone and aldol could be reduced to the resulting product using both aldehyde and corresponding benzylic alcohol (Scheme 7b-e). Aldehyde reduced aldol intermediate faster than enone (Scheme 7b vs 7c). However, alcohol **29** was more efficient reductant for enone **27** and less efficient for aldol **28** (Scheme 7d vs 7e). These results are consistent with paths **I** and **II,** where reduction of aldol occurs with one equivalent of CO formed via decarbonylation reaction of aldehyde and reduction of enone proceeds with alcohol. Nevertheless, in all cases it is proved that these species could play role as intermediates in this transformation.

Additionally, D-labeling experiments were carried out (Scheme 7f, 7g). In both cases benzylic position is isotope enriched more than it should be. Observed kinetic isotope effect (KIE) in both D-labeling reactions is moderate (2.6 and 3.3 respectively) proving primary KIE and postulating that the key transition state is the formation of benzylic C–H bond (**G** → **H,** $_{\Delta\Delta}G_{2}^{\neq}$ 11.96 kcal/mol). An additional 52 % D-incorporation in case of reaction on Scheme 7f could be explained by large amount of acetone-D_6 in the reaction mixture which could provide formation of deuterated water *via* its condensation in basic conditions (Scheme 7h), which plays role in the protonation step of ruthenium enolate forming in both mechanisms **I** and **II**. This proves our hypothesis that two mechanisms operate at the same time.

Moreover, reaction mixtures contained decarbonylative products (Scheme 7i), for example, chlorobenzene**,** which formation supports mechanism **I** and products of aldehyde conversion – cesium carboxylates, alcohols and their transformations products (*i.e.,* esters), which supports mechanism **II**.

3. Conclusions

In summary, we developed a conceptually novel reductive alkylation methodology that employs readily available aldehydes in a dual role: alkylating and reducing agent. In contrast to conventional approaches, our ruthenium-catalyzed protocol operates under neat conditions and employs readily available aldehydes themselves as internal reductants. This simplifies the reaction conditions and enhances sustainability by eliminating hazardous or sensitive reducing agents.

The applicability of developed method is demonstrated by reductive alkylation of five different nucleophiles: ketones, amines, amides, sulfonamides and nitriles. In the case of ketones alkylation this methodology demonstrates broad applicability across diverse classes of ketones and aldehydes, including challenging aliphatic aldehydes and substrates bearing sensitive functional groups. Possible ways of the target process were proposed, supported by DFT-calculations and control experiments. Overall, this work challenges the traditional perception of aldehydes as merely electrophilic partners by positioning them as versatile and sustainable reducing agents. It opens new trajectories for aldehyde-based redox processes and expands the conceptual borders of reductive alkylation chemistry.

CRediT authorship contribution statement

Fedor S. Kliuev: Writing – original draft, Methodology, Investigation, Formal analysis. **Sofiya A. Runikhina:** Investigation. **Oleg I. Afanasyev:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Denis Chusov:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcat.2025.116495.

Data availability

The data supporting this article have been included as part of the Supplementary Information: optimization details, experimental procedures, calculation details and copies of NMR spectra. The authors have cited additional references within the supplementary material [49,64,67,68,74-102].

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