Redox surrogate methods for sustainable amine N-alkylation

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Redox Surrogate Methods for Sustainable Amine *N*-Alkylation

Rebecca E. Ruscoe[1], Jeremy I. Ramsden[1] and Nicholas J. Turner[1]

Abstract

The *N*-alkylation of amines constitutes one of the most widely applied transformations in synthetic chemistry, but established methods often utilise non-renewable feedstocks and must be adapted for a post fossil fuel world. This review is focused on emerging methodologies in which redox surrogate reagents to carbonyl compounds are used which may be more readily sourced from nature. The review considers both chemocatalytic and biocatalytic approaches and considers challenges such as application and the development of sustainable methodology with low carbon impact.

Addresses

[1] School of Chemistry, University of Manchester, Manchester Institute of Biotechnology, 131 Princess Street, Manchester M1 7DN, United Kingdom

Corresponding author:
N. J. Turner (nicholas.turner@manchester.ac.uk)

1.0 Introduction

The formation of highly valued structural motifs often dictates the trends of synthetic organic chemistry and dominates the research carried out in both academia and industry. *N*-alkylamines are extremely important building blocks, ubiquitous in alkaloids, amino acids and nucleotides.[1] It is therefore unsurprising that these moieties are ever-present in compounds of pharmaceutical interest (Figure 1a).[2–4] Their synthetic versatility has meant that research into the synthesis of these products has been extensive. However, in recent years scientists have become increasingly aware of a need to shift to a bio-based economy that makes use of more renewable feedstocks.[5] In response, recent research into the alkylation of amines has been focused on the development of more sustainable and efficient methodology.

Much of the recent focus from researchers has been on performing *N*-alkylation with redox surrogate reagents to non-renewable carbonyl compounds. This review seeks to compare chemocatalytic and biocatalytic methods of achieving this, with the benefits and limitations of each being discussed (Figure 1b).

2.0 Chemical *N*-alkylation of Amines

There are many well-established methods for amine *N*-alkylation; here we will only be introducing those that are used routinely, due to their generality. There are further methods that are not discussed in this review, such as nitrile reduction, hydroamination of alkenes/alkynes and the Chan-Lam cross coupling reaction.[6–8]

2.1 S_N2 Reactions

Classical *N*-alkylations of amines typically involve the use of alkyl halides (although other reagents have been used, such as diazo compounds[9] and triflates[8]) as the alkylating reagent under basic conditions (Figure 2a). Although these S_N2 transformations can be effective syntheses to many *N*-alkylated amines, they are deemed unsustainable due to their need for harsh reaction conditions, production of stoichiometric acidic waste and the genotoxic nature of alkyl halides.[10]

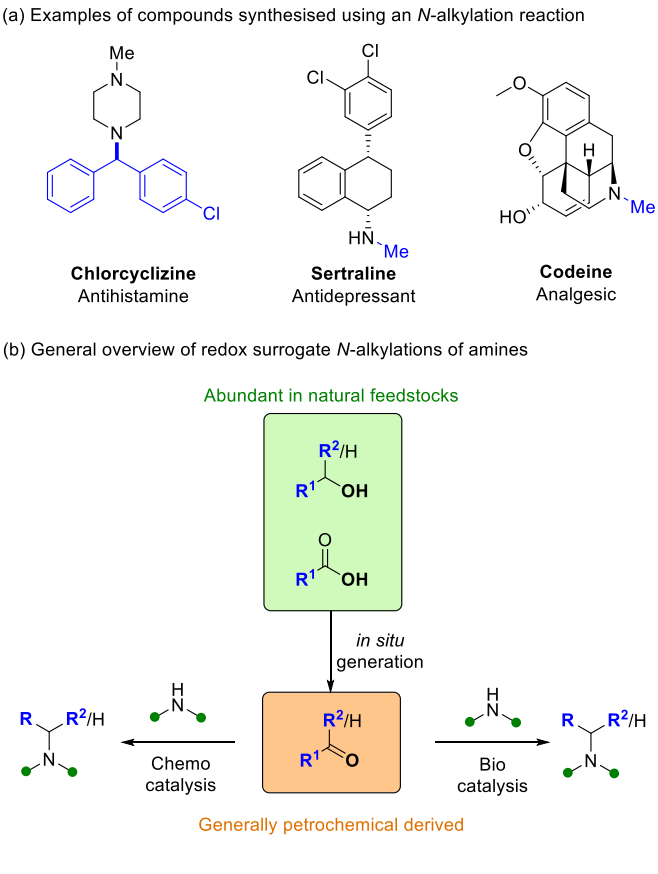

Figure 1 (a) Three examples of high valued compounds that require an *N*-alkylation in their synthesis, (b) Overview of chemical and biological approaches to *N*-alkylations.

This, along with common over-alkylation and often pre-functionalisation of alcohols to form the alkylating reagents, attests to the need for alternative methodologies. The use of milder and generally safer electrophilic reagents has been investigated, resulting in

the use of trialkyl orthoesters[11,12], dialkyl carbonates[13,14] and dimethyl sulfoxide[15].

2.2 Reductive Amination of Aldehydes and Ketones

The reductive amination of carbonyl compounds is a powerful alternative (Figure 2b) which is commonly used in the pharmaceutical sector,[16] with recent works quoting that this is the procedure chosen to form a quarter of all C-N bonds in the industry.[17] These reactions typically employ borohydride reagents as the reducing agent of choice, with the most common being bench stable solids: $NaBH_4$, $NaBH(OAc)_3$ and $NaBH_3CN$.[18] However, these bulky reagents have poor atom economy and can generate toxic side-products during work-up. Alternatives have been demonstrated with reducing agents such as zinc [19] and the use of formic acid (Leuckart-Wallach, Eschweiler Clarke reactions) [20,21] but often these reactions have a more limited scope.

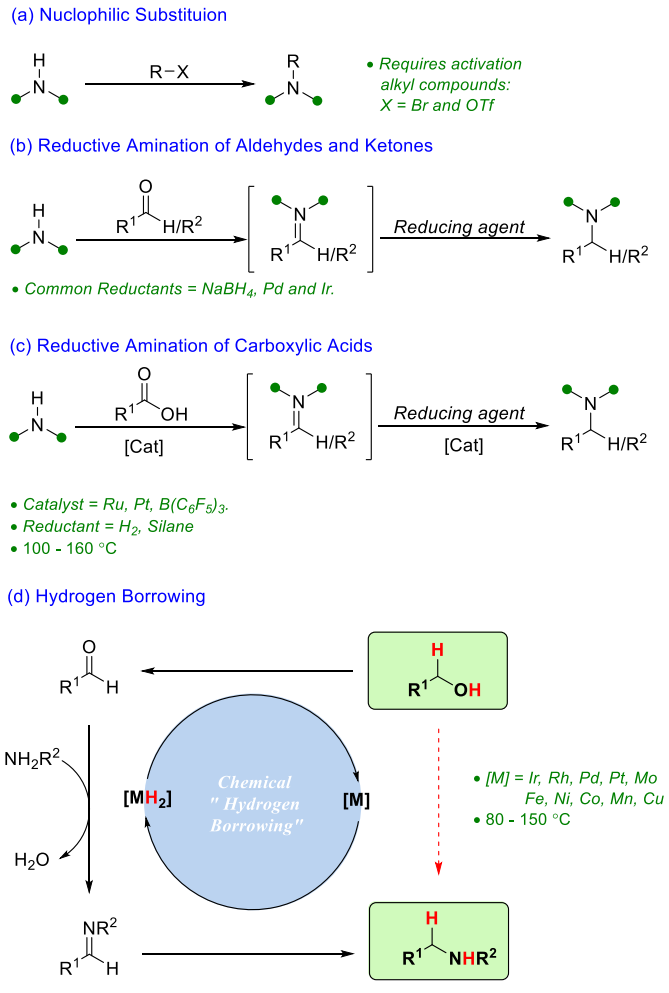

Figure 2 Methods for the *N*-alkylation of amines *via* (a) nucleophilic substitution (b) reductive amination (c) reductive amination of carboxylic acids and (d) hydrogen borrowing.

Catalytic reductive aminations can be achieved using hydrogen gas in the presence of a metal catalyst such as palladium, iridium and ruthenium.[18] Asymmetric catalytic methods have also been developed incorporating chiral ligands[22–24] and auxiliaries,[25][26] as well as metal catalysts geared towards sustainability,[27,28] the ability to recycle and recover the catalyst,[29–31] and even immobilisation of the catalyst within flow chemistry apparatus.[32] Additionally, methodologies utilising organocatalysts have been developed for the synthesis of chiral N-alkylated amines.[22,33–35]

Many carbonyl compounds however may require prior synthesis, particularly aldehyde reagents of which storage is complicated by a tendency to undergo aerobic oxidation. These issues, alongside a higher abundance of alcohol and carboxylic acid reagents in natural feedstocks have been the main driving force for the development of redox surrogate methodology.

2.3 Reductive Amination of Carboxylic Acids

More recently, there has been increased research into the catalysed reductive amination of higher oxidation alternatives (carbonic/carboxylic acids and CO_2) where the aldehyde may be generated *in situ*. Usually, these compounds are more stable, easily accessible and non-toxic.[36–38]

Following methods that utilised CO_2 for *N*-methylation,[39,40] initial reports of this strategy as a general platform for *N*-alkylation first came from the Beller group, who reported systems that used either platinum and silanes [41] or ruthenium and molecular hydrogen in combination.[42] This was followed by a metal-free version which achieved the transformation through boron based frustrated Lewis pair catalysis.[43,44] A method utilising iridium as the catalyst has also been reported [45] but still faces a requirement for harsh conditions. While the transformation has been demonstrated under benign conditions with rhodium catalysis,[46] the substrate scope is limited to arylamines. Although carboxylic acids are easily sourced from nature, their energetic stability is likely to continue to frustrate the development of methodology with high atom economy and green conditions.

2.4 Hydrogen Borrowing

N-alkylation reactions can also be performed *via* a hydrogen borrowing process. Hydrogen borrowing (HB), also referred to as 'hydrogen auto-transfer' is a process which involves an oxidation reaction, an intermediate transformation and is terminated by a reduction reaction (Figure 1c).[47] This redox-neutral cascade is an effective way of forming more complex molecules, whilst avoiding the use of molecular hydrogen or the preformation of reactive intermediates.

The HB *N*-alkylation of amines has been achieved using metals such as iridium, rhodium and palladium.[47] However, requiring the use of a metal catalyst is both financially and environmentally undesirable. Additives

such as ligands, acids or bases are generally necessary (more commonly with homogeneous catalysis), which impacts on the true atom economy of these procedures. This, combined with a general need for high temperatures and long reaction times, speaks to the necessary scope for improvement.

As we have become more environmentally aware, focus has shifted to more sustainable metal catalysts such as iron,[48] nickel,[49] cobalt,[50] manganese,[51] and copper.[52,53] Manganese and copper are relatively new catalysts to HB processes and show promise from examples shown in the literature that highlight a good substrate scope. Reaction conditions, however, remain harsh. As these catalysts are underdeveloped compared to the other metals utilised, further research could provide reactions able to tolerate milder reaction conditions. More recent examples have involved metal and oxidant free HB processes, which demonstrates further potential improvements for sustainability.[54] A HB mechanism has also been shown to operate using electrochemical conditions, which provides a solution to some of the drawbacks.[55] While successfully applied on kilogram scale by Pfizer, HB is yet to see widespread application on the process scale.[56,57]

3.0 Sustainable Biocatalytic *N*-alkylation of Amines

In the pursuit of lower carbon chemistry, biocatalysis possesses a distinct advantage due to the benign conditions at which the chemistry of life tends to operate. In combination with an intrinsic ability for enzymes to utilise feedstocks sourced from nature, biocatalysis possesses huge potential as a platform for fine synthesis in a post fossil fuel dependent world. As amine synthesis represents a field in which the biocatalytic toolbox is most developed, it follows that enzymatic methods for amine alkylation through cascade reactions are emerging as a model demonstration of this potential.

3.1 Biocatalytic Hydrogen Borrowing

In combination with enzymes capable of the amination of carbonyl compounds, redox enzymes capable of generating the preceding carbonyl *in situ* allow for the mimicking of chemical HB systems. The first enzyme cascade system to demonstrate this utilised three enzymes.[58] An alcohol dehydrogenase (ADH) capable of generating aldehydes from primary alcohols was combined with a transaminase, alongside an alanine dehydrogenase which was capable of simultaneously regenerating the alanine required as an amine donor for the transaminase step and the NAD^+ required for alcohol oxidation. The unique mechanism allowed the use of diol substrates yielding diamine products as opposed to the heterocyclic products generated by

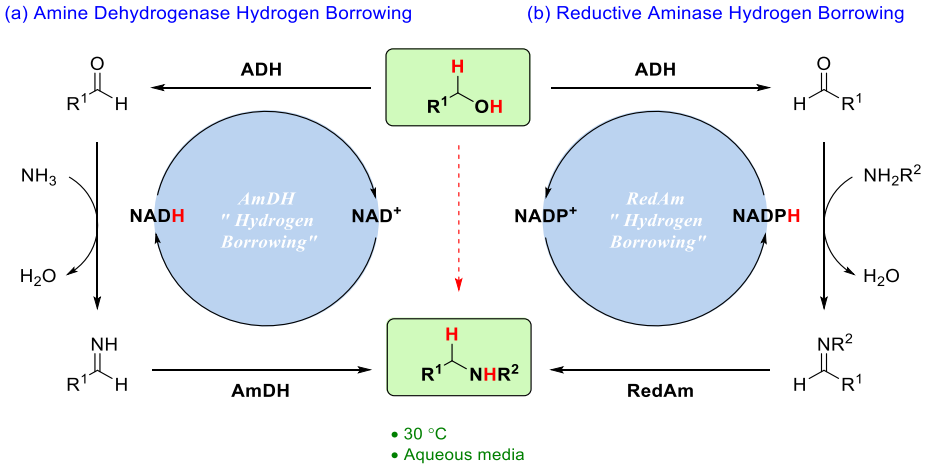

Figure 3 Biocatalytic hydrogen borrowing methods for the alkylation of (a) ammonia and (b) primary amines.

equivalent chemical systems.[59]

This was followed by a landmark paper in which the same transformation was achieved by the combination of an amine dehydrogenase (AmDH) with a co-factor complementary ADH.[60] This allows for the nicotinamide cofactor to take on the role of a hydride shuttle yielding the first true biocatalytic HB system (Figure 3a). Crucially, this work extended the substrate scope to secondary alcohols, allowing for their amination with consistently excellent enantioselectivity. However, the innate stereoselectivity of enzymes also proved a hindrance to these systems when a racemic mixture of alcohol substrates was used. This limitation was overcome through the use of a single non-enantioselective ADH.[61,62]

Whilst primary amination is a well-established biocatalytic transformation, biocatalysis has long been limited by a lack of options for performing reductive amination with more complex amines. Imine reductases (IREDs) had been envisaged as a potential solution, but initial difficulty in pre-forming an exocyclic imine in aqueous media remained a challenge.[63] This changed in 2017 when Turner and co-workers published a sub-class of IRED known as “reductive aminases”

(RedAms), capable of catalysing the prior formation of an imine in addition to reduction.[64] The same group followed this work with a hydrogen borrowing system that combined a RedAm with a range of non-selective single ADHs to affect the alkylation of primary amines with a range of both primary and secondary alcohols (Figure 3b).[65] This was further extended through the addition of a cytochrome p450 monooxygenase, yielding a HB system capable of employing unfunctionalised and non-activated cycloalkanes as alkylating agents.[66]

3.2 Irreversible Biocatalytic Aldehyde Generation

Although biocatalysis allows for HB chemistry to be performed under more benign conditions than transition metal equivalents, these systems remain limited by an inherent flaw. As biocatalytic HB systems are completely reversible, conversion is dictated by thermodynamics.[67] Therefore, to reach quantitative conversion a large excess of amine donor is required. This may lead to the chemistry becoming economically non-viable for process application, as was reported by GlaxoSmithKline who investigated the possibility of extending an asymmetric reductive amination step catalysed by an engineered RedAm to include prior biocatalytic alcohol oxidation.[68] In 2019, the Turner group reported a system to overcome this, in which "*Asp*RedAm" was applied in combination with an alcohol oxidase (AO) for the alkylation of amines with primary alcohols (Figure 4b).[69] Unlike ADHs, AOs perform the oxidation of alcohols irreversibly, utilising molecular oxygen as an oxidant. Directed evolution was used to generate a more general catalyst with a broader substrate scope.[70] While not a hydrogen borrowing system, requiring instead three enzymes, this methodology demonstrated the potential for the *N*-alkylation of amines using alcohols with low amine loading. The exemplary chemoselectivity of enzyme catalysts constitutes a potential large advantage over chemocatalytic systems and should be explored further, particularly with some members of the RedAm/IRED sub-class capable of performing the selective single alkylation of diamine substrates.[71]

This manuscript also reports a biocatalytic system for the reductive amination of carboxylic acids through the combination of *Asp*RedAm with a wild-type carboxylic acid reductase (CAR) (Figure 4a). While the CAR can perform the initial reduction selectively and irreversibly, the reaction requires ATP to turn over, necessitating the addition of further enzymes to recycle the resulting AMP. This results in a five-enzyme system, which may prove challenging in scaling, particularly as biocatalytic ATP recycling is yet to be

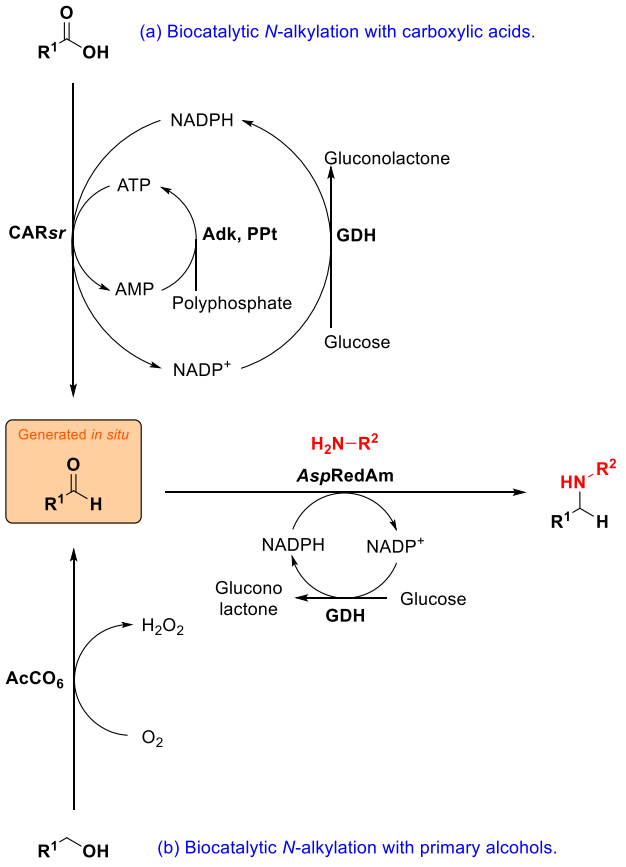

Figure 4 Irreversible redox surrogate biocatalytic *N*-alkylation methods using either (a) carboxylic acid reductases (CARs) or (b) alcohol oxidases (AOs).

reported on scale. Despite this, a complementary product scope is achieved again with low amine loading.

4. 0 Conclusions and Future Perspective

There are many methods for alkylating amines that have been developed over the years and these methods have generally moved towards more environmentally friendly protocols. The chemical methods discussed have their drawbacks, whether this is due to the reagents used, the harsh reaction conditions or the requirement for precious metals. There is potential for further advancement in this area that will allow chemists to produce these high value compounds with significantly reduced impact on the environment. This may be achieved by exploring more sustainable metals for hydrogen borrowing procedures, using carboxylic acids as aldehyde precursors or exploiting enzymes as catalyst alternatives.

While the past decade has seen rapid advancement in the development of biocatalytic systems for sustainable amine alkylation, a number of challenges remain to be overcome before the methodology reported finds common application in synthetic laboratories and on the process scale. For hydrogen borrowing systems, shifting the equilibrium continues to be the key limitation, and will require innovative solutions to remove the amine

product and drive the reaction. For alternative systems, the limitations of recycling enzymes must be addressed. The solution may be the use of enzymes as whole-cell biocatalysts, potentially in a single recombinant organism in systems akin to synthetic biology.

The implementation of enzymatic methodology also remains limited by the catalysts available in the biocatalytic toolbox, therefore more enzymes suitable for synthesis must either be discovered or engineered. For substrates with low aqueous solubility this suitability is extended to solvent tolerance, which often requires further engineering, disadvantaging a biocatalytic approach.

Biocatalysis continues to demonstrate huge potential to be a key technology in realising the goals of a greener platform for the synthesis of the future, both through sustainable transformations and mild conditions. *N*-alkylation represents a model synthetic method to realise this potential, and the willingness of chemical researchers to explore this will define its success.

Conflict of Interest Statement

The authors declare no conflict of interest.

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